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Subphenotype-Dependent Benefits of Bariatric Surgery for Individuals at Risk for Type 2 Diabetes

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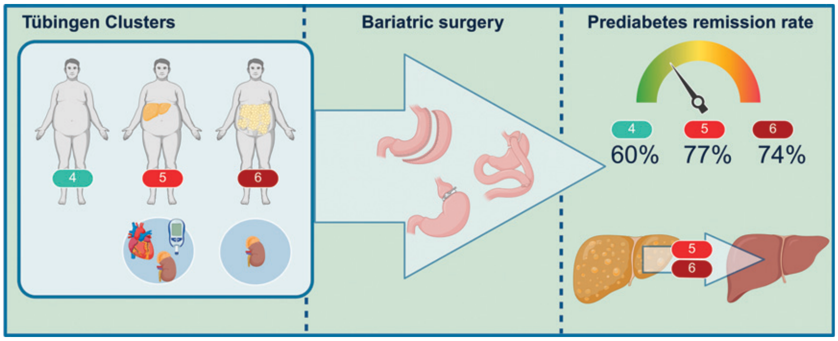

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Today, prediction of the metabolic benefit of bariatric surgery for the individual without type 2 diabetes (T2D) is difficult. This study aimed to identify differences in metabolic improvements in people from different risk strata without T2D.
- **What is the specific question we wanted to answer?**
  How do individuals from different risk strata for T2D (Tübingen Clusters) respond to bariatric surgery?
- **What did we find?**
  High-risk clusters had the highest prediabetes remission rates and strongest reduction of liver fat. Furthermore, the majority of high-risk clusters converted to low-risk clusters after bariatric surgery in contrast to outcomes of behavioral modification only.
- **What are the implications of our findings?**
  These findings might help with understanding mechanisms of prediabetes remission after bariatric surgery and identifying individuals who might specifically benefit from bariatric surgery.

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Leontine Sandforth,[1,2,3]
Violeta Raverdy,[4,5] Arvid Sandforth,[1,2,3]
Pierre Bauvin,[6] Estelle Chatelain,[7]
Helene Verkindt,[4,5]
Geltrude Mingrone,[8,9,10]
Caterina Guidone,[9] Ornella Verrastro,[8]
Karin Zhou,[1,2,3] Rami Archid,[11]
André Mihaljevic,[11] Robert Caiazzo,[4,5]
Gregory Baud,[4,5] Camille Marciniak,[4,5]
Mikael Chetboun,[4,5]
Marlene Ganslmeier,[1,2,3]
Vitória Minelli Faiao,[1,2,3]
Martin Heni,[12,13] Louise Fritsche,[2,3]
Anja Moller,[1,2,3]
Konstantinos Kantartzis,[1,2,3]
Andreas Peter,[2,3,12] Rainer Lehmann,[2,3,12]
Robert Wagner,[3,14,15]
Katsiaryna Prystupa,[3,14,15]
Andreas Fritsche,[1,2,3] Norbert Stefan,[1,2,3]
Hubert Preissl,[1,2,3,16]
Andreas L. Birkenfeld,[1,2,3,17]
Reiner Jumpertz von Schwartzenberg,[1,2,3,18,19]
and François Pattou[4,5]

OBJECTIVE

Bariatric surgery is an effective treatment option for individuals with obesity and type 2 diabetes (T2D). However, whether outcomes in subtypes of individuals at risk for T2D and/or comorbidities (Tübingen Clusters) differ, is unknown. Of these, cluster 5 (C5) and cluster 6 (C6) are high-risk clusters for developing T2D and/or comorbidities, while cluster 4 (C4) is a low-risk cluster. We investigated bariatric surgery outcomes, hypothesizing that high-risk clusters benefit most due to great potential for metabolic improvement.

RESEARCH DESIGN AND METHODS

We allocated participants without T2D but at risk for T2D, defined by elevated BMI, to the Tübingen Clusters. Participants had normal glucose regulation or prediabetes according to American Diabetes Association criteria. Two cohorts underwent bariatric surgery: a discovery (Lille, France) and a replication cohort (Rome, Italy). A control cohort (Tübingen, Germany) received behavioral modification counseling. Main outcomes included alteration of glucose regulation parameters and prediabetes remission.

RESULTS

In the discovery cohort, 15.0% of participants (*n* = 121) were allocated to C4, 22.3% (*n* = 180) to C5, and 62.4% (*n* = 503) to C6. Relative body weight loss was similar among all clusters; however, reduction of insulin resistance and improvement of β-cell function were strongest in C5. Prediabetes remission rate was lowest in low-risk C4 and highest in high-risk C5. Individuals from high-risk clusters changed to low-risk clusters in both bariatric surgery cohorts but not in the control cohort.

CONCLUSIONS

Participants in C5 had the highest benefit from bariatric surgery in terms of improvement in insulin resistance, β-cell function, and prediabetes remission. This novel classification might help identify individuals who will benefit specifically from bariatric surgery.

[1]Internal Medicine IV, Endocrinology, Diabetology and Nephrology, University Hospital of Tübingen, Tübingen, Germany
[2]Institute for Diabetes Research and Metabolic Diseases (IDM), Helmholtz Center Munich, University of Tübingen, Tübingen, Germany
[3]German Center for Diabetes Research (DZD), Neuherberg, Germany
[4]INSERM, CHU Lille, Institut Pasteur de Lille, UMR 1190 Translational Research for Diabetes, European Genomic Institute for Diabetes, University Lille, Lille, France
[5]Integrated Center for Obesity, General and Endocrine Surgery, CHU Lille, Lille, France
[6]INSERM, CHU Lille, Institut Pasteur de Lille, U1190-EGID, University Lille, Lille, France
[7]CNRS, INSERM, CHU Lille, Institut Pasteur de Lille, US 41-UAR 2014-PLBS, University Lille, Lille, France
[8]Department of Internal Medicine, Catholic University of the Sacred Heart, Rome, Italy
[9]Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[10]Division of Diabetes and Nutritional Sciences, School of Cardiovascular and Metabolic Medicine & Sciences, King's College London, London, U.K.
[11]Department of General, Visceral, and Transplant Surgery, University Hospital of Tübingen, Tübingen, Germany
[12]Institute for Clinical Chemistry and Pathobiochemistry, Department for Diagnostic Laboratory Medicine, University Hospital of Tübingen, Tübingen, Germany

