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Original Article

Lipid profiles and the risk of endometrial cancer in the Swedish AMORIS study

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Abstract: Background: While the association between obesity and endometrial cancer (EC) is well established, the underlying mechanisms require further study. We assessed possible links between lipid profiles and EC risk, while also taking into account BMI, parity, and menopausal status at baseline. Methods: Using the information available from the Swedish Apolipoprotein MOrtality RISk (AMORIS) study we created a cohort of 225,432 women with baseline values for glucose, triglycerides (TG), and total cholesterol (TC). Two subgroups of 31,792 and 26,317 had, in addition, baseline measurements of HDL, LDL, apolipoprotein A-I and apoB and BMI, respectively. We used Multivariate Cox proportional hazards models to analyze quartiles and dichotomized values of these lipid components for a link to EC risk. Results: During mean follow-up of 12 years (SD: 4.15), 1,144 persons developed endometrial cancer. A statistically significant association was found between TG and EC risk when using both quartiles and a clinical cut-off (Hazard Ratio (HR): 1.10 (95%CI: 0.88-1.37), 1.34 (1.09-1.63), and 1.57 (1.28-1.92)) for the 2nd, 3rd, and 4th quartile, compared to the 1st, with P-value for trend: <0.001). The association remained after exclusion of the first three years of follow-up. Also total cholesterol and TG/HDL ratio were positively associated with EC risk, but no link was found for the other lipid components studied. Conclusion: This detailed analysis of lipid components showed a consistent relation between TG levels and EC risk. Future research should continue to analyze the metabolic pathway and its relation to EC risk, as a pathway to further understand the relation of obesity and disease.

Keywords: Lipid profiles, risk factor, endometrial cancer, Swedish AMORIS study

Introduction

Increasing body mass index (BMI) is strongly associated with endometrial cancer (EC) incidence and death [1]. A meta-analysis including 19 reviews and prospective studies showed that per 5kg/m^2 increase in BMI a woman's risk of development of EC increased with 59% (RR: 1.59 (95%CI: 1.50-1.68) [2]. The molecular mechanisms underlying how adipose tissue and obesity contribute to the pathogenesis of EC are becoming better understood and have revealed a number of rational strategies, both behavioral and pharmaceutical, for the prevention of both primary and recurrent disease.

A greater amount of adipose tissue is thought to improve efficiency by which androstenedione converts into estrone, resulting in higher estrogen levels, which are positively associated with EC risk [3, 4]. Additionally, estrogen is thought to inhibit actions of peroxisome proliferator-activated receptor alpha (PPAR-alpha), a ligand-activated transcription factor that is heavily involved in catabolism of fatty acids and lipoproteins [5]. However, few epidemiological studies have investigated whether commonly measured markers of the lipid metabolism as well as glucose, which may have changed following overweight or obesity, are associated with the risk of EC.

A prospective cohort study of 31, 473 women found no association between low-density lipo-

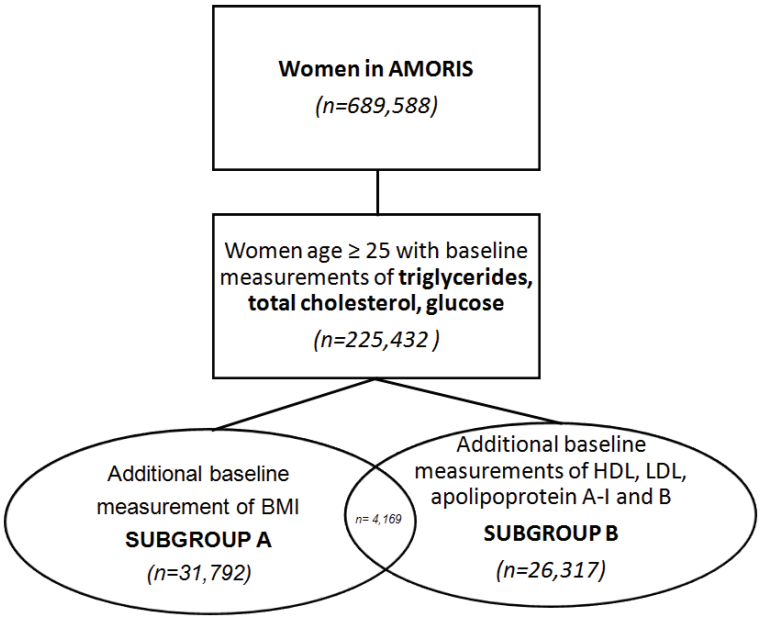

Figure 1. Overview of study population.

protein (LDL) or high-density lipoprotein (HDL) cholesterol and EC risk, but showed a positive relation between levels of triglycerides (TG) and EC after adjusting for age and BMI (HR: 1.79 (95% CI: 1.04-5.28)) [6]. In contrast, low serum cholesterol and low LDL cholesterol were associated with greater EC risk for women above 55 years of age in a case-control study with 256 cases (OR: 4.15 (95% CI: 1.8-9.7) and 3.06 (95% CI: 1.3-7.0), respectively) [7, 8]. To improve the understanding of mechanisms linking obesity and EC risk, we investigated associations between serum lipids and EC risk in a large prospective cohort.

