

# **SUPPLEMENTAL MATERIAL**

**Table S1. Correlations between serum LBP levels and other variables (n=2,568), 2002.**

Variable	Unadjusted		Adjusted for age and sex	
	Correlation coefficient	<i>P</i>	Correlation coefficient	<i>P</i>
Age	0.19	<0.0001	-	-
Male sex	0.10	<0.0001	-	-
Systolic blood pressure	0.17	<0.0001	0.11	<0.0001
Diastolic blood pressure	0.15	<0.0001	0.13	<0.0001
Use of antihypertensive agents	0.14	<0.0001	0.09	<0.0001
Diabetes mellitus	0.13	<0.0001	0.10	<0.0001
Serum total cholesterol	0.08	<0.0001	0.11	<0.0001
Serum HDL cholesterol	-0.17	<0.0001	-0.14	<0.0001
Serum triglycerides (log-transformed)	0.19	<0.0001	0.18	<0.0001
Use of lipid-modifying agents	0.06	0.002	0.04	0.07
Body mass index	0.17	<0.0001	0.20	<0.0001
Estimated glomerular filtration rate	-0.10	<0.0001	-0.04	0.07
Electrocardiogram abnormality	0.09	<0.0001	0.04	0.05
Smoking habits	0.03	0.16	0.03	0.19
Alcohol intake	-0.001	0.97	-0.01	0.73
Regular exercise	0.01	0.51	-0.01	0.88
HOMA-IR (log-transformed)	0.16	<0.0001	0.18	<0.0001
Serum hs-CRP (log-transformed)	0.62	<0.0001	0.60	<0.0001

HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; LBP, lipopolysaccharide-binding protein

The correlation coefficient was assessed by Pearson's correlation for continuous variables or Spearman's rank correlation for categorical variables.

**Table S2. Association between serum lipopolysaccharide-binding protein levels and the development of cardiovascular disease and its subtypes after excluding the subjects with white blood cell count of  $\geq 8600/\mu\text{l}$  (n=2,432), 2002-2012.**

LBP ( $\mu\text{g/mL}$ )	Persons at risk	No. of events	Hazard ratio (95% CI)
			Multivariable-adjusted*
<b>Cardiovascular disease</b>			
Q1 (2.20-9.68)	623	22	1.00 (Reference)
Q2 (9.69-10.93)	621	32	1.06 (0.61-1.83)
Q3 (10.94-12.40)	610	50	1.56 (0.93-2.60)
Q4 (12.41-24.34)	578	66	1.94 (1.18-3.20)
<i>P</i> for trend			0.01
Per 1-SD increment in serum LBP concentrations	2432	170	1.25 (1.08-1.44)
<b>Coronary heart disease</b>			
Q1 (2.20-9.68)	623	10	1.00 (Reference)
Q2 (9.69-10.93)	621	14	0.99 (0.43-2.25)
Q3 (10.94-12.40)	610	30	1.80 (0.86-3.76)
Q4 (12.41-24.34)	578	27	1.46 (0.69-3.08)
<i>P</i> for trend			0.20
Per 1-SD increment in serum LBP concentrations	2432	81	1.25 (1.01-1.53)
<b>Stroke</b>			
Q1 (2.20-9.68)	623	13	1.00 (Reference)
Q2 (9.69-10.93)	621	21	1.17 (0.58-2.36)
Q3 (10.94-12.40)	610	22	1.23 (0.61-2.48)
Q4 (12.41-24.34)	578	45	2.47 (1.30-4.68)
<i>P</i> for trend			0.003
Per 1-SD increment in serum LBP concentrations	2432	101	1.27 (1.06-1.53)

CI, confidence interval; LBP, lipopolysaccharide-binding protein

\*Adjusted for age, sex, systolic blood pressure, use of antihypertensive agents, diabetes mellitus, serum total cholesterol, serum high-density lipoprotein cholesterol, serum triglycerides, use of lipid-modifying agents, body mass index, estimated glomerular filtration rate, electrocardiogram abnormalities, smoking habits, alcohol intake, and regular exercise.

