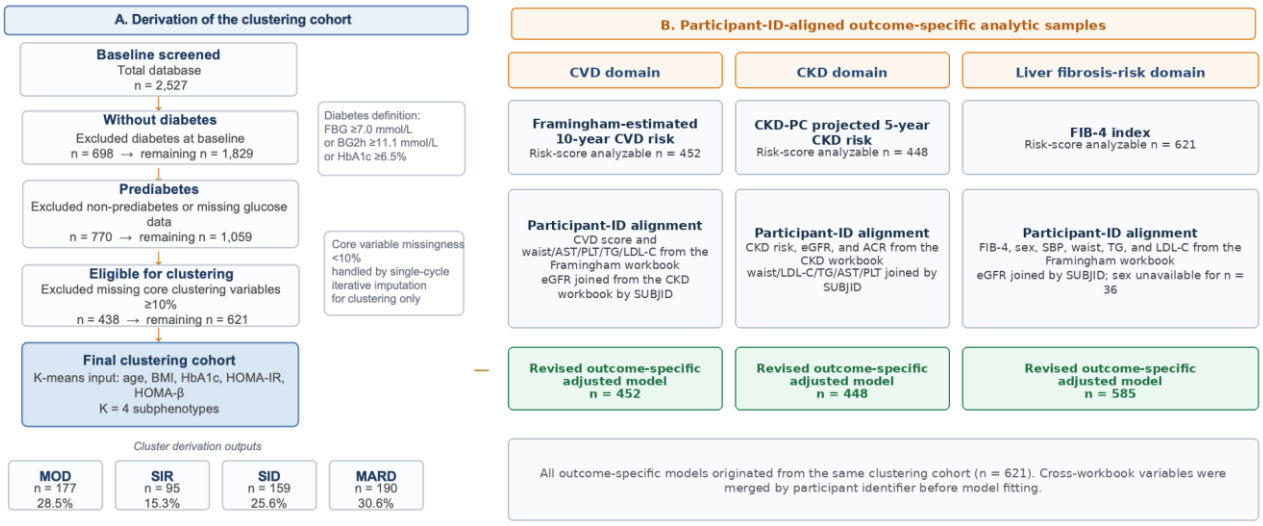
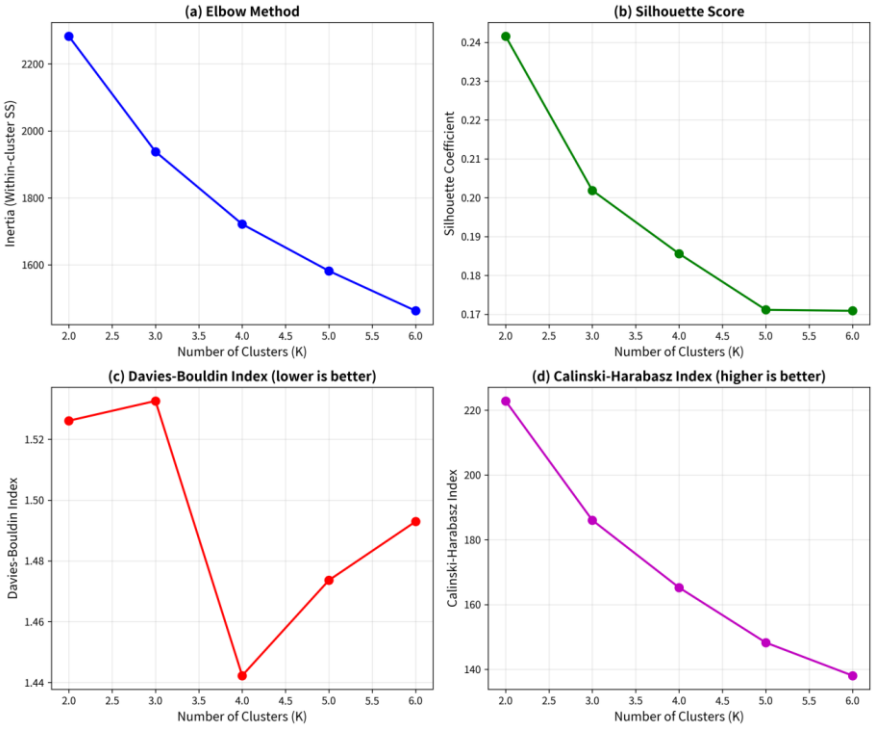
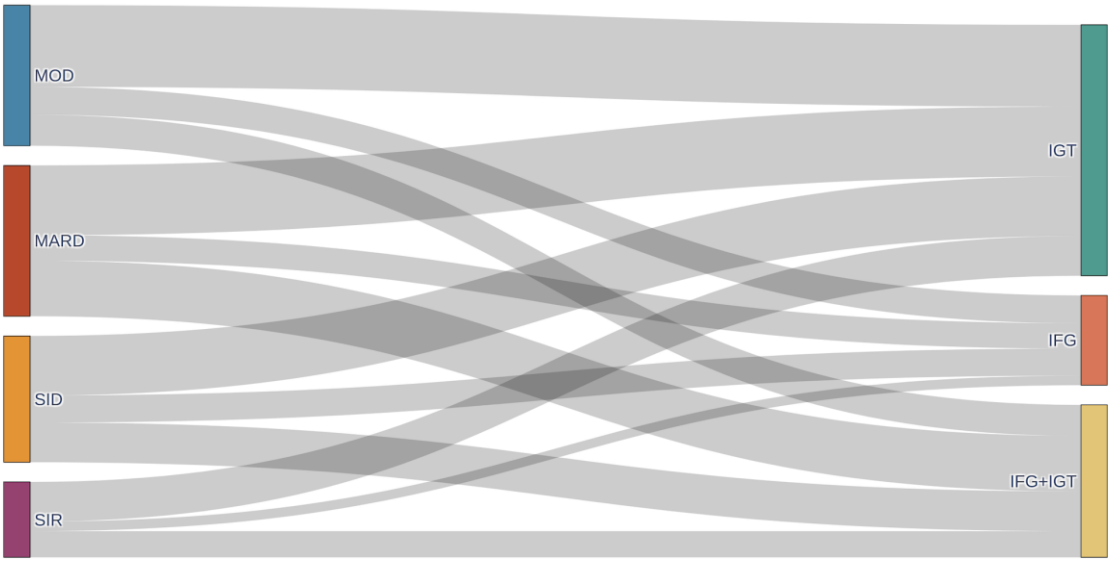


Supplementary Figure 1 Participant flow for clustering and outcome-specific analyses. A: Participant flow from 2527 screened individuals to the final clustering cohort of 621 adults with prediabetes and their allocation to four metabolic subphenotypes; B: Participant-ID–aligned analytic samples for Framingham-estimated 10-year cardiovascular disease risk, chronic kidney disease prognosis consortium -projected 5-year chronic kidney disease risk, and fibrosis-4 index -defined liver fibrosis risk. All outcome-specific samples originated from the same clustering cohort.



Supplementary Figure 2 The determination result of the optimal number of clusters in K-means clustering (K = 4). A: Elbow method; B:Silhouette score; C: Davies-Bouldin index (lower is better); D: Calinski-Harabasz index (higher is better). Elbow, silhouette, Davies-Bouldin, and Calinski-Harabasz indices were evaluated for candidate solutions with two to six clusters. The four-cluster solution was selected based on the elbow inflection and the lowest Davies–Bouldin index, together with clinical interpretability and downstream cluster-stability analyses.



Supplementary Figure 3 Sankey Diagram-Cluster *vs* prediabetes type. Sankey diagram showing the distribution of participants from the mild obesity-related dysmetabolism, mild age-related dysmetabolism, severe insulin-deficient dysmetabolism, and severe insulin-resistant dysmetabolism subphenotypes across isolated impaired fasting glucose, isolated impaired glucose tolerance, and combined impaired fasting glucose and impaired glucose tolerance categories. Flow widths are proportional to participant numbers. IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; MARD: Mild age-related dysmetabolism; MOD: Mild obesity-related dysmetabolism; SID: Severe insulin-deficient dysmetabolism; SIR: Severe insulin-resistant dysmetabolism.

Supplementary Table 1 Variable-level summary of imputation and winsorization

for covariates used in the outcome-specific models

Variable	Imputed after original missingness	Imputed after implausible-value cleaning	Total imputed	Winsorized	Remaining missing
Waist circumference	65	5	70	0	0
Systolic blood pressure	59	2	61	0	0
AST	12	0	12	12	0
Platelet count	30	7	37	3	0
Triglycerides	9	0	9	0	0
LDL-C	10	0	10	0	0
Creatinine and derived eGFR	13	4	17	0	0
Total variable-level records	198	18	216	15	0

Values are variable-level record counts rather than numbers of unique participants; the same participant may contribute to more than one variable. Originally missing values were imputed after participant-identifier alignment. Implausible values were first recoded as missing and then replaced with participant-specific imputed values. Winsorization denotes replacement of observed extreme values with a fixed upper boundary (aspartate aminotransferase, 45; platelet count, 498). Values of waist circumference, systolic blood pressure, low platelet count, and low creatinine that were recoded as missing and then imputed were not classified as winsorized. Estimated glomerular filtration rate was recalculated from cleaned creatinine for all participants; the 17 records shown represent participants whose estimated glomerular filtration rate was derived from imputed creatinine. AST: Aspartate aminotransferase; LDL-C: Low-density lipoprotein cholesterol; eGFR: Estimated glomerular filtration rate.

