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# Weight Loss by Telemonitoring of Nutrition and Physical Activity in Patients with Metabolic Syndrome for 1 Year

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### **Original Research**

# Weight Loss by Telemonitoring of Nutrition and Physical Activity in Patients with Metabolic Syndrome for 1 Year

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Key words: metabolic syndrome, weight loss, telemonitoring

**Objective:** Mobile technology can improve lifestyle programs, but the monitoring techniques and carer feedback need to be optimized. To this end, we investigated the efficacy of telemonitoring physical activity and nutrition over 12 months in patients with metabolic syndrome in a randomized, parallel-group, open trial.

**Methods:** Screening all over Germany yielded 184 patients with metabolic syndrome. All patients attended a single 2-hour instruction meeting in their region concerning a combination diet and the importance of physical activity. Thereafter they were randomized into a control group (controls, n = 62) or one of 2 different intervention groups. Both intervention groups were issued accelerometers, which measured physical activity, recorded daily weight and calorie intake, and transmitted these data to a central server for use by patient carers. In the Active Body Control Program of University of Magdeburg (ABC) intervention group (n = 60), information and motivation was ensured by weekly letters. In the 4sigma telephone coaching (4S) intervention group (n = 58), this was accomplished by monthly telephone calls from the carers. Clinical and biochemical data for all patients were collected at 0, 4, 8, and 12 months without any regular face-to-face meetings between patients and carers. The primary endpoint was weight loss and the secondary endpoint was the presence of metabolic syndrome.

**Results:** After 12 months the dropout rates in the control, 4S, and ABC groups were respectively 35%, 17%, and 18%. The adjusted relative weight losses after 12 months were respectively 3.7%, 8.6%, and 11.4% (all p < 0.000 versus baseline). ABC was more effective than 4S (p = 0.041); 43% of the patients completing the study in the ABC group lost more than 15% of their baseline weight. The diagnosis of metabolic syndrome was no longer applicable in 58% of the cases in the ABC group, in 41% of the 4S group, and in 33% of the controls.

**Conclusions:** Telemonitoring of physical activity and nutrition markedly improves weight loss and markers of metabolic syndrome.

#### INTRODUCTION

A diagnosis of metabolic syndrome is made when abdominal overweight occurs together with at least 2 additional risk factors such as elevated triglycerides, blood glucose, blood pressure, and low high-density lipoprotein cholesterol [1]. Although the exact criteria for the presence or absence of these risk factors are still the subject of discussion, there is broad agreement that metabolic syndrome carries an increased risk of developing obesity-associated disorders, in particular type 2 diabetes mellitus and cardiovascular diseases.

The central cause of metabolic syndrome is obesity, which has evolved into a worldwide epidemic [2]. The steady increase in its prevalence indicates that the measures used at present are unable to curb this development and that new and more effective alternatives are urgently needed.

Obesity has 2 basic causes: an excessive calorie intake and insufficient calorie expenditure by physical activity. Though there are numerous programs aimed at modification and control of calorie intake, the number of measures for increasing calorie consumption by increasing physical activity is limited. One major reason for this is that activity programs require a

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considerable time input from both patients and coaches. Therefore, approaches that use mobile technology and the Internet for lifestyle improvements are being developed and tested. Three recent reviews [3–5] agree that in the short-term weight loss can be improved by these programs. They also agree, however, that the published data differ markedly with respect to technologies used, patient groups studied, and study durations and that further research is needed in order to optimize telemonitoring as an effective tool for the management of obesity.

The Active Body Control (ABC) program is a lifestyle program that combines such telemonitoring with a combination diet, the Magdeburg Dual Diet. This program was first shown to be effective in obese adults [6] and subsequently in patients with type 2 diabetes mellitus [7]. In the present work we investigated the effects of telemonitoring over a period of 12 months in patients with metabolic syndrome in an open, randomized trial with parallel groups. We also compared 2 different ways of communicating with the patients: by weekly letters, as routinely done in the ABC program, and by monthly telephone calls from a specialized enterprise, 4sigma (4S), as an alternative communication pathway.

#### MATERIALS AND METHODS

#### **Patients and Interventions**

The patients were recruited by advertising in several major companies in southern and western Germany and by a newspaper advertisement in the region of Magdeburg in northeast Germany. Interested persons visited either their company doctors or the lipid clinic of Magdeburg University Hospital. None of these patients had participated in an earlier study carried out by the authors. Five hundred sixty-four individuals were screened and received condensed information about the trial, and fasting blood samples were then collected to test for inclusion or exclusion criteria concerning the metabolic syndrome (see the flowchart in Fig. 1).

The criteria for diagnosis of metabolic syndrome according to the International Diabetes Federation recommendations [8] were as follows: waist circumference > 80 cm in females and > 94 cm in males plus any 2 of the following 4 factors: triglycerides  $\geq 150$  mg/dl (1.7 mmol/L), high-density lipoprotein cholesterol < 50 mg/dl (1.29 mmol/L) in females and < 40 mg/dl (1.03 mmol/L) in males, systolic blood pressure (BP)  $\geq 130$  or diastolic BP  $\geq 85$  mmHg or treatment of any of the above conditions, and fasting blood glucose  $\geq 100$  mg/dl (5.6 mmol/L). A telephone and access to the Internet via a personal computer were required. The exclusion criteria were age less than 30 or over 60 years and diagnosis of diabetes mellitus, coronary heart disease, chronic heart failure, or cerebrovascular disorders, as well as other conditions possibly co-influencing physical activity or body weight, such as psychiatric disorders,

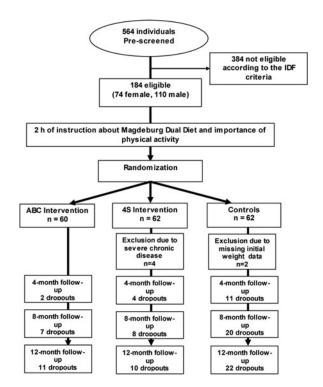


Fig. 1. Flowchart from screening to the end of the study.

use of antidepressants, neuroleptic or cortisol therapy, thyroid dysfunction, active cancer or other severe and life-threatening diseases, disabling disorders of the motor system, pregnancy, or changes in oral contraception. One hundred eighty-four persons met these criteria and were invited to a 2-hour instruction meeting. These meetings were held only once in each of the participating 8 regions. The instruction consisted of 2 parts. All individuals participated in the first part, which included an explanation of the Magdeburg Dual Diet and the importance of physical activity (details of both are given below). After this basic instruction the subjects were randomized by lot to one of 3 groups: controls (n = 62), ABC (n = 60), or 4S (n = 62). The different final group sizes after the 8 meetings are a consequence of the fact that the cohorts in each of the 8 participating regions were not necessarily a multiple of 3. The patients in the control group then left, and the remaining subjects received their accelerometers and instructions on their operation and data transmission. Because the intervention investigated in this trial was purely telemedical, there were no additional appointments with the patients except for determination of their biochemical and clinical parameters after 4, 8, and 12 months. It should be emphasized that all 3 groups received identical instructions about the Magdeburg Dual Diet and identical recommendations concerning physical activity. The difference between the 2 intervention groups and the control group was merely the telemonitoring of physical activity and nutrition by means of the Aipermotion instruments and the regular feedback from carers,

either by weekly letters (ABC group) or by monthly telephone calls (4S group).

The Magdeburg Dual Diet is a combination of 2 diets. The first consists of conventional calorie restriction, lowering the calorie intake by 500 kcal per day. The second is a low-carbohydrate diet, developed originally by Ludwig [9] and modified by Worm [10]. Emphasis was placed on preference for carbohydrates with low glycemic index (GI) but not on avoidance of carbohydrates as in the Atkins diet [11]. Many practical examples were presented, and a booklet was distributed containing an overview of the aims and background of the study, a table of calorie contents, and a table of GI values for a broad range of carbohydrates.

As far as exercise was concerned, the subjects were advised to increase their usual daily physical activity, like walking or cycling, rather than to engage in particular sports. The recommendation was to perform these activities moderately but steadily, slowly enough to be able to talk at the same time [12], and to keep the pulse below 120/min.

The accelerometer used was an Aipermotion 440 model from Aipermon GmbH (Munich, Germany). The accelerometers were programmed individually for each patient, with an allowance for age, sex, weight, and individual step lengths for 3 walking speeds: normal, fast, and jogging. The instruments calculate the current and daily distances at the 3 walking speeds and the current and daily exercise-related energy expenditure in kilocalories and displays the results on a screen. Movements that are only inadequately recorded by the instrument, such as swimming or cycling, are manually keyed in according to their duration and intensity. The validity of these measurements has been satisfactorily demonstrated by comparison with spiroergometry in different patient groups with heart failure [13] and by comparison with the 6-minute-walk test [14]. The patients were required to carry the matchbox-sized instrument in a little holster tied to the belt from the time they dressed in the morning until they undressed in the evening. The instrument measured the daily duration of active usage and transmitted it to the carer, expressed as percentage of 24 hours. An additional feature of the instrument is the recording of meal calories in a simplified form. The registration of nutritional calories occurs first by selection of the meal; for example, "breakfast," "snack," "main meal," or "drink" followed by choice of "mini," "normal," or "maxi." How to determine mini, normal, or maxi was covered in the 2-hour training. Although the actual calorie intake can only be roughly assessed by this approach, there is a satisfactory psychological effect because the patients are continuously aware of their nutritional behavior. Finally, the patients can read on the display the actual balance between the total calorie intake and the calories used up by the basal metabolic rate plus their physical activity.

These data and the daily body weights from the subjects' personal scales were transmitted once a week to a server in Magdeburg University Hospital by means of a USB connection to a home computer with automatic extraction of new data.

Using the ABC platform on this server, the ABC carer generated weekly individual report letters, which were sent out to all ABC patients by mail. Each letter showed the patient's weight loss curve from the beginning of the intervention (a red line) together with weight loss curves of the other participants in this group (black lines). A second graph showed, for each day of the preceding week, the duration of sensor use as a percentage of 24 hours, the kilocalories used up by exercise with 4 coloured bars reflecting the 4 activity intensities from "passive" to "jogging," and the distance covered in kilometers. A third graph showed the cumulative number of kilocalories from nutrition. Finally, the letter also contained comments assessing progress over the past week aiming to motivate the patients.

