

SUPPLEMENTARY MATERIAL

Table S1. Serum/plasma metabolites associated with any DR.

Category of metabolites	Name of metabolytes	Chinese		Malay		Indian		Pooled			After Bonferroni Correction
		OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	P - value	
Ketone bodies	3-hydroxybutyrate	1.51	1.14 - 2.01	1.16	0.95 - 1.41	1.26	1.07 - 1.48	1.26	1.13 - 1.41	0.00007	select
Fluid Balance	Creatinine	1.45	1.09 - 1.95	1.50	1.18 - 1.9	1.40	1.17 - 1.67	1.44	1.26 - 1.63	0.00000	select
Fatty acids (%)	Ratio of 22:6 docosahexaenoic acid to total fatty acids	1.02	0.79 - 1.31	1.11	0.92 - 1.34	1.26	1.08 - 1.48	1.16	1.04 - 1.29	0.00827	
Cholesterol	Esterified cholesterol	0.88	0.68 - 1.14	0.71	0.59 - 0.87	0.97	0.84 - 1.13	0.87	0.78 - 0.97	0.01294	
Fatty acids by saturation	Omega-6 fatty acids	0.80	0.61 - 1.05	0.77	0.63 - 0.93	0.99	0.86 - 1.16	0.88	0.79 - 0.99	0.02747	
Lipoprotein subclasses	& Total cholesterol in IDL	0.84	0.64 - 1.10	0.74	0.60 - 0.90	0.95	0.82 - 1.1	0.86	0.77 - 0.96	0.00921	
Cholesterol											
Lipoprotein subclasses	Total cholesterol to total lipids ratio in IDL	0.87	0.68 - 1.12	0.70	0.56 - 0.87	0.87	0.74 - 1.01	0.82	0.73 - 0.92	0.00056	select
Lipoprotein subclasses	Cholesterol esters in IDL	0.85	0.65 - 1.09	0.72	0.59 - 0.88	0.96	0.83 - 1.11	0.86	0.78 - 0.96	0.00839	
Lipoprotein subclasses	Cholesterol esters to total lipids ratio in IDL	0.75	0.58 - 0.98	0.69	0.56 - 0.86	0.86	0.74 - 1.01	0.79	0.71 - 0.89	0.00007	select
Lipoprotein subclasses	Free cholesterol in IDL	0.95	0.72 - 1.25	0.78	0.64 - 0.95	0.95	0.82 - 1.11	0.90	0.80 - 1.00	0.05121	
Lipoprotein subclasses	Total lipids in IDL	0.88	0.68 - 1.14	0.75	0.62 - 0.91	0.97	0.83 - 1.12	0.88	0.79 - 0.98	0.01879	
Lipoprotein subclasses	Concentration of IDL particles	0.87	0.67 - 1.12	0.78	0.65 - 0.95	0.97	0.83 - 1.13	0.89	0.80 - 0.99	0.03083	

Lipoprotein subclasses	Phospholipids in IDL	0.91	0.71 - 1.17	0.75	0.62 - 0.91	0.97	0.84 - 1.13	0.89	0.80 - 0.99	0.02956
Lipoprotein subclasses	Triglycerides to total lipids ratio in IDL	1.07	0.84 - 1.37	1.33	1.10 - 1.61	1.13	0.98 - 1.30	1.18	1.06 - 1.30	0.00204
Fatty acids	18:2, linoleic acid	0.82	0.63 - 1.07	0.77	0.63 - 0.93	0.99	0.85 - 1.16	0.88	0.79 - 0.99	0.02714
Cholesterol	Total cholesterol in LDL	0.88	0.67 - 1.16	0.71	0.58 - 0.87	0.97	0.84 - 1.13	0.87	0.78 - 0.97	0.01522
Lipoprotein subclasses	Free cholesterol to total lipids ratio in large HDL	1.12	0.83 - 1.52	1.28	1.01 - 1.62	1.04	0.87 - 1.24	1.12	0.99 - 1.28	0.08041
Lipoprotein subclasses	Total cholesterol in large LDL	0.86	0.65 - 1.13	0.71	0.57 - 0.87	0.96	0.83 - 1.12	0.87	0.78 - 0.97	0.01123
Lipoprotein subclasses	Total cholesterol to total lipids ratio in large LDL	0.88	0.61 - 1.29	0.68	0.54 - 0.86	0.95	0.81 - 1.11	0.86	0.76 - 0.97	0.01790
Lipoprotein subclasses	Cholesterol esters in large LDL	0.85	0.65 - 1.11	0.69	0.56 - 0.86	0.97	0.83 - 1.12	0.86	0.77 - 0.97	0.01115
Lipoprotein subclasses	Cholesterol esters to total lipids ratio in large LDL	0.79	0.58 - 1.08	0.62	0.48 - 0.80	0.95	0.81 - 1.12	0.83	0.73 - 0.94	0.00401
Lipoprotein subclasses	Free cholesterol in large LDL	0.91	0.68 - 1.22	0.75	0.62 - 0.91	0.96	0.83 - 1.11	0.88	0.79 - 0.98	0.02488
Lipoprotein subclasses	Total lipids in large LDL	0.86	0.66 - 1.12	0.72	0.59 - 0.88	0.98	0.84 - 1.13	0.88	0.78 - 0.98	0.01600
Lipoprotein subclasses	Concentration of large LDL particles	0.88	0.68 - 1.14	0.72	0.59 - 0.88	0.98	0.84 - 1.14	0.88	0.79 - 0.98	0.02035
Lipoprotein subclasses	Phospholipids in large LDL	0.87	0.67 - 1.13	0.75	0.61 - 0.90	0.97	0.83 - 1.12	0.88	0.79 - 0.97	0.01515
Lipoprotein subclasses	Phospholipids to total lipids ratio in large LDL	1.11	0.83 - 1.47	1.29	1.05 - 1.58	1.00	0.86 - 1.17	1.10	0.98 - 1.23	0.10656
Lipoprotein subclasses	Triglycerides to total lipids ratio in large LDL	1.05	0.80 - 1.37	1.34	1.11 - 1.62	1.10	0.94 - 1.27	1.16	1.04 - 1.29	0.00705