Supplementary Table 2 Pairwise post hoc comparisons of core clustering variables across metabolic subtypes (Mann-Whitney *U* test; false discovery rate-corrected)

Variable	Group 1	Group 2	Cliff's Δ	P Value	FDR-Corrected *P* value
Age (years)	MOD	SIR	0.057	0.443	0.443
	MOD	SID	−0.724	$< 1\times10^{-16}$	$< 1\times10^{-16}$
	MOD	MARD	−0.816	$< 1\times10^{-16}$	$< 1\times10^{-16}$
	SIR	SID	−0.686	$< 1\times10^{-16}$	$< 1\times10^{-16}$
	SIR	MARD	−0.769	$< 1\times10^{-16}$	$< 1\times10^{-16}$
	SID	MARD	−0.147	0.019	0.022
BMI (kg/m²)	MOD	SIR	−0.758	$< 1\times10^{-16}$	$< 1\times10^{-16}$
	MOD	SID	0.530	$< 1\times10^{-16}$	$< 1\times10^{-16}$
	MOD	MARD	−0.214	3.73×10^{-4}	3.73×10^{-4}
	SIR	SID	0.951	$< 1\times10^{-16}$	$< 1\times10^{-16}$
	SIR	MARD	0.654	$< 1\times10^{-16}$	$< 1\times10^{-16}$
	SID	MARD	−0.696	$< 1\times10^{-16}$	$< 1\times10^{-16}$
HbA1c (%)	MOD	SIR	−0.567	1.31×10^{-14}	2.62×10^{-14}
	MOD	SID	−0.671	$<1\times10^{-16}$	$<1\times10^{-16}$
	MOD	MARD	−0.774	$<1\times10^{-16}$	$<1\times10^{-16}$
	SIR	SID	−0.085	0.258	0.258
	SIR	MARD	−0.203	0.006	0.008
	SID	MARD	−0.126	0.042	0.050
HOMA-IR	MOD	SIR	−0.931	$< 1\times10^{-16}$	$< 1\times10^{-16}$
	MOD	SID	0.579	$< 1\times10^{-16}$	$< 1\times10^{-16}$
	MOD	MARD	−0.519	$< 1\times10^{-16}$	$< 1\times10^{-16}$
	SIR	SID	0.999	$< 1\times10^{-16}$	$< 1\times10^{-16}$
	SIR	MARD	0.679	$< 1\times10^{-16}$	$< 1\times10^{-16}$
	SID	MARD	−0.896	$< 1\times10^{-16}$	$< 1\times10^{-16}$

HOMA-β	MOD	SIR	−0.856	$< 1\times10^{-16}$	$< 1\times10^{-16}$
	MOD	SID	0.724	$< 1\times10^{-16}$	$< 1\times10^{-16}$
	MOD	MARD	−0.369	8.08×10^{-10}	8.08×10^{-10}
	SIR	SID	0.994	$< 1\times10^{-16}$	$< 1\times10^{-16}$
	SIR	MARD	0.716	$< 1\times10^{-16}$	$< 1\times10^{-16}$
	SID	MARD	−0.923	$< 1\times10^{-16}$	$< 1\times10^{-16}$

Pairwise comparisons were performed using the Mann–Whitney U test with Benjamini-Hochberg false discovery rate correction. Cliff's Δ is a nonparametric effect size (range -1 to 1); positive values indicate that Group 1 had higher values than Group 2. BMI: body mass index; HbA1c: Glycated hemoglobin; HOMA-IR: Homeostasis model assessment of insulin resistance; HOMA-β: Homeostasis model assessment of β-cell function; MOD: Mild obesity-related dysmetabolism; SIR: Severe insulin resistance; SID: Severe insulin deficiency; MARD: Mild age-related dysmetabolism; FDR: False discovery rate.

Supplementary Table 3 Overall differences in oral glucose tolerance test-derived indicators across metabolic subtypes (Kruskal-Wallis test)

Variable	H statistic	*P* value	Effect size (ε^2)
1-hour glucose (mmol/L)	23.305	3.49×10^{-5}	0.033
2-hour glucose (mmol/L)	10.842	0.013	0.013
1-hour insulin (mIU/L)	202.165	1.44×10^{-43}	0.326
2-hour insulin (mIU/L)	205.140	3.27×10^{-44}	0.328

The Kruskal-Wallis test was used to assess overall differences across the four metabolic subtypes. ε^2 (epsilon-squared) quantifies the magnitude of between-subtype differences (range 0 to 1). oral glucose tolerance test -derived indicators were not included in the clustering algorithm and serve as external biological validation markers.

Supplementary Table 4 Pairwise *post hoc* comparisons of oral glucose tolerance

test-derived indicators across metabolic subtypes (Mann-Whitney *U* test; false discovery rate-corrected)

Variable	Comparison	Cliff's Δ	*P* value	FDR-corrected *P* value
1-hour glucose (mmol/L)	MOD vs SIR	−0.317	2.14×10^{-5}	3.96×10^{-5}
	MOD vs SID	−0.178	0.005	0.007
	MOD vs MARD	−0.247	4.63×10^{-5}	7.93×10^{-5}
	SIR vs SID	0.107	0.159	0.200
	SIR vs MARD	0.050	0.500	0.522
	SID vs MARD	−0.048	0.437	0.477
2-hour glucose (mmol/L)	MOD vs SIR	−0.219	0.003	0.005
	MOD vs SID	0.007	0.908	0.908
	MOD vs MARD	−0.072	0.233	0.267
	SIR vs SID	0.219	0.004	0.005
	SIR vs MARD	0.141	0.053	0.071
	SID vs MARD	−0.079	0.205	0.246
1-hour insulin (mIU/L)	MOD vs SIR	−0.711	$< 1\times10^{-16}$	$< 1\times10^{-16}$
	MOD vs SID	0.311	8.87×10^{-7}	1.77×10^{-6}
	MOD vs MARD	−0.411	1.26×10^{-11}	4.31×10^{-11}
	SIR vs SID	0.855	$< 1\times10^{-16}$	$< 1\times10^{-16}$
	SIR vs MARD	0.374	3.76×10^{-7}	8.20×10^{-7}
	SID vs MARD	−0.640	$< 1\times10^{-16}$	$< 1\times10^{-16}$
2-hour insulin (mIU/L)	MOD vs SIR	−0.728	$< 1\times10^{-16}$	$< 1\times10^{-16}$
	MOD vs SID	0.354	2.14×10^{-8}	5.72×10^{-8}
	MOD vs MARD	−0.322	9.81×10^{-8}	2.35×10^{-7}
	SIR vs SID	0.874	$< 1\times10^{-16}$	$< 1\times10^{-16}$
	SIR vs MARD	0.476	5.67×10^{-11}	1.70×10^{-10}
	SID vs MARD	−0.615	$< 1\times10^{-16}$	$< 1\times10^{-16}$

Pairwise comparisons were performed using the Mann-Whitney *U* test with

Benjamini-Hochberg false discovery rate correction. Cliff's Δ is a nonparametric effect size (range -1 to 1); positive values indicate that the first group in the comparison had higher values. oral glucose tolerance test -derived indicators were not included in the clustering algorithm and serve as external biological validation markers. MOD: Mild obesity-related dysmetabolism; SIR: Severe insulin resistance; SID: Severe insulin deficiency; MARD: Mild age-related dysmetabolism; FDR: False discovery rate.

Supplementary Table 5 Cluster stability (bootstrap Jaccard index)

Cluster	Jaccard (mean)	Jaccard (median)	Jaccard (Q1-Q3)	Jaccard (min) /ARI summary
MOD	0.847	0.869	0.816–0.913	0.411–0.979
SIR	0.779	0.800	0.677–0.916	0.235–1.000
SID	0.810	0.841	0.727–0.930	0.282–0.992
MARD	0.815	0.828	0.631–0.918	0.478–0.979

MOD: Mild obesity-related dysmetabolism; SIR: Severe insulin resistance; SID: Severe insulin deficiency; MARD: Mild age-related dysmetabolism.

Supplementary Table 6 Random seed sensitivity (adjusted Rand index)

Item	Mean	Median	Q1–Q3	ARI summary
Overall ARI	0.972	0.973	0.959–0.983	0.954–1.000

Cluster stability was assessed by bootstrap resampling (80% subsample, 500 iterations). A mean Jaccard index > 0.75 indicates a stable cluster assignment. The adjusted Rand index evaluates the consistency of clustering results across different random seed initializations. ARI: Adjusted Rand index.

Supplementary Table 7 Availability of measured albumin-to-creatinine ratio for chronic kidney disease prognosis consortium risk estimation

Item	Value	Explanation
Full clustering sample	621	Participants classified into metabolic subtypes

Participants with measured ACR	453	Calculated from urinary albumin and urinary creatinine when both were available
Participants with positive measured ACR	452	Used for log10 transformation where applicable
CKD-PC analyzable sample	448	Participants included in CKD-PC projected 5-year CKD risk analysis
Participants with positive measured ACR in the risk-estimation sample	426 (95.1%)	Measured log10 ACR entered the equation through the ACR deviation term
Participants handled using the nondiabetic patch approach	22 (4.9%)	The ACR deviation term was set to zero
CKD-PC ≥ 5% events in the primary analysis	117/448 (26.1%)	Primary threshold-defined kidney-risk outcome
Measured-ACR-only sensitivity analysis	113/426 (26.5%)	Participants requiring the patch approach were excluded

ACR: Albumin-to-creatinine ratio; CKD-PC: Chronic kidney disease prognosis consortium; CKD: Chronic kidney disease.

Supplementary Table 8 Comparison of participants included and excluded from outcome-specific adjusted-model analytic samples, *n* (%)/median (interquartile range)

Variable	CVD included (*n* = 452)	CVD excluded (*n* = 169)	*P* value	CKD included (*n* = 448)	CKD excluded (*n* = 173)	*P* value	FIB-4 included (*n* = 585)	FIB-4 excluded (*n* = 36)	*P* value
Age (years)	53.00 (43.00–59.00)	49.00 (47.00–56.00)	0.092	52.00 (43.00–59.00)	49.00 (47.00–56.00)	0.378	52.00 (44.00–59.00)	49.00 (49.00–49.00)	0.031
Sex, male	222/452 (49.1)	44/133 (33.1)	0.001	220/448 (49.1)	46/137 (33.6)	0.001	266/585 (45.5)	Not available	NE

BMI (kg/m²)	25.20 (23.10–27.50)	25.26 (24.41–26.95)	0.200	25.20 (23.18–27.50)		25.19 (24.30–26.80)		0.438	25.20 (23.30–27.50)	25.18 (24.91–25.58)	0.960
Waist circumference (cm)	89.00 (82.00–94.72)	90.00 (85.00–96.00)	0.097	89.00 (82.00–94.90)		90.00 (85.00–96.00)		0.196	89.00 (82.50–95.00)	80.00 (73.50–86.50)	0.487
Fasting glucose (mmol/L)	6.10 (5.58–6.46)	5.90 (5.40–6.30)	0.036	6.10 (5.59–6.46)		5.90 (5.40–6.30)		0.038	6.03 (5.56–6.39)	6.23 (6.10–6.40)	0.017
2-hour glucose (mmol/L)	8.96 (8.11–9.74)	8.45 (7.90–9.70)	0.015	8.96 (8.11–9.74)		8.49 (7.80–9.70)		0.017	8.90 (8.10–9.76)	6.30 (5.67–7.25)	< 0.001
Creatinine (µmol/L)	66.95 (57.40–78.72)	73.00 (66.00–85.00)	<0.001	66.50 (57.30–78.40)		74.00 (66.00–87.00)		<0.001	68.70 (58.80–80.00)	77.00 (70.50–93.50)	< 0.001
Cluster distribution	MOD: 132 (29.2); MARD: 138 (30.5); SID: 108 (23.9); SIR: 74 (16.4)	MOD: 45 (26.6); MARD: 52 (30.8); SID: 51 (30.2); SIR: 21 (12.4)	0.329	MOD: 133 (29.7); MARD: 133 (29.7); SID: 107 (23.9); SIR: 75 (16.7)		MOD: 44 (25.4); MARD: 57 (32.9); SID: 52 (30.1); SIR: 20 (11.6)		0.153	MOD: 165 (28.2); MARD: 177 (30.3); SID: 149 (25.5); SIR: 94 (16.1)	MOD: 12 (33.3); MARD: 13 (36.1); SID: 10 (27.8); SIR: 1 (2.8)	0.197

P values are from Mann–Whitney *U* tests (continuous variables) or χ^2 tests (categorical variables). Denominators vary where original measurements were missing; sex was unavailable for all 36 participants excluded from the corrected FIB-4 adjusted model because sex itself was a required covariate. Included participants are those included in the outcome-specific adjusted model after participant-identifier alignment of the required covariates; excluded participants lacked the

outcome score or at least one required covariate. CVD: Cardiovascular disease; CKD: Chronic kidney disease; FIB-4: Fibrosis-4 index; BMI: Body mass index; FBG: Fasting blood glucose.

