RESEARCH

Cardio-psycho-metabolic outcomes of bariatric surgery: design and baseline of the WAS trial

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Abstract

Obesity is a rapidly emerging health problem and an established risk factor for cardiovascular diseases. Bariatric surgery profoundly reduces body weight and mitigates sequelae of obesity. The open, randomized controlled Würzburg Adipositas Studie (WAS) trial compares the effects of Roux-en-Y gastric bypass (RYGB) vs psychotherapy-supported lifestyle modification in morbidly obese patients. The co-primary endpoint addresses 1-year changes in cardiovascular function (peak VO_2 during cardiopulmonary exercise testing) and the quality of life (QoL) (Short-Form-36 physical functioning scale). Prior to randomization, all included patients underwent a multimodal anti-obesity treatment for 6–12 months. Thereafter, the patients were randomized and followed through month 12 to collect the primary endpoints. Afterwards, patients in the lifestyle group could opt for surgery, and final visit was scheduled for all patients 24 months after randomization. Sample size calculation suggested to enroll 90 patients in order to arrive at minimally 22 patients per group evaluable for the primary endpoint. Secondary objectives were to quantify changes in body weight, left ventricular hypertrophy, systolic and diastolic function (by echocardiography and cardiac MRI), functional brain MRI, psychometric scales, and endothelial and metabolic function. WAS enrolled 93 patients (72 women, median age 38 years, BMI 47.5 kg/m^2) exhibiting a relevantly compromised exercise capacity (median peakVO_2 18.3 mL/min/kg) and the QoL (median physical functioning scale 50). WAS is the first randomized controlled trial focusing on the effects of RYGB on cardiovascular function beyond hypertension. In addition, it will provide a wealth of high-quality data on the cerebral, psychiatric, hepatic, and metabolic function in obese patients after RYGB.

Key Words

- randomized controlled trial
- morbid obesity
- Roux-en-Y gastric bypass
- lifestyle intervention
- heart failure
- cardiovascular and brain function
- quality of life

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Introduction

Obesity has emerged as a major global health concern, with a growing impact on morbidity and mortality (1). A recent study forecasted that nearly half of all adults in the US will be obese by 2030 and that nearly one out of four will suffer from severe obesity, that is BMI ≥35 kg/m^2 (2). Obesity is an established risk factor for type 2 diabetes and cardiovascular diseases such as arterial hypertension, coronary heart disease, or stroke (3). Furthermore, obesity increases the risk of new-onset heart failure, particularly heart failure with preserved ejection fraction (4, 5). Patients with morbid obesity appear to carry a significantly higher mortality risk (6, 7).

Currently, bariatric surgery is the only treatment for morbid obesity conveying a substantial and sustained weight loss and long-term remission of obesity-related comorbidities (8, 9, 10, 11). Bariatric surgery is, therefore, recommended for patients with BMI ≥40 kg/m^2 or ≥35 kg/m^2 with associated obesity-related comorbidities (8, 12, 13). Although a wide range of surgical procedures has been described, Roux-en-Y gastric bypass (RYGB) is the best investigated and the second most frequently performed bariatric procedure worldwide (14, 15). Lifestyle intervention was not able to reduce the rate of cardiovascular events in obese patients with type 2 diabetes (16), but mortality might be reduced by bariatric surgery (11, 17). Large Swedish registries found that obese patients undergoing bariatric surgery had a 2–5 times lower incidence of heart failure when compared with non-surgical patients (18, 19). Two recent meta-analyses of cohort studies confirmed that intentional weight loss is associated with improvements in New York Heart Association (NYHA) classification, diastolic function, reductions in left ventricular (LV) mass index, and left atrial size (20, 21). The beneficial effects of weight loss may further include improvements in metabolic and neurohormonal regulation, exercise capacity, hemodynamic parameters, cardiac remodeling, and the quality of life (QoL). However, the evidence base explaining the influence of weight loss surgery on the heart remains poorly defined and mainly relies on non-randomized studies (22, 23).

So far, randomized trials in bariatric surgery have mainly focused on weight loss and diabetes remission (10, 24, 25, 26, 27, 28, 29). One trial compared bariatric surgery and lifestyle intervention in 100 patients with a BMI between 30.0 and 39.9 kg/m^2 and demonstrated that RYGB resulted in improved blood pressure control and remission of hypertension (30). However, no randomized trial primarily investigated the effects of RYGB on additional cardiopulmonary and cardiac function. Furthermore, the effect of bariatric surgery on several other obesity-related diseases as non-alcoholic fatty liver disease (NAFLD) or psycho-emotional stressors as depression has not been investigated in randomized trials.

We here report the study rationale and design of the Würzburg Adipositas Studie (WAS) trial, provide the baseline characteristics of all enrolled participants, and discuss the relevance of the expected findings from this multidisciplinary intervention study focusing on cardio–psycho–metabolic outcomes. One particular strength of the WAS trial is its control arm that receives a 12-month psychotherapy-supported lifestyle intervention, rendering this trial unique also for analyzing the QoL and other psychometric measures. Due to its highly multidisciplinary approach, the WAS trial will also provide a multitude of secondary, clinically relevant results on brain and liver function in morbidly obese patients after RYGB.

Methods

Study design and patients

The WAS trial is an open, randomized, single-center trial comparing an intensive lifestyle intervention to RYGB surgery in morbidly obese patients. The study protocol was approved by the local ethics committee (ethics committee of the Julius-Maximilians-Universität Würzburg, Germany, #182/08) and complied with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to any study-related investigation. Patients were eligible if they suffered from obesity and fulfilled the criteria for gastric bypass surgery. The eligibility criteria are summarized in Table 1. The trial was registered at ClinicalTrials.gov (NCT01352403).

Study flow

Figure 1 visualizes the study flow. At the screening visit, all selection criteria were assessed including cardiopulmonary exercise testing (CPET). During the study period, in Germany, cost coverage by the individual health insurance of the patient had to be granted prior to bariatric surgery. This presumed participation in a multimodal anti-obesity treatment phase for a period of 6–12 months (see details in 'Multimodal anti-obesity treatment and counseling'). Therefore, each patient had to enroll (visit 1) in a pre-randomization run-in period until cost coverage had been received. After bestowed cost coverage, the patient could

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Table 1 Selection criteria.