Worldwide, 2.5 billion adults are affected by overweight and obesity (1). Many of these individuals develop type 2 diabetes (T2D), which is among the leading causes of death globally (2). Most individuals have already established T2D-associated comorbidities, such as nephropathy or macrovascular disease, at the time of diagnosis (3). Therefore, it is of utmost importance to improve T2D prevention and treat individuals earlier in the course of metabolic disease, specifically in prediabetes, since lifetime T2D risk in people aged >35 years with prediabetes is >70% (4). Bariatric surgery is a well-established therapy to decelerate disease progression of obesity-associated sequelae, such as cardiovascular events, renal disease, or mortality, via body weight reduction. It has been shown to improve glycemic control in people with T2D and even promote T2D remission. A recent data-driven classification of individuals with T2D has defined five clusters that show different disease progression patterns and diverging risks of diabetes complications (5). Importantly, T2D clusters benefit from bariatric surgery to different extents and in differential manners (6). Participants from the severe insulin-resistant diabetes (SIRD) cluster benefited more from bariatric surgery in terms of both T2D remission and renal function compared with the remaining clusters.

However, complications such as nephropathy can occur even before the onset of T2D (3). Thus, it is important to further characterize and understand subphenotypes and treatment responses before T2D onset. In individuals at risk for T2D, defined by prediabetes, a history of gestational diabetes mellitus, familial risk for T2D, and/or elevated BMI, data-driven clusters differing in T2D risk and related complications have been identified. Clustering variables include anthropometrics, glucose and insulin measures from oral glucose tolerance tests (OGTTs), and fasting lipid levels (7). From these six clusters, cluster 4 (C4), cluster 5 (C5), and cluster 6 (C6) are linked with obesity, and cluster 3 (C3), C5, and C6 show a high risk for developing T2D and/or complications. C5 is characterized by high liver fat content and insulin resistance and high cardiovascular risk ("high liver fat content and insulin resistance-related cluster"). C6 shows a high nephropathy risk and high insulin secretion despite a relatively low risk to develop T2D ("nephropathy risk and high insulin secretion-related cluster"). C4, however, belongs to the low-risk clusters associated with severe obesity but with a low risk of developing T2D or related complications ("low risk obesity cluster"). An overview of these Tübingen Clusters is provided in Supplementary Fig. 1. Similar to individuals with T2D, individuals with prediabetes can achieve a reduction of insulin resistance via weight loss after bariatric surgery and may thereby significantly reduce their elevated T2D risk, as has been shown previously (8). While current guidelines recognize T2D as a comorbidity guiding clinical decision-making about bariatric surgery, prediabetes representing an independent risk factor for cardiovascular events, kidney disease, or even mortality is currently not recognized as a relevant obesity-associated comorbidity, partially due to its heterogeneity (2,9). To account for this heterogeneity and to evaluate therapeutic responses to bariatric surgery, participants with prediabetes were assigned to the Tübingen Clusters. In this study, we aimed to examine the cluster-specific impact of bariatric surgery on glucose regulation parameters, prediabetes remission, and cluster change in individuals with an elevated risk for T2D, specifically in two cohorts undergoing bariatric surgery and a control cohort (10). We hypothesized that high-risk clusters benefit most from bariatric surgery due to their potential to improve a previously deleterious metabolic state.

RESEARCH DESIGN AND METHODS

Study Design and Participants

In this multicohort study, we investigated the postoperative outcomes of novel data-driven subphenotypes of individuals without T2D but at risk for T2D (defined by elevated BMI >27 kg/m^2) in two cohorts undergoing bariatric surgery: the A Biological Atlas of Severe Obesity (ABOS) cohort in Lille, France (ClinicalTrials.gov identifier: NCT01129297); the Bariatric Surgery and Reactive Hypoglycemia study cohort in Rome, Italy (ClinicalTrials.gov identifier: NCT01581801); and the Clinical and Metabolic Characterization of Long-Term Courses of Obesity Patients (AdipFollowup) cohort in Tübingen, Germany (ClinicalTrials.gov identifier: NCT04375371) as control. ABOS participants were followed up after 1 and 2 years, Rome cohort participants were followed up for a mean (SD) of 15.3 (4.5) months, and control cohort participants were followed up for ∼10 years (mean [SD] 128.9 [30.1] months).

ABOS is an ongoing prospective study that aims to identify determinants of outcomes of bariatric surgery. ABOS participants without T2D (n = 806) who underwent Roux-en-Y gastric bypass, sleeve gastrectomy, or gastric banding be-

[13]Division of Endocrinology and Diabetology, Department of Internal Medicine I, University Hospital Ulm, Ulm, Germany
[14]Institute for Clinical Diabetology, German Diabetes Center, Leibniz Institute for Diabetes Research at Heinrich Heine University Düsseldorf (DDZ), Düsseldorf, Germany
[15]Department of Endocrinology and Diabetology, Medical Faculty, Heinrich Heine University Hospital, Düsseldorf, Germany
[16]Department of Pharmacy and Biochemistry, Institute of Pharmaceutical Sciences, and Interfaculty Centre for Pharmacogenomics and Pharma Research, Eberhard Karls University Tübingen, Tübingen, Germany
[17]School of Cardiovascular and Metabolic Medicine and Sciences, King's College London, London, U.K.
[18]Cluster of Excellence EXC 2124 "Controlling Microbes to Fight Infections" (CMFI), University of Tübingen, Tübingen, Germany
[19]M3 Research Center, Tübingen, Germany

Corresponding authors: Reiner Jumpertz von Schwartzenberg, reiner.jumpertz-vs@med.uni-tuebingen.de, and François Pattou, francois.pattou@univ-lille.fr

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L.S., V.R., R.J.v.S., and F.P. contributed equally.

tween 1 January 2006 and 12 December 2017 were included in the current study (Supplementary Fig. 2). Participant data were prospectively collected at the time of surgery and 1 and 2 years after surgery. A 75-g OGTT was performed at baseline and at follow-up. A description of the laboratory assessments has been published previously (11).

