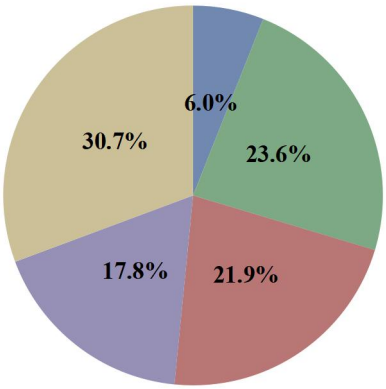
Supplementary appendix 1

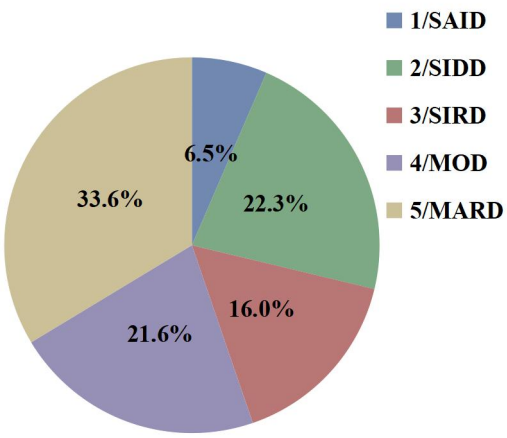
Validation of the Swedish diabetes regrouping scheme in adult-onset diabetes in China