Inclusion criteria
• Age ≥18 years
• BMI >40 kg/m^2 or
• BMI >35 kg/m^2 with severe comorbidities
• Indication for Roux-en-Y gastric bypass surgery
• Ability to perform cardiopulmonary exercise testing
• Written informed consent
Exclusion criteria
• Pregnancy or breast feeding
• Unstable angina pectoris
• Life expectancy <12 months
• Endocrine or psychiatric disorder as cause of obesity
• Systemic glucocorticoid treatment (with exception of glucocorticoid replacement therapy)
• Abuse of drugs or alcohol within the last 5 years
• Inability to attend regular study visits for logistic reasons
• Participation in competing trials

be randomized (visit 2). Randomization was performed into early RYGB surgery (see details in 'Surgery' section) vs continuation of the multimodal treatment concept augmented by an additional intensive psychotherapeutic intervention (see details in 'Psychotherapy-supported lifestyle intervention'). Twelve months after randomization (visit 4), patients in the lifestyle group could opt for surgery, too, if surgery was still indicated. The final visit 5 was scheduled 24 months after randomization. However, an extended follow-up is offered to all patients in order to acquire long-term results. All study visits were performed at the outpatient clinics of the Comprehensive Heart Failure Center and included an extensive list of investigations, usually carried out during 2 consecutive days. Details are presented below and an overview of investigations is given in Table 2.

Endpoints

The primary objective of the WAS trial is to compare the impact of RYGB surgery vs an intensified lifestyle intervention on cardiovascular performance and QoL in patients with morbid obesity. Thus, in the WAS trial, two independent primary endpoints were specified: (i) 12-month change (visit 2 vs visit 4) in peak VO_2 (mL/min/kg) at CPET; (ii) 12-month change (visit 2 vs visit 4) in the physical functioning scale (PFS) of the 36-item short form health survey (SF-36). An increase of 5 mL/min/kg in peak VO_2 and of 10 points in the PFS of the SF-36 were assumed to be clinically meaningful differences for 12-month changes of these markers, respectively. Secondary endpoints are 12-month changes in 6-min walk test distance, cardiac characteristics assessed by echocardiography and cardiac MRI, body weight, comorbidities (e.g. diabetes, hypertension), depressed mood, eating behavior, pre-frontal brain

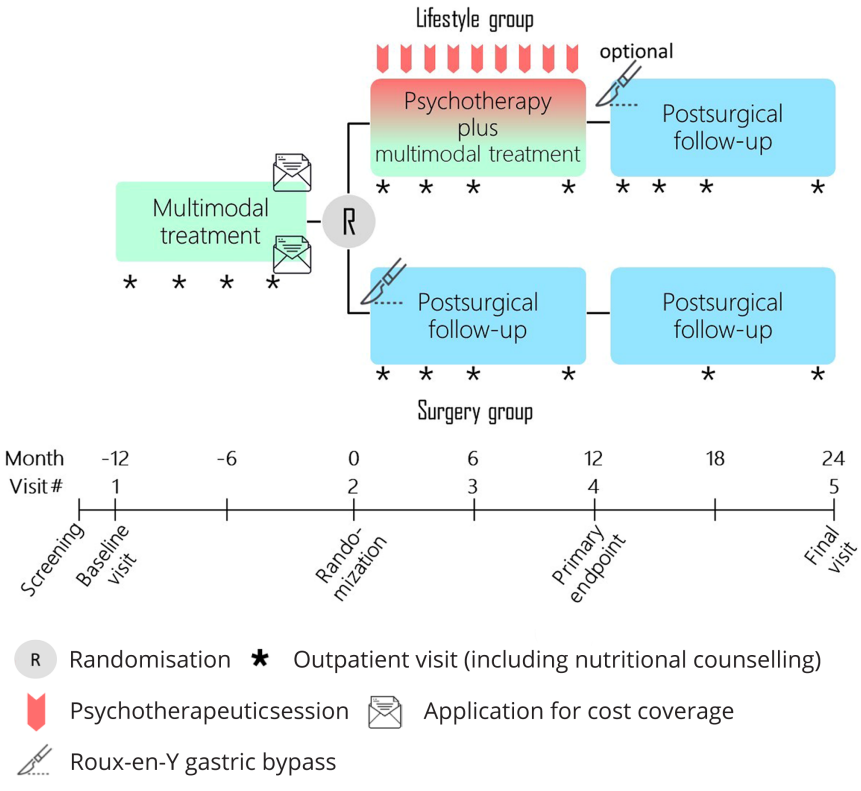

Figure 1
Time schedule of the WAS trial for the individual patient. Each study visit included a comprehensive evaluation stretched over 2 consecutive days. At the screening visit, selection criteria were checked (incl. cardio-pulmonary exercise test). Since cost coverage for bariatric surgery required documented failure of multimodal anti-obesity treatment, all patients engaged in such an intervention period (at least 6 months) until insurance issues were solved. Only then, at visit 2, patients could be randomized. Patients in the surgery arm were scheduled for timely gastric bypass surgery, whereas patients in the lifestyle arm continued with multimodal treatment concept augmented by an intensive psychotherapeutic intervention. Twelve months after randomization, the primary endpoint was evaluated, and patients in the lifestyle group could then also opt for surgery. The final assessment of all patients was scheduled 24 months after randomization. Hence, total study duration was 36 months. Extended long-term follow-up will be offered to all participants.

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Table 2 Key assessments in the WAS trial.

	Visit 1 (up to 12 months prior to randomization)	**Visit 2** (0 months, randomization)	**Visit 3** (6 months)	**Visit 4** (12 months)	**Visit 5** (24 months)
Clinical examination	●	●	●	●	●
Dietary records	●	●	●	●	●
CPET	●[a]	●		●	●
SF-36	●	●	●	●	●
Echocardiography	●	●	●	●	●
Cardiac MRI	●	●		●	●
6-min walk test	●	●	●	●	●
ECG	●	●	●	●	●
Assessment of endothelial dysfunction	●	●		●	●
Psychometric assessment[b]	●	●	●	●	●
Brain near infrared spectroscopy	●	●		●	●
Functional brain MRI		●		●	●
Laboratory analysis for metabolomic and endocrine assessment	●	●	●	●	●
Gut microbiome		●		●	●
Bioelectrical impedance analysis	●	●	●	●	●
Additional laboratory analyses[c]	●	●		●	●
Liver MR spectroscopy	●	●		●	●
Liver elastography		●		●	●
Liver biopsy		●[d]		●[d]	
Assessment of obesity-related diseases	●	●	●	●	●
Adverse events[e]			●	●	●

[a]CPET performed at screening visit. [b]Details see Table 3. [c]Details see Supplementary Table 2 (including biobanking of plasma, serum, spot urine, and saliva). [d]Intra-operatively performed for patients randomized to the surgical group after visit 2 and for patients in the lifestyle group after visit 4. [e]Only adverse events associated with metabolic-bariatric surgery were recorded.
CPET, cardiopulmonary exercise testing; SF-36, short form health survey 36.

activity, liver function and stiffness, endothelial function, gut microbiota, peripheral immune cells, markers of carbohydrate metabolism, adipokines, natriuretic peptides, and other hormones, as well as vitamin D metabolism. Key primary and secondary efficacy measures are described in more detail in Table 3.