Patients in the 4S group received a monthly telephone call from specialist doctors and nurses from the 4sigma company in Munich, Germany. This company specializes in telephone-based health coaching including the use of telemonitoring. The calls took on average 20 minutes each, and the carers used the same ABC platform described above but communicated and commented on the data verbally.

The study was approved by the Ethics Committee of the School of Medicine and all subjects provided written informed consent

#### **Blood Sampling and Laboratory Measurements**

Blood samples were taken from the antecubital vein after a 12-hour overnight fast and sent by mail to the central laboratory at Magdeburg University Hospital. All laboratory tests were done by commercial enzymatic methods in a random-access analyzer (Modular, Roche Diagnostics, Mannheim, Germany) in serum for all parameters except glucose, which was determined in sodium fluoride plasma. Hb<sub>A1c</sub> was determined in EDTA tubes by high-performance liquid chromatography (Variant II, Bio-Rad, Munich, Germany). The homeostasis model of assessment (HOMA) index was calculated according to Haffner et al. [15]. Body weight, height, waist circumference, and blood pressure were measured by the investigating doctors at baseline and then at 4, 8, and 12 months. Blood pressure was determined using manual sphygmomanometers.

#### **Statistical Analysis**

The primary aim of the analyses was to compare the results between the different treatment arms. The primary endpoint was the weight loss from baseline to month 12 as a percentage from baseline. The main secondary endpoint was the presence of metabolic syndrome. Further secondary endpoints were absolute weight loss and changes in body mass index (BMI), waist circumference, and laboratory parameters.

The study was designed to detect differences in weight loss at the 12-month visit between the 3 treatment arms with a power of at least 80% if the difference amounted to 5 kg or more.

As a simplified scenario for the sample size calculation we used Bonferroni-corrected pairwise t tests at the 2-sided level 0.05/3 = 0.0167 and assumed a common standard deviation of 7 kg in all treatments. This would require about 45 persons per treatment arm; with a supposed dropout rate of 25% this meant that 60 patients had to be recruited for each treatment arm.

We begin with a description of demographic and baseline parameters stratified by treatment arm, completed by a comparison of these parameters between the treatment arms in Bonferronicorrected chi-squared tests for gender and Tukey tests for all continuous parameters.

The main analysis for the primary endpoint, the percentage weight loss, is the comparison between the 3 treatment arms. Patients were allocated to the 3 groups according to the intention-to-treat principle. Weight loss at the 4-month, 8-month, and 12-month visits were modeled in a mixed linear model with a random patient effect (intercept) and fixed effects for treatment arm, visit, baseline value (covariable), and interactions between treatment arm and visit as well as between visit and baseline value. Although values from all visits were included in the analyses, the main focus was on the results at the 12month visit. A Bonferroni correction was used to adjust the 3 pairwise comparisons between the treatment arms at 12 months and also for corresponding confidence intervals for the pairwise differences. In addition, estimates of the groupwise means with unadjusted confidence intervals and unadjusted p values for the tests versus 0 (i.e., no weight loss) were taken from the mixed model for all visits. In a secondary consideration, in each group

the weight loss was compared between the 3 visits based on the same mixed model (also with Bonferroni adjustment for 3 pairwise visit comparisons).

Because dropout is an essential issue in this study (as in nearly all diet studies), several missing value strategies were considered simultaneously. The primary analysis ("original" estimates in the results tables) used all available measurements at corresponding visits (note that the mixed model approach does not require complete data from all visits). In sensitivity analyses, we substituted missing values from dropouts by multiple imputation and by the last observation carried forward strategy (LOCF) as well as by baseline observation carried forward (BOCF). For multiple imputations we used 5 replications, where missing values were substituted in a Markov chain Monte Carlo method based on the available measurements for the patient at other visits and a random disturbance.

Analogous analyses were carried out with the continuous secondary endpoints but with absolute differences from baseline. For variables with skewed distributions (triglycerides, apo B, ALT, AST, C-reactive protein [CRP], glucose, Hb<sub>Alc</sub>, insulin, and HOMA), the test results (*p* values) were taken from analyses with log-transformed data, but the estimates and confidence intervals were derived from additional analyses with the original data for more convenient presentation uniform over all variables.

The main secondary outcome variable, metabolic syndrome, was considered in pairwise Bonferroni-corrected chi-squared tests. Missing values were treated by the LOCF protocol.

Table 1. Baseline Demographics of the Patients

| N                           | ABC 60                 | 4S 58                  | Controls 60            | p ABC<br>vs 4S | p ABC<br>vs Controls | p 4S<br>vs Controls |
|-----------------------------|------------------------|------------------------|------------------------|----------------|----------------------|---------------------|
| Gender: No. (%)             | F: 18 (30); M: 42 (70) | F: 27 (47); M: 31 (53) | F: 28 (47); M: 32 (53) | NS             | NS                   | NS                  |
| Age (years)                 | $50.3 \pm 7.8$         | $50.3 \pm 8.0$         | $50.1 \pm 8.1$         | NS             | NS                   | NS                  |
| Weight (kg)                 | $104.8 \pm 18.5$       | $97.8 \pm 16.3$        | $96.1 \pm 19.7$        | NS             | 0,025                | NS                  |
| BMI (m <sup>2</sup> /kg)    | $34.0 \pm 4.9$         | $33.3 \pm 5.8$         | $32.6 \pm 4.9$         | NS             | NS                   | NS                  |
| Waist (cm)                  | $111.8 \pm 11.8$       | $109.8 \pm 11.8$       | $107.9 \pm 13.1$       | NS             | NS                   | NS                  |
| BP systolic (mmHg)          | $142.0 \pm 16.8$       | $144.2 \pm 21.0$       | $140.9 \pm 17.6$       | NS             | NS                   | NS                  |
| BP diastolic (mmHg)         | $88.3 \pm 10.2$        | $90.2 \pm 11.2$        | $88.1 \pm 12.6$        | NS             | NS                   | NS                  |
| Triglycerides (mmol/L)      | $2.45 \pm 1.41$        | $2.22 \pm 0.97$        | $2.12 \pm 0.81$        | NS             | NS                   | NS                  |
| Cholesterol (mmol/L)        | $5.86 \pm 1.08$        | $5.82 \pm 1.22$        | $5.77 \pm 1.19$        | NS             | NS                   | NS                  |
| HDL cholesterol (mmol/L)    | $1.14 \pm 0.30$        | $1.21 \pm 0.32$        | $1.19 \pm 0.25$        | NS             | NS                   | NS                  |
| LDL cholesterol (mmol/L)    | $3.72 \pm 0.92$        | $3.67 \pm 1.02$        | $3.62 \pm 1.06$        | NS             | NS                   | NS                  |
| Uric acid (µmol/L)          | $354.1 \pm 85.2$       | $357.9 \pm 87.4$       | $342.9 \pm 81.0$       | NS             | NS                   | NS                  |
| AST ( $\mu$ mol/s * L)      | $0.51 \pm 0.16$        | $0.56 \pm 0.23$        | $0.53 \pm 0.20$        | NS             | NS                   | NS                  |
| ALT (µmol/s * L)            | $0.65 \pm 0.34$        | $0.72 \pm 0.54$        | $0.61 \pm 0.39$        | NS             | NS                   | NS                  |
| Apolipoprotein B (g/L)      | $1.15 \pm 0.23$        | $1.16 \pm 0.28$        | $1.12 \pm 0.28$        | NS             | NS                   | NS                  |
| CRP high-sensitivity (mg/L) | $5.62 \pm 8.72$        | $3.93 \pm 5.85$        | $3.69 \pm 5.03$        | NS             | NS                   | NS                  |
| Glucose (mmol/L)            | $4.18 \pm 0.53$        | $4.21 \pm 0.77$        | $4.22 \pm 0.77$        | NS             | NS                   | NS                  |
| Hba1c IFCC (mmol/mol)       | $39.6 \pm 4.8$         | $38.9 \pm 5.8$         | $39.2 \pm 6.1$         | NS             | NS                   | NS                  |
| Insulin (pmol/L)            | $93.8 \pm 54.0$        | $88.5 \pm 60.3$        | $82.6 \pm 54.4$        | NS             | NS                   | NS                  |
| HOMA                        | $2.42 \pm 1.32$        | $2.37 \pm 1.92$        | $2.16 \pm 1.55$        | NS             | NS                   | NS                  |

ABC = Active Body Control Program of University of Magdeburg, 4S = 4sigma telephone coaching, BMI = body mass index, BP = blood pressure, HDL = high-density lipoprotein, LDL = low-density lipoprotein, AST = Aspartat-Aminotransferase, ALT = Alanin-Aminotransferase, CRP = C-reactive protein, IFCC = International Federation of Clinical Chemistry, HOMA = homeostasis model of assessment.

All analyses were carried out using SAS Version 9.2 (SAS Institute Inc., Cary, NC; procedures FREQ, GLM, MEAN, MIXED, MI, MIANALYZE). The tests were carried out at a significance level of 0.05.

#### **RESULTS**

A flowchart of the study is presented in Fig. 1. Six of the randomized patients were excluded from the final evaluation. Documentation of the baseline data was lost in 2 cases (both in the control group). Four more patients were found during the first 4 months to suffer from severe preexisting conditions having an effect on body weight at the baseline visit: 2 severe depressions, 1 amyotrophic lateral sclerosis, and 1 cancer of the colon (all 4S group).

Table 1 gives the baseline data for the remaining patients for the 3 groups. A statistically significant difference between the groups was observed for the baseline weight, which was higher in the ABC group than in the controls. The difference is due to an incidental higher proportion of men in the ABC group: (70%) vs 53% in both the 4S group and the controls. To compensate for this imbalance, we analyzed the different primary and secondary metrical endpoints not only as the change from the baseline but additionally included the baseline value as a covariable. In addition, the relative weight loss and the decrease in BMI are reported, both of which are less influenced by the absolute baseline weight. Table 2a gives the dropout rates in the 3 groups. These increased in the course of the study and after 12 months became almost equal at 18% and 17% in the ABC and 4S group but at 35% were twice as high in the control group. Table 2b shows the reasons for dropout. Loss of sensor was the prevailing technical reason with a consecutive unwillingness to pay a second security deposit for a replacement instrument.

