Supplementary Table 1. Baseline characteristics of the randomly selected subcohort (Japan, n = 658), by fat-distribution cluster

	Cluster 1 Hepatic steatosis (n = 118)	Cluster 2 Pancreatic steatosis (n = 62)	Cluster 3 Trunk myosteatosis (n = 224)	Cluster 4 Steatopenia (n = 254)	P-value
Age (years)	50 (43-57)	61 (55-64)	56 (50-60)	45 (40-53)	< 0.001
Male, n (%)	92 (78.0)	49 (79.0)	160 (71.4)	183 (72.0)	0.42
Body mass index (kg/m^2)	26.6 (24.7-29.0)	26.1 (24.3-27.6)	23.5 (22.1-25.4)	22.3 (20.6-23.9)	< 0.001
Height (cm)	167.0 (160.9-171.0)	165.5 (159.5-170.4)	166.3 (160.4-170.9)	167.4 (161.2-172.7)	0.17
Weight (kg)	75.1 (67.6-83.9)	71.7 (64.9-77.9)	65.1 (56.8-72.5)	63.2 (54.1-70.0)	<0.001
Waist circumference (cm)	92.4 (87.0-98.5)	92.5 (88.5-96.5)	85.7 (82.0-90.5)	80.6 (75.9-85.0)	<0.001
Liver fat (HU)	51.6 (43.3-56.8)	61.4 (55.0-66.3)	65.6 (62.7-68.4)	67.2 (64.3-70.9)	< 0.001
Pancreas fat (HU)	46.3 (41.5-49.5)	26.8 (18.5-33.0)	47.2 (43.2-50.1)	52.1 (49.7-54.6)	< 0.001
Muscle fat (HU)	40.7 (37.4-43.3)	34.1 (30.2-37.4)	36.8 (33.7-39.5)	45.3 (42.8-47.8)	< 0.001
Visceral fat (cm^2)	171.0 (123.5-217.6)	167.1 (118.9-215.0)	96.8 (53.4-140.1)	42.7 (16.2-87.8)	< 0.001
Muscle area (cm^2)	160.7 (139.0-173.2)	148.3 (123.3-161.5)	138.4 (105.5-155.9)	140.8 (108.9-161.1)	< 0.001
Fasting plasma glucose (mg/dL)	93.0 (87.0-101.0)	94.5 (90.0-98.0)	91.0 (86.5-96.0)	88.0 (81.0-93.0)	< 0.001
Fasting plasma glucose (mmol/L)	5.2 (4.8-5.6)	5.3 (5.0-5.4)	5.1 (4.8-5.3)	4.9 (4.5-5.2)	< 0.001
HbA1c (%)	5.4 (5.2-5.6)	5.4 (5.3-5.6)	5.3 (5.1-5.5)	5.2 (5.0-5.4)	< 0.001
HbA1c (mmol/mol)	36 (33-38)	36 (34-38)	34 (32-37)	33 (31-36)	< 0.001
Triglycerides (mg/dL)	134.0 (98.0-189.0)	121.5 (86.0-172.0)	88.0 (66.0-121.5)	79.5 (56.0-115.0)	< 0.001
HDL cholesterol (mg/dL)	51.0 (44.0-59.0)	51.0 (45.0-62.0)	57.0 (48.5-68.0)	59.0 (48.0-69.0)	< 0.001
LDL cholesterol (mg/dL)	125.5 (109.0-144.0)	129.0 (109.0-153.0)	125.0 (105.0-142.0)	115.0 (96.0-135.0)	< 0.001
Systolic blood pressure (mmHg)	124.0 (118.0-132.0)	120.0 (114.0-132.0)	120.0 (110.0-130.0)	112.0 (104.0-124.0)	< 0.001
Diastolic blood pressure (mmHg)	80.0 (74.0-86.0)	79.0 (70.0-84.0)	78.0 (70.0-84.0)	72.0 (68.0-80.0)	< 0.001
Current smoker, n (%)	36 (30.5)	11 (17.7)	59 (26.3)	90 (35.4)	0.023
Alcohol intake, n (%)	35 (29.7)	16 (25.8)	89 (39.7)	86 (33.9)	0.11
Physical activity, n (%)	15 (12.7)	16 (25.8)	51 (22.9)	56 (22.0)	0.077

