Supplementary methods

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Content

1 Surgery
2 Psychotherapy
3 Cardiopulmonary exercise testing (CPET)
4 Additional neuropsychological assessments
5 Transthoracic echocardiography
6 Cardiac MRI
7 Evaluation of endothelial dysfunction and arterial stiffness
8 Near infrared spectroscopy
9 Brain MRI
10 Metabolomic and endocrine assessment
11 Evaluation of liver function
12 Assessment of obesity-related and other concomitant diseases

1 Surgery

All patients received general anesthesia including endotracheal intubation. Patients were positioned in a modified beach-chair position. Abdominal access and insufflation was achieved with an optical-
viewing non-bladed trocar. Five further ports were positioned including a retractor for the left liver lobe. An antecolic and antegastric Roux-en-Y loop was created. The proximal jejunum was divided 50 cm distally to the ligament of Treitz, and a 150-cm Roux limb was constructed in all cases (1). Therefore, a stapled side-to-side jejuno-jejunostomy was created and the enterotomy as well as the mesenteric defect were closed with running sutures.

For the creation of the pouch, the dissection started with incision of the phrenico-gastric peritoneal reflection at the angle of His. Starting 4 cm from the gastroesophageal junction at the lesser curvature, dissection was performed medial to the nerve of Latarjet to reach the bursa omentalis. The circular stapler anvil was passed through the anterior stomach adjacent to the lesser curve. A linear stapler was then fired transversely across the stomach just distal to the anvil. The gastric pouch with an estimated size of 15-25 ml was then completed by repeat firing of a two 60 mm linear cutting stapler thus yielding an oblique partition of the stomach to the angle of His. The gastrotomy on the greater curve of the stomach was closed with a running suture. The gastro-jejunostomy was created with a circular stapler passed into the opened Roux limb through the left-sided lateral port-site. The abdominal wall fascia at this port-site had to be manually dilated to accommodate this stapler. After creating a short 'Krückstock' using a linear stapler, the gastro-jejunostomy was tested by advancing an oro-gastric tube into the Roux-limb and injecting methylene-blue through the tube.

2 Psychotherapy

Psychotherapy-supported lifestyle modification was performed jointly by psychologists and psychiatrists. It was designed as cognitive behavioral psychotherapy (2-4). Over a period of about 9 months, 3 individual and 9 group sessions were performed. The main goal of the individual sessions at the beginning of the intervention was to build a deeper understanding of the underlying patterns leading to individual obesity. After giving basic information, a model of the patient's individual factors causing and maintaining obesity was developed. Therefore, the patient's case history was assessed, focusing on cues regarding genetic predispositions, dysfunctional eating behavior and dysfunctional problem solving strategies in the past. An analysis of a current problem behavior, such as overeating or having eating attacks, was conducted as well, using cognitive behavioral techniques (5). Individual sessions were completed by assessing different kinds of dysfunctional eating habits, coping strategies
and pointing out the difference between diets and a recommended long-term adoption of healthier nutrition patterns.

Afterwards, patients were assigned to groups of 2-4 people. The superior goal during group sessions was to get patients into action, aiming to modify or replace dysfunctional habits, maladaptive coping strategies and dysfunctional thinking or attitudes. Between sessions, patients had to engage in therapeutic homework. Group therapy was structured into 7 modules: reward system (3 modules), self-concept, social skills, relapse strategies, and preparation for (potential) bariatric surgery.

During the first three sessions, patients learned about the reward system and its dysfunction in morbidly obese people (6). In order to deal with craving, patients were guided to practice mindfulness exercises and were supported to learn individual skills to master stressful situations. A behavioral experiment was conducted, using a food cue to induce craving. Patients thus could experience success in overcoming craving by using their newly acquired skills. Furthermore, patients were supported to identify and practice alternative ways to feel reward in order to replace eating without physiological need, such as pursue a hobby or enjoying a hot wellness bath. Next, patients learned about self-management techniques (7), e.g. finding positive self-commitments to resist overeating. Another module of the therapeutic group concept was improving self-concept and self-image. As an example, patients had to speak friendly to themselves, assuming being a valued friend. Group therapy sessions also aimed to enhance patients’ social skills to reduce social sources of stress that lead to dysfunctional eating behavior. Based on the circumplex model (8), patients were trained to show friendly assertive behavior to reach their goals in the interaction with other people. Towards the end of group sessions, patients were prepared to deal with relapse situations to dysfunctional eating habits in order to build up further motivation to eat healthy in the long run. The last session was held by a physician, who provided information about the potentially upcoming bypass operation and its consequences.