Lipoprotein subclasses	Cholesterol esters to total lipids ratio in chylomicrons and large VLDL	1.14	0.85 - 1.51	1.29	1.05 - 1.58	1.06	0.91 - 1.23	1.14	1.02 - 1.27	0.02421
Lipoprotein subclasses	Total cholesterol in medium LDL	0.93	0.72 - 1.20	0.71	0.59 - 0.87	1.00	0.86 - 1.15	0.89	0.80 - 0.99	0.03888
Lipoprotein subclasses	Cholesterol esters in medium LDL	0.90	0.68 - 1.19	0.71	0.57 - 0.88	0.98	0.83 - 1.16	0.88	0.78 - 0.99	0.03447
Lipoprotein subclasses	Cholesterol esters to total lipids ratio in medium LDL	0.93	0.71 - 1.21	0.74	0.58 - 0.94	0.99	0.84 - 1.18	0.90	0.80 - 1.02	0.11005
Lipoprotein subclasses	Free cholesterol in medium LDL	0.89	0.69 - 1.16	0.76	0.63 - 0.91	0.97	0.84 - 1.12	0.88	0.80 - 0.98	0.02282
Lipoprotein subclasses	Total lipids in medium LDL	0.89	0.69 - 1.16	0.71	0.59 - 0.87	0.99	0.86 - 1.15	0.88	0.79 - 0.98	0.02378
Lipoprotein subclasses	Concentration of medium LDL particles	0.89	0.69 - 1.15	0.78	0.65 - 0.94	1.00	0.86 - 1.15	0.90	0.81 - 1.00	0.05714
Lipoprotein subclasses	Phospholipids in medium LDL	0.81	0.62 - 1.06	0.74	0.61 - 0.90	0.98	0.84 - 1.13	0.87	0.78 - 0.97	0.01047
Lipoprotein subclasses	Triglycerides to total lipids ratio in medium LDL	1.06	0.82 - 1.37	1.33	1.11 - 1.60	1.08	0.93 - 1.24	1.15	1.04 - 1.27	0.00860
Glycerides and phospholipids	Phosphatidylcholine and other cholines	0.84	0.65 - 1.08	0.79	0.65 - 0.96	0.98	0.85 - 1.14	0.90	0.80 - 1.00	0.04394
Cholesterol	Serum total cholesterol	0.86	0.67 - 1.11	0.76	0.62 - 0.92	0.98	0.85 - 1.14	0.89	0.80 - 0.99	0.02697
Fatty acids by saturation	Saturated fatty acids	0.76	0.58 - 1.00	0.78	0.65 - 0.95	0.99	0.85 - 1.15	0.88	0.79 - 0.98	0.02238
Lipoprotein subclasses	Total cholesterol in small LDL	0.95	0.74 - 1.23	0.72	0.59 - 0.87	1.00	0.86 - 1.15	0.90	0.81 - 1.00	0.04639
Lipoprotein subclasses	Cholesterol esters in small LDL	0.91	0.67 - 1.24	0.73	0.59 - 0.90	0.97	0.82 - 1.15	0.88	0.78 - 0.99	0.03090
Lipoprotein subclasses	Free cholesterol in small LDL	0.92	0.71 - 1.18	0.68	0.55 - 0.85	0.97	0.84 - 1.13	0.88	0.79 - 0.98	0.02148

Lipoprotein subclasses	Total lipids in small LDL	0.89	0.69 - 1.15	0.78	0.65 - 0.93	0.98	0.85 - 1.14	0.90	0.81 - 1.00	0.04046	
Lipoprotein subclasses	Concentration of small LDL particles	0.88	0.68 - 1.14	0.78	0.65 - 0.93	0.98	0.85 - 1.14	0.89	0.81 - 0.99	0.03836	
Lipoprotein subclasses	Phospholipids in small LDL	0.82	0.63 - 1.06	0.65	0.53 - 0.81	0.95	0.82 - 1.11	0.84	0.75 - 0.94	0.00219	
Glycerides and phospholipids	Sphingomyelins	0.86	0.67 - 1.11	0.76	0.63 - 0.92	0.93	0.80 - 1.09	0.86	0.77 - 0.96	0.00782	
Glycerides and phospholipids	Total cholines	0.84	0.65 - 1.08	0.81	0.66 - 0.98	0.99	0.85 - 1.15	0.90	0.81 - 1.01	0.06736	
Glycerides and phospholipids	Total phosphoglycerides	0.81	0.62 - 1.05	0.77	0.63 - 0.94	1.00	0.86 - 1.16	0.89	0.80 - 0.99	0.03292	
Aromatic amino acids	Tyrosine	0.70	0.54 - 0.91	0.72	0.59 - 0.87	0.73	0.63 - 0.85	0.72	0.65 - 0.81	0.00000	select
Lipoprotein subclasses	Total cholesterol in very large HDL	0.85	0.67 - 1.08	0.97	0.79 - 1.20	0.85	0.74 - 0.98	0.88	0.79 - 0.98	0.01618	
Lipoprotein subclasses	Cholesterol esters in very large HDL	0.85	0.67 - 1.07	0.95	0.76 - 1.18	0.85	0.74 - 0.97	0.87	0.78 - 0.97	0.00937	
Lipoprotein subclasses	Triglycerides in very large HDL	0.81	0.64 - 1.02	0.92	0.71 - 1.19	0.86	0.75 - 0.99	0.86	0.77 - 0.96	0.00546	
Lipoprotein subclasses	Cholesterol esters to total lipids ratio in chylomicrons and very large VLDL	1.21	0.85 - 1.72	1.42	1.13 - 1.77	1.04	0.84 - 1.28	1.20	1.04 - 1.38	0.01041	
Lipoprotein subclasses	Total lipids in very large VLDL	0.83	0.65 - 1.05	0.79	0.64 - 0.97	0.99	0.85 - 1.15	0.90	0.81 - 1.00	0.05325	
Lipoprotein subclasses	Concentration of very large VLDL particles	0.83	0.65 - 1.05	0.78	0.63 - 0.97	0.99	0.86 - 1.16	0.90	0.81 - 1.00	0.05364	
Lipoprotein subclasses	Phospholipids in very large VLDL	0.84	0.66 - 1.06	0.77	0.62 - 0.96	1.00	0.86 - 1.16	0.90	0.81 - 1.00	0.05576	