Supplementary Table 9 Continuous organ-risk distributions across metabolic subtypes

Organ-risk measure	Subtype	*n*	Mean ± SD	Median (interquartile range)	Range	Kruskal–Wallis *H*	*P* value
Framingham 10-year CVD risk	MARD	138	13.05 ± 10.50	10.28 (5.68–16.55)	1.90–53.71	78.56	< 0.001
Framingham 10-year CVD risk	SID	108	9.20 ± 8.39	6.13 (3.97–10.16)	0.23–41.91	78.56	< 0.001
Framingham 10-year CVD risk	SIR	74	6.57 ± 5.70	5.46 (2.64–8.23)	0.85–30.57	78.56	< 0.001
Framingham 10-year CVD risk	MOD	132	5.50 ± 5.06	3.39 (2.02–7.61)	0.56–31.35	78.56	< 0.001
Framingham 10-year CVD risk	Overall	452	8.87 ± 8.51	6.13 (3.17–11.26)	0.23–53.71	78.56	< 0.001
CKD-PC projected 5-year CKD risk	MARD	133	9.43 ± 13.81	4.86 (2.77–8.43)	0.42–74.49	161.35	< 0.001
CKD-PC projected 5-year CKD risk	SID	107	7.51 ± 11.71	3.60 (1.72–6.15)	0.08–59.87	161.35	< 0.001
CKD-PC projected 5-year CKD risk	SIR	75	3.49 ± 8.19	1.12 (0.63–2.69)	0.08–50.56	161.35	< 0.001
CKD-PC	MOD	133	1.68 ± 2.69	0.95 (0.49–	0.05–	161.35	< 0.001

projected 5-year CKD risk				1.89)	21.86		
CKD-PC projected 5-year CKD risk	Overall	448	5.68 10.61	± 2.32 (0.97–5.26)	0.05–74.49	161.35	< 0.001
FIB-4 index	MARD	190	1.1896 0.4656	± 1.1114 (0.8988–1.4071)	0.4003–3.6742	139.48	< 0.001
FIB-4 index	SID	159	1.2284 0.5123	± 1.1520 (0.9558–1.3978)	0.3502–3.8274	139.48	< 0.001
FIB-4 index	SIR	95	0.7514 0.3545	± 0.6717 (0.4678–0.8907)	0.2242–2.0277	139.48	< 0.001
FIB-4 index	MOD	177	0.8542 0.4190	± 0.7698 (0.5881–1.0115)	0.2846–3.9880	139.48	< 0.001
FIB-4 index	Overall	621	1.0369 0.4903	± 0.9710 (0.6933–1.2892)	0.2242–3.9880	139.48	< 0.001

Framingham 10-year CVD risk was analyzable in 452 participants; CKD-PC projected 5-year CKD risk in 448 participants; FIB-4 index in all 621 participants. P values were derived from the Kruskal–Wallis test across the four subtypes. Pairwise comparisons (Dunn test with Bonferroni correction): CVD risk: MARD vs MOD (P<0.001), MARD vs SID (P=0.001), MARD vs SIR (P<0.001), MOD vs SID (P<0.001), MOD vs SIR (P=0.601), SID vs SIR (P=0.199). CKD risk: MARD vs MOD (P<0.001), MARD vs SID (P=0.148), MARD vs SIR (P<0.001), SID vs MOD (P<0.001), SID vs SIR (P<0.001), SIR vs MOD (P=0.456). FIB-4: MARD vs MOD (P<0.001), MARD vs SID (P=1.000), MARD vs SIR (P<0.001), SID vs MOD (P<0.001), SID vs SIR (P<0.001), MOD vs SIR (P=0.383). CVD: Cardiovascular disease; CKD-PC: Chronic kidney

disease prognosis consortium; CKD: Chronic kidney disease; FIB-4: Fibrosis-4 index.

Supplementary Table 10 Risk-category composition across metabolic subtypes by organ system, *n* (%)

Organ-risk measure	Risk category	MARD	SID	SIR	MOD	Overall	χ^2	*P* value
Framingham 10-year CVD risk (*n* = 452)	Low risk (< 10%)	67 (48.6)	80 (74.1)	64 (86.5)	110 (83.3)	321 (71.0)	58.34	< 0.001
Framingham 10-year CVD risk (*n* = 452)	Intermediate (10–< 20%)	46 (33.3)	15 (13.9)	7 (9.5)	20 (15.2)	88 (19.5)	58.34	< 0.001
Framingham 10-year CVD risk (*n* = 452)	High risk (≥ 20%)	25 (18.1)	13 (12.0)	3 (4.1)	2 (1.5)	43 (9.5)	58.34	< 0.001
CKD-PC projected 5-year CKD risk (*n* = 448)	Low risk (< 2.5%)	30 (22.6)	38 (35.5)	54 (72)	112 (84.2)	234 (52.2)	132.19	< 0.001
CKD-PC projected 5-year CKD risk (*n* = 448)	Intermediate (2.5–< 5%)	38 (28.6)	33 (30.8)	12 (16.0)	14 (10.5)	97 (21.7)	132.19	< 0.001
CKD-PC projected 5-year CKD risk (*n* = 448)	Elevated risk (≥ 5%)	65 (48.9)	36 (33.6)	9 (12.0)	7 (5.3)	117 (26.1)	132.19	< 0.001
FIB-4 index (*n* = 621)	Low risk (< 1.30)	136 (71.6)	107 (67.3)	86 (90.5)	160 (90.4)	489 (78.7)	41.37	< 0.001
FIB-4 index (*n* = 621)	Indeterminate (1.30–< 2.00)	53 (27.9)	50 (31.4)	9 (9.5)	16 (9.0)	128 (20.6)	41.37	< 0.001
FIB-4 index (*n* = 621)	High risk (≥ 2.00)	1 (0.5)	2 (1.3)	0 (0.0)	1 (0.6)	4 (0.6)	41.37	< 0.001

χ^2 tests compare risk-category distributions across the four subtypes. Subtype-

specific n varies by outcome because of differing analytic sample requirements: CVD (*n* = 452), CKD (*n* = 448), FIB-4 (*n* = 621). Column headers show the full-cohort subtype sizes (*n* = 621). CVD risk categories: low (< 10%), intermediate (10–< 20%), high (≥ 20%), based on Framingham 10-year risk. CKD risk categories: low (< 2.5%), intermediate (2.5–< 5%), elevated (≥ 5%), based on CKD-PC projected 5-year risk. FIB-4 categories: low risk (< 1.30), indeterminate (1.30–< 2.00), high risk (≥ 2.00).

Supplementary Table 11 Event rate and source contribution to the elevated organ-risk burden across metabolic subtypes

Organ-risk measure	Primary threshold	Subtype	*n*	Events	Event rate, %	Source contribution, %
Framingham 10-year CVD risk	≥ 10%	MARD	138	71	51.45	54.2
Framingham 10-year CVD risk	≥ 10%	SID	108	28	25.93	21.4
Framingham 10-year CVD risk	≥ 10%	SIR	74	10	13.51	7.6
Framingham 10-year CVD risk	≥ 10%	MOD	132	22	16.67	16.8
Framingham 10-year CVD risk	≥ 10%	Overall	452	131	28.98	100.0
CKD-PC projected 5-year	≥ 5%	MARD	133	65	48.9	55.6
CKD-PC projected 5-year	≥ 5%	SID	107	36	33.6	30.8
CKD-PC projected 5-year	≥ 5%	SIR	75	9	12.0	7.7
CKD-PC projected 5-year	≥ 5%	MOD	133	7	5.3	6.0
CKD-PC projected 5-year	≥ 5%	Overall	448	117	26.1	100.0
FIB-4 index	≥ 1.30	MARD	190	68	35.79	44.7
FIB-4 index	≥ 1.30	SID	159	58	36.48	38.2
FIB-4 index	≥ 1.30	SIR	95	9	9.47	5.9
FIB-4 index	≥ 1.30	MOD	177	17	9.60	11.2
FIB-4 index	≥ 1.30	Overall	621	152	24.48	100.0

Event rate = number of participants at or above the threshold/subtype-specific analytic *n* × 100. Source contribution = events in a subtype/total events across all subtypes × 100. Primary thresholds: Framingham 10-year cardiovascular disease risk

≥ 10%; chronic kidney disease prognosis consortium projected 5-year cardiovascular disease risk ≥ 5%; FIB-4 index ≥ 1.30. CVD: Cardiovascular disease; CKD-PC: Chronic kidney disease prognosis consortium; CKD: Chronic kidney disease; FIB-4: Fibrosis-4 index.

Supplementary Table 12 Multicollinearity diagnostics for the outcome-specific adjusted models

Variable	VIF
CVD model	
MARD vs MOD	1.739
SID vs MOD	1.672
SIR vs MOD	1.602
Waist circumference	1.520
AST	1.075
Platelet count	1.105
eGFR	1.281
Triglycerides	1.100
LDL-C	1.043
CKD model	
MARD vs MOD	1.488
SID vs MOD	1.503
SIR vs MOD	1.600
Waist circumference	1.521
LDL-C	1.040
Triglycerides	1.100
AST	1.061

Platelet count	1.099
FIB-4 model	
MARD vs MOD	1.752
SID vs MOD	1.643
SIR vs MOD	1.653
Waist circumference	1.855
Male sex	1.284
Systolic blood pressure	1.124
eGFR	1.237
Triglycerides	1.085
LDL-C	1.010

Variance inflation factors were calculated for the participant-ID-aligned outcome-specific adjusted models. All VIFs were below 2, indicating no meaningful multicollinearity among retained covariates. Clinical variable names are shown; internal database column names are not displayed.