Family history of diabetes, n (%)	23 (19.5)	16 (25.8)	39 (17.4)	56 (22.0)	0.40
Antihypertensive drug, n (%)	28 (23.7)	16 (25.8)	42 (18.8)	13 (5.1)	< 0.001
Lipid-lowering drug, n (%)	26 (22.0)	9 (14.5)	30 (13.4)	11 (4.3)	< 0.001

Continuous data are expressed as medians and interquartile ranges. Fisher's exact test was used for categorical data. The Kruskal-Wallis test was used for continuous data. We regarded participants who met all of the following criteria as "physically active": length of each physical-exercise session ≥ 30 minutes, frequency of physical exercise ≥ 2 times a week, and duration of physical exercise ≥ 1 year. Missing data: waist circumference (n = 3), LDL-cholesterol (n = 2), physical activity (n = 1)

HU, Hounsfield unit

Supplementary Table 2. Baseline characteristics of the cohort in Germany (n = 319), by fat-distribution cluster

	Cluster 1 Hepatic steatosis (n = 39)	Cluster 2 Pancreatic steatosis (n = 21)	Cluster 3 Trunk myosteatosis (n = 103)	Cluster 4 Steatopenia (n = 156)	P-value
Age (years)	55 (40-62)	56 (49-64)	58 (43-65)	36 (29-44)	< 0.001
Male, n (%)	8 (20.5)	8 (38.1)	29 (28.2)	42 (26.9)	0.53
Body mass index (kg/m^2)	32.4 (29.7-35.2)	34.0 (29.7-39.7)	29.4 (25.9-32.7)	23.1 (21.1-26.5)	< 0.001
Height (cm)	164.8 (160.0-172.0)	170.0 (164.0-176.0)	168.0 (164.0-174.8)	168.0 (164.0-175.5)	0.16
Weight (kg)	88.9 (78.7-109.1)	105.5 (85.8-113.5)	82.4 (72.6-94.9)	67.5 (60.5-78.3)	<0.001
Waist circumference (cm)	99.0 (93.5-114.0)	113.5 (98.5-118.0)	96.0 (87.5-104.0)	78.0 (73.0-86.0)	<0.001
Liver fat (%)	13.8 (10.9-19.2)	6.1 (3.2-7.2)	3.0 (1.6-5.2)	0.9 (0.6-2.0)	< 0.001
Pancreas fat (%)	6.4 (3.9-8.7)	17.4 (15.0-20.3)	4.3 (3.2-7.2)	2.2 (1.5-3.1)	< 0.001
Muscle fat (%)	8.1 (6.4-9.3)	9.0 (8.3-9.7)	8.4 (7.6-9.3)	5.9 (5.1-6.8)	< 0.001
Visceral fat (L)	4.6 (4.2-5.6)	6.5 (4.8-7.3)	3.7 (2.9-4.8)	1.6 (1.0-2.1)	< 0.001
Muscle area (cm^2)	140.2 (128.4-168.1)	145.5 (131.6-206.7)	138.5 (122.8-161.0)	129.8 (121.8-148.8)	0.015
Fasting plasma glucose (mg/dL)	93.6 (91.8-100.8)	95.4 (91.8-100.8)	95.4 (90.0-100.8)	86.4 (82.8-91.8)	< 0.001
Fasting plasma glucose (mmol/L)	5.2 (5.1-5.6)	5.3 (5.1-5.6)	5.3 (5.0-5.6)	4.8 (4.6-5.1)	< 0.001
HbA1c (%)	5.7 (5.3-6.0)	5.6 (5.3-6.0)	5.7 (5.4-5.9)	5.4 (5.2-5.6)	< 0.001
HbA1c (mmol/mol)	39 (34-42)	38 (34-42)	39 (36-41)	36 (33-38)	< 0.001
Triglycerides (mg/dL)	117.0 (92.0-161.0)	123.0 (96.0-155.0)	98.0 (77.0-136.0)	72.0 (56.0-97.5)	< 0.001
HDL cholesterol (mg/dL)	48.0 (41.0-58.0)	53.0 (47.0-58.0)	54.0 (45.0-67.0)	55.5 (48.0-69.5)	0.002
LDL cholesterol (mg/dL)	124.0 (105.0-158.0)	145.0 (120.0-163.0)	125.0 (108.0-157.0)	104.5 (90.0-125.0)	< 0.001
Systolic blood pressure (mmHg)	136.0 (125.0-151.0)	141.0 (135.0-145.0)	134.0 (124.0-144.0)	124.0 (115.0-134.0)	< 0.001
Diastolic blood pressure (mmHg)	89.0 (82.0-101.0)	90.0 (86.0-97.0)	86.0 (80.0-95.0)	82.0 (74.0-90.0)	< 0.001
Current smoker, n (%)	4 (10.5)	0 (0.0)	5 (5.2)	13 (8.7)	0.39
Alcohol intake, n (%)	3 (7.9)	4 (19.0)	4 (4.1)	3 (2.0)	0.007
Habitual physical activity score*	8.2 (7.0-9.0)	7.8 (6.9-8.4)	8.5 (7.1-9.4)	8.1 (7.3-9.0)	0.25