3 Cardiopulmonary exercise testing (CPET)

General conditions and preparation: Gas calibration was performed once daily, according the vendor’s manual. After exclusion of contraindications regarding physical stress, the participant sat down on a chair on the treadmill. In the sitting position, capillary blood for blood gas analysis was drawn from the hyperemized ear lobe (ABL 80, Radiometer Krefeld, Germany). The blood pressure was taken (manual brachial measurement), a 12 lead ECG was applied, and a mask was selected to properly fit
the participant’s face. After starting the exercise program, the technician entered sex, date of birth, height, and weight (measurements from the respective day) and selected one out of two pre-specified CPET protocols (Supplementary Table 1) aiming a symptom limited exercise period of 8 to 12 minutes targeting a respiratory exchange ratio (RER) >1.0.

After the automatic gas exchange calibration, a clip was placed on the participant’s nose and the mouthpiece was inserted to perform the calibration of the volume sensor (Triple V). After successful calibration, the Triple V was inserted into the mask, which then was placed on the participant’s face. Care was taken to maintain a tight seal around the mask thus ensuring correct measurements. All data was collected and analyzed using the SentrySuite software (VIASYS Healthcare GmbH, Höchberg Germany) with reference to recommendations of the American Heart Association (9).

Resting period: During the resting phase (sitting position, 5 minutes), key metabolic variables (heart rate, oxygen uptake, carbon dioxide output, respiratory rate) and the RER were observed and checked for consistency and plausibility. The participant then stood up and the chair was taken from the treadmill.

Exercise period and stopping criteria: We used two different protocols according to the patient’s anticipated exercise capacity (P1 “low” and P2 “high”) judged by the study physician. For warming up, the treadmill was started on a very slow pace with the participant adopting slow walking speed for 4 or 2 minutes, respectively, for P1 or P2. Then, the incremental exercise program started with iterative increases in pace and grade (Supplementary Table 1). During the warm-up phase and the incremental exercise phase, blood pressure was taken every 2 minutes (manual brachial measurement). Stopping criteria were either perceived maximum exertion or meeting one of the following safety stopping criteria: significant ECG alterations, angina pectoris, systolic blood pressure >220 mmHg, reaching the target heart rate, or the feeling of the patient that he/she could no longer walk safely on the treadmill. Borg's rating of perceived exertion was filled in by the patient directly after termination of the examination and capillary blood was taken for blood gas analysis. After complete stop of treadmill, the chair was put back on the treadmill and the patient sat back down on the chair until blood pressure and heart rate had normalized and RER fell below 1.00.

Documentation and assessment: The full information of the CPET was saved and printed. A pneumologist cross-checked and verified all results used for clinical evaluation in the trial.
4 Additional neuropsychological assessments

**Eating behavior.** Eating habits were assessed by two questionnaires. First, the German version of the Three-factor Eating Questionnaire (TFEQ) (10), Fragebogen zum Essverhalten (FEV) (11) containing 60 questions was used to measure dietary restraint, disinhibition and hunger. Second, to assess for restraint, emotional eating and external eating, the 30 questions comprising German version of the Dutch Eating Behavior Questionnaire (DEBO) (12), Fragebogen zum Ernährungsverhalten (FEV-II), was administered (13, 14).

**Food craving.** The Food Cravings Questionnaire Trait (FCQ-T) (15) addresses 39 questions to describe motivational states (16).

**Sleep disturbance.** The Epworth Sleepiness Scale (ESS) assesses sleepiness during daytime by an 8-item questionnaire (17).

**Additional neuropsychological tests.** The Multiple Choice Vocabulary Test, “Mehrfachwortschatz-Test B” (MWT-B) (18) was performed to determine the intelligence of the participants. The digitspan test, a part of the WIE/WAIS-IIIIR assesses attention and auditory memory function (19). The Stroop test (20, 21) was performed to explore executive functions as attention and inhibition.

