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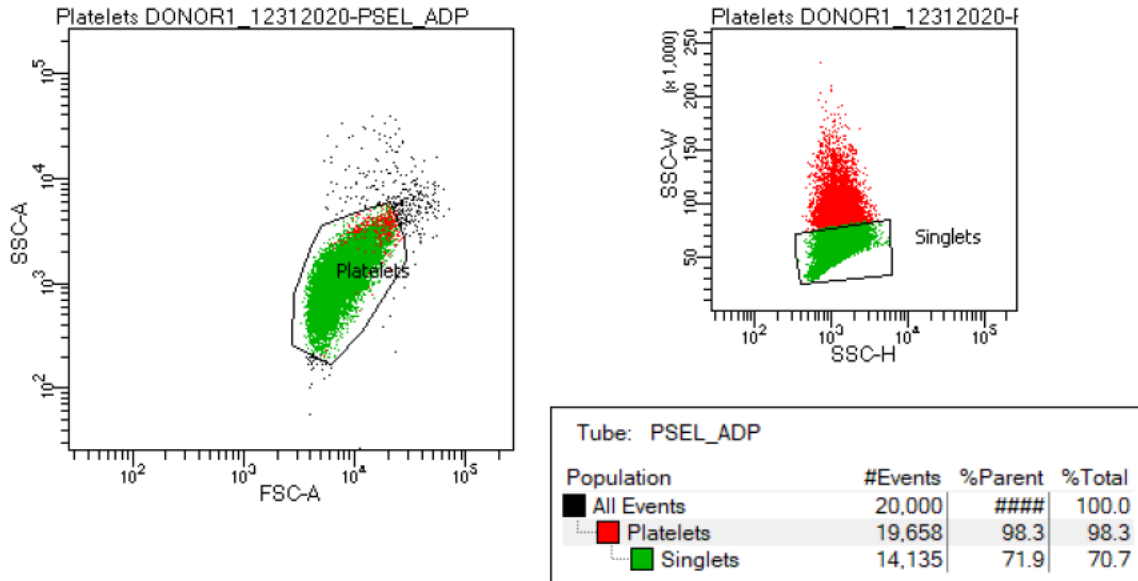

Figure S1: Example of the gating strategy used for platelet flow cytometry experiments. Human washed platelets were exposed to vehicle (saline), stimulated with 2 µM ADP and incubated with anti-P-selectin antibody (CD62P-PE). The sample was analyzed on a FACS LSR Fortessa flow cytometer. Platelets were gated to exclude doublets and the raw mean fluorescent intensity (MFI) was quantified. Twenty thousand events were collected.

Supplementary tables:

Table S1: Clinic characteristics of the discovery cohort

Characteristics	Quartile 1 (n=290)	Quartile 2 (n=289)	Quartile 3 (n=289)	Quartile 4 (n=289)	p
Age (yr)	59.8(51.9-69)	61.3(54.1-70.5)	66.5(57.4-72.5)	70.2(61.8-76)	<0.001
Male (%)	69.3	68.5	62.3	54.3	<0.001
BMI (kg/m^2)	27.8(24.9-31.6)	28.4(25.2-31.2)	28.7(25.6-31.9)	28.7(25.9-33.6)	0.04
Diabetes mellitus (%)	14.8	13.1	23.5	36.7	<0.001
Hypertension (%)	59.7	61.9	67.1	65.4	0.24
Current smoking (%)	15.9	17.3	12.1	9.4	0.02
CAD (%)	75.9	78.2	70.6	77.5	0.14
Heart failure (%)	22.1	21.0	24.3	33.3	0.02
History of MI (%)	45.5	44.7	45.1	50.0	0.57
LDL-c (mg/dl)	100(82-118)	96(80-117)	97(83-112)	93(76-114)	0.05
HDL-c (mg/dl)	34(29-42)	34(28-40)	34(28-41)	33.9(27-40)	0.22
Total cholesterol (mg/dl)	163(145-187)	160(141-188)	164(143-185)	161(139-188)	0.86
Triglycerides (mg/dl)	110(75-153)	119(82-170)	123(85-161)	136(96-201)	<0.001

The baseline characteristics of participants in the discovery cohort are shown stratified by erythritol quartiles. Continuous data are presented as median (interquartile range). Categorical variables are presented as %. BMI, body mass index; CAD, coronary artery disease; HDL, high density lipoprotein; LDL, low density lipoprotein; MI, myocardial infarction. Two-sided P values were calculated by Kruskal-Wallis test for numerical data and Chi-Square test for categorical data comparing erythritol quartiles. n=1,157.