Methods

Study population and data collection

The Swedish AMORIS database has been described in detail elsewhere [9-11]. Briefly, this database is based on linkage of the Central Automation Laboratory (CALAB) database (1985 -1996) to several Swedish national registries such as the National Cancer Register, Cause of Death Register, consecutive Swedish Censuses during 1970-1990, Patient Register, Multi-Generation Register, and National Register of Emigration by using the Swedish 10-digit personal identity number to provide information on cancer diagnosis, vital status, socio-economic status (SES), hospitalization, parity, and emigration [12]. The CALAB database includes data from 351,487 male and 338,101 female healthy individuals having clinical laboratory testing as part of a general health check-up or outpatients referred for laboratory testing. This study complied with the Declaration of Helsinki and was approved by the ethics review board of the Karolinska Institute.

We selected all females aged 25+, whose levels of triglycerides (TG) (mmol/L), total cholesterol (TC) (mmol/L), and glucose (mmol/L) were measured at baseline and who did not have hysterectomy, as registered in the Patient Register, prior to this index examination (n=225,432). Of those, 26,317 had baseline measurement of body-mass index (BMI, kg/m^2) (Subgroup A) and 32,659 persons had baseline information of LDL (mmol/L), HDL (mmol/L), apolipoprotein (apo) B (g/L), and apoA-I (g/L) (Subgroup B) (**Figure 1**). Follow-up started six months after baseline examination and subjects were followed until date of EC diagnosis, hysterectomy, death, emigration out of Sweden or study closing date (31 December 2002), whichever occurred first.

Endometrial cancer diagnosis was taken from the National Cancer Registry (ICD-7: 172), which has an underreporting of <4%. All incident cases of cancer in Sweden must be separately reported to the cancer register by the responsible clinician as well as the respective pathologist/cytologist. All cancers are thus histologically or cytologically confirmed and record linkage by means of the personal identity number ensures that each tumour is only registered once [13, 14]. SES is based on the occupational group recorded in the census information, which classifies gainfully employed subjects into manual and non-manual workers, designated here as blue-collar and white-collar workers [15]. Number of children and mother's age at birth of first child, as measures of parity, were obtained from the Swedish Multi-Generation Register. The concentrations of LDL and HDL were calculated and validation procedures have been reported [11].

Table 1. Laboratory methods used to assess the biomarkers used in AMORIS.

	Instrument	Method	Total imprecision
Triglycerides	Technicon DAX™ 96 Multichannel Analyzer (Bayer Diagnostics, Tarrytown, USA)	GPO-PAP: Enzymatic determination of glycerol with glycerol-phosphate-oxidase (GPO) after hydrolysis with lipoprotein lipase	≤5.0% CV
Total cholesterol	Technicon DAX™ 96 Multichannel Analyzer (Bayer Diagnostics, Tarrytown, USA)	CHOD-PAP: Enzymatic cholesterol assay based on cholesterol esterase and cholesterol oxidase conversion followed by a Trinder-type sequence of reactions	≤2.7% CV
Glucose	Technicon DAX™ 96 Multichannel Analyzer (Bayer Diagnostics, Tarrytown, USA)	GOD-PAP method: Enzymatic colorimetric test in which glucose in serum reacts with oxygen to give gluconate and hydrogen peroxide in the presence of glucose oxidase	<2.2% CV
Apolipoprotein A-I	Technicon DAX™ 96 Multichannel Analyzer (Bayer Diagnostics, Tarrytown, USA)	Immunoturbidimetry using polyclonal antisera from Orion (Helsinki, Finland)	<4.0% CV
Apolipoprotein B	Technicon DAX™ 96 Multichannel Analyzer (Bayer Diagnostics, Tarrytown, USA)	Immunoturbidimetry using polyclonal antisera from Orion (Helsinki, Finland)	<4.0% CV

The balance of cholesterol can be assessed either by ratios of TC to HDL (TC/HDL) or LDL to HDL cholesterol (LDL/HDL) or by using a ratio of apoB/apoA-I, which are component particles of LDL and HDL that bind and transport cholesterol [16].

To measure total cholesterol and TG we applied enzymatic methods whereas apoB and apoA-I were measured by immunoturbidimetric methods [9, 10]. Glucose was measured enzymatically with a glucose-oxidase/peroxidase method. All methods were fully automated with automatic calibration and performed at one accredited laboratory [9] (**Table 1**).

Data analysis

Associations between quartiles of lipid components and EC risk were studied by using multivariate Cox proportional hazards models. All models were adjusted for continuous levels of glucose, TG and TC, as well as age, parity, fasting status, and SES. The association between glucose and EC risk has been studied in detail previously in AMORIS [12]. An analysis of lipid components in relation to EC risk was also carried out using dichotomized values based on cut-offs used in cardiovascular disease prevention (cut-offs: 1.03 mmol/L, 4.10 mmol/L, 5.00, 3.50, 1.50, 1.05, 1.00, and 0.50 for HDL, LDL, TC/HDL, LDL/HDL, apoB, apoA-I, apoB/apoA-I, and log(TG/HDL), respectively) [10, 17, 18]. Levels of TG and TC were also dichotomized based on the National Cholesterol Education Program (NCEP) (cut-offs: 1.71 and 6.50mmol/L) [18].