Family history of diabetes, n (%)	25 (64.1)	14 (66.7)	62 (60.2)	79 (50.6)	0.21
Antihypertensive drug, n (%)	2 (5.1)	2 (9.5)	7 (6.8)	7 (4.5)	0.59
Lipid-lowering drug, n (%)	0 (0.0)	0 (0.0)	3 (2.9)	4 (2.6)	0.85

Continuous data are expressed as medians and interquartile ranges. Fisher's exact test was used for categorical data. The Kruskal-Wallis test was used for continuous data.

Missing data: muscle volume (n = 9), systolic blood pressure (n = 1), diastolic blood pressure (n = 1), current smoker (n = 14), alcohol intake (n = 13), habitual physical activity score (n = 17)

* J A Baecke, J Burema, J E Frijters. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. Am J Clin Nutr. 1982;36(5):936-42.

Supplementary Table 3. Hazard ratios and 95% confidence intervals for pairwise comparisons: the association between membership in a fat-distribution cluster at baseline and the incidence of diabetes mellitus, from the case-cohort study in Japan (n = 754)

HRs (95% CIs), P-values	Cluster 1 vs Cluster 3*	Cluster 2 vs Cluster 3*	Cluster 1 vs Cluster 2*
Unadjusted analysis	2.33 (1.49-3.64), < 0.001	2.19 (1.24-3.87), 0.007	1.07 (0.61-1.87), 0.82
Age-and-sex-adjusted analysis	2.60 (1.61-4.21), < 0.001	1.89 (1.05-3.39), 0.033	1.38 (0.75-2.52), 0.30
Multivariable-adjusted model 1	2.06 (1.26-3.39), 0.004	1.73 (0.96-3.13), 0.067	1.19 (0.65-2.19), 0.58
Multivariable-adjusted model 2	1.83 (1.08-3.10), 0.024	1.51 (0.80-2.83), 0.20	1.22 (0.66-2.25), 0.53
Multivariable-adjusted model 3	1.96 (1.11-3.44), 0.020	1.52 (0.80-2.90), 0.20	1.28 (0.67-2.46), 0.45

*The reference cluster for each comparison.

Cluster 1: Hepatic steatosis, Cluster 2: Pancreatic steatosis, Cluster 3: Trunk myosteatosis

Pairwise comparisons in addition to table 2 in the main manuscript are shown.

Weighted Cox regression analyses were conducted to estimate the hazard ratios, 95% confidence intervals, and P-values.

Model 1: Adjusted for age, sex, alcohol intake, current smoking, and muscle area

Model 2: Adjusted for age, sex, alcohol intake, current smoking, muscle area, and body mass index

Model 3: Adjusted for age, sex, alcohol intake, current smoking, muscle area, body mass index, systolic blood pressure, diastolic blood pressure, triglycerides, HDL-cholesterol, LDL-cholesterol, antihypertensive drugs, and lipid-lowering drugs

Supplementary Table 4. Pairwise interactions of fat compartments regarding type-2 diabetes risk (Japan, n = 754)

