Biomarkers and prediction models for type 2 diabetes and diabetes related outcomes

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Chapter 7

Plasma procalcitonin is associated with obesity, insulin resistance and the metabolic syndrome

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Abstract

Background Procalcitonin, a well-known biomarker of sepsis and bacterial infections, is produced by adipose tissue and has potential as a marker for chronic low-grade inflammation. The objective of this study was to investigate whether plasma procalcitonin levels in the normal range are associated with obesity, insulin resistance and metabolic syndrome (MS) in the general population.

Methods Plasma procalcitonin (0.006-0.1 ng/ml) was measured in 3197 men and 3638 women (aged 28 to 75 years) of the Prevention of Renal and Vascular End-stage Disease (PREVEND) study using an ultra-sensitive immunoluminometric assay. MS was defined according to Adult Treatment Panel III criteria.

Results Median (interquartile range) plasma procalcitonin was 0.018 (0.015-0.022) ng/ml in men and 0.014 (0.012-0.017) ng/ml in women (P <0.001). Plasma procalcitonin was positively associated with BMI and waist circumference. In both sexes, cross-sectional associations of plasma procalcitonin with insulin resistance and components of the MS remained significant after adjustment for age, BMI, waist circumference and other covariates. The age-adjusted odds ratio (OR) for MS was 3.2 (95% confidence interval [CI]=2.5-4.2) in men and 4.1 (95%CI, 3.0-5.5) in women, when comparing the highest to the lowest quartile of plasma procalcitonin. The multivariate-adjusted OR for MS was 1.9 (95%CI= 1.4-2.6) in men and 2.3 (95%CI= 1.6-3.3) in women. The multivariate-adjusted OR for insulin resistance was 3.3 (95%CI=2.4-4.3) in men and 2.5 (95%CI= 1.9-3.4) in women.

Conclusions Elevated plasma procalcitonin levels in the normal range are associated with measures of obesity, insulin resistance and metabolic syndrome in the general population.

Introduction

There are strong links between obesity, insulin resistance and components of the metabolic syndrome. Chronic low grade inflammation has been implicated in the pathophysiology of these three intertwined entities [1, 2].

Procalcitonin, a 116-aminoacid polypeptide, is the precursor of calcitonin hormone produced by neuroendocrine C-cells of the thyroid and K-cells of the lung, encoded from the calcitonin I (*CALC I*) gene on chromosome 11 [3-5]. Procalcitonin is best known as a biomarker of infection and severe systemic inflammation [6, 7]. Recent studies show that adipose tissue is capable of expressing and secreting procalcitonin [8-10]. This makes procalcitonin a potential biomarker for obesity-related low grade-inflammation.

There are no data addressing the significance of variation in plasma procalcitonin levels in the general population. So far, procalcitonin level in the normal population has been studied only in a small sample, and only an association of procalcitonin with sex was acknowledged [11]. We hypothesize that plasma procalcitonin may be associated with measures of obesity, insulin resistance and metabolic risk factors.

Methods

This cross-sectional analysis was conducted on the participants from the Prevention of Renal and Vascular Endstage Disease (PREVEND) study in the general population (age ranged between 28 and 75 years) of the city of Groningen, the Netherlands. Details of the study design, recruitment, and procedures have been published elsewhere [12]. Plasma procalcitonin was measured in 7,690 participants from the samples of the baseline screening. At first, we excluded 25 participants with procalcitonin level > 0.1 ng/ml. Further exclusion was for 385 individuals who had no documented fasting blood samples or missing data for other variables, leaving 3,137 men and 3,638 women (total, n=6,835) for the present analysis. The PREVEND study was approved by the local medical ethics committee, University Medical Center Groningen, and conformed to the principles outlined in the Declaration of Helsinki. All participants gave written informed consent.