Supplementary figures

A

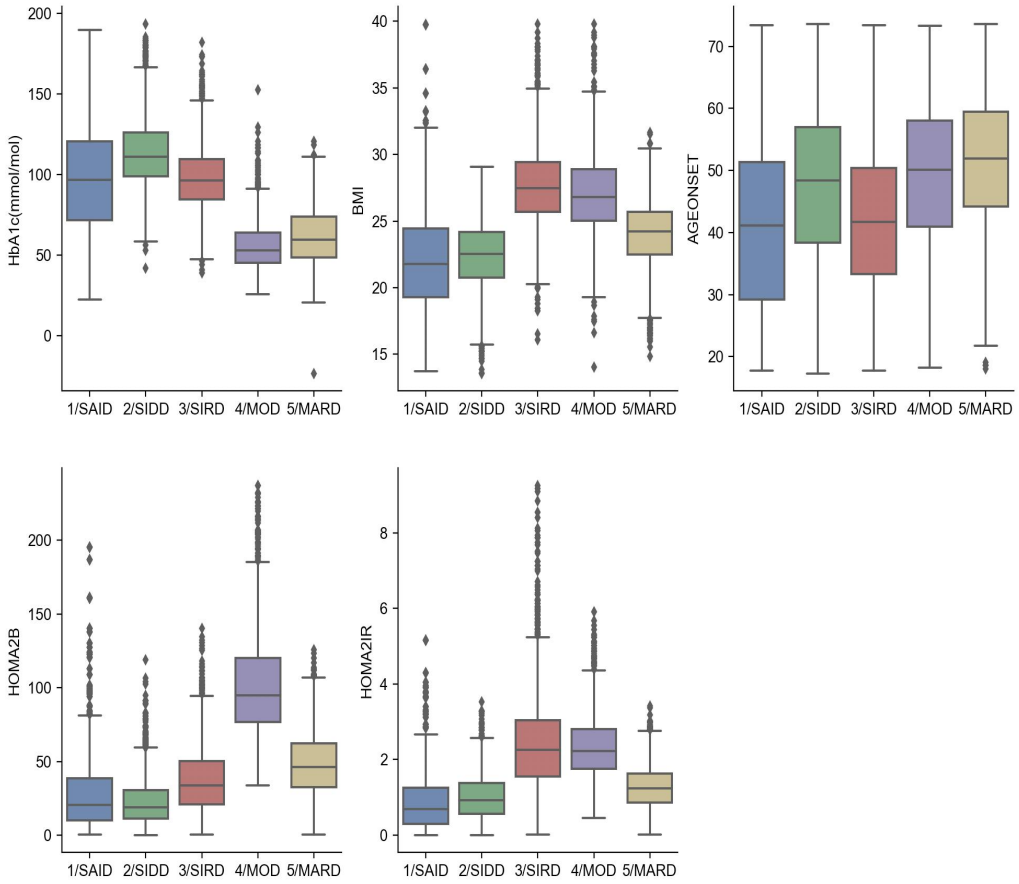


B



36 **C**

37


HbA1c(mmol/mol)
BMI
AGEONSET
HOMA2B
HOMA2IR
1/SAID
2/SIDD
3/SIRD
4/MOD
5/MARD

D

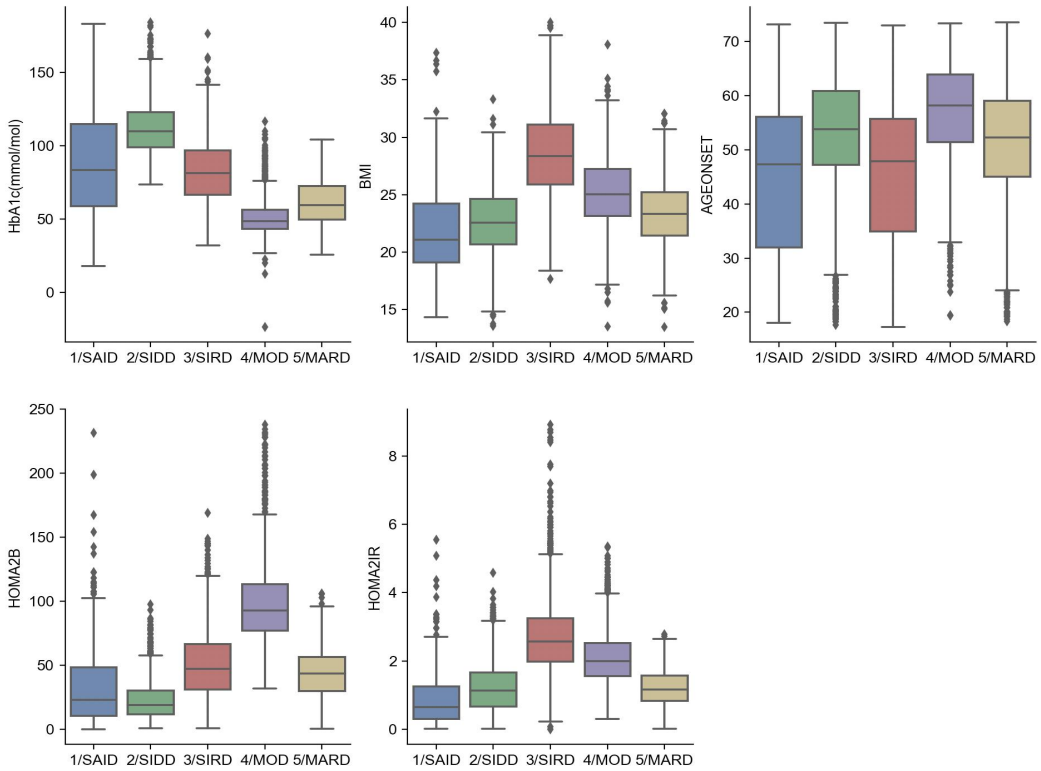


Figure S1: Sex stratified TwoStep clustering in patients. The patients were with similar distributions and clinical patterns for males (A, C) and females (B, D) in each cluster.