Standard of care and intervention

Multimodal anti-obesity treatment and counseling

After enrollment in the trial (visit 1), all patients commenced a standardized multimodal anti-obesity treatment. The program included regular nutritional advice shared during group meetings. It covered more general topics (nutritional basics, calorie-restricted healthy diet, eating out, etc.) as well as individual counseling based on a food diary and provided by a dietician. Each patient was expected to attend at least three group meetings and three individual sessions. Patients received individualized recommendations regarding physical activities and were provided with a pedometer to track their daily step count. Additionally, patients attended outpatient visits every 8–12 weeks. There, they were clinically re-evaluated by a study physician including measurement of body weight and adjustment of medication. This program was offered throughout the trial to all patients that had not undergone surgery yet. Patients subjected to RYGB received specific information on the expected changes after surgery in accordance with the then-current recommendations (31, 32). During postoperative follow-up, patients underwent regular re-evaluations regarding food intolerance, eating behavior, and potential malnutrition.

Surgery

Surgery was performed by experienced laparoscopic surgeons with more than 300 completed bariatric procedures prior to this trial. After the creation of a small pouch of 20–40 mL, an antecolic RYGB with a Roux limb of 150 cm and a biliopancreatic limb of 50 cm was created (14). Diet started with liquids on the day of surgery. Typically, patients were discharged on days 5–6 after surgery when sufficient post-gastric bypass diet was tolerated. For details, please refer to Supplementary methods (see section on supplementary materials given at the end of this article).

Psychotherapy-supported lifestyle intervention

Lifestyle intervention was designed as cognitive behavioral psychotherapy (33, 34, 35) and consisted of three single

Table 3 Efficacy measures of the WAS trial: domains, instruments, characteristics, and targets.

Domain	Instrument	Characteristics	Target
Cardiovascular characterization	Cardiopulmonary exercise testing	Ramp protocol, peak VO_2	Cardiopulmonary performance
	Echocardiography	Left ventricular & atrial dimensions; systolic and diastolic function	Heart failure etiology and severity
	Cardiac MRI (including spectroscopy)	Left and right ventricular mass and dimensions; systolic function	Heart failure etiology and severity, intracellular cardiac lipid content
	Six-min walk test	Walking distance	Physical capacity
	Office blood pressure measurement	After 5 min of rest	Blood pressure control
	Twenty four-h ambulatory blood pressure measurement		Blood pressure control, dipping status
	EndoPAT®	Reactive hyperemia index Augmentation index	Endothelial dysfunction, vascular stiffness
	12-lead resting ECG		
Psychomorphometry	SF-36	SQ, 36 items, 8 domains	Generic health-related quality of life
	PHQ-9	SQ, nine items, mirrors symptoms during the past 2 weeks	Vital exhaustion, depressive symptoms
	BDI	SQ, 21 items	Depressive symptoms
	FEV questionnaire	SQ, 60 items	Eating behavior
	FEV II questionnaire	SQ, 30 items	Eating behavior
	FCQ-T	SQ, 39 items	Food craving, motivational status
	ESS	SQ, eight items	Day sleepiness
	Multiple choice vocabulary test – MWT-B	32 words	Intelligence
	Digitspan test	Number of memorized digits	Attention and auditory memory function
	Stroop test	Time in sec	Executive functions: interference control
	fNIRS	Frontal cortical oxygenation during resting and functional conditions – VFT and TMT, resting state	Executive functions: cognitive flexibility, selective attention, very low frequency oscillation
	Brain (f)MRI	Structural imaging and functional imaging using a cue paradigm in resting state and food picture processing DTI	Functional changes in connectivity VBM Functional alteration in reward system Structural changes in connectivity
Metabolic and endocrine function	Oral glucose tolerance test	Blood analysis after a 75 g glucose challenge	Blood sugar control
	Metabolic profiling	Blood analysis with LC-MS/MS[a]	Metabolic dysfunction
	Hormone measurements	Blood and saliva analysis with LC-MS/MS and immunoassays[a]	Endocrine dysfunction
	Gut microbiome	Stool analysis	Characterization of gut microbiome
	Bioelectrical impedance analysis	Determination of electrical impedance	Body composition
Liver function	Liver MRI spectroscopy	Liver tissue analysis for chemical composition	Liver triglyceride content
	Liver elastography	Vibration controlled transient elastography; quantification of liver stiffness	Liver fibrosis
	Liver biopsy	Histology, gene expression	Liver fibrosis

(Continued)

Table 3 Continued.

Domain	Instrument	Characteristics	Target
Comorbidities	Medical history (incl. documentation of concomitant drugs)	Open and standardized questions	Obesity-related comorbidities
	Comprehensive laboratory assessment	Blood analysis[a]	For example, adverse events and comorbidities
	Obstructive sleep apnea screening	Apnea–hypopnea index, desaturation index	Obstructive sleep apnea
	Polysomnography	Apnea–hypopnea index, desaturation index	Confirmation of obstructive sleep apnea in case of pathologic findings in obstructive sleep apnea screening

[a]See Supplementary Table 2.
BDI, Beck depression inventory; DTI, diffusion tensor imaging; ESS, Epworth sleepiness scale; FCQ-T, food cravings questionnaire trait; (f)MRI, (functional) magnetic resonance imaging; fNIRS, functional near infrared spectroscopy; LC-MS/MS, liquid chromatography mass spectrometry; MWT-B, Mehrfachwortschatz-Test B; PHQ, patient health questionnaire; SF-36, short form health survey 36; SQ, standardized questionnaire; TMT, trail-making-tests; VBM, Voxel-based morphometry; VFT, verbal fluency task.

sessions and nine group sessions spread over a period of 9 months. The content and aims of this intervention were based on the core assumption of a disordered reward system in morbidly obese persons (36). Major aims were informing about obesity and its etiology, providing an individual problem analysis of obesity and disturbed eating behavior, improving motivation for a change of behavior, promoting alternatives to overeating, improving self-concept and self-image, social competence, and self-efficacy including existing and external resources, transfer of behavioral modification to everyday life, and improvement of strategies for coping with relapses. Details are presented in Supplementary methods.

Diagnostic procedures and technical investigations

Table 3 gives an overview of all efficacy measures of the WAS trial. A short description of the key methods is given in the following sections. Details regarding the methodology used can also be found in Supplementary methods.