Blood pressure was measured in supine position with an automatic device (Dinamap XL Model 9300, Johnson-Johnson Medical, Tampa, FL). Smoking and alcohol use were based on self-reports. Metabolic syndrome was defined according to the National Cholesterol Education Program's Adult Treatment Panel III report (ATP III) criteria [13], as participants having at least 3 of the following: 1) Waist circumference > 35 inches (> 88 cm) in women or > 40 inches (> 102 cm) in men, 2) blood pressure ≥ 130/≥85 mmHg or treatment for hypertension, 3) fasting triglycerides ≥ 150 mg/dL (≥ 1.7 mmol/L), 4) HDL cholesterol ≤ 40mg/dL (≤ 1.0 mmol/L) in men or ≤ 50 mg/dL

(≤ 1.3 mmol/L) in women, and 5) fasting blood glucose ≥ 110 mg/dL (≥ 6.1 mmol/L) or treatment for type 2 diabetes. Insulin resistance was assessed based on the homeostasis model assessment for insulin resisatnce (HOMA-IR) that is calculated using the following formula: [glucose (mmol/l)×insulin (mU/ml)]/22.5] [14]. We defined insulin resistance as a HOMA-IR score in upper sex-specific quartiles.

In baseline samples, serum and urinary creatinine, total cholesterol, and plasma glucose were measured by dry chemistry (Eastman Kodak, Rochester, New York). High density lipoprotein (HDL) cholesterol was measured with a homogeneous method (direct HDL, Aeroset TM System, Abbott Laboratories, Abbott Park, Illinois). Triglycerides were measured enzymatically. High-sensitivity C-reactive protein (hs-CRP) was determined by nephelometry (BN II, Dade Behring, Marburg, Germany). Urinary albumin excretion (UAE) was measured as the mean of two 24-hour urine collections by nephelometry with a threshold of 2.3 mg/l (Dade Behring Diagnostic, Marburg, Germany). Insulin was measured with an AxSym® auto-analyzer (Abbott Diagnostics, Amstelveen, The Netherlands). Procalcitonin was measured by a novel commercially available immuno-luminometric assays (B.R.A.H.M.S PCT sensitive LIA, Hennigsdorf, Germany). Assays were performed in EDTA-plasma aliquots that had been stored frozen at -80°C, without prior thawing and re-freezing. The intraassay CV at 0.1 ng/mL was 6% and at 0.03 ng/mL it was 8%. The Functional assay sensitivity, defined as the lowest concentration to be determined with an interassay CV of 20% was 0.007 ng/ml. The lowest detection limit was 0.006 ng/ml. The assay technique has been described previously [11]. All technicians were blinded to the participants' characteristics.

Continuous variables were compared by using one-way ANOVA or a Kruskal-Wallis test and a χ^2 test was used for the categorical variables to test for differences across quartiles of procalcitonin. We evaluated the association of log2 procalcitonin level with the components (continuous) of the metabolic syndrome using univariate and multivariate-adjusted linear regression models in sex-stratified analyses. Regression coefficients with 95%confidence intervals (CIs) were determined. We performed univariate and multivariate-adjusted logistic regression models to test the association between plasma procalcitonin level and presence of the metabolic syndrome and insulin resistance. The models were adjusted for age, measures of obesity, hs-CRP, tobacco smoking, alcohol use, history of cardiovascular disease and hormone replacement therapy (for women). A *P* value of 0.05 or less from two-sided tests was considered statistically significant. The statistical analyses were performed using SPSS 16.0 statistical software (SPSS Inc., Chicago, IL).

Results

Of 3,197 men and 3,638 women, 631 (19.7%) and 616 (16.9%) had metabolic syndrome, respectively. Median (IQR) procalcitonin levels were 0.018 (0.015-0.022) ng/ml in men and 0.014 (0.012-0.017) ng/ml in women (*P* <0.001). Anthropometric and clinical characteristics of the study population are summarized in Table 1 for men

and women separately. Participants with high procalcitonin levels were older, more obese and more likely to fulfill criteria for the metabolic syndrome. They also had lower insulin sensitivity, lower creatinine clearance, higher hs-CRP and higher UAE. Men with high procalcitonin were more likely to be smoker or ex-smoker, whereas women with high procalcitonin were less likely to use alcohol.