Fig. 2 shows the unadjusted individual weight loss curves in kilograms in the 2 intervention groups over the year; the mean is shown in red. Weight loss did not differ between men and women in any of the groups, either in absolute (kg) or in relative (%) terms. The adjusted relative weight losses according to the mixed model evaluation are given in Fig. 3 at months 0, 4, 8, and 12. It is apparent that weight loss was greatest in the ABC group

Table 2a. Dropout Rates

|          |          | Dropout Rates, n (%) | )         |
|----------|----------|----------------------|-----------|
|          | 4 Months | 8 Months             | 12 Months |
| ABC      | 2 (3%)** | 7 (12%)**            | 11 (18%)* |
| 4S       | 4 (6%)*  | 8 (13%)*             | 10 (16%)* |
| Controls | 11 (18%) | 20 (32%)             | 22 (35%)  |

 $\label{eq:ABC} ABC = Active\ Body\ Control\ Program\ of\ University\ of\ Magdeburg,\ 4S = 4 sigma\ telephone\ coaching.$ 

p vs. controls: \*p < 0.05. \*\*p < 0.01.

Table 2b. Reasons for Dropout

|                                      | ABC    | 4S     | Controls |
|--------------------------------------|--------|--------|----------|
| Contact not possible after 12 months | 5 (8%) | 4 (7%) | 16 (28%) |
| Technical issues                     | 5 (8%) | 2 (3%) | 0        |
| Not satisfied with the program       | 0      | 1 (2%) | 3 (4%)   |
| Familial/professional                | 1 (2%) | 2 (3%) | 0        |
| Metformin therapy                    | 0      | 1 (2%) | 3 (4%)   |

ABC = Active Body Control Program of University of Magdeburg, 4S = 4sigma telephone coaching.

and decreased in the control group between 8 and 12 months, whereas in the 2 intervention groups they increased further.

The data collected from the accelerometers were generally in line with the greater weight loss in the ABC group. This group had longer walking distances (ABC: 6.5 km/day, 4S: 5.9 km/day) and a lower nutritional energy input (ABC: 1487 kcal/day, 4S: 1510 kcal/day). None of these differences reached statistical significance; however, the minor daily difference in calorie intake and exercise-induced calorie burn added up over one year to approximately an average of additional negative balance of 24,000 kcal and is, therefore, in line with the additional weight loss in the ABC group.

Table 3 shows the proportion of completing patients whose relative weight loss exceeded 5%, 10%, or 15%. Highest values were again observed in the ABC group, in which almost every other patient lost more than 15% of their baseline weight.

Table 4 shows the changes in various clinical and biochemical parameters after 12 months. Four patients developed diabetes mellitus (3 controls, 1 4S). They remained in the evaluation with their original data until the beginning of therapy with metformin, which is known to influence body weight and associated parameters. Thereafter they were treated as dropouts. The changes from baseline in Table 4 are given as adjusted means after different approaches to account for the dropouts. The original estimates from the mixed model approach used all available measurements at corresponding visits. MI shows values after multiple imputation, and LOCF and BOCF give values after the last observation carried forward and baseline observation carried forward procedure. In all 3 groups body weight, blood pressure, and most of the obesity-related biochemical parameters improved relative to baseline (first 3 columns). Compared with the controls (columns 4 and 5), the groups with telemonitoring showed statistically

**Table 3.** Proportions (%) of Patients Completing the Study Whose Weight Loss Exceeded 5%, 10%, or 15% of Their Baseline Weight after 12 Months

| Weight Loss | ABC | 4S | Controls |
|-------------|-----|----|----------|
| ≥5%         | 82  | 68 | 32       |
| _<br>≥10%   | 57  | 43 | 8        |
| ≥15%        | 43  | 19 | 5        |

ABC = Active Body Control Program of University of Magdeburg, 4S = 4sigma telephone coaching.

Table 4. Changes in Weight, Blood Pressure, and Biochemistry after 12 Months in the Groups ABC and 4S and in the Controls<sup>a</sup>