Cardiopulmonary exercise testing

CPET was conducted according to standard operating procedures by a trained technician at time points indicated in Table 2. A motorized treadmill system was used (h/p/cosmos, sports & medical GmbH, Nussdorf-Traunstein, Germany) that was run on dedicated exercise program software (CardioSoft, GE) in combination with a spirometry unit (Oxycon Pro Delta, VIASYS Healthcare GmbH, Höchberg Germany). One out of two pre-specified CPET protocols was selected aiming at an exercise period of 8–12 min. CPET was performed symptom-limited and targeting a respiratory exchange ratio >1.0. Peak VO_2 values (mL/kg body mass/min) will be calculated as the average of measures from the last 30 sec during peak exercise (37). Capillary blood gas analysis was performed before exercise testing and at maximum load. Borg's rating of perceived exertion was filled in by the patient directly after the termination of the examination. Stopping criteria were ECG alterations, angina pectoris, systolic blood pressure >220 mmHg, reaching the target heart rate, perceived maximum exertion, or the feeling of the patient that he/she could no longer walk safely on the treadmill. All data were collected and analyzed using the SentrySuite software (VIASYS Healthcare GmbH, Höchberg Germany) with reference to recommendations of the American Heart Association (38).

Quality of life assessment and neuropsychological evaluation

All questionnaires were filled out by patients themselves at respective study visits. Validated German versions were used throughout.

Quality of Life The SF-36 (39) measures generic health-related QoL (40). It comprises 36 questions and contains eight subscales: physical functioning scale, role-physical, bodily pain, general health, vitality, role emotional, social function, and mental health. Two summary scales can be derived, that is the physical health and the mental health component scores.

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Depressed mood/depression The Patient Health Questionnaire 9 (PHQ-9) is a nine-item self-administered questionnaire asking for symptoms of depression according to Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria, using a Likert scale from '0' (not at all) to '3' (nearly every day) over the previous 2 weeks (41). The Beck Depression Inventory also registers depressive symptoms covering 21 questions to form a summary score (42).

Additional standardized questionnaires on eating behavior, sleep disturbance, and additional neuropsychological tests are described in the Supplementary methods.

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 prespecified protocol using the same system presets over time. Standard two-dimensional images (LV parasternal long- and short axis, LV apical 4-, 2-, 3-chamber, and subcostal view) and Doppler recordings (pulsed-wave Doppler of the mitral valve inflow (E and A wave velocity), continuous-wave Doppler through the aortic and tricuspid valves, pulsed tissue Doppler of the septal and lateral mitral (e' velocity) and the lateral tricuspid annulus) were obtained and analyzed according to current guidelines (43).

Cardiac MR imaging

Cardiac MR imaging was performed to analyze the LV function and to quantify intracellular cardiac lipid content by ^{1}H-MR spectroscopy using a 12-channel phased array body coil on a 3T MRI unit (MAGNETOM Skyra, Siemens Sector Healthcare, Erlangen, Germany) with subjects in the supine position. Functional imaging was carried out using cine MRI of the short- and long heart axis and a steady-state free precession sequence (field of view adjusted individually; matrix size 256×216; slice thickness 8 mm; TR 3.5 ms; TE 1.48 ms; flip angle 45°). LV mass and LVEF, stroke volume, end-systolic volume, end-diastolic volume, cardiac output expressed in L/min) were analyzed using Argus Function software (Siemens Healthcare). For ^{1}H-MR, spectroscopy data acquisition, a double-triggered single voxel spin-echo spectroscopic sequence (PRESS) was applied (TR 1500 ms, TE 35 ms; 32 averages; flip-angle 90°).

The 6-min walk test

The 6-min walk test was performed according to the standard operating procedure implemented at the CHFC that is based on international guidelines (44), in a 20-m indoor course. Participants were encouraged to cover as much ground as possible and were informed about the remaining time after 3 min. Before and after the test, heart rate, oxygen saturation, and breathing frequency were measured. The 6-min walk distance was recorded. In case the patient had terminated the test prematurely, the achieved distance and walking time were recorded as well as the reason for premature termination.

Functional near-infrared spectroscopy

Brain activity was measured in the study population as well as in a healthy, lean control group (n = 60) over the prefrontal cortex using functional near-infrared spectroscopy (fNIRS) (Hitachi ETG-4000; Hitachi Medical Co., Japan) with a sampling rate of 10 Hz (45). The positioning of the fNIRS probe set with 3×11 optodes was aligned with the EEG position FPz according to the international 10–20 system (46). The fNIRS acquisition process started with measurements at rest over a period of 5 min, with participants sitting relaxed and with closed eyes (47). Thereafter, fNIRS was measured during the following neuropsychological test sequence: (i) verbal fluency task (48) and (ii) trail-making-tests (49, 50).

MRI of the brain

Structural, as well as functional MRI of the brain, were measured in a part of the study population (n = 19 completed with additional three drop-outs during the fMRI) as well as in a healthy, lean control group (n = 22). Data were obtained using a Siemens Skyra 3 Tesla whole-body scanner (Siemens Medical Systems, Erlangen, Germany). After a 5-min resting-state measurement, a structural image as well as functional measurements during a task, in which high- and low-caloric and non-food pictures were presented (51), were measured. Additionally, diffusion tensor imaging was applied.

Evaluation of liver function

Hepatic function, fat content, and fibrosis stage were assessed as standardized in our liver center. Liver function tests included routine parameters such as serum transaminases and bilirubin as well as the apoptosis

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marker, CK18-M30. Composite tests such as FibroMAX™ (BioPredictive S.A.S., Paris, France) allow the blood-based assessment of inflammatory activity and fibrosis (52). Exploratory analyses included peripheral immune cell abundance and enterohepatic hormones. Hepatic triglyceride content was quantified by magnetic resonance spectroscopy (MRS, MAGNETOM Skyra, Siemens Sector Healthcare, Erlangen, Germany) (53) and controlled attenuation parameter measurement (FibroScan® 502 Touch, Echosens, Paris, France) (54). Hepatic MRS was performed in the same session as cardiac MRI/MRS. Hepatic fibrosis staging was performed using vibration-controlled transient elastography (52). Exploratory liver tissue gene expression profiles will be analyzed from a biopsy taken during bariatric surgery.

Additional investigations

As indicated in Table 2, each patient was evaluated regularly by standard 12-channel ECG, 24-h ambulatory blood pressure monitoring, and a bioelectrical impedance analysis. In addition, endothelial dysfunction and arterial stiffness were evaluated using EndoPAT®. Furthermore, sampling of blood was performed in fasting condition and during a glucose tolerance test, and urine, stool, and saliva were collected at the time points indicated in Supplementary Table 2. For the documentation of changes in obesity-related conditions, we applied definitions given in Supplementary Table 3.