Supplementary Table 13 Sensitivity analysis: prevalence ratios at alternative risk thresholds across metabolic subtypes

Variable	Model	*n*	Events	PR	95%CI (PR)	*P* value
Framingham-estimated 10-year CVD risk ≥ 7.5%						
MOD (reference)	Model 1	452	185	Ref	—	—
MARD vs MOD	Model 1	452	185	2.448	1.783–3.359	<0.001
SID vs MOD	Model 1	452	185	1.546	1.067–2.240	0.021
SIR vs MOD	Model 1	452	185	1.102	0.693–1.751	0.682
MOD (reference)	Model 2	452	185	Ref	—	—
MARD vs MOD	Model 2	452	185	1.709	1.254–2.329	<0.001

SID vs MOD	Model 2	452	185	1.633	1.147–2.326	0.007
SIR vs MOD	Model 2	452	185	0.696	0.431–1.123	0.138
Framingham-estimated 10-year CVD risk ≥ 10%						
MOD (reference)	Model 1	452	131	Ref	—	—
MARD vs MOD	Model 1	452	131	3.087	2.040–4.672	<0.001
SID vs MOD	Model 1	452	131	1.556	0.946–2.557	0.082
SIR vs MOD	Model 1	452	131	0.811	0.406–1.618	0.552
MOD (reference)	Model 2	452	131	Ref	—	—
MARD vs MOD	Model 2	452	131	1.942	1.283–2.940	0.002
SID vs MOD	Model 2	452	131	1.805	1.116–2.921	0.016
SIR vs MOD	Model 2	452	131	0.399	0.206–0.772	0.006
Framingham-estimated 10-year CVD risk ≥ 15%						
MOD (reference)	Model 1	452	74	Ref	—	—
MARD vs MOD	Model 1	452	74	5.141	2.513–10.520	<0.001
SID vs MOD	Model 1	452	74	2.750	1.244–6.078	0.012
SIR vs MOD	Model 1	452	74	1.115	0.378–3.285	0.844
MOD (reference)	Model 2	452	74	Ref	—	—
MARD vs MOD	Model 2	452	74	2.708	1.270–5.775	0.010
SID vs MOD	Model 2	452	74	3.124	1.412–6.910	0.005
SIR vs MOD	Model 2	452	74	0.461	0.169–1.263	0.132
Framingham-estimated 10-year CVD risk ≥ 20%						
MOD (reference)	Model 1	452	43	Ref	—	—
MARD vs MOD	Model 1	452	43	11.957	2.889–49.484	<0.001
SID vs MOD	Model 1	452	43	7.944	1.832–34.442	0.006
SIR vs MOD	Model 1	452	43	2.676	0.457–15.652	0.275

MOD (reference)	Model 2	452	43	Ref	—	—
MARD vs MOD	Model 2	452	43	5.388	1.279–22.692	0.022
SID vs MOD	Model 2	452	43	10.609	2.320–48.509	0.002
SIR vs MOD	Model 2	452	43	0.756	0.144–3.961	0.741
CKD-PC-estimated projected 5-year CKD risk ≥ 5%						
MOD (reference)	Model 1	448	117	Ref	—	—
MARD vs MOD	Model 1	448	117	9.286	4.423–19.495	<0.001
SID vs MOD	Model 1	448	117	6.393	2.964–13.787	<0.001
SIR vs MOD	Model 1	448	117	2.280	0.885–5.874	0.088
MOD (reference)	Model 2	448	117	Ref	—	—
MARD vs MOD	Model 2	448	117	8.748	4.123–18.560	<0.001
SID vs MOD	Model 2	448	117	6.407	2.990–13.728	<0.001
SIR vs MOD	Model 2	448	117	2.095	0.790–5.555	0.137
CKD-PC-estimated projected 5-year CKD risk ≥ 10%						
MOD (reference)	Model 1	448	55	Ref	—	—
MARD vs MOD	Model 1	448	55	13.500	3.276–55.632	<0.001
SID vs MOD	Model 1	448	55	13.673	3.289–56.849	<0.001
SIR vs MOD	Model 1	448	55	3.547	0.665–18.909	0.138
MOD (reference)	Model 2	448	55	Ref	—	—
MARD vs MOD	Model 2	448	55	12.618	3.044–52.312	<0.001
SID vs MOD	Model 2	448	55	13.908	3.311–58.423	<0.001
SIR vs MOD	Model 2	448	55	3.264	0.589–18.080	0.176
CKD-PC-estimated projected 5-year CKD risk ≥ P90 (11.4%)						
MOD (reference)	Model 1	448	45	Ref	—	—
MARD vs MOD	Model 1	448	45	11.500	2.766–47.805	<0.001

SID vs MOD	Model 1	448	45	9.944	2.338–42.298	0.002
SIR vs MOD	Model 1	448	45	3.547	0.665–18.909	0.138
MOD (reference)	Model 2	448	45	Ref	—	—
MARD vs MOD	Model 2	448	45	10.525	2.508–44.174	0.001
SID vs MOD	Model 2	448	45	10.711	2.465–46.543	0.002
SIR vs MOD	Model 2	448	45	2.945	0.525–16.528	0.220
CKD-PC-estimated projected 5-year CKD risk ≥ P95 (22.8%)						
MOD (reference)	Model 1	448	23	Ref	—	—
MARD vs MOD	Model 1	448	23	NE	—	NE
SID vs MOD	Model 1	448	23	NE	—	NE
SIR vs MOD	Model 1	448	23	NE	—	NE
MOD (reference)	Model 2	448	23	Ref	—	—
MARD vs MOD	Model 2	448	23	NE	—	NE
SID vs MOD	Model 2	448	23	NE	—	NE
SIR vs MOD	Model 2	448	23	NE	—	NE
FIB-4 ≥ 1.30						
MOD (reference)	Model 1	621	152	Ref	—	—
MARD vs MOD	Model 1	621	152	3.726	2.282–6.085	<0.001
SID vs MOD	Model 1	621	152	3.798	2.312–6.239	<0.001
SIR vs MOD	Model 1	621	152	0.986	0.457–2.127	0.972
MOD (reference)	Model 2	585	150	Ref	—	—
MARD vs MOD	Model 2	585	150	3.002	1.758–5.127	<0.001
SID vs MOD	Model 2	585	150	3.505	2.100–5.849	<0.001
SIR vs MOD	Model 2	585	150	0.912	0.410–2.028	0.821
FIB-4 ≥ 2.00						

MOD (reference)	Model 1	621	24	Ref	—	—
MARD vs MOD	Model 1	621	24	3.416	0.969–12.043	0.056
SID vs MOD	Model 1	621	24	3.340	0.920–12.120	0.067
SIR vs MOD	Model 1	621	24	0.621	0.065–5.889	0.678
MOD (reference)	Model 2	585	24	Ref	—	—
MARD vs MOD	Model 2	585	24	2.719	0.746–9.912	0.130
SID vs MOD	Model 2	585	24	2.678	0.697–10.293	0.152
SIR vs MOD	Model 2	585	24	0.617	0.065–5.847	0.674

Poisson regression with robust standard errors; prevalence ratios and 95%CI are reported. Reference group: MOD for all analyses. Model 2 covariates were waist circumference, aspartate aminotransferase, platelet count, estimated glomerular filtration rate, triglycerides, and low-density lipoprotein cholesterol for the cardiovascular disease model; waist circumference, aspartate aminotransferase, platelet count, triglycerides, and low-density lipoprotein cholesterol for the chronic kidney disease model; and waist circumference, sex, systolic blood pressure, estimated glomerular filtration rate, triglycerides, and low-density lipoprotein cholesterol for the FIB-4 model. Estimates were reported as not estimable when sparse or zero-event cells precluded stable estimation. PR: Prevalence ratio; CVD: Cardiovascular disease; CKD: Chronic kidney disease; FIB-4: Fibrosis-4 index; Ref.: Reference.

Supplementary Table 14 Sensitivity analysis: continuous organ-risk differences across metabolic subtypes

Organ-risk measure	Method	Subtype	β (95%CI)	*P* value	*n*
Framingham 10-year CVD risk, %	Robust OLS (HC3)	MARD	β=7.55 (5.59–9.51)	< 0.001	452
Framingham 10-year CVD risk, %	Robust OLS (HC3)	SID	β=3.70 (1.89–5.51)	< 0.001	452
Framingham 10-year CVD risk, %	Robust OLS (HC3)	SIR	β=1.07 (-0.50–2.64)	0.181	452
Framingham 10-year CVD risk, %	Robust OLS (HC3)	MOD	0.00 (Ref.)	—	452

CKD-PC projected 5-year CKD risk, %			Robust OLS (HC3)	MARD	β=7.75 (5.35–10.15)	< 0.001	448
CKD-PC projected 5-year CKD risk, %			Robust OLS (HC3)	SID	β=5.84 (3.56–8.11)	< 0.001	448
CKD-PC projected 5-year CKD risk, %			Robust OLS (HC3)	SIR	β=1.82 (-0.1–3.74)	0.064	448
CKD-PC projected 5-year CKD risk, %			Robust OLS (HC3)	MOD	0.00 (Ref.)	—	448
FIB-4 index			Robust OLS (HC3)	MARD	0.3355 (0.2447–0.4262)	< 0.001	621
FIB-4 index			Robust OLS (HC3)	SID	0.3742 (0.2732–0.4753)	< 0.001	621
FIB-4 index			Robust OLS (HC3)	SIR	-0.1027 (-0.1974–-0.008)	0.0335	621
FIB-4 index			Median regression	MARD	0.3429 (0.2473–0.4386)	< 0.001	621
FIB-4 index			Median regression	SID	0.3822 (0.2822–0.4823)	< 0.001	621
FIB-4 index			Median regression	SIR	-0.0981 (-0.2146–0.0183)	0.0985	621

β coefficients represent the mean (robust OLS) or median (median regression) difference in continuous risk relative to MOD (reference). Robust OLS uses heteroscedasticity-consistent standard errors (HC3). Median regression (quantile regression at the 50th percentile) is reported for FIB-4 as an additional robustness check. OLS: Ordinary least squares; CVD: Cardiovascular disease; CKD-PC: Chronic kidney disease prognosis consortium; CKD: Chronic kidney disease; FIB-4: Fibrosis-4 index; Ref.: Reference.

Supplementary Table 15 Complete-case sensitivity analysis of threshold-defined

organ-risk outcomes across metabolic subtypes using observed non-imputed covariates

Organ-risk measure	Threshold	Model	*n*	Events	MARD PR (95%CI)	SID PR (95%CI)	SIR PR (95%CI)
CVD risk	≥ 10%	Model 1	407	126	3.02 (2.00–4.54)	1.49 (0.91–2.46)	0.79 (0.40–1.57)
		Model 2			1.87 (1.23–2.83)	1.68 (1.05–2.71)	0.38 (0.20–0.74)
CKD risk	≥ 5%	Model 1	409	108	10.42 (4.68–23.18)	6.69 (2.91–15.37)	2.67 (0.99–7.20)
		Model 2			9.88 (4.40–22.14)	6.78 (2.98–15.43)	2.41 (0.86–6.70)
FIB-4	≥ 1.30	Model 1	531	140	4.34 (2.55–7.41)	4.39 (2.55–7.54)	1.16 (0.52–2.56)
		Model 2			3.13 (1.76–5.57)	3.72 (2.15–6.41)	1.09 (0.48–2.46)

Complete-case samples were defined separately for each outcome and were fixed across Model 1 and Revised Model 2. Participants were required to have an available outcome, a metabolic subtype assignment, and observed non-imputed values for all covariates included in the corresponding revised outcome-specific model. Observed extreme AST and platelet-count values retained the same prespecified winsorization used in the primary analysis; records in which a covariate was replaced by imputation were excluded. Poisson regression with HC3 robust standard errors was used to estimate prevalence ratios and 95% confidence intervals, with MOD as the reference group. Revised Model 2 included waist circumference, AST, platelet count, eGFR, triglycerides, and LDL-C for the CVD outcome; waist circumference, LDL-C, triglycerides, AST, and platelet count for the CKD outcome; and waist circumference, sex, systolic blood pressure, eGFR, triglycerides, and LDL-C for the FIB-4 outcome. AST: Aspartate aminotransferase; CVD: Cardiovascular disease; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate; FIB-4: Fibrosis-4 index; LDL-C: Low-density lipoprotein cholesterol; MARD: Mild age-related dysmetabolism; MOD: Mild obesity-related dysmetabolism; SID: Severe insulin deficiency; SIR: Severe insulin resistance.