|  | AB                               | ABC Group 12 Months<br>Minus Baseline   | 12 Mor  | nths  | 4S  | 4S Group 12 Months<br>Minus Baseline  | 2 Month<br>aseline               | SL                                   | Contro   | ol Group 12 M<br>Minus Baseline       | Control Group 12 Months<br>Minus Baseline | ıths                                     |  | ABC<br>Minus 4S                                      | S   |  | AB   | ABC Minus<br>Controls                    |   |                               | 4S N<br>Con                              | 4S Minus<br>Controls  |   |
|--|----------------------------------|---|---|---|---|---|----------------------------------|--------------------------------------|--|---------------------------------------|---|--|--|--|---|--|--|--|---|-------------------------------|--|---|---|
| Estimate                                   | ⊲                                | d   | 95%   | כו  | ◁   | d   | 95%                              | CI                                   | ◁  | 6 d                                   | 95%                                       | [ ]                                      | 7  | p 95   | 95% CI  |  | d  | 95%                                      | CI  | ◁                             | d  | %56   | CI  |
| Weight loss (%) Original MI LOCF           | 11.4                             | 0.000   | 9.8<br>9.2<br>9.5   | 12.9<br>12.5<br>12.5  |   | 0.000   | 7.0<br>6.9<br>6.6                | 10.2<br>10.3<br>9.6                  | 3.7 0<br>4.4 0<br>3.0 0                              | 0.000                                 | 2.1                                       | 4.8.4<br>4.8.3                           | 2.8 0.04<br>2.3 NS<br>2.9 0.02                 | - 7  | 0.1 5.5<br>0.6 5.2<br>0.3 5.6   | 5 7.7<br>2 6.4<br>6 8.0                              |  |  | 10.5<br>9.5<br>10.6   | 4.9<br>4.1<br>5.1             | 0.000<br>0.002<br>0.000                  | 2.1   | 7.7   |
| BOCF                                       | 10.3                             | 0.000   | 8.7   | 11.8  | 7.2   | 0.000   | 5.6                              | 8.7                                  |  | 0.002                                 |   |  |  |  |   |  |  | 5.1                                      | 10.5  | 4.7                           | 0.000                                    | 2.1   | 7.4   |
| weignt loss (kg) Original MI LOCF BOCF     | -12.2 $-11.7$ $-11.8$ $-11.0$    | 0.000 0 0.000 0 0.000 0 0.000 0   | -13.8<br>-13.4<br>-13.4   | -10.5 $-10.0$ $-10.2$ $-9.4$                                    | -8.8<br>-8.6<br>-8.3<br>-7.3                                  | 0.000 - 0.000 - 0.000 0.000 0.000   | -10.4<br>-10.4<br>-9.9<br>-8.9   | -7.1 -<br>-6.8 -<br>-6.6 -           | -4.2 0<br>-4.6 0<br>-3.3 0<br>-2.7 0                 | 0.000 - 0.000 - 0.000 - 0.000 - 0.001 | -6.0 -<br>-6.6 -<br>-4.9 -                | -2.5 -<br>-2.6 -<br>-1.7 -<br>-1.1 -     | 3.4 0.0<br>3.1 0.0<br>3.6 0.0<br>3.8 0.0       | 0.013 -6.2<br>0.039 -6.1<br>0.007 -6.4<br>0.005 -6.6 | .2 -0.6<br>.1 -0.1<br>.4 -0.8<br>.6 -0.9  | 6 -7.9<br>11 -7.1<br>8 -8.6<br>9 -8.3                | 9 0.000<br>1 0.000<br>6 0.000<br>3 0.000   | 0 -10.9<br>0 -10.3<br>0 -11.3<br>0 -11.1 | -5.0<br>-3.9<br>-5.8<br>-5.4                                  | -4.5<br>-5.0<br>-4.5          | 0.001<br>0.004<br>0.000<br>0.000         | 7.5<br>-7.0<br>-7.8<br>-7.4   | $\begin{array}{c} -1.6 \\ -1.0 \\ -2.2 \\ -1.7 \end{array}$ |
| DMI (III7/kg) Original MI LOCF BOCF        | -4.1<br>-3.9<br>-3.9<br>-3.7     | 0.000<br>0.000<br>0.000<br>0.000  |   | -3.6<br>-3.3<br>-3.4<br>-3.1                                    | -2.8<br>-2.8<br>-2.7<br>-2.3                                  | 0.000<br>0.000<br>0.000<br>0.000  | -3.4<br>-3.2<br>-2.9             | -2.3<br>-2.2<br>-2.2<br>-1.8         | $\begin{array}{cccccccccccccccccccccccccccccccccccc$ | 0.000 - 0.000 - 0.000 - 0.000 - 0.000 | -1.8<br>-2.0<br>-1.5<br>-1.3              | -0.6<br>-0.8<br>-0.5<br>-0.3             | -1.2 0.0<br>-1.1 0.0<br>-1.2 0.0<br>-1.3 0.0   | 0.004 -2<br>0.023 -2<br>0.004 -2<br>0.002 -2         | 2.2 -0.3<br>2.1 -0.1<br>2.1 -0.3<br>2.3 -0.4  | 3 -2.9<br>3 -2.5<br>3 -2.9<br>4 -2.9                 | 9 0.000<br>5 0.000<br>9 0.000<br>9 0.000   | -3.5<br>-3.5<br>-3.8<br>-3.8             | $ \begin{array}{c} -2.0 \\ -1.5 \\ -2.0 \\ -2.0 \end{array} $ | -1.7<br>-1.4<br>-1.5          | 0.000<br>0.006<br>0.000<br>0.000         | -2.6<br>-2.5<br>-2.6  | -0.7<br>-0.3<br>-0.8  |
| Waist (cm) Original MI LOCF BOCF           | -14.3 $-13.7$ $-13.0$ $-11.3$    | 0.000 - | -16.2<br>-15.8<br>-14.9<br>-13.2                                    | -12.3 -<br>-11.5 -<br>-11.2 -9.4                                | $\begin{array}{c} -10.8 \\ -10.2 \\ -9.8 \\ -9.3 \end{array}$ | 0.000 - | -12.8<br>-12.2<br>-11.6          | - 8.9<br>- 8.2<br>- 8.0<br>- 7.4     | -6.7 0<br>-7.7 0<br>-5.4 0<br>-4.1 0                 | 00.00                                 | -8.8 -<br>-10.2 -<br>-7.3 -<br>-6.0 -     | - 4.5<br>- 5.1<br>- 3.5<br>- 2.2         | 3.4 0.0<br>3.4 NS<br>3.2 0.0<br>2.1 NS         | - 7t<br>- 3t<br>1                                    | 6.8 0.0<br>7.1 0.2<br>6.4 -0.1<br>5.3 1.2   | 0 -7.6<br>2 -6.0<br>1 -7.6<br>2 -7.2                 | 6 0.000<br>0 0.004<br>6 0.000<br>2 0.000   | ) -11.2<br>4 -10.3<br>0 -10.8<br>0 -10.5 | - 4.0<br>- 4.4<br>- 4.0                                       | -4.2<br>-2.6<br>-4.4<br>-5.2  | 0.017<br>NS<br>0.003<br>0.001            | -7.8<br>-6.1<br>-7.6<br>-8.5  | -0.6 $0.9$ $-1.2$ $-1.9$                                    |
| Systolic BP (mmHg) Original MI LOCF BOCF   | -11.0 $-10.7$ $-9.3$ $-9.9$      | 0.000 - 0.000 - 0.000 - 0.000 - 0.000 - 0.000   | -15.2<br>-15.4<br>-13.2<br>-13.7                                    | -6.7<br>-6.0<br>-5.4<br>-6.1                                    | -12.4<br>-12.5<br>-11.8<br>-9.9                               | 0.000<br>0.001<br>0.000<br>0.000  | -16.7<br>-18.8<br>-15.8<br>-13.8 | -8.0<br>-6.2<br>-7.9<br>-6.0         | -5.8 0<br>-6.1 0<br>-4.6 0<br>-3.5 N                 | 0.020 –<br>0.013 –<br>0.022 –<br>NS   | -10.7 -<br>-10.7 -<br>-8.6 -              | -0.9<br>-1.4<br>-0.7                     | 1.4 NS<br>1.8 NS<br>2.5 NS<br>0.0 NS           | S -6.1<br>S -7.2<br>S -4.2<br>S -6.6                 | .1 8.9<br>.2 10.8<br>.2 9.3<br>.6 6.7   | 9 -5.2<br>8 -4.7<br>3 -4.7<br>7 -6.4                 | 2  | -13.1<br>-13.0<br>-11.4<br>-13.0         | 2.8<br>3.6<br>2.1<br>0.3                                      | -6.6<br>-6.4<br>-7.2<br>-6.4  | NS<br>NS<br>0.036                        | -14.6<br>-18.5<br>-14.0<br>-13.1                                    | 1.5<br>5.6<br>-0.3<br>0.3                                   |
| Diastolic BP (mmHg) Original MI LOCF BOCF  | -6.0<br>-5.7<br>-4.7<br>-5.8     | 0.000   | -8.4<br>-8.3<br>-6.9<br>-7.9  | -3.6<br>-3.1<br>-2.5<br>-3.7                                    | -6.2<br>-6.3<br>-5.7<br>-5.0                                  | 0.000<br>0.002<br>0.000<br>0.000  | -8.7<br>-9.8<br>-7.9             | - 3.8<br>- 3.5<br>- 2.9<br>- 2.8     | -3.9 0<br>-3.8 0<br>-3.3 0<br>-2.2 0                 | 0.005 - 0.003 - 0.004 - 0.044 -       | -6.7 -<br>-6.3 -<br>-5.5 -                | -1.2<br>-1.3<br>-0.1 -0                  | 0.2 NS<br>0.6 NS<br>1.0 NS<br>-0.8 NS          | 8 - 4.4.0<br>4.4.1.0<br>8.4.4.0                      | 0. 4.4<br>4.7 5.7<br>8. 4.7<br>6. 2.9   | 7 -1.9<br>7 -1.4<br>9 -3.55                          | 0 NS<br>9 NS<br>4 NS<br>55 NS              | -6.5<br>-6.3<br>-5.2<br>-7.28            | 2.4<br>2.6<br>2.3<br>0.17                                     | -2.3<br>-2.5<br>-2.4<br>-2.73 | NS N | -6.8<br>-8.9<br>-6.2<br>-6.50                                       | 2.2<br>3.8<br>1.4<br>1.03                                   |
| Inglycendes (mmol/L) Original MI LOCF BOCF | _                                | -0.56 0.000<br>-0.55 0.000<br>-0.58 0.000<br>-0.45 0.000  | $ \begin{array}{c} -0.87 \\ -0.95 \\ -0.85 \\ -0.71 \end{array} $   | -0.24<br>-0.15<br>-0.30<br>-0.19                                | 0.00 0.007<br>-0.04 0.005<br>-0.07 0.002<br>0.00 0.010        | 0.007<br>0.005<br>0.002<br>0.010  | -0.33<br>-0.39<br>-0.35<br>-0.27 | 0.32 -<br>0.31 -<br>0.20 -<br>0.26 - | -0.19 0<br>-0.13 0<br>-0.16 0<br>-0.16 0             | 0.034 - 0.024 - 0.023 - 0.042 - 0.042 | -0.54<br>-0.44<br>-0.43                   | 0.16 –(<br>0.17 –(<br>0.11 –(<br>0.10 –( | -0.55 NS<br>-0.51 NS<br>-0.50 0.00<br>-0.45 NS | 5  | I   | 0.00 -0.37<br>0.23 -0.41<br>0.03 -0.41<br>0.01 -0.29 | 37 0.036<br>41 NS<br>41 0.006<br>29 0.024  | 5 -0.94<br>-1.07<br>5 -0.89<br>1 -0.75   | 0.21<br>0.24<br>0.06<br>0.16                                  | 0.19<br>0.09<br>0.09<br>0.15  | NS NS NS NS                              | -0.39<br>-0.44<br>-0.38<br>-0.30                                    | 0.77<br>0.63<br>0.56<br>0.61                                |
| Cholesterol (mmol/L) Original MI LOCF BOCF | -0.30<br>-0.29<br>-0.28<br>-0.29 | $\begin{array}{cccc} -0.30 & 0.003 \\ -0.29 & 0.016 \\ -0.28 & 0.003 \\ -0.29 & 0.001 \end{array}$  | $ \begin{array}{ccc} -0.50 \\ -0.53 \\ -0.46 \\ -0.46 \end{array} $ | $\begin{array}{c} -0.10 \\ -0.06 \\ -0.10 \\ -0.12 \end{array}$ | -0.08 NS<br>-0.10 NS<br>-0.07 NS<br>-0.08 NS                  | NS N  | -0.28<br>-0.30<br>-0.26<br>-0.25 | 0.12 -<br>0.10 -<br>0.11 -<br>0.10 - | -0.37 0<br>-0.28 0<br>-0.28 0<br>-0.26 0             | 0.001<br>0.006<br>0.002<br>0.003      | -0.59 -<br>-0.48 -<br>-0.46 -<br>-0.43 -  | -0.15 -(<br>-0.08 -(<br>-0.10 -(         | -0.22 NS<br>-0.19 NS<br>-0.20 NS<br>-0.22 NS   |  | $\begin{array}{ccc} -0.57 & 0. \\ -0.61 & 0. \\ -0.52 & 0. \\ -0.51 & 0. \end{array}$ | 0.13 0.0<br>0.22 -0.0<br>0.11 0.0<br>0.08 -0.0       | 0.07 NS<br>-0.01 NS<br>0.00 NS<br>-0.03 NS | -0.29<br>-0.42<br>-0.31<br>-0.32         | 0.43<br>0.32<br>0.26  | 0.29<br>0.18<br>0.21<br>0.18  | NS N | $ \begin{array}{ccc} -0.07 \\ -0.15 \\ -0.11 \\ -0.11 \end{array} $ | 0.66<br>0.51<br>0.52<br>0.48                                |