Table S2: Clinical characteristics of the US validation cohort

Characteristics	Quartile 1 (n=542)	Quartile 2 (n=534)	Quartile 3 (n=540)	Quartile 4 (n=533)	p
Age (yr)	57.5(51-64)	60.5(54-67)	64.8(57-72)	70(60-76)	<0.001
Male (%)	66.6	65.9	65.0	58.5	0.02
BMI (kg/m^2)	28.5(25.1-31.9)	28.3(25.6-31.6)	28.7(25.9-32.5)	28.1(25.3-32.9)	0.30
Diabetes mellitus (%)	12.4	15.7	23.9	36.6	<0.001
Hypertension (%)	61.4	62.7	64.3	64	0.76
Current smoking (%)	16.4	14.5	8.6	11.4	0.001
CAD (%)	66.7	71.1	77.4	85.0	<0.001
Heart failure (%)	16.1	21.2	26.7	37.9	<0.001
History of MI (%)	30.9	35.9	41.2	50.1	<0.001
LDL-c (mg/dl)	99(80-120)	99.5(79-120)	94(76-116)	93(73-111)	<0.001
HDL-c (mg/dl)	35(29-43)	35(29-42)	34(28-41)	32(26-38)	<0.001
Total cholesterol (mg/dl)	162(140-187)	163(143-191)	160(137-186)	158(132-184)	0.005
Triglycerides (mg/dl)	103(77-139)	111(82-161)	119(87-159)	131(93-188)	<0.001

The baseline characteristics of participants in the US validation cohort are shown stratified by erythritol quartiles. Continuous data are presented as median (interquartile range). Categorical variables are presented as %. BMI, body mass index; CAD, coronary artery disease; HDL, high density lipoprotein; LDL, low density lipoprotein; MI, myocardial infarction. Two-sided P values were calculated by Kruskal-Wallis test for numerical data and Chi-Square test for categorical data comparing erythritol quartiles. n=2,149.

Table S3: Clinical characteristics of the European validation cohort

Characteristics	Quartile 1 (n=209)	Quartile 2 (n=211)	Quartile 3 (n=205)	Quartile 4 (n=208)	p
Age-yr	67(59-76)	72(65-79)	77(69-82)	79(73-85)	<0.001
Male (%)	71.8	73.5	64.9	70.2	0.25
Diabetes mellitus (%)	13.4	19.4	32.2	46.6	<0.001
Hypertension (%)	75.6	79.6	82.4	84.1	0.14
Current smoking (%)	29.7	14.7	10.2	12.5	<0.001
CAD (%)	64.6	65.4	68.3	78.8	0.005
Heart failure (%)	54.3	60.7	68.8	83.6	<0.001
History of MI (%)	44.0	46.4	46.6	61.5	0.001
LDL-c (mg/dl)	98(71-131)	96(71-130)	91(72-121)	82(64-105)	<0.001
HDL-c (mg/dl)	49(40-62)	49(39-60)	48(40-62)	45(36-57)	0.06
Total cholesterol (mg/dl)	162(137-197)	165(136-199)	167(136-198)	156(129-180)	0.05
Triglycerides (mg/dl)	121(89-172)	111(87-163)	115(90-160)	133(95-174)	0.19

The baseline characteristics of participants in the European validation cohort are shown stratified by erythritol quartiles. Continuous data are presented as median (interquartile range). Categorical variables are presented as %. BMI, body mass index; CAD, coronary artery disease; HDL, high density lipoprotein; LDL, low density lipoprotein; MI, myocardial infarction. Two-sided P values were calculated by Kruskal-Wallis test for numerical data and Chi-Square test for categorical data comparing erythritol quartiles. n=833.

Table S4: Hazard ratios for 3-year MACE for the covariates used in the adjusted

Cox models in the discovery cohort

	HR with 95% CI	P value
Age	1.06 (0.85 - 1.34)	0.59
Gender	1.10 (0.70 - 1.72)	0.69
Blood pressure	1.05 (0.88 - 1.26)	0.59
Diabetes	1.23 (0.79 - 1.91)	0.36
Smoking	1.28 (0.73 - 2.25)	0.39
LDL cholesterol	1.02 (0.83 - 1.26)	0.83
HDL cholesterol	1.03 (0.80 - 1.31)	0.84
Triglycerides	1.09 (0.96 - 1.23)	0.18
BMI	0.90 (0.72 - 1.13)	0.36

BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein. Two-sided P

values for the adjusted Cox model are indicated. n=1,157.