Supplementary Table 16 Sensitivity analysis: prevalence ratios with alternative reference group across metabolic subtypes

Variable	Model	*n*	Events	PR	95%CI (PR)	*P* value
Framingham-estimated 10-year CVD risk ≥ 10%						
SIR (reference)	Model 1	452	131	Ref	—	—
MOD vs SIR	Model 1	452	131	1.233	0.618–2.462	0.552
MARD vs SIR	Model 1	452	131	3.807	2.092–6.929	<0.001
SID vs SIR	Model 1	452	131	1.919	0.993–3.707	0.053
SIR (reference)	Model 2	452	131	Ref	—	—
MOD vs SIR	Model 2	452	131	2.508	1.295–4.858	0.006
MARD vs SIR	Model 2	452	131	4.872	2.761–8.597	<0.001
SID vs SIR	Model 2	452	131	4.528	2.281–8.990	<0.001
CKD-PC-estimated projected 5-year CKD risk ≥ 5%						
SIR (reference)	Model 1	448	117	Ref	—	—
MOD vs SIR	Model 1	448	117	0.439	0.170–1.130	0.088
MARD vs SIR	Model 1	448	117	4.073	2.154–7.701	<0.001
SID vs SIR	Model 1	448	117	2.804	1.437–5.469	0.002
SIR (reference)	Model 2	448	117	Ref	—	—
MOD vs SIR	Model 2	448	117	0.477	0.180–1.265	0.137
MARD vs SIR	Model 2	448	117	4.175	2.196–7.937	<0.001
SID vs SIR	Model 2	448	117	3.058	1.476–6.334	0.003
FIB-4 ≥ 1.30						
SIR (reference)	Model 1	621	152	Ref	—	—
MOD vs SIR	Model 1	621	152	1.014	0.470–2.186	0.972
MARD vs SIR	Model 1	621	152	3.778	1.972–7.237	<0.001
SID vs SIR	Model 1	621	152	3.850	2.001–7.409	<0.001

SIR (reference)	Model 2	585	150	Ref	—	—
MOD vs SIR	Model 2	585	150	1.096	0.493–2.439	0.821
MARD vs SIR	Model 2	585	150	3.292	1.691–6.411	<0.001
SID vs SIR	Model 2	585	150	3.843	1.898–7.782	<0.001

Poisson regression with robust standard errors (HC3); prevalence ratios (PR) and 95% confidence intervals are reported. Reference group: SIR. This analysis tests whether the subtype ranking observed in the Primary analysis (ref = MOD) is robust to the choice of reference group. PR: Prevalence ratio; CVD: Cardiovascular disease; CKD: Chronic kidney disease; FIB-4: Fibrosis-4 index.

Supplementary Table 17 Age distribution in the full cohort and cardiovascular disease analysis samples, mean ± SD/median (P25, P75)

Sample	*n*	Age	Age	Range
Full cohort	621	51.08 ± 10.14	52 (45, 58)	22–70
CVD analytic sample	452	51.29 ± 10.73	53 (43, 59)	22–70
Adjusted-model sample	452	51.29 ± 10.73	53 (43, 59)	22–70

The full-cohort median age was 52 years. The cardiovascular disease analytic sample median was 53 years; the prespecified stratification nevertheless used the full-cohort cutoff of 52 years. CVD: Cardiovascular disease.

Supplementary Table 18 Age distribution across metabolic subtypes in the cardiovascular disease analytic sample, *n* (%)/median (P25, P75)

Subtype	*n*	Age	Age	Range	< 52 years	≥ 52 years
MOD	132	43.49 ± 8.48	43.5 (37, 50)	26-64	105 (79.5)	27 (20.5)
MARD	138	58.93 ± 6.84	59 (54, 64.75)	36-70	18 (13.0)	120 (87.0)
SID	108	56.22 ± 8.06	57 (51.75, 62)	26-69	27 (25.0)	81 (75.0)
SIR	74	43.76 ± 9.26	42.5 (37.25, 50.75)	22-64	56 (75.7)	18 (24.3)

Age composition was highly imbalanced across subtypes: MARD and SID were

concentrated in the older stratum, whereas MOD and SIR were concentrated in the younger stratum.

Supplementary Table 19 Overall subtype associations with Framingham-defined intermediate/high cardiovascular disease risk

Model	*n*	Events	Comparison	PR (95%CI)	*P* value
Model 1	452	131	MARD vs MOD	3.087 (2.040–4.672)	< 0.001
Model 1	452	131	SID vs MOD	1.556 (0.946–2.557)	0.082
Model 1	452	131	SIR vs MOD	0.811 (0.406–1.618)	0.552
Model 2	452	131	MARD vs MOD	1.942 (1.283–2.940)	0.002
Model 2	452	131	SID vs MOD	1.805 (1.116–2.921)	0.016
Model 2	452	131	SIR vs MOD	0.399 (0.206–0.772)	0.006

Model 1 was unadjusted. Model 2 adjusted for waist circumference, AST, platelet count, eGFR, triglycerides, and LDL-C. These estimates average across the observed and highly unequal age distributions of the subtypes.

Supplementary Table 20 Median-age-stratified sensitivity analysis of Framingham-defined intermediate/high cardiovascular disease risk

Age stratum	Model	Subtype	*n*	Events	Event rate, %	PR (95% CI)	*P* value
< 52 years	Model 1	MOD	105	11	10.5	1.00 (Ref.)	—
< 52 years	Model 1	MARD	18	11	61.1	5.83 (2.99–11.40)	<0.001
< 52 years	Model 1	SID	27	0	0.0	NE	NE
< 52 years	Model 1	SIR	56	3	5.4	0.51 (0.15–1.76)	0.287
< 52 years	Model 2	MOD	105	11	10.5	1.00 (Ref.)	—
< 52 years	Model 2	MARD	18	11	61.1	2.85 (1.49–5.42)	0.001
< 52 years	Model 2	SID	27	0	0.0	NE	NE

< 52 years	Model 2	SIR	56	3	5.4	0.20 (0.05–0.76)	0.018
≥ 52 years	Model 1	MOD	27	11	40.7	1.00 (Ref.)	—
≥ 52 years	Model 1	MARD	120	60	50.0	1.23 (0.75–2.00)	0.412
≥ 52 years	Model 1	SID	81	28	34.6	0.85 (0.49–1.46)	0.554
≥ 52 years	Model 1	SIR	18	7	38.9	0.95 (0.46–1.99)	0.901
≥ 52 years	Model 2	MOD	27	11	40.7	1.00 (Ref.)	—
≥ 52 years	Model 2	MARD	120	60	50.0	1.09 (0.68–1.74)	0.719
≥ 52 years	Model 2	SID	81	28	34.6	1.22 (0.73–2.03)	0.454
≥ 52 years	Model 2	SIR	18	7	38.9	0.50 (0.26–0.98)	0.045

The age cutoff was the full-cohort median (52 years). NE indicates that a formal PR was not estimated because the SID subgroup had zero events in participants aged < 52 years. Binary stratification does not remove residual age imbalance within each stratum.

Supplementary Table 21 Global interaction between median-age stratum and metabolic subtype

Model	**Interaction**	***P* for interaction**	**Interpretation**	**Caution**
Model 1	Subtype × age stratum	NE	Not interpreted because the < 52-year SID cell had zero events.	Binary interaction estimates were separation-sensitive; the continuous-age interaction is reported in Supplementary Table 20
Model 2	Subtype × age stratum	NE	Not interpreted because the < 52-year SID cell had zero events.	Sparse cells precluded a stable joint Wald test

The categorical age-stratum interaction was not interpreted because the younger SID cell contained zero events, producing separation-sensitive estimates. The formal

continuous-age interaction model in Supplementary Table 20 provides the primary interaction test.

Supplementary Table 22 Continuous age-by-subtype interaction analysis

Model	Term	Wald χ^2	df	*P* value	Interaction PR per year (95%CI)
Model 1	Global subtype × continuous age	34.798	3	1.34e-07	—
Model 1	MARD × age	—	—	2.86e-07	0.895 (0.858–0.934)
Model 1	SID × age	—	—	0.339	0.974 (0.922–1.028)
Model 1	SIR × age	—	—	0.975	0.999 (0.933–1.069)
Model 2	Global subtype × continuous age	23.674	3	2.92e-05	—
Model 2	MARD × age	—	—	1.01e-05	0.908 (0.869–0.948)
Model 2	SID × age	—	—	0.383	0.976 (0.924–1.031)
Model 2	SIR × age	—	—	0.629	0.985 (0.929–1.046)

Age was centered at 52 years. An interaction PR below 1 indicates that the subtype-to-MOD prevalence ratio decreases with each additional year of age. The adjusted global interaction remained significant and was driven primarily by MARD × age.

Supplementary Table 23 Conditional subtype effects at age 52 and subtype-specific age slopes

Model	Estimand	Subtype/comparison	PR (95%CI)	*P* value
Model 1	Subtype contrast at age 52	MARD vs MOD	1.645 (1.078–2.511)	0.021
Model 1	Subtype contrast at age 52	SID vs MOD	0.473 (0.260–0.860)	0.014
Model 1	Subtype contrast at age 52	SIR vs MOD	0.680 (0.356–1.297)	0.241
Model 1	Within-subtype age slope	MOD	1.132 (1.093–1.172)	< 0.001
Model 1	Within-subtype age slope	MARD	1.013 (0.989–1.038)	0.300

Model 1	Within-subtype age slope	SID	1.102 (1.058–1.149)	< 0.001
Model 1	Within-subtype age slope	SIR	1.131 (1.067–1.199)	< 0.001
Model 2	Subtype contrast at age 52	MARD vs MOD	1.343 (0.898–2.008)	0.151
Model 2	Subtype contrast at age 52	SID vs MOD	0.713 (0.395–1.288)	0.262
Model 2	Subtype contrast at age 52	SIR vs MOD	0.353 (0.187–0.669)	0.001
Model 2	Within-subtype age slope	MOD	1.120 (1.081–1.161)	< 0.001
Model 2	Within-subtype age slope	MARD	1.017 (0.989–1.045)	0.236
Model 2	Within-subtype age slope	SID	1.093 (1.045–1.143)	< 0.001
Model 2	Within-subtype age slope	SIR	1.104 (1.050–1.161)	< 0.001

The subtype contrasts at age 52 are conditional effects from the interaction model and are not directly comparable with the overall non-interaction Model 2 estimates. Within-subtype age slopes quantify the change in score-defined high-risk prevalence per 1-year increase in age.