| Fig. 2   |   |   |   |   |  |  |   |
|--|---|---|---|---|--|--|---|
| 0.13 0.000 0.007 0.18 0.12 0.000 0.06 0.18 0.09 0.003 0.15 0.01 NS -0.09 0.10 0.03 NS -0.09 0.13 0.12 0.000 0.06 0.18 0.10 0.001 0.04 0.14 0.10 0.01 NS -0.01 0.01 0.02 0.13 0.13 0.000 0.08 0.18 0.12 0.000 0.05 0.15 0.10 0.001 0.04 0.14 0.10 0.00 NS -0.018 0.09 0.01 0.13 0.000 0.08 0.18 0.12 0.000 0.09 0.15 0.15 0.00 0.01 0.10 0.00 NS -0.02 0.08 0.08 0.09 0.01 0.03 0.13 0.000 0.00 0.05 0.15 0.00 0.01 0.01 0.10 0.00 NS -0.02 0.01 0.00 0.05 0.15 0.00 0.01 0.01 0.00 NS -0.02 0.02 0.17 NS -0.02 0.01 0.00 0.00 0.00 0.00 0.02 0.01 0.00 0.02 0.17 NS -0.02 0.10 0.00 0.00 0.00 0.00 0.00 0.00   | 0.13<br>0.11<br>0.12<br>0.13  | 0.58<br>0.54<br>0.48<br>0.39  | 0.12<br>0.11<br>0.10<br>0.09                                    | 25.8<br>24.3<br>24.7<br>14.1                                    | 0.03<br>0.05<br>0.00<br>0.03   | 0.01<br>0.03<br>-0.01<br>0.00                    | 1.45<br>1.90<br>2.51<br>1.05<br>page)                             |
| 0.13 0.000 0.007 0.18 0.12 0.000 0.06 0.18 0.09 0.003 0.15 0.01 NS -0.09 0.10 0.03 NS -0.09 0.13 0.12 0.000 0.06 0.18 0.10 0.001 0.04 0.14 0.10 0.01 NS -0.01 0.01 0.02 0.13 0.13 0.000 0.08 0.18 0.12 0.000 0.05 0.15 0.10 0.001 0.04 0.14 0.10 0.00 NS -0.018 0.09 0.01 0.13 0.000 0.08 0.18 0.12 0.000 0.09 0.15 0.15 0.00 0.01 0.10 0.00 NS -0.02 0.08 0.08 0.09 0.01 0.03 0.13 0.000 0.00 0.05 0.15 0.00 0.01 0.01 0.10 0.00 NS -0.02 0.01 0.00 0.05 0.15 0.00 0.01 0.01 0.00 NS -0.02 0.02 0.17 NS -0.02 0.01 0.00 0.00 0.00 0.00 0.02 0.01 0.00 0.02 0.17 NS -0.02 0.10 0.00 0.00 0.00 0.00 0.00 0.00   | -0.07<br>-0.07<br>-0.05<br>-0.04  | -0.04<br>-0.18<br>-0.03<br>-0.10  | $\begin{array}{c} -0.04 \\ -0.06 \\ -0.05 \\ -0.05 \end{array}$ | -26.3<br>-29.2<br>-19.8<br>-28.7                                | $\begin{array}{c} -0.15 \\ -0.14 \\ -0.20 \\ -0.17 \end{array}$  | -0.11<br>-0.10<br>-0.12                          | -3.70<br>-2.90<br>-1.92<br>-3.00                                  |
| 0.13 0.000 0.007 0.18 0.12 0.000 0.06 0.18 0.09 0.003 0.15 0.01 NS -0.09 0.10 0.03 NS -0.09 0.13 0.12 0.000 0.06 0.18 0.10 0.001 0.04 0.14 0.10 0.01 NS -0.01 0.01 0.02 0.13 0.13 0.000 0.08 0.18 0.12 0.000 0.05 0.15 0.10 0.001 0.04 0.14 0.10 0.00 NS -0.018 0.09 0.01 0.13 0.000 0.08 0.18 0.12 0.000 0.09 0.15 0.15 0.00 0.01 0.10 0.00 NS -0.02 0.08 0.08 0.09 0.01 0.03 0.13 0.000 0.00 0.05 0.15 0.00 0.01 0.01 0.10 0.00 NS -0.02 0.01 0.00 0.05 0.15 0.00 0.01 0.01 0.00 NS -0.02 0.02 0.17 NS -0.02 0.01 0.00 0.00 0.00 0.00 0.02 0.01 0.00 0.02 0.17 NS -0.02 0.10 0.00 0.00 0.00 0.00 0.00 0.00   | N N N N N N N N N N N N N N N N N N N   | N N N N N N N N N N N N N N N N N N N   | NS N                        |   | 0.007<br>NS<br>0.001<br>0.011  | NS<br>NS<br>0.012<br>0.044                       | NS<br>NS<br>NS<br>NS  |
| 0.13 0.000 0.007 0.18 0.12 0.000 0.06 0.18 0.09 0.003 0.15 0.01 NS -0.09 0.10 0.03 NS -0.09 0.13 0.12 0.000 0.06 0.18 0.09 0.001 0.04 0.14 0.01 NS -0.01 0.11 0.10 NS -0.09 0.13 0.12 0.000 0.005 0.13 0.12 0.000 0.005 0.13 0.12 0.000 0.007 0.17 0.09 0.001 0.04 0.14 0.01 NS -0.01 0.10 1.01 0.00 NS -0.01 0.11 0.008 NS -0.04 0.13 0.12 0.000 0.007 0.17 0.09 0.001 0.04 0.14 0.01 0.10 0.00 NS -0.02 0.03 0.03 NS -0.03 0.03 0.17 0.09 0.001 0.04 0.04 0.00 NS -0.01 0.00 0.05 0.13 0.00 0.00 0.00 0.00 0.00 0.00 0.00  | 0.03<br>0.02<br>0.03<br>0.04  | 0.27<br>0.18<br>0.23<br>0.15  | 0.04<br>0.03<br>0.03<br>0.02                                    | -0.3<br>-2.5<br>2.4<br>-7.3                                     |  |  | -1.12<br>-0.50<br>0.29<br>-0.97<br>(Co                            |
| 0.13 0.000 0.07 0.18 0.12 0.000 0.06 0.18 0.09 0.003 0.15 0.01 NS -0.09 0.10 0.03 NS -0.09 0.12 0.000 0.06 0.18 0.12 0.000 0.06 0.18 0.12 0.000 0.06 0.18 0.12 0.000 0.06 0.18 0.12 0.000 0.00 0.06 0.18 0.12 0.000 0.005 0.18 0.12 0.000 0.005 0.18 0.12 0.000 0.005 0.18 0.12 0.000 0.005 0.18 0.12 0.000 0.005 0.18 0.12 0.000 0.005 0.18 0.12 0.000 0.005 0.18 0.12 0.000 0.005 0.18 0.12 0.000 0.005 0.18 0.12 0.000 0.005 0.17 0.005 0.001 0.004 0.10 0.00 NS -0.08 0.08 0.05 0.05 0.005 0   | 0.13<br>0.13<br>0.12<br>0.13  | 0.55<br>0.48<br>0.47<br>0.33  | 0.02<br>0.04<br>0.01<br>0.01                                    |   |  |  |   |
| 0.13 0.000 0.007 0.18 0.12 0.000 0.06 0.18 0.09 0.003 0.15 0.01 NS -0.09 0.10 0.00 0.12 0.000 0.06 0.18 0.12 0.000 0.06 0.18 0.10 0.000 0.04 0.16 0.00 NS -0.11 0.11 0.00 0.13 0.000 0.06 0.18 0.12 0.000 0.06 0.18 0.12 0.000 0.06 0.18 0.12 0.000 0.06 0.18 0.12 0.000 0.06 0.19 0.10 0.000 0.06 0.19 0.10 0.000 0.06 0.19 0.10 0.000 0.06 0.19 0.10 0.000 0.05 0.17 0.06 0.01 0.10 0.00 NS -0.08 0.09 0.00 0.06 0.19 0.10 0.000 0.05 0.17 0.06 0.01 0.10 0.00 NS -0.03 0.29 0.11 0.000 NS -0.02 0.00 0.00 0.05 0.00 0.00 0.00 0.02 0.00 0.00  | -0.07<br>-0.09<br>-0.05<br>-0.04  | -0.06<br>-0.14<br>-0.05<br>-0.16  | -0.14<br>-0.16<br>-0.13<br>-0.13                                |   | $\begin{array}{c} -0.11 \\ -0.11 \\ -0.18 \\ -0.15 \end{array}$  | -0.06<br>-0.06<br>-0.07<br>-0.06                 | -4.65<br>-4.14<br>-3.30<br>-3.77                                  |
| 0.13 0.000 0.007 0.18 0.12 0.000 0.06 0.18 0.09 0.003 0.15 0.01 NS -0.09 0.10 0.00 0.12 0.000 0.06 0.18 0.12 0.000 0.06 0.18 0.10 0.000 0.04 0.16 0.00 NS -0.11 0.11 0.00 0.13 0.000 0.06 0.18 0.12 0.000 0.06 0.18 0.12 0.000 0.06 0.18 0.12 0.000 0.06 0.18 0.12 0.000 0.06 0.19 0.10 0.000 0.06 0.19 0.10 0.000 0.06 0.19 0.10 0.000 0.06 0.19 0.10 0.000 0.05 0.17 0.06 0.01 0.10 0.00 NS -0.08 0.09 0.00 0.06 0.19 0.10 0.000 0.05 0.17 0.06 0.01 0.10 0.00 NS -0.03 0.29 0.11 0.000 NS -0.02 0.00 0.00 0.05 0.00 0.00 0.00 0.02 0.00 0.00  | $\overset{\text{N}}{\overset{\text{N}}}{\overset{\text{N}}{\overset{\text{N}}{\overset{\text{N}}{\overset{\text{N}}}{\overset{\text{N}}{\overset{\text{N}}{\overset{\text{N}}{\overset{\text{N}}}{\overset{\text{N}}{\overset{\text{N}}{\overset{\text{N}}}{\overset{\text{N}}{\overset{\text{N}}{\overset{\text{N}}}{\overset{\text{N}}{\overset{\text{N}}{\overset{\text{N}}}{\overset{\text{N}}{\overset{\text{N}}}{\overset{\text{N}}{\overset{\text{N}}}{\overset{\text{N}}{\overset{\text{N}}}{\overset{\text{N}}{\overset{\text{N}}}{\overset{\text{N}}{\overset{\text{N}}}{\overset{\text{N}}{\overset{\text{N}}}{\overset{\text{N}}}{\overset{\text{N}}{\overset{\text{N}}}{\overset{\text{N}}}{\overset{\text{N}}}{\overset{\text{N}}}{\overset{\text{N}}}{\overset{\text{N}}}{\overset{\text{N}}}{\overset{\text{N}}}{\overset{\text{N}}}{\overset{\text{N}}}{\overset{\text{N}}{\overset{\text{N}}}{\overset{\text{N}}{\overset{\text{N}}{\overset{\text{N}}{\overset{N}}}{\overset{\text{N}}{\overset{N}}}}{\overset{\text{N}}{\overset{N}}}}\overset{\text{N}}}{\overset{\text{N}}}{\overset{N}}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}{\overset{N}}\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}{\overset{N}}{\overset{N}}}{\overset{N}}{\overset{N}}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}{\overset{N}}}{\overset{N}}}{\overset{N}}{\overset{N}}}{\overset{N}}{\overset{N}}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}{\overset{N}}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}}{\overset{N}}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}{\overset{N}}}{\overset{N}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}{\overset{N}}{\overset{N}}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}{$ | $\overset{\text{N}}{\overset{\text{N}}}{\overset{\text{N}}{\overset{\text{N}}{\overset{\text{N}}}{\overset{\text{N}}{\overset{\text{N}}{\overset{\text{N}}{\overset{\text{N}}{\overset{\text{N}}{\overset{\text{N}}{\overset{\text{N}}{\overset{\text{N}}}{\overset{\text{N}}{\overset{\text{N}}}{\overset{\text{N}}{\overset{\text{N}}}{\overset{\text{N}}{\overset{\text{N}}}{\overset{\text{N}}{\overset{\text{N}}{\overset{\text{N}}}{\overset{\text{N}}{\overset{\text{N}}}{\overset{\text{N}}{\overset{\text{N}}}{\overset{\text{N}}{\overset{\text{N}}}{\overset{\text{N}}{\overset{\text{N}}}{\overset{\text{N}}}{\overset{\text{N}}}{\overset{\text{N}}}{\overset{\text{N}}}{\overset{\text{N}}}{\overset{\text{N}}{\overset{\text{N}}}{\overset{\text{N}}}{\overset{\text{N}}}{\overset{\text{N}}}{\overset{\text{N}}}}}{\overset{\text{N}}}{\overset{\text{N}}{\overset{\text{N}}{\overset{\text{N}}{\overset{\text{N}}{\overset{\text{N}}}{\overset{\text{N}}{\overset{\text{N}}}{\overset{\text{N}}}{\overset{\text{N}}}}}{\overset{\text{N}}}{\overset{\text{N}}{\overset{\text{N}}}{\overset{\text{N}}{\overset{N}}}}{\overset{\text{N}}{\overset{N}}}{\overset{N}}}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}{\overset{N}}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}{\overset{N}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}{\overset{N}}}{\overset{N}}{\overset{N}}{\overset{N}$ | NS<br>NS<br>NS<br>0.033   | $\begin{array}{c} X & X \\ X & X \\ X & X \\ X & X \end{array}$ | $\overset{\text{NS}}{\overset{\text{NS}}}}{\overset{\text{NS}}{\overset{\text{NS}}}{\overset{\text{NS}}{\overset{\text{NS}}{\overset{\text{NS}}{\overset{\text{NS}}{\overset{\text{NS}}{\overset{\text{NS}}{\overset{\text{NS}}{\overset{\text{NS}}{\overset{\text{NS}}{\overset{\text{NS}}{\overset{\text{NS}}{\overset{\text{NS}}{\overset{\text{NS}}{\overset{\text{NS}}{\overset{\text{NS}}{\overset{\text{NS}}{\overset{\text{NS}}{\overset{\text{NS}}{\overset{N}}}}}{\overset{\text{NS}}{\overset{N}}}}}{\overset{N}}{\overset{N}}{\overset{N}}}{\overset{N}}}}{\overset{N}}}{\overset{N}}}{\overset{N}}}}}}}}$ | NS N         | 0.040<br>NS<br>0.046<br>0.026                                     |
| 0.13 0.000 0.007 0.18 0.12 0.000 0.06 0.18 0.09 0.003 0.03 0.15 0.01 NS -0.09 0.10 0.12 0.000 0.06 0.18 0.12 0.000 0.06 0.18 0.10 0.000 0.04 0.16 0.00 NS -0.11 0.11 0.11 0.13 0.000 0.06 0.18 0.12 0.000 0.05 0.15 0.00 0.04 0.16 0.00 NS -0.08 0.09 0.10 0.000 0.06 0.18 0.12 0.000 0.05 0.15 0.00 0.04 0.14 0.01 NS -0.08 0.09 0.00 0.06 0.15 0.00 0.05 0.15 0.00 0.00 0.05 0.15 0.00 0.00  | 0.03<br>0.02<br>0.04<br>0.05  | 0.25<br>0.17<br>0.21<br>0.08  | -0.06<br>-0.06<br>-0.06   | -2.6<br>-4.0<br>-6.3<br>-5.3                                    | $\begin{array}{c} -0.03 \\ -0.02 \\ -0.08 \\ -0.05 \end{array}$  | 0.00<br>0.00<br>-0.02<br>-0.01                   |   |