In men, across quartiles of body mass index (BMI) median (IQR) procalcitonin levels gradually increased from 0.016 (0.014-0.020) ng/ml in the first to 0.020 (0.016-0.024) ng/ml in the fourth quartile (P<0.001) (Figure S1). In women, this was from 0.013 (0.011-0.015) ng/ml in the first to 0.016 (0.014-0.019) ng/ml in the fourth quartile (P<0.001). In men, across quartiles of waist circumference, median (IQR) procalcitonin increased from 0.016 (0.014-0.020) ng/ml in the first to 0.019 (0.016-0.022) ng/ml in the fourth quartile (P<0.001). In women, this was from 0.013 (0.011-0.015) ng/ml in the first to 0.016 (0.014-0.020) ng/ml in the fourth quartile (P<0.001). Associations of components of the metabolic syndrome – waist circumference, systolic blood pressure, diastolic blood pressure, triglycerides, HDL cholesterol, glucose – and insulin resistance – fasting insulin, HOMA-IR – with procalcitonin were independent of age in linear regression analyses. Further adjustment for BMI attenuated these associations, but they remained statistically significant. Subsequent further adjustments for hs-CRP, smoking status, alcohol intake, history of cardiovascular disease and hormone replacement therapy (for women) did not materially change these associations except for blood pressure, which lost significance in women (Table S1).

Logistic regression analyses (Table 2) show that risk for the metabolic syndrome and insulin resistance increased across procalcitonin quartiles. In multivariate-adjusted models, the odds ratio's (ORs) for metabolic syndrome and insulin resistance in the highest quartile compared with the lowest were 1.9 (95% CI, 1.4-2.6) and 3.3 (95% CI, 2.4-4.3) in men, and 2.3 (95% CI, 1.6-3.3) and 2.5 (95%CI, 1.9-3.4) in women, respectively.

Discussion

To the best of our knowledge, this study explored for the first time the association of plasma procalcitonin with measures of obesity and metabolic and cardiovascular risk factors in a large sample of the general population. An important finding is that variation in plasma procalcitonin within the normal range is associated with insulin resistance and the metabolic syndrome in apparently healthy men and women. The association of plasma procalcitonin with insulin resistance and metabolic syndrome was independent of age, measures of obesity, hs-CRP, history of cardiovascular disease and health behaviors.

The current results are in line with experimental and observational data that suggest that plasma procalcitonin can be an inflammatory biomarker even in the absence of signs of systemic infection or sepsis [8-10, 15, 16]. Human adipose tissue depots have been identified as major non-neuroendocrine calcitonin mRNA expression sites [8, 9], and *in vitro* secretion of procalcitonin by adipocytes was stimulated by activated

Table 1. Anthropometric and clinical characteristics of participants according to sex-specific quartiles of plasma procalcitonin (n=6,835)