A B

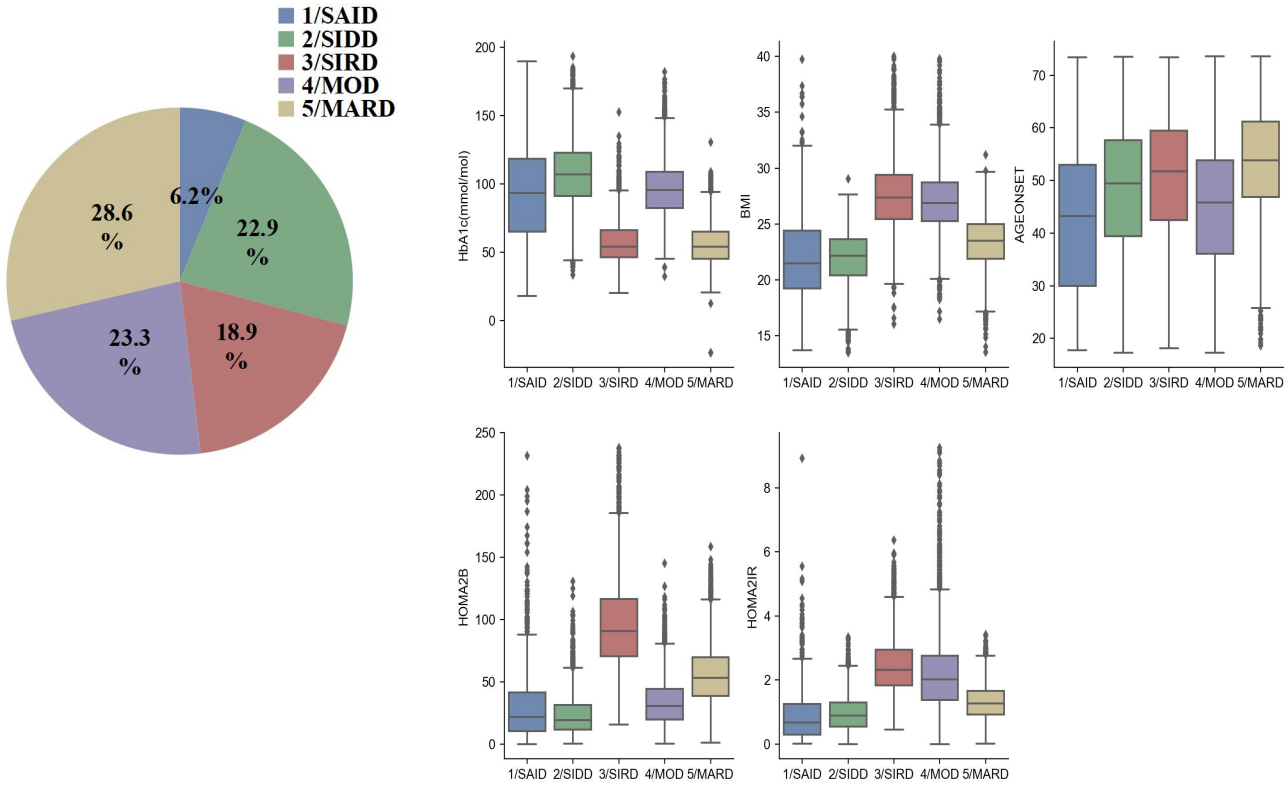
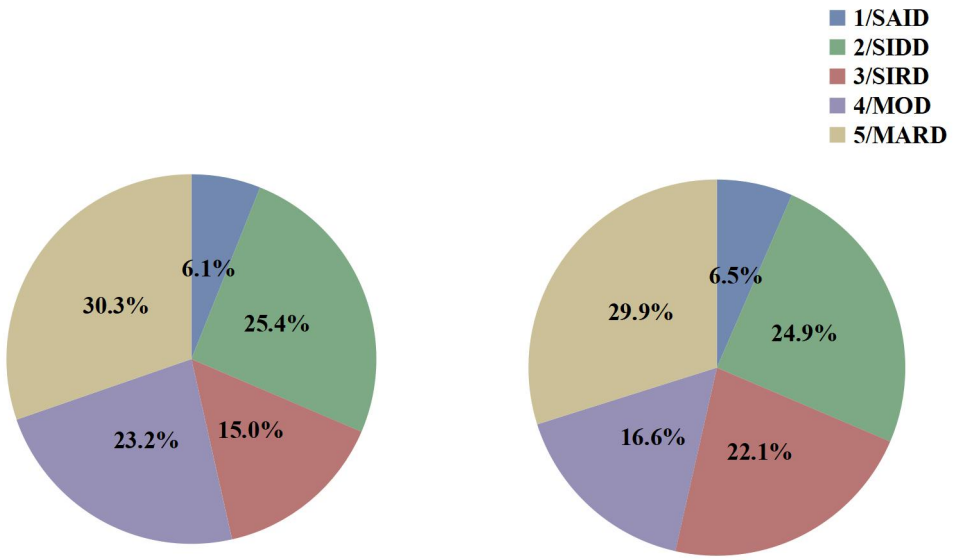
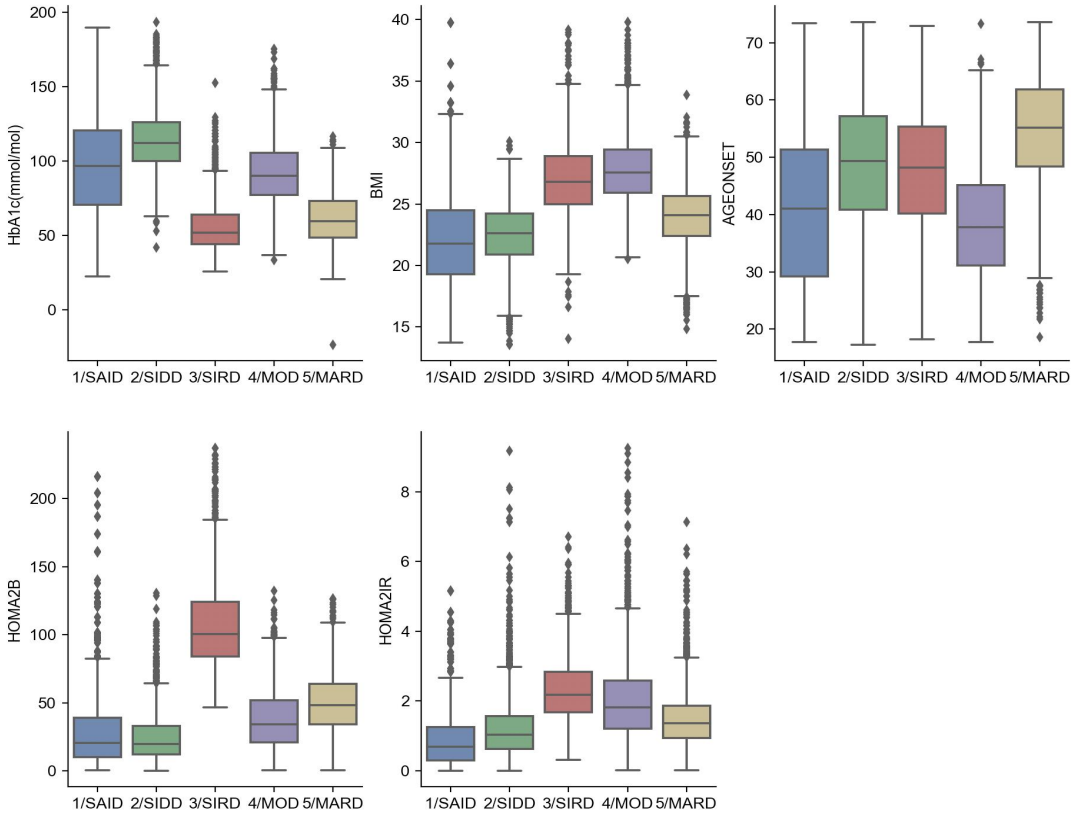


Figure S2: Cluster distributions and characteristics by TwoStep clustering. Frequencies (A) and distributions of variables used for clustering (B) were sharing the similar pattern with sex stratified clustering.