| 0.13 0.000 0.07 0.18 0.12 0.000 0.06 0.18 0.09 0.003 0.03 0.15 0.01 NS -0.09 0.12 0.000 0.06 0.18 0.12 0.000 0.06 0.18 0.12 0.000 0.06 0.18 0.12 0.000 0.06 0.18 0.12 0.000 0.06 0.18 0.12 0.000 0.06 0.18 0.12 0.000 0.06 0.18 0.12 0.000 0.06 0.18 0.10 0.001 0.04 0.16 0.00 NS -0.08 0.19 0.00 0.06 0.15 0.10 0.000 0.05 0.17 0.01 0.10 0.00 NS -0.08 0.10 0.00 0.05 0.15 0.00 0.00 0.01 0.10 0.00 NS -0.03 0.00 0.00 0.00 0.01 0.10 0.00 NS -0.23 0.00 0.02 0.00 0.0   | 0.10<br>0.11<br>0.09<br>0.08  | 0.28<br>0.29<br>0.25<br>0.19  | -0.02<br>0.00<br>-0.01  | 22.6<br>22.0<br>13.3<br>23.2                                    |  |  |   |
| 0.13 0.000 0.07 0.18 0.12 0.000 0.06 0.18 0.09 0.003 0.03 0.15 0.00 0.12 0.000 0.06 0.18 0.12 0.000 0.06 0.18 0.12 0.000 0.06 0.18 0.12 0.000 0.06 0.18 0.12 0.000 0.06 0.18 0.12 0.000 0.07 0.17 0.09 0.001 0.04 0.14 0.01 0.10 0.000 0.08 0.18 0.12 0.000 0.07 0.17 0.09 0.001 0.04 0.14 0.01 0.000 0.03 0.18 0.12 0.000 0.07 0.17 0.09 0.001 0.04 0.14 0.01 0.000 0.03 0.11 0.08 0.02 0.01 0.08 0.02 0.01 0.08 0.02 0.01 0.08 0.02 0.01 0.02 0.00 0.02 0.001 0.02 0.001 0.00 0.02 0.01 0.00 0.02 0.01 0.00 0.02 0.01 0.00 0.02 0.01 0.00 0.00   | -0.09<br>-0.11<br>-0.08<br>-0.08  | -0.32<br>-0.30<br>-0.28<br>-0.31  |   |   | $\begin{array}{c} -0.05 \\ -0.05 \\ -0.08 \\ -0.08 \end{array}$  | -0.01<br>-0.02<br>-0.01<br>-0.01                 | -3.44<br>-3.64<br>-3.59<br>-2.79                                  |
| 0.13 0.000 0.07 0.18 0.12 0.000 0.06 0.18 0.10 0.001 0.04 0.15 0.12 0.000 0.06 0.18 0.12 0.000 0.06 0.18 0.10 0.001 0.04 0.14 0.13 0.000 0.06 0.18 0.12 0.000 0.05 0.15 0.06 0.017 0.01 0.01 0.10 0.10 0.000 0.06 0.18 0.12 0.000 0.07 0.17 0.09 0.001 0.04 0.14 0.10 0.000 0.06 0.18 0.10 0.000 0.05 0.15 0.06 0.017 0.01 0.10 0.10 0.000 0.06 0.15 0.10 0.000 0.05 0.15 0.06 0.017 0.010 0.000   | $\begin{array}{c} \mathbf{N} \\ $   | NS N  | 0.011<br>0.032<br>0.013<br>0.022                                | N N N N N N N N N N N N N N N N N N N                           | $\overset{N}{\overset{N}{\overset{N}{\overset{N}{\overset{N}{\overset{N}{\overset{N}{\overset{N}$  | 0.046<br>NS<br>NS<br>NS                          | N N N N N N N N N N N N N N N N N N N                             |
| 0.13 0.000 0.07 0.18 0.12 0.000 0.06 0.18 0.10 0.001 0.04 0.15 0.12 0.000 0.06 0.18 0.12 0.000 0.06 0.18 0.10 0.001 0.04 0.14 0.13 0.000 0.06 0.18 0.12 0.000 0.05 0.15 0.06 0.017 0.01 0.01 0.10 0.10 0.000 0.06 0.18 0.12 0.000 0.07 0.17 0.09 0.001 0.04 0.14 0.10 0.000 0.06 0.18 0.10 0.000 0.05 0.15 0.06 0.017 0.01 0.10 0.10 0.000 0.06 0.15 0.10 0.000 0.05 0.15 0.06 0.017 0.010 0.000   | 0.01<br>0.00<br>0.01<br>0.00  | -0.02<br>-0.01<br>-0.02<br>-0.06  |   | -2.3<br>-1.6<br>-8.7<br>2.1                                     | 0.03<br>0.03<br>0.02<br>0.02   | 0.05<br>0.04<br>0.04<br>0.04                     | -0.94<br>-1.16<br>-1.39<br>-0.78                                  |
| 0.13 0.000 0.007 0.18 0.12 0.000 0.06 0.18 0.09 0.003 0.003 0.12 0.000 0.06 0.18 0.10 0.004 0.10 0.004 0.13 0.000 0.06 0.18 0.12 0.000 0.06 0.18 0.10 0.001 0.004 0.10 0.006 0.08 0.18 0.12 0.000 0.07 0.17 0.09 0.001 0.04 0.10 0.000 0.06 0.15 0.10 0.000 0.07 0.17 0.09 0.001 0.04 0.10 0.000 0.06 0.15 0.10 0.000 0.05 0.15 0.00 0.05 0.10 0.034 0.000 0.052 0.00 0.00 0.022 0.00 0.002 0.003 0.00 0.00  | 0.15<br>0.16<br>0.14<br>0.10  |   |   | 0.1<br>1.0<br>-1.6<br>3.3                                       | -0.09<br>-0.11<br>-0.04  | -0.01<br>-0.02<br>-0.01<br>0.01                  |   |
| 0.13 0.000 0.07 0.18 0.12 0.000 0.06 0.18 0.09 0.12 0.000 0.06 0.18 0.10 0.012 0.000 0.06 0.18 0.12 0.000 0.06 0.18 0.12 0.000 0.05 0.15 0.10 0.09 0.10 0.000 0.06 0.15 0.10 0.000 0.05 0.15 0.00 0.00 0.0   | 0.03<br>0.04<br>0.04<br>0.01  |   |   |   |  |  | -1.68<br>-1.72<br>-2.11<br>-1.11                                  |
| 0.13 0.000 0.07 0.18 0.12 0.000 0.06 0.18 0.09 0.12 0.000 0.06 0.18 0.10 0.012 0.000 0.06 0.18 0.12 0.000 0.06 0.18 0.12 0.000 0.05 0.15 0.10 0.09 0.10 0.000 0.06 0.15 0.10 0.000 0.05 0.15 0.00 0.00 0.0   | 0.003<br>0.001<br>0.001<br>0.017  | 0.000<br>0.038<br>0.000<br>0.004  | 0.002<br>0.024<br>0.003<br>0.005                                | NS<br>NS<br>0.028<br>NS   | 0.000<br>0.000<br>0.001<br>0.006   | 0.005<br>0.002<br>0.002<br>0.050                 | NS<br>0.028<br>0.028<br>NS  |
| 0.13 0.000 0.07 0.18 0.12 0.000 0.06 0.18 0.12 0.000 0.06 0.18 0.12 0.000 0.06 0.18 0.12 0.000 0.06 0.18 0.12 0.000 0.07 0.17 0.10 0.000 0.08 0.18 0.12 0.000 0.07 0.17 0.10 0.000 0.06 0.18 0.12 0.000 0.07 0.17 0.10 0.000 0.06 0.18 0.12 0.000 0.07 0.19 0.00 0.06 0.18 0.10 0.000 0.07 0.19 0.01 0.02 0.01 0.008 0.18 0.02 0.01 0.00 0.01 0.02 0.01 0.00 0.02 0.11 0.00 0.05 0.01 0.00 0.01 0.02 0.01 0.00 0.01 0.02 0.01 0.00 0.00 0.01 0.00 0.00 0.01 0.00 0.00 0.01 0.00 0.00 0.01 0.00 0.00 0.00 0.01 0.00 0.00 0.01 0.00 0.00 0.01 0.00 0.00 0.01 0.00 0.00 0.00 0.00 0.00 0.01 0.00 0.   |   |   |   | -15.6<br>-14.2<br>-14.4<br>-9.0                                 |  |  |   |
| 0.13 0.000 0.07 0.18 0.12 0.000 0.06 0.13 0.000 0.06 0.18 0.12 0.000 0.06 0.13 0.02 0.000 0.06 0.18 0.12 0.000 0.07 0.13 0.000 0.08 0.18 0.12 0.000 0.07 0.10 0.000 0.05 0.13 0.000 0.06 0.15 0.10 0.000 0.05 0.05 0.009 0.005 0.03 0.025 0.09 0.03 0.00 0.03 0.02 0.03 0.000 0.018 0.02 0.005 0.03 0.02 0.013 0.000 0.018 0.08 0.02 0.005 0.041 0.09 0.013 0.000 0.017 0.09 0.040 0.045 0.09 0.013 0.000 0.017 0.09 0.040 0.045 0.09 0.013 0.000 0.017 0.09 0.040 0.045 0.09 0.013 0.000 0.017 0.09 0.040 0.045 0.09 0.017 0.009 0.017 0.09 0.005 0.010 0.09 0.013 0.000 0.017 0.09 0.02 0.010 0.009 0.013 0.000 0.025 0.010 0.000 0.025 0.010 0.000 0.025 0.010 0.000 0.025 0.010 0.000 0.025 0.010 0.000 0.025 0.000 0.025 0.000 0.025 0.000 0.025 0.000 0.025 0.000 0.025 0.000 0.025 0.000  | 0.18<br>0.18<br>0.17<br>0.15  | 0.10<br>0.08<br>0.10<br>0.08  | 0.00<br>0.00<br>0.00<br>-0.01                                   |   | -0.15<br>-0.16<br>-0.14<br>-0.10   | -0.06<br>-0.07<br>-0.07                          | 0.18<br>0.50<br>0.75<br>0.26                                      |
| 0.13 0.000 0.07 0.18 0.12 0.000 0.06 0.18 0.13 0.000 0.06 0.18 0.10 0.000 0.06 0.18 0.10 0.000 0.06 0.18 0.10 0.000 0.06 0.18 0.009 NS   | 0.06<br>0.06<br>0.07<br>0.05  | $\begin{array}{c} -0.25 \\ -0.25 \\ -0.20 \\ -0.21 \end{array}$   | -0.09<br>-0.09<br>-0.09   |   |  |  | $ \begin{array}{r} -2.72 \\ -2.20 \\ -1.82 \\ -2.08 \end{array} $ |
| 0.13 0.000 0.07 0.18 0.12 0.000 0.06 0.18 0.13 0.000 0.06 0.18 0.10 0.000 0.06 0.18 0.10 0.000 0.06 0.18 0.10 0.000 0.06 0.18 0.009 NS   | 0.000<br>0.000<br>0.000<br>0.000  | N N N N N N N N N N N N N N N N N N N   | 0.031<br>0.041<br>0.045<br>0.010                                | 0.031<br>0.029<br>NS<br>0.010                                   | 0.000<br>0.000<br>0.000<br>0.000   | 0.000<br>0.000<br>0.000<br>0.000                 | 0.001<br>0.000<br>0.001<br>0.004                                  |
| 0.13 0.000 0.07 0.18 0.12 0.000 0.06 0.18 0.13 0.000 0.06 0.18 0.10 0.000 0.06 0.18 0.10 0.000 0.06 0.18 0.10 0.000 0.06 0.18 0.009 NS   | 0.12<br>0.12<br>0.12<br>0.10  | -0.07<br>-0.08<br>-0.05<br>-0.06  | -0.05<br>-0.05<br>-0.04<br>-0.05                                |   | -0.20<br>-0.21<br>-0.20<br>-0.15   | -0.10<br>-0.10<br>-0.10<br>-0.08                 | -1.27<br>-0.85<br>-0.53<br>-0.91                                  |
| 0.13 0.000 0.07 0.12 0.000 0.06 0.13 0.000 0.008 0.10 0.000 0.008 0.10 0.000 0.008 0.009 NS -0.29 -0.07 NS -0.29 -0.13 0.000 -0.19 -0.13 0.000 -0.13 -0.13 0.000 -0.13 -0.13 0.000 -0.17 -18.1 0.014 -32.6 -18.2 0.019 -33.3 -20.7 0.001 -33.2 -14.3 0.000 -0.21 -0.13 0.000 -0.21 -0.13 0.000 -0.23 -0.13 0.000 -0.23 -0.13 0.000 -0.23 -0.13 0.000 -0.23 -0.00 0.001 -0.09 -0.05 0.000 -0.09 -0.05 0.000 -0.09 -0.06 0.001 -0.09 -0.06 0.001 -0.09 -0.06 0.001 -0.09 -0.06 0.001 -0.09 -0.06 0.001 -0.09 -0.06 0.000 -3.51 -1.92 0.000 -3.83   | 0.18<br>0.18<br>0.18  | 0.08<br>0.11<br>0.09<br>0.02  |   |   |  |  |   |
| 0.13 0.000 0.12 0.000 0.13 0.000 0.10 0.000 0.10 0.000 0.10 0.000 0.11 0.000 0.11 0.000 0.13 0.000 0.13 0.000 0.13 0.000 0.13 0.000 0.13 0.000 0.14 0.014 0.18 0.000 0.017 0.000 0.018 0.000 0.018 0.000 0.018 0.000 0.018 0.000 0.018 0.000 0.018 0.000 0.018 0.000 0.018 0.000 0.018 0.000 0.018 0.000 0.019 0.000 0.019 0.000 0.010 0.000 0.010 0.000 0.010 0.000 0.010 0.000 0.010 0.000 0.010 0.000 0.010 0.000 0.010 0.000 0.010 0.000 0.010 0.000 0.010 0.000 0.010 0.000 0.010 0.000 0.010 0.000 0.010 0.000 0.010 0.000   | 0.07<br>0.06<br>0.08<br>0.06  | -0.26<br>-0.29<br>-0.22<br>-0.27  |   |   |  |  | -3.63 -<br>-3.51 -<br>-3.18 -<br>-2.84 -                          |
| 0.13<br>0.10<br>0.13<br>0.10<br>0.00<br>-0.09<br>-0.07<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.13<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10<br>-0.10 | 0.000<br>0.000<br>0.000   | NS<br>NS<br>NS<br>NS  | 0.000<br>0.000<br>0.000<br>0.000                                | 0.014 -<br>0.019 -<br>0.001 -<br>0.020 -                        | 0.000<br>0.000<br>0.000  | 0.005<br>0.001<br>0.000<br>0.017                 |   |
|  | 0.13<br>0.12<br>0.13<br>0.10  | -0.09<br>-0.09<br>-0.07<br>-0.13  | $\begin{array}{c} -0.15 \\ -0.13 \\ -0.13 \\ -0.13 \end{array}$ |   | $\begin{array}{c} -0.17 \\ -0.18 \\ -0.18 \\ -0.13 \end{array}$  | -0.05<br>-0.06<br>-0.06<br>-0.03                 | -2.21<br>-2.01<br>-1.92<br>-1.70                                  |
|  | HDL cholesterol (mmol/L) Original MI LOCF BOCF LDL cholesterol  | (mmol/L) Original MI LOCF BOCF Apolipoprotein B   | ( la  |   | _  | AST (µmol/s * L) Original MI LOCF BOCF CRP high- | vity  |