Following our study on the association between glucose and EC risk, we also conducted an analysis stratified by glucose levels with 6.11 mmol/L as the cut-off [12]. In subgroup A, the association between TG, TC, and EC risk was also stratified by BMI. We chose BMI stratification rather than BMI adjustment because we wanted to test whether overweight (BMI≥25kg/m^2) was associated with increased EC risk via changes in lipid components. Overweight rather than obesity (BMI≥30kg/m^2) was chosen because there were too few obese persons in the cohort. The number of EC cases in subgroup B was too small to allow for stratification by BMI. Wald Tests were used to check for statistical significance of the interaction terms tested above.

Since parity at baseline is thought to be inversely associated with EC risk [19], we conducted a stratified analysis by parity status (0 versus ≥1 children) in which an additional adjustment for age at first birth was made. To account for the unfavorable effects of menopause

on the lipid profile [20], we also did an age-stratified analysis as a proxy for menopausal status at time of baseline [21]. In the analysis of premenopausal women, individuals were followed to age 50 after which they were censored [12]. In the assessment of postmenopausal risk, individuals with a baseline measurement taken before age 50 entered the study at age 50 by means of delayed entry. We evaluated reverse causation by excluding all women with follow-up < 3 years [22]. All Cox proportional hazard models were tested for proportionality by visual inspection of the log(-log(survival) versus log(time) plot and there were no signs of model violations. All statistical methods are consistent with our studies on lipid profiles and risk of prostate and kidney cancer [23-25] and were conducted with Statistical Analysis Systems (SAS) release 9.1.3 (SAS Institute, Cary, NC) and R version 2.7.2 (R Foundation for Statistical Computing, Vienna, Austria). This study complied with the Declaration of Helsinki and was approved by the ethics review board of the Karolinska Institute.

Results

A total of 1,144 women developed EC during mean follow-up of 12.16 years (SD: 4.15) . Descriptive statistics of the study population are shown in **Table 2**. These baseline characteristics were similar for both subgroups A and B (results not shown).

Hazard ratios (HR) for the associations between lipid components and EC risk are presented in **Table 3**. A statistically significant positive association was noted for quartiles of TG and TC (e.g. HR for TG: 1.10 (95%CI: 0.88-1.37), 1.34 (95%CI: 1.09-1.63), 1.57 (95%CI: 1.28-1.92) for the 2nd, 3rd, and 4th quartile compared to the 1st, P-value for trend: <0.001). The TG/HDL ratio was the only lipid ratio found to be statistically significantly positively associated with EC risk (HR: 1.18 (95%CI: 0.71-1.95), 1.38 (95%CI: 0.86-2.24), 1.67 (95%CI: 1.05-2.66) for the 2nd, 3rd, and 4th quartile compared to the 1st, P-value for trend: 0.021). In **Table 4** we show how lipid components are associated with EC risk in relation to clinical cut-off points. We found a positive association between elevated levels of TG, TG/HDL ratio, and EC risk (**Table 4**).

No effect modification by levels of glucose was seen for the association between TG, TC, and EC risk (**Table 5**). In subgroup A, we found no effect modification by BMI levels (</≥ 25kg/m^2) (**Table 5**). **Figure 2** provides further insight into the associations between quartiles of TG and TC, and EC risk by strata of BMI (</≥25.) For TG it can be seen that those with BMI ≥ 25 had a higher cumulative incidence for all quartiles while the difference between quartiles is smaller, particularly among the first and fourth quartiles, explaining why relative risk estimates are slightly larger for those with BMI<25.

Next, we determined how parity or menopausal status may alter associations between lipids and EC risk (**Table 5**). While confidence intervals overlapped where there were lower levels of TC, EC risk was positively associated with high levels of TG for both categories of parity, with the risk being slightly higher among nulliparous women. In the group of pre-menopausal women, HR for EC was only statistically significant for the highest quartile of TG levels, but for the post-menopausal women it was statistically significant for both the 3rd and 4th quartiles of TG (**Table 5**).

Finally, excluding those with follow-up time < 3 years, in order to assess reverse causality, did not affect the above findings (results not shown).

Discussion

This study found consistent evidence for a positive association between elevated TG levels and EC risk, both when using quartiles and dichotomous values of TG as well as when conducting stratified analysis by parity or menopausal status.

A series of contradictory observations have emerged regarding the relation between lipids and EC. In a prospective study of 5,209 subjects, no association was found between TC and any female cancer, while others have found both negative and positive associations between TC and EC risk [26-28]. Most recently, a prospective cohort study including 31,473 women found no association between TC, LDL, or HDL and EC risk, but there was a positive association of TG levels and EC risk (RR: 2.34 (95% CI: 1.04-5.28)) [6].

Our findings of an association between TG and EC risk corroborate this most recent study, but

Table 2. Descriptive statistics by endometrial cancer status.