Lipoprotein subclasses	Triglycerides in very large VLDL	0.83	0.65 - 1.05	0.79	0.63 - 0.99	0.98	0.84 - 1.13	0.90	0.80 - 1.00	0.04821
Lipoprotein subclasses	Cholesterol esters in very small VLDL	0.83	0.64 - 1.07	0.79	0.63 - 0.98	0.96	0.82 - 1.12	0.89	0.79 - 0.99	0.03451
Lipoprotein subclasses	Cholesterol esters to total lipids ratio in chylomicrons and very small VLDL	0.88	0.67 - 1.14	0.91	0.74 - 1.11	0.86	0.74 - 0.99	0.87	0.78 - 0.97	0.01460
Lipoprotein subclasses	Total cholesterol to total lipids ratio in chylomicrons and extremely large VLDL	1.11	0.82 - 1.51	1.19	0.94 - 1.51	1.28	1.08 - 1.51	1.22	1.08 - 1.39	0.00140
Lipoprotein subclasses	Cholesterol esters to total lipids ratio in chylomicrons and extremely large VLDL	1.04	0.79 - 1.38	1.22	0.96 - 1.56	1.21	1.02 - 1.44	1.18	1.04 - 1.33	0.00999
Lipoprotein subclasses	Free cholesterol in chylomicrons and extremely large VLDL	0.83	0.65 - 1.06	0.80	0.65 - 0.99	0.98	0.84 - 1.14	0.90	0.81 - 1.00	0.04830
Lipoprotein subclasses	Total lipids in chylomicrons and extremely large VLDL	0.79	0.62 - 1.00	0.82	0.68 - 0.99	0.95	0.82 - 1.11	0.88	0.79 - 0.98	0.01581
Lipoprotein subclasses	Concentration of chylomicrons and extremely large VLDL particles	0.78	0.61 - 1.00	0.82	0.68 - 0.99	0.95	0.82 - 1.10	0.87	0.79 - 0.97	0.01305
Lipoprotein subclasses	Phospholipids in chylomicrons and extremely large VLDL	0.82	0.64 - 1.04	0.81	0.67 - 0.99	0.95	0.82 - 1.11	0.88	0.79 - 0.98	0.02339
Lipoprotein subclasses	Triglycerides in chylomicrons and extremely large VLDL	0.78	0.61 - 0.99	0.80	0.66 - 0.98	0.94	0.81 - 1.09	0.87	0.78 - 0.96	0.00827
Lipoprotein subclasses	Triglycerides to total lipids ratio in chylomicrons and extremely large VLDL	0.98	0.63 - 1.52	0.91	0.74 - 1.12	0.72	0.60 - 0.88	0.82	0.71 - 0.94	0.00336

Table S2. Serum/plasma metabolites associated with moderate and above DR

Category of metabolites	Name of metabolytes	Chinese		Malay		Indian		Pooled			After Bonferroni
		OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	P - value	Correction
Apolipoproteins	Apolipoprotein A-I	0.74	0.52 - 1.05	0.63	0.49 - 0.82	0.88	0.70 - 1.09	0.76	0.65 - 0.88	0.00033	select
Apolipoproteins	Apolipoprotein B	0.90	0.63 - 1.28	0.71	0.56 - 0.90	0.96	0.78 - 1.19	0.85	0.73 - 0.98	0.02565	
Ketone bodies	3-hydroxybutyrate	1.91	1.30 - 2.81	1.16	0.92 - 1.48	1.10	0.87 - 1.38	1.22	1.05 - 1.42	0.00868	
Fluid Balance	Creatinine	1.68	1.14 - 2.47	1.44	1.09 - 1.89	1.95	1.53 - 2.48	1.70	1.45 - 2.01	0.00000	select
Cholesterol	Esterified cholesterol	0.96	0.67 - 1.36	0.60	0.47 - 0.77	0.90	0.74 - 1.11	0.79	0.69 - 0.92	0.00177	
Fatty acids by saturation (%)	Ratio of omega-3 fatty acids to total fatty acids	1.00	0.71 - 1.43	1.24	0.97 - 1.57	1.27	1.02 - 1.59	1.21	1.04 - 1.40	0.01223	
Fatty acids by saturation	Omega-6 fatty acids	0.97	0.67 - 1.39	0.67	0.53 - 0.85	0.89	0.72 - 1.10	0.81	0.70 - 0.94	0.00498	
Cholesterol	Free cholesterol	0.96	0.67 - 1.36	0.73	0.58 - 0.92	0.96	0.78 - 1.18	0.87	0.75 - 1.00	0.04740	
Glycolysis related metabolites	Glucose	1.43	0.93 - 2.19	1.59	1.14 - 2.20	1.16	0.92 - 1.47	1.32	1.10 - 1.57	0.00211	
Cholesterol	Total cholesterol in HDL2	0.80	0.53 - 1.20	0.76	0.59 - 0.97	0.94	0.75 - 1.17	0.84	0.72 - 0.98	0.02798	
Cholesterol	Total cholesterol in HDL3	0.96	0.67 - 1.39	0.63	0.49 - 0.81	0.98	0.79 - 1.21	0.84	0.72 - 0.97	0.02123	
Cholesterol	Total cholesterol in HDL	0.80	0.56 - 1.13	0.74	0.58 - 0.95	0.90	0.73 - 1.12	0.82	0.71 - 0.95	0.00953	
Lipoprotein subclasses & Cholesterol	Total cholesterol in IDL	1.00	0.69 - 1.44	0.66	0.51 - 0.85	0.90	0.72 - 1.11	0.82	0.71 - 0.95	0.00843	
Lipoprotein subclasses	Total cholesterol to total lipids ratio in IDL	0.94	0.68 - 1.31	0.58	0.44 - 0.76	0.73	0.59 - 0.90	0.72	0.62 - 0.83	0.00001	select
Lipoprotein subclasses	Cholesterol esters in IDL	0.98	0.69 - 1.40	0.63	0.49 - 0.81	0.90	0.73 - 1.11	0.81	0.70 - 0.94	0.00429	