**Table 4.** Changes in Weight, Blood Pressure, and Biochemistry after 12 Months in the Groups ABC and 4S and in the Controls<sup>a</sup> (Continued)

|                  | ABC Group 12 Months<br>Minus Baseline | C Group 12 Mor<br>Minus Baseline | nths  | 4S Group<br>Minus | p 12 Months<br>s Baseline | hs    | Control<br>Mi | rol Group 12 Me<br>Minus Baseline | Control Group 12 Months<br>Minus Baseline |       | A<br>Min | ABC<br>Minus 4S |        | 1       | ABC Minus<br>Controls | inus<br>ols |       |               | 4S Minus<br>Controls | slo:    |       |
|------------------|---------------------------------------|----------------------------------|-------|-------------------|---------------------------|-------|---------------|-----------------------------------|---|-------|----------|-----------------|--------|---------|-----------------------|-------------|-------|---------------|----------------------|---------|-------|
|                  | $\Delta$ $D$                          | 95%                              | CI    | $\Delta$ $D$      | 95%                       | CI    | ◁             | р                                 | 95% CI                                    | ◁     | d        | 95%             | CI     | ◁       | <i>b</i>              | 95%         | CI    | ◁             | р                    | 95%     | CI    |
| Flucose (mmol/L) | 0.00 0.000                            |                                  |       | -022 0013         |                           | 900   | 010           | SZ.                               |   | 2     |          | _0.23           | 0.31   | 86.0    |                       |             | 10 0  |               | SZ.                  | 090     | 0.03  |
| MI               | $-0.18 \ 0.026$                       | -0.35                            | -0.02 | $-0.17 \ 0.038$   | 0.33                      | -0.02 | 0.03          | SS                                | -0.07 0.27<br>-0.19 0.26                  | -0.01 | SZ       | -0.20           | 0.29   | -0.23   | SS                    | -0.52       | 0.19  | -0.52 $-0.21$ | SZ                   | -0.51   | 0.10  |
| LOCF             | $-0.16\ 0.030$                        |                                  |       | -0.16 NS          |                           | -0.02 | 0.11          | SN                                |   | 0.00  |          | -0.24           | 0.24   | -0.26   | Ċ                     |             | .0.03 |               | NS                   | -0.50   | -0.02 |
| BOCF             | -0.12 NS                              |                                  |       | -0.20  0.001      |                           | -0.07 | 90.0          | SN                                |   | 0.08  |          | -0.15           | 0.31   | -0.18   |                       |             | 0.04  | $\overline{}$ | 0.031                | -0.49   | -0.03 |
| IbA1c IFCC       |                                       |                                  |       |                   |                           |       |               |                                   |   |       |          |                 |        |         |                       |             |       |               |                      |         |       |
| (mmol/mol)       |                                       |                                  |       |                   |                           |       |               |                                   |   |       |          |                 |        |         |                       |             |       |               |                      |         |       |
| Original         |                                       | -1.73                            | 0.08  |                   | -1.32                     | 0.50  |               | .013                              | 0.34 2.31                                 |       | SN       | -1.99           | 1.16   | -2.150  |                       |             | 0.51  | -1.73         | SZ                   | -3.37   | -0.10 |
|                  |                                       | -1.61                            | 0.55  |                   | -1.26                     | 0.53  |               | 016                               | 0.29 2.06                                 |       | SZ       | -1.85           | 1.53   |         |                       |             | 0.01  | -1.54         | SZ                   | -3.05 - | -0.03 |
| LOCF             | -0.66 NS                              | -1.52                            | 0.21  | -0.44 NS          | -1.33                     | 0.44  | 1.08          | 0.018                             | 0.20 1.95                                 | -0.21 | SZ       | -1.73           | 1.30   | _       | . 210.0               | -3.24 $-$   | -0.23 | -1.52         | SZ                   | -3.04   | 0.00  |
| BOCF             |                                       | -1.47                            | 0.03  |                   | -1.13                     | 0.41  |               | SN                                | -0.01 1.51                                |       | SZ       | -1.68           | 0.95   | _       |                       |             | 0.16  | -1.11         | SN                   | -2.43   | 0.22  |
| omol/L)          |                                       |                                  |       |                   |                           |       |               |                                   |   |       |          |                 |        |         |                       |             |       |               |                      |         |       |
|                  | -32.8 0.000                           |                                  |       | -25.9 0.000       |                           | '     | _             |                                   | _   | -6.9  | 0.045    | ı               | - 5.81 | _       | - 1                   | 49.8        |       | -15.9         |                      | -42.9   | 11.1  |
|                  | -32.0 0.000                           |                                  | -17.2 |                   | .42.5                     | - 9.6 | -13.4 (       |                                   | -30.6 3.7                                 | -5.9  | SN       | -33.9           | - 0.22 | -18.5 0 | -0.023                | -44.6       | 7.5   | -12.6         | SN                   | -41.1   | 15.8  |
|                  | -23.4 0.000                           |                                  |       |                   |                           |       | _             |                                   | _   | 9.0   | SN       | - 1             | - 6.22 | _       | - 1                   | 39.2        |       | -17.6         |                      | -40.0   | 8.4   |
|                  | -23.4 0.000                           | 0.000 - 36.0                     |       | -24.0 0.000       |                           |       | _             | 0.029                             | _   | 9.0   | SN       | - 1             | - 6.22 | _       | - 1                   | 39.2        |       | -17.6         |                      | -40.0   | 4.8   |
|                  |                                       |                                  |       |                   |                           |       |               |                                   |   |       |          |                 |        |         |                       |             |       |               |                      |         |       |
| Original         | $-0.91 \ 0.000$                       | -1.32                            | -0.50 | -0.780.000        | -1.18                     | -0.38 | -0.23 (       | 0.019                             | -0.67 0.21                                | -0.13 | SZ       | -0.84           | 0.58   | -0.68 0 | 0.004                 | -1.42       | 0.07  | -0.55         | SZ                   | -1.29   | 0.19  |
|                  | -0.880.000                            |                                  |       | -0.720.000        |                           | -0.32 |               | .002                              |   | -0.16 |          | -0.81           | 0.48   |         | .050                  | -1.28       | 0.24  | -0.36         | SZ                   | -1.07   | 0.35  |
|                  | -0.620.000                            |                                  |       | -0.71  0.000      | 1                         | -0.35 |               | SZ                                |   | 0.00  |          | -0.51           | 0.70   |         | .005                  | -1.10       | 0.11  | -0.59         | SZ                   | -1.20   | 0.03  |
| BOCF             | -0.620.000                            |                                  |       | -0.71  0.000      |                           | -0.35 |               | SZ                                |   | 0.00  |          | -0.51           | 0.70   |         | . 500.                | -1.10       | 0.11  | -0.59         | SZ                   | -1.20   | 0.03  |

