Meal Replacement by Formula Diet Reduces Weight more than a Lifestyle Intervention Alone in Patients with Overweight or Obesity and Accompanied Cardiovascular Risk Factors – the ACOORH Trial

Running title: Formula diet and lifestyle intervention in obesity

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Abstract

Background: As formula diets have demonstrated to be effective in reducing weight, we hypothesized that in patients with overweight or obesity and accompanied cardiovascular risk factors, combining a liquid formula diet with a lifestyle intervention is superior in reducing weight and improving cardiovascular risk factors than lifestyle intervention alone.

Methods: In this multicenter RCT 463 participants with overweight or obesity (BMI: 27-35 kg/m²; at least one additional co-morbidity of the metabolic syndrome) were randomized (1:2) into either a control group with lifestyle intervention only (CON, n=155) or a lifestyle intervention group including a liquid meal replacement (INT, n=308). Both groups used telemonitoring devices (scales and pedometers), received information on healthy diet and were instructed to increase physical activity. Telemonitoring devices automatically transferred data into a personalised online portal and acquired data were discussed. INT obtained a liquid meal replacement substituting three meals/day (~1,200 kcal) within the first week. During weeks 2-4, participants replaced two meals/day and during weeks 5-26 only one meal/day was substituted (1,300-1,500 kcal/day). Follow-up was conducted after 52 weeks. Intention-to-treat analyses were performed. Primary outcome was weight change. Secondary outcomes comprised changes in cardiometabolic risk factors including body composition and laboratory parameters.

Results: From the starting cohort 360 (78%, INT: n=244; CON: n=116) and 317 (68%, INT: n=216; CON: n=101) participants completed the 26-weeks intervention phase and the 52-weeks follow-up. The estimated treatment difference (ETD) between both groups was -3.2 kg [-4.0; -2.5] (P<0.001) after 12 weeks and -1.8 kg [-2.8; -0.8] (P<0.001) after 52 weeks.

Conclusions: A low-intensity lifestyle intervention combined with a liquid meal replacement is superior regarding weight reduction and improvement of cardiovascular risk factors than lifestyle intervention alone.

Introduction

A high energy intake combined with low physical activity are major determinants for overweight and obesity and contribute to the overall increase of non-communicable diseases [1].

Although lifestyle interventions have been shown to induce clinically relevant effects, adherence to these approaches remains low overall. Therefore, alternative treatment strategies need to be considered [2, 3]. In this context, liquid meal replacements have been shown to be an useful treatment option to manage obesity and diseases such as type 2 diabetes [4-6], leading to improvements in fat mass, blood pressure, HbA_{1c}, or insulin [7, 8]. Furthermore, there is a positive association between partial and complete meal replacement with weight reduction which was shown in favor of complete meal replacement in patients with type 2 diabetes [9]. Based on their positive effects in the management of patients with type 2 diabetes, liquid meal replacements have been included into current guidelines for baseline treatment of type 2 diabetes [10-12], but not uniformly for the routine management of overweight and obesity [3]. In this regard, there is still uncertainty about weight maintenance and long-term effectivity of formula diets [13, 14] and whether there is a beneficial effect of adding a formula diet to an lifestyle intervention and/or nutrition counseling alone in patients with overweight and obesity [12].

Hence, an international and multicenter RCT, the *Almased Concept against Overweight and Obesity and Related Health Risk* (ACOORH)-study, was conducted to examine the impact of a liquid meal replacement together with a low-intensity lifestyle intervention compared to a low-intensity lifestyle intervention alone on weight loss in patients with overweight or obesity and accompanied cardiovascular risk factors.

Materials/Subjects and Methods

Study design and population

Participating volunteers (n=463) were randomly allocated with a ratio of 1:2 into either a lifestyle intervention group (CON, n=155) or a meal replacement-based lifestyle intervention group (INT, n=308). The lifestyle intervention was characterized by a 26-week intervention phase and a follow-up phase until week 52 and the study design has been described in detail previously in a predefined subanalysis of the ACOORH study focusing solely on patients with prediabetes [15]. This multicenter RCT received ethical approval (registered at *drks.de*; ID: DRKS00006811) for each participating center and the study reporting adheres to CONSORT guidelines. Informed consent was obtained from all participating volunteers. Study participants were recruited in all study centers either through direct contacting based on existing patient files, (2) proactive study enquiry by the participants via the study center homepages, or (3) advertisements in newspapers. Inclusion and exclusion criteria have been described in detail previously [15].

Intervention and diet regime

Both groups were provided with guideline booklets about healthy cooking, received advices regarding physical activity and a healthy lifestyle including encouragement to lose weight, and were equipped with telemetric scales (smartLAB scale W; HMM Holding AG, Dossenheim, Germany) and pedometers (smartLAB walk P+; HMM Holding AG, Dossenheim, Germany). Probands were recommended to note down a 4-day, unweighted diet record at baseline and after 12, and 52 weeks of the study and all records (including steps and body

weight) were discussed during the study visits (personal contact time ≈ 1-2 h per visit). A detailed description of the study can be found elsewhere [15] and is illustrated in Fig. 1.