Supplementary Table 24 Conditional subtype contrasts at representative ages

Model	Age (years)	Comparison	PR (95%CI)	*P* value
Model 1	40	MARD vs MOD	6.244 (2.823–13.815)	< 0.001
Model 1	40	SID vs MOD	0.649 (0.212–1.986)	0.449
Model 1	40	SIR vs MOD	0.689 (0.205–2.319)	0.547
Model 1	52	MARD vs MOD	1.645 (1.078–2.511)	0.021
Model 1	52	SID vs MOD	0.473 (0.260–0.860)	0.014
Model 1	52	SIR vs MOD	0.680 (0.356–1.297)	0.241
Model 1	65	MARD vs MOD	0.388 (0.230–0.655)	< 0.001
Model 1	65	SID vs MOD	0.335 (0.186–0.605)	< 0.001
Model 1	65	SIR vs MOD	0.670 (0.279–1.612)	0.372
Model 2	40	MARD vs MOD	4.301 (1.965–9.411)	< 0.001

Model 2	40	SID vs MOD	0.955 (0.310–2.946)	0.937
Model 2	40	SIR vs MOD	0.421 (0.136–1.303)	0.134
Model 2	52	MARD vs MOD	1.343 (0.898–2.008)	0.151
Model 2	52	SID vs MOD	0.713 (0.395–1.288)	0.262
Model 2	52	SIR vs MOD	0.353 (0.187–0.669)	0.001
Model 2	65	MARD vs MOD	0.381 (0.225–0.644)	< 0.001
Model 2	65	SID vs MOD	0.519 (0.291–0.925)	0.026
Model 2	65	SIR vs MOD	0.292 (0.133–0.641)	0.002

These are exploratory marginal contrasts. The age-65 comparisons involving MOD are extrapolative because the observed maximum age in the cardiovascular disease - analytic MOD group was 64 years. Therefore, PRs below 1 at age 65 must not be interpreted as evidence that MARD, SID, or SIR is protective.

Supplementary Table 25 Diagnostics of continuous age-by-subtype interaction models

Model	***n***	**Events**	**Pearson χ^2/df**	**Deviance/df**	**Minimum fitted mean**	**Maximum fitted mean**	**Fitted means > 1**	**SE type**	**Maximum VIF**
Model 1	452	131	0.612	0.551	0.005	1.262	2	HC3	—
Model 2	452	131	0.529	0.480	0.003	2.635	12	HC3	5.96

Poisson log-link models were used to estimate prevalence ratios. Fitted means above 1 indicate that model-based fitted values should not be interpreted as probabilities. All VIFs in the non-interaction Model 2 were below 2.

Supplementary Table 26 Cross-framework synthesis of adjusted cardiovascular disease estimates

Analytic framework	**Age condition**	**Comparison**	**PR (95%CI)**	***P* value**

Overall non-interaction Model 2	Observed distribution	age	MARD vs MOD	1.942	(1.283–2.940)	0.002
Overall non-interaction Model 2	Observed distribution	age	SID vs MOD	1.805	(1.116–2.921)	0.016
Overall non-interaction Model 2	Observed distribution	age	SIR vs MOD	0.399	(0.206–0.772)	0.006
Age-stratified Model 2	< 52 years		MARD vs MOD	2.85	(1.49–5.42)	0.001
Age-stratified Model 2	< 52 years		SID vs MOD	NE		NE
Age-stratified Model 2	< 52 years		SIR vs MOD	0.20	(0.05–0.76)	0.018
Age-stratified Model 2	≥ 52 years		MARD vs MOD	1.09	(0.68–1.74)	0.719
Age-stratified Model 2	≥ 52 years		SID vs MOD	1.22	(0.73–2.03)	0.454
Age-stratified Model 2	≥ 52 years		SIR vs MOD	0.50	(0.26–0.98)	0.045
Continuous-interaction Model 2	Age 52		MARD vs MOD	1.343	(0.898–2.008)	0.151
Continuous-interaction Model 2	Age 52		SID vs MOD	0.713	(0.395–1.288)	0.262
Continuous-interaction Model 2	Age 52		SIR vs MOD	0.353	(0.187–0.669)	0.001

The three frameworks estimate different quantities. The overall model averages over observed age distributions; the stratified model compares subtypes within broad age bands; the interaction model estimates subtype contrasts at a specific age. Their differences are expected and collectively demonstrate strong age dependence.

Supplementary Table 27 Age distribution in the full cohort and chronic kidney disease analytic sample, mean ± SD/ median (P25, P75)/ *n* (%)

Sample	Subtype	*n*	Age	Age	Range	< 52 years	≥ 52 years
Full cohort	Overall	621	51.08 ± 10.14	52 (45, 58)	22–70	310 (49.9)	311 (50.1)
Full cohort	MOD	177	44.04 ± 7.84	45 (38, 50)	26–64	147 (83.1)	30 (16.9)
Full cohort	MARD	190	57.85 ± 6.82	57 (53, 63.75)	36–70	35 (18.4)	155 (81.6)
Full cohort	SID	159	55.42 ± 7.90	56 (50, 62)	26–70	54 (34.0)	105 (66.0)
Full cohort	SIR	95	43.39 ± 9.33	43 (36.5, 50)	22–64	74 (77.9)	21 (22.1)
CKD analytic sample	Overall	448	51.10 ± 10.73	52 (43, 59)	22–70	208 (46.4)	240 (53.6)
CKD analytic sample	MOD	133	43.49 ± 8.45	44 (37, 50)	26–64	106 (79.7)	27 (20.3)
CKD analytic sample	MARD	133	58.79 ± 6.84	59 (54, 64)	36–70	18 (13.5)	115 (86.5)
CKD analytic sample	SID	107	56.23 ± 8.10	57 (51.5, 62)	26–69	27 (25.2)	80 (74.8)
CKD analytic sample	SIR	75	43.64 ± 9.25	42 (37, 50.5)	22–64	57 (76.0)	18 (24.0)

The 52-year cutoff was the full-cohort median. P25 and P75 denote the 25th and 75th percentiles.

Supplementary Table 28 Distribution of chronic kidney disease prognosis consortium-defined intermediate/high-risk events by median-age stratum and subtype

Age stratum	Subtype	*n*	Events	Event prevalence, %	Contribution within age stratum, %	Contribution to all 117 events, %
< 52 years	Overall	208	9	4.33	100.00	7.69
< 52 years	MOD	106	3	2.83	33.33	2.56
< 52 years	MARD	18	2	11.11	22.22	1.71
< 52 years	SID	27	1	3.70	11.11	0.85
< 52 years	SIR	57	3	5.26	33.33	2.56
≥ 52 years	Overall	240	108	45.00	100.00	92.31
≥ 52 years	MOD	27	4	14.81	3.70	3.42

≥ 52 years	MARD	115	63	54.78	58.33	53.85
≥ 52 years	SID	80	35	43.75	32.41	29.91
≥ 52 years	SIR	18	6	33.33	5.56	5.13

Note. Within-stratum contributions sum to 100%. Overall, 9/117 events (7.69%) occurred before age 52 and 108/117 (92.31%) occurred at age 52 or older.

Supplementary Table 29 Overall and median-age-stratified sensitivity analyses of chronic kidney disease prognosis consortium-defined intermediate/high risk

Analysis population	Model	Comparison	PR (95%CI)	*P* value
Overall	Model 1	MARD vs MOD	9.29 (4.42–19.50)	< 0.001
Overall	Model 1	SID vs MOD	6.39 (2.96–13.79)	< 0.001
Overall	Model 1	SIR vs MOD	2.28 (0.89–5.87)	0.088
Overall	Model 2	MARD vs MOD	8.75 (4.12–18.56)	< 0.001
Overall	Model 2	SID vs MOD	6.41 (2.99–13.73)	< 0.001
Overall	Model 2	SIR vs MOD	2.10 (0.79–5.55)	0.137
< 52 years	Model 1	MARD vs MOD	3.93 (0.70–21.88)	0.119
< 52 years	Model 1	SID vs MOD	1.31 (0.14–12.09)	0.813
< 52 years	Model 1	SIR vs MOD	1.86 (0.39–8.92)	0.438
< 52 years	Model 2	MARD vs MOD	5.98 (1.11–32.23)	0.038
< 52 years	Model 2	SID vs MOD	1.07 (0.14–8.23)	0.946
< 52 years	Model 2	SIR vs MOD	2.86 (0.48–17.13)	0.249
≥ 52 years	Model 1	MARD vs MOD	3.70 (1.47–9.28)	0.005
≥ 52 years	Model 1	SID vs MOD	2.95 (1.16–7.54)	0.024
≥ 52 years	Model 1	SIR vs MOD	2.25 (0.74–6.87)	0.154
≥ 52 years	Model 2	MARD vs MOD	3.69 (1.47–9.27)	0.005
≥ 52 years	Model 2	SID vs MOD	3.06 (1.20–7.80)	0.019

≥ 52 years	Model 2	SIR vs MOD	2.05 (0.66–6.33)	0.213

Model 1 was unadjusted. Model 2 adjusted for waist circumference, LDL-C, triglycerides, AST, and platelet count. The < 52-year stratum included only 9 events; its estimates are imprecise.

Supplementary Table 30 Global interaction between median-age stratum and metabolic subtype

Model	Interaction term	Wald χ^2	df	*P* for interaction	*n*	Events
Model 1	Subtype × age stratum	0.593	3	0.898	448	117
Model 2	Subtype × age stratum	0.577	3	0.902	448	117

Age stratum was coded as < 52 *vs* ≥ 52 years. Non-significance indicates no statistical evidence of multiplicative effect modification by the binary age stratum.

Supplementary Table 31 Continuous age-by-subtype interaction analysis

Model	Conditional effect or interaction term	PR (95%CI)	*P* value	Global *P* for interaction
Model 1	MARD vs MOD at age 52	2.15 (0.88–5.27)	0.095	0.456
Model 1	SID vs MOD at age 52	1.43 (0.52–3.93)	0.493	
Model 1	SIR vs MOD at age 52	2.07 (0.78–5.48)	0.145	
Model 1	Age per 1 year within MOD	1.21 (1.09–1.34)	< 0.001	
Model 1	MARD × age (ratio of age slopes)	0.92 (0.83–1.03)	0.136	
Model 1	SID × age (ratio of age slopes)	0.95 (0.85–1.06)	0.356	
Model 1	SIR × age (ratio of age slopes)	0.94 (0.82–1.06)	0.310	
Model 2	MARD vs MOD at age 52	2.09 (0.84–5.21)	0.112	0.500
Model 2	SID vs MOD at age 52	1.44 (0.52–3.96)	0.484	
Model 2	SIR vs MOD at age 52	1.89 (0.68–5.23)	0.222	
Model 2	Age per 1 year within MOD	1.21 (1.09–1.33)	< 0.001	
Model 2	MARD × age (ratio of age slopes)	0.93 (0.84–1.03)	0.161	

Model 2	SID × age (ratio of age slopes)	0.95 (0.85–1.06)	0.388
Model 2	SIR × age (ratio of age slopes)	0.93 (0.82–1.06)	0.265

Age was centered at 52 years. Subtype main effects are conditional contrasts at age 52; the age main effect is the per-year effect within MOD; interaction PRs are ratios of age slopes. Model 2 adjusted for waist circumference, LDL-C, triglycerides, AST, and platelet count.