A **B**


1/SAID
2/SIDD
3/SIRD
4/MOD
5/MARD
6.1%
25.4%
15.0%
23.2%
30.3%
6.5%
24.9%
22.1%
16.6%
29.9%

C


HbA1c(mmol/mol)
BMI
AGEONSET
HOMA2B
HOMA2IR
1/SAID
2/SIDD
3/SIRD
4/MOD
5/MARD

D

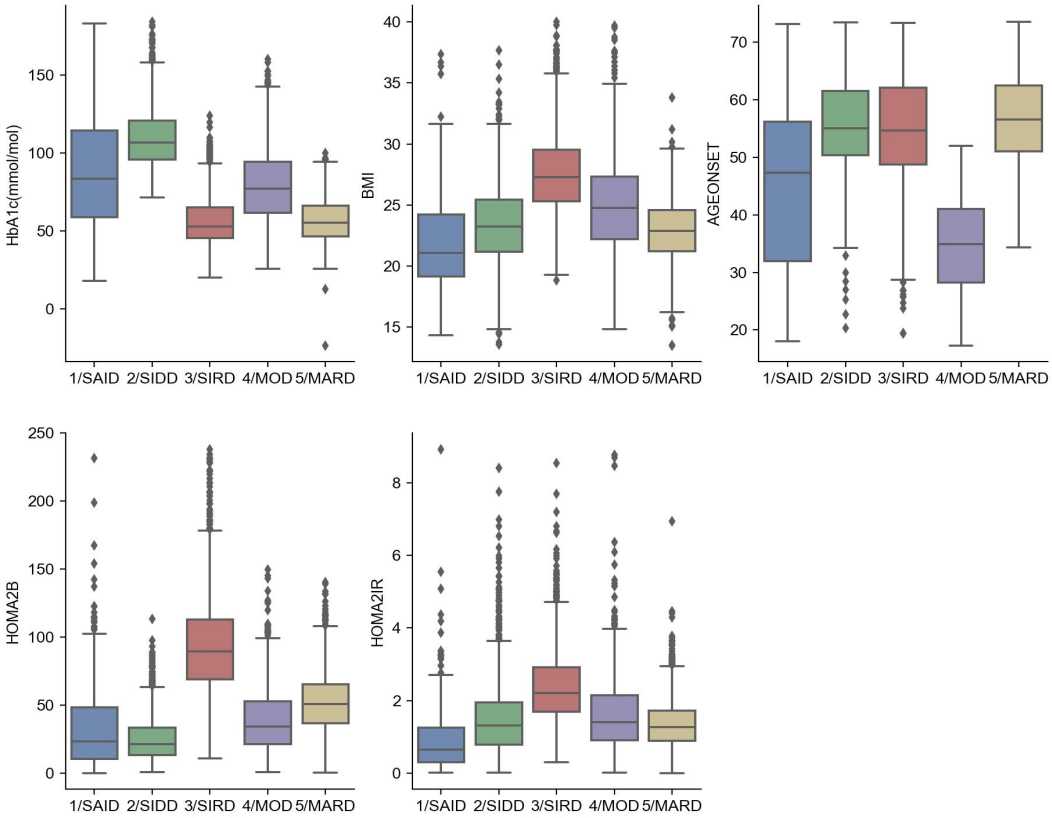
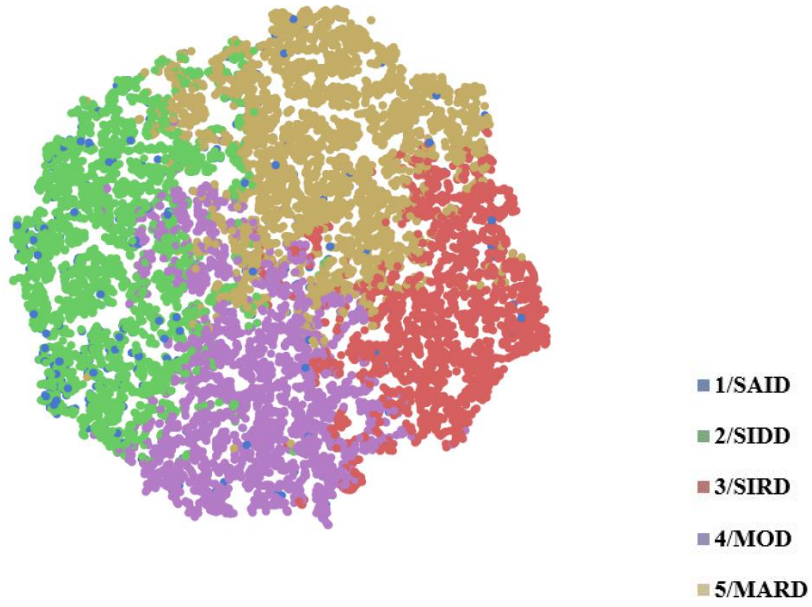