Additionally, the INT group was provided with the liquid soy-yogurt-honey-based meal replacement Almased-Vitalkost® (protein content: 53.3% (83 % soy-protein-isolate, and 17% milk protein), glycemic index (GI): 27, energy per 100 g powder: 1507 kJ (360 kcal), Almased-Wellness-GmbH, Bienenbüttel, Germany [16]) for the first 26 weeks and received an accompanying booklet containing information about preparing and applying the liquid formula diet and general advices about low-carbohydrate, low-glycemic and protein-rich meals. The management of the liquid formula diet regime during the study is described in detail elsewhere [15]. All booklet records were evaluated at each visit by study nurses and used for nutritional and lifestyle counselling.

Measurements

Measurements were performed at baseline as well as after 4, 12, 26, and after 52 weeks as described in detail elsewhere [15]. Body composition (Seca medical Body Composition Analyzer® (seca-mBCA 115), Hamburg, Germany [17]) and blood pressure (Mobil-O-Graph PWA; I.E.M. GmbH, Stolberg, Germany) were determined by using validated devices. Biochemical blood parameters were determined by venous blood sampling. Adverse and serious adverse events [18] were documented continuously (participant questionnaire) and were reviewed by an external monitor.

Statistics

Sample size calculation was based on the results of a previous study [19] and its assumptions, including randomization and number of dropouts, are described in detail elsewhere [15]. Final sample size per group comprised at least 19 participants for each study center. However, based on previous experiences in all participating centers with dropout rates greater than 50% for long-term adherence to weight management programs, at least a number of 40 participants per center was targeted.

Primary outcome of the ACOORH study was body weight in kg after 4, 12, 26 and 52 weeks of intervention. Power calculation was performed for the difference of body weight change after 12 weeks of intervention between INT and CON. Secondary outcomes comprised changes in anthropometric (fat mass (FM), fat free mass (FFM), and waist circumference (WC)) and clinical parameters (fasting blood glucose (FBG), systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol, HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), TG) after 4, 12, 26 and 52 weeks of intervention.

An independent institute (ACOMED statistik®, Leipzig, Germany) executed the statistical analysis and a detailed description including statistical tests applied (for parametric and non-parametric data) and software used can be found elsewhere [15]. Completer (per-protocol (PP)) and intention-to-treat (ITT) analyses were applied. All statistical tests were two-sided and significance was assumed at $\alpha<0.05$. Participants who visited all follow-up assessments were integrated into the PP analysis. Primary analysis focused on the ITT approach as these values are of more clinical relevance. Last-observation-carried-forward (LOCF) method was applied to replace missing data for the ITT analysis.

Results

Four hundred thirty-nine (95%, INT: n=299; CON: n=140) from the starting cohort finished the first 4 weeks of the intervention phase. Follow-up data after 12, 26 and 52 weeks were available from 396 (86%, INT: n=270; CON: n=126), 360 (78%, INT: n=244; CON: n=116) and 317 participants (68%, INT: n=216; CON: n=101). Anthropometric and clinical parameters of INT and CON at baseline are illustrated in Table 1. Dropouts demonstrated no statistical difference in comparison to the non-dropout group (Supplementary Table 1). Participants dropped out because of (1) health issues, (2) work-related issues, (3) personal issues and (4) other reasons. No acute cardiac event, hospitalization for cardiovascular disease, or other serious adverse events related to the study participation occurred.

Compared to CON, INT significantly lost more weight after 4 weeks (-4.0 kg with 95% CI [-4.3;-3.8] vs. -1.4 kg [-1.8;-1.1]; P<0.001), 12 weeks (-5.8 kg with 95% CI [-6.3;-5.3] vs. -2.7 kg [-3.3;-2.1]; P<0.001), 26 weeks (-5.9 kg with 95% CI [-6.5;-5.4] vs. -3.0 kg [-3.8;-2.2]; P<0.001) and 52 weeks (-4.4 kg [-5.0;-3.8] vs. -2.7 kg [-3.0;-2.0]; P<0.001) in the ITT analysis. The estimated treatment difference (ETD) between both groups was -2.6 kg [-3.5; -1.8] (P<0.001) after 4 weeks, -3.2 kg [-4.0; -2.5] (P<0.001) after 12 weeks, -2.9 kg [-3.7; -2.1] (P<0.001) after 26 weeks and -1.8 kg [-2.8; -0.8] (P<0.001) after 52 weeks. These differences were even stronger in the PP analysis after 4 weeks (-4.5 kg with 95% CI [-4.8;-4.2] vs. -1.6 kg [-2.0;-1.2] P<0.001), 12 weeks (-6.3 kg with 95% CI [-6.8;-5.8] vs. -3.2 kg [-3.9;-2.6] P<0.001), 26 weeks (-6.8 kg with 95% CI [-7.5;-6.2] vs. -3.6 kg [-4.6;-2.7] P<0.001) and 52 weeks (-5.0 kg [-5.7;-4.2] vs. -3.5 kg [-4.5;-2.5] P=0.021).

