SUPPLEMENTARY DATA

Supplementary Table 1: Pearson correlation coefficient of serum ethylamine concentration with risk factors taken as a continuous variable.

Variables	Serum ethylamine concentration (log-transformed) , log[ng/mL]
Age, years	r= 0.200, p<0.001
Insulinogenic index (log-transformed)	r= -0.061, p=0.005
HOMA-IR (log-transformed)	r= -0.067, p=0.002
Systolic blood pressure, mmHg	r= 0.082, p<0.001
Diastolic blood pressure, mmHg	r= 0.068, p=0.001
Serum total cholesterol, mmol/L	r= -0.017, p=0.43
Serum HDL cholesterol, mmol/L	r= 0.015, p=0.47
Serum triglycerides (log-transformed), log[mmol/L]	r= 0.031, p=0.14
Body mass index, kg/m^2	r= -0.057, p=0.006
Total energy intake, kcal/day	r= 0.069, p=0.001

SUPPLEMENTARY DATA

Supplementary Table 2: Subgroup analyses of the associations between serum ethylamine levels and the risk of incident type 2 diabetes

		Serum ethylamine level, ng/mL				p for trend	p for hetero.[c)]
		Q1 (≤0.86)	Q2 (0.87-2.10)	Q3 (2.11-5.28)	Q4 (≥5.29)		
Age							
<65 years	N of events/subjects	53/406	43/376	43/330	30/293		
	Incidence rate (100PYs)[a)]	2.30	1.60	1.75	1.25	0.02	
	HR (95% CI) [b)]	1.00 (reference)	0.83 (0.55-1.28)	0.78 (0.51-1.20)	0.62 (0.39-0.99)*	0.04	0.16
≥65 years	N of events/subjects	23/157	24/187	27/233	39/271		
	Incidence rate (100PYs)[a)]	2.64	2.20	1.90	2.35	0.69	
	HR (95% CI) [b)]	1.00 (reference)	0.75 (0.42-1.35)	0.74 (0.42-1.32)	0.89 (0.52-1.52)	0.84	
Sex							
Women	N of events/subjects	44/413	29/324	24/290	29/296		
	Incidence rate (100PYs)[a)]	1.84	1.44	1.23	1.43	0.22	
	HR (95% CI) [b)]	1.00 (reference)	0.86 (0.53-1.39)	0.82 (0.49-1.37)	0.76 (0.47-1.25)	0.27	0.60
Men	N of events/subjects	32/150	38/239	46/273	40/268		
	Incidence rate (100PYs)[a)]	3.98	2.83	2.93	2.44	0.07	
	HR (95% CI) [b)]	1.00 (reference)	0.68 (0.41-1.11)	0.62 (0.38-0.99)*	0.61 (0.38-1.00)	0.07	
Glucose tolerance status							
Normal	N of events/subjects	16/416	17/402	16/391	19/392		
	Incidence rate (100PYs)[a)]	0.67	0.67	0.60	0.67	0.94	
	HR (95% CI) [b)]	1.00 (reference)	0.99 (0.50-2.00)	0.91 (0.45-1.85)	1.01 (0.50-2.02)	0.96	0.20
Prediabetes	N of events/subjects	60/147	50/161	54/172	50/172		
	Incidence rate (100PYs)[a)]	8.41	6.04	5.51	5.37	0.02	
	HR (95% CI) [b)]	1.00 (reference)	0.71 (0.48-1.05)	0.66 (0.45-0.98)*	0.61 (0.41-0.91)*	0.02	
Obesity（BMI ≥25 kg/m^2）							
No	N of events/subjects	39/418	45/439	47/437	44/433		
	Incidence rate (100PYs)[a)]	1.70	1.59	1.52	1.38	0.34	
	HR (95% CI) [b)]	1.00 (reference)	0.96 (0.61-1.50)	0.87 (0.56-1.35)	0.93 (0.59-1.45)	0.65	0.048
Yes	N of events/subjects	37/145	22/124	23/126	25/131		
	Incidence rate (100PYs)[a)]	5.02	3.05	2.97	3.01	0.06	