Lipoprotein subclasses	Cholesterol esters to total lipids ratio in IDL	0.80	0.57 - 1.13	0.57	0.43 - 0.74	0.72	0.58 - 0.89	0.68	0.59 - 0.79	0.00000	select
Fatty acids	18:2, linoleic acid	0.99	0.69 - 1.43	0.68	0.54 - 0.86	0.92	0.74 - 1.14	0.83	0.72 - 0.96	0.01136	
Lipoprotein subclasses	Total cholesterol in large VLDL	0.76	0.55 - 1.04	0.75	0.58 - 0.96	0.99	0.80 - 1.22	0.86	0.74 - 0.99	0.03280	
Lipoprotein subclasses	Cholesterol esters to total lipids ratio in chylomicrons and large VLDL	1.31	0.89 - 1.92	1.57	1.22 - 2.03	1.25	1.02 - 1.54	1.36	1.17 - 1.58	0.00005	select
Lipoprotein subclasses	Free cholesterol in large VLDL	0.75	0.55 - 1.03	0.71	0.54 - 0.93	0.99	0.81 - 1.23	0.85	0.73 - 0.98	0.02801	
Lipoprotein subclasses	Free cholesterol to total lipids ratio in chylomicrons and large VLDL	0.61	0.40 - 0.94	0.66	0.50 - 0.88	0.97	0.74 - 1.28	0.77	0.64 - 0.92	0.00390	
Lipoprotein subclasses	Total lipids in large VLDL	0.76	0.55 - 1.05	0.71	0.55 - 0.91	0.95	0.77 - 1.18	0.83	0.72 - 0.96	0.01039	
Lipoprotein subclasses	Concentration of large VLDL particles	0.76	0.55 - 1.06	0.71	0.55 - 0.91	0.95	0.77 - 1.17	0.83	0.72 - 0.95	0.00973	
Lipoprotein subclasses	Phospholipids in large VLDL	0.76	0.55 - 1.05	0.77	0.61 - 0.97	0.96	0.78 - 1.19	0.85	0.74 - 0.98	0.02092	
Lipoprotein subclasses	Triglycerides in large VLDL	0.76	0.55 - 1.06	0.70	0.54 - 0.90	0.95	0.77 - 1.17	0.82	0.71 - 0.95	0.00802	
Lipoprotein subclasses	Total cholesterol in medium HDL	0.83	0.59 - 1.18	0.72	0.56 - 0.92	0.93	0.74 - 1.15	0.83	0.71 - 0.96	0.01286	
Lipoprotein subclasses	Cholesterol esters in medium HDL	0.81	0.57 - 1.16	0.71	0.56 - 0.91	0.91	0.73 - 1.14	0.81	0.70 - 0.95	0.00712	
Lipoprotein subclasses	Total lipids in medium HDL	0.79	0.55 - 1.13	0.70	0.55 - 0.90	0.97	0.78 - 1.20	0.84	0.72 - 0.97	0.01633	

Lipoprotein subclasses		Concentration of medium HDL particles	0.77	0.54 - 1.11	0.70	0.55 - 0.90	0.97	0.79 - 1.20	0.84	0.72 - 0.97	0.01624	
Lipoprotein subclasses		Phospholipids in medium HDL	0.74	0.53 - 1.04	0.71	0.56 - 0.91	0.99	0.80 - 1.23	0.84	0.73 - 0.97	0.01901	
Lipoprotein subclasses		Phospholipids in medium LDL	0.95	0.66 - 1.37	0.66	0.52 - 0.83	0.90	0.73 - 1.12	0.81	0.70 - 0.94	0.00411	
Lipoprotein subclasses		Triglycerides in medium VLDL	0.81	0.58 - 1.13	0.79	0.63 - 1.00	0.95	0.76 - 1.17	0.86	0.74 - 0.99	0.03507	
Glycerides and phospholipids		Phosphatidylcholine and other cholines	0.81	0.57 - 1.15	0.67	0.53 - 0.86	0.92	0.74 - 1.14	0.80	0.69 - 0.93	0.00302	
Fatty acids saturation	by	Polyunsaturated fatty acids	0.95	0.66 - 1.36	0.69	0.55 - 0.88	0.94	0.77 - 1.16	0.85	0.73 - 0.98	0.02284	
Cholesterol		Remnant cholesterol (non-HDL, non-LDL -cholesterol)	0.89	0.63 - 1.27	0.72	0.57 - 0.91	0.99	0.80 - 1.23	0.86	0.75 - 1.00	0.04373	
Cholesterol		Serum total cholesterol	0.94	0.66 - 1.33	0.66	0.52 - 0.83	0.92	0.75 - 1.13	0.82	0.71 - 0.94	0.00568	
Fatty acids saturation	by	Saturated fatty acids	0.83	0.58 - 1.19	0.65	0.51 - 0.83	0.90	0.73 - 1.12	0.79	0.68 - 0.92	0.00182	
Fatty acids saturation (%)	by	Ratio of saturated fatty acids to total fatty acids	0.69	0.47 - 1.00	0.81	0.64 - 1.03	0.74	0.59 - 0.91	0.76	0.65 - 0.88	0.00019	select
Lipoprotein subclasses		Free cholesterol in small HDL	0.80	0.56 - 1.15	0.76	0.60 - 0.96	0.93	0.75 - 1.16	0.84	0.72 - 0.97	0.01718	
Lipoprotein subclasses		Total lipids in small HDL	0.94	0.68 - 1.31	0.64	0.50 - 0.82	0.95	0.77 - 1.17	0.83	0.72 - 0.96	0.01057	
Lipoprotein subclasses		Concentration of small HDL particles	0.93	0.67 - 1.29	0.66	0.52 - 0.86	0.95	0.77 - 1.18	0.84	0.73 - 0.97	0.01975	