Weight reduction was accompanied with changes in WC, FM, FBG, SBP, DBP, total cholesterol, TG, and LDL-C in both groups following the intervention, with a particularly

pronounced effect within the first 12 weeks (Fig. 2) (ITT analysis). These effects were already evident after 4 weeks of intervention in all parameters in the INT group (all P<0.001) (ITT analysis), but not in the CON group. Only FM, WC, and SBP (all P<0.001) as well as DBP and total cholesterol (both P<0.01) significantly changed after 4 weeks in CON (ITT analysis). The aforementioned 12-week changes remained significantly altered after 26 weeks of intervention in the INT group in all parameters (P<0.001) (ITT analysis). In contrast, only FM, WC, and SBP remained significantly changed after 26 weeks in the CON group (all P<0.01) (ITT analysis).

Compared to CON, INT significantly reduced more WC, FM, FFM, total cholesterol, and LDL-C after 12 weeks of intervention (Table 2). These differences remained significant after 52 weeks in FM, FFM, and. INT reduced FM by -3.3 kg with 95% CI [-3.9; -2.7] vs. -2.4 kg [-3.2; -1.5] P=0.020) and) compared to CON after 52 weeks. INT showed a pronounced loss in FFM compared to CON after 52 weeks (-0.9 kg [-1.3; -0.6] vs. -0.3 kg [-0.9; 0.2] P<0.001).

Discussion

The results of the ACOORH trial show that a low-intensity lifestyle intervention accompanied with a liquid formula diet contributes to larger reductions in body weight in patients with overweight or obesity and accompanied cardiovascular risk factors compared to a low-intensity lifestyle intervention alone and these findings remain significantly superior even after 52 weeks.

The weight reduction after 1 year (-5.8 kg [-6.3; -5.3] (ITT analysis)) is comparable to other lifestyle intervention programs with smaller cohorts (n=19-167), which have also shown a significant weight loss ranging from -1.43 kg to -12.1 kg [20]. In particular, very intense lifestyle programs with rigorous meal replacement regimen [21] or intensive support [22] led to mean

weight losses greater than 10 kg. Furthermore, study effects and weight loss show a dose-response pattern in relation to program duration [23] and intensity of support [20]. The longer the intensive intervention phase and the greater the level of support, the greater the weight loss.

A recently published systematic review and meta-analysis demonstrated larger weight reductions following either very low (<800 kcal/day) or low-calorie (>800 kcal/day) liquid meal replacements (ranging from 8.9 to 15.0 kg) in patients with obesity (BMI: 36-43 kg/m²) [24]. Compared to the present study can be assumed that the weight reduction difference to the studies in the meta-analysis is resulted by a higher calorie intake per day (1300-1500 kcal/day). In addition, we chose a more moderate daily energy intake target to increase study compliance and adherence as well as to minimise dropout rates. In support of this approach, it has been shown that a moderate and continuous weight loss reduces the risk for adverse outcomes in the long-term compared to a fast and severe weight loss [25].

In the present study, weight reduction was accompanied with further improvements, (predominantly achieved in the INT-group) during the 12-week intervention phase in cardiometabolic parameters, including FM, WC, DBP and LDL-C and TC. Furthermore, after 52 weeks of follow-up there was still a significant difference in FM loss between both groups. These findings are in line with other lifestyle intervention trials with low-calorie diets in patients with prediabetes [7] or type 2 diabetes [26, 27] or lifestyle interventions with physical activity in patients with obesity [28].

The ACCORH trial and its strengths are characterized by (1) a comparably large sample size in an (2) international and multicenter design with (3) a randomized controlled trial approach. Moreover, (4) two intervention groups were followed up over a period of 52 weeks and this trial was conducted in a (5) real-world setting in which a low-intensity lifestyle

intervention was combined with liquid meal replacement. The intention was to design a practical lifestyle-based intervention program which could be easily implemented into present health care programs. Moreover, the (6) inclusion of only high-risk participants with at least one additional co-morbidity of the metabolic syndrome indicates a further strength of the study.

There are also limitations in the present trial that have to be considered. We did not constantly (i) controlled the participants for decreased energy intake or for false food compositions (e.g., amount of carbohydrates or proteins) by monitoring diet diaries. As it is well-known that dietary records of patients with obesity are characterized by systematic errors, we, therefore, had purposely chosen not to constantly monitor these records [29]. However, the prepared 4-day diet diaries of the probands were used in each study visit as a resource of information for the lifestyle counseling. Moreover, volunteers of the INT group should record the number of containers and amount of meal replacement consumed. Thus, we were able, at least, to evaluate the intake of liquid meal replacement within the first 12 weeks. A second limitation was the imputation of missing values by the LOCF approach. More sophisticated imputation methods like multiple imputation could have been performed as this imputation technique takes the uncertainty of the imputed values more realistic into account. However, the LOCF procedure was consciously chosen as it is a conservative statistical approach to estimate treatment effects, which might have even underestimated the results. Concomitantly, the ITT analysis method performed prevents the overestimation of data and takes the number of dropouts into account.

In sum, a low-intensity lifestyle intervention accompanied with a liquid meal replacement contributes to a long-term and clinically relevant weight reduction in patients with overweight and obesity and further cardiovascular risk factors. Furthermore, this weight reduction was

characterized with improvements in cardiovascular and cardiometabolic risk factors. The present findings underline the efficacy of the liquid formula diet tested in individuals with overweight or obesity and accompanied cardiovascular risk factors when included in a lifestyle intervention program. This therapy approach should be considered as a valid option for management of overweight and obesity in clinical, community and health care settings.

