

SUPPLEMENTARY DATA

Supplementary Table S1. Antibodies for immunoblotting (Western blot).

Enzyme	Catalog number	Dilution	Provider
PKM1	7067	1:1,000	Cell Signaling Technology, Beverly, MA
PKM2	4053	1:1,000	Cell Signaling Technology, Beverly, MA
GAPDH	sc-48166	1:1,000	Santa Cruz Biotechnology, Dallas, TX
TPI1	31470	1:1,000	Novus Biologicals, Littleton, CO
ENO1	ab155102	1:1,000	Abcam, Cambridge, MA
AR	ab71405	1:100	Abcam, Cambridge, MA
GLO1	MA1-13029	1:1,000	Thermo Fisher Scientific, Waltham, MA
MT-CO2	ab79393	1:5,000	Abcam, Cambridge, MA
β -actin	sc-1616 HRP	1:1,000	Santa Cruz Biotechnology, Dallas, TX

Bio-Rad Mini-PROTEAN TGX (Bio-Rad Laboratories, Hercules, CA) precast gels were used for all the western blotting. ImageJ software was applied to quantify the amounts of protein in the western blotting.

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Supplementary Table S2. Clinical characteristics of non-Medalist subjects with WB of glomeruli in recovered kidneys.

Characteristic	Non-DM Subjects N=5	T2D N=19	T1D N=15	P- value
Gender (M/F)	2/3	13/6	10/5	0.70
Age (years)	63 (63, 74)	63.0 (54.0, 67.0)	67 (45, 80)	0.61
Duration (years)	na	10.0 (4.0, 15.0)	50 (26, 63)	<0.001
Height (cm)	163.2 (160.0, 167.6)	170.2 (165.0, 173.0)	170.2 (164.0, 182.9)	0.32
Weight (kg)	65.8 (52.2, 79.8)	84.0 (69.0, 93.0)	77.1 (69.0, 97.5)	0.20
BMI (kg/m ²)	22.1 (20.4, 30.0)	28.2 (25.3, 31.5)	26.5 (23.3, 32.3)	0.34
eGFR (ml/min/1.73m ²)	69.6 (60.1, 95.6)	40.0 (14.9, 58.5)	24.6 (13.6, 76.2)	0.23
Renal function by eGFR*				
eGFR High group (≥30 ml/min/1.73m ²)	3	12	6	-
eGFR Low group (<30 ml/min/1.73m ²)	0	7	8	-
Renal histology†				
DN class no to mild (0-IIA)	4	14	6	-
DN class moderate to severe (IIB-IV)	0	5	8	-

Median (25th -75th percentile range) or n. P-values (Anova) show the difference between the groups (Non-DM Subjects, T2D, T1D). na; not applicable. eGFR; estimated glomerular filtration rate. DN Class; Histological classification of DN by Taervart et al [ref]. *Data missing on two non-DM subjects. †Data missing on one individual with T1D and one non-DM subject.

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Supplementary Table S3. Clinical characteristics of Joslin Medalists for SOMAscan analysis.

Clinical Characteristics	Overall Cohort N=1008	SOMAscan Yes (N=180)	SOMAscan No (N=828)	P-value
Male, %	46	50	45	0.24
Age (Years)	65.8±7.6	66.8 ±7.5	65.6±7.6	0.06
Duration (Years)	54.7±5.7	55.4±6.2	54.5±5.6	0.05
BMI (kg/m ²)	26.2±4.7	27.2±5.2	25.9±4.6	0.002
Insulin dose (units/kg)	0.46±0.17	0.46±0.2	0.46±0.2	0.76
HbA _{1c} (%)	7.2±1.0	7.5±0.9	7.1±1.0	<.001
HbA _{1c} (mmol/mol)	55.1±10.51	58.2±9.6	54.4±10.6	<.001
Total cholesterol (mg/dl)	161.5±32.8	161.4±34.88	161.5±32.3	0.95
LDL cholesterol (mg/dl)	81.0±23.8	82.5±25.3	80.7±23.49	0.35
HDL cholesterol (mg/dl)	65.3±19.9	62.4±21.6	66.0±19.5	0.03
Triglycerides (mg/dl)	74.7±37.2	82.5±44.2	73.0±35.3	0.002
eGFR (ml/min/1.73 m ²)	69.8±20.2	58.2±24.2	72.4±18.3	<.001
ACR (ug/mg)	12.1 (6.8-33.9)	13.4 (8.0-48.9)	11.9 (6.2-31)	0.01
Systolic BP (mmHg)	132.2±16.9	132.3±17.4	132.2±16.8	0.94
Diastolic BP (mmHg)	64.2±8.5	63.3±8.4	64.37±8.6	0.13
CVD, %	40	50	38	0.002
PDR, %	53	62	51	0.02
Neuropathy (MNSI≥2), %	70	74	69	0.16
Detectable c-peptide, %	33	42	31	0.003
Hypertensive Medication, %	65	70	64	0.13
Lipid lowering medication, %	70	73	69	0.22
Exercise, %	80	74	81	0.03

Data are mean±SD or median (IQR) for continuous variables or % for categorical variables where noted. P-values between those with and without SOMAscan data. eGFR; estimated glomerular filtration rate, ACR; albumin-to-creatinine ratio; BP; blood pressure, CVD cardiovascular disease, PDR; proliferative diabetic retinopathy.

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Supplementary Table S4. Replication of enzymes in CKD-protected Medalists plasma (SOMAscan).

Protein	NoCKDvsCKD.p	NoCKDvsCKD.FC	Enzyme
Pyruvate kinase M2	0.000669	1.52	PKM2
Isoform 1 of Triosephosphate isomerase	0.00128	1.31	TPI1
L-lactate dehydrogenase B chain	0.00625	1.16	LDHB
Phosphoglycerate mutase 1	0.0011	2.37	PGAM1
Cytochrome C	0.146	1.06	Cytochrome C
Glyceraldehyde-3-phosphate dehydrogenase	0.392	1.18	GAPDH

FC: Fold change. 6/14 enzymes part of the glycolysis, glucose metabolism and TCA pathways earlier identified in protected Medalists glomeruli were part of the SOMAscan platform and specifically analyzed. CKD refers to Chronic kidney Disease Stage 3b, as defined by $eGFR < 45 \text{ ml/min/1.73 m}^2$.

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Supplementary Table S5. Up-regulated proteins (FDR<0.05) in the plasma from Joslin Medalists who were CKD Protected vs. Non-protected (SOMAscan) – unadjusted and adjusted analyses.

Target	Target full name	Unadjusted			Adjusted*		
		FC	p	FDR	FC	p	FDR
Testican-2	Testican-2	1.37	3.88E-16	1.75E-14	1.28	5.44E-08	1.2E-06
ON	SPARC	1.5	1.56E-07	2.21E-06	1.71	1E-08	2.75E-07
DUS3	Dual specificity protein phosphatase 3	1.6	1.96E-07	2.66E-06	1.69	5.03E-07	7.48E-06
Cathepsin V	Cathepsin L2	1.29	4.85E-07	5.88E-06	1.2	0.00205	0.00807
LGMN	Legumain	1.16	1.03E-06	1.17E-05	1.18	9.04E-06	8.72E-05
ERBB1	Epidermal growth factor receptor	1.15	1.38E-06	1.54E-05	1.07	0.0341	0.0871
SGTA	Small glutamine-rich tetratricopeptide repeat-containing protein alpha	1.69	1.39E-06	1.54E-05	1.72	1.09E-05	0.000103
Mammaglobin 2	Mammaglobin-B	1.14	1.92E-06	2.08E-05	1.19	2.09E-07	3.63E-06
TWEAK	Tumor necrosis factor ligand superfamily member 12	1.14	2.14E-06	2.26E-05	1.13	0.000217	0.00127
Apo D	Apolipoprotein D	1.14	2.29E-06	2.39E-05	1.16	0.000023	0.000187
amyloid precursor protein	Amyloid beta A4 protein	1.4	3.81E-06	3.81E-05	1.6	1.03E-07	2.01E-06
Glutamate carboxypeptidase	Cytosolic non-specific dipeptidase	1.26	5.69E-06	5.44E-05	1.32	1.11E-05	0.000104
PDE11	Dual 3',5'-cyclic-AMP and -GMP phosphodiesterase 11A	1.4	5.81E-06	5.46E-05	1.57	1.27E-07	2.38E-06
6-Phosphogluconate dehydrogenase	6-phosphogluconate dehydrogenase, decarboxylating	1.94	8.21E-06	7.54E-05	1.75	0.000997	0.00446
Cathepsin A	Lysosomal protective protein	1.27	8.44E-06	7.69E-05	1.36	9.51E-06	0.000091
C1QBP	Complement component 1 Q subcomponent-binding protein, mitochondrial	1.1	8.52E-06	0.000077	1.14	1.72E-06	2.25E-05
SRCN1	Proto-oncogene tyrosine-protein kinase Src	2.08	9.23E-06	8.27E-05	2.03	0.000334	0.00181
NCC27	Chloride intracellular channel protein 1	1.66	1.07E-05	9.48E-05	2.01	2.36E-07	3.98E-06
BAFF Receptor	Tumor necrosis factor receptor superfamily member 13C	1.23	1.18E-05	0.000104	1.21	0.000845	0.00396
kallikrein 14	Kallikrein-14	1.15	1.21E-05	0.000105	1.14	0.000447	0.00237
PK3CG	Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit gamma isoform	1.18	1.28E-05	0.00011	1.2	7.19E-05	0.000507
PKB a/b/g	RAC-alpha/beta/gamma serine/threonine-protein kinase	1.42	0.000013	0.000111	1.63	1.21E-07	2.31E-06
P-Selectin	P-selectin	1.22	0.000014	0.000119	1.3	1.93E-06	2.48E-05
Glypican 3	Glypican-3	1.31	1.62E-05	0.000135	1.13	0.0496	0.117
MAPKAPK3	MAP kinase-activated protein kinase 3	1.36	1.83E-05	0.000151	1.49	6.63E-06	6.93E-05
MIF	Macrophage migration inhibitory factor	1.23	1.92E-05	0.000157	1.34	2.73E-06	3.33E-05