	HR (95% CI) [b]	1.00 (reference)	0.55 (0.31-0.95)*	0.50 (0.28-0.88)*	0.46 (0.26-0.80)**	0.008	
Insulinogenic index							
≥0.40	N of events/subjects	42/414	32/384	31/380	34/385		
	Incidence rate (100PYs)[a]	1.78	1.30	1.24	1.28	0.16	
	HR (95% CI) [b]	1.00 (reference)	0.70 (0.43-1.12)	0.64 (0.39-1.05)	0.71 (0.44-1.15)	0.16	0.63
<0.40	N of events/subjects	32/125	34/151	36/165	34/155		
	Incidence rate (100PYs)[a]	5.34	4.09	3.28	3.36	0.05	
	HR (95% CI) [b]	1.00 (reference)	0.88 (0.53-1.48)	0.72 (0.43-1.21)	0.76 (0.45-1.27)	0.22	
HOMA-IR							
<1.60	N of events/subjects	27/371	34/370	33/380	35/388		
	Incidence rate (100PYs)[a]	1.33	1.31	1.11	1.00	0.20	
	HR (95% CI) [b]	1.00 (reference)	1.03 (0.61-1.75)	0.87 (0.51-1.49)	0.81 (0.47-1.38)	0.32	0.22
≥1.60	N of events/subjects	49/192	33/193	37/183	34/176		
	Incidence rate (100PYs)[a]	4.83	2.97	3.28	3.34	0.14	
	HR (95% CI) [b]	1.00 (reference)	0.54 (0.34-0.85)**	0.60 (0.38-0.94)*	0.58 (0.37-0.92)*	0.04	

Abbreviations: BMI, body mass index; CI, confidence interval; hetero., heterogeneity; HOMA-IR, homeostatic model assessment-insulin resistance; HR, hazard ratio

*p<0.05, **p<0.01 vs. Q1

a) Adjusted for age and sex.

b) Adjusted for age, sex, family history of diabetes, systolic blood pressure, use of antihypertensive agents, use of angiotensin II receptor blockers, prediabetes, serum total cholesterol, serum high density lipoprotein cholesterol, serum triglycerides (log-transformed), use of statins, obesity, current smoking, current drinking, and regular exercise. The variable relevant to the subgroup was excluded from each model.

c) Heterogeneities in the association between serum ethylamine levels and multivariable-adjusted hazard ratio on the development of type 2 diabetes between subgroups were tested by using the relevant Cox model including a multiplicative interaction term.

SUPPLEMENTARY DATA

Supplementary Table 3: Baseline characteristics of subjects eligible for the study

Variables	Values (n=12)
Male, n (%)	6 (50%)
Age, years	56.5 (7.6)
Body mass index , kg/m^2	23.4 (2.8)
Systolic blood pressure, mmHg	123.5 (14.2)
Diastolic blood pressure, mmHg	74.7 (10.7)
Heart rate , beats/min	67.5 (15.2)

Values are presented as the means (standard deviation) or a number (percentage).