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Conflict of Interest

W Banzer, A Berg, KM Braumann, M Halle, K Kempf, D McCarthy, HG Predel, J Scholze, D Führer-Sakel, and H Toplak received research support for their departments from the Almased-Wellness-GmbH to perform the study. A Berg, M Halle, D McCarthy, and H Toplak have also received speakers´ honoraria (category: *personal financial interests*) from Almased-Wellness-GmbH. All four authors declare that their honoraria had no influence on their contribution to the study design, data collection, data analysis, manuscript preparation and/or publication decisions. Nina Schaller and M Röhling declare no conflict of interest regarding the publication of this article.

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Author contributions

A Berg had the initial idea for the study design and initiated the study. The protocol was designed together with H Toplak and with additional contributions of S Martin. M Halle and M Röhling drafted the manuscript. All authors critically revised the manuscript and approved the final version. W Banzer, A Berg, KM Braumann, D McCarthy, M Halle, K Kempf, S Martin, HG Predel, J Scholze, D Führer-Sakel, and H Toplak collected data at their local sites. A Berg is the guarantor of this work and all co-authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A et al. Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med. 2017; 377: 13–27.
2. Konig D, Hörmann J, Predel HG, Berg A. A 12-Month Lifestyle Intervention Program Improves Body Composition and Reduces the Prevalence of Prediabetes in Obese Patients. Obes Facts. 2018; 11: 393-399.
3. Astbury NM, Piernas C. A systematic review and meta-analysis of the effectiveness of meal replacements for weight loss. Obes. Rev. 2019; 20: 569-587.
4. Lean ME, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet. 2017; 391: 541–551.
5. Steven S, Hollingsworth KG, Al-Mrabeh A, Avery L, Aribisala B, Caslake M et al. Very Low-Calorie Diet and 6 Months of Weight Stability in Type 2 Diabetes: Pathophysiological Changes in Responders and Nonresponders. Diabetes Care. 2016; 39: 808-815.
6. Kempf K, Schloot NC, Gartner B, Keil R, Schadewaldt P, Martin S. Meal replacement reduces insulin requirement, HbA1c and weight long-term in type 2 diabetes patients with >100 U insulin per day. J Hum Nutr Diet. 2014; 27 Suppl 2: 21-27.
7. Konig D, Kookhan S, Schaffner D, Deibert P, Berg A. A meal replacement regimen improves blood glucose levels in prediabetic healthy individuals with impaired fasting glucose. Nutrition. 2014; 30: 1306-1309.
8. Kempf K, Altpeter B, Berger J, Reuss O, Fuchs M, Schneider M et al. Efficacy of the Telemedical Lifestyle intervention Program TeLiPro in Advanced Stages of Type 2 Diabetes: A Randomized Controlled Trial. Diabetes Care. 2017; 40: 863-871.
9. Kempf K, Rohling M. Individualized Meal Replacement Therapy Improves Clinically Relevant Long-Term Glycemic Control in Poorly Controlled Type 2 Diabetes Patients. Nutrients. 2018; 10:
10. American Diabetes Association. 4. Lifestyle management: standards of medical care in diabetes-2018. Diabetes Care. 2018; 41: S38–S50.
11. Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American diabetes association (ADA) and the European association for the study of diabetes (EASD). Diabetes Care. 2018; 41: 2669–2701.
12. Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G et al. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2018; 61: 2461-2498.
13. Lean MEJ, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L et al. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. Lancet Diabetes Endocrinol. 2019; 7: 344–355.
14. Yumuk V, Tsigos C, Fried M, Schindler K, Busetto L, Micic D et al. European Guidelines for Obesity Management in Adults. Obes Facts. 2015; 8: 402-424.
15. Röhling M, Kempf K, Banzer W, Berg A, Braumann KM, Tan S et al. Prediabetes Conversion to Normoglycemia Is Superior Adding a Low-Carbohydrate and Energy Deficit Formula Diet to Lifestyle Intervention-A 12-Month Subanalysis of the ACOORH Trial. Nutrients. 2020; 12:
16. Koohkan S, McCarthy D, Berg A. The effect of a soy-yoghurt-honey product on excess weight and related Page health risk factors - A review. J Nutrition Health Food Sci. 2017; 5: 1-10.