Sample size calculation, power analysis, and adaptation of the statistical plan during the trial

For the mean-value comparison of the change in peak VO_2 between patients under lifestyle intervention vs bariatric surgery, we based our sample size calculation conservatively on a two-sided *t*-test for independent samples. For the experimental group (bariatric surgery), we originally postulated a peak VO_2 of 16 ± 6 mL/min/kg before and 24 ± 6 mL/min/kg after intervention (55), hence a mean change of 8 mL/min/kg with a S.D. of 6 mL/min/kg. Assuming a moderate correlation between the measurement before and after the intervention, quantified by a Pearson correlation coefficient of 0.5, we postulated the same S.D. of 6 mL/min/kg also for the change score as for the difference obtainable in the control (lifestyle) group. Then, 22 patients per group, 44 in total, are needed to detect a difference of 6.6 mL/min/kg in the mean VO_2 changes of both groups (corresponding to a mean change of 8.0 mL/min/kg vs 1.4 mL/min/kg for experimental group vs control group, respectively) as significant deviance from the null hypothesis of equal mean changes in both groups, with $\alpha = 0.025$ (co-primary endpoint CPET) and power = 0.90. For changes in the QoL, non-randomized evidence available at the time of designing the trial already suggested major improvements of health-related QoL in the order of 30–35 points (56, 57). We also expected a relevant improvement in the control group, in the order of 20 points of the physical function scale. A total sample of 44 evaluable patients (22 per group) would allow to detect a difference of 10 (S.D. 9) points as significant deviance from the null hypothesis of equal mean changes in both groups, with $\alpha = 0.025$ (co-primary endpoint QoL; Mann–Whitney *U* test) and power = 0.90.

The primary analysis consists of a comparison of the respective mean change (peak VO_2 or physical functional scale) from randomization (visit 2) to visit 4 between the two treatment groups using a baseline-adjusted comparison of the mean change by analysis of covariance (ANCOVA), with change in peak VO_2 or physical functional scale as the response variable, treatment group as a factor, and respective baseline value (peak VO_2 or physical functional scale) as the covariate. We will use this method because ANCOVA is unbiased, and since this is a randomized study, applying ANCOVA better preserves power compared to change score analysis (be two-sided *t*-test).

We had expected a drop-out rate of 25%. Thus, 60 patients had to be randomized to ensure at least 22 patients per group for analysis. Considering the required prolonged pre-trial run-in phase, we assumed to enroll 90 patients to enable randomization of the required 60 patients. Whereas this assumption was correct, we experienced an uneven drop-out rate. From the first 29 randomized patients, only 1 (7%) in the surgery group, but 7 (47%) in the lifestyle group dropped out. Based on these proportions, we adopted an unequal randomization procedure for the remainder of the recruitment in order to maintain statistical power, that is equal conditional expected values for both group sizes at the time of statistical analysis. We applied an approximation algorithm to meet this criterion because two equations had to be fulfilled by only one parameter. The respective amendment to the study protocol was approved by the Ethics committee in October 2014. The adjusted randomization scheme yielded satisfactory group sizes. A centralized randomization algorithm applying SAS Software 9.4 was used throughout the study.

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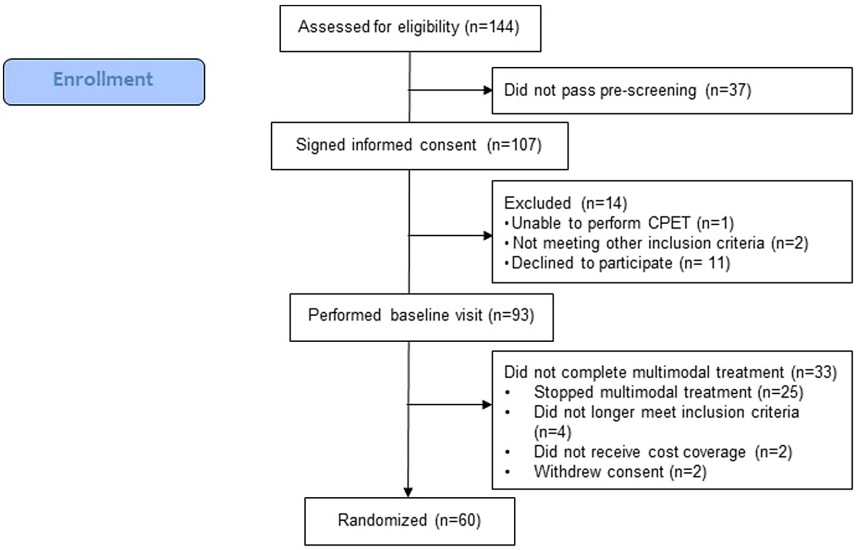

Figure 2
CONSORT diagram of the WAS trial.

Results

Screening of patients for WAS started in spring 2011, and 107 signed their informed consent between July 2011 and November 2015 (Fig. 2). Three patients were excluded, because they did not meet all inclusion criteria, and 11 patients withdrew their consent. Of the remaining 93 patients, 89 completed visit 1, whereas 4 patients started directly at visit 2, as they had already undergone the multimodal anti-obesity treatment outside of the trial and thus received cost coverage for bariatric surgery by their health insurance. Thirty-three patients (36%) dropped out during the run-in phase prior to randomization. The reasons were stopping with the multimodal treatment (n = 25), no longer meeting all inclusion criteria (n = 4), not receiving cost coverage (n = 2), and patient's wish (n = 2). This enabled the randomization of 60 patients, as planned.

The key baseline characteristics of the entire cohort are depicted in Table 4. The overall trial population was predominantly female (77.4%), with a median age of 38 years (range 21–63). The mean body weight was 137 kg resulting in a median BMI of 48.6 kg/m^2 (range 37–70 kg/m^2). Despite the young mean age of the study sample, 73% of the patients were already diagnosed with arterial hypertension, 23% with type 2 diabetes mellitus, 44% with dyslipidemia, and 52% with sleep apnea. A relevant proportion of the study participants received new diagnoses of comorbid conditions during the trial, especially sleep apnea. Using NYHA functional class, 44% of patients were judged as class II and 22% even as class III. Consistently, the majority of patients (66%) suffered from exercise-induced dyspnea, most likely due to the high body weight.

Metabolic functions were also impaired in a relevant proportion of patients (Table 4). For instance, HOMA-IR was >2.5 in all but 9% of patients indicating insulin resistance in over 90% of study participants. Furthermore, 22% of patients were already medically treated for diabetes mellitus and 16% had triglycerides ≥200 mg/dL. In only one-quarter of patients, the NAFLD fibrosis score (58) provided no evidence of liver fibrosis. In 29% of premenopausal women, polycystic ovarian syndrome was diagnosed and 60% of men had a testosterone below 10 nmol/L.

Cardiovascular function was compromised in a large proportion of patients (Table 5). Eleven percent of patients had a peak VO_2 during CPET of equal or less than 14 mL/min/kg, consistent with a generally accepted threshold which places heart failure patients on the evaluation list for transplant (59). By contrast, only 22% reached more than 20 mL/min/kg. Of note, due to the high body weight of the patients, the median achieved maximum load was quite high, with more than 170% of predicted load. However, a markedly reduced exercise capacity was evident when judged by the median 6-min walking distance of only 420 m in the whole group, which is well below the tenth percentile of healthy age-matched adults (i.e. >510 m in men and >490 m in women) (60, 61). In fact, 20% of patients were able to walk less than <350 m. LV ejection fraction was >50% in all patients, whereas in 60% a diastolic dysfunction was diagnosed. Serum NT-proBNP levels were >125 ng/L in 23% and >300 ng/L in 5% of the patients.