Procalcitonin Quartiles, ng/ml		1	2	3	4	
	M	(0.008-0.015)	(0.016-0.018)	(0.019-0.022)	(0.023-0.098)	***P* value***
Characteristic	**F**	(0.006-0.012)	(0.013-0.014)	(0.015-0.017)	(0.018-0.098)	
No. of participants	M	887	806	769	735	-
	F	1043	906	868	821	-
Age, yr	M	46.0±12.0	48.9±12.5	51.1±12.9	52.8±12.9	<0.001
	F	42.5±9.7	45.6±10.8	49.6±12.3	55.2±12.3	<0.001
History of Cardiovascular disease, no. (%)	M	60 (6.8)	58 (7.2)	75 (9.8)	81 (11.0)	0.005
	F	16 (1.5)	20 (2.2)	35 (4.0)	38 (4.6)	<0.001
BMI, kg/m^2	M	25.0±3.3	26.0±3.3	26.8±3.6	27.3±3.8	<0.001
	F	24.4±3.8	25.2±4.2	26.3±4.8	27.8±5.2	<0.001
Normal weight, no. (%)	M	465 (52.4)	314 (39.0)	247 (32.1)	198 (26.9)	<0.001
Overweight, no. (%)		365 (41.1)	402 (49.9)	390 (50.7)	374 (50.9)	
Obese, no. (%)		57 (6.4)	90 (11.2)	132 (17.2)	163 (22.2)	
Normal weight, no. (%)	F	668 (64.0)	498 (55.0)	391 (45.0)	259 (31.5)	<0.001
Overweight, no. (%)		293 (28.1)	294 (32.5)	316 (36.4)	319 (38.9)	
Obese, no. (%)		82 (7.9)	114 (12.6)	161 (18.5)	243 (29.6)	
Waist circumference, cm	M	89.6±10.2	93.0±10.1	95.6±10.7	97.1±11.5	<0.001
	F	80.0±10.8	84.8±11.9	90.2±12.2	94.6±12.3	<0.001
Systolic blood pressure, mmHg	M	124.9±16.1	126.9±16.6	129.9±18.1	132.5±18.6	<0.001
	F	113.6±15.9	116.9±17.8	121.0±20.1	127.9±21.4	<0.001
Diastolic blood pressure, mmHg	M	72.3±9.1	73.5±8.9	75.3±9.3	76.8±9.9	<0.001
	F	66.7±8.4	68.1±8.7	69.4±9.1	71.4±8.5	<0.001
Total Cholestrol, mmol/l	M	5.4±1.0	5.6±1.1	5.8±1.0	5.8±1.1	<0.001
	F	5.3±1.0	5.5±1.1	5.7±1.2	6.0±1.2	<0.001
HDL cholesterol, mmol/l	M	1.2±0.3	1.1±0.3	1.1±0.3	1.1±0.3	<0.001
	F	1.6±0.4	1.5±0.4	1.5±0.4	1.4±0.4	<0.001
Triglyceride, mmol/l	M	1.3±0.8	1.5±0.9	1.7±1.1	1.8±1.5	<0.001
	F	1.0±0.4	1.1±0.7	1.3±0.7	1.6±1.0	<0.001
Glucose, mmol/l	M	4.8±0.8	4.9±1.0	5.0±1.0	5.3±1.6	<0.001
	F	4.5±0.7	4.6±0.7	4.7±0.9	5.2±1.6	<0.001
Insulin, mU/l	M	6.8 (4.9-9.7)	7.9 (5.6-11.9)	9.2 (6.2-13.2)	10.5 (6.9-15.6)	<0.001