	Endometrial Cancer N=1144	No Endometrial Cancer N=224288
Age (years)		
Mean (SD)	56.09 (10.06)	46.52 (13.78)
Parity, n (%)		
0 children	316 (31.98)	62139 (32.08)
1 child	247 (25)	43991 (22.71)
2 children	372 (37.65)	77083 (39.79)
3+ children	53 (5.36)	10516 (5.43)
Age at Birth of First Child		
<21	24.86 (4.63)	24.69 (4.84)
BMI (kg/m^2)^		
<18.5	1 (0.09)	822 (0.37)
18.5- 24.99	61 (5.33)	17661 (7.87)
25-29.99	33 (2.88)	5831 (2.60)
>30	20 (1.75)	1888 (0.84)
Missing	1029 (89.95)	198086 (88.32)
SES		
White Collar	325 (28.41)	66216 (29.52)
Blue Collar	643 (56.21)	120583 (53.76)
Not gainfully employed or Missing	176 (15.38)	37489 (16.71)
Follow-up time (years)		
Mean (SD)	8.23 (4.46)	12.18 (4.14)
Fasting status		
Fasting	724 (63.29)	124650 (55.58)
Non-fasting	309 (27.01)	74232 (33.10)
Missing	111 (9.70)	25406 (11.33)
Glucose (mmol/l)		
Mean (SD)	5.15 (1.47)	4.86 (1.13)
Triglycerides (mmol/l)		
Mean (SD)	1.36 (0.835)	1.11(0.72)
Total cholesterol (mmol/l)		
Mean (SD)	6.12 (1.13)	5.59 (1.17)
Apolipoprotein A-I (mmol/l)*		
Mean (SD)	1.54 (0.25)	1.51 (0.24)
Apolipoprotein B (mmol/l)*		
Mean (SD)	1.32 (0.36)	1.16 (0.34)
HDL-cholesterol (mmol/l)*		
Mean (SD)	1.72 (0.46)	1.72 (0.43)
LDL-cholesterol (mmol/l)*		
Mean (SD)	3.84 (1.13)	3.48 (4.14)
ApoB/apoA-I ratio*		
Mean (SD)	0.87(0.30)	0.79 (0.27)
LDL/HDL ratio*		
Mean (SD)	2.47 (1.26)	2.21 (1.22)
Total Cholesterol/HDL ratio*		
Mean (SD)	3.89 (1.60)	3.56 (1.61)
Triglycerides/HDL ratio*		
Mean (SD)	0.93 (0.91)	0.77 (1.08)

^ Measured in subgroup A; * Measured in subgroup B

we also found an association between TC and EC, albeit not when using medical cut-offs [6]. Certain nuclear receptors, such as perioxisome activated receptors (PPAR), have been found to modulate lipid levels [6, 29, 30]. One form of PPAR, PPAR gamma, is expressed in adipose tissue and is activated by endogenous ligands, such as fatty acids, and is involved in lipid metabolism [31]. In EC, as among several other cancers, it has been noted that PPAR gamma

Table 3. Hazard ratios of endometrial cancer in quartiles of lipoprotein components and ratios, adjusted for age, parity, glucose (continuous), triglycerides (continuous), total cholesterol (continuous), fasting status, and SES.

	N(%)		Hazard Ratio (95% CI)
	Endometrial Cancer	No Endometrial Cancer	
Triglycerides (mmol/L)[1]			
<0.70	148 (12.94)	53155 (23.70)	1.00 (Ref)