Supplementary Table 32 Association of age with chronic kidney disease prognosis consortium-defined intermediate/high risk within each subtype

Model	Subtype	PR per 1-year age increase (95%CI)	*P* value
Model 1	MOD	1.21 (1.09–1.34)	< 0.001
Model 1	MARD	1.12 (1.08–1.15)	< 0.001
Model 1	SID	1.15 (1.09–1.21)	< 0.001
Model 1	SIR	1.13 (1.04–1.23)	0.003
Model 2	MOD	1.21 (1.09–1.33)	< 0.001
Model 2	MARD	1.12 (1.08–1.16)	< 0.001
Model 2	SID	1.15 (1.09–1.21)	< 0.001
Model 2	SIR	1.12 (1.04–1.22)	0.004

Subtype-specific slopes were derived from the continuous age-by-subtype interaction models.

Supplementary Table 33 Conditional subtype contrasts at selected ages

Model	Age (years)	Comparison	PR (95% CI)	*P* value
Model 1	40	MARD vs MOD	5.654 (0.736–43.416)	0.096
Model 1	40	SID vs MOD	2.710 (0.286–25.659)	0.385
Model 1	40	SIR vs MOD	4.626 (0.436–49.058)	0.204
Model 1	52	MARD vs MOD	2.148 (0.876–5.268)	0.095

Model 1	52	SID vs MOD	1.426 (0.517–3.929)	0.493
Model 1	52	SIR vs MOD	2.066 (0.778–5.484)	0.145
Model 1	65	MARD vs MOD	0.753 (0.302–1.874)	0.542
Model 1	65	SID vs MOD	0.711 (0.282–1.792)	0.470
Model 1	65	SIR vs MOD	0.862 (0.264–2.822)	0.807
Model 2	40	MARD vs MOD	5.163 (0.670–39.770)	0.115
Model 2	40	SID vs MOD	2.599 (0.278–24.290)	0.402
Model 2	40	SIR vs MOD	4.415 (0.427–45.663)	0.213
Model 2	52	MARD vs MOD	2.094 (0.842–5.209)	0.112
Model 2	52	SID vs MOD	1.437 (0.521–3.962)	0.484
Model 2	52	SIR vs MOD	1.886 (0.681–5.225)	0.222
Model 2	65	MARD vs MOD	0.788 (0.322–1.928)	0.602
Model 2	65	SID vs MOD	0.756 (0.307–1.864)	0.543
Model 2	65	SIR vs MOD	0.751 (0.239–2.354)	0.623

These are exploratory marginal estimates. Because age distributions differed markedly across subtypes, estimates at 40 and 65 years may rely on limited common support and should not be used as primary evidence.

Supplementary Table 34 Diagnostics of the continuous age-by-subtype interaction models

Model	***n***	**Events**	**Convergence**	**Iterations**	**Pearson χ^2/df**	**Zero-event cells**	**Standard errors**	**Maximum VIF**
Model 1	448	117	Converged	7	0.840	No zero-event subtype cells	HC3 robust standard errors	—

Model 2	448	117	Converg ed	7	0.769	No zero-event subtype cells	HC3 standard errors	robust 5.61

Note. In the adjusted continuous-age chronic kidney disease model, the maximum VIF was 5.61; inflation was concentrated in centered age and interaction terms rather than the non-age covariates. HC3 robust standard errors were used.

Supplementary Table 35 Sensitivity analysis restricted to participants with measured albumin-to-creatinine ratio

Outcome	Model	*n*	Events	Comparison	PR (95%CI)	*P* value
CKD-PC projected 5-year CKD risk ≥ 5% (measured positive ACR only)	Model 1	426	113	MOD (reference)	1.00 (Ref.)	—
CKD-PC projected 5-year CKD risk ≥ 5% (measured positive ACR only)	Model 1	426	113	MARD vs MOD	9.215 (4.394–19.326)	< 0.001
CKD-PC projected 5-year CKD risk ≥ 5% (measured positive ACR only)	Model 1	426	113	SID vs MOD	5.916 (2.731–12.815)	< 0.001
CKD-PC projected 5-year CKD risk ≥ 5% (measured positive ACR only)	Model 1	426	113	SIR vs MOD	2.385 (0.929–6.126)	0.071
CKD-PC projected 5-year CKD risk ≥ 5% (measured positive ACR only)	Model 2	426	113	MOD (reference)	1.00 (Ref.)	—
CKD-PC projected 5-year CKD risk ≥ 5% (measured positive ACR only)	Model 2	426	113	MARD vs MOD	8.628 (4.065–18.310)	< 0.001
CKD-PC projected 5-year CKD risk ≥ 5% (measured positive ACR only)	Model 2	426	113	SID vs MOD	5.987 (2.781–12.890)	< 0.001
CKD-PC projected 5-year CKD risk ≥ 5% (measured positive ACR only)	Model 2	426	113	SIR vs MOD	2.114 (0.795–5.621)	0.134

This sensitivity analysis excluded participants who required the chronic kidney

disease prognosis consortium patch approach and included only participants with positive quality-controlled measured ACR. The adjusted model used participant-ID-aligned waist circumference, LDL-C, triglycerides, AST, and platelet count.

Supplementary Table 36 Event rate and source contribution for projected 5-year chronic kidney disease risk across metabolic subtypes

Analysis chain	Subtype	*n*	Events	Event rate, %	Source contribution, %
Primary analysis	MARD	133	65	48.9	55.6
Primary analysis	MOD	133	7	5.3	6.0
Primary analysis	SID	107	36	33.6	30.8
Primary analysis	SIR	75	9	12.0	7.7
Measured-ACR-only analysis	MARD	127	64	50.4	56.6
Measured-ACR-only analysis	MOD	128	7	5.5	6.2
Measured-ACR-only analysis	SID	102	33	32.4	29.2
Measured-ACR-only analysis	SIR	69	9	13.0	8.0

Event rate = number of participants with chronic kidney disease prognosis consortium projected 5-year chronic kidney disease risk ≥5% divided by subtype-specific analytic n. Source contribution = events in a subtype divided by total events across all subtypes. MARD: Mild age-related dysmetabolism; MOD: Mild obesity-related dysmetabolism; SID: Severe insulin deficiency; SIR: Severe insulin resistance.

Supplementary Table 37 Descriptive age and fibrosis-4 index distributions by metabolic subtype, mean ± SD/ median (P25, P75)

Group	*n*	Age	Age	Age range	FIB-4	FIB-4
Overall	621	51.08 ± 10.14	52 (45, 58)	22–70	1.037 ± 0.490	0.971 (0.693, 1.289)
MOD	177	44.04 ± 7.84	45 (38, 50)	26–64	0.854 ± 0.419	0.770 (0.588, 1.011)
MARD	190	57.85 ± 6.82	57 (53, 64)	36–70	1.190 ± 0.466	1.111 (0.899, 1.407)
SID	159	55.42 ± 7.90	56 (50, 62)	26–70	1.228 ± 0.512	1.152 (0.956, 1.398)

SIR	95	43.39 ± 9.33	43 (36.5, 50)	22–64	0.751 ± 0.354	0.672 (0.468, 0.891)

MOD: Mild obesity-related dysmetabolism; MARD: Mild age-related dysmetabolism; SID: Severe insulin deficiency; SIR: Severe insulin resistance.

Supplementary Table 38 Event rates under standard and age-aware fibrosis-4 index thresholds by subtype and age stratum

Age stratum	Subtype	*n*	Standard threshold events	Standard threshold rate	Age-aware threshold events	Age-aware threshold rate	Fewer events
Full sample	MOD	177	17	9.6%	17	9.6%	0
Full sample	MARD	190	68	35.8%	51	26.8%	17
Full sample	SID	159	58	36.5%	46	28.9%	12
Full sample	SIR	95	9	9.5%	9	9.5%	0
< 52 years	MOD	147	11	7.5%	11	7.5%	0
< 52 years	MARD	35	1	2.9%	1	2.9%	0
< 52 years	SID	54	8	14.8%	8	14.8%	0
< 52 years	SIR	74	3	4.1%	3	4.1%	0
≥ 52 years	MOD	30	6	20.0%	6	20.0%	0
≥ 52 years	MARD	155	67	43.2%	50	32.3%	17
≥ 52 years	SID	105	50	47.6%	38	36.2%	12
≥ 52 years	SIR	21	6	28.6%	6	28.6%	0

The standard threshold was FIB-4 index ≥ 1.30. The age-aware threshold was FIB-4 index ≥ 1.30 for participants aged < 65 years and ≥ 2.00 for participants aged ≥ 65 years. Fewer events indicate participants reclassified from event to non-event by the age-aware threshold.

Supplementary Table 39 Full-sample poisson regression under standard and age-

aware fibrosis-4 index thresholds

Threshold definition	Model	Subtype	Model N	Model events	Subtype n	Subtype events	Event rate	PR	95%CI	*P* value
Standard threshold	Model 1	MOD	621	152	177	17	9.6%	Ref	—	—
Standard threshold	Model 1	MARD	621	152	190	68	35.8%	3.73	2.28–6.09	< 0.001
Standard threshold	Model 1	SID	621	152	159	58	36.5%	3.80	2.31–6.24	< 0.001
Standard threshold	Model 1	SIR	621	152	95	9	9.5%	0.99	0.46–2.13	0.972
Standard threshold	Model 2	MOD	585	150	165	16	9.7%	Ref	—	—
Standard threshold	Model 2	MARD	585	150	177	67	37.9%	3.00	1.76–5.13	< 0.001
Standard threshold	Model 2	SID	585	150	149	58	38.9%	3.50	2.10–5.85	< 0.001
Standard threshold	Model 2	SIR	585	150	94	9	9.6%	0.91	0.41–2.03	0.821
Age-aware threshold	Model 1	MOD	621	123	177	17	9.6%	Ref	—	—
Age-aware threshold	Model 1	MARD	621	123	190	51	26.8%	2.79	1.68–4.65	< 0.001
Age-aware threshold	Model 1	SID	621	123	159	46	28.9%	3.01	1.80–5.03	< 0.001
Age-aware threshold	Model 1	SIR	621	123	95	9	9.5%	0.99	0.46–2.13	0.972

Age-aware threshold	Model 2	MOD	585	121	165	16	9.7%	Ref	—	—
Age-aware threshold	Model 2	MARD	585	121	177	50	28.2%	2.36	1.33–4.19	0.003
Age-aware threshold	Model 2	SID	585	121	149	46	30.9%	3.10	1.80–5.32	< 0.001
Age-aware threshold	Model 2	SIR	585	121	94	9	9.6%	0.82	0.36–1.85	0.626

Values are prevalence ratios with 95%CI. MOD was the reference group. Model 1 was unadjusted. Model 2 adjusted for waist circumference, sex, systolic blood pressure, estimated glomerular filtration rate, triglycerides, and low-density lipoprotein cholesterol. Robust Poisson regression with HC3 standard errors was used.