	F	6.5 (4.8-8.7)	7.1 (5.2-10.1)	7.8 (5.5-11.2)	9.9 (6.5-15.4)	<0.001
HOMA-IR	M	1.4 (1.0-2.1)	1.7 (1.2-2.6)	2.0 (1.3-3.1)	2.4 (1.5-3.7)	<0.001
	F	1.3 (0.9-1.8)	1.4 (1.0-2.1)	1.6 (1.1-2.5)	2.2 (1.3-3.6)	<0.001
Tobacco smoking, no. (%)	M					
Never		266 (30.0)	216 (26.8)	175 (22.8)	167 (22.7)	
Quitted		318 (35.9)	301 (37.3)	310 (40.3)	348 (47.3)	<0.001
Current smoker		303 (34.2)	289 (35.9)	284 (36.9)	220 (29.9)	
	F					
Never		356 (34.1)	294 (32.5)	313 (36.1)	279 (34.0)	
Quitted		344 (33.0)	285 (31.5)	285 (32.8)	271 (33.0)	0.861
Current smoker		343 (32.9)	327 (36.1)	270 (31.1)	271 (33.0)	
Alcohol use, no. (%)	M					
Never		125 (14.1)	143 (17.7)	143 (18.6)	136 (18.5)	
1 to 4 drinks per month		90 (10.1)	94 (11.7)	88 (11.4)	97 (13.2)	
2 to 7 drinks per week		370 (41.7)	307 (38.1)	263 (34.2)	253 (34.4)	0.118
1 to 3 drinks per day		223 (25.1)	201 (24.9)	211 (27.4)	181 (24.6)	
≥ 4 drinks per day		79 (8.9)	61 (7.6)	64 (8.3)	68 (9.3)	
	F					
Never		280 (26.8)	265 (29.2)	308 (35.5)	313 (38.1)	
1 to 4 drinks per month		200 (19.2)	183 (20.2)	155 (17.9)	167 (20.3)	
2 to 7 drinks per week		375 (36.0)	305 (33.7)	245 (28.2)	216 (26.3)	<0.001
1 to 3 drinks per day		173 (16.6)	130 (14.3)	147 (16.9)	105 (12.8)	
≥ 4 drinks per day		15 (1.4)	23 (2.5)	13 (1.5)	20 (2.4)	
Creatinine clearance, ml/min	M	117.4±26.5	114.3±25.8	113.8±28.1	111.5±27.4	<0.001
	F	98.1±21.4	99.1±21.3	96.1±25.1	91.4±24.5	<0.001
Urine albumin excretion, mg/24h	M	9.1 (6.6-16.7)	9.9 (6.8-17.3)	10.7 (7.1-20.9)	13.0 (7.5-31.9)	<0.001
	F	7.8 (5.7-12.1)	8.1 (5.7-13.2)	8.5 (6.0-14.0)	10.0 (6.4-18.6)	<0.001
hs-CRP, mg/l (n=6617)	M	0.7 (0.3-1.7)	1.0 (0.5-2.4)	1.3 (0.7-2.7)	2.0 (1.0-4.4)	<0.001
	F	0.9 (0.4-2.2)	1.1 (0.5-2.5)	1.4 (0.6-3.3)	2.3 (1.0-5.1)	<0.001

Abbreviations: M, male; F, female; BMI, body mass index; HDL, high-density lipoprotein; hs-CRP, high –sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment for insulin resistance. *P values are based on χ^2 test for categorical data, spearman rank correlation for ordinal data and ANOVA or Kruskal-Wallis for continuous data; depending on the normality of the data, which were presented by mean±S.D. or median (interquartile range).

Table 2. Odds ratios for metabolic syndrome and insulin resistance according to sex-specific quartiles of plasma procalcitonin

	Procalcitonin Quartiles, ng/ml				
	1	2	3	4	*P* value for trend
Men					
No. of person	887	806	769	735	
Metabolic syndrome,					
No. of cases	94	137	169	231	
Unadjusted OR (95% CI)	1.00	1.7 (1.3-2.3)	2.4 (1.8-3.1)	3.9 (3.0-5.0)	<0.001
Age-adjusted OR (95% CI)	1.00	1.6 (1.2-2.1)	2.1 (1.6-2.7)	3.2 (2.5-4.2)	<0.001
Multivariate OR (95% CI) †	1.00	1.2 (0.9-1.7)	1.3 (0.9-1.8)	1.9 (1.4-2.6)	<0.001
Insulin resistance, *					
No of cases	103	168	223	303	
Unadjusted OR (95% CI)	1.00	2.0 (1.5-2.6)	3.1 (2.4-4.0)	5.3 (4.1-6.9)	<0.001
Age-adjusted OR (95% CI)	1.00	1.9 (1.4-2.5)	2.8 (2.2-3.6)	4.7 (3.6-6.0)	<0.001
Multivariate OR (95% CI) †	1.00	1.6 (1.2-2.1)	2.1 (1.6-2.8)	3.3 (2.4-4.3)	<0.001
Women					
No. of person	1043	906	868	821	
Metabolic syndrome,					
No. of cases	66	102	160	288	
Unadjusted OR (95% CI)	1.00	1.9 (1.4-2.6)	3.3 (2.5-4.5)	8.0 (6.0-10.7)	<0.001
Age-adjusted OR (95% CI)	1.00	1.5 (1.1-2.2)	2.2 (1.6-3.0)	4.1 (3.0-5.5)	<0.001
Multivariate OR (95% CI) †	1.00	1.3 (0.9-1.8)	1.3 (0.9-1.9)	2.3 (1.6-3.4)	<0.001
Insulin resistance, *					
No of cases	132	168	242	367	
Unadjusted OR (95% CI)	1.00	1.6 (1.2-2.0)	2.7 (2.1-3.4)	5.6 (4.4-7.0)	<0.001
Age-adjusted OR (95% CI)	1.00	1.4 (1.1-1.8)	2.1 (1.7-2.7)	3.9 (3.0-4.9)	<0.001
Multivariate OR (95% CI) †	1.00	1.2 (0.9-1.7)	1.4 (1.2-1.9)	2.5 (1.9-3.4)	<0.001