For the analysis of prediabetes remission, all individuals with prediabetes at baseline were included (n = 423). Prediabetes status was defined at baseline based on a fasting plasma glucose (PG) of 100–125 mg/dL (5.6–6.9 mmol/L) and/or a 2-h PG of 140–199 mg/dL (7.8–11.0 mmol/L) during OGTT and/or an HbA_{1c} of 5.7–6.4% (39–46 mmol/mol) according to American Diabetes Association recommendations (12). Glucose area under the curve (AUC) during OGTT was determined using the trapezoidal rule ($AUC_{Glucose\ 0–120\ min}$) (13). Peripheral insulin sensitivity was estimated by the modified Matsuda index ($ISI_{Matsmod}$) according to the following equation: $10{,}000 / \sqrt{([glucose_{0\ min} \times insulin_{0\ min}] \times [(glucose_{0\ min} + glucose_{30\ min} + glucose_{120\ min}) / 3] \times [(insulin_{0\ min} + insulin_{30\ min} + insulin_{120\ min}) / 3])}$ (14,15). Insulin resistance was assessed by the HOMA of insulin resistance (HOMA-IR), which was calculated according to the following equation: $insulin_{0\ min} \times glucose_{0\ min} / 22.5$ (16). The disposition index as a measure of β-cell function was calculated as the product of the C-peptidogenic index and Matsuda index (17) and the C-peptide/glucose AUC using the trapezoidal rule as a proxy for insulin secretion ($AUC_{C\text{-}peptide\ 0–30\ min} / AUC_{Glucose\ 0–30\ min}$) (18).

The independent replication cohort from Rome consisted of 60 individuals with obesity without T2D who were randomly assigned 1:1 to either Roux-en-Y gastric bypass or sleeve gastrectomy at the Catholic University School of Medicine in Rome between December 2012 and December 2014 (19). A description of the analytic procedures of samples has been published previously (19).

The independent control cohort from Tübingen consisted of 46 individuals with obesity who received behavioral modification counseling for body weight reduction. This included 10 group sessions with nutrition, physical activity, and lifestyle counseling over 6 months. A detailed description of the laboratory assessments has been published elsewhere (20). Individuals of the control cohort were retrospectively contacted for rephenotyping between 27 January and 23 October 2020.

The studies were reviewed and approved by the regional human ethics committees (Lille: Comité de Protection des Personnes Nord Ouest VI; Rome: Rome Catholic University Ethical Committee; Tübingen: Ethics Committee at the Eberhard-Karls University of Tübingen) in accordance with national guidelines and the provisions of the Declaration of Helsinki as revised in 2000. All participants provided written informed consent to participate in the respective studies.

Clustering

Clinical clustering variables of the Tübingen Clusters were BMI, hip and waist circumference, fasting PG and insulin, 2-h PG and insulin, fasting triglycerides, and HDL cholesterol (HDL-C) levels (7). The Tübingen Clusters were named after the first cohort in which they were described (Tübingen Family Study) (7,21). An online application for personal use or research purposes is accessible at https://prediabclusters.idm-tuebingen.org.

Participants were assigned to C3, C4, C5, or C6 at baseline. Owing to the low number of participants assigned to C3 (n = 2 each in ABOS and the control cohort), it was excluded from further analysis.

Surgery

All bariatric surgery procedures were done laparoscopically, as described previously (6).

Outcomes

Prediabetes remission was defined according to current American Diabetes Association criteria for normal glucose regulation, as below the described cutoffs for prediabetes, and without the use of glucose-lowering drugs (8,10,12). Chronic kidney disease (CKD) was assessed based on the estimated glomerular filtration rate (eGFR) calculated according to the MDRD equation (22). The general cardiovascular risk profile was estimated according to the Framingham sex-specific multivariable risk algorithm (23). Liver biopsies were done as previously described (24). The Nonalcoholic Fatty Liver Disease (NAFLD) Activity Score was defined as the unweighted summed scores for steatosis (0–3), lobular inflammation (0–3), and ballooning (25). Noninvasive tests (fatty liver index, AST-to-platelet ratio index [APRI], and NAFLD Fibrosis Score) were computed as described previously (24).

Statistical Analysis

Statistical analyses were performed using the R Version 4.2.2 software. Data are presented as mean (95% CI), median (interquartile range), or n (%) unless otherwise specified. Between-group comparisons over time were analyzed using linear mixed-effects models, with participant as a random effect using the lme4 package, or cross-sectionally using two-way ANOVA with a post hoc test for multiple comparisons (least significant difference), applying Bonferroni correction, or Wilcoxon signed rank or χ^2 test, as appropriate. The model included cluster, time point, and the interaction between the two as model terms, and main outcomes were evaluated in models with BMI, age, sex, and type of surgery as fixed effects and in the case of insulin secretion, with insulin sensitivity.

Data and Resource Availability

The data sets generated or analyzed during the current study are not publicly available since they are subject to national data protection laws and restrictions imposed by the ethics committees to ensure data privacy of study participants. They can be applied for through an individual project agreement with the principal investigator of the respective university hospital.

RESULTS

In all cohorts, the most abundant cluster was high-risk C6 (Fig. 1). Participant anthropometric and metabolic characteristics of ABOS at baseline are summarized in Table 1, and those of the remaining cohorts are combined in Supplementary Table 1. Low-risk C4 participants had lower BMI, liver fat content, triglycerides, insulin resistance, insulin secretion, and glycemia and higher HDL-C compared with C5 and C6 participants at baseline.

Since Tübingen Clusters depend on modifiable metabolic measures, we hypothesized that bariatric surgery would