0.70-0.90	183 (16.00)	47176 (21.03)	1.10 (0.88-1.37)
0.90-1.30	339 (29.63)	61508 (27.42)	1.34 (1.09-1.63)
≥1.30	474 (41.43)	62449 (27.84)	1.57 (1.28-1.92)
P-value for trend			<0.001
Total cholesterol (mmol/L)[2]			
<4.80	122 (10.66)	56221(25.07)	1.00 (Ref)
4.80-5.50	223 (19.49)	54931 (24.49)	1.28 (1.02-1.60)
5.50-6.30	324 (28.32)	55272 (24.64)	1.28 (1.03-1.59)
≥6.30	475 (41.52)	57864 (25.80)	1.15 (0.93-1.43)
P-value for trend			0.731
LDL-cholesterol (mmol/L)[b,2]			
<2.70	19 (11.45)	7726 (23.78)	1.00 (Ref)
2.70-3.36	41 (24.70)	8152 (25.09)	1.48 (0.85-2.56)
3.36-4.13	42 (25.30)	8204 (25.25)	1.11 (0.64-1.94)
≥4.13	64 (38.55)	8411 (25.89)	1.16 (0.67-2.00)
P-value for trend			0.857
HDL-cholesterol (mmol/L) [b,2]			
<1.45	49 (29.52)	8345 (25.68)	1.00 (Ref)
1.45-1.70	42 (25.30)	8240 (25.23)	1.03 (0.66-1.60)
1.70-1.98	29 (17.47)	7983 (24.57)	0.72 (0.44-1.19)
≥1.98	46 (27.71)	7925 (24.39)	0.97 (0.62-1.54)
P-value for trend			0.645
Apolipoprotein B (g/L)[b]			
<0.93	19 (11.46)	8071 (24.84)	1.00 (Ref)
0.93-1.11	34 (20.48)	8063 (24.81)	1.06 (0.60-1.89)
1.11-1.34	41 (24.70)	7841 (24.13)	0.90 (0.49-1.65)
≥1.34	72 (43.37)	8518 (26.21)	1.01 (0.50-2.03)
P-value for trend			0.885
Apolipoprotein A-I (g/L)[b]			
<1.35	37 (22.29)	8434 (25.96)	1.00 (Ref)
1.35-1.49	46 (27.71)	8128 (25.01)	1.14 (0.74-1.77)
1.49-1.65	36 (21.69)	7706 (26.72)	0.89 (0.56-1.42)
≥1.65	47 (28.31)	8225 (25.31)	0.96 (0.61-1.51)
P-value for trend			0.606
Total Cholesterol/HDL ratio [b,2]			
<2.69	30 (18.07)	7758 (23.88)	1.00 (Ref)
2.69-3.22	34 (20.48)	7951 (24.47)	0.93 (0.56-1.52)
3.22-3.98	40 (24.10)	8276 (25.34)	0.85 (0.52-1.39)
≥3.98	62 (37.35)	8508 (26.18)	0.88 (0.53-1.47)
P-value for trend			0.605
LDL/HDL ratio[b,2]			
<1.52	33 (19.88)	8210 (25.27)	1.00 (Ref)
1.52-2.00	31 (18.67)	8053 (24.78)	0.80 (0.49-1.31)
2.00-2.66	47 (28.31)	8161 (25.12)	0.97 (0.61-1.53)
≥2.66	55 (33.13)	8069 (24.88)	0.81 (0.50-1.31)
P-value for trend			0.564
ApoB/apoA-I ratio[b]			
<0.60	26 (15.66)	7988 (24.58)	1.00 (Ref)
0.60-0.75	38 (22.89)	8431 (25.95)	1.02 (0.62-1.68)
0.75-0.93	40 (24.10)	7830 (24.10)	0.86 (0.52-1.43)
≥0.93	62 (37.35)	8244 (25.37)	0.93 (0.56-1.54)
P-value for trend			0.657
Triglycerides/HDL ratio[b,2]			
<0.37	28 (16.87)	8359 (25.73)	1.00 (Ref)
0.37-0.54	34 (20.48)	7941 (24.44)	1.18 (0.71-1.95)
0.54-0.87	44 (26.51)	8124 (25.00)	1.38 (0.86-2.24)
≥0.87	60 (36.14)	8069 (24.83)	1.67 (1.05-2.66)
P-value for trend			0.021