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Table 4 Baseline characteristics of patients enrolled in the WAS trial. Values are *n* (%), mean (S.D.), or median (quartiles), as appropriate.

	Entire study cohort (*n* = 93)	**Women** (*n* = 72)	**Men** (*n* = 21)	**Reference range, if applicable**
Age (years)	38 (32; 46)	41 (33; 48)	36 (32; 42)	
Body height (cm)	170 (9)	167 (7)	179 (7)	
Body weigh, (kg)	140 (19)	135 (15)	157 (25)	
BMI (kg/m^2)	48.6 (6.1)	48.7 (6.0)	48.6 (6.2)	20.0–24.9
Waist circumference (cm)	133 (9)	129 (11)	146 (14)	W <80; M <94,
Heart rate (b.p.m.)	75 (11)	75 (10)	76 (12)	
NYHA functional class, *n* (%)				
I	32 (34.4)	22 (30.6)	10 (47.6)	
II	41 (44.1)	33 (45.8)	8 (38.1)	
III	20 (21.5)	17 (23.6)	3 (14.3)	
NT-proBNP (pg/mL)	67 (30; 119)	68 (35; 119)	43 (24; 120)	<125
Co-morbidities and risk factors				
Coronary heart disease, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	
Atrial fibrillation, *n* (%)	2 (2.2)	1 (1.4)	1 (4.8)	
Type 2 diabetes , *n* (%)	21 (22.7)	13 (18.1)	8 (38.1)	
Medically treated, *n* (%)	20 (21.5)[a]	12 (16.7)	8 (38.1)	
HbA1c (%)	5.8 (1.0)	5.8 (0,9)	6.1 (1.4)	<5.7
HOMA-IR[b]	5.9 (3.5)	5.3 (2.5)	8.7 (5.3)	<2.0
Lipid metabolism disturbances, *n* (%)	41 (44.1)	31 (43.1)	10 (47.6)	
Medically treated, *n* (%)	9 (9.7)	6 (8.3)	3 (14.3)	
LDL (mg/dL)	122 (33)	122 (34)	123 (38)	<160
HDL (mg/dL)	50 (12)	52 (12)	41 (9)	W >45, M >35
Triglycerides (mg/dL)	145 (86)	133 (67)	195 (147)	<150
Arterial hypertension, *n* (%)	67 (72.8)	52 (72.2)	15 (75)	
Medically treated, *n* (%)	48 (52.2)	36 (50)	12 (60)	
Systolic BP (mmHg)	135 (17)	135 (16)	133 (19)	<120
Diastolic BP (mmHg)	83 (11)	83 (11)	84 (13)	<80
Sleep apnea, *n* (%)	46 (51.7)	30 (43.5)	16 (80)	
Treated by CPAP, *n* (%)	10 (11.2)	4 (5.6)	6 (28.6)	
Polycystic ovary syndrome, *n* (%)		16 (28.6)[c]		
Male hypogonadism[d], *n* (%)			12 (60)	
Renal impairment, *n* (%)[e]	15 (17.0)	8 (11.8)	7 (35.0)	
Creatinine (serum) (mg/dL)	0.80 (0.12)	0.77 (0.12)	0.93 (0.29)	
eGFR[f], (mL/min/1.73 m^2)	95 (20)	92 (18)	105 (24)	>90
Albumin (mg/g) creatinine (spot urine)[g]	3 (3; 18.1)	3 (3; 12.5)	4.8 (3; 83.2)	<30
Liver function				
ALT (U/L)	30 (22.9; 42)	26 (18.5; 36.1)	47 (37; 53)	<35
No evidence of significant fibrosis[h] *n* (%)	24 (25.8)	19 (26.8)	5 (23.8)	
Evidence of significant fibrosis[h], *n* (%)	16 (17.4)	13 (18.3)	3 (14.3)	
Current smoker, *n* (%)	20 (21.3)	9 (12.5)	11 (52.4)	
Former smoker, *n* (%)	30 (32.6)	25 (34.7)	5 (23.8)	
Never smoker, *n* (%)	43 (46.1)	38 (52.8)	5 (23.8)	

[a]Additional six (6.5 %) were treated with metformin as off-label use for obesity treatment; [b]only in patients without medical antidiabetic treatment (*n* = 67); [c]of premenopausal women; [d]defined as morning total testosterone <10 nmol/L (2.88 ng/mL) (results available in 20 of 21 male patients); [e]Renal impairment was defined as eGFR <60 m/min/1.73 m^2 and/or >30 mg albumin/g creatinine in spot urine. However, only 1 patient had an eGFR <60 mL/min/1.73 m^2; [f]using the MDRD equation (63); [g]in 45 patients (36 women, 9 men) no albumin in spot urine was detectable; [h]defined by non-alcoholic fatty liver disease fibrosis score (58); in 1 patient data were missing; 52 patients (56.5%) had an indeterminate score between −1.455 and 0.675.
M, men; W, women.

Overall, QoL measured by the SF-36 questionnaire was markedly impaired. In particular, in both sexes, median scores of the physical functioning scale (i.e. the co-primary endpoint) were 35 points lower than a German reference sample (62). Consistently, in most other domains much poorer results than expected were observed, with the exception of a normal emotional status (Table 5). Based on the results of the PHQ-9 assessment, 50% of patients were judged as experiencing mild, 22% moderate, and 11% even severe depressive symptoms.

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Table 5 Cardiac and psychometric evaluation of the WAS trial cohort at baseline.