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TEC	Tyrosine-protein kinase Tec	1.43	2.13E-05	0.000172	1.69	1.8E-07	3.28E-06
GPVI	Platelet glycoprotein VI	1.36	3.12E-05	0.000248	1.61	9.48E-08	1.88E-06
Soggy-1	Dickkopf-like protein 1	1.2	0.000037	0.000292	1.22	0.000252	0.00141
Cytochrome P450 3A4	Cytochrome P450 3A4	1.36	5.07E-05	0.000395	1.6	1.85E-07	3.31E-06
GSK-3 alpha/beta	Glycogen synthase kinase-3 alpha/beta	1.56	5.13E-05	0.000397	1.77	7.28E-06	7.47E-05
NID2	Nidogen-2	1.13	7.18E-05	0.000552	1.18	1.97E-05	0.000165
Protein disulfide isomerase A3	Protein disulfide-isomerase A3	1.28	8.05E-05	0.000614	1.46	4.54E-07	6.92E-06
14-3-3	14-3-3 protein family	1.34	8.49E-05	0.000639	1.57	3.59E-07	5.71E-06
Mn SOD	Superoxide dismutase [Mn], mitochondrial	1.15	8.87E-05	0.000664	1.08	0.0444	0.106
NMT1	Glycylpeptide N-tetradecanoyltransferase 1	1.34	9.52E-05	0.000707	1.56	1.06E-06	0.000015
AIF1	Allograft inflammatory factor 1	1.15	0.000116	0.000849	1.23	4.99E-07	7.48E-06
Calcineurin B a	Calcineurin subunit B type 1	1.16	0.000128	0.00093	1.17	0.000514	0.00264
cGMP-stimulated PDE	cGMP-dependent 3',5'-cyclic phosphodiesterase	1.15	0.000138	0.001	1.17	0.000538	0.00271
MAPK14	Mitogen-activated protein kinase 14	1.3	0.00014	0.00101	1.52	3.52E-07	5.68E-06
Carbonic anhydrase XIII	Carbonic anhydrase 13	1.61	0.000146	0.00104	1.62	0.00118	0.00506
HSP 90a/b	Heat shock protein HSP 90-alpha/beta	1.28	0.000147	0.00104	1.44	1.32E-06	1.82E-05
Angiopoietin-1	Angiopoietin-1	1.24	0.000192	0.00132	1.31	3.97E-05	0.000297
DBNL	Drebrin-like protein	1.24	0.000194	0.00132	1.36	2.78E-05	0.000221
BARK1	beta-adrenergic receptor kinase 1	1.45	0.000252	0.0017	1.7	8.14E-06	8.13E-05
DC-SIGNR	C-type lectin domain family 4 member M	1.1	0.000298	0.00199	1.04	0.153	0.284
NAP-2	Neutrophil-activating peptide 2	1.53	0.000329	0.00219	1.94	4.97E-06	5.51E-05
CTAP-III	Connective tissue-activating peptide III	1.53	0.000341	0.00225	1.95	3.82E-06	0.000044
PDE5A	cGMP-specific 3',5'-cyclic phosphodiesterase	1.5	0.000403	0.00263	1.57	0.00072	0.00344
PA2G4	Proliferation-associated protein 2G4	1.42	0.000445	0.00287	1.76	1.56E-06	2.12E-05
IL-19	Interleukin-19	1.13	0.000454	0.00291	1.11	0.00799	0.0258
HDAC8	Histone deacetylase 8	1.13	0.000546	0.00344	1.15	0.00221	0.00859
ATS13	A disintegrin and metalloproteinase with thrombospondin motifs 13	1.15	0.000602	0.00374	1.04	0.37	0.541
PPID	Peptidyl-prolyl cis-trans isomerase D	1.62	0.000641	0.00393	1.78	0.000366	0.00198
M2-PK	Pyruvate kinase PKM	1.52	0.000669	0.00408	1.74	6.65E-05	0.000475
Calcineurin	Calcineurin	1.32	0.000692	0.0042	1.44	9.08E-05	0.000618
TIMP-3	Metalloproteinase inhibitor 3	1.38	0.00077	0.00465	1.39	0.0037	0.0135
Aflatoxin B1 aldehyde reductase	Aflatoxin B1 aldehyde reductase member 2	1.5	0.000774	0.00465	1.91	4.52E-06	5.05E-05
BTK	Tyrosine-protein kinase BTK	1.49	0.000847	0.00503	1.89	2.92E-06	3.51E-05
Nidogen	Nidogen-1	1.11	0.000909	0.00532	1.15	0.000267	0.00148
PKC-B-II	Protein kinase C beta type	1.54	0.000923	0.00537	1.92	2.97E-05	0.000235

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	(splice variant beta-II)						
Cyclophilin A	Peptidyl-prolyl cis-trans isomerase A	1.2	0.00094	0.00541	1.35	1.65E-05	0.000143
FGF-20	Fibroblast growth factor 20	1.14	0.000965	0.00553	1.1	0.000779	0.00369
Stress-induced-phosphoprotein 1	Stress-induced-phosphoprotein 1	1.36	0.00102	0.00583	1.65	7.35E-06	7.47E-05
SNAA	Alpha-soluble NSF attachment protein	1.37	0.00103	0.00587	1.69	3.16E-06	3.71E-05
PDGF-AA	Platelet-derived growth factor subunit A	1.37	0.00105	0.00593	1.66	1.34E-05	0.000121
Phosphoglycerate mutase 1	Phosphoglycerate mutase 1	2.37	0.0011	0.00615	4.2	1.68E-05	0.000145
Transketolase	Transketolase	1.28	0.00113	0.00628	1.54	1.69E-06	2.24E-05
Afamin	Afamin	1.1	0.00119	0.00657	1.05	0.181	0.322
BASI	Basigin	1.12	0.00124	0.00679	1.17	0.000222	0.0013
Triosephosphate isomerase	Triosephosphate isomerase	1.31	0.00128	0.00699	1.61	2.19E-06	2.74E-05
ASM3A	Acid sphingomyelinase-like phosphodiesterase 3a	1.17	0.00129	0.00699	1.23	3.13E-06	3.71E-05
Factor B	Complement factor B	1.08	0.00142	0.00761	1.09	0.00125	0.00529
HMG-1	High mobility group protein B1	1.19	0.00154	0.00821	1.28	0.000149	0.000921
HGFA	Hepatocyte growth factor activator	1.23	0.00156	0.00829	1.24	0.0117	0.0357
IF4G2	Eukaryotic translation initiation factor 4 gamma 2	1.39	0.00166	0.00875	1.63	0.000083	0.000575
PKC-A	Protein kinase C alpha type	1.4	0.00169	0.00889	1.61	0.000226	0.00132
TCTP	Translationally-controlled tumor protein	1.31	0.00182	0.00946	1.63	3.33E-06	3.88E-05
phosphoglycerate kinase 1	Phosphoglycerate kinase 1	1.22	0.00189	0.00977	1.26	0.00107	0.00475
Testican-1	Testican-1	1.12	0.0019	0.0098	1.21	1.43E-05	0.000128
Sphingosine kinase 1	Sphingosine kinase 1	1.41	0.00192	0.00984	1.69	4.41E-05	0.000325
IMB1	Importin subunit beta-1	1.4	0.00194	0.00992	1.52	0.000857	0.00397
LY86	Lymphocyte antigen 86	1.08	0.00214	0.0108	1.13	0.000121	0.000777
BAFF	Tumor necrosis factor ligand superfamily member 13B	1.15	0.00227	0.0114	1.07	0.218	0.37
4EBP2	Eukaryotic translation initiation factor 4E-binding protein 2	1.14	0.00229	0.0115	1.19	0.000928	0.00423
RANTES	C-C motif chemokine 5	1.43	0.00247	0.0123	1.89	1.24E-05	0.000115
Protease nexin I	Glia-derived nexin	1.17	0.00259	0.0128	1.21	0.0027	0.0101
SBDS	Ribosome maturation protein SBDS	1.41	0.0027	0.0133	1.68	0.000103	0.000683
Thrombospondin-1	Thrombospondin-1	1.38	0.00307	0.0149	1.66	8.27E-05	0.000575
CDK8/cyclin C	Cyclin-dependent kinase 8:Cyclin-C complex	1.14	0.00304	0.0149	1.21	0.000293	0.00161
ALT	Alanine aminotransferase 1	1.11	0.00316	0.0153	1.19	0.000195	0.00115
Calpain I	Calpain I	1.32	0.00329	0.0157	1.64	6.34E-06	6.69E-05
BDNF	Brain-derived neurotrophic factor	1.2	0.00329	0.0157	1.38	4.32E-06	4.88E-05
Esterase D	S-formylglutathione hydrolase	1.32	0.00328	0.0157	1.43	0.00172	0.00703
SHBG	Sex hormone-binding	1.25	0.00336	0.0159	-1.01	0.895	0.935