5 Transthoracic echocardiography

A standardized transthoracic echocardiogram was performed (Vivid E9 and E95 GE, Vingmed, Horten, Norway) by well-trained sonographers from the Comprehensive Heart Failure Center according to a pre-specified protocol and using the same system presets. A minimum of three cardiac cycles was recorded and stored in a digital raw-data format. Standard left ventricular (LV) apical views (4-, 2-, and 3-chamber views) were acquired avoiding LV foreshortening. Interventricular septal and posterior wall thickness as well as LV end-diastolic and end-systolic diameters (LVEDD and LVESD) were determined from M-mode recordings of the parasternal long axis view with the ultrasound beam
perpendicular to the interventricular septum at the level of the mitral valve leaflet tips. LV mass was estimated as: $0.0008 \times (1.04 \times (LVDd [mm] + IVSd [mm] + LVPWd [mm])^3 - LVDd [mm]^3) + 0.6$. LV end-diastolic and end-systolic volumes (LVEDV and LVESV) were measured using the biplane disc summation method (i.e., modified Simpson’s rule) from 2D images of apical 4- and 2-chamber views, and LV stroke volume (LVSV) and ejection fraction (LVEF) were calculated accordingly: $LVSV = LVEDV - LVESV$; $LVEF = LVSV / LVEDV \times 100$. In case of suboptimal quality, LVEF was measured monoplane, or estimated visually. Global longitudinal peak systolic strain was obtained from the apical 3-, 4-, and 2-chamber views using Automated Function Imaging. Left atrial (LA) end-systolic volume was obtained in the apical 4- and 2-chamber views using the biplane disc summation method. In case of suboptimal image quality, LA diameter was measured in the parasternal long axis view.

Transmitral inflow pattern with E and A wave velocities and E wave deceleration time was obtained by pulsed wave (PW) Doppler with the sample volume positioned at the mitral leaflets tips. PW tissue Doppler imaging was recorded at the septal and lateral mitral annulus in the apical 4-chamber view ($e'\)$. Maximal tricuspid valve regurgitation velocity was assessed using continuous wave Doppler.

According to current guidelines, reduced systolic function was defined as LVEF ≤50%. Since indication to body surface area might underestimate deviation from normal in this collective, we used definitions based on crude measurements: LV hypertrophy: LV mass >224 g in men and >162 g in women or diameter of interventricular septum or posterior LV wall >10 mm in men and >9 mm in women; LV dilation: LV end-diastolic volume >150 ml in men and >106 ml in women or LV end-diastolic diameter >58 mm in men and >52 mm in women, respectively. Left atrial (LA) diameter was defined as LA volume >69 ml in men and >63 ml in women, LA area >30 cm$^2$, or LA Diameter >47 mm in men and >43 mm in women, respectively (22).

Diastolic dysfunction was diagnosed in patients with reduced LVEF, LV hypertrophy, or LV dilation as well as if three out of the following four criteria were fulfilled (23): LA dilation, average E/e’ >14, lateral e’ <0.1 m/s or septal e’ <0.07 m/s, tricuspid regurgitation maximal flow velocity >2.8 m/s.

Valve disease was diagnosed according to current guidelines using the PISA and the pressure half time method for the quantification of mitral and aortic valve regurgitation (24), respectively, and the maximal antegrade velocity, pressure gradient, and valve area for the quantification of mitral and aortic valve stenosis (25).
1H-MR spectroscopy data acquisition used a double-triggered single voxel spin-echo spectroscopic sequence (PRESS) with TR 1500 ms, TE 35 ms; 32 averages; flip-angle 90°. The 20×5×14 mm$^3$ (1.4 ml) voxel was positioned within the septum on diastolic cine images avoiding contamination by epicardial fat, additional saturation blocks were positioned on all 6 sides of the voxel. To enable free-breathing during the measurement, a navigator was positioned on the lung-liver interface of the right diaphragm for respiratory motion gating. Measurements were acquired at end-systole and end-expiration. 1H MR spectra with and without water suppression were acquired. A vendor-specific software (Siemens Healthcare, Erlangen, Germany) was used for post-processing of 1HMRS data. Determination of resonance signals was supported by previous experience at our center (26). The water signal was set at 4.7 ppm, for methylene group containing intramyocardial lipids at 1.3 ppm, and for methyl group containing lipids at 0.9 ppm. The total myocardial lipid content results from the addition of the area under the curve (AUC) of the resonance signals of both peaks and was expressed as 100% x (AUC [lipid 1.3 ppm] + AUC [lipid 0.9 ppm])/(AUC [water] + AUC [lipid 1.3 ppm] + AUC [lipid 0.9 ppm]). Pericardial fat was visually quantified and categorized as no, slight, moderate, or pronounced lipomatosis.