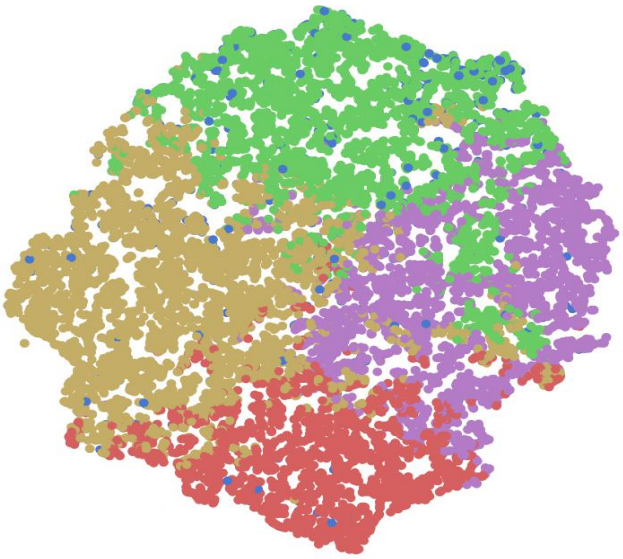
Figure S3: Sex stratified k-means clustering. Distributions and clinical characteristics were similar in males (A, C) and females (B, D).

A



103

B



104

105 **Figure S4: The distributions of clusters visualized by t-SNE.** The results analyzed by TwoStep (A) and

106 k-means (B) clustering methods were visualized by T-distributed stochastic neighbor embedding (t-SNE) in

107 three dimensions.

108

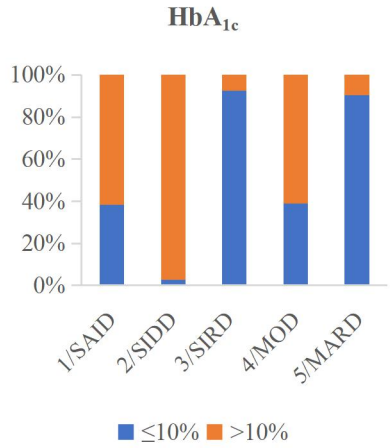


Figure S5: Distributions of HbA1c by cluster. The distributions of HbA1c with 10% as the cut-off in each of the five subgroups. Cluster 2 had the highest proportion of 97.29% (vs. cluster 5, p<0.0001), followed by cluster 1 (61.65%, vs. cluster 5, p<0.0001) and cluster 4 (61.18%, vs. cluster 5, p<0.0001), and cluster 3 and 5 had the lowest proportions of 7.67% (vs. cluster 5, p=0.154) and 9.66% respectively.

A **B**

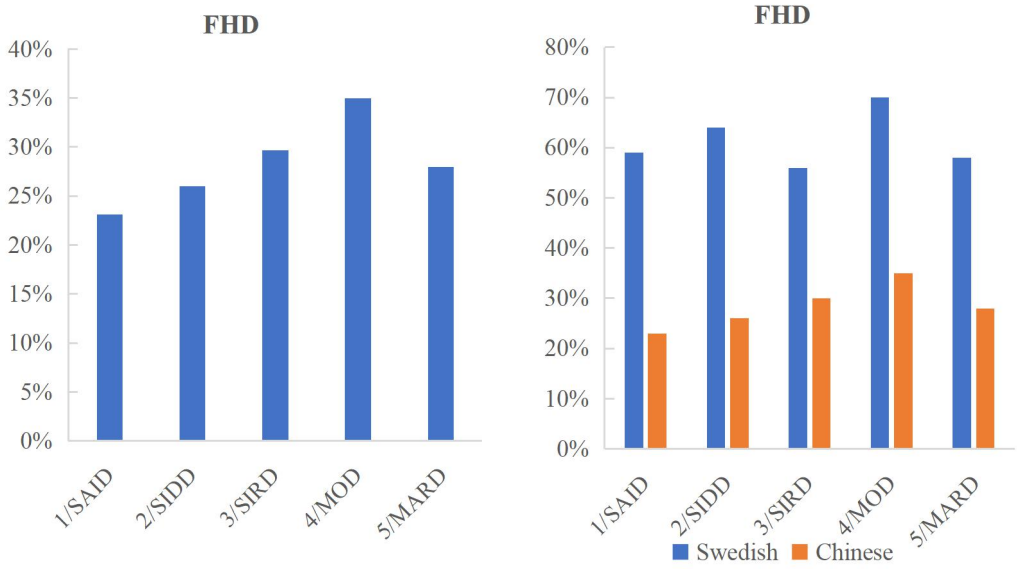


Figure S6: Distributions of FHD by clusters. (A) The rate of FHD in Chinese. It was highest in cluster 4 [35.6% (1190/3343), vs cluster 5, p<0.0001], followed by cluster 3 [30.3% (775/2559), vs cluster 5, p<0.0001], lowest in cluster 1[23.3% (227/975), vs cluster 5, p<0.0001]. (B) The comparison of FHD rate in Chinese and