17. Bosy-Westphal A, Schautz B, Later W, Kehayias JJ, Gallagher D, Müller MJ. What makes a BIA equation unique? Validity of eight-electrode multifrequency BIA to estimate body composition in a healthy adult population. Eur J Clin Nutr. 2013; 67 Suppl 1: S14-21.
18. U.S. Food and Drug Administration, *Investigational New Drug Application (IND). Sec. 312.32 IND Safety Reporting*. 2018: U.S. Food and Drug Administration.
19. Berg A, Deibert P, Landmann U, König D, Schmidt-Trucksäss A, Rücker G et al. Gewichtsreduktion ist machbar. Halbjahresergebnisse einer klinisch kontrollierten, randomisierten Interventionsstudie mit übergewichtigen Erwachsenen. Ernährungs-Umschau. 2003; 50: 386-393.
20. Astbury NM, Piernas C. A systematic review and meta-analysis of the effectiveness of meal replacements for weight loss. Obes Rev. 2019; 20: 569–587.
21. Lowe MR, Butryn ML, Zhang F. Evaluation of meal replacements and a home food environment intervention for long-term weight loss: a randomized controlled trial. Am J Clin Nutr. 2018; 107: 12-19.
22. Rock CL, Flatt SW, Sherwood NE, Karanja N, Pakiz B, Thomson CA. Effect of a free prepared meal and incentivized weight loss program on weight loss and weight loss maintenance in obese and overweight women: a randomized controlled trial. Jama. 2010; 304: 1803-1810.
23. Ahern AL, Wheeler GM, Aveyard P, Boyland EJ, Halford JCG, Mander AP et al. Extended and standard duration weight-loss programme referrals for adults in primary care (WRAP): a randomised controlled trial. Lancet. 2017; 389: 2214-2225.
24. Leslie WS, Taylor R, Harris L, Lean ME. Weight losses with low-energy formula diets in obese patients with and without type 2 diabetes: systematic review and meta-analysis. Int J Obes (Lond). 2017; 41: 96-101.
25. Stefan N, Haring HU, Schulze MB. Metabolically healthy obesity: the low-hanging fruit in obesity treatment? Lancet Diabetes Endocrinol. 2017; 6: 249–258.
26. Sellahewa L, Khan C, Lakkunarajah S, Idris I. A systematic review of evidence on the use of very low calorie diets in people with diabetes. Curr Diabetes Rev. 2017; 13: 35–46.
27. Jackness C, Karmally W, Febres G, Conwell IM, Ahmed L, Bessler M et al. Very low-calorie diet mimics the early beneficial effect of Roux-en-Y gastric bypass on insulin sensitivity and beta-cell Function in type 2 diabetic patients. Diabetes. 2013; 62: 3027-3032.
28. Baillot A, Romain AJ, Boisvert-Vigneault K, Audet M, Baillargeon JP, Dionne IJ et al. Effects of lifestyle interventions that include a physical activity component in class II and III obese individuals: a systematic review and meta-analysis. PLoS One. 2015; 10: e0119017.
29. Bhanpuri NH, Hallberg SJ, Williams PT, McKenzie AL, Ballard KD, Campbell WW et al. Cardiovascular disease risk factor responses to a type 2 diabetes care model including nutritional ketosis induced by sustained carbohydrate restriction at 1 year: an open label, non-randomized, controlled study. Cardiovasc Diabetol. 2018; 17: 56.

Figure legends

Fig.1. Flow diagram.

Fig. 2. Mean changes in secondary outcomes.

(A) weight, (B) systolic blood pressure (C) diastolic blood pressure, (D) LDL-C, (E) total cholesterol, (F) fasting blood glucose, (G) waist circumference, (H) triglycerides, and (I) fat mass after 4, 12, 26, and 52 weeks. Within-group changes were analyzed using ANOVA with repeated measures. ***p<0.001 vs. baseline; **p<0.01 vs. baseline; *p<0.05 vs. baseline; ITT, intention-to-treat analysis

Table legends

Table 1. Baseline characteristics.

Data are presented as means ± standard deviations, or percentages. BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; FM, fat mass; FFM, fat free mass; HC, hip circumference; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; SBP, systolic blood pressure; WC, waist circumference; WHR, waist-to-hip ratio

Table 2. Intra and intergroup changes in the INT and CON-group after 12 and 52 weeks compared to baseline

Data are shown as mean [95% CI]. ***p<0.001 vs. baseline; **p<0.01 vs. baseline; *p<0.05 vs. baseline. Differences in changes after 12 as well as 52 weeks between both groups were analyzed using ANCOVAs adjusting for baseline values. DBP, diastolic blood pressure; FBG, fasting

402 blood glucose; FM, fat mass; FFM, fat free mass; HDL-C, HDL cholesterol; LDL-C, LDL

403 cholesterol; n.a., not available; SBP, systolic blood pressure; WC, waist circumference