Table S5: Hazard ratios for 3-year MACE for the covariates used

in the adjusted Cox models in the US validation cohort

	HR with 95% CI	P value
Age	1.60 (1.35 - 1.89)	<0.001
Gender	0.77 (0.57 - 1.05)	0.10
Blood pressure	1.01 (0.87 - 1.19)	0.86
Diabetes	0.83 (0.59 - 1.17)	0.29
Smoking	2.02 (1.39 - 2.92)	<0.001
LDL cholesterol	1.01 (0.86 - 1.17)	0.95
HDL cholesterol	0.81 (0.69 - 0.96)	0.02
Triglycerides	0.88 (0.73 - 1.06)	0.17
BMI	0.94 (0.81 - 1.11)	0.48

BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein. Two-sided P values for the adjusted Cox model are indicated. n=2,149.

Table S6: Hazard ratios for 3-year MACE for the covariates used

in the adjusted Cox models in the European validation cohort

	HR with 95% CI	P value
Age	1.78 (1.40 - 2.28)	<0.001
Gender	1.06 (0.70 - 1.61)	0.77
Hypertension	1.25 (0.74 - 2.11)	0.40
Diabetes	1.53 (1.04 - 2.24)	0.03
Smoking	1.66 (1 .00- 2.74)	0.05
LDL cholesterol	1.12 (0.89 - 1.42)	0.32
HDL cholesterol	0.94 (0.73 - 1.22)	0.66
Triglycerides	1.06 (0.87 - 1.29)	0.54

LDL, low-density lipoprotein; HDL, high-density lipoprotein. Two-sided P values for the adjusted

Cox model are indicated. n=833.

Table S7: Gender-stratified Cox models for 3-year MACE in the discovery cohort

Female (n=421)	Quartile 1 (n=106)	Q2 (n=105)	Q3 (n=105)	Q4 (n=105)
Unadjusted HR	1	2.35 (0.83 - 6.65)	1.35 (0.43 - 4.25)	4.46 (1.68 - 11.86)**
Adjusted HR	1	2.46 (0.84 - 7.19)	1.46 (0.41 - 5.11)	5.00 (1.68 - 14.9)**

Male (n=736)	Q1 (n=185)	Q2 (n=184)	Q3 (n=183)	Q4 (n=184)
Unadjusted HR	1	1.19 (0.55 - 2.57)	0.64 (0.26 - 1.56)	3.25 (1.69 - 6.24)***
Adjusted HR	1	1.17 (0.53 - 2.58)	0.59 (0.24 - 1.46)	2.69 (1.34 - 5.41)**

The adjustment included age, sex, diabetes mellitus, blood pressure, low-density and high-density lipoprotein cholesterol levels, triglyceride levels, current smoking status and BMI.

Two-sided P values for the Cox model are indicated as follows ***$P<0.001$, **$P<0.01$. n=1,157.

Table S8: Gender-stratified Cox models for 3-year MACE in the US validation cohort

Female (n=773)	Q1 (n=194)	Q2 (n=194)	Q3 (n=195)	Q4 (n=190)
Unadjusted HR	1	1.11 (0.56 - 2.22)	1.41 (0.73 - 2.74)	2.30 (1.25 - 4.23)**
Adjusted HR	1	1.02 (0.52 - 2)	1.18 (0.61 - 2.31)	1.59 (0.79 - 3.2)

Male (n=1376)	Q1 (n=344)	Q2 (n=348)	Q3 (n=340)	Q4 (n=344)
Unadjusted HR	1	1.08 (0.59 - 1.99)	1.7 (0.98 - 2.94)	2.82 (1.70 - 4.70)***
Adjusted HR	1	1.02 (0.55 - 1.90)	1.38 (0.79 - 2.43)	1.96(1.13 - 3.39)*

The adjustment included age, sex, diabetes mellitus, blood pressure, low-density and high-density lipoprotein cholesterol levels, triglyceride levels, current smoking status and BMI. Two-sided P values for the Cox model are indicated as follows ***$P<0.001$, **$P<0.01$, *$P<0.05$. n=2,149.