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	globulin						
LYNB	Tyrosine-protein kinase Lyn, isoform B	1.26	0.00386	0.018	1.36	0.000594	0.00294
METAP1	Methionine aminopeptidase 1	1.3	0.00392	0.0182	1.28	0.0262	0.0706
DKK1	Dickkopf-related protein 1	1.24	0.00404	0.0186	1.4	0.000195	0.00115
RAN	GTP-binding nuclear protein Ran	1.47	0.00403	0.0186	1.63	0.000902	0.00414
a2-HS-Glycoprotein	Alpha-2-HS-glycoprotein	1.07	0.00419	0.0192	1.05	0.0668	0.147
Bone proteoglycan II	Decorin	1.09	0.00432	0.0197	1.09	0.0114	0.0351
Myokinase, human	Adenylate kinase isoenzyme 1	1.31	0.00431	0.0197	1.53	9.35E-05	0.000628
PF-4	Platelet factor 4	1.74	0.00444	0.0199	2.69	1.32E-05	0.00012
annexin VI	Annexin A6	1.36	0.00441	0.0199	1.65	7.18E-05	0.000507
HPG-	15-hydroxyprostaglandin dehydrogenase [NAD(+)]	1.09	0.00442	0.0199	1.15	0.0003	0.00164
WISP-1	WNT1-inducible-signaling pathway protein 1	1.12	0.00453	0.0202	1.15	0.00381	0.0138
Cadherin-6	Cadherin-6	1.13	0.00456	0.0203	1.17	0.000889	0.0041
UBC9	SUMO-conjugating enzyme UBC9	1.23	0.0051	0.0224	1.48	8.7E-06	8.54E-05
ARP19	cAMP-regulated phosphoprotein 19	1.28	0.00535	0.0233	1.55	1.56E-05	0.000138
RAC1	Ras-related C3 botulinum toxin substrate 1	1.35	0.00545	0.0236	1.73	1.01E-05	9.57E-05
Aminoacylase-1	Aminoacylase-1	1.26	0.00561	0.0243	1.07	0.521	0.686
BCL2-like 1 protein	Bcl-2-like protein 1	1.18	0.00572	0.0247	1.29	0.000227	0.00132
Caspase-3	Caspase-3	1.3	0.00578	0.0248	1.44	0.0012	0.00509
ERK-1	Mitogen-activated protein kinase 3	1.25	0.00607	0.0259	1.42	0.000165	0.00101
ARTS1	Endoplasmic reticulum aminopeptidase 1	1.21	0.00609	0.0259	1.18	0.0603	0.135
LDH-H 1	L-lactate dehydrogenase B chain	1.16	0.00625	0.0264	1.3	5.86E-05	0.000424
FER	Tyrosine-protein kinase Fer	1.29	0.00639	0.0269	1.35	0.00467	0.0165
sICAM-3	Intercellular adhesion molecule 3	1.12	0.00662	0.0276	1.09	0.11	0.218
Rab GDP dissociation inhibitor beta	Rab GDP dissociation inhibitor beta	1.19	0.00662	0.0276	1.39	1.47E-05	0.00013
RET	Proto-oncogene tyrosine-protein kinase receptor Ret	1.13	0.00689	0.0285	1.03	0.564	0.725
MDHC	Malate dehydrogenase, cytoplasmic	1.17	0.00701	0.0289	1.33	4.83E-05	0.000352
ERBB3	Receptor tyrosine-protein kinase erbB-3	1.07	0.00728	0.0298	1.02	0.553	0.718
NDP kinase B	Nucleoside diphosphate kinase B	1.29	0.00755	0.0308	1.55	0.000121	0.000777
Thyroxine-Binding Globulin	Thyroxine-binding globulin	1.07	0.00773	0.0314	1.03	0.415	0.583
NAGK	N-acetyl-D-glucosamine kinase	1.12	0.00782	0.0316	1.16	0.00234	0.00898
PDPK1	3-phosphoinositide-dependent protein kinase 1	1.27	0.00783	0.0316	1.48	0.000115	0.000762

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LYN	Tyrosine-protein kinase Lyn	1.27	0.00819	0.0327	1.43	0.00048	0.00249
CPNE1	Copine-1	1.4	0.00818	0.0327	1.69	0.000189	0.00113
CNTN2	Contactin-2	1.15	0.00843	0.0334	1.04	0.5	0.675
FGF-8B	Fibroblast growth factor 8 isoform B	1.12	0.00851	0.0336	1.1	0.101	0.204
Cyclophilin F	Peptidyl-prolyl cis-trans isomerase F, mitochondrial	1.38	0.00862	0.0339	1.68	0.000572	0.00284
PAI-1	Plasminogen activator inhibitor 1	1.45	0.0088	0.0344	1.74	0.000535	0.00271
UBE2N	Ubiquitin-conjugating enzyme E2 N	1.27	0.00904	0.0351	1.59	1.94E-05	0.000164
AMPK a2b2g1	AMP Kinase (alpha2beta2gamma1)	1.21	0.00957	0.037	1.37	0.000411	0.00219
CSK	Tyrosine-protein kinase CSK	1.34	0.0104	0.0397	1.77	0.00002	0.000166
PTP-1B	Tyrosine-protein phosphatase non-receptor type 1	1.12	0.0105	0.0399	1.18	0.00242	0.00928
FYN	Tyrosine-protein kinase Fyn	1.27	0.0106	0.0402	1.34	0.00875	0.0277
OBCAM	Opioid-binding protein/cell adhesion molecule	1.09	0.0107	0.0406	1.08	0.0372	0.0935
KYNU	Kynureninase	1.12	0.0118	0.0445	1.16	0.00372	0.0135
C6	Complement component C6	1.1	0.0126	0.0471	1.1	0.0572	0.13

P: p-value, FDR: False Discovery Rate, FC: Fold Change. CKD refers to Chronic kidney Disease Stage 3b, as defined by eGFR<45 ml/min/1.73 m².

*Adjusted analyses included covariates HbA1c, BMI, HDL, triglycerides, c-peptide, exercise and hypertensive meds.

SUPPLEMENTARY DATA

Supplementary Table S6. Down-regulated proteins (FDR<0.05) in the plasma from Joslin Medalists who were CKD Protected vs. Non-protected (SOMAscan) – unadjusted and adjusted analyses.

Target	Target full name	Unadjusted			Adjusted*		
		FC	p	FDR	FC	p	FDR
Cystatin C	Cystatin-C	-1.7	2.13E-28	2.41E-25	-1.54	8.18E-20	9.23E-17
UNC5H3	Netrin receptor UNC5C	-1.41	2.73E-23	1.54E-20	-1.39	9.76E-17	3.83E-14
EphB6	Ephrin type-B receptor 6	-1.35	9.12E-23	3.43E-20	-1.33	2.92E-15	3.3E-13
Epithelial cell kinase	Ephrin type-A receptor 2	-1.7	1.37E-22	3.88E-20	-1.65	1.02E-16	3.83E-14
FSTL3	Follistatin-related protein 3	-1.53	1.06E-21	2.39E-19	-1.45	2.69E-16	4.53E-14
TNF sR-I	Tumor necrosis factor receptor superfamily member 1A	-1.69	1.42E-21	2.66E-19	-1.54	2.59E-16	4.53E-14
Endostatin	Endostatin	-1.42	3.14E-21	5.07E-19	-1.34	6.68E-13	3.59E-11
b2-Microglobulin	Beta-2-microglobulin	-1.82	6.19E-21	8.74E-19	-1.65	1.74E-14	1.64E-12
TNF sR-II	Tumor necrosis factor receptor superfamily member 1B	-1.55	1.1E-20	1.38E-18	-1.48	3.48E-14	2.62E-12
RELT	Tumor necrosis factor receptor superfamily member 19L	-1.68	1.54E-20	1.74E-18	-1.6	1.08E-13	7.03E-12
TFF3	Trefoil factor 3	-1.87	4.76E-20	4.88E-18	-1.73	1.77E-15	2.21E-13
DAN	Neuroblastoma suppressor of tumorigenicity 1	-2.77	1.24E-19	1.17E-17	-2.62	2.81E-16	4.53E-14
Ephrin-A4	Ephrin-A4	-1.59	2.07E-19	1.79E-17	-1.5	3.36E-14	2.62E-12
Cathepsin H	Cathepsin H	-1.42	3.43E-19	2.77E-17	-1.33	1.12E-13	7.03E-12
UNC5H4	Netrin receptor UNC5D	-1.59	4.62E-19	3.48E-17	-1.63	1.08E-15	1.53E-13
IGFBP-6	Insulin-like growth factor-binding protein 6	-1.51	5.81E-19	4.1E-17	-1.42	4.69E-13	2.65E-11
JAM-B	Junctional adhesion molecule B	-1.41	1.26E-18	8.37E-17	-1.35	4.44E-12	2.18E-10
DAF	Complement decay-accelerating factor	-1.33	6.77E-18	4.25E-16	-1.37	1.14E-14	1.17E-12
Lipocalin 2	Neutrophil gelatinase-associated lipocalin	-1.74	1.48E-17	8.78E-16	-1.58	3.47E-11	1.45E-09
Ephrin-A5	Ephrin-A5	-1.52	2.41E-17	1.31E-15	-1.54	1.94E-16	4.53E-14
DR6	Tumor necrosis factor receptor superfamily member 21	-1.28	2.43E-17	1.31E-15	-1.3	3.16E-13	1.88E-11
SLPI	Antileukoproteinase	-1.33	4.66E-17	2.29E-15	-1.28	1.06E-11	4.6E-10
TAJ	Tumor necrosis factor receptor superfamily member 19	-1.8	4.52E-17	2.29E-15	-1.85	3.16E-14	2.62E-12
Layilin	Layilin	-1.55	7.74E-17	3.64E-15	-1.51	1.44E-12	7.36E-11
DERM	Dermatopontin	-1.36	6.15E-16	2.67E-14	-1.32	1.05E-10	4.1E-09
MATN2	Matrilin-2	-1.32	7.1E-16	2.97E-14	-1.35	9.54E-14	6.73E-12
RGMB	RGM domain family member B	-1.3	9.58E-16	3.86E-14	-1.33	7.75E-12	3.5E-10
ROR1	Tyrosine-protein kinase transmembrane receptor ROR1	-1.29	1.04E-15	4.05E-14	-1.31	4.95E-12	2.33E-10
Cystatin M	Cystatin-M	-1.66	1.2E-15	4.51E-14	-1.46	8.06E-08	1.62E-06
ARMEL	Cerebral dopamine neurotrophic factor	-1.49	1.72E-15	6.26E-14	-1.4	3.03E-08	7.43E-07