Lipoprotein subclasses	Phospholipids in small HDL	0.77	0.53 - 1.11	0.78	0.62 - 0.99	0.95	0.76 - 1.18	0.85	0.74 - 0.99	0.03276	
Lipoprotein subclasses	Phospholipids in small LDL	0.90	0.63 - 1.29	0.52	0.39 - 0.69	0.85	0.69 - 1.05	0.74	0.64 - 0.87	0.00013	select
Glycerides and phospholipids	Sphingomyelins	0.98	0.69 - 1.39	0.66	0.51 - 0.84	0.80	0.64 - 1.00	0.77	0.67 - 0.89	0.00058	select
Glycerides and phospholipids	Total cholines	0.84	0.59 - 1.20	0.69	0.54 - 0.88	0.92	0.74 - 1.14	0.82	0.71 - 0.94	0.00649	
Total fatty acids and saturation measures	Total fatty acids	0.87	0.61 - 1.25	0.67	0.53 - 0.86	0.95	0.77 - 1.18	0.83	0.72 - 0.96	0.01125	
Glycerides and phospholipids	Total phosphoglycerides	0.79	0.55 - 1.12	0.65	0.51 - 0.83	0.92	0.74 - 1.14	0.79	0.68 - 0.92	0.00172	
Aromatic amino acids	Tyrosine	0.57	0.40 - 0.82	0.67	0.53 - 0.85	0.76	0.62 - 0.93	0.69	0.60 - 0.80	0.00000	select
Total fatty acids and saturation measures	Estimated degree of unsaturation	1.14	0.80- 1.62	1.38	1.10 - 1.74	1.23	0.98 - 1.54	1.27	1.10 - 1.47	0.00138	
Lipoprotein subclasses	Total cholesterol in very large HDL	0.89	0.65 - 1.22	0.75	0.59 - 0.96	0.82	0.68 - 0.99	0.81	0.71 - 0.93	0.00273	
Lipoprotein subclasses	Total cholesterol to total lipids ratio in very large HDL	0.78	0.53 - 1.15	0.73	0.57 - 0.93	0.76	0.60 - 0.98	0.75	0.64 - 0.88	0.00044	select
Lipoprotein subclasses	Cholesterol esters in very large HDL	0.90	0.65 - 1.23	0.73	0.56 - 0.94	0.81	0.67 - 0.98	0.80	0.70 - 0.92	0.00177	
Lipoprotein subclasses	Cholesterol esters to total lipids ratio in very large HDL	0.85	0.58 - 1.26	0.74	0.58 - 0.95	0.76	0.59 - 0.98	0.77	0.65 - 0.90	0.00125	

Lipoprotein subclasses	Free cholesterol to total lipids ratio in very large HDL	0.70	0.45 - 1.08	0.75	0.58 - 0.97	0.81	0.64 - 1.03	0.77	0.66 - 0.91	0.00161	
Lipoprotein subclasses	Phospholipids to total lipids ratio in very large HDL	1.13	0.69 - 1.86	1.31	0.97 - 1.76	1.48	1.06 - 2.08	1.34	1.09 - 1.64	0.00537	
Lipoprotein subclasses	Cholesterol esters to total lipids ratio in chylomicrons and very large VLDL	1.46	0.91 - 2.33	1.72	1.30 - 2.28	1.38	1.03 - 1.85	1.54	1.28 - 1.85	0.00001	select
Lipoprotein subclasses	Total lipids in very large VLDL	0.74	0.54 - 1.00	0.68	0.53 - 0.88	0.95	0.77 - 1.16	0.81	0.70 - 0.94	0.00416	
Lipoprotein subclasses	Concentration of very large VLDL particles	0.74	0.54 - 1.00	0.68	0.52 - 0.88	0.95	0.77 - 1.16	0.81	0.70 - 0.93	0.00393	
Lipoprotein subclasses	Phospholipids in very large VLDL	0.75	0.55 - 1.03	0.66	0.51 - 0.86	0.97	0.79 - 1.19	0.82	0.71 - 0.94	0.00531	
Lipoprotein subclasses	Phospholipids to total lipids ratio in chylomicrons and very large VLDL	0.54	0.31 - 0.96	0.70	0.52 - 0.95	0.96	0.70 - 1.32	0.77	0.63 - 0.95	0.01471	
Lipoprotein subclasses	Triglycerides in very large VLDL	0.74	0.54 - 1.00	0.68	0.52 - 0.91	0.90	0.73 - 1.10	0.80	0.69 - 0.92	0.00231	
Lipoprotein subclasses	Total cholesterol to total lipids ratio in chylomicrons and extremely large VLDL	1.19	0.76 - 1.86	1.42	1.05 - 1.92	1.54	1.24 - 1.93	1.45	1.23 - 1.71	0.00001	select
Lipoprotein subclasses	Cholesterol esters to total lipids ratio in chylomicrons and extremely large VLDL	1.00	0.68 - 1.49	1.56	1.14 - 2.13	1.52	1.20 - 1.92	1.42	1.20 - 1.68	0.00005	select
Lipoprotein subclasses	Free cholesterol in chylomicrons and extremely large VLDL	0.75	0.55 - 1.02	0.73	0.57 - 0.93	0.94	0.77 - 1.16	0.83	0.72 - 0.95	0.00803	
Lipoprotein subclasses	Total lipids in chylomicrons and extremely large VLDL	0.74	0.54 - 1.02	0.74	0.59 - 0.93	0.94	0.76 - 1.15	0.83	0.72 - 0.95	0.00664	
Lipoprotein subclasses	Concentration of chylomicrons and extremely large VLDL particles	0.74	0.54 - 1.02	0.74	0.58 - 0.93	0.93	0.76 - 1.14	0.82	0.71 - 0.94	0.00545	

Lipoprotein subclasses	Phospholipids in chylomicrons and extremely large VLDL	0.75	0.55 - 1.03	0.73	0.57 - 0.93	0.92	0.75 - 1.13	0.82	0.71 - 0.94	0.00569
Lipoprotein subclasses	Phospholipids to total lipids ratio in chylomicrons and extremely large VLDL	0.53	0.30 - 0.94	0.84	0.61 - 1.15	0.93	0.68 - 1.26	0.83	0.67 - 1.02	0.06963
Lipoprotein subclasses	Triglycerides in chylomicrons and extremely large VLDL	0.74	0.54 - 1.02	0.71	0.56 - 0.91	0.91	0.74 - 1.11	0.81	0.70 - 0.93	0.00268