Abbreviation: OR, odds ratio; CI, confidence interval; hs-CRP, high –sensitivity C-reactive protein.

* Insulin resistance defined as cases with homeostasis model assessment score in upper quartile, namely above 2.8 and 2.3 for men and women, respectively.

† odds ratios with corresponding 95% confidence intervals (95% CIs) has been adjusted for age, BMI, hs-CRP, tobacco smoking, alcohol use, history of cardiovascular diseases and hormone replacement therapy (for women) in 6,617 participants with hs-CRP availabe.

macrophages [9]. Since obesity is associated with increased macrophage infiltration into adipose tissue, a similar scenario may play a role *in vivo*. In a recent publication, an association of plasma procalcitonin with central body fat distribution was found in women with polycystic ovary syndrome [15]. In line with this, we found a significant independent association of waist circumference with procalcitonin in both sexes.

The associations of plasma procalcitonin levels with insulin resistance and components of the metabolic syndrome were attenuated after adjustment for BMI and therefore dependent on BMI. This supports our view that circulating levels of procalcitonin are partly dependent on adipose tissue mass. However, another part of the associations was independent of BMI. Possible explanations are that circulating levels of procalcitonin are related to adipocyte function rather than mass, or that other factors that link inflammation to the metabolic syndrome play a role, e.g. non-assessed atherosclerosis [17] or periodontitis [18].

This study extends the available information for procalcitonin to a role as a biomarker of non-infectious conditions, namely the metabolic and cardiovascular arena. Moreover, since plasma procalcitonin can now be measured within the normal range, it warrants further research into its potential to identify individuals at risk of cardiovascular and chronic metabolic disease.

There are several limitations of this study. The study is a cross-sectional investigation and causal relationships of procalcitonin as a novel biomarker of the metabolic syndrome and insulin resistance can not be inferred. Another limitation is the use of insulin resistance based on HOMA-IR instead of the gold standard hyperinsulinemic euglycemic clamp technique. While our study included apparently healthy adults, mostly recruited from Caucasians in the Netherlands, it is unclear if our findings would be replicable in other regions and among un-healthy individuals with cardiovascular or other comorbidities.

In conclusion, our findings based on community-based data show that higher plasma procalcitonin levels in the normal range are associated with increased measures of obesity, components of the metabolic syndrome, and greater risk of having metabolic syndrome and insulin resistance. Because associations only partly depend on BMI, plasma procalcitonin may serve as a new marker for adipocyte dysfunction, chronic low-grade inflammation or both.

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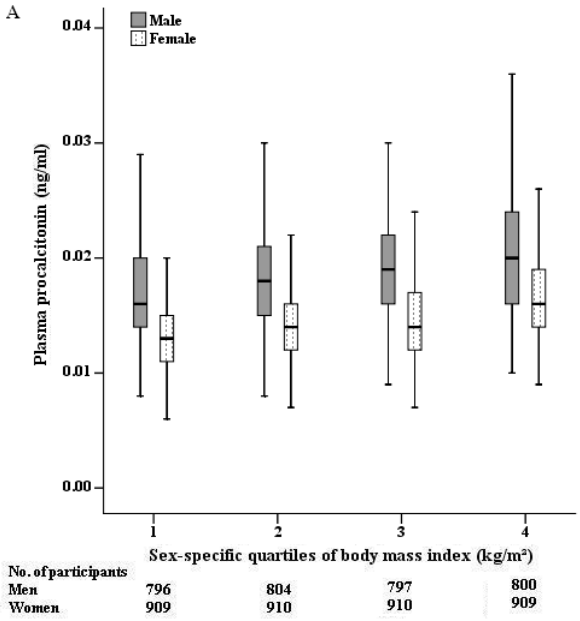
Appendix