Supplementary Table 40 Restricted sensitivity analysis of fibrosis-4 index ≥ 1.30 in participants aged 35-64 years

Subtype	Model	*n*	PR	95% CI	*P* value
MOD	Model 1	521	Ref	—	—
MARD	Model 1	521	2.695	1.585–4.580	< 0.001
SID	Model 1	521	3.134	1.856–5.292	< 0.001
SIR	Model 1	521	1.104	0.511–2.385	0.802
MOD	Model 2	485	Ref	—	—
MARD	Model 2	485	2.291	1.283–4.092	0.005
SID	Model 2	485	3.212	1.869–5.521	< 0.001
SIR	Model 2	485	0.914	0.399–2.091	0.831

Values are prevalence ratios with 95% confidence intervals. MOD was the reference group. Model 1 was unadjusted. Model 2 adjusted for waist circumference, sex, systolic blood pressure, estimated glomerular filtration rate, triglycerides, and low-density lipoprotein cholesterol. The analysis was restricted to participants aged 35–

64 years.

Supplementary Table 41 Median-age stratified Poisson regression for fibrosis-4 index ≥ 1.30

Age stratum	Model	Subtype	Model *n*	Model events	Event/*n*	Event rate	PR	95%CI	*P* value
< 52 years	Model 1	MOD	310	23	11/147	7.5%	Ref	—	—
< 52 years	Model 1	MARD	310	23	1/35	2.9%	0.38	0.05–2.86	0.349
< 52 years	Model 1	SID	310	23	8/54	14.8%	1.98	0.84–4.66	0.118
< 52 years	Model 1	SIR	310	23	3/74	4.1%	0.54	0.16–1.88	0.335
< 52 years	Model 2	MOD	276	21	10/135	7.4%	Ref	—	—
< 52 years	Model 2	MARD	276	21	0/23	0.0%	NE	—	NE
< 52 years	Model 2	SID	276	21	8/45	17.8%	2.25	0.93–5.44	0.073
< 52 years	Model 2	SIR	276	21	3/73	4.1%	0.60	0.12–3.07	0.538
≥ 52 years	Model 1	MOD	311	129	6/30	20.0%	Ref	—	—
≥ 52 years	Model 1	MARD	311	129	67/155	43.2%	2.16	1.03–4.52	0.041
≥ 52 years	Model 1	SID	311	129	50/105	47.6%	2.38	1.13–5.01	0.022
≥ 52 years	Model 1	SIR	311	129	6/21	28.6%	1.43	0.53–3.82	0.478
≥ 52 years	Model 2	MOD	309	129	6/30	20.0%	Ref	—	—
≥ 52 years	Model 2	MARD	309	129	67/154	43.5%	2.00	0.95–4.20	0.067
≥ 52 years	Model 2	SID	309	129	50/104	48.1%	2.26	1.07–4.75	0.032
≥ 52 years	Model 2	SIR	309	129	6/21	28.6%	1.41	0.52–3.83	0.501

Values are prevalence ratios with 95%CI. MOD was the reference group within each age stratum and model. The age cut point was the full-sample median of 52 years. Model 1 was unadjusted. Model 2 adjusted for waist circumference, sex, systolic blood pressure, estimated glomerular filtration rate, triglycerides, and low-density lipoprotein cholesterol. NE indicates not estimable because of zero events.

Supplementary Table 42 Formal continuous-age-by-subtype interaction tests in fibrosis-4 index analyses

Outcome definition	Model	Age term	Interaction test	χ^2	df	*P* value	Interpretation
Standard threshold	Model 1	Continuous age centered at 52 years	Subtype × age	4.946	3	0.176	No formal interaction evidence
Standard threshold	Model 2	Continuous age centered at 52 years	Subtype × age	5.608	3	0.132	No formal interaction evidence
Age-aware threshold	Model 1	Continuous age centered at 52 years	Subtype × age	10.874	3	0.012	Evidence of interaction
Age-aware threshold	Model 2	Continuous age centered at 52 years	Subtype × age	12.569	3	0.006	Evidence of interaction

This table reports the global formal interaction tests for continuous age and metabolic subtype. Continuous age was centered at 52 years. The standard threshold was FIB-4 index ≥ 1.30; the age-aware threshold was FIB-4 index ≥ 1.30 for participants aged < 65 years and ≥ 2.00 for participants aged ≥ 65 years. Model 2 adjusted for waist circumference, sex, systolic blood pressure, estimated glomerular filtration rate, triglycerides, and low-density lipoprotein cholesterol.

Supplementary Table 43 Individual continuous-age-by-subtype interaction terms in adjusted fibrosis-4 index models

Outcome definition	Interaction term	β per year	PR per year	95%CI	*P* value
Standard threshold	MARD × age	-0.00481	0.995	0.926–1.069	0.895

Standard threshold	SID × age	-0.03446	0.966	0.899–1.038	0.347
Standard threshold	SIR × age	0.04073	1.042	0.952–1.140	0.376
Age-aware threshold	MARD × age	-0.05556	0.946	0.879–1.018	0.139
Age-aware threshold	SID × age	-0.06993	0.932	0.868–1.002	0.057
Age-aware threshold	SIR × age	0.04025	1.041	0.950–1.140	0.386

Rows show the subtype-specific interaction terms relative to the MOD reference slope from adjusted continuous-age interaction models. Continuous age was centered at 52 years. The borderline SID × age term under the age-aware threshold should be interpreted together with the global test and the marginal estimates, rather than as a standalone subgroup conclusion.

Supplementary Table 44 Median-age-stratum-by-subtype interaction tests in fibrosis-4 index analyses

Outcome definition	**Model**	**Age term**	**Interaction test**	χ^2	**df**	***P* value**	**Interpretation**
Standard threshold	Model 1	< 52 *vs* ≥ 52 years	Subtype × age stratum	3.623	3	0.305	No strong categorical interaction evidence
Standard threshold	Model 2	< 52 *vs* ≥ 52 years	Subtype × age stratum	NE	3	NE	Not interpreted because a younger-stratum subtype cell had zero events
Age-aware threshold	Model 1	< 52 *vs* ≥ 52 years	Subtype × age stratum	3.774	3	0.287	No strong categorical interaction evidence

Age-aware threshold	Model 2	< 52 vs ≥ 52 years	Subtype × age stratum	NE	3	NE	Not interpreted because a younger-stratum subtype cell had zero events

Categorical age-stratum interaction tests are distinct from the continuous-age tests in Supplementary Table 40. Adjusted categorical tests were not interpreted because the younger MARD cell contained zero events after complete-case restriction, producing separation-sensitive estimates. NE indicates not estimable.

Supplementary Table 45 Subtype-specific age slopes in continuous-age Poisson models

Outcome definition	Model	Subtype	β per year	PR per year	95%CI	*P* value
Standard threshold	Model 1	MOD	0.100	1.106	1.035–1.182	0.003
Standard threshold	Model 1	MARD	0.106	1.112	1.080–1.144	< 0.001
Standard threshold	Model 1	SID	0.075	1.078	1.047–1.110	< 0.001
Standard threshold	Model 1	SIR	0.144	1.155	1.089–1.226	< 0.001
Standard threshold	Model 2	MOD	0.105	1.111	1.040–1.186	0.002
Standard threshold	Model 2	MARD	0.100	1.105	1.072–1.140	< 0.001
Standard threshold	Model 2	SID	0.070	1.073	1.041–1.106	< 0.001
Standard threshold	Model 2	SIR	0.146	1.157	1.089–1.228	< 0.001
Age-aware threshold	Model 1	MOD	0.100	1.106	1.035–1.182	0.003
Age-aware threshold	Model 1	MARD	0.058	1.060	1.028–1.094	< 0.001
Age-aware threshold	Model 1	SID	0.040	1.040	1.010–1.072	0.008
Age-aware threshold	Model 1	SIR	0.144	1.155	1.089–1.226	< 0.001
Age-aware threshold	Model 2	MOD	0.106	1.112	1.041–1.188	0.002
Age-aware threshold	Model 2	MARD	0.051	1.052	1.016–1.089	0.004
Age-aware threshold	Model 2	SID	0.036	1.037	1.005–1.070	0.024

Age-aware threshold	Model 2	SIR	0.146	1.158	1.089–1.231	< 0.001

The PR per year represents the within-subtype relative change in the probability of meeting the Fibrosis-4 index event definition for each 1-year increase in age. Values are derived from models containing subtype, continuous age, and subtype-by-age interaction terms.

Supplementary Table 46 Adjusted marginal subtype prevalence ratios at representative ages

Outcome definition	Age point	Comparison	PR	95%CI	*P* value	Extrapolation flag
Standard threshold	40 years	MARD vs MOD	1.00	0.34–2.99	0.994	No
Standard threshold	40 years	SID vs MOD	2.36	0.85–6.51	0.098	No
Standard threshold	40 years	SIR vs MOD	0.52	0.14–1.93	0.333	No
Standard threshold	52 years	MARD vs MOD	0.95	0.50–1.80	0.870	No
Standard threshold	52 years	SID vs MOD	1.56	0.88–2.76	0.128	No
Standard threshold	52 years	SIR vs MOD	0.86	0.37–1.96	0.711	No
Standard threshold	65 years	MARD vs MOD	0.89	0.29–2.71	0.838	Yes
Standard threshold	65 years	SID vs MOD	1.00	0.33–3.03	0.994	Yes
Standard threshold	65 years	SIR vs MOD	1.45	0.33–6.44	0.623	Yes
Age-aware threshold	40 years	MARD vs MOD	2.20	0.74–6.50	0.154	No
Age-aware threshold	40 years	SID vs MOD	3.82	1.42–10.30	0.008	No
Age-aware threshold	40 years	SIR vs MOD	0.46	0.12–1.76	0.256	No
Age-aware threshold	52 years	MARD vs MOD	1.13	0.60–2.13	0.709	No
Age-aware threshold	52 years	SID vs MOD	1.65	0.93–2.92	0.085	No
Age-aware threshold	52 years	SIR vs MOD	0.75	0.32–1.76	0.504	No
Age-aware threshold	65 years	MARD vs MOD	0.55	0.17–1.73	0.305	Yes
Age-aware threshold	65 years	SID vs MOD	0.67	0.21–2.08	0.484	Yes

Age-aware threshold	65 years	SIR vs MOD	1.26	0.28–5.71	0.766	Yes

Values are adjusted marginal prevalence ratios with 95% confidence intervals from continuous-age interaction models. Age points were 40 years, 52 years, and 65 years. The 65-year estimate is a mild extrapolation for MOD and SIR because the maximum observed ages for these subtypes were 64 years.