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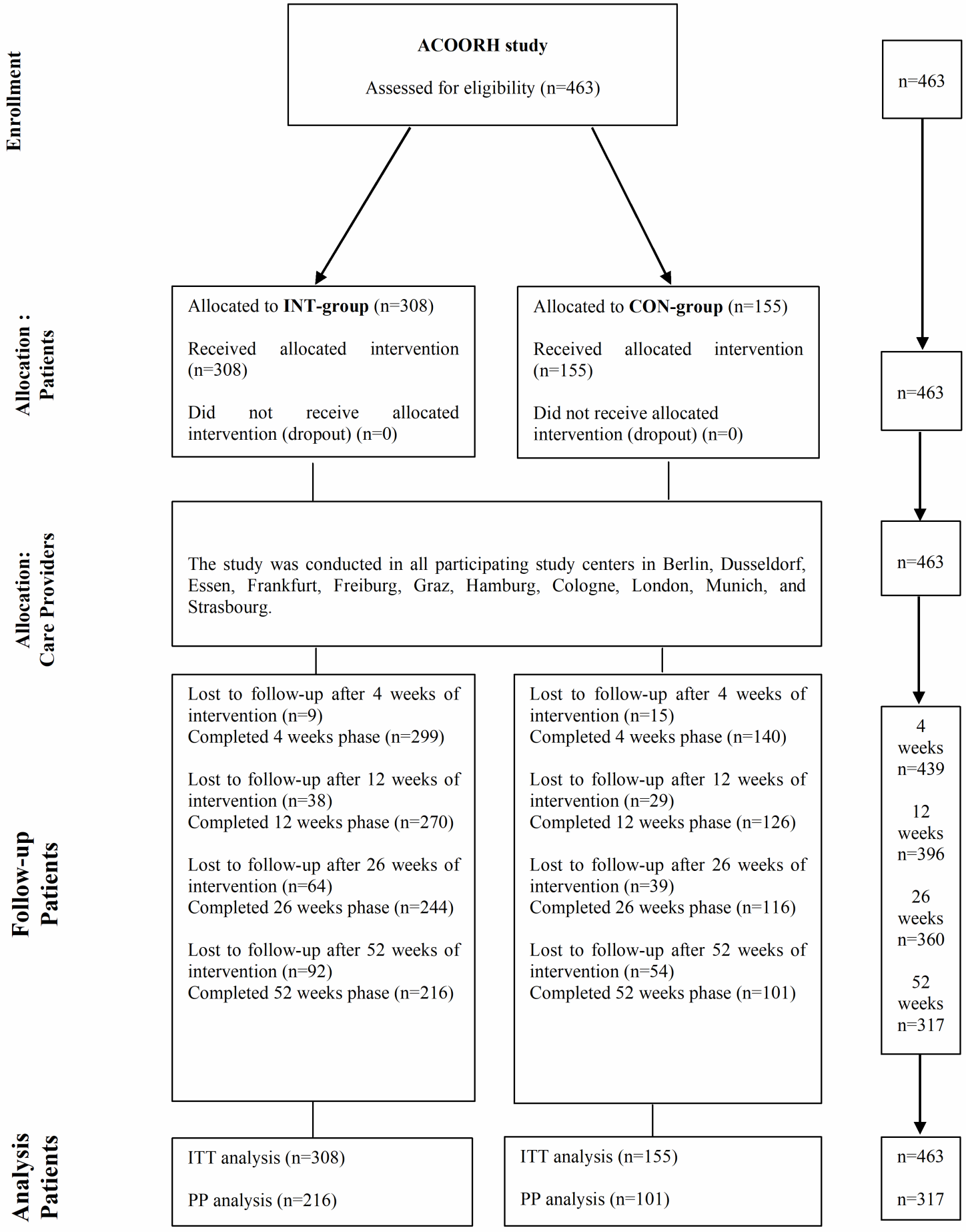
Enrollment
ACOORH study
Assessed for eligibility (n=463)
n=463
Allocation : Patients
Allocated to INT-group (n=308)
Received allocated intervention (n=308)
Did not receive allocated intervention (dropout) (n=0)
Allocated to CON-group (n=155)
Received allocated intervention (n=155)
Did not receive allocated intervention (dropout) (n=0)
n=463
Allocation: Care Providers
The study was conducted in all participating study centers in Berlin, Dusseldorf, Essen, Frankfurt, Freiburg, Graz, Hamburg, Cologne, London, Munich, and Strasbourg.
n=463
Follow-up Patients
Lost to follow-up after 4 weeks of intervention (n=9)
Completed 4 weeks phase (n=299)
Lost to follow-up after 12 weeks of intervention (n=38)
Completed 12 weeks phase (n=270)
Lost to follow-up after 26 weeks of intervention (n=64)
Completed 26 weeks phase (n=244)
Lost to follow-up after 52 weeks of intervention (n=92)
Completed 52 weeks phase (n=216)
Lost to follow-up after 4 weeks of intervention (n=15)
Completed 4 weeks phase (n=140)
Lost to follow-up after 12 weeks of intervention (n=29)
Completed 12 weeks phase (n=126)
Lost to follow-up after 26 weeks of intervention (n=39)
Completed 26 weeks phase (n=116)
Lost to follow-up after 52 weeks of intervention (n=54)
Completed 52 weeks phase (n=101)
4 weeks n=439
12 weeks n=396
26 weeks n=360
52 weeks n=317
Analysis Patients
ITT analysis (n=308)
PP analysis (n=216)
ITT analysis (n=155)
PP analysis (n=101)
n=463
n=317