HR (95% CI), P-value	Visceral fat (per 1 SD)	Liver fat (per 1 SD)	Pancreas fat (per 1 SD)
Liver fat (per 1 SD)	Visceral fat: 1.76 (1.46-2.13), < 0.001 Liver fat: 1.53 (1.23-1.91), < 0.001 Interaction: 0.90 (0.78-1.04), 0.17		
Pancreas fat (per 1 SD)	Visceral fat: 1.98 (1.65-2.39), < 0.001 Pancreas fat: 1.48 (1.18-1.86), 0.001 Interaction: 0.79 (0.67-0.93), 0.004	Liver fat: 1.69 (1.48-1.92), < 0.001 Pancreas fat: 1.36 (1.16-1.59), < 0.001 Interaction: 0.88 (0.78-1.00), 0.055	
Muscle fat (per 1 SD)	Visceral fat: 1.99 (1.69-2.35), < 0.001 Muscle fat: 1.23 (1.02-1.48), 0.029 Interaction: 0.93 (0.82-1.06), 0.26	Liver fat: 1.68 (1.47-1.92), < 0.001 Muscle fat: 1.27 (1.07-1.50), 0.006 Interaction: 1.02 (0.90-1.17), 0.71	Pancreas fat: 1.48 (1.29-1.69), < 0.001 Muscle fat: 1.23 (1.03-1.47), 0.020 Interaction: 0.77 (0.66-0.90), 0.001

Weighted Cox regression analyses were conducted to estimate the hazard ratios, 95% confidence intervals, and P-values for the association of fat deposits with incident type-2 diabetes.

Visceral fat area, liver attenuation, pancreas attenuation, and muscle attenuation were used as fat variables.

Liver attenuation, pancreas attenuation, and muscle attenuation were "flipped" such that higher value would correspond to more fat.

Each fat variable was standardized (mean = 0, SD = 1) and analyzed as a continuous variable.

Mean (1 SD): 100.7 (70.3) cm^2 for visceral fat, 62.8 (9.3) HU for liver fat, 46.1 (10.5) HU for pancreas fat, and 40.2 (6.3) HU for muscle fat.

SD, standard deviation; HR, hazard ratio; CI, confidence interval; HU, Hounsfield unit

Supplementary Table 5. P-values for pairwise comparisons: glycemia, insulin sensitivity, and insulin secretion based on results of 75g oral glucose tolerance tests, across fat-distribution clusters in Germany (n = 319)

P-values	Cluster 1 vs Cluster 3	Cluster 2 vs Cluster 3	Cluster 1 vs Cluster 2
Glycemia	0.022	0.55	0.27
Insulin sensitivity	< 0.001	0.087	0.016
Insulin secretion	< 0.001	0.79	0.010
Sensitivity-adjusted insulin secretion	0.15	0.49	0.091

Cluster 1: Hepatic steatosis, Cluster 2: Pancreatic steatosis, Cluster 3: Trunk myosteatosis

Pairwise comparisons in addition to table 3 in the main manuscript are shown.

P-values were calculated from Wilcoxon's rank-sum tests.

Supplementary Table 6. Pairwise interactions of fat compartments regarding glycemia (Germany, n = 319)

β (95% CI), P-value	Visceral fat (per 1 SD)	Liver fat (per 1 SD)	Pancreas fat (per 1 SD)
Liver fat (per 1 SD)	Visceral fat: 83.3 (58.6-108.0), < 0.001 Liver fat: 54.0 (25.7-82.3), < 0.001 Interaction: -23.6 (-40.0- -7.16), 0.005		
Pancreas fat (per 1 SD)	Visceral fat: 100.1 (76.7-123.5), < 0.001 Pancreas fat: 31.7 (4.53-58.8), 0.022 Interaction: -34.7 (-53.6- -15.7), < 0.001	Liver fat: 77.5 (54.8-100.1), < 0.001 Pancreas fat: 44.0 (20.7-67.3), < 0.001 Interaction: -23.4 (-41.0- -5.92), 0.009	
Muscle fat (per 1 SD)	Visceral fat: 95.0 (71.8-118.1), < 0.001 Muscle fat: 23.6 (0.93-46.3), 0.041 Interaction: -30.6 (-51.8- -9.35), 0.005	Liver fat: 70.5 (49.3-91.6), < 0.001 Muscle fat: 51.0 (30.0-72.0), < 0.001 Interaction: -9.83 (-30.0-10.4), 0.34	Pancreas fat: 65.4 (35.1-95.7), < 0.001 Muscle fat: 44.7 (20.5-68.9), < 0.001 Interaction: -36.4 (-58.7- -14.1), 0.001

Glycemia was evaluated by AUC Glucose$_{0-120}$ from a 75 g oral glucose tolerance test, and the unit is mmol*min/ml.

