CORRECTION:

This corrects table 2 (RR and 95% CI under model 2 for Triglyceride) of paper V

(Borena W, Edlinger M, Bjørge T, Ha¨ggstro¨m C, Lindkvist B, et al. (2014) A Prospective Study on Metabolic Risk Factors and Gallbladder Cancer in theMetabolic Syndrome and Cancer (Me-Can) Collaborative Study. PLoS ONE 9(2): e89368. doi:10.1371/journal.pone.0089368).

Table 2. Risk of primary gallbladder cancer (n=184) in relation to quintiles of metabolic factors (n=575,390)

Exposure	Quintile level	Mean (SD)	n	Model 1 [1] RR	95% CI	Model 2 [2] RR	95% CI
BMI (kg/m^2)	1	20.7 (1.3)	20	1.00			
	2	23.0 (0.8)	26	1.12	0.58, 2.19		
	3	24.7 (0.8)	38	1.49	0.80, 2.76		
	4	26.8 (0.9)	47	1.70	0.93, 3.09		
	5	31.3 (2.6)	53	1.94	1.08, 3.51		
				P_{trend} = 0.08			
Mid-BP [3] (mmHg)	1	88.2 (4.9)	20	1.00		1.00	
	2	96.9 (2.4)	27	1.37	0.48, 4.01	1.27	0.44, 3.74
	3	102.7 (2.3)	41	2.11	0.77, 5.75	1.86	0.68, 5.04
	4	109.8 (2.9)	35	1.02	0.36, 2.86	0.82	0.29, 2.32
	5	124.5 (9.5)	60	1.81	0.68, 4.81	1.25	0.45, 3.45
				P_{trend} = 0.47		P_{trend} = 0.92	
Glucose (mmol/l)	1	4.2 (0.5)	31	1.00		1.00	
	2	4.8 (0.3)	34	2.51	0.47, 13.5	2.32	0.43, 12.7
	3	5.1 (0.3)	28	1.18	0.20, 7.11	1.07	0.18, 6.33
	4	5.5 (0.4)	38	3.14	0.60, 16.5	2.64	0.49, 13.9
	5	6.8 (2.0)	53	7.52	1.56, 36.1	5.38	1.11, 26.5
				P_{trend} = 0.01		P_{trend} = 0.04	
Cholesterol (mmol/l)	1	4.2 (0.5)	27	1.00		1.00	
	2	5.0 (0.3)	37	1.14	0.53, 2.47	1.11	0.52, 2.38
	3	5.6 (0.3)	34	0.74	0.33, 1.61	0.70	0.32, 1.53
	4	6.2 (0.3)	40	0.71	0.35, 1.53	0.66	0.31, 1.42
	5	7.4 (0.8)	46	0.67	0.32, 1.46	0.62	0.29, 1.32
				P_{trend} = 0.14		P_{trend} = 0.08	
Triglycerides [4] (mmol/l)	1	0.7 (0.2)	22	1.00		1.00	
	2	1.0 (0.2)	30	1.48	0.45, 4.88	1.38	0.38, 2.00
	3	1.3 (0.3)	34	1.40	0.44, 4.49	1.20	0.37, 3.84
	4	1.9 (0.4)	46	2.50	0.84, 7.61	1.94	0.64, 5.94
	5	3.1 (1.7)	48	2.06	0.67, 6.28	1.38	0.44, 4.34
				P_{trend} = 0.12		P_{trend} = 0.50	

[1] RRs were estimated from Cox PH regression models with attained age as time scale after excluding the first year after baseline measurement; RRs are adjusted for smoking status and age at baseline, and stratified by cohort, sex and categories of birth year; RRs are corrected for regression dilution bias by use of the regression dilution ratio; conversion into uncorrected RR = exp (log(RR)*RDR); BMI RDR=0.90, mid-BP RDR=0.54, glucose RDR=0.29, cholesterol RDR=0.66, triglycerides RDR=0.47

[2] Additionally adjusted for quintile levels of BMI (except for BMI)

[3] Mid-BP is (systolic BP + diastolic BP) / 2; value missing for 1 GBC case

[4] Value missing for 4 GBC cases

Abbreviations: BMI=body mass index; BP=blood pressure; GBC=gallbladder cancer; RDR=regression dilution ratio; RR=relative risk; SD=standard deviation