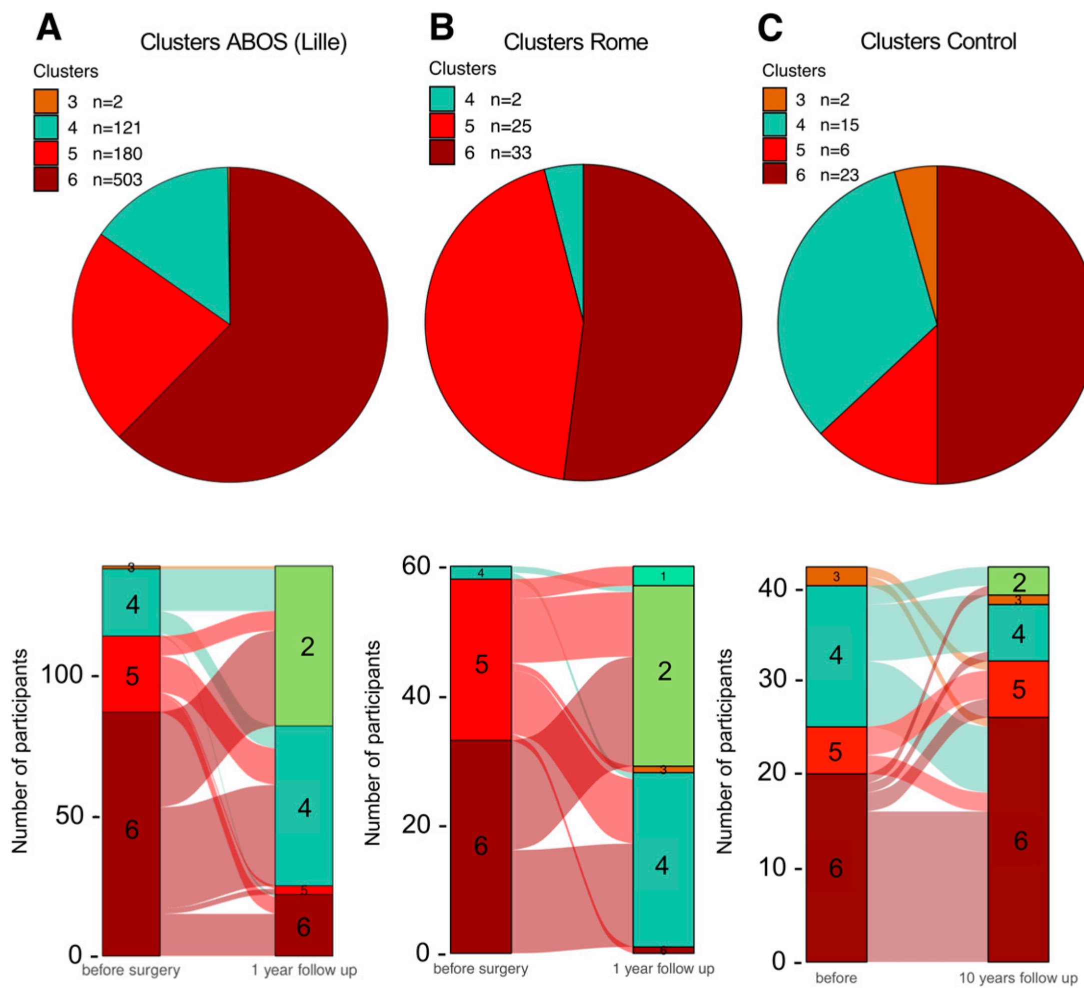

Figure 1—Tübingen Clusters distribution at baseline and change of cluster assignment over time in the ABOS cohort (*A*), Rome cohort (*B*), and control cohort (*C*).

lead to reassignment of high-risk clusters to low-risk clusters. In the ABOS and Rome cohorts, bariatric surgery led to a switch from high-risk to low-risk clusters in most participants (Fig. 1*A* and *B*). Equal fractions of C5 and C6 participants remained in high-risk clusters in ABOS, but nearly all C5 participants who did not convert to a low-risk cluster converted to C6 (Fig. 1*A*). Finally, in the control cohort, most participants stayed in high-risk clusters, and nearly one-half of C4 participants converted to C6 after long-term follow-up (Fig. 1*C*).

Next, we investigated cluster-specific anthropometric outcomes of bariatric surgery. One year after surgery, C5 and C6 participants had a higher BMI than C4 participants (mean [SD]: C5 33.2 [6.2] vs. C6 33.6 [6.2] [$P > 0.99$] and C4 30.6 [5.6] [each P vs. C5 and C6 <0.001]), while relative body weight loss was similar among all clusters (mean [SD]: C4 27.9% [11.0%] vs. C5 27.7% [10.9%] vs. C6 27.9% [11.1%]; $P = 0.81$) (Fig. 2*A*).

We further examined parameters of glucose regulation and insulin sensitivity. Initially, $AUC_{Glucose\ 0–120\ min}$ was highest in C5 and C6 (Table 1) and reduced in both clusters after surgery, with the most pronounced relative reduction in C5 versus the other clusters (Fig. 2*B*). $AUC_{Glucose\ 0–120\ min}$ was lowest in C4 (Table 1), but $AUC_{Glucose\ 0–120\ min}$ did not change significantly 1 year after bariatric surgery in this cluster (mean [SD]: 761 [155] min × mmol/L; $P = 0.9$). PG levels after bariatric surgery decreased to similar values between C6 and C4 but remained slightly higher in C5 versus C4 and C6 (Fig. 2*G* and *I*). As expected based on cluster characteristics, HOMA-IR was highest in C5 and lowest in C4 (P for each comparison <0.001) (Table 1). After bariatric surgery, C5 achieved the most pronounced reductions in HOMA-IR, with both C5 and C6 exhibiting stronger reductions in HOMA-IR than C4 (ΔHOMA-IR: C4 −29.52% vs. C5 −53.82% vs. C6 −53.00%; P C4 vs. C5 or C6 <0.001, P C5 vs. C6 >0.99) (Fig. 2*C*). Similarly, $ISI_{Matsmod}$ increased more strongly in C5 and C6 after bariatric surgery ($\Delta ISI_{Matsmod}$: C4 66.44% vs. C5 227.88% vs. C6 150.80%; P for each comparison <0.001) (Fig. 2*D*). However, HOMA-IR and $ISI_{Matsmod}$ did not change significantly in C4 (Fig. 2*C* and *D*). The disposition index was highest in C4 and C6 at baseline, while C4 was the only cluster not to show a significant increase in β-cell function after bariatric surgery (mean [SD]: C4 104.93% [274.70%] vs. C5 254.73% [311.10%] vs. C6 133.52% [394.26%]; C4 vs. C5 $P = 0.03$, C4 vs. C6 $P = 0.62$, C5 vs. C6 $P = 0.01$) (Fig. 2*E*). $AUC_{C\text{-}peptide\ 0–30\ min}$ / $AUC_{Glucose\ 0–30\ min}$ was highest in C6 and lowest in C5 and C4 (Supplementary Fig. 6*D*). Only C5 increased insulin sensitivity–adjusted insulin secretion after bariatric surgery, which