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TIMD3	Hepatitis A virus cellular receptor 2	-1.43	1.99E-15	7.02E-14	-1.42	2.01E-10	7.34E-09
MIP-5	C-C motif chemokine 15	-1.56	4.76E-15	1.63E-13	-1.47	8.39E-09	2.43E-07
HCC-1	C-C motif chemokine 14	-1.77	4.82E-14	1.6E-12	-1.67	8.57E-11	3.46E-09
Elafin	Elafin	-1.75	5.01E-14	1.61E-12	-1.6	6.93E-09	2.06E-07
Trypsin 2	Trypsin-2	-1.9	2.67E-13	8.38E-12	-1.73	9.2E-09	2.6E-07
URB	Coiled-coil domain-containing protein 80	-1.29	7.88E-13	2.4E-11	-1.29	1.14E-08	3.07E-07
EPHB2	Ephrin type-B receptor 2	-1.33	1.25E-12	3.7E-11	-1.37	4.59E-10	1.62E-08
CAPG	Macrophage-capping protein	-1.74	1.53E-12	4.42E-11	-1.37	0.00016	0.000981
DLL1	Delta-like protein 1	-1.23	3.07E-12	8.67E-11	-1.23	2.8E-09	8.8E-08
VEGF	Vascular endothelial growth factor A	-1.24	3.92E-12	1.08E-10	-1.18	1.93E-06	2.48E-05
MMP-7	Matrilysin	-1.71	5.71E-12	1.53E-10	-1.68	6.16E-09	1.88E-07
PYY	Peptide YY	-1.51	1.3E-11	3.42E-10	-1.45	1.92E-07	3.39E-06
CATZ	Cathepsin Z	-1.32	2.05E-11	5.26E-10	-1.33	3.24E-08	7.61E-07
Factor D	Complement factor D	-1.36	2.46E-11	6.17E-10	-1.24	0.00012	0.000777
IL-15 Ra	Interleukin-15 receptor subunit alpha	-1.31	3.48E-11	8.54E-10	-1.29	2.47E-09	8.13E-08
CNTFR alpha	Ciliary neurotrophic factor receptor subunit alpha	-1.33	4.17E-11	1E-09	-1.34	2.31E-08	5.8E-07
IL-16	Interleukin-16	-1.33	4.72E-11	1.11E-09	-1.25	5.1E-06	5.59E-05
NRX1B	Neurexin-1-beta	-1.39	6.61E-11	1.52E-09	-1.41	1.64E-08	4.31E-07
PAPP-A	Pappalysin-1	-1.49	1.05E-10	2.33E-09	-1.42	1.11E-06	1.55E-05
NRX3B	Neurexin-3-beta	-1.26	1.03E-10	2.33E-09	-1.32	2.52E-09	8.13E-08
IL-18 BPa	Interleukin-18-binding protein	-1.35	1.74E-10	3.78E-09	-1.36	2.8E-07	4.59E-06
TIG2	Retinoic acid receptor responder protein 2	-1.39	2.56E-10	5.45E-09	-1.29	2.39E-05	0.000192
MP2K2	Dual specificity mitogen-activated protein kinase 2	-1.49	4.07E-10	8.5E-09	-1.27	0.00109	0.00479
BSSP4	Brain-specific serine protease 4	-1.35	4.91E-10	1.01E-08	-1.35	1.33E-07	2.45E-06
Angiogenin	Angiogenin	-1.31	5.4E-10	1.09E-08	-1.19	0.000183	0.0011
CD70	CD70 antigen	-1.23	6.5E-10	1.29E-08	-1.17	3.62E-05	0.000276
TF	Tissue Factor	-1.48	1.2E-09	2.33E-08	-1.31	0.00025	0.00141
IL-17 RC	Interleukin-17 receptor C	-1.41	1.25E-09	2.4E-08	-1.34	2.21E-05	0.000182
RGMA	Repulsive guidance molecule A	-1.24	1.49E-09	2.81E-08	-1.29	1.26E-09	4.31E-08
FABP	Fatty acid-binding protein, heart	-1.57	3.04E-09	5.62E-08	-1.51	2.58E-07	4.28E-06
XEDAR	Tumor necrosis factor receptor superfamily member 27	-1.45	3.78E-09	6.89E-08	-1.38	7.23E-06	7.47E-05
Nogo Receptor	Reticulon-4 receptor	-1.28	3.88E-09	6.94E-08	-1.22	2.36E-05	0.00019
IL-13 Ra1	Interleukin-13 receptor subunit alpha-1	-1.28	4.38E-09	7.73E-08	-1.3	4.48E-08	1.01E-06
Stanniocalcin-1	Stanniocalcin-1	-1.27	6.96E-09	1.21E-07	-1.23	1.6E-06	2.15E-05
CRDL1	Chordin-like protein 1	-1.26	9.11E-09	1.56E-07	-1.35	1.84E-10	6.91E-09
Renin	Renin	-2.05	1.15E-08	1.94E-07	-1.82	3.46E-05	0.000267
TNR4	Tumor necrosis factor receptor superfamily	-1.48	1.69E-08	2.8E-07	-1.59	7.67E-08	1.6E-06

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	member 4						
MK11	Mitogen-activated protein kinase 11	-1.56	1.79E-08	2.93E-07	-1.39	0.000262	0.00147
IGFBP-4	Insulin-like growth factor-binding protein 4	-1.21	3.62E-08	5.84E-07	-1.13	0.00154	0.00637
CXCL16, soluble	C-X-C motif chemokine 16	-1.19	3.94E-08	6.26E-07	-1.16	3.27E-05	0.000255
resistin	Resistin	-1.34	4.97E-08	7.69E-07	-1.26	0.000149	0.000921
CLM6	CMRF35-like molecule 6	-1.25	4.97E-08	7.69E-07	-1.31	6.93E-08	1.48E-06
EphA5	Ephrin type-A receptor 5	-1.3	5.63E-08	8.58E-07	-1.34	8.47E-07	1.23E-05
Ck-b-8-1	Ck-beta-8-1	-1.27	6.23E-08	9.38E-07	-1.24	3.61E-05	0.000276
EphA1	Ephrin type-A receptor 1	-1.51	9.17E-08	1.36E-06	-1.47	1.98E-06	2.51E-05
Kallikrein 11	Kallikrein-11	-1.35	1.04E-07	1.53E-06	-1.4	5.71E-08	1.24E-06
kallikrein 8	Kallikrein-8	-1.39	1.14E-07	1.65E-06	-1.48	3.44E-08	7.93E-07
TSP2	Thrombospondin-2	-1.48	1.47E-07	2.09E-06	-1.47	2.15E-07	3.69E-06
MMP-12	Macrophage metalloelastase	-1.54	1.63E-07	2.27E-06	-1.65	9.81E-07	0.000014
PTN	Pleiotrophin	-1.26	1.68E-07	2.32E-06	-1.21	8.19E-05	0.000574
IGFBP-5	Insulin-like growth factor-binding protein 5	-1.16	2.3E-07	3.09E-06	-1.15	3.15E-05	0.000247
TGF- β R III	Transforming growth factor beta receptor type 3	-1.15	2.39E-07	3.18E-06	-1.18	6.5E-07	9.53E-06
PKC-G	Protein kinase C gamma type	-1.23	2.51E-07	3.3E-06	-1.21	0.00013	0.000817
Nectin-like protein 1	Cell adhesion molecule 3	-1.33	3.24E-07	4.21E-06	-1.39	3.67E-07	5.75E-06
Periostin	Periostin	-1.28	3.3E-07	4.23E-06	-1.25	0.000118	0.000775
MPIF-1	C-C motif chemokine 23	-1.23	3.47E-07	4.4E-06	-1.16	0.00194	0.00773
RGM-C	Hemojuvelin	-1.17	3.93E-07	4.93E-06	-1.23	1.79E-08	4.6E-07
bFGF-R	Fibroblast growth factor receptor 1	-1.14	4.71E-07	5.81E-06	-1.18	7.87E-08	1.62E-06
IL-17F	Interleukin-17F	-1.52	4.73E-07	5.81E-06	-1.49	3.21E-08	7.61E-07
HVEM	Tumor necrosis factor receptor superfamily member 14	-1.27	5.15E-07	6.18E-06	-1.29	5.99E-06	0.000065
Lysozyme	Lysozyme C	-1.15	5.89E-07	0.000007	-1.16	0.000023	0.000187
ERP29	Endoplasmic reticulum resident protein 29	-1.21	7.37E-07	8.66E-06	-1.13	0.0036	0.0132
TSP4	Thrombospondin-4	-1.21	7.67E-07	8.92E-06	-1.17	0.000568	0.00284
NKp30	Natural cytotoxicity triggering receptor 3	-1.38	9.11E-07	1.05E-05	-1.48	7.5E-06	7.56E-05
CSF-1	Macrophage colony-stimulating factor 1	-1.31	1.11E-06	1.25E-05	-1.31	1.58E-05	0.000139
Fractalkine/CX3CL-1	Fractalkine	-1.24	1.67E-06	1.84E-05	-1.26	1.86E-05	0.000159
TIMP-1	Metalloproteinase inhibitor 1	-1.17	2.06E-06	0.000022	-1.11	0.00211	0.00826
TNFSF15	Tumor necrosis factor ligand superfamily member 15	-1.38	2.07E-06	0.000022	-1.46	4.13E-07	6.38E-06
suPAR	Urokinase plasminogen activator surface receptor	-1.24	2.33E-06	2.42E-05	-1.29	8.4E-06	8.32E-05
Trypsin	Trypsin-1	-1.53	3.22E-06	3.28E-05	-1.42	0.0019	0.00761
4-1BB	Tumor necrosis factor receptor superfamily member 9	-1.28	3.23E-06	3.28E-05	-1.21	0.000518	0.00265