7 Evaluation of endothelial dysfunction and arterial stiffness

Endothelial function and arterial stiffness was analyzed using EndoPAT® (Itamar Medical Ltd, Israel). Examinations took place after an overnight fast and discontinuation of medication affecting vascular tone (betablockers, statins, nitrates, calcium channel blockers) for 24 hrs in a thermo-neutral, quiet setting, with the patient in a half-sitting position. Sensors were placed on the fingertips of both index fingers. The signal was measured from the fingertip of the index finger of the non-dominant arm. After 6 minutes of examination, the brachial artery of the non-dominant arm was occluded for 5 minutes using a standard blood pressure cuff (pressure at least 200 mmHg or 60 mmHg above systolic blood pressure measured on the contra-lateral arm). After cuff release, probes measured the endothelium-mediated changes in vascular tone elicited by the down-stream hyperemic response. Measurements form the contra-lateral arm were used to control for concurrent non-endothelial dependent changes in vascular tone. The EndoPAT software was used for both online acquisition and offline analysis.
8 Near infrared spectroscopy

The VFT (27) consists of three subtasks. In the letter version, subjects were instructed to pronounce as many German nouns as possible beginning with the letters “A”, “F” and “S” without using proper names. In the category version, subjects were required to list German nouns belonging to the categories “animals”, “fruits”, and “flowers”. In the third task, subjects were asked to repeat all days of the week at a moderate speed in a consecutive manner. Each task was presented as one block of 60 s consisting of 30 s activation and 30 s of rest. The number of correct verbal responses was counted, representing behavioral performance. The TMT (28, 29) is a paper and pen test comprising part A and B, and a control task (part C). Part A consists of a sheet of paper imprinted with numbers (1 to 30), which have to be connected in ascending numerical order. Part B consists of a sheet of paper imprinted with numbers (1 to 15) and letters (A to O), which have to be connected in ascending and alternating order (1-A, 2-B, 3-C, …, 15-O). Part C consists of a sheet of paper imprinted with 18 circles, one auxiliary line between the circles, separated in 5 rows. Time for preparation for each part is 30 s with 30 s resting time between every part. All parts were repeated 3 times. For analyses of the functional data, a moving average was applied with a time window of 5 seconds for high-frequency artefacts, and a discrete cosine filter to remove signal drifts. For statistical analysis, the mean value for each channel, condition, and participant was calculated separately over the block length of 30 s. To detect activation, we calculated one-tailed t-tests against zero for each condition and channel. To compare the brain activation patterns between conditions, we used t-tests for paired samples.

9 Brain MRI

For structural data, an MPRAGE sequence with a 3D-magnetization prepared rapid gradient echo and anisotropic spatial resolution of 1 mm3 was used with the following parameter: echo time 2.26 ms; repetition time 1900 ms; flip angle 9°; field of view 256 mm2. Data will be analyzed with the CAT12 toolbox (http://dbm.neuro.uni-jena.de/cat/). Diffusion tensor imaging data were measured with a resolution of 2.2 mm3. The following parameters were used: echo time 94.0 ms; repetition time 8700 ms; 64 slices. For resting state measurements, T2-weighted images with the following parameters were acquired: echo time 30.0 ms; repetition time 1800 ms; flip angle 90°; field of view 210 mm; 28 slices; slice thickness 4.0mm; voxel size 3.3x3.3x4.0 mm3. Images were obtained in ascending,
interleaved order, and a total of 160 measurements were recorded over 5 minutes with the instruction to close the eyes and to relax. Data will be analyzed with the CONN toolbox (30). For functional measurements T2- weighted images the following parameters were acquired: echo time 30.0 ms; repetition time 2000 ms; flip angle 90°; field of view 230mm; 37 slices; slice thickness 3.0 mm; voxel size 3.6x3.6x3.0 mm3. Images were obtained in ascending, interleaved order, and a total of 565 measurements were recorded for each participant during a task, in which high- and low-caloric and non-food pictures were presented in a block design (31).

10 Metabolomic and endocrine assessment

Venous blood samples were drawn to allow for metabolic, metabolomic and endocrine profiling. To ensure comparability, we used standardized pre-analytic procedures, and all samples were stored at -80°C immediately after centrifugation, if applicable. Supplementary Table 2 summarizes all parameters that were measured according the protocol. As standard parameters of glucose metabolism, we measured levels of fasting glucose, fasting insulin and glycated hemoglobin (HbA1c). As a surrogate of insulin resistance, the homeostasis model assessment (HOMA) index was calculated as follows: Fasting insulin (µIU/ml) * fasting glucose (mg/dl) / 405. Additionally, a glucose tolerance test was performed measuring glucose immediately before and two hours after ingestion of 75 g glucose. To evaluate lipid metabolism, levels of cholesterol, high-density and low-density lipoproteins (HDL-C, LDL-C) and triglycerides were measured. Several hormones and peptides are known to control food intake, mainly via interaction with integrative hypothalamic nuclei and/or direct effects on gastrointestinal motility. Primary markers in that context were: glucagon like peptide 1 (GLP-1), peptide tyrosine tyrosine (PYY), gastric inhibitory polypeptide (GIP), leptin, adiponectin, neurotensin, ghrelin, amylin, pancreatic polypeptide, agouti-related peptide (AgrP).