Multiple linear regression models were used to estimate β, 95% CI, and P-values for the associations of fat deposits with glycemia.

Each fat variable was standardized (mean = 0, SD = 1) and analyzed as a continuous variable.

Mean (1 SD): 3.1 (2.1) L for visceral fat, 4.3 (5.2) % for liver fat, 5.0 (4.8) % for pancreas fat, 7.1 (1.7) % for muscle fat, and 894.9 (207.1)

mmol*min/ml for the AUC Glucose$_{0-120}$.

SD, standard deviation; CI, confidence interval; AUC, area under the curve

Supplementary Table 7. Regression coefficients (β) and 95% confidence intervals for the associations of fat deposits with insulin sensitivity, insulin secretion, and aerobic capacity (Germany, n = 319)

|	Insulin sensitivity	Insulin secretion	Adjusted insulin secretion	Aerobic capacity
	β (95% CI), P-value	β (95% CI), P-value	β (95% CI), P-value	β (95% CI), P-value
Visceral fat (per 1SD)	-1.29 (-1.47- -1.10), < 0.001	16.5 (9.72-23.2), < 0.001	-5.83 (-11.7-0.038), 0.052	-2.02 (-3.06- -0.98), < 0.001
Liver fat (per 1 SD)	-1.19 (-1.38- -1.00), < 0.001	21.9 (15.4-28.4), < 0.001	-0.25 (-6.08- 5.58), 0.93	-2.25 (-3.56- -0.95), 0.001
Pancreas fat (per 1 SD)	-0.74 (-0.95- -0.52), < 0.001	4.92 (-2.00-11.8), 0.16	-7.18 (-13.0- -1.37), 0.016	-1.02 (-2.03- -0.0017), 0.050
Muscle fat (per 1 SD)	-0.90 (-1.11- -0.70), < 0.001	9.41 (2.54-16.3), 0.007	-5.22 (-11.1-0.61), 0.079	-2.48 (-3.52- -1.44), < 0.001

Insulin sensitivity and insulin secretion were assessed by NEFA-ISI and AUC C-peptide$_{0-30}$/AUC Glucose$_{0-30}$, respectively. To estimate insulin secretion adjusted for insulin sensitivity, we calculated AUC C-peptide$_{0-30}$/AUC Glucose$_{0-30}$ residuals from regression of AUC C-peptide$_{0-30}$/AUC Glucose$_{0-30}$ on NEFA-ISI and its quadratic term. Aerobic capacity was quantified as VO2 max. Insulin sensitivity and secretion are in arbitrary units, and the unit of VO2 max is mL/kg/min. Linear regression models were used to estimate β, 95% CI, and P-values. Each fat variable was standardized (mean = 0, SD = 1) and analyzed as a continuous variable.

Mean (1 SD): 3.1 (2.1) L for visceral fat, 4.3 (5.2) % for liver fat, 5.0 (4.8) % for pancreas fat, 7.1 (1.7) % for muscle fat, 4.3 (2.1) for NRFA-ISI, 163.7 (62.8) for the AUC C-peptide$_{0-30}$/AUC Glucose$_{0-30}$, 0 (52.6) for the AUC C-peptide$_{0-30}$/AUC Glucose$_{0-30}$ residuals, and 20.1 (6.2) mL/kg/min for the VO2 max.