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HCC-4	C-C motif chemokine 16	-1.29	3.4E-06	3.43E-05	-1.28	0.000182	0.0011
Carbonic anhydrase III	Carbonic anhydrase 3	-1.56	3.98E-06	3.94E-05	-1.38	0.00355	0.0131
PARC	C-C motif chemokine 18	-1.32	5.25E-06	5.16E-05	-1.28	0.000481	0.00249
WFKN2	WAP, Kazal, immunoglobulin, Kunitz and NTR domain-containing protein 2	-1.24	5.45E-06	5.31E-05	-1.3	6.06E-06	6.51E-05
MIA	Melanoma-derived growth regulatory protein	-1.2	5.65E-06	5.44E-05	-1.21	0.000122	0.000777
IL-27	Interleukin-27	-1.2	5.75E-06	5.46E-05	-1.14	0.00315	0.0117
Troponin I, skeletal, fast twitch	Troponin I, fast skeletal muscle	-1.51	7.59E-06	7.08E-05	-1.49	0.000248	0.00141
Myoglobin	Myoglobin	-1.35	7.88E-06	7.29E-05	-1.29	0.000383	0.00206
C34 gp41 HIV Fragment	gp41 C34 peptide, HIV	-1.22	1.17E-05	0.000103	-1.27	4.26E-06	4.86E-05
SLIK5	SLIT and NTRK-like protein 5	-1.25	1.45E-05	0.000122	-1.32	2.41E-06	2.99E-05
NKp46	Natural cytotoxicity triggering receptor 1	-1.23	1.73E-05	0.000144	-1.26	0.00013	0.000817
Angiopoietin-2	Angiopoietin-2	-1.3	2.07E-05	0.000168	-1.25	0.000171	0.00104
CD23	Low affinity immunoglobulin epsilon Fc receptor	-1.36	2.43E-05	0.000194	-1.33	0.00162	0.00669
IMDH1	Inosine-5'-monophosphate dehydrogenase 1	-1.51	3.73E-05	0.000293	-1.32	0.0259	0.0704
Spondin-1	Spondin-1	-1.18	8.12E-05	0.000615	-1.12	0.0272	0.0728
OX2G	OX-2 membrane glycoprotein	-1.16	0.000108	0.000796	-1.21	3.77E-05	0.000284
BGH3	Transforming growth factor-beta-induced protein ig-h3	-1.15	0.000153	0.00108	-1.14	0.00362	0.0132
G-CSF	Granulocyte colony-stimulating factor	-1.35	0.000165	0.00116	-1.29	9.19E-05	0.000621
Nectin-like protein 2	Cell adhesion molecule 1	-1.18	0.000169	0.00118	-1.26	0.000013	0.000119
ART	Agouti-related protein	-1.2	0.000189	0.00131	-1.22	0.000522	0.00266
GPNMB	Transmembrane glycoprotein NMB	-1.16	0.000243	0.00166	-1.19	0.000268	0.00148
HSP 70	Heat shock 70 kDa protein 1A	-1.19	0.00028	0.00188	-1.15	0.0139	0.0414
CD48	CD48 antigen	-1.14	0.000376	0.00247	-1.19	9.81E-05	0.000656
Prolactin Receptor	Prolactin receptor	-1.16	0.000424	0.00275	-1.14	0.0139	0.0414
Glucagon	Glucagon	-1.5	0.000456	0.00291	-1.58	0.00118	0.00506
IL-11 RA	Interleukin-11 receptor subunit alpha	-1.17	0.000463	0.00294	-1.23	5.98E-05	0.00043
LSAMP	Limbic system-associated membrane protein	-1.11	0.000549	0.00345	-1.18	6.21E-06	6.62E-05
BCMA	Tumor necrosis factor receptor superfamily member 17	-1.15	0.000599	0.00374	-1.22	4.39E-05	0.000325
CYTT	Cystatin-SA	-1.32	0.000627	0.00387	-1.35	0.00171	0.00703
pTEN	Phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase and dual-	-1.25	0.000825	0.00493	-1.23	0.00767	0.0248

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	specificity protein phosphatase PTEN						
BSP	Bone sialoprotein 2	-1.3	0.000851	0.00503	-1.34	0.00137	0.00577
CYTN	Cystatin-SN	-1.31	0.000892	0.00525	-1.3	0.00649	0.0217
IGFBP-2	Insulin-like growth factor-binding protein 2	-1.17	0.000933	0.0054	-1.15	0.00943	0.0294
CYTD	Cystatin-D	-1.37	0.00111	0.00618	-1.43	0.00152	0.00629
PD-L2	Programmed cell death 1 ligand 2	-1.12	0.00119	0.00657	-1.17	0.000146	0.00091
sCD4	T-cell surface glycoprotein CD4	-1.08	0.00141	0.00761	-1.06	0.0354	0.0899
GRN	Granulins	-1.08	0.00154	0.00821	-1.13	0.000126	0.000802
OMD	Osteomodulin	-1.17	0.00176	0.00917	-1.25	0.000465	0.00243
IL-17E	Interleukin-25	-1.17	0.00207	0.0105	-1.17	0.0112	0.0346
calgranulin B	Protein S100-A9	-1.29	0.00212	0.0108	-1.03	0.769	0.861
IL-22	Interleukin-22	-1.26	0.00301	0.0148	-1.22	0.00598	0.0202
DLL4	Delta-like protein 4	-1.14	0.00335	0.0159	-1.18	0.000751	0.00358
Eotaxin	Eotaxin	-1.22	0.00364	0.0172	-1.36	0.000119	0.000777
b-NGF	beta-nerve growth factor	-1.17	0.00379	0.0178	-1.21	0.00291	0.0109
GSTA3	Glutathione S-transferase A3	-1.35	0.00378	0.0178	-1.19	0.166	0.302
FGF-19	Fibroblast growth factor 19	-1.31	0.00441	0.0199	-1.45	0.00187	0.00752
TECK	C-C motif chemokine 25	-1.21	0.00483	0.0214	-1.21	0.0277	0.0739
HDGR2	Hepatoma-derived growth factor-related protein 2	-1.14	0.0049	0.0216	-1.03	0.529	0.694
PDE9A	High affinity cGMP-specific 3',5'-cyclic phosphodiesterase 9A	-1.22	0.00524	0.0229	-1.23	0.00728	0.0237
CLC7A	C-type lectin domain family 7 member A	-1.17	0.00582	0.0249	-1.04	0.565	0.725
LKHA4	Leukotriene A-4 hydrolase	-1.42	0.00655	0.0275	-1.58	0.00292	0.0109
IGF-I sR	Insulin-like growth factor 1 receptor	-1.11	0.00674	0.028	-1.17	0.000618	0.00303
GIB	Phospholipase A2	-1.24	0.00724	0.0297	-1.35	0.00132	0.00555
MMP-16	Matrix metalloproteinase-16	-1.17	0.00816	0.0327	-1.14	0.0784	0.169
LAG-3	Lymphocyte activation gene 3 protein	-1.19	0.00835	0.0332	-1.29	0.00191	0.00761
Activin A	Inhibin beta A chain	-1.17	0.00878	0.0344	-1.11	0.134	0.256
calreticulin	Calreticulin	-1.12	0.0089	0.0346	-1.15	0.00559	0.0191
SIG14	Sialic acid-binding Ig-like lectin 14	-1.22	0.0099	0.0382	-1.36	0.000911	0.00417
Galectin-3	Galectin-3	-1.08	0.0102	0.0392	-1.13	0.00173	0.00705
IL-1 sRI	Interleukin-1 receptor type 1	-1.13	0.0108	0.0406	-1.22	0.000245	0.00141
MMP-14	Matrix metalloproteinase-14	-1.21	0.0126	0.0471	-1.3	0.00695	0.0228

P: p-value, FDR: False Discovery Rate, FC: Fold Change. CKD refers to Chronic kidney Disease Stage 3b, as defined by eGFR<45 ml/min/1.73 m².

*Adjusted analyses included covariates HbA1c, BMI, HDL, triglycerides, c-peptide, exercise, and hypertensive medications.

SUPPLEMENTARY DATA

Supplementary Table S7. Correlations of ACR with glycolytic enzymes in DN strata.

Enzyme	Spearman Rank-Order Correlation with ACR (n=144)					
	Overall		No CKD (n=79)		CKD (n=65)	
	<i>rho</i>	<i>p</i>	<i>rho</i>	<i>p</i>	<i>rho</i>	<i>p</i>
TPI1	-0.1	0.21	0.01	0.93	-0.03	0.84
LDHB	-0.04	0.6	0.07	0.54	0.07	0.56
MDH1	-0.1	0.21	-0.05	0.64	0.02	0.89
PKM2	-0.18	0.03	0.1	0.38	-0.15	0.23
PGAM1	-0.09	0.28	-0.11	0.33	0.03	0.84
Cytochrome C	-0.25	0.002	0.21	0.06	-0.21	0.09
GAPDH	-0.08	0.35	-0.1	0.36	-0.002	0.99

CKD defined as Chronic Kidney Disease stage 3b, that is, CKD-EPI eGFR<45mL/min/1.73m²; rho is the correlation coefficient.

SUPPLEMENTARY DATA

Supplementary Table S8. Clinical characteristics of Joslin Medalists with and without Metabolomics data.