1: Not adjusted for TG; 2 Not adjusted for TC; b: Measured in subgroup B

Table 4. Hazard ratios of endometrial cancer for lipid components and lipid ratios using cut-off points used in cardiovascular disease prevention, adjusted for age, glucose (continuous), triglycerides (continuous), fasting status, and SES.

	N(%)		Hazard Ratio (95% CI)
	Endometrial cancer	No Endometrial cancer	
Triglycerides (mmol/L)[1]			
<1.71	875 (76.49)	196146 (87.45)	1.00 (Ref)
≥1.71	269 (23.51)	28142 (12.55)	1.54 (1.33-1.79)
Total cholesterol (mmol/L)[2]			
<6.50	724 (63.29)	176582 (78.33)	1.00 (Ref)
≥6.50	420 (36.71)	47706 (21.16)	0.99 (0.87-1.12)
LDL-cholesterol (mmol/L)[b2]			
<4.10	100 (60.24)	23812 (73.28)	1.00 (Ref)
≥4.10	66 (39.76)	8681 (26.72)	0.96 (0.69-1.34)
HDL-cholesterol (mmol/L) [b2]			
≥1.03	156 (93.98)	31061 (95.59)	1.00 (Ref)
<1.03	10 (6.02)	1432 (4.41)	0.86 (0.41-1.81)
Apolipoprotein B (mmol/L) [b]			
<1.50	116 (69.88)	27570 (84.85)	1.00 (Ref)
≥1.50	50 (30.12)	4923 (15.15)	1.36 (0.86-2.14)
Apolipoprotein A-I (mmol/L) [b]			
≥1.05	166 (100.0)	32103 (98.80)	1.00 (Ref)
<1.05	0 (0)	390 (1.20)	NA
TC/HDL [b2]			
<5.00	133 (80.12)	29019 (89.31)	1.00 (Ref)
≥5.00	33 (19.88)	3474 (10.69)	1.23 (0.77-1.98)
LDL/HDL [b2]			
<3.5	138 (83.13)	29281 (90.11)	1.00 (Ref)
≥3.50	28 (16.87)	3212 (9.89)	1.08 (0.68-1.73)
ApoB/apoA-I [b]			
<1.00	111 (66.87)	26382 (81.19)	1.00 (Ref)
≥1.00	55 (33.13)	6111 (18.81)	1.31 (0.89-1.94)
Log(TG/HDL) [b2]			
<0.50	143 (86.14)	30017 (92.38)	1.00 (Ref)
≥0.50	23 (13.86)	2476 (7.62)	1.62 (1.03-2.54)

1: Not adjusted for TG; 2: Not adjusted for TC; b: Measured in subgroup B.

expression is downregulated, which suggests that, since PPAR-gamma has also been found to regulate expression of p21 in EC cells, down-regulation of PPAR-gamma supports EC while preventing the clearing of TG [30, 32]. Such a mechanism would suggest that increased triglyceride levels may possibly cause a decrease in PPAR-gamma levels, causing adverse effects on regulation of cell cycle, as is present in cancerous cells. PPAR-alpha, another form of PPAR, is also expressed in adipose tissue and facilitates catabolism of TG [33]. Furthermore, in mice fed ligands for PPAR-alpha, increased expression of proteins such as CDK-1 and CDK-4 in murine hepatic cells was noted, which are over-expressed in cancer cells [31]. As fatty acids are recognized ligands for PPAR-alpha and it has been noted that PPAR-alpha levels are elevated in endometrial cancer, it could be speculated that PPAR-alpha may be a possible explanation to the association between TG and EC risk [31, 34].