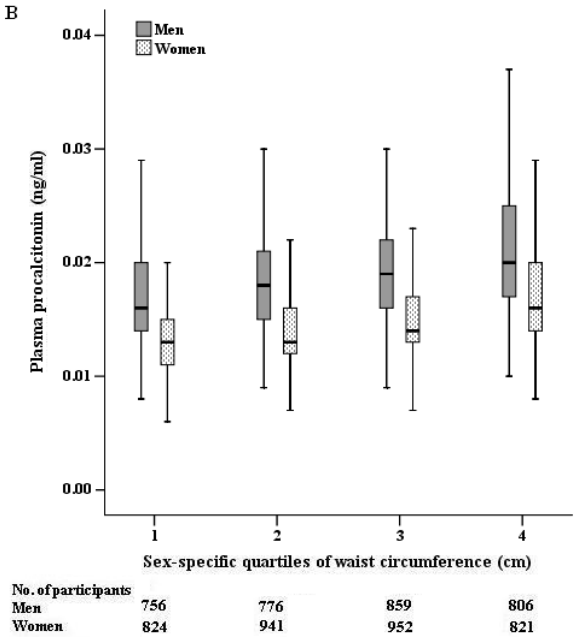


Figure S1. Association of plasma procalcitonin levels with body mass index (A) and waist circumference (B) in men and women

Table S1. Regression coefficients for Log_2 procalcitonin with components of metabolic syndrome, fasting insulin and HOMA-IR*

	Men			Women		
	Unstandardized β (95%CI)	Standardized β	*P* value	Unstandardized β (95%CI)	Standardized β	*P* value
Glucose, mmol/l						
Model 1	0.45 (0.37-0.54)	0.18	<0.001	0.64 (0.56-0.72)	0.26	<0.001
Model 2	0.34 (0.26-0.43)	0.13	<0.001	0.42 (0.33-0.50)	0.17	<0.001
Model 3	0.24 (0.51-0.32)	0.09	<0.001	0.31 (0.23-0.39)	0.12	<0.001
Model 4	0.23 (0.14-0.32)	0.09	<0.001	0.29 (0.21-0.37)	0.12	<0.001
Model 5	0.22 (0.13-0.31)	0.08	<0.001	0.24 (0.15-0.32)	0.10	<0.001
Insulin, mU/l						
Model 1	3.15 (2.63-3.68)	0.21	<0.001	4.21 (3.77-4.66)	0.29	<0.001
Model 2	2.88 (2.36-3.40)	0.19	<0.001	3.65 (3.18-4.13)	0.25	<0.001
Model 3	1.53 (1.06-2.01)	0.10	<0.001	2.21 (1.80-2.62)	0.15	<0.001
Model 4	1.43 (0.96-1.90)	0.09	<0.001	2.05 (1.64-2.45)	0.14	<0.001
Model 5	1.42 (0.94-1.92)	0.09	<0.001	1.85 (1.42-2.28)	0.13	<0.001
HOMA-IR						
Model 1	1.04 (0.88-1.19)	0.22	<0.001	1.34 (1.21-1.47)	0.32	<0.001
Model 2	0.92 (0.76-1.08)	0.19	<0.001	1.11 (0.98-1.25)	0.27	<0.001
Model 3	0.55 (0.40-0.70)	0.12	<0.001	0.73 (0.61-0.85)	0.18	<0.001
Model 4	0.52 (0.37-0.67)	0.11	<0.001	0.69 (0.57-0.81)	0.16	<0.001
Model 5	0.52 (0.37-0.67)	0.11	<0.001	0.60 (0.48-0.73)	0.15	<0.001
Waist circumference, cm						
Model 1	5.97 (5.14-6.80)	0.24	<0.001	9.15 (8.19-10.11)	0.30	<0.001
Model 2	4.50 (3.71-5.30)	0.18	<0.001	5.76 (4.78-6.74)	0.19	<0.001
Model 3	-	-	-	-	-	-
Model 4	-	-	-	-	-	-
Model 5	4.21 (3.39-5.03)	0.17	<0.001	4.09 (3.08-5.09)	0.14	<0.001
Systolic blood pressure, mmHg						
Model 1	6.18 (4.83-7.52)	0.16	<0.001	12.09 (10.63-13.54)	0.26	<0.001
Model 2	3.60 (2.33-4.88)	0.09	<0.001	3.90 (2.52-5.29)	0.08	<0.001
Model 3	1.60 (0.35-2.84)	0.04	0.012	2.17 (0.80-3.55)	0.05	0.002