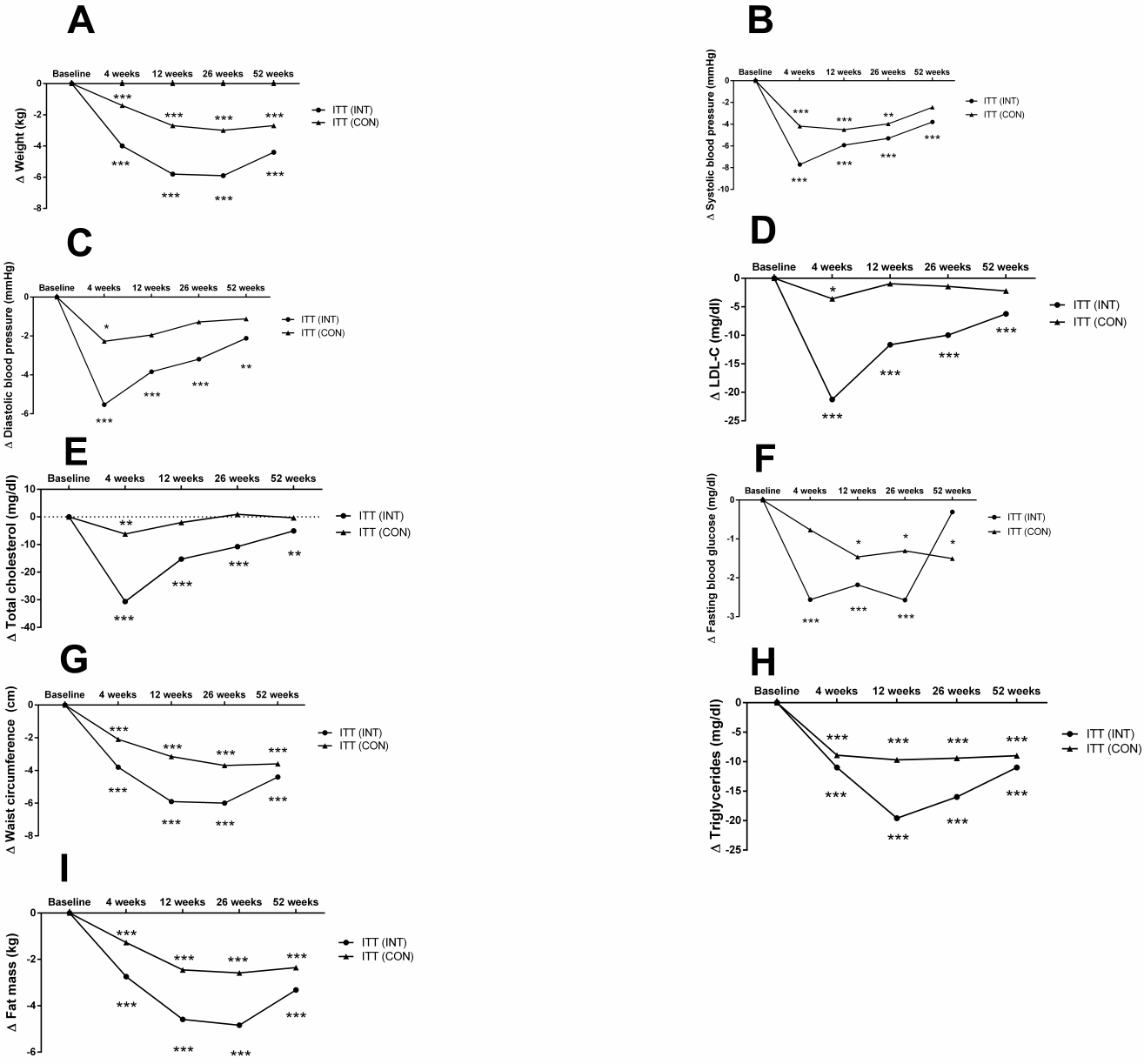
A
Baseline
4 weeks
12 weeks
26 weeks
52 weeks
Δ Weight (kg)
ITT (INT)
ITT (CON)
B
Δ Systolic blood pressure (mmHg)
C
Δ Diastolic blood pressure (mmHg)
D
Δ LDL-C (mg/dl)
E
Δ Total cholesterol (mg/dl)
F
Δ Fasting blood glucose (mg/dl)
G
Δ Waist circumference (cm)
H
Δ Triglycerides (mg/dl)
I
Δ Fat mass (kg)

Table 1. Baseline characteristics

	INT-group (n=308)	CON-group (n=155)
Sex (% male)	32.8	41.3
Age (years)	51 ± 10	50 ± 10
Weight (kg)	92 ± 14	94 ± 12
BMI (kg/m²)	31.7 ± 2.4	31.5 ± 2.4
WC (cm)	106 ± 10	107 ± 8
HC (cm)	113 ± 8	112 ± 7
WHR	0.94 ± 0.08	0.95 ± 0.08
FM (kg)	37.0 ± 6.7	37.0 ± 6.6
FFM (kg)	54.9 ± 11.7	56.7 ± 11.5
FBG (mg/dl)	94 ± 12	94 ± 11
SBP (mmHg)	134 ± 15	134 ± 13
DBP (mmHg)	89 ± 12	89 ± 10
Total cholesterol (mg/dl)	221 ± 39	220 ± 45
HDL-C (mg/dl)	56 ± 15	56 ± 15
LDL-C (mg/dl)	141 ± 34	139 ± 39
Triglycerides (mg/dl)	145 ± 83	147 ± 68

Data are presented as means ± standard deviations, or percentages. BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; FM, fat mass; FFM, fat free mass; HC, hip circumference; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; SBP, systolic blood pressure; WC, waist circumference; WHR, waist-to-hip ratio

Table 2. Intra and intergroup changes in the INT and CON-group after 12 and 52 weeks compared to baseline