Following the studies investigating the association between the metabolic syndrome and EC risk [35-37], we performed a glucose-stratified analysis. Despite the rather consistent positive association between serum glucose levels and EC risk, our study did not find evidence for effect modification. The association between TG and EC remained for those with normal glucose levels, but the lack of an association among those with high glucose is likely due to the small number of cases with high glucose levels. Besides the PPAR mechanism mentioned above, it was recently suggested that dendritic cells, responsible for initiation and maintenance of immune response, from tumour-bearing mice and persons with cancer have high amounts of TG compared with those from tumour free mice and healthy individuals [38]. These findings suggest that manipulating lipid levels in den-

Table 5. Hazard ratios of endometrial cancer in quartiles of lipoprotein components and ratios, adjusted for age, parity, glucose (continuous), triglycerides (continuous), total cholesterol (continuous), fasting status, and SES, stratified by parity (nulliparous vs. parous) or menopausal stage.

	N(%)		Hazard Ratio (95% CI)	N(%)		Hazard Ratio (95% CI)	P-values for Interaction
	Endometrial Cancer	No Endometrial Cancer		Endometrial Cancer	No Endometrial Cancer		
	Glucose <6.11 mmol/L			Glucose ≥6.11 mmol/L			
Triglycerides (mmol/L)[1]							
<0.70	142 (13.63)	52368 (24.51)	1.00 (Ref)	6 (5.88)	787 (7.42)	1.00 (Ref)	0.922
0.70-0.90	178 (17.08)	46142 (21.59)	1.12 (0.90-1.40)	5 (4.90)	1034 (9.75)	0.46 (0.13-1.64)	
0.90-1.30	322 (30.90)	59102 (27.66)	1.35 (1.10-1.66)	17 (16.67)	2406 (22.69)	0.66 (0.25-1.74)	
≥1.30	400 (38.39)	56070 (26.24)	1.56 (1.27-1.92)	74 (72.55)	6279 (60.15)	0.91 (0.37-2.20)	
P-value for trend			<0.001			0.482	
Total cholesterol (mmol/L)[2]							
<4.80	113 (10.84)	54673 (25.59)	1.00 (Ref)	9 (8.82)	1548 (14.60)	1.00 (Ref)	0.084
4.80-5.50	206 (19.77)	52916 (24.76)	1.27 (1.01-1.60)	17 (16.67)	2015 (19.00)	1.23 (0.49-3.09)	
5.50-6.30	293 (28.12)	52505 (24.57)	1.24 (0.99-1.55)	31 (30.39)	2767 (26.09)	1.57 (0.67-3.67)	
≥6.30	430 (41.27)	52588 (25.08)	1.12 (0.89-1.40)	45 (44.12)	4276 (40.32)	1.11 (0.47-2.61)	
P-value for trend			0.974			0.997	
	BMI <25			BMI ≥25			
Triglycerides (mmol/L)[1,a]			1.00 (Ref)			1.00 (Ref)	
<0.70	12 (19.35)	5445 (29.46)	1.16 (0.53-2.56)	4 (7.55)	915 (11.85)	0.85 (0.23-3.19)	0.438
0.70-0.90	13 (20.97)	4388 (23.74)	1.09 (0.50-2.36)	5 (9.43)	1146 (14.85)	0.91 (0.28-2.88)	
0.90-1.30	16 (25.81)	5053 (27.34)	1.73 (0.79-3.78)	11 (20.75)	2140 (27.72)	1.51 (0.51-4.44)	
≥1.30	21 (33.87)	3597 (19.46)	0.198	33 (62.26)	3518 (45.58)	0.190	
P-value for trend							
Total cholesterol (mmol/L)[2,a]							
<4.80	8 (12.90)	5299 (28.67)	1.00 (Ref)	6 (11.32)	1260 (16.32)	1.00 (Ref)	0.547
4.80-5.50	20 (32.26)	5014 (27.13)	1.92 (0.84-4.40)	7 (13.21)	1680 (21.76)	0.63 (0.21-1.90)	
5.50-6.30	19 (30.65)	4575 (24.75)	1.35 (0.57-3.20)	18 (33.96)	2141 (27.75)	0.92 (0.36-2.39)	
≥6.30	15 (24.19)	3595 (19.45)	0.84 (0.33-2.16)	22 (41.51)	2637 (34/16)	0.65 (0.25-1.72)	
P-value for trend			0.309			0.524	
	Nulliparous			Parous			
Triglycerides (mmol/L)[1]							
<0.70	45 (14.24)	16586 (26.69)	1.00 (Ref)	77 (13.25)	26651 (22.56)	1.00 (Ref)	0.667
0.70-0.90	45 (14.24)	13489 (21.71)	0.94 (0.62-1.43)	99 (17.04)	24639 (20.85)	1.13 (0.83-1.52)	
0.90-1.30	87 (27.53)	16573 (26.67)	1.23 (0.85-1.79)	173 (29.78)	32695 (27.67)	1.29 (0.98-1.70)	
≥1.30	139 (43.99)	15491 (24.93)	1.73 (1.19-2.50)	232 (39.93)	34173 (28.92)	1.45 (1.09-1.92)	
P-value for trend			<0.001			0.005	
Total cholesterol (mmol/L)[2]							
<4.80	37 (11.71)	19013 (30.60)	1.00 (Ref)	65 (11.19)	26713 (22.61)	1.00 (Ref)	0.405
4.80-5.50	58 (18.35)	15783 (25.40)	1.18 (0.78-1.79)	120 (20.65)	28692 (24.28)	1.24 (0.92-1.68)	
5.50-6.30	82 (25.95)	13764 (22.15)	1.18 (0.79-1.78)	169 (29.09)	30608 (25.90)	1.18 (0.88-1.58)	
≥6.30	139 (43.99)	13579 (21.85)	1.15 (0.77-1.73)	227 (39.07)	32145 (27.21)	1.01 (0.75-1.36)	
P-value for trend			0.656			0.455	
	Pre-Menopausal			Post-Menopausal			
Triglycerides (mmol/L)[1]							
<0.70	66 (23.32)	43160 (30.72)	1.00 (Ref)	188 (16.43)	61695 (27.51)	1.00 (Ref)	
0.70-0.90	64 (22.61)	33019 (23.51)	1.12 (0.79-1.58)	183 (16.00)	47176 (21.03)	1.07 (0.86-1.32)	
0.90-1.30	75 (26.50)	36393 (25.91)	1.15 (0.82-1.62)	339 (29.63)	61508 (27.42)	1.31 (1.09-1.58)	
≥1.30	78 (27.56)	27904 (19.86)	1.41 (0.99-2.01)	434 (37.94)	53909 (24.04)	1.57 (1.30-1.90)	
P-value for trend			0.066			<0.0001	
Total cholesterol (mmol/L)[2]							
<4.80	63 (22.26)	49716 (35.39)	1.00 (Ref)	142 (12.41)	61022 (27.21)	1.00 (Ref)	
4.80-5.50	80 (28.27)	41710 (29.69)	1.06 (0.76-1.48)	223 (19.49)	54931 (24.49)	1.26 (1.01-1.58)	
5.50-6.30	81 (28.62)	31644 (22.53)	1.12 (0.80-1.57)	324 (28.32)	55275 (24.64)	1.23 (1.00-1.52)	
≥6.30	59 (20.85)	17406 (12.39)	1.17 (0.81-1.71)	455 (39.77)	53060 (23.66)	1.13 (0.92-1.39)	
P-value for trend			0.368			0.671	