This corrects the sub-section „Comparison with literature" of the "Discussion" section of paper V

(Borena W, Edlinger M, Bjørge T, Ha¨ggstro¨m C, Lindkvist B, et al. (2014) A Prospective Study on Metabolic Risk Factors and Gallbladder Cancer in the Metabolic Syndrome and Cancer (Me-Can) Collaborative Study. PLoS ONE 9(2): e89368. doi:10.1371/journal.pone.0089368)

Comparisons with the literature

The observed significant association between metabolic syndrome and GBC in this study with large number of participants and adequately long follow-up period strengthens reports by a previous case-control study based on over 600 biliary tract cancers which also found significant role of Mets on GBC. (17,) However, such studies may be limited by the timing of exposure and outcome not being able to exclude reverse causality. This may probably be the case with the lack of association between waist circumference and risk of GBC. Such deficiencies are better dealt with prospective studies of long follow up period. Although several prospective studies exist on individual metabolic factors (31, 32), literatures on the association between MetS as an entity and GBC are scarce (13). In a previous prospective study(13) MetS was defined as simultaneous exposure to antihypertensive, hypoglycaemic and hypolypemic treatments which is a rather rough approximation of MetS. Compared to ours this previous study did not find statistically significant association between MetS and GBC which is a rather questionable finding in the face of evident significant association with most of the individual components.

Although several independent mechanisms are depicted to underpin the association between obesity and cancer, the mechanisms that link obesity with gallbladder cancer risk are unclear (34-36). Many studies have identified obesity as a risk to be more pronounced in women, and suggested a possible role of sex hormones (mainly oestrogen) in the pathogenesis of GBC (8, 13, 29, 36-41). There are even indications that sex hormone receptors exist on the tumour tissue (42). Our

results, that increasing BMI poses greater risk mainly in younger women of premenopausal age group, might be supportive of this mechanism. This finding is supported by another cohort study in Norway (13).

In tumours that depend on oestrogen for their growth, like breast and endometrial cancers, obesity is shown to be of greater risk in postmenopausal women (43-46). In our study, however, the risk for GBC was higher for younger women below the age of 50. This observation might be due to chance, as we did not find a significant interaction between age and BMI. However, if confirmed in further studies, the clinicopathological mechanisms may be entirely different for GBC.

Blood glucose levels were shown to be associated with incidence of cancer overall and in several specific sites like the colon, pancreas, liver, and endometrium in previous studies (11, 28, 47-48). Studies reporting specifically a link between GBC and blood glucose levels are almost inexistent (28). The association between glucose and cancer risk in our study remained after adjustment for major putative confounders like BMI, smoking and age, indicating a possible causal link. However, biological mechanisms in the association between blood glucose and cancer are poorly understood. A large case-control study by Shebl et al indicated that although diabetes could be a risk factor for gallstone formation, the association between diabetes and GBC can be explained only partly by the positive association between diabetes and gallstones (14).

The inverse association we observed between total cholesterol and GBC in women may be largely due to preclinical effects of the cancer on total serum cholesterol (49). A lag-time sub-analysis excluding 3 years of follow up after baseline measurement, rendered the association non-significant although the direction of association persisted. This was also shown in another recently published Me-Can study on total serum cholesterol and cancer (50).

Studies on the association between blood pressure and GBC incidence are scarce (48, 51). Although it was shown that several cancer sites might be significantly associated with high blood pressure, none of these studies identified blood pressure as risk for GBC.

A case-control study on serum lipids and biliary tract cancers including gallbladder cancer showed that compared to controls, cases had significantly higher mean levels of serum triglyceride (STG) (15). However, our study, based on prospective data analyses as well as other similar cohort studies did not confirm this finding (48, 52). In the study by Andreotti et al serum measurement took place shortly after cancer diagnosis. In this constellation one cannot rule out a possible reverse causation due to disease effect (53).

In conclusion, our study showed that increasing BMI and blood glucose levels are possible risk factors for GBC. Obesity was seen to pose a greater risk among women in the premenopausal age. Beyond the individual factors, the results of our study show that the metabolic syndrome as an entity presents a risk constellation for the occurrence of gallbladder cancer. Considering the rise in temporal trend of BMI and blood glucose levels (48, 54), we would anticipate that the incidence of GBC might also increase.