In addition, we will perform liquid chromatography-mass spectrometry (LC-MS) analyses facilitating the measurement of a large number of metabolites (substrates or products of biological processes). Of special interest are the branch chained amino acids (BCAAs), as it is well known, that their spectrum changes after bariatric surgery. Such changes in BCAA levels can be correlated with modification of insulin resistance and other significant metabolic parameters (32, 33). In addition, steroid hormones, thyroid specific hormones and natriuretic peptides will be measured. The intestinal microbiome is intrinsically linked with overall health, including obesity risk (34). Obesity and obesity-related metabolic
disorders (e.g. non-alcoholic steatohepatitis (NASH)) are characterized by specific alterations of the human gut microbiome. To assess the interaction of gut microbiome with the intervention-induced changes as an exploratory endpoint, further integrative analysis of fecal microbiota composition and the serum metabolome fingerprint will be performed. Furthermore, aliquots of plasma, serum, spot urine, and saliva were biobanked for future studies.

**Supplementary Table 2: Laboratory workup during the WAS trial**

### 11 Evaluation of liver function

Following the standards of our liver center, liver function tests included routine biochemical parameters such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT) and bilirubin as well as the apoptosis marker cytokeratin 18 fragments (M30) (35). Composite tests such as FibroMax allowed assessment of inflammatory activity and fibrosis by blood-based measures (36). Exploratory analyses focused on flow cytometry to quantify peripheral immune cell abundance and analysis of enterohepatic signaling by measurement of fibroblast growth factor (FGF) hormones. Hepatic triglyceride content was quantified by both magnetic resonance spectroscopy (MRS) using a 3T MRI unit (MAGNETOM Skyra, Siemens Sector Healthcare, Erlangen, Germany) and Controlled Attenuation Parameter (CAP) measurement (Fibroscan 502 Touch) (37, 38). Both methods are characterized by a high sensitivity for the quantification of hepatic lipid content with a threshold as low as 5% steatosis and will be analyzed in a complementary fashion in those patients where only one measurement can be obtained. Quantification of hepatic fibrosis stage was performed using Vibration-Controlled Transient Elastography (VCTE) of the Fibroscan device (39). As an exploratory endpoint, liver tissue gene expression profiles will be analyzed and correlated with clinical parameters. For this purpose, a liver biopsy was taken during bariatric surgery.

### 12 Assessment of obesity-related and other concomitant diseases

Concomitant diseases were documented in details at baseline and at each study visit. For the documentation of changes in obesity-related conditions, we will apply definitions given in **Supplementary Table 3**. For the definition of “response” we adapted the criteria suggested by the American Society for Metabolic and Bariatric Surgery (ASMBS) (40) and will judge the changes during
follow-up in three categories: (i) complete response, (ii) partial response, and (iii) no significant change or worsening.

To simplify accounting of drugs, each drug will be counted as one drug (independent of the actual dosage) and will then be summed per indication and reported as drug count (DC) with the following exceptions: insulin 1-50 IU/d will be counted as 1, 51-100 IU/d as 2, and >101 IU/d as 3 drugs; high-dose statin therapy (e.g. 80 mg simvastatin, 40 mg atorvastatin, 20 mg rosuvastatin) will be judged as 2 drugs. Drugs that are clearly used for other purposes (e.g. beta-blocker for migraine, but not blood pressure; or metformin for obesity, but not diabetes mellitus) will not be considered as drug in this context. For the primary analysis of response the evaluation at the time of randomization (visit 2) will be compared to visit 4 (12 months after randomization).

In addition, all patients were asked at any study visit, if they ever had experienced coronary heart disease, cardiac intervention or surgery, stroke/TIA, loss of consciousness, pulmonary hypertension, suffered from inborn cardiac disease or peripheral arterial disease, had a malignant tumor or if they were experiencing symptoms of gastroesophageal reflux, had a known liver cirrhosis or infectious diseases like HIV or hepatitis B/C. All concomitant drugs were entered at every visit in the case report forms. Any previous abdominal surgery was also documented.

Supplementary Table 3: Obesity-related disease and response criteria during follow-up

Supplementary Table 4: Baseline characteristics of patients enrolled in the WAS trial (comparing randomized patients to patients leaving the study before randomization)

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