ITT (INT, n=307; CON, n=154) PP (INT, n=266; CON, n=126) 12w PP (INT, n=214; CON, n=101) 52w	12 weeks			52 weeks		
	INT	CON	P (INT vs. CON)	INT	CON	P (INT vs. CON)
Weight (kg) ITT	-5.8 [-6.3; -5.3]***	-2.7 [-3.3; -2.1]***	**<0.001**	-4.4 [-5.0; -3.8]***	-2.7 [-3.4; -2.0]***	**<0.001**
PP	-6.3 [-6.8; -5.8]***	-3.2 [-3.9; -2.6]***	**<0.001**	-5.0 [-5.7; -4.2]***	-3.5 [-4.5; -2.5]***	**0.021**
WC (cm) ITT	-5.9 [-6.5; -5.2]***	-3.1 [-3.9; -2.4]***	**<0.001**	-4.4 [-5.2; -3.7]***	-3.6 [-4.7; -2.6]***	0.175
PP	-6.3 [-7.1; -5.6]***	-3.6 [-4.5; -2.7]***	**<0.001**	-4.8 [-5.7; -3.8]***	-4.6 [-5.9; -3.3]***	0.725
FM (kg) ITT	-4.6 [-5.1; -4.1]***	-2.5 [-3.1; -1.8]***	**<0.001**	-3.3 [-3.9; -2.7]***	-2.4 [-3.2; -1.5]***	**0.020**
PP	-5.1 [-5.5; -4.7]***	-2.9 [-3.5; -2.3]***	**<0.001**	-3.7 [-4.5; -3.0]***	-3.1 [-4.2; -2.0]***	0.248
FFM (kg) ITT	-1.0 [-1.4; -0.6]***	-0.2 [-0.8; 0.3]	**<0.001**	-0.9 [-1.3; -0.6]***	-0.3 [-0.9; 0.2]	**<0.001**
PP	-1.0 [-1.4; -0.7]***	-0.3 [-0.8; 0.2]	**<0.001**	-1.0 [-1.6; -0.5]***	-0.4 [-1.2; 0.3]	**<0.001**
FBG (mg/dl) ITT	-2.2 [-3.5; -0.9]***	-1.5 [-3.0; 0.0]*	0.577	-0.3 [-1.7; 1.1]	-1.5 [-2.9; -0.1]*	0.169
PP	-2.5 [-3.8; -1.1]***	-1.7 [-3.5; 0.1]*	0.433	-0.3 [-2.0; 1.4]	-1.4 [-3.4; 0.5]	0.305
SBP (mmHg) ITT	-5.9 [-8.0; -3.3]***	-4.5 [-7.5; -1.5]**	0.191	-3.8 [-5.9; -1.7]***	-2.4 [-5.4; 0.5]	0.218
PP	-6.4 [-8.3; -4.5]***	-5.1 [-7.9; -2.3]***	0.207	-4.1 [-6.8; -1.4]**	-1.7 [-5.6; 2.2]	0.093
DBP (mmHg) ITT	-3.8 [-5.3; -2.3]***	-1.9 [-4.1; 0.2]	**0.022**	-2.1 [-3.5; -0.7]***	-1.1 [-3.1; 0.9]	0.172
PP	-4.0 [-5.4; -2.7]***	-2.4 [-4.3; -0.4]*	0.069	-2.0 [-3.8; -0.2]*	-0.9 [-3.5; 1.7]	0.221
Total cholesterol (mg/dl) ITT	-16 [-19; -13]***	-2 [-6; 2]	**<0.001**	-6 [-9; -2]**	-0 [-5; 4]	0.076
PP	-15[-18; -12]***	-2 [-7; 3]	**<0.001**	-1 [-5; 3]	2 [-8; 4]	0.639
HDL-C (mg/dl) ITT	-1 [-2; 0]	0 [-1; 2]	**0.002**	2 [1; 3]**	2 [0; 3]*	0.858
PP	-0 [-1; 1]	1 [-1; 2]	**0.004**	3 [1; 4]***	2 [1; 4]**	0.907

LDL-C (mg/dl)	ITT	-12 [-15; -10]***	-1 [-4; 2]	**<0.001**	-7 [-10; -4]***	-2 [-6; 1]	0.067
	PP	-12 [-15; -9]***	-0 [-4; 3]	**<0.001**	-4 [-7; -1]*	-4 [-8; 1]	0.736
Triglycerides (mg/dl)	ITT	-19 [-27; -11]***	-10 [-25; 5]***	0.161	-11 [-20; -3]***	-9 [-20; 3]*	0.618
	PP	-22 [-30; -14]***	-11 [-29; 8]***	0.132	-12 [-21; -4]**	-15 [-30; -1]*	0.840

Data are shown as mean [95% CI]. ***p<0.001 vs. baseline; **p<0.01 vs. baseline; *p<0.05 vs. baseline. Differences in changes after 12 as well as 52 weeks between both groups were analyzed using ANCOVAs adjusting for baseline values. DBP, diastolic blood pressure; FBG, fasting blood glucose; FM, fat mass; FFM, fat free mass; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; n.a., not available; SBP, systolic blood pressure; WC, waist circumference