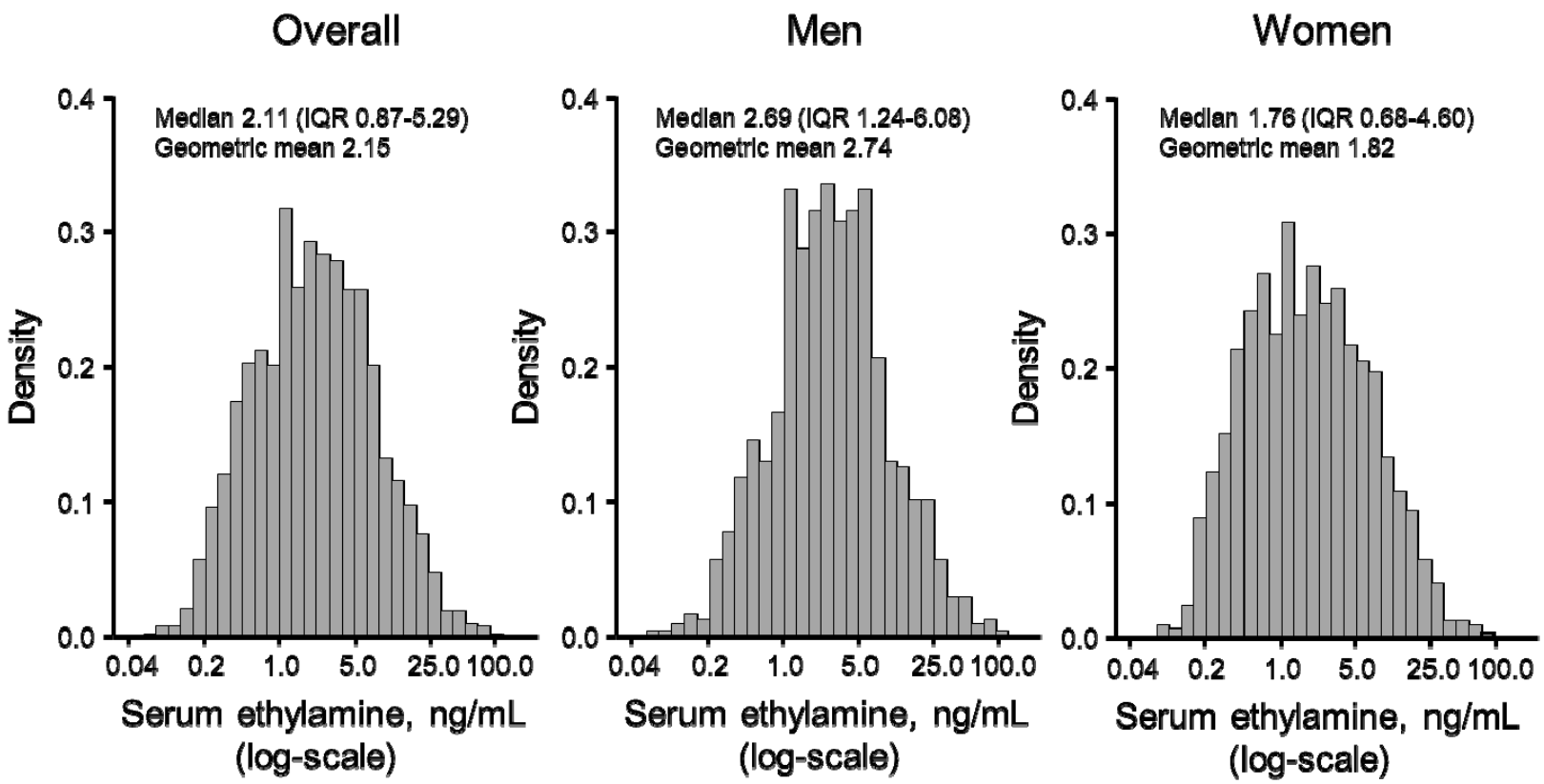
Supplementary Table 4: Kinetic parameters of ethylamine in the subjects after ingestion of L-theanine-rich green tea products.

Parameter	Values (n=12)
t_{max} (hours)	1.67 (0.89)
C_{max} (ng/mL)	5.86 (1.19)
AUC_{0-t} (hours*ng/mL)	86.0 (22.3)
$AUC_{0-\infty}$ (hours*ng/mL)	93.4 (22.5)
$t_{1/2}$ (hours)	12.4 (2.4)

Values are presented as the means (standard deviation).