Parameter	Entire study cohort (*n* = 93)	Women (*n* = 72)	Men (*n* = 21)	Reference ranges or predicted values, if applicable
Exercise testing (values at maximum load) (*n* = 90)[a]				
Peak VO_2 (mL/min/kg)	18.1 (3.1)	17.8 (3.0)	18.9 (3.3)	
Peak VO_2, % of predicted	105 (20)	110 (18)	88 (17)	100
Load (W)	231 (66)	222 (63)	256 (73)	
Load, % of predicted	171 (56)	190 (48)	110 (28)	100
Heart rate (b.p.m.)	147 (24)	147 (22)	146 (29)	
VO_2 (mL/min)	2516 (477)	2389 (401)	2936 (475)	
VO_2, % of predicted	105 (20)	110 (18)	87 (14)	100
VCO_2	2421 (547)	2299 (491)	2820 (542)	
VE (L/min)	66 (15)	63 (14)	74 (16)	
VE max, % of predicted	70 (17)	73 (18)	62 (14)	100
BR[b], %	36 (13)	35 (13)	40 (13)	
BR[b], % of predicted	134 (54)	132 (57)	140 (49)	100
O_2 pulse (O_2/HR) (mL)	17 (4)	16 (3)	20 (4)	
O_2 pulse, % of predicted	129 (26)	135 (25)	111 (20)	100
RER (VCO_2/VO_2)	0.96 (0.10)	0.96 (0.09)	0.96 (0.10)	
RER >1.0, *n* (%)	24 (26.7)	19 (27.5)	5 (23.8)	
6-min walking distance, m (*n* = 93)	403 (66)	402 (72)	409 (70)	W >630; M >640
Echocardiography[c] (*n* = 93)				
LV mass (g)	189 (170; 220)	186 (167; 213)	247 (188; 281)	W ≤162; M ≤224
LV mass index (g/m^2)	78 (69; 89)	75 (68; 83)	89 (76; 105)	W ≤95; M ≤115
LV hypertrophy[d], *n* (%)				
Based on LV mass	64 (68.8)	54 (75.0)	10 (47.6)	
Based on LV mass index	7 (7.5)	6 (8.3)	1 (4.8)	
LV end-diastolic volume (mL)	93 (28)	92 (28)	100 (27)	W ≤106; M ≤150
LV end-diastolic volume index (mL/m^2)	37 (10)	37 (10)	38 (10)	W ≤61; M ≤74
LV dilation[e], *n* (%)	34 (36.6)	29 (40.3)	5 (23.8)	
LV ejection fraction (%)	60 (5)	61 (5)	58 (4)	W 54–74; M 52–72
Reduced LV ejection fraction[f], *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	
Global longitudinal strain (*n* = 43) (%)	−18.4 (3.1)	−17.1 (2.2)	−18.6 (3.2)	≤−17
LA diameter (mm)	40 (3)	39 (3)	42 (4)	W ≤43 mm; M ≤47 mm
LA dilation[g], *n* (%)	28 (30.1)	21 (29.2)	7 (33.3)	
Diastolic dysfunction[h], *n* (%)	56 (60.2)	46 (63.9)	10 (47.6)	
E/e'	7.7 (2.2)	7.6 (2.1)	8.0 (2.7)	≤8
e' $_{lateral}$ (cm/s)	11.8 (3.1)	11.9 (3.1)	11.6 (3.2)	>10
TR Vmax (m/s)	2.4 (0.3)	2.4 (0.3)	2.2 (0.2)	≤2.8
Cardiac MRI (*n* = 59)[i]				
LV mass (g)	150 (125; 178)	136 (118; 159)	180 (168; 204)	W 75–175; M 118–230
LV mass index (g/m$^{2)}$	61 (53; 71)	57 (52; 71)	66 (65; 80)	W 63–95; M 70–113
EndoPAT (*n* = 93)				
LnRHI	0.60 (0.26)	0.60 (0.28)	0.58 (0.22)	>0.51
Quality of life: SF-36[j] (*n* = 88)				
Physical functioning scale	50 (35; 65)	50 (35; 65)	53 (40; 69)	W 95 (70; 100); M 95 (85; 100)
Role physical	71 (0; 100)	50 (0; 100)	75 (0; 100)	W 100 (75; 100); M 100 (100; 100)
Bodily pain	51 (39; 62)	43 (41; 62)	62 (32; 70)	W 84 (51; 100); M 100 (62; 100)
General health	44 (30; 58)	45 (31; 60)	35 (22; 52)	W 67 (52; 82); M 72 (55; 82)
Vitality	40 (30; 52)	40 (25; 60)	40 (30; 45)	W 60 (45; 75); M 70 (55; 80)
Role emotional	100 (42; 100)	100 (50; 100)	100 (25; 100)	W 100 (100; 100); M 100 (100; 100)
Social function	63 (50; 88)	63 (50; 88)	63 (41; 97)	W 100 (75; 100); M 100 (88; 100)
Mental health	68 (52; 76)	68 (62; 76)	68 (52; 80)	W 72 (60; 84); M 80 (68; 88)
Physical health component summary score	35 (29; 44)	35 (28; 44)	37 (33; 42)	W 53 (42; 57); M 54 (47; 57)
Mental health component summary score	50 (38; 55)	50 (38; 55)	37 (33; 55)	W 52 (46; 70); M 54 (50; 57)

(Continued)

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Table 5 Continued.

Parameter	Entire study cohort (n = 93)	Women (n = 72)	Men (n = 21)	Reference ranges or predicted values, if applicable
Depression screening (n = 88)				
PHQ-9 (sum score)[k]	8 (6; 11)	7 (6; 11)	8 (5; 12)	F 3.1 (3.5); M 2.7 (3.5)

Values are mean (SD) or median (quartiles), unless indicated otherwise.
[a]In three patients, not all CPET values could be derived due to technical problems. [b]Due to technical problems results were only available in 48 patients (35 women). [c]Reference values for echocardiography (64), except for diastolic function (65). [d]Defined as LVEF <50%. [e]Defined as LV enddiastolic volume >150 mL in men and >106 mL in women or LV enddiastolic diameter >58 mm in men and >52 mm in women, respectively. [f]Defined as 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. [g]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. [h]Defined as reduced LVEF, LV hypertrophy, or LV dilation, as well as if three out of the following four criteria were fulfilled (65): 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. [i]Patients were excluded from cardiac MRI in case of a tattoo or relevant claustrophobia. [j]Reference values for SF-36 (62). [k]Reference values for PHQ-9 were only available as mean (s.d.) (69, 70); depression severity was categorized as: 5–9 mild; 10–14 moderate; 15–27 severe.
BR, breathing reserve; E/e', filling index; LA, left atrial; lnRHI, natural logarithm of the reactive hyperemia index; LV, left ventricular; M, men; RER, respiratory exchange ratio; TR Vmax tricuspid regurgitation maximal flow velocity; VO_2, oxygen consumption; VCO_2, carbon dioxide production; VE, minute ventilation; W, women.

Apart from the expected differences in some cardiac and psychometric parameters, predominantly men were diagnosed with diabetes, sleep apnea, and were active smokers. However, the distribution of other cardiovascular risk factors showed no relevant difference between the sexes. Most baseline characteristics of patients who terminated study participation before randomization were readily comparable, such as age, BMI, and primary outcome measures. However, more men than women terminated the study early, leading also to a higher percentage of obstructive sleep apnea among drop-outs.

Discussion

The prevalence of obesity is continuously increasing and its association with cardiovascular disease is well established. Obesity acts through the development of risk factors, such as hypertension, dyslipidemia, and glucose intolerance or type 2 diabetes, but may also mediate damage independently through the promotion of systemic inflammation or increased sympathetic tone (68). WAS is the first randomized controlled trial specifically designed to investigate the impact of RYGB vs psychotherapy-supported intensive lifestyle intervention on 12-month changes in cardiovascular performance measured by standardized CPET. The second equivalently powered co-primary endpoint addresses the physical function domain of generic health-related QoL. While several RCTs testing bariatric and metabolic surgery have investigated QoL as a secondary endpoint and suggested significant benefits by the surgical approach, none of these studies addressed it as a predefined primary outcome.