Table S9: Gender-stratified Cox models for 3-year MACE in the European validation cohort

Female (n=249)	Q1 (n=63)	Q2 (n=62)	Q3 (n=62)	Q4 (n=62)
Unadjusted HR	1	1.64 (0.64 - 4.2)	1.67 (0.65 - 4.30)	3.77 (1.61 - 8.80)**
Adjusted HR	1	1.82 (0.48 – 7.0)	1.66 (0.53 - 5.19)	2.27 (0.75 - 6.82)

Male (n=584)	Q1 (n=150)	Q2 (n=142)	Q3 (n=146)	Q4 (n=146)
Unadjusted HR	1	1.22 (0.65 - 2.32)	2.09(1.17 - 3.72)*	4.92 (2.89 - 8.35)***
Adjusted HR	1	0.98 (0.46 - 2.09)	0.93 (0.43 - 1.98)	2.37(1.16 - 4.84)*

The adjustment included age, sex, diabetes mellitus, hypertension, low-density and high-density lipoprotein cholesterol levels, triglyceride level and current smoking status. Two-sided P values for the Cox model are indicated as follows ***P<0.001, **P<0.01, *P<0.05. n=833.

Table S10: Hazard ratios for 3-year MACE for erythritol in different subgroups of the US validation cohort

Subgroup	n	Q4 vs. Q1 HR (95% CI)	P value	P for interaction
Age ≥ 70	608	2.06 (1.22 - 3.49)	0.007	0.61
Age < 70	1541	1.86 (1.12 - 3.08)	0.02	
Female	773	2.30 (1.25 - 4.23)	0.007	0.43
Male	1356	2.82 (1.70 - 4.70)	<0.001	
Hypertension	652	3.12 (1.25 - 7.76)	0.01	0.95
No Hypertension	1489	2.69 (1.71 - 4.24)	<0.001	
Diabetes	475	2.07 (0.93 - 4.57)	0.07	0.55
No Diabetes	1674	2.63 (1.69 - 4.09)	<0.001	
HbA1C≥5.7 %	1081	2.48 (1.45 - 4.24)	0.001	0.20
HbA1C<5.7 %	952	3.04 (1.62 - 5.68)	0.001	
GFR ≥ 60 ml/min/1.73m^3	1834	1.83 (1.18 - 2.85)	0.007	0.11
GFR <60 ml/min/1.73m^3	315	4.47 (1.82 – 11.0)	0.001	
BMI ≥27 kg/m^2	1346	2.69 (1.57 - 4.61)	<0.001	0.68
BMI <27 kg/m^2	803	2.81 (1.58 - 4.98)	<0.001	
CAD	1610	2.56 (1.67 - 3.94)	<0.001	0.58
No CAD	539	2.74 (0.98 - 7.64)	0.05	
Prior MI	797	2.17 (1.22 - 3.86)	0.008	0.12
No Prior MI	1223	3.26 (1.83 - 5.81)	<0.001	
LDL-c≥ 100 mg/dL	974	2.03 (1.18 - 3.52)	0.011	0.76
LDL-c<100 mg/dL	1175	3.23 (1.87 - 5.57)	<0.001	
HDL- c≥ 40 mg/dL	645	2.02 (1.04 - 3.92)	0.04	0.75
HDL-c<40 mg/dL	1504	2.96 (1.82 - 4.80)	<0.001	
Triglycerides ≥ 150	665	2.86 (1.38 - 5.92)	0.005	0.41
Triglycerides <150	1494	2.82 (1.76 - 4.53)	<0.001	

BMI, body mass index; CAD, coronary artery disease; GFR, glomerular filtration rate; HbA1C, hemoglobin A1C; HDL, high density lipoprotein; LDL, low density lipoprotein; MI, myocardial infarction. Two-sided P values are shown for the Cox model and for interaction with the groups. N numbers for each subset are indicated.

Table S11: Hazard ratios for 3-year MACE for erythritol in different subgroups of the European validation cohort