Table 1—Baseline characteristics of ABOS cohort

Characteristic	C4 (*n* = 121)	C5 (*n* = 180)	C6 (*n* = 503)	*P*
Age (years)				
Mean (SD)	37.5 (10.6)	41.1 (11.6)	36.9 (11.3)	<0.001
Median (IQR)	37.0 (15.0)	41.0 (17.3)	35.0 (18.0)	
Sex				
Female	103 (85.1%)	152 (84.4%)	389 (77.3%)	0.0396
Male	18 (14.9%)	28 (15.6%)	114 (22.7%)	
BMI (kg/m^2)				
Mean (SD)	42.7 (5.2)	46.4 (6.6)	47.5 (7.6)	<0.001
Median (IQR)	41.3 (4.5)	45.2 (7.8)	45.7 (9.0)	
Waist-to-hip ratio				
Mean (SD)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	<0.001
Median (IQR)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	
eGFR by MDRD (mL/min)				
Mean (SD)	100.3 (21.6)	95.9 (20.2)	101.0 (21.3)	0.0195
Median (IQR)	97.2 (26.7)	95.3 (24.3)	98.3 (24.7)	
Liver fat content (%)				
Mean (SD)	14.8 (22.6)	28.8 (24.9)	21.6 (21.9)	<0.001
Median (IQR)	5.0 (19.0)	20.0 (35.0)	15.0 (26.0)	
Type of surgery				
Gastric banding	36 (29.8%)	34 (18.9%)	112 (22.3%)	0.0546
Gastric bypass	67 (55.4%)	105 (58.3%)	264 (52.5%)	
Sleeve gastrectomy	18 (14.9%)	41 (22.8%)	127 (25.2%)	
Triglycerides (mmol/L)				
Mean (SD)	1.1 (0.5)	1.9 (0.9)	1.3 (0.5)	<0.001
Median (IQR)	1.0 (0.6)	1.7 (0.9)	1.2 (0.6)	
HDL-C (mmol/L)				
Mean (SD)	1.3 (0.3)	1.1 (0.2)	1.2 (0.2)	<0.001
Median (IQR)	1.2 (0.4)	1.0 (0.3)	1.2 (0.3)	
HOMA-IR				
Mean (SD)	1.7 (0.6)	5.0 (3.0)	3.8 (2.0)	<0.001
Median (IQR)	1.7 (0.9)	4.4 (2.8)	3.3 (2.2)	
HOMA of β-cell function				
Mean (SD)	108.3 (77.5)	184.0 (112.1)	213.4 (118.7)	<0.001
Median (IQR)	98.7 (52.2)	155.2 (114.9)	186.5 (130.4)	
Glucose AUC				
Mean (SD)	780.1 (113.2)	1061.0 (107.6)	862.0 (109.4)	<0.001
Median (IQR)	784.6 (116.0)	1067.2 (132.5)	865.5 (139.9)	
Fasting PG (mmol/L)				
Mean (SD)	5.0 (0.4)	5.8 (0.6)	5.2 (0.5)	<0.001
Median (IQR)	5.1 (0.5)	5.8 (0.9)	5.2 (0.7)	
2-h PG (mmol/L)				
Mean (SD)	5.2 (1.1)	8.6 (1.2)	6.2 (1.2)	<0.001
Median (IQR)	5.1 (1.4)	8.5 (1.5)	6.2 (1.6)	
Fasting plasma insulin (mU/L)				
Mean (SD)	7.5 (2.6)	19.6 (11.0)	16.5 (8.1)	<0.001
Median (IQR)	7.6 (3.6)	17.3 (12.0)	14.7 (9.1)	
2-h Plasma insulin (mU/L)				
Mean (SD)	21.9 (14.2)	133.0 (104.0)	74.9 (62.1)	<0.001
Median (IQR)	18.2 (16.0)	101.2 (104.5)	62.2 (57.9)	
Fasting c-peptide (ng/mL)				
Mean (SD)	2.9 (1.9)	4.0 (1.1)	3.7 (1.1)	<0.001
Median (IQR)	2.7 (1.0)	3.8 (1.3)	3.5 (1.3)	
2-h C-peptide (ng/mL)				
Mean (SD)	7.3 (4.7)	12.9 (3.9)	10.2 (3.2)	<0.001
Median (IQR)	6.5 (3.0)	12.7 (4.1)	10.2 (4.2)	

Continued on p. 6

was not observed in C4 and C6, while the latter was characterized by high insulin secretion (Fig. 2*F*, Supplementary Fig. 5*F*, and Supplementary Fig. 6*D*). Changes in the remaining glucose regulation parameters of the Rome cohort are shown in Supplementary Fig. 5.

We next analyzed glucose regulation trajectories of C4, C5, and C6. Changes in glucose regulation status 1 year after bariatric surgery are shown in Fig. 3*A*–*C*. Despite exhibiting the lowest prediabetes prevalence, C4 had the lowest prediabetes remission rate of all participants who met prediabetes criteria at baseline, while C5 and C6 had the highest remission rate 1 year (C4 60% vs. C5 77% [P = 0.045]; C4 vs. C6 74% [P = 0.09]) (Fig. 3*D*) and 2 years (C4 61% vs C5 82% [P = 0.007]; C4 vs. C6 79% [P = 0.047]) (Fig. 3*E*) after bariatric surgery.

To further understand the underlying mechanisms contributing to prediabetes remission, we investigated anthropometric and metabolic parameters by prediabetes remission status (i.e., responder vs. nonresponder). In all clusters, responders had more body weight loss than nonresponders (mean [SD] Δbody weight: C4 responders 35 [5] kg vs. nonresponders 29 [8] kg [P group over time <0.05]; C5 responders 38 [3] kg vs. nonresponders 25 [6] kg [P group over time <0.001]; C6 responders 42 [2.5] kg vs. nonresponders 26 [5] kg [P group over time <0.001]) (Fig. 3*F*), indicating that weight loss is important for prediabetes remission in all clusters. Insulin resistance and sensitivity (HOMA-IR and $ISI_{Matsmod}$) showed a stronger improvement in C6 responders than in nonresponders (Fig. 3*G* and *H*); however, improvement did not differ between C5 and C4 nonresponders and responders. Furthermore, β-cell function improved more strongly in C5 responders than nonresponders but was not different between C4 responders and nonresponders (disposition index: C4 responders vs. nonresponders P group over time = 0.07; C5 responders vs. nonresponders P group over time = 0.02; C6 responders vs. nonresponders P group over time = 0.33) (Fig. 3*J*). $AUC_{C\text{-peptide } 0–30 \text{ min}}/AUC_{Glucose\ 0–30\ min}$ increased only in C5 responders.