Swedish (1). Abbreviation: FHD: family history of diabetes.

A **B**

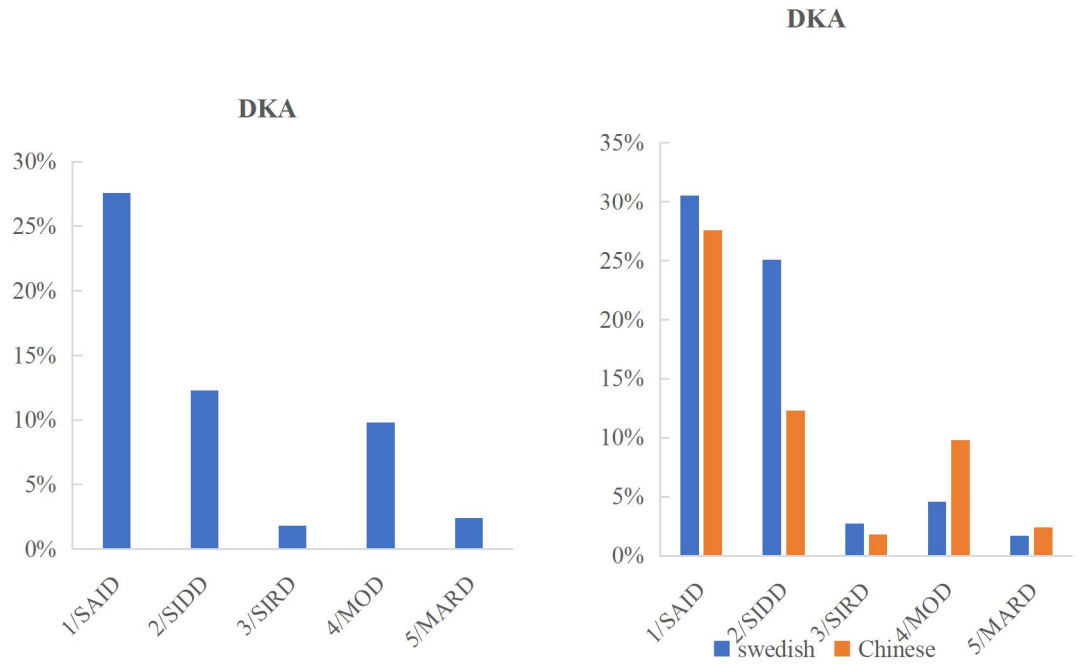


Figure S7: Distributions of DKA by clusters. (A) The rate of DKA occurrence in Chinese. It was highest in cluster 1 [27.7% (271/977), vs cluster 5, p<0.0001], followed by cluster 2 [12.4% (480/3863), vs cluster 5, p<0.0001]. The rate in cluster 4 was 10.0% (334/3348, vs cluster 5, p<0.0001), but less than 5% in cluster 3 (1.8%) and cluster 5 (2.5%). (B) The comparison of DKA occurrence in Swedish (1) and Chinese. Abbreviation: DKA: diabetic ketoacidosis.

Supplementary Tables

Table S1: Data of six variables used for clustering by TwoStep analysis.

Cluster	Age (year)	BMI (kg/m^2)	HOMA-2B (%)	HOMA-IR	HbA_{1c} (mmol/mol)	HbA_{1c} (%)	GADA	Number
1/SAID	43.20876	21.48438	21.8	0.677512	93.42	10.70	1	982
2/SIDD	49.40315	22.14533	19.5	0.888889	106.92	11.93	0	3614
3/SIRD	51.77002	27.35885	90.8	2.317501	54.19	7.11	0	2986
4/MOD	45.79329	26.89232	30.8	2.024291	95.61	10.90	0	3673
5/MARD	53.83162	23.52941	53.3	1.270648	54.08	7.10	0	4517

Table S2: Data of six variables used for clustering by TwoStep analysis in males.

Cluster	Age (year)	BMI (kg/m^2)	HbA_{1c} (mmol/mol)	HbA_{1c} (%)	HOMA2B (%)	HOMA-IR	GADA	Number
1/SAID	41.12526	21.7757	96.69945	11.00	20.7	0.686107	1	572
2/SIDD	48.38467	22.52334	110.9071	12.30	19	0.932836	0	2244
3/SIRD	41.68378	27.46562	96.2623	10.96	33.7	2.262443	0	2083
4/MOD	50.11636	26.78676	52.98361	7.00	94.9	2.227171	0	1688
5/MARD	51.94387	24.2101	59.54098	7.60	46.2	1.236094	0	2914

Table S3: Data of six variables used for clustering by TwoStep analysis in females.