**Table S3. Association between serum lipopolysaccharide-binding protein levels and the development of cardiovascular disease and its subtypes after excluding the subjects who died due to fatal infection during the follow-up (n=2,522), 2002-2012.**

LBP ( $\mu\text{g/mL}$ )	Persons at risk	No. of events	Hazard ratio (95% CI)
			Multivariable-adjusted*
<b>Cardiovascular disease</b>			
Q1 (2.20-9.68)	635	23	1.00 (Reference)
Q2 (9.69-10.93)	629	30	0.95 (0.55-1.65)
Q3 (10.94-12.40)	628	52	1.51 (0.91-2.50)
Q4 (12.41-24.34)	630	66	1.74 (1.06-2.84)
<i>P</i> for trend			0.02
Per 1-SD increment in serum LBP concentrations	2522	171	1.21 (1.05-1.39)
<b>Coronary heart disease</b>			
Q1 (2.20-9.68)	635	10	1.00 (Reference)
Q2 (9.69-10.93)	629	13	0.92 (0.40-2.13)
Q3 (10.94-12.40)	628	32	1.89 (0.91-3.91)
Q4 (12.41-24.34)	630	26	1.30 (0.61-2.75)
<i>P</i> for trend			0.10
Per 1-SD increment in serum LBP concentrations	2522	81	1.16 (0.94-1.43)
<b>Stroke</b>			
Q1 (2.20-9.68)	635	14	1.00 (Reference)
Q2 (9.69-10.93)	629	21	1.09 (0.55-2.16)
Q3 (10.94-12.40)	628	24	1.20 (0.61-2.36)
Q4 (12.41-24.34)	630	44	2.09 (1.12-3.90)
<i>P</i> for trend			0.02
Per 1-SD increment in serum LBP concentrations	2522	103	1.24 (1.03-1.49)

CI, confidence interval; LBP, lipopolysaccharide-binding protein

\*Adjusted for age, sex, systolic blood pressure, use of antihypertensive agents, diabetes mellitus, serum total cholesterol, serum high-density lipoprotein cholesterol, serum triglycerides, use of lipid-modifying agents, body mass index, estimated glomerular filtration rate, electrocardiogram abnormalities, smoking habits, alcohol intake, and regular exercise.

**Table S4. Risk of cardiovascular disease and its subtypes according to serum lipopolysaccharide-binding protein levels using the method proposed by Fine and Gray (n=2,568), 2002-2012.**

LBP ( $\mu\text{g/mL}$ )	Persons at risk	No. of events	Hazard ratio (95% CI)
			Multivariable-adjusted*
<b>Cardiovascular disease</b>			
Q1 (2.20-9.68)	641	23	1.00 (Reference)
Q2 (9.69-10.93)	643	33	1.02 (0.59-1.76)
Q3 (10.94-12.40)	639	52	1.52 (0.91-2.51)
Q4 (12.41-24.34)	645	72	1.94 (1.20-3.16)
<i>P</i> for trend			0.005
<b>Coronary heart disease</b>			
Q1 (2.20-9.68)	641	10	1.00 (Reference)
Q2 (9.69-10.93)	643	15	1.02 (0.45-2.28)
Q3 (10.94-12.40)	639	32	1.88 (0.90-3.93)
Q4 (12.41-24.34)	645	30	1.54 (0.73-3.24)
<i>P</i> for trend			0.15
<b>Stroke</b>			
Q1 (2.20-9.68)	641	14	1.00 (Reference)
Q2 (9.69-10.93)	643	22	1.12 (0.56-2.28)
Q3 (10.94-12.40)	639	24	1.23 (0.62-2.44)
Q4 (12.41-24.34)	645	48	2.34 (1.26-4.38)
<i>P</i> for trend			0.004

CI, confidence interval; LBP, lipopolysaccharide-binding protein

\*Adjusted for age, sex, systolic blood pressure, use of antihypertensive agents, diabetes mellitus, serum total cholesterol, serum high-density lipoprotein cholesterol, serum triglycerides, use of lipid-modifying agents, body mass index, estimated glomerular filtration rate, electrocardiogram abnormalities, smoking habits, alcohol intake, and regular exercise.