1: Not adjusted for TG; 2: Not adjusted for TC; [a]Measured in subgroup A.

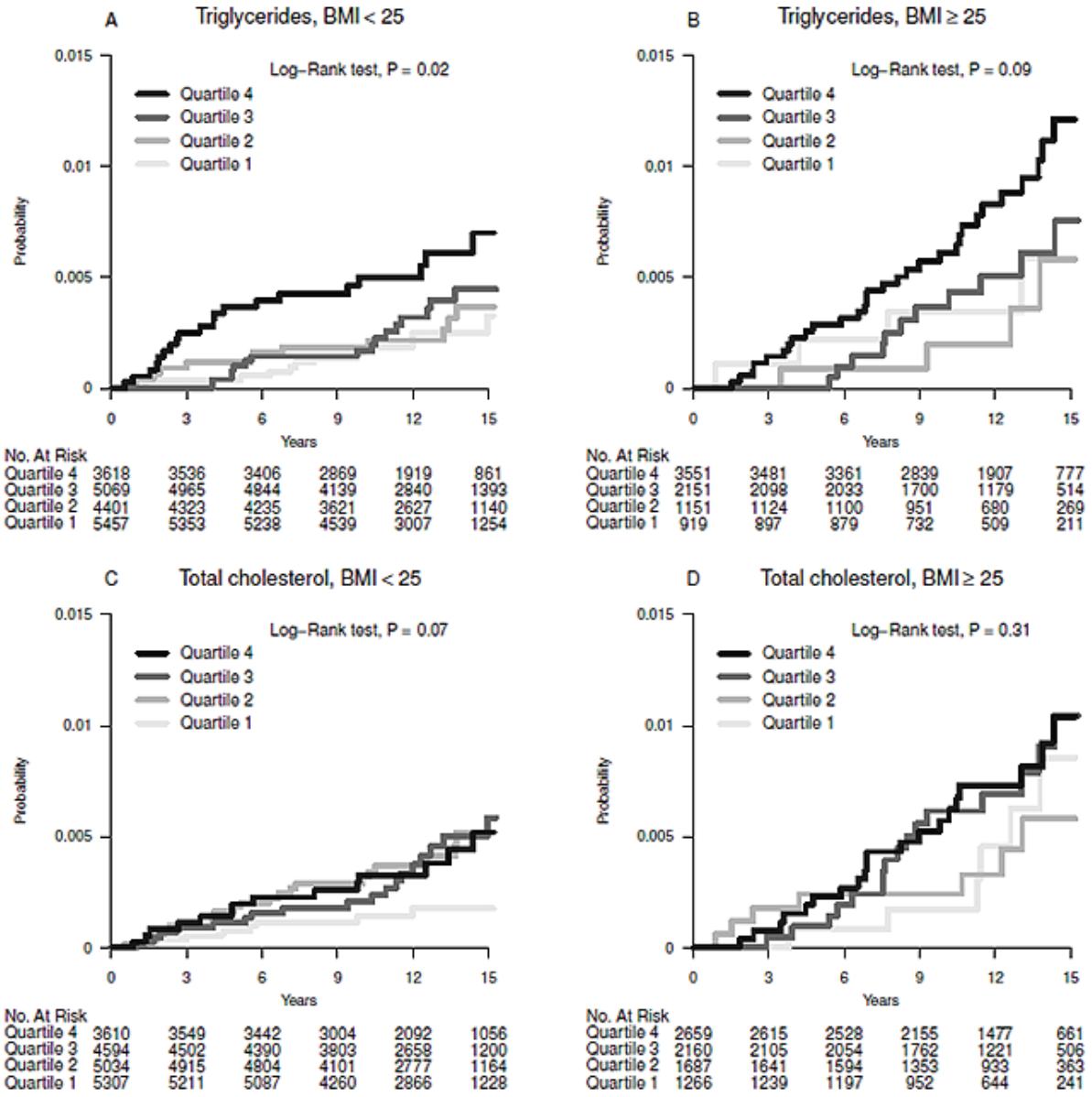

Figure 2. Cumulative incidence of endometrial cancer for quartiles of triglycerides and total cholesterol, stratified by levels of BMI (</≥ 25kg/m^2).

dritic cells may improve immune responses in cancer and illustrate the importance of assessing reverse causality when assessing the link between lipid components and risk of cancer. We did not find evidence for reverse causation, however to verify the findings by Herber et al. [38], we lack information on tumour stage in this database.

In our study, upon stratification by BMI, the positive association between TG and EC risk was attenuated for overweight women; this may be due to the difference in baseline levels of triglyceride-associated EC risk between overweight and non-overweight individuals. Our results have to be interpreted carefully, as there is already a higher EC risk associated with obese individuals, which is not represented in our calculated hazard ratios, but can be seen in **Figure 2**.

We found that the association between TG and EC risk was slightly greater in women who were nulli-parous at baseline, which may suggest that

parity may affect the association of TG and EC. However, as this was observed for only one quartile, it may not be conclusive and TG may be a proxy of another metabolic marker such as obesity. Several studies have noted the protective effect of parity on EC risk [39, 40]. As EC is associated with high levels of unopposed estrogen, the protective effect of parity may be due to the high levels of progesterone that are present during the course of pregnancy [19]. Protection due to parity may also arise from the shedding of malignant cells through childbirth [40]. Experiments in mice have shown a decrease in elevated TG levels in mice injected with progesterone, which while speculative, could explain the protective effect of parity on the association of TG with greater EC risk [41].

Additionally, we noted a stronger association between TG and EC risk for postmenopausal women compared to premenopausal women. However, this observation was limited to the highest quartile of TG. In addition, one has to be aware that we did not have detailed information on menopausal status and used age as a proxy. Among premenopausal women, obesity is related to an increased number of anovulatory menstrual cycles [42]. Our observation of an association between menopause and EC risk via TG is in line with previous research, which found menopause to be positively associated with increased TG, possibly related to increased hepatic production of TG-rich particles [43, 44]. The increase in TG and possible subsequent downstream increases in PPAR-alpha and cancer-associated proteins is a potential mechanism of association between possible effect-modification of menopause status at baseline and association between TG and EC risk.

The large number of women with prospective measurements of lipid biomarkers, all measured at the same clinical laboratory, is a major advantage of our analysis. The AMORIS population covers a range of SES and ethnicity similar to that of the general working population of Stockholm county. During the study period the population selected for AMORIS had an all-cause mortality about 14% lower than in the general population of Stockholm county when taking age, gender, and calendar year into account [45], but this does not affect the internal validity of our study. Another strength of this prospective study was its ability to account for parity, menopausal status, and BMI as potential confounders. However, only limited data on BMI was available which confined the statistical power when also studying BMI (n=31,792) and age was used as a proxy for menopausal status. The latter approximation has been used previously and is based on a previously estimated median age at menopause of 50 [12, 21]. All models were adjusted for fasting status, however it was missing for about 10% of the study population. Lack of possible confounding variables, such as age at menarche, oral contraceptive use, measurements of different hormone levels, and hormonal use are limitations of this study.

Conclusion

Triglycerides were consistently associated with a greater EC risk in this prospective study. These results suggest that lipid metabolism, particularly TG, is a possible mechanism through which obesity is linked to EC. Future research should continue to analyze the metabolic pathway and its relation to EC risk, as a pathway to further understand the relation of obesity and disease.

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