

## List of Online Supplemental Materials

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**Online Supplementary Figure 2:** Glucose metabolism of *cd93*<sup>+/-</sup> female mice compared to *cd93*<sup>+/+</sup> female mice (black dots and black squares respectively). A) Glucose tolerance test of *cd93*<sup>+/-</sup> and *cd93*<sup>+/+</sup> female mice (n=5-10), aged 4 months, before given a western diet. B) Glucose tolerance test of *cd93*<sup>+/-</sup> and *cd93*<sup>+/+</sup> female mice (n=5-10 respectively), after 16 weeks of western diet.

**Online Supplementary Figure 3:** Effect of normo-glycaemia or hyper-glycaemia on release of sCD93 from endothelial cells. A. Human carotid artery endothelial cells (HctAEC) were cultured in the presence of 5nM or 30nM glucose, with and without inflammatory stimuli (50nM PMA or 50ug/ml LPS) for 24 hours. B. Human endothelial hybrid cells EA.Hy 926 were cultured in the presence of 5nM or 30nM glucose, with and without inflammatory stimuli (50nM PMA) for 24 hours.

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**Online Supplemental Table 1:** Cell populations in mice with one or 2 copies of the *cd93* gene

	<i>cd93</i> <sup>+/-</sup>	<i>cd93</i> <sup>+/+</sup>	P value
scd93 (ng/mL)	104 (18)	254 (63)	<b>0.008</b>
% <i>cd93</i> <sup>+</sup> B cells*	2.79 (1.08)	6.43 (1.61)	<b>0.018</b>
% iNKT cells#	2.49 (1.29)	3.43 (2.45)	0.410
% IgG <sup>+</sup> B cells*	79 (8.02)	81 (8.64)	0.590
% IgM <sup>+</sup> B cells*	0.81 (0.29)	1.08 (0.75)	0.270

Where: \*, Defined as CD45R<sup>+</sup>CD19<sup>+</sup> from spleen; #, Defined as CD4<sup>+</sup>α-galCer tetramer <sup>+</sup> from liver. Values are presented as mean (standard deviation).

**Online Supplemental Table 2:** Multiple regression analyses of metabolic markers on sCD93 levels

	without diabetes			type 2 diabetes		
	Beta	Se	P	Beta	Se	P
BMI (kg/m <sup>2</sup> )	-0.003	0.001	0.0740	0.000	0.002	0.9500
HDL cholesterol (mmol/L)#	0.031	0.026	0.2320	-0.120	0.040	0.7680
Triglycerides (mmol/L)#	-0.049	0.014	<b>&lt;0.0001</b>	-0.021	0.020	0.2980
fasting glucose (mmol/L)*	-0.136	0.044	<b>0.0020</b>	0.007	0.032	0.8290
fasting proinsulin (pmol/L)*	-0.005	0.009	0.5780	-0.007	0.012	0.5400
fasting insulin (pmol/L)*	-0.027	0.006	<b>&lt;0.0001</b>	0.001	0.009	0.8780
HOMA B*	-0.028	0.009	<b>0.0010</b>	0.000	0.010	0.9950
HOMA IR*	-0.028	0.006	<b>&lt;0.0001</b>	0.001	0.009	0.0883
C reactive protein (mmol/L)	-0.002	0.004	0.6310	0.009	0.007	0.1930
Creatinine (micromol/L)	0.359	0.030	<b>&lt;0.0001</b>	0.371	0.045	<b>&lt;0.0001</b>
Uric acid (mmol/L)	0.045	0.026	0.0830	0.032	0.036	0.3720
Adiponectin (ug/mL)	0.022	0.008	<b>0.0030</b>	0.015	0.011	0.1770
Leptin (ng/mL)	-0.009	0.009	0.2900	0.014	0.013	0.2920
IL-5 (pg/mL)	0.035	0.007	<b>&lt;0.0001</b>	0.005	0.010	0.6040

Where: all multiple regression analyses were adjusted for age and sex; # subjects not on lipid lowering medication (n= 1426); \*as glucose, proinsulin and insulin measures are not informative in subjects with T2D, these variables have been omitted from the analysis of subjects with T2D.