The main hypothesis of WAS is that the major weight loss induced by RYGB in severely obese patients will lead to a combined and clinically relevant improvement of cardiovascular performance and physical functioning. WAS is powered to answer both questions if the resulted changes are clinically meaningful. Accordingly, we *a priori* defined a net improvement of peak VO_2 by 5 mL/min/kg and of 10 points in the SF-36 physical functioning scale between both groups; 5 mL/min/kg may be considered a remarkable increase in peak VO_2, when compared to other studies, for example in the area of heart failure (69, 70). However, WAS also claims to provide mechanistic explanations to the improved primary endpoints. The detailed cardiologic phenotyping in the WAS trial design includes biomarkers, electro- and echocardiography, and exercise testing, as well as cardiac MRI. This will allow to comprehensively assess the cardiac morphology and function of severely obese patients and to determine the changes associated with substantial weight loss. Of note, the study sample also prominently illustrates the difficulties arising when physiological measurements are compared between obese and non-obese subjects. Put differently, what should be considered a normal value in an obese person? For example, CPET derived parameters were partly supra-normal or only mildly reduced if judged by % values of predicted, but were markedly reduced if indexed by weight, for example, peak VO_2 (mL/min/kg). In fact, the obtained mean peak VO_2 values were consistent with a major, obesity-induced cardiopulmonary mismatch also found in symptomatic heart failure (59, 71). Consistently, the distance walked in 6 min was 30% lower than anticipated for individuals of comparable age. By contrast, however, mean LV mass was normal when indexed to body surface area (BSA), whereas

it was markedly increased when calculated from crude measurements. Hence, the objectively hypertrophied heart becomes 'normal' because the BSA is grossly increased. It will be important to appropriately weigh these associations against each other when the WAS trial reports on the outcomes of operated and non-operated patients. As such, we expect that the marked weight loss induced by surgery will improve the crude, but not necessarily the indexed values.

Because body weight is such a major contributor to the executed workload generated during CPET via treadmill, the observed mean maximum load of 231 W was expectedly very high, in fact much higher than the maximum load anticipated for cycle ergometry. However, CPET via treadmill was chosen for the following reasons: walking as a weight-bearing exercise in contrast to cycling reflects the physiological load of these patients, who have to carry and move their weight permanently. Furthermore, at the time of study initiation, the available cycle ergometers were only approved for a body weight ≤150 kg and thus not regarded safe for this study population.

Furthermore, the comprehensive psychometric evaluation of the patients at the different study visits will shed additional light on obesity-induced alterations of psycho-emotional health. The patients of the WAS cohort had lower QoL in virtually all domains of the SF-36 and more pronounced depressive symptoms in psychometric self-reported PHQ-9 testing compared to normal values. These findings underline the profound impact of obesity on both physical and mental conditions. Together with the extensive data derived from complementary technical investigations, WAS offers the opportunity for new insights into the brain-body interaction. In addition, WAS addresses hitherto unanswered questions in several other obesity-related diseases. A specific focus will be the evaluation of the improvements of metabolic and endocrine dysfunction, but also liver impairment. Potential resolution of PCOS in women and changes in steroid patterns will be part of the investigation, as well as remission of the very frequent insulin resistance. The fact that all but two patients in the lifestyle group opted for surgery at visit 4, will improve the statistical power for the analyses of several secondary endpoints, as these patients will be 1 year after surgery at visit 5 and might complement visit 4 data of the surgery group.

Strengths and limitations

The major strength of WAS is its comprehensive cardiovascular characterization employing multiple state-of-the-art tools of all patients at four time points over a period of 3 years in total. WAS is quite unique due to its control group with a dedicated lifestyle intervention, professionally led by psychiatrists and psychologists experienced in obesity care. This contrasts with most other RCTs in the field that solely mandated standard medical therapy (e.g. for diabetes or hypertension) in the control group (30, 72, 73). It is possible that the need to undergo a multimodal anti-obesity treatment already prior to randomization reduces the effect of the psychotherapy-augmented lifestyle intervention in the conservative treatment group as individual patients had already lost weight during the pre-randomization phase that plateaued during the randomized period.

Cardiopulmonary exercise capacity might often be limited in extremely obese persons and the lactate threshold may not be reached. To reduce the bias potentially introduced by symptom-limited exercise, we followed strict rules of patient motivation. We further will report the change in VO_2 (from visits 2 to 4) at the peak exercise RER of the baseline visit. The number of patients in our sample is not sufficient to investigate endpoints like mortality or incident cardiovascular events. However, important surrogate endpoints will be studied that are expected to shed new light on mechanistic associations in areas like psychometric outcomes, brain and liver function and morphology, and metabolomics. This is made possible by a highly interdisciplinary team of investigators enriching the trial with state-of-the-art methodology allowing to study multiple important secondary endpoints. The sex distribution is typical of a bariatric collective. However, this also means that sex-specific findings may not be reliably detected due to the relatively small number of male participants. The WAS trial was designed as an open-randomized trial since respective sham procedures were not considered feasible. We cannot exclude selection bias, because the complex study design required a significant commitment on the side of the patient, possibly leading to a disproportionate enrollment of highly motivated patients. However, as such a bias is expected to improve the effect size (i.e. weight loss) predominantly in the lifestyle group, it will rather lead to an underestimation of the difference between conservative and surgical therapy rather than to an overestimation. Recruitment was challenging and took 11 months longer than the estimated 42 months. Although we anticipated the drop-out rate quite accurately, we did not foresee the markedly uneven distribution of drop-outs for reasons detailed above. However, we successfully adapted the statistical concept and adopted an unequal randomization procedure. Due to unequal drop-out, an

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intention-to-treat analysis will not be reasonable. A high drop-out rate may make it difficult to generalize results. Therefore, an important aspect of the main analysis will be to detect any differences between patients who remained in the study after randomization and those who terminated participation.

Conclusion

The majority of severely obese patients suffer from highly relevant cardio–psycho–metabolic consequences of this disabling condition. Bariatric surgery is currently the most effective method to achieve a sustained body weight reduction. Furthermore, this intervention improves cardiovascular risk factors like diabetes and hypertension, and yet there is no evidence from randomized trials regarding respective effects on cardiovascular performance. Due to its comprehensive assessment of cardio-metabolic function and its detailed psychometric evaluation, WAS will significantly advance our understanding of the underlying consequences of established and resolved severe obesity.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EC-21-0338.

Declarations of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

S Störk and M Fassnacht contributed equally to this work.

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