Model 4	1.53 (0.28-2.78)	0.04	0.016	1.98 (0.60-3.36)	0.04	0.005
Model 5	1.65 (0.37-2.93)	0.04	0.010	1.31 (-0.19-2.80)	0.03	0.087
Diastolic blood pressure, mmHg						
Model 1	3.37 (2.65-4.09)	0.16	<0.001	3.87 (3.20-4.55)	0.18	<0.001
Model 2	1.87 (1.19-2.54)	0.09	<0.001	1.43 (0.74-2.12)	0.07	<0.001
Model 3	0.95 (0.28-1.62)	0.04	0.005	0.92 (0.22-1.61)	0.04	0.010
Model 4	0.88 (0.21-1.54)	0.04	0.010	0.80 (0.10-1.50)	0.04	0.025
Model 5	0.84 (0.16-1.52)	0.04	0.012	0.73 (-0.02-1.48)	0.03	0.055
HDL cholesterol, mmol/l						
Model 1	-0.10 (-0.12- -0.07)	-0.14	<0.001	-0.18 (-0.21- -0.15)	-0.19	<0.001
Model 2	-0.10 (-0.12- -0.07)	-0.14	<0.001	-0.18 (-0.21- -0.15)	-0.19	<0.001
Model 3	-0.06 (-0.08- -0.03)	-0.08	<0.001	-0.13 (-0.16- -0.10)	-0.13	<0.001
Model 4	-0.05 (-0.08- -0.03)	-0.08	<0.001	-0.11 (-0.15- -0.08)	-0.12	<0.001
Model 5	-0.05 (-0.07- -0.02)	-0.06	<0.001	-0.10 (-0.13- -0.06)	-0.10	<0.001
Triglyceride, mmol/l						
Model 1	0.46 (0.37-0.54)	0.18	<0.001	0.54 (0.48-0.59)	0.30	<0.001
Model 2	0.45 (0.36-0.54)	0.18	<0.001	0.42 (0.36-0.48)	0.24	<0.001
Model 3	0.32 (0.23-0.40)	0.12	<0.001	0.34 (0.28-0.40)	0.19	<0.001
Model 4	0.30 (0.22-0.39)	0.12	<0.001	0.32 (0.26-0.38)	0.18	<0.001
Model 5	0.31 (0.22-0.39)	0.12	<0.001	0.29 (0.23-0.35)	0.16	<0.001

Abbreviations: HOMA-IR, homeostasis model assessment for insulin resistance; HDL, high density cholesterol; hs-CRP, high –sensitivity C-reactive protein.
*Per doubling increase of procalcitonin level, unstandardized regression coefficients, β, represents the every unit change of metabolic risk factors.
Model 1 is the unadjusted β for Log2 procalcitonin level with the variables. Model 2 presents the age-adjusted β. In model 3, BMI is added to model 2 (not for waist circumference). In model 4, waist circumference is added to model 3 (not for waist circumference). In model 5, hs-CRP, tobacco smoking, alcohol use, history of cardiovascular disease and hormone replacement therapy (for women) are added to model 4 in 6617 participants with hs-CRP availabe.