Missing data: insulin sensitivity (n = 3), sensitivity-adjusted insulin secretion (n = 7), aerobic capacity (n = 168)

SD, standard deviation; BMI, body mass index; NEFA-ISI, non-esterified fatty acids-based insulin sensitivity index; AUC, area under the curve;

VO2 max, maximal oxygen uptake
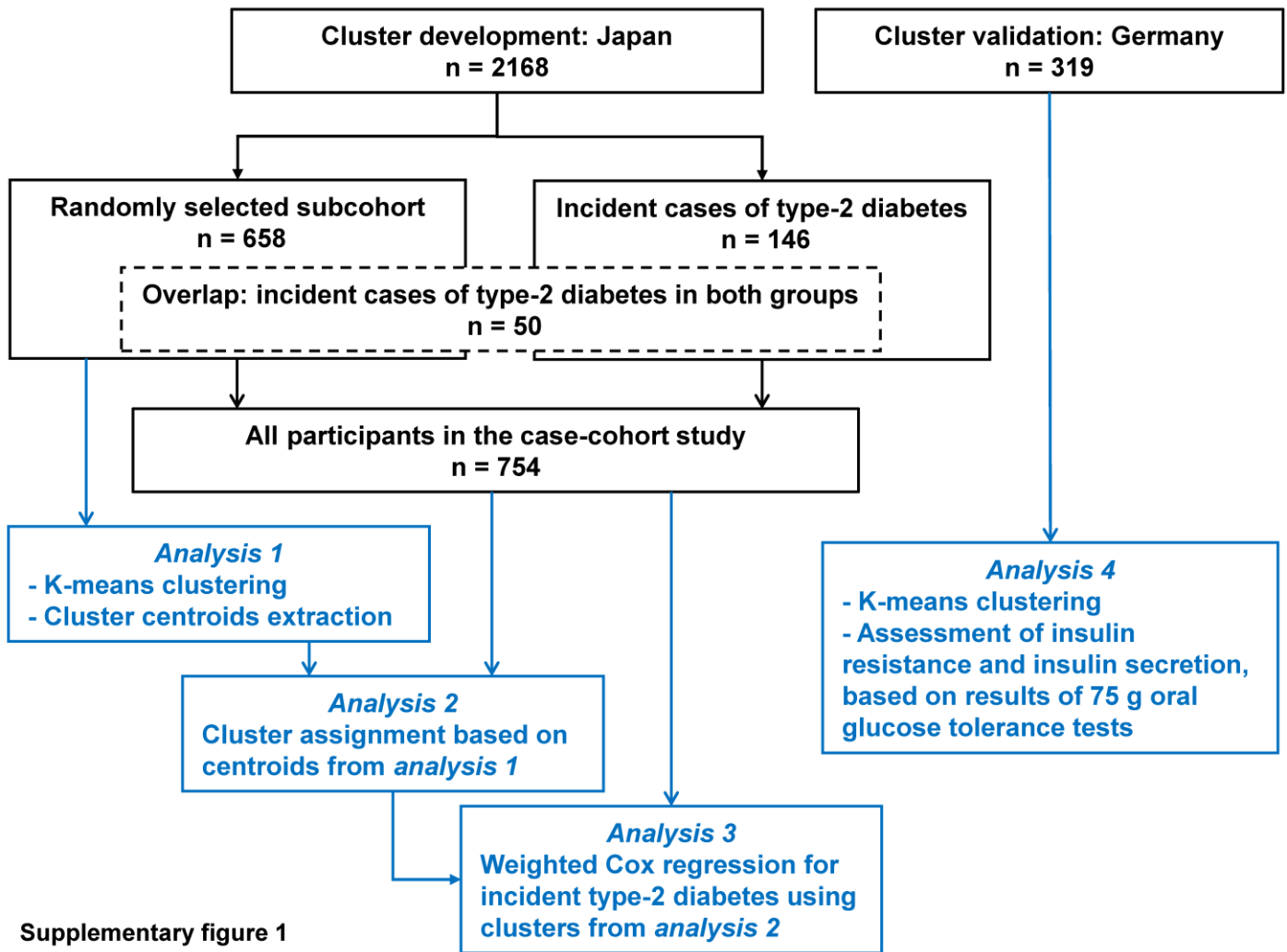
Supplementary Figure 1. Study flow diagram.

Incident cases of type-2 diabetes (n = 146) are within and outside of the randomly selected subcohort.

The case-cohort study in Japan comprised 754 participants of whom 658 were in the randomly selected subcohort. There were 146 incident cases of type-2 diabetes, including 50 "overlap" cases.

Analysis 1 was conducted using data from the randomly selected subcohort (Japan, n = 658).