Table S3. Serum/plasma metabolites associated with VTDR

Category of metabolites	Name of metabolites	Chinese		Malay		Indian		Pooled			After Bonferroni Correction
		OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	P - value	
Apolipoproteins	Apolipoprotein A-I	0.55	0.34 - 0.88	0.82	0.61 - 1.11	0.97	0.76 - 1.23	0.85	0.71 - 1.01	0.06079	
Ketone bodies	3-hydroxybutyrate	2.76	1.67 - 4.56	1.29	0.97 - 1.71	1.16	0.90 - 1.49	1.34	1.13 - 1.60	0.00097	select
Fluid Balance	Creatinine	1.79	1.08 - 2.97	1.79	1.30 - 2.47	2.14	1.65 - 2.76	1.96	1.63 - 2.37	0.00000	select
Glycolysis related metabolites	Glucose	1.16	0.68 - 1.97	1.85	1.21 - 2.83	1.07	0.83 - 1.39	1.23	1.00 - 1.51	0.04508	
Cholesterol	Total cholesterol in HDL2	0.59	0.35 - 1.00	0.74	0.55 - 1.00	0.90	0.70 - 1.15	0.80	0.67 - 0.95	0.01367	
Cholesterol	Total cholesterol in HDL	0.60	0.38 - 0.93	0.77	0.57 - 1.04	0.93	0.73 - 1.18	0.82	0.69 - 0.97	0.02154	
Lipoprotein subclasses	Total cholesterol to total lipids ratio in IDL	0.73	0.49 - 1.09	0.69	0.50 - 0.96	0.89	0.70 - 1.12	0.80	0.67 - 0.95	0.01045	
Lipoprotein subclasses	Cholesterol esters to total lipids ratio in IDL	0.71	0.46 - 1.09	0.66	0.48 - 0.90	0.84	0.66 - 1.06	0.76	0.64 - 0.90	0.00157	select
Glycerides and phospholipids & Lipoprotein subclasses	Triglycerides in IDL	1.11	0.71 - 1.74	1.53	1.15 - 2.04	1.32	1.04 - 1.68	1.36	1.14 - 1.61	0.00044	select
Lipoprotein subclasses	Triglycerides in large LDL	1.02	0.65 - 1.60	1.47	1.10 - 1.95	1.30	1.00 - 1.68	1.31	1.10 - 1.56	0.00281	
Lipoprotein subclasses	Triglycerides to total lipids ratio in large LDL	1.31	0.84 - 2.04	1.41	1.05 - 1.90	1.16	0.92 - 1.48	1.26	1.06 - 1.50	0.00744	
Lipoprotein subclasses	Cholesterol esters to total lipids ratio in chylomicrons and large VLDL	1.21	0.74 - 1.97	1.69	1.23 - 2.32	1.11	0.88 - 1.39	1.27	1.07 - 1.51	0.00682	

Lipoprotein subclasses	Total cholesterol in medium HDL	0.66	0.43 - 1.03	0.63	0.47 - 0.85	0.95	0.75 - 1.22	0.78	0.66 - 0.93	0.00624	
Lipoprotein subclasses	Total cholesterol to total lipids ratio in medium HDL	0.84	0.55 - 1.29	0.68	0.50 - 0.92	0.88	0.69 - 1.14	0.80	0.67 - 0.96	0.01373	
Lipoprotein subclasses	Cholesterol esters in medium HDL	0.64	0.41 - 1.01	0.62	0.46 - 0.83	0.94	0.74 - 1.21	0.77	0.64 - 0.91	0.00303	
Lipoprotein subclasses	Cholesterol esters to total lipids ratio in medium HDL	0.86	0.56 - 1.33	0.66	0.49 - 0.89	0.84	0.65 - 1.09	0.78	0.65 - 0.93	0.00585	
Lipoprotein subclasses	Free cholesterol in medium HDL	0.68	0.42 - 1.09	0.69	0.51 - 0.93	0.97	0.76 - 1.25	0.82	0.69 - 0.98	0.02895	
Lipoprotein subclasses	Total lipids in medium HDL	0.61	0.38 - 0.97	0.63	0.46 - 0.85	1.00	0.79 - 1.26	0.80	0.67 - 0.95	0.01233	
Lipoprotein subclasses	Triglycerides to total lipids ratio in medium HDL	1.04	0.68 - 1.60	1.41	1.07 - 1.86	1.14	0.90 - 1.44	1.21	1.03 - 1.43	0.02253	
Lipoprotein subclasses	Triglycerides in medium LDL	1.02	0.65 - 1.62	1.38	1.02 - 1.88	1.29	1.01 - 1.66	1.28	1.07 - 1.53	0.00738	
Lipoprotein subclasses	Triglycerides to total lipids ratio in medium LDL	1.28	0.84 - 1.97	1.34	1.00 - 1.79	1.15	0.92 - 1.45	1.23	1.04 - 1.45	0.01336	
Lipoprotein subclasses	Phospholipids to total lipids ratio in chylomicrons and medium VLDL	1.16	0.77 - 1.74	1.37	1.04 - 1.81	1.17	0.89 - 1.54	1.24	1.04 - 1.48	0.01485	
Fatty acids by saturation (%)	Ratio of saturated fatty acids to total fatty acids	0.70	0.42 - 1.16	0.73	0.54 - 0.98	0.71	0.56 - 0.90	0.71	0.60 - 0.85	0.00015	select
Lipoprotein subclasses	Free cholesterol in small HDL	0.69	0.44 - 1.09	0.70	0.53 - 0.93	0.95	0.74 - 1.21	0.81	0.68 - 0.96	0.01749	
Lipoprotein subclasses	Phospholipids in small HDL	0.71	0.44 - 1.13	0.66	0.50 - 0.89	0.97	0.76 - 1.23	0.81	0.68 - 0.96	0.01808	