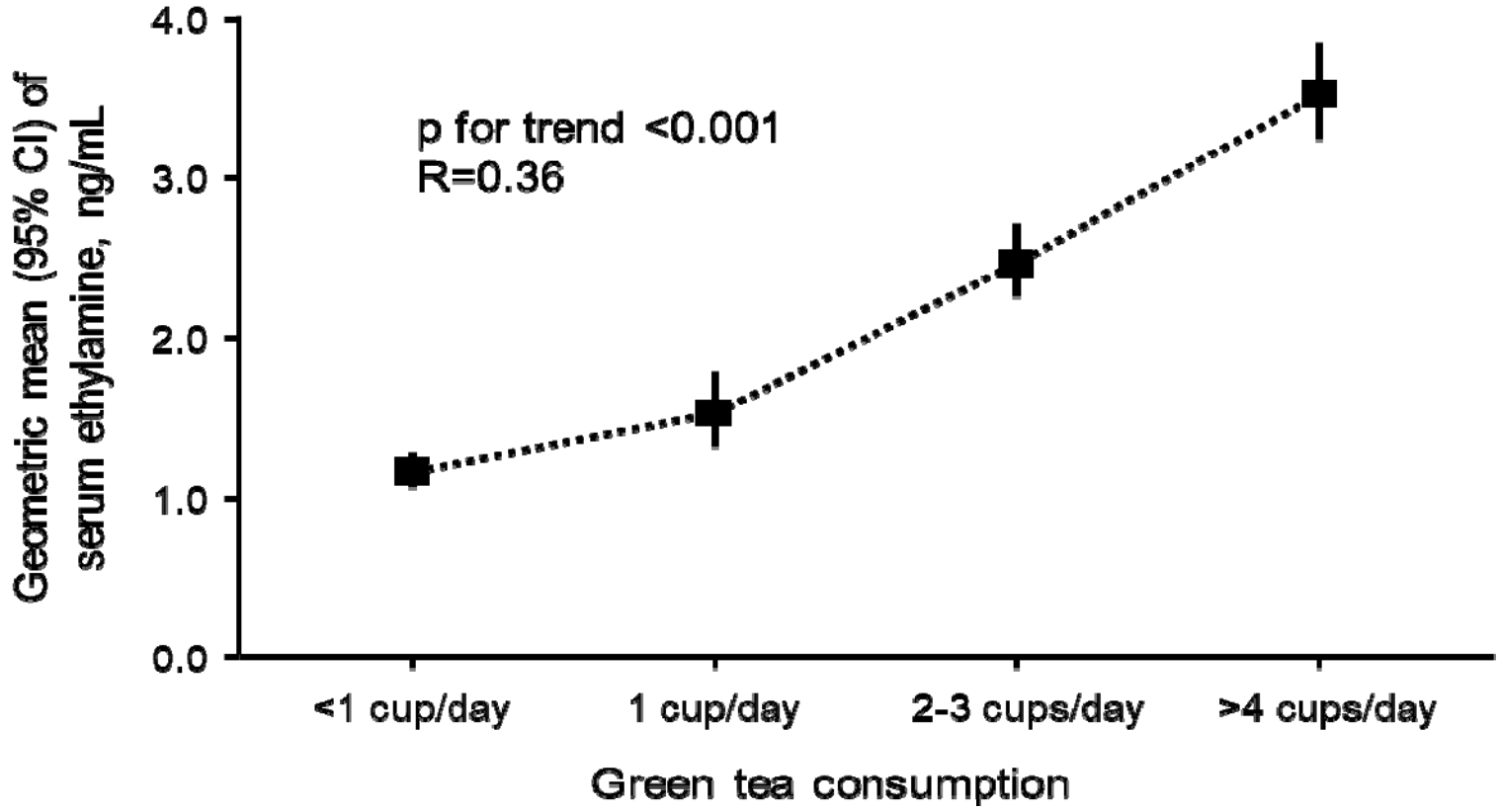
SUPPLEMENTARY DATA

Supplementary Figure S1. Distributions of serum ethylamine concentrations in overall subjects and in either sex
X-bars are shown in log-scale.



SUPPLEMENTARY DATA

Supplementary Figure S2. Association between green tea consumption and serum ethylamine concentrations
Vertical bars denote 95% confidence intervals.



SUPPLEMENTARY DATA

Supplementary Figure 3: Simulation curves of serum ethylamine concentrations after multiple ingestion in the case of (a) twice-daily ingestion with an interval of 12 hours or (b) five-times daily consecutive ingestion at intervals of 1 hour