Cluster	Age (year)	BMI (kg/m^2)	HbA_{1c} (mmol/mol)	HbA_{1c} (%)	HOMA-2B (%)	HOMA-IR	GADA	Number
1/SAID	47.2909	21.09619	83.5847	9.80	23.2	0.646831	1	407
2/SIDD	53.84942	22.58271	109.8142	12.20	19.1	1.133787	0	1396
3/SIRD	47.90691	28.35306	81.39891	9.60	47.1	2.564103	0	1003
4/MOD	58.16838	25.03605	48.61202	6.60	92.6	2.000000	0	1355
5/MARD	52.23956	23.34501	59.54098	7.60	43.5	1.168224	0	2110

Table S4: Data of six variables used for clustering by k-means analysis in males.

Cluster	Age (year)	BMI (kg/m^2)	HbA_{1c} (mmol/mol)	HbA_{1c} (%)	HOMA-2B (%)	HOMA2IR	GADA	Number
1/SAID	40.99932	21.79931	96.69945	11.00	20.7	0.68918	1	575
2/SIDD	49.35661	22.64153	112	12.40	19.9	1.040042	0	2412
3/SIRD	48.21081	26.81661	51.89071	6.90	100.4	2.178649	0	1429
4/MOD	37.7577	27.54821	90.14208	10.40	34.2	1.818182	0	2205
5/MARD	55.20192	24.09297	59.43169	7.59	48.3	1.362398	0	2880

Table S5: Data of six variables used for clustering by k-means analysis in females.

Cluster	Age (year)	BMI (kg/m^2)	HbA_{1c} (mmol/mol)	HbA_{1c} (%)	HOMA-2B (%)	HOMA2IR	GADA	Number
1/SAID	47.3128	21.09619	83.5847	9.80	23.3	0.6515	1	408
2/SIDD	55.06366	23.23346	106.5355	11.90	21.6	1.30719	0	1563
3/SIRD	54.66119	27.30411	52.98361	7.00	89.6	2.205075	0	1386
4/MOD	34.88843	24.75546	77.02732	9.20	34.3	1.402525	0	1041
5/MARD	56.61054	22.89282	55.1694	7.20	50.9	1.264223	0	1873

166 **Table S6: Patient characteristics in clusters analyzed by k-means method.**

	1/SAID	2/SIDD	3/SIRD	4/MOD	5/MARD
N (%)	983(6.20)	3908(24.80)	2615(16.60)	3400(21.60)	4866(30.90)
Age (year)	42.70 ± 14.04	50.53 ± 11.59	51.80± 11.01	39.12 ± 10.16	54.77 ± 9.75
BMI ($kg/m^{2)}$	22.01 ± 3.77	22.51 ± 2.62	26.95 ± 3.24	27.85 ± 3.02	23.38 ± 2.55
Smoke%	314(32.30)	1273(32.96)	775(29.94)	1185(35.36)	1228(25.49)
HbA_{1c}(mmol/mol)	93.46 ± 33.88	112.92 ± 19.97	54.71 ± 16.07	87.32 ± 21.38	59.14 ± 14.92
HbA_{1c} (%)	10.70 ± 5.25	12.48 ± 3.98	7.16 ± 3.62	10.14 ± 4.11	7.56 ± 3.52
HOMA2-B (%)	21.90(10.60-42.80)	20.20(12.40-32.60)	98.60(83.40-122.10)	36.00(22.80-53.40)	48.80(34.90-64.25)
HOMA2-IR	0.68(0.30-1.26)	1.09(0.65-1.68)	2.18(1.68-2.86)	1.81(1.21-2.55)	1.30(0.89-1.78)
SBP (mmHg)	120.95 ± 15.36	124.94 ± 16.08	129.66 ± 16.21	127.63 ± 15.21	127.73 ± 16.37
DBP (mmHg)	76.74 ± 10.15	79.25 ± 10.31	80.97 ± 10.48	82.10 ± 10.77	79.14 ± 10.12
TG (mmol/l)	1.58 ± 1.35	2.17 ± 1.75	2.29 ± 1.61	2.87 ± 2.07	1.94 ± 1.39
TC (mmol/l)	4.50 ± 1.31	4.96 ± 1.41	4.68 ± 1.27	4.95 ± 1.39	4.71 ± 1.25
LDL (mmol/l)	2.73 ± 1.00	3.05 ± 1.03	2.76 ± 0.95	2.89 ± 1.01	2.76 ± 0.95
HDL (mmol/l)	1.26 ± 0.41	1.20 ± 0.40	1.14 ± 0.33	1.08 ± 0.36	1.23 ± 0.37
Insulin (%)	468(47.76)	1635(41.91)	237(9.08)	920(27.15)	670(13.81)
Metformin (%)	260(26.53)	1327(34.02)	917(35.13)	1401(41.34)	1449(29.88)
Sulphonyl (%)	106(10.81)	558(14.30)	307(11.76)	332(9.80)	720(14.85)
Acarbose (%)	189(19.29)	742(19.02)	415(15.90)	4749(13.99)	765(15.77)
GLP1 receptor agonist (%)	8(0.82)	10(0.26)	44(1.69)	103(3.04)	8(0.16)