Subgroup	n	Q4 vs. Q1 HR (95% CI)	P value	P for interaction
Age ≥ 70	540	3.49 (2.12 - 5.73)	<0.001	0.86
Age < 70	293	3.08 (1.22 - 7.78)	0.02	
Female	249	3.77 (1.61 - 8.80)	0.002	0.28
Male	584	4.92 (2.89 - 8.35)	<0.001	
Hypertension	670	6.08 (1.31 – 28.1)	<0.001	0.61
No Hypertension	163	4.97 (3.05 - 8.09)	0.02	
Diabetes	232	5.16 (2.4 - 11.1)	<0.001	0.35
No Diabetes	601	2.96 (1.72 - 5.10)	<0.001	
HbA1C≥5.7 %	439	5.39 (2.96 - 9.81)	<0.001	0.05
HbA1C<5.7 %	394	2.13 (1.06 - 4.25)	0.03	
GFR ≥ 60 ml/min/1.73m^3	559	2.38 (1.32 - 4.31)	0.004	0.21
GFR <60 ml/min/1.73m^3	274	5.25 (2.82 - 9.76)	<0.001	
CAD	577	4.22 (2.58 - 6.89)	<0.001	0.86
No CAD	256	5.97 (1.75 - 20.4)	0.004	
Prior MI	413	4.69 (2.54 - 8.66)	<0.001	0.69
No Prior MI	419	3.48 (1.77 - 6.87)	<0.001	
LDL-c≥ 100 mg/dL	333	4.27 (1.94 - 9.37)	<0.001	0.98
LDL-c<100 mg/dL	479	3.92 (2.25 - 6.83)	<0.001	
HDL- c≥ 40 mg/dL	594	4.28 (2.4 - 7.62)	<0.001	0.99
HDL-c<40 mg/dL	216	4.15 (1.91 - 8.99)	<0.001	
Triglycerides ≥ 150	193	3.85 (1.50 - 9.87)	0.005	0.74
Triglycerides <150	388	3.71 (1.93 - 7.14)	<0.001	

CAD, coronary artery disease; GFR, glomerular filtration rate; HbA1C, hemoglobin A1C; HDL, high density lipoprotein; LDL, low density lipoprotein; MI, myocardial infarction. Two-sided P values are shown for the Cox model and for interaction with the groups. N numbers for each subset are indicated.

Table S12. Cox regression models in the discovery cohort

	HR with 95% CI	P value
Erythritol	1.31 (1.17 - 1.46)	<0.001
Age	1.20 (0.96 - 1.49)	0.12
Gender	1.10 (0.70 - 1.73)	0.68
Blood pressure	1.04 (0.87 - 1.24)	0.67
Diabetes	1.16 (0.73 - 1.84)	0.54
Smoking	1.41 (0.82 - 2.42)	0.22
LDL cholesterol	1.04 (0.84 - 1.28)	0.72
HDL cholesterol	1.04 (0.81 - 1.32)	0.77
Triglycerides	1.11 (0.99 - 1.25)	0.09
BMI	0.97 (0.78 - 1.21)	0.79

Hazard ratio for 3-year MACE per arbitrary unit of Erythritol (untargeted metabolomics) with covariates used for adjustment. BMI, body mass index; HDL, high density lipoprotein; LDL, low density lipoprotein. Two-sided P values are shown for the adjusted Cox model. n=1,157.

Table S13. Cox regression analysis in US validation cohort

	HR with 95% CI	P value
Erythritol	1.21 (1.12 - 1.31)	<0.001
Age	1.69 (1.44 - 1.98)	<0.001
Gender	0.76 (0.56 - 1.03)	0.08
Blood pressure	1.00 (0.86 - 1.17)	0.98
Diabetes	0.82 (0.58 - 1.16)	0.26
Smoking	1.97 (1.35 - 2.88)	<0.001
LDL cholesterol	1.03 (0.88 - 1.19)	0.74
HDL cholesterol	0.80 (0.68 - 0.95)	0.01
Triglycerides	0.89 (0.74 - 1.07)	0.22
BMI	0.96 (0.82 - 1.12)	0.60

Hazard ratio for 3-year MACE per μM of erythritol with covariates used for adjustment. BMI, body mass index; HDL, high density lipoprotein; LDL, low density lipoprotein. Two-sided P values are shown for the adjusted Cox model. n=2,149.

Table S14. Cox regression analysis in the European validation cohort

	HR with 95% CI	P value
Erythritol	1.16 (1.05 - 1.30)	0.005
Age	2.01 (1.6 - 2.54)	<0.001
Gender	1.07 (0.7 - 1.63)	0.76
Hypertension	1.25 (0.73 - 2.13)	0.41
Diabetes	1.68 (1.14 - 2.47)	0.009
Smoking	1.65 (1.01 - 2.71)	0.05
LDL cholesterol	1.09 (0.82 - 1.43)	0.57
HDL cholesterol	0.96 (0.74 - 1.24)	0.75
Triglycerides	1.14 (0.95 - 1.36)	0.16

Hazard ratio for 3-year MACE per µM of erythritol with covariates used for adjustment. HDL, high density lipoprotein; LDL, low density lipoprotein. Two-sided P values are shown for the adjusted Cox model. n=833.