Next, since glucose levels are critically regulated by the liver and partly depend on hepatic lipid content, local inflammation, and fibrosis, we analyzed in a subgroup of participants

Table 1—Continued

Characteristic	C4 (n = 121)	C5 (n = 180)	C6 (n = 503)	P
HbA_{1c} (%)				
Mean (SD)	5.5 (0.4)	5.7 (0.4)	5.6 (0.4)	<0.001
Median (IQR)	5.5 (0.5)	5.8 (0.5)	5.6 (0.5)	

IQR, interquartile range.

who underwent initial and rebiopsy of the liver 1 year after bariatric surgery (n = 104). Here, C5 showed the highest liver steatosis severity and NAFLD Activity Score but not Kleiner Liver Fibrosis Score at baseline (liver steatosis severity: C4 vs. C5 $P < 0.001$; C4 vs. C6 $P < 0.001$; C5 vs. C6 $P = 0.003$) (Supplementary Fig. 3*A*–*C*). Most C5 and C6 participants achieved a liver fat percentage reduction into the normal or near-normal range (Supplementary Fig. 3*D*). C4 had a liver fat content corresponding to grade 1 macroscopic steatosis, which decreased by trend into the normal range. These findings were similar when assessed by noninvasive tests for steatosis and fibrosis (Supplementary Fig. 3*E*–*G*). Scores for advanced metabolic dysfunction–associated steatotic liver disease (MASLD), such as the APRI and Fibrosis-4 (FIB-4), were significantly reduced in C6 nonresponders, while the FIB-4 score increased in C5 and C6 responders (Supplementary Fig. 4*A*–*C*).

The highest prediabetes remission and the high conversion rates from high- to low-risk clusters in C5 were also accompanied by the strongest reduction in relative Framingham Risk Score (rFRS), although C5 participants were older (Supplementary Fig. 6*A*). Furthermore, C5 and C6 participants had a slight increase in eGFR (Supplementary Fig. 6*B*). Trajectories of insulin sensitivity and secretion of ABOS are shown in Supplementary Fig. 6*C* and *D*, and glucose regulation trajectories and prediabetes remission rates of the Rome and control cohorts in Supplementary Fig. 7.

CONCLUSIONS

In this study, we show that novel, data-driven clusters of individuals at risk for T2D (Tübingen Clusters) differ in their response to bariatric surgery. As body weight loss was similar among all clusters, differences in the alteration of glucose regulation parameters were independent of differences in relative body weight loss. While high-risk C5 and C6 ameliorated both insulin resistance and β-cell function, specifically low-risk C4 participants with prediabetes did not benefit from bariatric surgery to the same extent, which is demonstrated by their lower prediabetes remission rate. C4 achieved a moderate improvement in insulin resistance (despite basal HOMA-IR being in the normal range), but neither C4 responders nor nonresponders had improved insulin secretion or β-cell function after bariatric surgery. Whether this was due to, for example, a lack of improved β-cell sensitivity to incretins or changes in hepatic VLDL-palmitate export remains to be demonstrated (26,27). However, metabolic dysfunction was less severe in C4 already before surgery and may reflect a state of metabolically healthy obesity (28). Nonetheless, since prediabetes remission via weight loss is beneficial in terms of T2D risk reduction and potential complications (8), C4 individuals with prediabetes may benefit from prediabetes remission despite the overall less severe metabolic dysfunction of the whole cluster. C5 benefited most from bariatric surgery in terms of improvement in insulin resistance, prediabetes remission, and cardiovascular risk as reflected by the rFRS. Despite that overall prediabetes remission rates were lower than expected after bariatric surgery, participants achieving prediabetes remission primarily had improved insulin sensitivity in C6 and insulin secretion in C5. Thus, for C6 individuals, improving insulin sensitivity in light of already high insulin secretion is sufficient to achieve prediabetes remission. Vice versa, increasing insulin secretion appears to be a key mechanistic underpinning for those achieving remission in C5. Considering the slightly lower insulin secretion in C5 versus C6 at baseline, we cannot rule out that cluster definition may be associated with this outcome.

Hepatic phenotypes of Tübingen Clusters previously assessed by ^1H magnetic resonance spectroscopy are validated here for the first time via liver biopsies (7). We observed that C5 participants indeed had the highest liver fat content, followed by C6, which reduced into the near-normal range after bariatric surgery. The differential response to bariatric surgery may result from stronger metabolic perturbances in C5 at baseline combined with the high effectiveness of bariatric surgery in improving MASLD, as shown to be associated with higher remission of T2D after bariatric surgery (29). This reduction in liver fat may be associated with an increase in insulin secretion, as has been demonstrated previously (30–32). Importantly, the noninvasive fatty liver index shows a similar pattern as liver steatosis determined by liver biopsy. However, liver fibrosis assessed both by liver biopsy (Kleiner Liver Fibrosis Score) and noninvasively (APRI and NAFLD Fibrosis Score) did not differ among clusters, reflecting the relatively low prevalence of liver fibrosis in this cohort. Additionally, noninvasive tests for hepatic fibrosis in MASLD may not be suitable for adequately reflecting an elevated MASLD risk after bariatric surgery (e.g., increasing FIB-4 scores in C5 and C6 responders) (24).

Weight loss was higher in individuals achieving prediabetes remission in all clusters, indicating that weight loss can mediate prediabetes remission, which has previously been demonstrated for lifestyle intervention (8). Although weight loss mediated prediabetes remission at least in part in all clusters, mechanisms resulting in prediabetes remission differed among clusters. Specifically, in C4, insulin resistance only improved marginally, while in C6, change in insulin sensitivity was a discriminator between response and nonresponse. This was not the case in C5. Furthermore, neither C4 nonresponders nor responders significantly increased insulin secretion or β-cell function, while in C5 and C6, responders increased β-cell function in particular. As the prediabetic state delineates a higher risk for T2D, the primary aim, besides weight loss, should be remission of prediabetes as one of the most effective ways to reduce T2D risk (8,10). As shown here, prediabetes remission rates after bariatric surgery differed between low-risk and high-risk clusters. This is surprising since C4 participants were younger compared with