Aromatic acids	amino	Tyrosine	0.54	0.34 - 0.85	0.74	0.55 - 0.99	0.72	0.58 - 0.90	0.70	0.59 - 0.83	0.00002	select
Lipoprotein size	particle	Mean diameter for VLDL particles	0.90	0.59 - 1.37	0.72	0.54 - 0.97	0.92	0.73 - 1.16	0.85	0.72 - 1.00	0.05348	
Lipoprotein subclasses		Triglycerides in very small VLDL	1.06	0.69 - 1.63	1.39	1.05 - 1.85	1.22	0.97 - 1.55	1.25	1.06 - 1.48	0.00852	
Lipoprotein subclasses		Total cholesterol to total lipids ratio in chylomicrons and extremely large VLDL	1.41	0.80 - 2.48	1.74	1.19 - 2.53	1.35	1.06 - 1.72	1.45	1.20 - 1.76	0.00015	select
Lipoprotein subclasses		Cholesterol esters to total lipids ratio in chylomicrons and extremely large VLDL	1.32	0.78 - 2.21	1.86	1.25 - 2.75	1.36	1.05 - 1.77	1.47	1.20 - 1.79	0.00016	select
Lipoprotein subclasses		Triglycerides to total lipids ratio in chylomicrons and extremely large VLDL	0.69	0.30 - 1.59	0.58	0.41 - 0.82	0.74	0.57 - 0.97	0.68	0.55 - 0.83	0.00019	select

Table S4. Urinary metabolites associated with any DR

Category of metabolites	Name of metabolytes	Chinese		Indian		Pooled		P - value	After Bonferroni Correction
		OR	95%CI	OR	95%CI	OR	95%CI		
Glycolysis related metabolites	Citrate	1.28	1.01 - 1.63	1.33	1.08 - 1.64	1.31	1.12 - 1.53	0.00073	select
Miscellaneous	Ethanolamine	1.35	1.04 - 1.77	1.28	1.09 - 1.49	1.30	1.13 - 1.48	0.00015	select
Miscellaneous	Formate	1.53	1.08 - 2.18	1.30	1.09 - 1.54	1.34	1.15 - 1.57	0.00023	select
Other amino acids	Glutamine	1.33	1.01 - 1.74	1.16	1.00 - 1.36	1.20	1.05 - 1.38	0.00702	select
Miscellaneous	Hypoxanthine	1.34	1.02 - 1.74	1.25	1.06 - 1.47	1.27	1.11 - 1.46	0.00065	select
Other amino acids	Taurine	1.15	0.85 - 1.56	1.21	1.01 - 1.44	1.19	1.02 - 1.39	0.02418	
Microbial metabolism	Trimethylamine-N-oxide	0.84	0.64 - 1.11	0.85	0.73 - 0.99	0.85	0.74 - 0.97	0.01390	

Table S5. Urinary metabolites associated with moderate and above DR

Category of metabolites	Name of metabolytes	Chinese		Indian		Pooled		P - value	After Bonferroni Correction
		OR	95% CI	OR	95% CI	OR	95% CI		
Other amino acids	Alanine	1.32	0.90 - 1.93	1.53	1.22 - 1.92	1.47	1.21 - 1.79	0.00010	select
Pyrimidine metabolism	3-Hydroxyisobutyrate	1.29	0.91 - 1.82	1.55	1.25 - 1.92	1.48	1.23 - 1.77	0.00003	select
Miscellaneous	3-Hydroxyisovalerate	1.39	0.86 - 2.22	1.46	1.22 - 1.76	1.45	1.23 - 1.73	0.00002	select
Glycolysis related metabolites	Citrate	1.17	0.84 - 1.62	1.99	1.50 - 2.63	1.59	1.29 - 1.97	0.00002	select
Miscellaneous	Ethanolamine	1.46	1.00 - 2.12	1.95	1.52 - 2.49	1.78	1.45 - 2.19	0.00000	select
Miscellaneous	Formate	1.56	0.97 - 2.51	1.84	1.43 - 2.36	1.78	1.43 - 2.21	0.00000	select
Other amino acids	Glutamine	1.22	0.85 - 1.77	1.31	1.02 - 1.67	1.28	1.05 - 1.57	0.01718	
Miscellaneous	Glycolic acid	1.07	0.75 - 1.53	1.44	1.15 - 1.79	1.33	1.10 - 1.60	0.00333	select
Miscellaneous	Hypoxanthine	1.43	0.99 - 2.07	1.67	1.28 - 2.18	1.59	1.28 - 1.97	0.00003	select
Branched-chain amino acids	Leucine	1.15	0.79 - 1.69	1.32	1.04 - 1.67	1.27	1.04 - 1.55	0.01915	
Pyrimidine metabolism	Uracil	1.08	0.74 - 1.57	1.36	1.08 - 1.72	1.28	1.05 - 1.56	0.01584	
Branched-chain amino acids	Valine	1.20	0.84 - 1.7	1.28	1.04 - 1.58	1.26	1.05 - 1.51	0.01261	

Table S6. Urinary metabolites associated with VTDR

Category of metabolites	Name of metabolytes	Chinese		Indian		Pooled			After Bonferroni Correction
		OR	95%CI	OR	95%CI	OR	95%CI	P - value	
Other amino acids	Alanine	1.01	0.60 - 1.68	1.41	1.10 - 1.81	1.32	1.06 - 1.66	0.01433	
Miscellaneous	3-Hydroxyisobutyrate	1.13	0.70 - 1.82	1.44	1.14 - 1.82	1.38	1.11 - 1.70	0.00295	select
Miscellaneous	3-Hydroxyisovalerate	1.39	0.76 - 2.55	1.48	1.22 - 1.80	1.47	1.22 - 1.77	0.00004	select
Glycolysis related metabolites	Citrate	1.05	0.65 - 1.69	1.91	1.41 - 2.57	1.61	1.25 - 2.08	0.00023	select
Miscellaneous	Ethanolamine	1.59	0.96 - 2.65	1.80	1.37 - 2.36	1.75	1.38 - 2.22	0.00001	select
Miscellaneous	Formate	1.17	0.61 - 2.22	1.81	1.38 - 2.37	1.70	1.32 - 2.18	0.00003	select
Miscellaneous	Hypoxanthine	1.37	0.85 - 2.21	2.00	1.45 - 2.75	1.78	1.37 - 2.32	0.00002	select
Branched-chain amino acids	Leucine	1.13	0.68 - 1.87	1.33	1.02 - 1.73	1.28	1.01 - 1.62	0.03892	
Dietary metabolites	3-Methylhistidine	0.65	0.44 - 0.96	0.88	0.70 - 1.11	0.81	0.66 - 0.99	0.04364	
Pyrimidine metabolism	Uracil	1.05	0.63 - 1.74	1.54	1.17 - 2.02	1.41	1.11 - 1.79	0.00463	select



Figure S1. Association between serum/plasma metabolites and moderate/above diabetic retinopathy in Chinese, Indians and Malay cohorts.