Analysis 2 and analysis 3 were conducted using data from all participants in the case-cohort study (Japan, n = 754).

Analysis 4 was conducted using data from the cohort in Germany (n = 319)
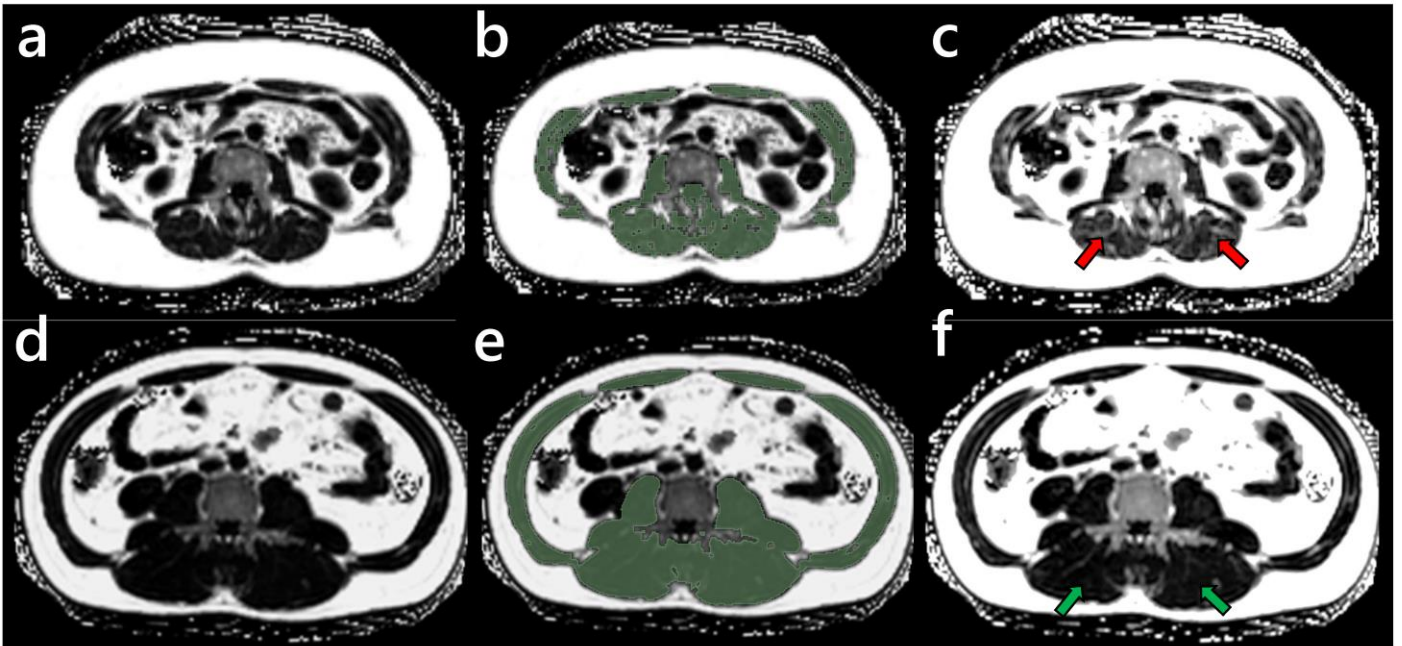
Supplementary figure 2

Supplementary Figure 2. Axial PDFF images at the level of the L3 lumbar segment.

PDFF images from a 50-year-old woman (a-c) and a 34-year-old man (d-f) show the muscle area in green (b

and e) and muscle fat (c and f) resulting in a mean of 11.7% in the woman and 4.8% in the man.