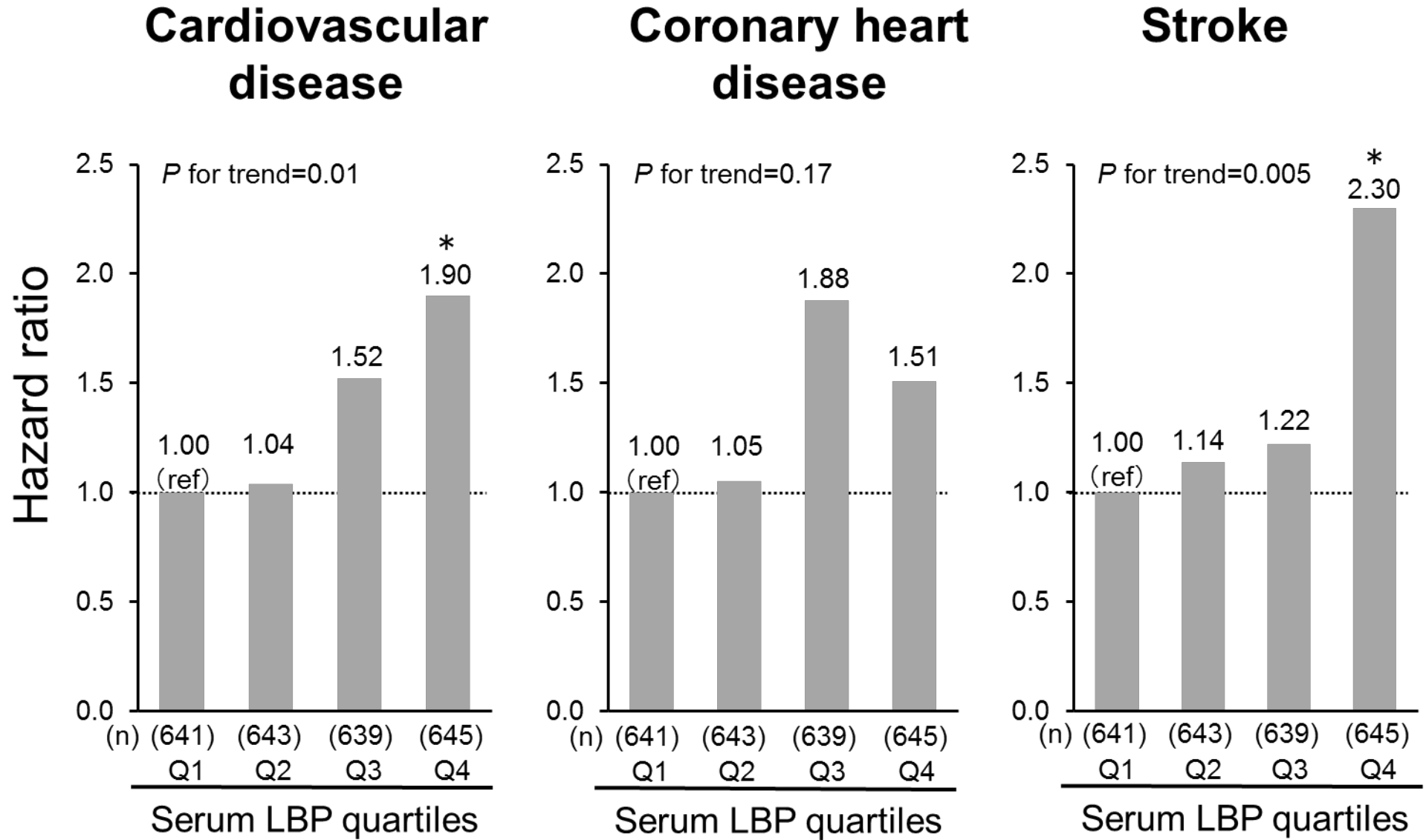
**Table S5. Multivariable-adjusted hazard ratios per 1-SD increment in serum lipopolysaccharide-binding protein level for cardiovascular disease according to amount of alcohol consumption among subjects with available data (n=2,551), 2002-2012.**

Subgroups	Persons at risk	No. of events	Hazard ratio (95% CI) per 1-SD increment in serum LBP	<i>P</i> for heterogeneity
Alcohol intake_No	1432	104	1.36 (1.14-1.61)	
Alcohol intake_Yes				0.16
<18g ethanol/day	541	39	1.04 (0.72-1.48)	
≥18g ethanol/day	578	37	1.13 (0.83-1.54)	

CI, confidence interval; LBP, lipopolysaccharide-binding protein; SD, standard deviation

The model was adjusted for age, sex, systolic blood pressure, use of antihypertensive agents, diabetes mellitus, serum total cholesterol, serum high-density lipoprotein cholesterol, serum triglycerides, use of lipid-modifying agents, body mass index, estimated glomerular filtration rate, electrocardiogram abnormalities, smoking habits, and regular exercise.

Figure S1. Risk of cardiovascular disease and its subtypes according to serum lipopolysaccharide-binding protein levels (n=2,568), 2002-2012.



Q1 to Q4 indicate ascending quartiles of LBP levels (Q1: 2.20-9.68 µg/mL; Q2: 9.69-10.93 µg/mL; Q3: 10.94-12.40 µg/mL; Q4: 12.41-24.34 µg/mL).

\*P<0.05 vs Q1.

The hazard ratios were adjusted for age, sex, systolic blood pressure, use of antihypertensive agents, diabetes mellitus, serum total cholesterol, serum high-density lipoprotein cholesterol, serum triglycerides, use of lipid-modifying agents, body mass index, estimated glomerular filtration rate, electrocardiogram abnormalities, smoking habits, alcohol intake, and regular exercise.