OR estimate corresponds to per SD ↑ in serum metabolites
OR estimates adjusted for age, sex, systolic BP, duration of diabetes and HbA1c%

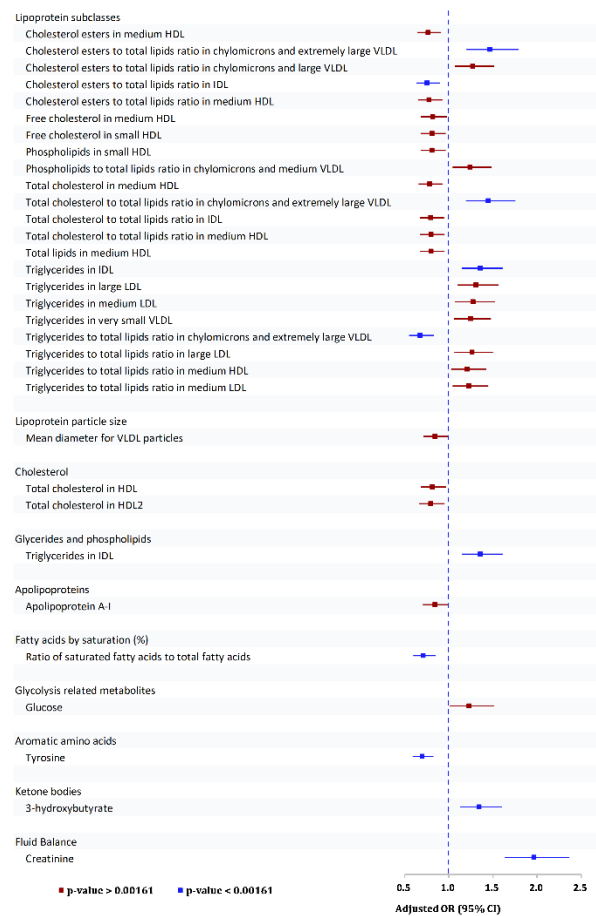


Figure S2. Association between serum/plasma metabolites and vision-threatening diabetic retinopathy in Chinese, Indians and Malay cohorts.

OR estimate corresponds to per SD ↑ in serum metabolites, and per SD ↓ in urine and metabolites
OR estimates adjusted for age, sex, systolic BP, duration of diabetes and HbA1c%

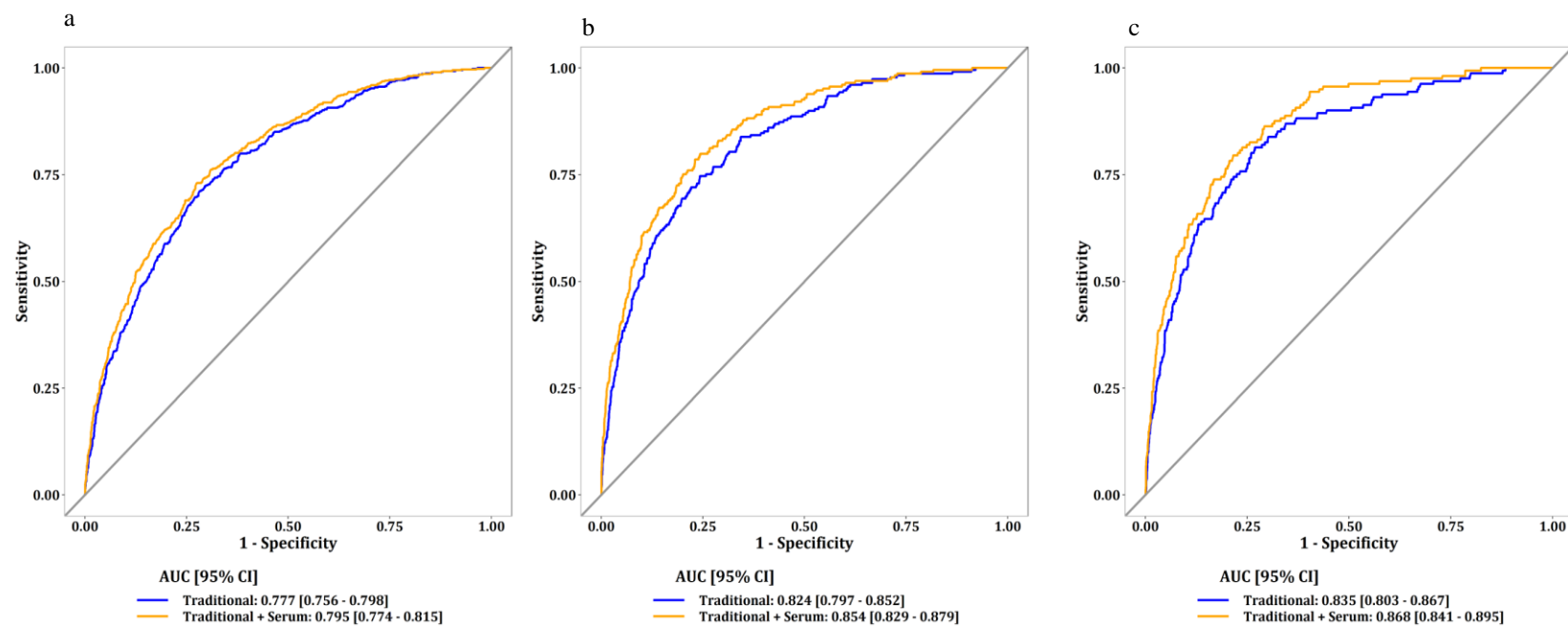


Figure S3. ROC curves – metabolites and a) any DR b) Moderate and above DR c) VTDR.