Characteristic	Overall Cohort N=1008	Metabolomic set (N=214)	Non-Metabolomic set (N=794)	P-value
Male, %	46	56	43	<.001
Age (Years)	65.8±7.6	66.3±8.0	65.7±7.5	0.31
Duration (Years)	54.7±5.7	55.21±6.3	54.53±5.6	0.12
BMI (kg/m ²)	26.2±4.7	26.2±4.8	26.20±4.2	0.96
Insulin dose (units/kg)	0.46±0.17	0.46±0.2	0.46±0.2	0.93
HbA _{1c} (%)	7.2±1.0	7.23±1.0	7.18±1.0	0.50
HbA _{1c} (mmol/mol)	55.1±10.5	55.55±10.9	55.01±10.4	0.50
Total cholesterol (mg/dl)	161.5±32.8	160.4±33.5	161.8±32.6	0.57
LDL cholesterol (mg/dl)	81.0±23.8	82.02±23.1	80.72±24.0	0.48
HDL cholesterol (mg/dl)	65.3±19.9	62.8±20.6	66.1±19.7	0.03
Triglycerides (mg/dl)	74.7±37.2	76.01±36.7	74.3±37.3	0.56
eGFR (ml/min/1.73 m ²)	69.8±20.2	65.8±24.1	70.9±18.9	0.004
ACR (ug/mg)	12.1 (6.8-33.9)	12 (7.6-29.0)	13 (6.6-36.0)	0.67
Systolic BP (mmHg)	132.2±16.9	132.3±18.2	132.2±16.6	0.94
Diastolic BP (mmHg)	64.2±8.5	63.1±8.0	64.4±8.7	0.07
CVD, %	40	42	39	0.38
PDR, %	53	55	53	0.59
Neuropathy (MNSI≥2), %	70	70	70	0.94
Detectable c-peptide, %	33	44	30	<.001
Hypertensive Medication, %	65	64	66	0.59
Lipid lowering medication, %	70	66	71	0.17
Exercise, %	80	78	80	0.49

P-values between those with and without Metabolomic data. Data are mean±SD or median (IQR) for continuous variables or % for categorical variables where noted. eGFR; estimated glomerular filtration rate, ACR; albumin-to-creatinine ratio; BP; blood pressure, CVD cardiovascular disease, PDR; proliferative diabetic retinopathy.

SUPPLEMENTARY DATA

Supplementary Table S9. Clinical characteristics of Joslin Medalists for Metabolomic analysis.

Characteristic	CKD +ve (N=57)	CKD -ve (N=157)	P-value
Male, %	61	54	0.34
Age (Years)	65.5±7.8	68.7±7.8	0.01
Duration (Years)	55.7 ±6.2	55.1±6.6	0.48
BMI (kg/m ²)	27.3±3.8	25.8±4.3	0.02
Insulin dose (units/kg)	0.43±0.2	0.47±0.2	0.27
HbA _{1c} (%)	6.7±0.9	7.41±1.0	<0.001
HbA _{1c} (mmol/mol)	50.0±39.6	57.5±10.7	<0.001
Total cholesterol (mg/dl)	153.9±37.1	162.7±31.9	0.09
LDL cholesterol (mg/dl)	78.0 ±24.2	83.5±22.7	0.13
HDL cholesterol (mg/dl)	57.0±19.7	64.8±20.7	0.01
Triglycerides (mg/dl)	87.6±38.2	71.6±35.4	0.01
eGFR (ml/min/1.73 m ²)	34.1±9.62	76.9±16.6	<0.001
ACR (ug/mg)*	24.0 (11-101)	10.7 (6.0-18.8)	<0.001
Systolic BP (mmHg)	134.3±20.7	131.6±17.3	0.37
Diastolic BP (mmHg)	62.9±8.0	63.2±7.99	0.79
CVD, %	61	36	0.001
PDR, %	68	50	0.04
Neuropathy (MNSI≥2), %	61	74	0.09
Detectable c-peptide, %	38	46	0.31
Hypertensive Medication, %	79	57	0.001
Lipid lowering medication, %	71	64	0.29
Exercise, %	72	80	0.21

Data are mean±SD or median (IQR) for continuous variables or % for categorical variables where noted. eGFR; estimated glomerular filtration rate, ACR; albumin-to-creatinine ratio; BP; blood pressure, CVD cardiovascular disease, PDR; proliferative diabetic retinopathy. CKD refers to Chronic kidney Disease Stage 3b, as defined by CKD-EPI eGFR<45 ml/min/1.73 m².

SUPPLEMENTARY DATA

Supplementary Table S10. Up- and downregulated metabolites in the plasma from Joslin Medalist CKD Protected vs. Non-protected – un-adjusted and adjusted analyses.

Metabolite	Unadjusted			Adjusted*		
	FC	p	FDR	FC	p	FDR
glucuronate	-2.32	1.4E-24	8.13E-23	-1.86	5.16E-12	7.49E-11
xanthurenate	-1.82	5.04E-22	1.46E-20	-1.73	2.11E-14	1.23E-12
quinolinate	-2.23	8.88E-20	1.72E-18	-1.83	8.01E-11	9.29E-10
thymine	-1.37	1.22E-15	1.76E-14	-1.35	3.68E-12	7.12E-11
hypoxanthine	-1.61	1.18E-14	1.37E-13	-1.58	2.51E-12	7.12E-11
urate	-1.23	8.12E-14	7.85E-13	-1.19	1.28E-08	1.23E-07
inositol	-1.6	3.34E-12	2.77E-11	-1.41	3.12E-06	1.39E-05
homovanillate	-1.51	5.43E-12	3.94E-11	-1.44	1.28E-07	1.06E-06
oxalate	-1.35	2.17E-11	1.4E-10	-1.26	9.52E-07	5.02E-06
sorbitol	-2.55	6.41E-11	3.72E-10	-2.33	2.72E-07	1.97E-06
suberate	-1.29	1.95E-10	1.03E-09	-1.25	1.81E-06	8.75E-06
indolelactate	-1.51	2.68E-10	1.29E-09	-1.45	5.29E-07	3.41E-06
indoxylsulfate	-1.87	9.57E-10	4.27E-09	-1.79	6.53E-07	3.79E-06
hydroxyphenylacetate	-3.19	9.13E-09	3.78E-08	-2.68	1.16E-05	4.81E-05
4-pyridoxate	-4.31	4.96E-08	1.92E-07	-3.22	8.73E-05	0.000337
sebacate	-1.35	9.56E-08	3.47E-07	-1.25	0.000379	0.00129
adenine	-2.74	3.41E-07	1.16E-06	-2.21	0.000167	0.000607
lactose	-1.77	4.94E-07	1.59E-06	-1.49	0.00183	0.00531
sucrose	-1.75	7.3E-07	2.23E-06	-1.44	0.00292	0.00807
3-methyladipate/pimelate	-1.11	1.03E-05	2.98E-05	-1.1	0.000747	0.00228
pantothenate	-1.76	1.18E-05	3.25E-05	-1.68	0.000468	0.00151
hippurate	-1.72	1.85E-05	4.87E-05	-1.37	0.0416	0.0805
4-hydroxymandelate	-1.43	5.62E-05	0.000142	-1.19	0.0806	0.142
homogentisate	-1.42	7.09E-05	0.000171	-1.18	0.0971	0.152
fumarate/maleate	-1.19	0.000278	0.000645	-1.15	0.00913	0.0241
aconitate	-1.17	0.000405	0.000903	-1.11	0.0365	0.0756
salicylurate	-3.64	0.00049	0.00105	-2.05	0.0946	0.152
ADP	1.59	0.000599	0.00124	1.33	0.0483	0.0903
4-hydroxybenzaldehyde	-1.55	0.00152	0.00304	-1.47	0.0139	0.0321
adipate	-1.16	0.00555	0.0107	-1.11	0.143	0.208
2-hydroxyglutarate	-1.08	0.00651	0.0122	-1.05	0.181	0.25
orotate	-1.58	0.00754	0.0137	-1.44	0.096	0.152
taurodeoxycholate/taurochenodeoxycholate	-2.36	0.0078	0.0137	-1.11	0.773	0.815
GDP	1.69	0.0124	0.0211	1.32	0.2	0.264
uridine	1.13	0.0325	0.0539	1.01	0.836	0.866
pyruvate	1.29	0.0358	0.0578	1.47	0.00995	0.0251
uracil	1.13	0.0574	0.09	1.03	0.751	0.807
2-aminoadipate	-1.15	0.0597	0.0911	-1.18	0.0398	0.0795
3-hydroxybenzoate	-2.08	0.0643	0.0957	-1.23	0.655	0.73
indole-3-propionate	-1.23	0.0877	0.127	-1.27	0.0908	0.152
gentisate	-1.3	0.117	0.166	-1.08	0.678	0.741
citrate	-1.06	0.157	0.216	-1	0.964	0.964
succinate	-1.04	0.221	0.298	-1.09	0.0235	0.0525

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alpha-hydroxybutyrate	-1.13	0.24	0.303	-1.31	0.0256	0.0551
IMP	1.36	0.239	0.303	-1.16	0.577	0.657
alpha-ketoglutarate	1.11	0.231	0.303	1.29	0.0138	0.0321
lactate	1.06	0.401	0.495	1.13	0.117	0.174
AMP	1.1	0.517	0.624	-1.12	0.429	0.529
fructose/glucose/galactose	-1.03	0.643	0.761	-1.04	0.462	0.559
xanthine	1.02	0.794	0.921	1.01	0.87	0.886
glycocholate	-1.05	0.836	0.931	1.18	0.504	0.597
PEP	1.05	0.851	0.931	-1.3	0.358	0.452
phosphoglycerate	1.04	0.82	0.931	-1.34	0.101	0.155
chenodeoxycholate/deoxycholate	1.04	0.889	0.955	1.43	0.227	0.292
hexose monophosphate	1	0.984	0.994	-1.23	0.191	0.258
malate	-1	0.994	0.994	1.06	0.531	0.616
2-phosphoglycerate	-1.01	0.955	0.994	-1.36	0.0748	0.136
glycodeoxycholate/glycochenodeoxycholate	1	0.976	0.994	1.28	0.176	0.248

P: p-value, FDR: False Discovery Rate, FC: Fold Change. CKD refers to Chronic kidney Disease Stage 3b, as defined by CKD-EPI eGFR<45 ml/min/1.73 m².

*Adjusted analyses included covariates for age, BMI, HbA1c, HDL, triglycerides, and hypertensive medications.