**Online Supplemental Table 3:** Association of sCD93 levels with measures of IMT

		without diabetes			type 2 diabetes		
		Beta	Se	P	Beta	Se	P
baseline	CC-IMT <sub>mean</sub>	0.007	0.005	0.168	-0.016	0.010	0.102
	BIF-IMT <sub>mean</sub>	-0.006	0.010	0.575	0.012	0.019	0.527
	IMT <sub>mean</sub>	0.002	0.006	0.706	0.006	0.012	0.606
	CC-IMT <sub>max</sub>	0.002	0.008	0.762	-0.012	0.016	0.438
	BIF-IMT <sub>max</sub>	-0.002	0.012	0.873	0.031	0.023	0.185
	IMT <sub>max</sub>	0.003	0.012	0.808	0.035	0.022	0.116
	IMT <sub>mean-max</sub>	0.002	0.007	0.716	0.008	0.013	0.536
Progression	CC-IMT <sub>mean</sub>	-0.002	0.002	0.296	-0.002	0.005	0.658
	BIF-IMT <sub>mean</sub>	-0.004	0.005	0.438	-0.005	0.013	0.698
	IMT <sub>mean</sub>	-0.001	0.002	0.547	-0.002	0.005	0.741
	CC-IMT <sub>max</sub>	0.004	0.007	0.573	-0.015	0.016	0.351
	BIF-IMT <sub>max</sub>	-0.008	0.012	0.463	-0.014	0.025	0.560
	IMT <sub>max</sub>	0.006	0.012	0.621	0.002	0.025	0.937
	IMT <sub>mean-max</sub>	0.002	0.004	0.642	-0.004	0.008	0.586
	fastest_progression	0.001	0.015	0.933	-0.045	0.030	0.136

Where: all multiple regression analyses were adjusted for age and sex; Progression variables also adjusted for their baseline counterparts; all IMT measurements in mm; CC-IMT, IMT of the common carotid artery excluding 1cm proximal to the bifurcation; BIF-IMT, IMT of the bifurcation; IMT, composite measure of the entire carotid tree; mean, average of measures; max, maximum of the measures; mean-max, mean of the maximum measures; Fastest

progression, segment with the largest change during follow-up.

**Online Supplemental Table 4:** SNPs associated with type 2 diabetes have little effect on sCD93 levels in subjects without type 2 diabetes

CHR	SNP	BP	Locus	proxy used	EAF	N	BETA	SE	L95	U95	P
1	rs17106184	50909985	<i>FAF1</i>	na	A	2470	0.000	0.014	-0.027	0.027	0.9753
1	rs2820446	219750717	<i>LYPLAL1</i>	rs4846567	T	2470	0.010	0.009	-0.007	0.027	0.2604
2	rs10190052	647760	<i>TMEM18</i>	rs4854348	A	2470	0.001	0.010	-0.018	0.021	0.9012
2	rs243088	60573870	<i>BCL11A</i>	rs243083	G	2470	-0.001	0.008	-0.016	0.014	0.8796
2	rs3923113	165555207	<i>GRB14</i>	rs7609045	A	2470	-0.002	0.008	-0.018	0.013	0.7622
2	rs2943640	227093585	<i>IRS1</i>	na	A	2470	0.007	0.008	-0.009	0.023	0.3904
3	rs1801282	12391583	<i>PPARG</i>	rs2197423	A	2470	0.009	0.012	-0.014	0.033	0.4366
3	rs11717195	123082398	<i>ADCY5</i>	na	C	2470	0.017	0.010	-0.002	0.036	0.0848
3	rs4402960	185511687	<i>IGF2BP2</i>	na	T	2470	0.001	0.008	-0.015	0.017	0.9104
3	rs6808574	187740523	<i>LPP</i>	na	T	2418	0.006	0.008	-0.009	0.022	0.4215
4	rs4458523	6293350	<i>WFS1</i>	rs10012946	T	2470	-0.001	0.008	-0.016	0.015	0.9313
4	rs6813195	153520475	<i>TMEM154</i>	na	T	2470	0.001	0.008	-0.015	0.017	0.8918
5	rs702634	53271420	<i>ARL15</i>	na	G	2470	0.015	0.008	-0.002	0.031	0.0769
5	rs319598	134240235	<i>PCBD2</i>	na	T	2470	-0.004	0.008	-0.020	0.011	0.5663