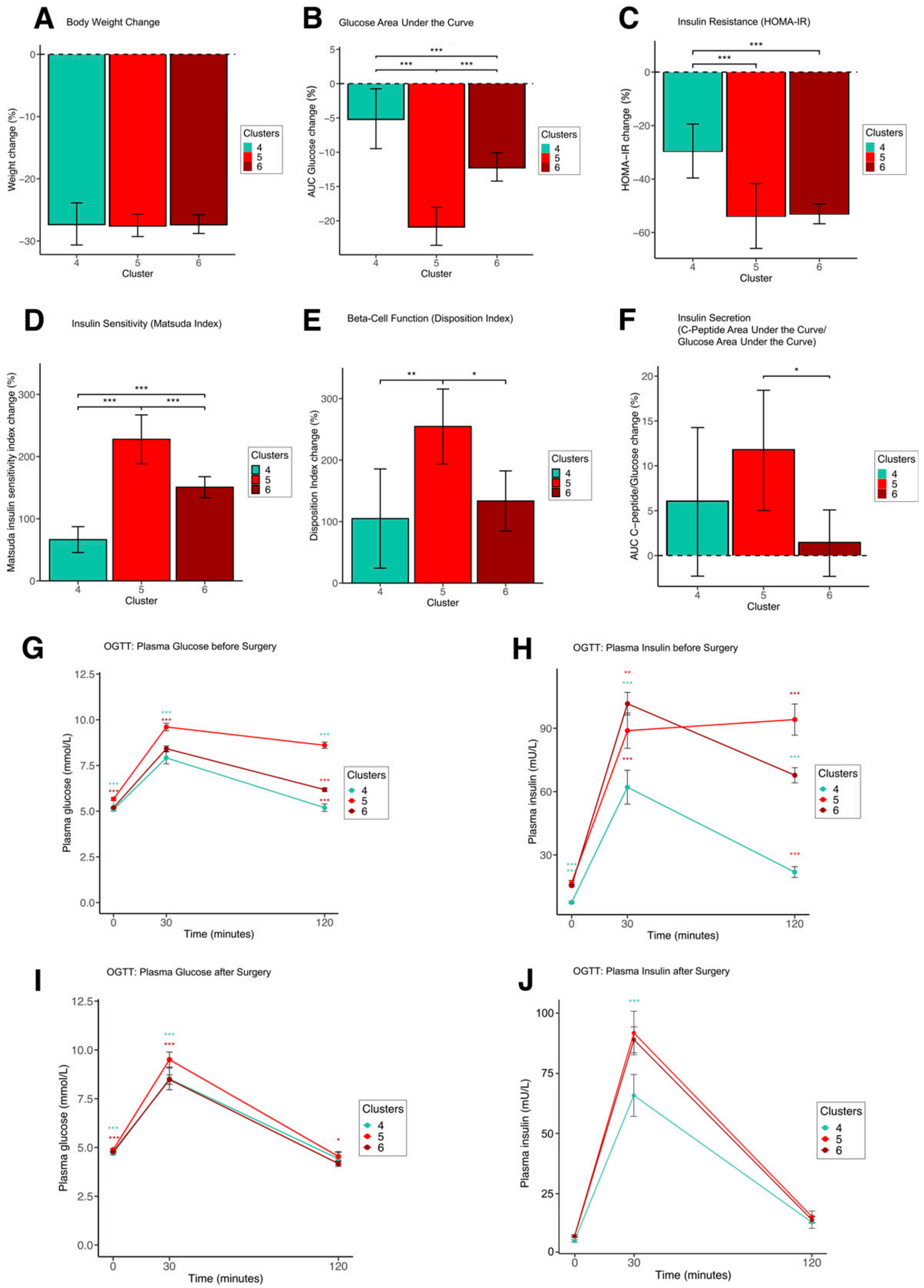

Figure 2—Weight and glucose regulation trajectories in ABOS (Lille) cohort. Percent change of the following parameters: weight loss (*A*), $AUC_{Glucose\ 0–120\ min}$ (*B*), HOMA-IR (*C*), Matsuda index (*D*), disposition index (*E*), and $AUC_{C\text{-}peptide\ 0–30\ min}$ / $AUC_{Glucose\ 0–30\ min}$ (*F*). PG and insulin trajectories over OGTT at baseline (*G* and *H*) and after 1 year (*I* and *J*). Data are mean (95% CI). Analyses were performed using two-way ANOVA or Wilcoxon signed rank test, as applicable. $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. Color of asterisks indicates comparison cluster (*G*–*J*).