SUPPLEMENTARY DATA

Supplementary Table S11. Baseline clinical characteristics of Joslin Medalists whose samples were used to replicate and validate TNFR1 and TNFR2 by ELISAs.

Characteristic	ELISA Replication	SOMAscan
	N=30	N=181
Male, N (%)	16 (53.33)	92 (50.83)
Age (years)	73.20 (9.17)	66.73 (7.55)
Duration (years)	65.10 (10.32)	55.40 (6.20)
BMI (kg/m ²)	26.79 (5.05)	27.18 (5.20)
Dose (kg)	0.46 (0.19)	0.46 (0.16)
HbA1c (mmol/mol)	57.09 (10.77)	58.17 (99.53)
HbA1c(%)	7.37 (0.98)	7.47 (0.87)
Total Cholesterol (mg/mmol)	3.99 (0.74)	4.19 (0.91)
Total Cholesterol (mg/dL)	154.00 (28.48)	161.64 (34.96)
LDLc (mmol/L)	2.05 (0.50)	2.14 (0.66)
LDLc (mg/dL)	79.25 (19.29)	82.75 (25.47)
HDLc (mmol/L)	1.52 (0.45)	1.61 (0.56)
HDLc (mg/dL)	58.600 (17.38)	62.37 (21.56)
Triglycerides (mg/dL)	0.91 (0.45)	0.93 (0.50)
Triglycerides (mmol/L)	80.67 (39.80)	82.61 (44.08)
eGFR (ml/min/1.73 m ²)	48.50 (20.39)	58.20 (24.11)
ACR (ug/mg)	15.07 (26.51)	13.18 (51.15)
ACR (mg/mmol)	133.26 (234.33)	116.51 (452.14)
Systolic BP (mmHg)	132.91 (22.49)	132.31 (17.43)
Diastolic BP (mmHg)	61.23 (8.99)	63.25 (8.43)
Nephropathy, N (%)	14 (46.67)	84 (46.41)
CVD, N (%)	22 (75.86)	87 (49.71)
PDR, N (%)	11 (57.89)	88 (61.97)
Neuropathy, N (%)	20 (74.07)	127 (74.71)
Detectable C-peptide, N (%)	13 (43.33)	76 (42.70)
Hypertensive Medication, N (%)	20 (68.97)	122 (69.71)
Lipid Lowering Medication, N (%)	20 (66.67)	128 (73.14)
Exercise*, N (%)	16 (55.17)	129 (73.30)

Data are mean±SD or median (IQR) for continuous variables or % for categorical variables where noted; eGFR: estimated glomerular filtration rate, ACR: albumin-to-creatinine ratio; BP: blood pressure, CVD: cardiovascular disease, PDR: proliferative diabetic retinopathy. *p<0.05 for difference between the groups.

SUPPLEMENTARY DATA

Supplementary Table S12. Correlation of TNF receptors with glycolytic enzymes

Enzyme	Correlation with TNF1		Correlation with TNF2	
	<i>Correlation coefficient</i>	<i>P</i>	<i>Correlation coefficient</i>	<i>P</i>
TPI1	-0.32	0.31	-0.47	0.12
LDHB	-0.12	0.70	-0.29	0.36
MDH1	-0.23	0.47	-0.35	0.27
PKM2	-0.63	0.03	-0.66	0.02
PGAM1	-0.42	0.18	-0.35	0.27
Cytochrome C	-0.59	0.05	-0.69	0.01
GAPDH	-0.39	0.21	-0.48	0.12

SUPPLEMENTARY DATA

Supplementary Table S13. Clinical characteristics of Joslin Medalists whose samples were used to replicate and validate APP by ELISAs.

Characteristic	ELISA N=40	SOMAscan N=181
Male, <i>N</i> (%)	13 (32.50)	92 (50.83)
Age (years)	67.1 (7.23)	66.73 (7.55)
Duration (years)	55.08 (6.14)	55.40 (6.20)
BMI (kg/m ²)	25.58 (4.06)	27.18 (5.20)
HbA1c (%)	7.16 (1.12)	7.47 (0.87)
HbA1c (mmol/mol)	54.70 (12.27)	58.17 (99.53)
LDLc (mg/dL)	74 (20.96)	82.75 (25.47)
LDLc (mmol/L)	1.92 (0.54)	2.14 (0.66)
HDLc (mg/dL)	63.85 (18.97)	62.37 (21.56)
HDLc (mmol/L)	1.6 (0.49)	1.61 (0.56)
Triglycerides (mg/dL)	75.85 (30.91)	82.61 (44.08)
Triglycerides (mmol/L)	0.86 (0.35)	0.93 (0.50)
Systolic BP (mmHg)	129.90 (17.11)	132.31 (17.43)
Diastolic BP (mmHg)	62.61 (9.95)	63.25 (8.43)
ACR (ug/mg)	78.30 (155.15)	116.51 (452.14)
ACR (mg/mmol)	8.86 (17.55)	13.18 (51.15)
Total Cholesterol (mg/dL)	153.53 (31.70)	161.64 (34.96)
Total Cholesterol (mmol/L)	3.97 (0.82)	4.19 (0.91)
Insulin dose (kg)	0.44 (0.14)	0.46 (0.16)
eGFR (mL/min per 1.73m ²)	58.04 (24.76)	58.20 (24.11)
Nephropathy, <i>N</i> (%)	20 (50.00)	84 (46.41)
Lipid Lowering Medication, <i>N</i> (%)	34 (85.00)	128 (73.14)
Hypertensive Medication, <i>N</i> (%)	29 (74.36)	122 (69.71)
Detectable C-peptide, <i>N</i> (%)	14 (35.00)	76 (42.70)
CVD, <i>N</i> (%)	19 (47.50)	87 (49.71)
PDR, <i>N</i> (%)	19 (51.35)	88 (61.97)
Neuropathy, <i>N</i> (%)	30 (78.95)	127 (74.71)
Exercise, <i>N</i> (%)	29 (74.36)	129 (73.30)

Data are mean±SD or median (IQR) for continuous variables or *N* (%) for categorical variables where noted. eGFR; estimated glomerular filtration rate, ACR; albumin-to-creatinine ratio; BP; blood pressure, CVD cardiovascular disease, PDR; proliferative diabetic retinopathy. **p*<0.05 for difference between the groups.

SUPPLEMENTARY DATA

Supplementary Table S14. Examining APP (ELISA) relationship to sample characteristics (N=159).

Characteristic	Correlation coefficient	P-value
Sex*	0.94	0.13
Duration (years)	-0.07	0.4
Age (Baseline)	-0.13	0.11
Insulin dose (kg)	0.16	0.06
<i>BMI</i> (kg/m ²)	0.22	0.01
HbA1c (%)	0.07	0.35
LDLc (mg/dL)	-0.01	0.99
Total Cholesterol (mg/dL)	-0.01	0.86
Triglycerides (mg/dL)	-0.13	0.11
HDLc (mg/dL)	0.02	0.83
<i>eGFR</i> (mL/min per 1.73m ²)	0.32	<.0001
ACR(ug/mg)	-0.16	0.06
Systolic BP (mmHg)	0.01	0.89
Diastolic BP (mmHg)	0.03	0.72
Lipid Lowering Medication*	0.68	0.45
Hypertensive Medication*	1.16	0.14
Detectable C-peptide*	-0.94	0.2
<i>CVD</i> *	1.56	0.02
<i>PDR</i> *	2.25	<0.01
Nephropathy*	2.89	<0.01
Neuropathy*	0.12	0.9

*mean difference and p-value from t-test

SUPPLEMENTARY DATA

Supplementary Table S15. Association between APP (ELISA) and Diabetic complications in the Medalists (N=159)

Outcome	Regression Estimate (95% CI)*	P-value
No PDR vs PDR	2.06 (0.55, 3.58)	0.01
No CVD vs CVD	1.25 (-0.22, 2.72)	0.09
No CKD vs CKD	3.28 (1.84, 4.72)	<.0001
No DPN vs DPN	-0.15 (-2.03, 1.73)	0.88

PDR=Proliferative diabetic retinopathy; CVD=Cardiovascular disease; CKD= Chronic kidney Disease Stage 3b, as defined by eGFR<45 ml/min/1.73 m²; DPN=diabetic peripheral neuropathy;

*model adjusted for age, sex, BMI, insulin dose.

SUPPLEMENTARY DATA

Supplementary Table S16. Correlation of APP (ELISA) with glycolytic enzymes [N=159]

Glycolytic enzyme	Pearson correlation coefficient	P value
TPI1	0.15995	0.0823
LDHB	0.19756	0.0313
MDH1	0.17042	0.0639
PKM2	0.06181	0.5042
PGAM1	0.02971	0.7484
Cytochrome C	-0.10683	0.2475
GAPDH	0.08753	0.3438