6	rs7756992	20679709	<i>CDKALI</i>	na	G	2470	0.005	0.009	-0.012	0.022	0.5535
6	rs9472138	43811762	<i>VEGFA</i>	na	T	2470	-0.012	0.009	-0.029	0.005	0.1677
6	rs4273712	126964510	<i>C6orf173</i>	na	G	2470	0.000	0.008	-0.016	0.017	0.9881
6	rs6937795	137299152	<i>IL20RA</i>	rs4407733	A	2470	0.006	0.008	-0.009	0.021	0.4567
7	rs7795991	13900731	<i>ETVI</i>	na	G	2470	-0.003	0.008	-0.019	0.012	0.6565
7	rs17168486	14898282	<i>DGKB</i>	na	T	2470	-0.011	0.010	-0.031	0.009	0.2819
7	rs849135	28196413	<i>JAZF1</i>	na	A	2470	-0.009	0.008	-0.024	0.007	0.2617
8	rs516946	41519248	<i>ANK1</i>	na	T	2470	-0.021	0.009	-0.039	-0.003	<b>0.0211</b>
8	rs7845219	95937502	<i>TP53INP1</i>	na	C	2470	-0.006	0.008	-0.021	0.009	0.4660
8	rs3802177	118185025	<i>SLC30A8</i>	na	A	2470	-0.009	0.008	-0.026	0.007	0.2682
8	rs1561927	129568078	<i>TMEM75</i>	na	C	2469	-0.007	0.009	-0.024	0.010	0.4307
9	rs7041847	4293150	<i>GLIS3</i>	rs10814916	A	2470	0.005	0.008	-0.011	0.020	0.5529
9	rs10811661	22132076	<i>CDKN2A,CDKN2B</i>	rs2383208	G	2470	-0.006	0.010	-0.025	0.013	0.5390
9	rs17791513	81905590	<i>TLE4</i>	na	G	2470	-0.006	0.014	-0.034	0.022	0.6781
9	rs2796441	84308948	<i>TLE1</i>	na	A	2470	0.015	0.008	-0.001	0.030	0.0636
10	rs11257655	12307894	<i>CDC123</i>	na	T	2470	-0.016	0.009	-0.035	0.002	0.0759

10	rs12571751	80942631	ZMIZ1	na	G	2470	0.006	0.008	-0.010	0.021	0.4758
10	rs10788575	89768584	PTEN	na	A	2470	0.027	0.012	0.004	0.049	<b>0.0213</b>
10	rs1111875	94462882	HHEX,IDE	na	T	2470	0.006	0.008	-0.009	0.021	0.4612
10	rs7903146	114758349	TCF7L2	na	T	2470	0.012	0.009	-0.005	0.029	0.1699
10	rs10510110	124193181	PLEKHA1	rs2280141	T	2470	-0.002	0.008	-0.017	0.014	0.8177
11	rs163184	2847069	KCNQ1	na	T	2469	-0.003	0.008	-0.018	0.013	0.7320
11	rs5215	17408630	KCNJ11	na	C	2469	0.004	0.008	-0.012	0.020	0.6120
11	rs1552224	72433098	ARAP1,CENTD2	na	C	2469	-0.004	0.010	-0.025	0.016	0.6800
11	rs10830963	92708710	MTNR1B	na	G	2470	-0.004	0.008	-0.021	0.012	0.5925
12	rs10842994	27965150	KLHDC5	na	T	2470	-0.011	0.010	-0.032	0.009	0.2689
12	rs2261181	66212318	HMG2	na	T	2470	-0.003	0.012	-0.028	0.021	0.7921
12	rs1727313	123616514	MPHOSPH9	rs1727294	A	2470	0.000	0.009	-0.018	0.018	0.9864
13	rs10507349	26781528	RNF6	na	A	2470	0.003	0.010	-0.016	0.022	0.7688
13	rs1359790	80717156	SPRY2	na	A	2470	-0.007	0.009	-0.024	0.010	0.4016
15	rs7163757	62383155	C2CD4A	rs4502156	C	2470	-0.009	0.008	-0.025	0.006	0.2485
15	rs7178572	77747190	HMG20A	na	A	2470	0.013	0.008	-0.003	0.030	0.1143