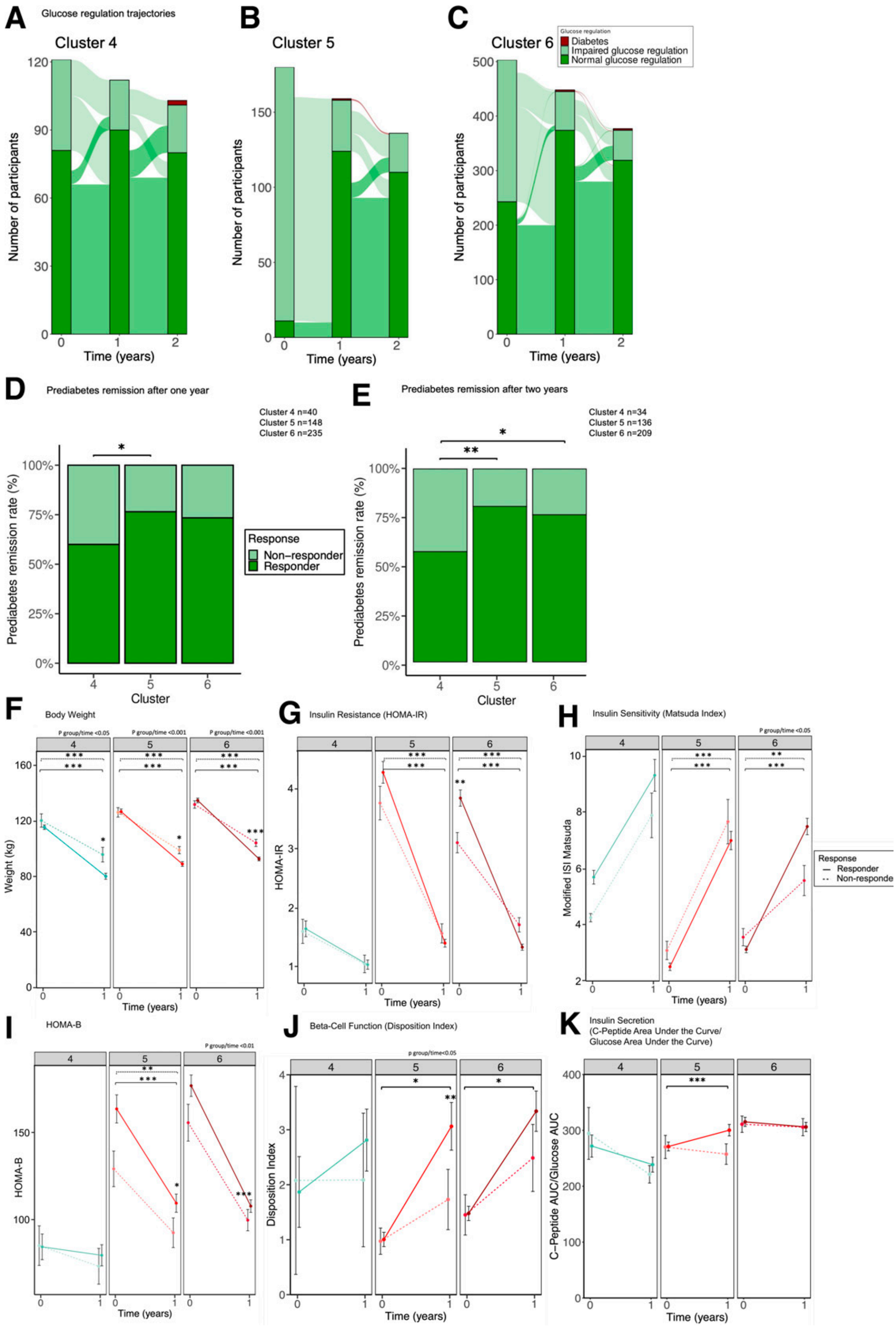

Figure 3—Glucose regulation trajectories, prediabetes remission, and glucose regulation indices by response in ABOS cohort. Glucose regulation status at baseline and 1 and 2 years after surgery in C4 (*A*), C5 (*B*), and C6 (*C*). Prediabetes remission after 1 year (*D*) and 2 years (*E*), weight (*F*), HOMA-IR (*G*), Matsuda index (*H*), HOMA of β-cell function (HOMA-B) (*I*), disposition index (*J*), and $AUC_{C\text{-peptide } 0–30 \text{ min}}$ / $AUC_{Glucose\ 0–30\ min}$ (*K*). This multivariable mixed-effects linear model included age, sex, type of surgery, time point, cluster, and the interaction between cluster and time point as main effects. Data are mean (95% CI). $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

C5 and younger age has been associated with higher prediabetes remission rates after bariatric surgery (33). Overall remission rates of prediabetes were similar to those observed after bariatric surgery in individuals with overt T2D (34). Since in prediabetes, metabolic derangements are not as severe as in T2D, a higher feasibility of prediabetes remission compared with T2D remission could be expected. However, similar remission rates suggest that prediabetes remission is as difficult to achieve as T2D remission. Similar to our findings, evidence on bariatric surgery–induced T2D remission in T2D subphenotypes showed that bariatric surgery induced a lower remission rate in low-risk mild obesity–related diabetes compared with the high-risk cluster SIRD (6). These findings indicate that other mechanisms apart from weight loss, which was similar among clusters in our study, might play a role in improving glucose regulation in C4. Specific characteristics of C4 that cannot or can only partly be improved by bariatric surgery may be decisive for this. As C4 participants had near-normal HOMA-IR values at baseline, insulin resistance may not have been the main driver of the prediabetic state in this cluster. Even though C4 participants had a slightly better β-cell function at baseline compared with C5 and C6 participants, a higher proportion in C4 still did not manage to gain further improvements in β-cell function as opposed to C5 and C6. Individuals with severe insulin deficient diabetes have been shown to have the lowest diabetes remission rate compared with mild obesity–related diabetes and SIRD (6). In line with this, lacking the ability to increase β-cell function could prevent C4 individuals from returning to normal glucose regulation (35). In previous studies by our group, C4 participants did not have a specific genetic risk of β-cell dysfunction (7). Since first-phase insulin secretion after bariatric surgery is also orchestrated by release of glucagon-like peptide 1, C4 might not promote or even be able to increase glucagon-like peptide 1 secretion after bariatric surgery as strongly as the other clusters (36). Therefore, further studies examining incretin responses after bariatric surgery between subphenotypes are needed to investigate whether tailored treatment (e.g., with incretin-based medication) might be a more effective treatment option in terms of prediabetes remission, specifically in C4 (37).

After short-term follow-up, most participants converted from high-risk to low-risk clusters, while those from low-risk clusters stayed in low-risk clusters, as expected. This cluster change is similar in both cohorts undergoing bariatric surgery (ABOS and Rome). However, in the control cohort, most participants changed to high-risk clusters over time, imposing an increasing metabolic risk without surgical intervention. This study is the first in our knowledge to show that individuals change clusters after bariatric surgery, which may reflect the reduced cardiometabolic risk upon bariatric surgery assessed by a reduction of the rFRS. Interestingly, rFRS was reduced to similar levels among all three clusters, although C5 had the highest rFRS before surgery. This is particularly important since C5 participants were the oldest, with age being part of the bariatric surgery–independent variables of the rFRS. Furthermore, both C5 and C6 participants increased kidney function represented by eGFR, which might reflect the kidney-protective effect of bariatric surgery specifically in these clusters and may not be the case for C4. After long-term follow-up in participants who did not undergo bariatric surgery, a switch from a high- to a low-risk cluster was rare, and many of the participants with former low risk converted to high-risk clusters. Thereby, reassignment to Tübingen Clusters could help reassess risk for T2D and complications after bariatric surgery and may guide therapeutic approaches postoperatively.

Our study has some limitations. First, most study participants were White Europeans, which may limit generalizability. Additionally, this study is the first to show cluster reassignment after bariatric surgery, which could be affected by alterations in gastrointestinal glucose absorption and insulin secretion. Still, high-risk clusters had the strongest improvement of rFRS and eGFR, possibly reflecting the reduced risk represented by cluster change. Similarly, not all dynamic glucose regulation indices have been validated after bariatric surgery. However, OGTT curves have been successfully compared with hyperinsulinemic-euglycemic clamp tests before and after bariatric surgery in individuals without diabetes (38). Thus, applied indices most likely reflect actual metabolic changes after bariatric surgery. Finally, different prediabetes definitions, for example, by World Health Organization criteria with fasting glucose 110–125 mg/dL (6.1–6.9 mmol/L) and without an HbA_{1c} cutoff or by 1-h PG, may result in different prediabetes remission rates (39,40).

In conclusion, our results support the relevance of this novel T2D risk classification in individuals with severe obesity and identified differing responses to surgery. Our analysis shows that participants classified as high-risk C5 benefited most from bariatric surgery in terms of amelioration of insulin resistance, insulin secretion, prediabetes remission, and risk cluster change. Low-risk C4 participants had the lowest prediabetes remission rate, suggesting that reaching weight loss targets may not be sufficient for achieving normal glucose regulation in this cluster. These findings may help advance precision medicine approaches in bariatric surgery.

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