FHD (%)	227(23.28)	1015(26.40)	775(30.29)	1190(35.60)	1360(28.46)
DKA (%)	271(27.74)	480(12.42)	47(1.83)	334(9.98)	118(2.46)
FRS (%)	4.05(1.54-9.44)	9.06(4.1-17.78)	9.89(4.41-17.78)	5.51(2.48-10.82)	9.61(5.05-18.69)
0-10(%)	704(76.44)	1956(54.30)	1213(50.48)	2274(72.31)	2333(51.74)
10-20(%)	143(15.53)	900(24.99)	636(26.47)	626(19.90)	1151(25.53)
>20(%)	74(8.03)	746(20.71)	554(20.05)	245(7.79)	1025(22.73)
GADA%	921(100)	0	0	0	0

Data were presented as number (percentage) for categorial variables and median (25th–75th percentile) for continuous variables. SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; BMI: body mass index; TG: triglyceride; TC: total cholesterol; LDL: low Density Lipoprotein; HDL: high density lipoprotein; DKA: diabetic ketoacidosis; GADA: Glutamic Acid Decarboxylase Antibody. FHD: Family history of diabetes; FRS: Framingham risk score.

Table S7: Comparison of variable distributions between Chinese and Swedish

Cluster	Cohort	Frequency (%)	Age of onset (year)	BMI (kg/m^2)	HbA_{1c} (mmol/mol)	HbA_{1c} (%)	HOMA2B (%)	HOMA-IR
1/SAID	ANDIS (1)	6.40	50.48	27.45	80.03	9.47	56.71	2.16
	Chinese	6.20*	41.82-43.58	21.78-22.26	91.34-95.58	10.51-10.90	29.87-33.86	0.87-0.98
2/SIDD	ANDIS (1)	17.50	56.74	28.86	101.85	11.47	47.64	3.18
	Chinese	24.80†	50.16-50.89	22.43-22.59	112.30-113.55	12.43-12.54	23.98-25.05	1.26-1.32
3/SIRD	ANDIS (1)	15.30	65.25	33.85	54.07	7.10	150.47	5.54
	Chinese	16.60†	51.38-52.22	26.83-27.08	54.10-55.33	7.10-7.21	104.91-107.47	2.31-2.38
4/MOD	ANDIS (1)	21.60	48.96	35.71	57.70	7.43	95.03	3.35
	Chinese	21.60*	38.78-39.46	27.75-27.96	86.61-88.05	10.08-10.21	38.77-40.23	1.97-2.05
5/MARD	ANDIS (1)	39.10	67.37	27.94	50.08	6.73	86.59	2.55
	Chinese	30.90†	54.50-55.05	23.31-23.45	58.72-59.56	7.52-7.60	49.21-50.39	1.38-1.42

Data were presented with mean in ANDIS (1) and 95% CI in Chinese. *P >0.05 compared with ANDIS (1), † P<0.05 compared with ANDIS (1).

Table S8: Comparison of insulin and metformin use, family history of diabetes, DKA occurrence between Chinese and Swedish diabetic populations

Cluster	Cohort	Insulin Use (%)	Metformin use (%)	Family history of diabetes (%)	DKA occurrence (%)
1/SAID	ANDIS (1)	41.9	44.7	59.0	30.5
	Chinese	45-51	24-29	21-26	25-30
2/SIDD	ANDIS (1)	29.1	77.8	64.0	25.1
	Chinese	40-43	33-36	25-28	11-13
3/SIRD	ANDIS (1)	3.7	48.8	56.0	2.7
	Chinese	8-10	33-37	28-32	1-2
4/MOD	ANDIS (1)	3.3	59.1	70.0	4.6
	Chinese	26-29	40-43	34-37	9-11
5/MARD	ANDIS (1)	1.6	44.0	58.0	1.7
	Chinese	13-15	29-31	27-30	2-3

Data was presented as means in ANDIS (1) and 95% CI in Chinese diabetic patients.

Reference

1. Ahlqvist E, Storm P, Karajamaki A, Martinell M, Dorkhan M, Carlsson A, Vikman P, Prasad RB, Aly DM, Almgren P, Wessman Y, Shaat N, Spegel P, Mulder H, Lindholm E, Melander O, Hansson O, Malmqvist U, Lernmark A, Lahti K, Forsen T, Tuomi T, Rosengren AH and Groop L. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. *Lancet Diabetes Endocrinol*. 2018;6(5):361-369.

Supplementary appendix 2

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