PDFF, proton density fat fraction
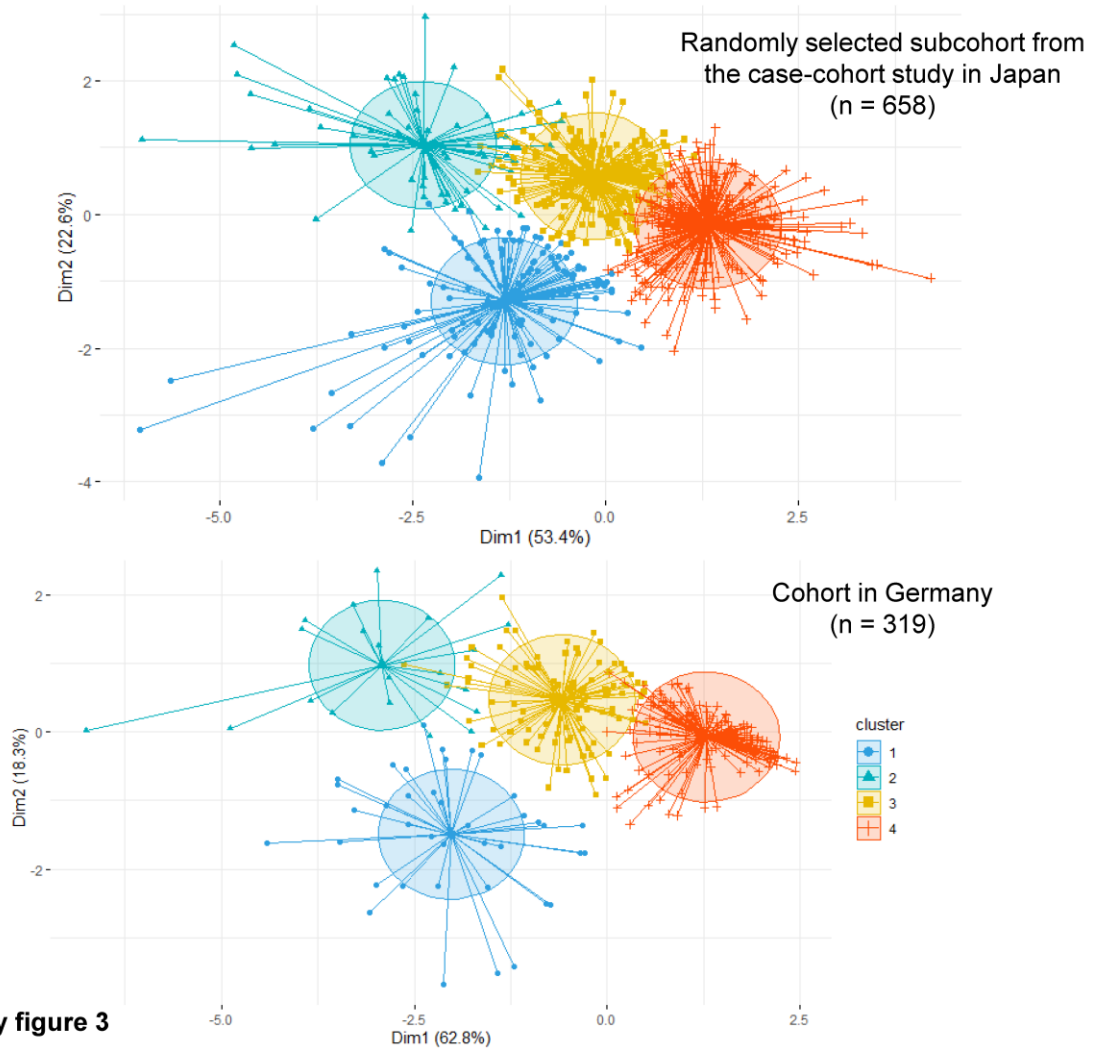
Supplementary figure 3

Supplementary Figure 3. Cluster plots

Four clusters based on k-means clustering are shown in each of the two cluster plots. Principal components analysis was conducted to project data onto the first two principal components. Data variation (%) of the first principal component (Dim1) and the second principal component (Dim2) are shown on the axes.

Cluster 1: Hepatic steatosis, Cluster 2: Pancreatic steatosis, Cluster 3: Trunk myosteatosis , Cluster 4: Steatopenia

	Cluster 1 Hepatic steatosis	Cluster 2 Pancreatic steatosis	Cluster 3 Trunk myosteatosis	Cluster 4 Steatopenia
Diabetes risk	⬆ ⬆	⬆ ⬆	⬆	Reference
Insulin sensitivity	⬇ ⬇ ⬇	⬇ ⬇	⬇	Reference
Insulin secretion adjusted for insulin sensitivity	➡	⬇	⬇	Reference

Supplementary figure 4

Supplementary Figure 4. Summary of metabolic characteristics in fat distribution clusters