15	rs12899811	91544076	<i>PRCI</i>	na	G	2469	0.005	0.008	-0.011	0.021	0.5474
16	rs9936385	53819198	<i>FTO</i>	rs9923233	C	2470	0.001	0.008	-0.014	0.017	0.8634
17	rs11651755	36099840	<i>HNF1B</i>	na	C	2470	-0.016	0.008	-0.032	-0.001	<b>0.0423</b>
18	rs12970134	57876227	<i>MC4R</i>	rs11663816	C	2470	-0.003	0.009	-0.021	0.015	0.7217
19	rs8108269	46158513	<i>GIPR</i>	na	G	2470	0.005	0.008	-0.012	0.021	0.5838
20	rs4812829	42989267	<i>HNF4A</i>	na	A	2470	-0.011	0.010	-0.030	0.009	0.2971

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Where: analyses adjusted for age, sex and population structure; EAF, type 2 diabetes risk-increasing allele; na, not applicable.

**Online Supplemental Table 5: SDPP baseline characteristics by baseline glucose regulation**

status

	without diabetes	prediabetes	type 2 diabetes
n*	843	326	113
Male (%)	489 (58)	180 (55)	63 (56)
Age (years)	47.8 (4.6)	48.5 (4.4)	49.5 (4.0)
Height (m)	1.73 (0.09)	1.72 (0.10)	1.71 (0.09)
Weight (kg)	79.5 (14.3)	85.7 (17.6)	88.2 (18.3)
BMI (kg/m <sup>2</sup> )	26.6 (4.12)	29.1 (5.4)	30.0 (5.8)
WHR	0.87 (0.07)	0.89 (0.08)	0.91 (0.07)
SBP (mmHg)	125 (15)	134 (19)	135 (17)
DBP (mmHg)	79 (10)	83 (11)	83 (9)
Fasting glucose (mmol/L)	4.82 (0.54)	5.54 (0.75)	7.71 (2.69)
Fasting insulin (mU/L)	16.8 (8.6)	21.7 (11.9)	29.9 (20.1)
sCD93 (ng/mL)	163 (44)	158 (44)	158 (41)
Current smokers (%)	257 (27.6)	85 (23.6)	46 (35.9)
BP treatment (%)	75 (8.1)	60 (16.7)	28 (21.9)

Where:\* smallest n for any variable; values are presented as mean (standard deviation) for continuous measures and n (%) for categorical measures

**Online Supplemental Table 6:** Effect of sCD93-associated SNPs (Mälarstig *et al* 2012) on sCD93 and HOMA indices.

SNP	EA	without diabetes (n=2474)									type 2 diabetes (n=900)					
		sCD93			HOMA B			HOMA S			HOMA IR			sCD93		
		Beta	Se	P	Beta	Se	P	Beta	Se	P	Beta	Se	P	Beta	Se	P
rs2749812	A	-0.018	0.010	0.0754	-0.003	0.022	0.8926	0.002	0.033	0.9612	-0.002	0.033	0.9612	0.003	0.015	0.8621
rs3746731	G	-0.006	0.008	0.4815	-0.005	0.017	0.7514	-0.014	0.026	0.5900	0.014	0.026	0.5900	0.009	0.012	0.4364

Where: analyses adjusted for age, sex and population structure; EA, effect allele; Homeostasis Model Assessment (HOMA) indices were computed using the HOMA2 calculator (<https://www.dtu.ox.ac.uk/homacalculator>). Effect allele frequency of rs2749812 =0.17 and rs3746731 =0.48.