SUPPLEMENTARY DATA

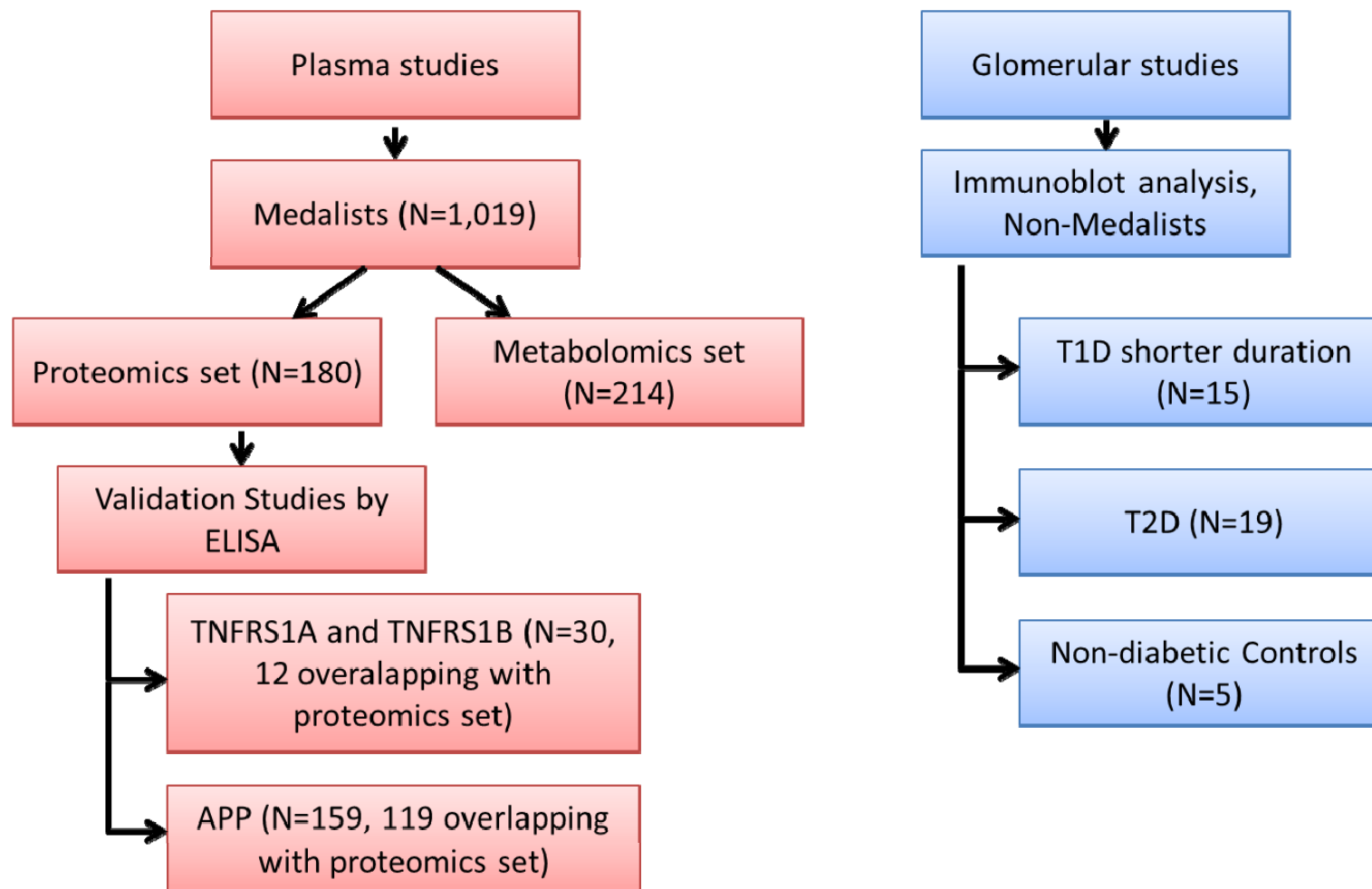
Supplementary Table S17. Pro-thrombotic Somalogic proteins that significantly correlated with APP, and their associations with CKD and PDR

Protein	Correlation with APP ELISA		No CKD vs. CKD		No PDR vs. PDR	
	<i>Correlation coefficient</i>	<i>P</i>	<i>Fold change</i>	<i>P</i>	<i>Fold change</i>	<i>P</i>
THBS2	-0.19	0.04	-1.48	1.5E-07	-1.13	0.17
THBS4	-0.25	0.01	-1.21	7.7E-07	-1.15	0.0019
TF	-0.18	0.05	-1.48	1.2E-09	-1.12	0.14
C5	0.19	0.04	1.02	0.38	-1.00	0.95
GP6	0.18	0.05	1.36	3.1E-05	1.01	0.88

THBS2=Thrombospondin-2; THBS4=Thrombospondin-4; TF=Tissue factor; C5=Complement C5; GP6=Platelet glycoprotein VI. CKD refers to Chronic kidney Disease Stage 3b, as defined by eGFR<45 ml/min/1.73 m². PDR=Proliferative diabetic retinopathy.

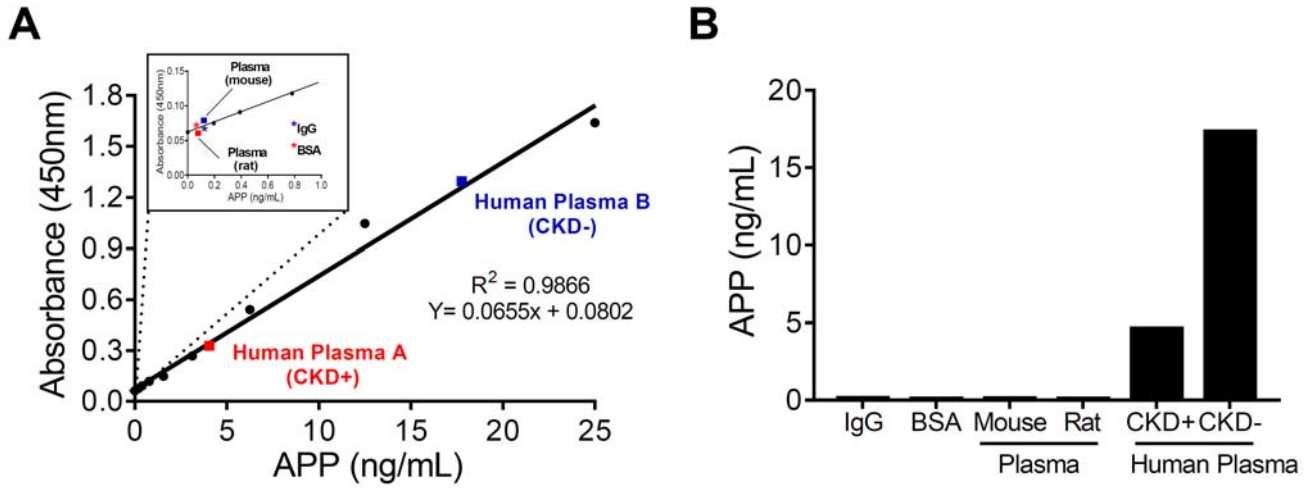
SUPPLEMENTARY DATA

Supplementary Figure S1. Flowchart of Study Design and Subsets



SUPPLEMENTARY DATA

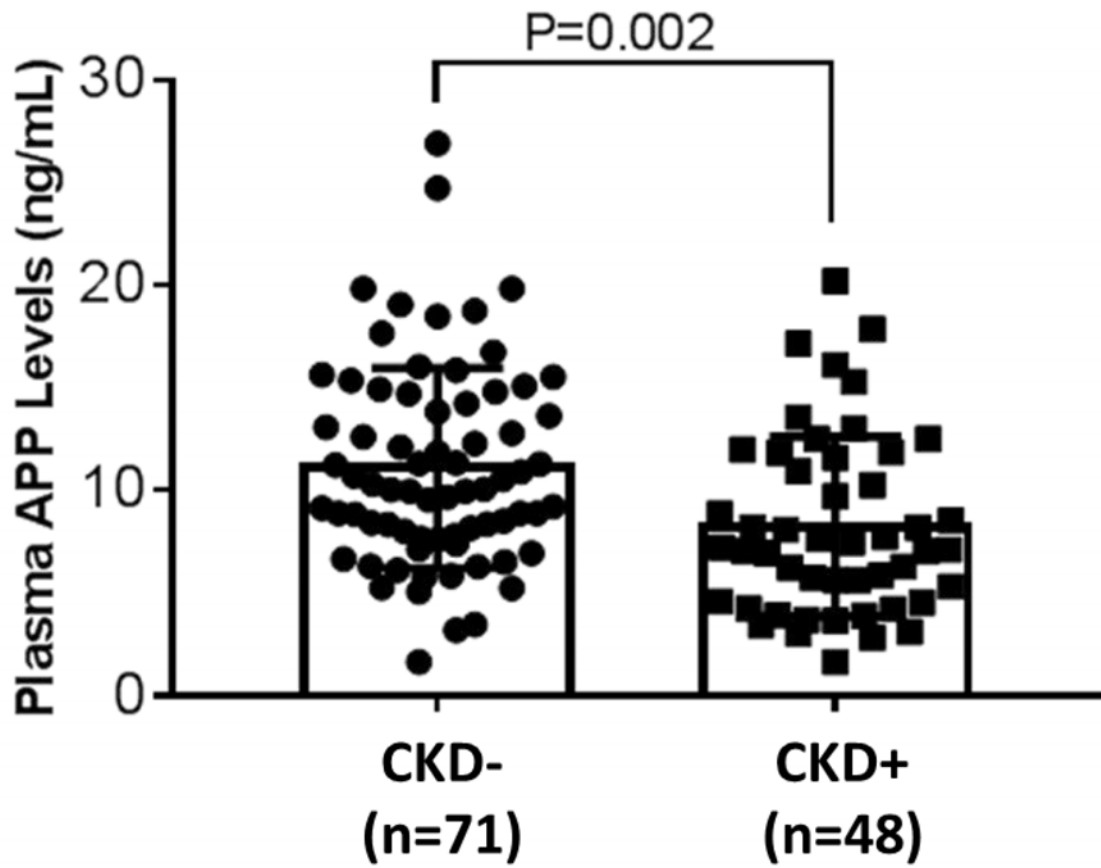
Supplementary Figure S2. Sensitivity and specificity of Human plasma APP ELISA. A) Standard Curve
B) Quantification of various validating samples



*CKD=Chronic kidney disease (diabetic nephropathy)

SUPPLEMENTARY DATA

Supplementary Figure S3. APP ELISA measurements in DN and no DN among 119 Medalists overlapping with SOMAscan samples [Validation Set]
CKD refers to Chronic kidney Disease Stage 3b, as defined by $eGFR < 45 \text{ ml/min/1.73 m}^2$



SUPPLEMENTARY DATA

Supplementary Figure S4. Correlations between APP and TNF receptors (ELISA) (N=13).