ABC = Active Body Control Program of University of Magdeburg, 4S = 4sigma telephone coaching, CI = confidence interval, MI = multiple imputation, LOCF = last observation carried forward, BOCF = baseline observation carried forward, BOCF = baseline observation carried forward, BMI = body mass index, BP = blood pressure, HDL = high-density lipoprotein, LDL = low-density lipoprotein, ALT = Alanin-Aminotransferase, AST = Aspartat-Aminotransferase, CRP = C-reactive protein, IFCC = International Federation of Clinical Chemistry, HOMA = homeostasis model of assessment.

\*All differences given here were adjusted to baseline levels to compensate for baseline differences between the groups. Original estimates are results taken from the mixed model approach, which uses all available data from all visits. To correct for dropouts, 3 approaches are presented: MI, LOCF, and BOCF. The 3 columns on the right give differences between the groups.

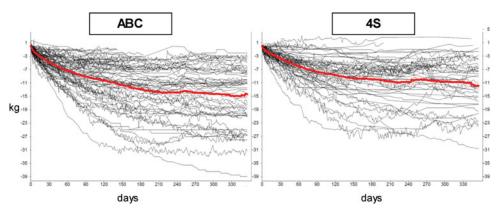


Fig. 2. Individual absolute weight losses in kilograms in the 2 intervention groups over the entire study. Red lines represent the mean weight loss (unadjusted kilograms) in each group. A frequent weight increase by 2 to 3 kg after 240 days reflects the time around Christmas and was corrected in most cases thereafter. (Color figure available online.)

greater effects on relative and absolute weight, BMI, and waist circumference and, in the ABC group only, on triglycerides, CRP,  $Hb_{Alc}$ , and the parameters of insulin resistance. The magnitude of the effects was greatest for the high-sensitivity CRP (-48% and -28%) and for the HOMA index (-38% and -36%) in the ABC and 4S groups, respectively. If we compare ABC with 4S, the former was more effective with respect to the absolute and the relative weight, BMI, as well as apolipoprotein B.

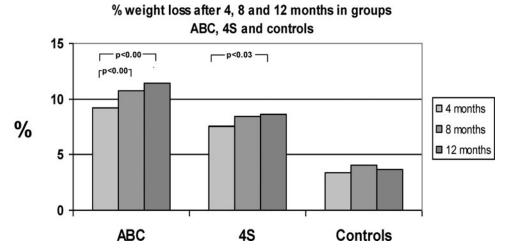
Quality of life was assessed by means of the WHO-5 questionnaire [16]. The return rates after 12 months were 62%, 57%, and 45% in groups ABC, 4S, and controls, respectively, and the well-being indices increased by 44% (p < 0.001), 33% (p < 0.001), and 20% (nonsignificant).

Fig. 4 shows the proportion of patients for whom a diagnosis of metabolic syndrome was no longer applicable after 12 months because one or more of the International Diabetes Federation criteria had disappeared. This rate was 33% in the control group, as opposed to 41% in the 4S group and 58% in the ABC group.

#### **DISCUSSION**

The major finding of this study is that telemonitoring of both physical activity and food intake considerably improves weight reduction and corrects metabolic syndrome in a majority of patients. With regard to communication with the patients, the weekly letters of the ABC program were more effective than the monthly telephone calls in the 4S group.

The magnitude of the observed weight loss can be regarded as quite satisfactory, in particular in the ABC group, with a reduction of adjusted body weight by 12.2 kg (11.4%). A weight reduction program is regarded as medically relevant when an individual loses more than 5% of the baseline weight [17–21]. This aim was achieved in 82% of the subjects completing the study in the ABC group and in 68% in the 4S group. The substantial > 15% weight loss was achieved by a remarkable 43% of the subjects in the ABC group.



**Fig. 3.** Relative weight losses in the 2 intervention groups and in the control group after 4, 8, and 12 months. These data are taken from the mixed model approach, which used all available data at all time points. The changes between months 8 and 12 are not statistically significant but the weight loss trends show a further increase in groups ABC and 4S but a decrease in the control group.

# syndrome 80 60 60 58% 41% 33%

% of patients free from the metabolic

**Fig. 4.** Proportions of patients free from metabolic syndrome after 12 months (data from LOCF evaluation).

Control

Mobile technology has been used repeatedly in weight loss studies, but the technical approaches differed considerably. Several studies used PDAs, mobile phones, and the Internet to exchange written information concerning meals, activities, and respective recommendations. Intervention studies of this kind during 1 year [22-27] report weight losses of between 1.3 kg [25] and 7.6 kg [24]. Studies using pedometers or accelerometers to measure physical activity are less frequent [28–31]. All included regular face-to-face counseling and were carried out for periods shorter than in the present study. Richardson et al. [29] achieved a weight loss of 4.1 lbs after 3 weeks in 12 participants (BMI 37), and Polzien et al. [28] reported a weight loss of 6.2 kg in 19 patients (BMI 32.6) after 12 weeks. Andersen et al. [31] reported data that can be compared with our results. They advised 20 women (BMI 32.4) to observe a 1200 kcal/d diet and to increase their moderate physical activity by 30 minutes per day over 16 weeks. In addition, the patients wore accelerometers whose readings were evaluated at each of 16 weekly counseling meetings. This group lost 8.7% (7.9 kg), which compares well with our 4-month weight reductions of 9.2% in the ABC group and of 7.5% in the 4S group. Our effects are, therefore, in line with satisfactory results obtained by other investigators. However, our study extends the knowledge taken from earlier studies in 2 respects: in the first place, higher weight losses can be achieved by longer interventions (Figs. 2 and 3). Secondly, this weight loss can be achieved by telemonitoring without faceto-face counseling, which is time-consuming for both patients and carers.

What are the major elements contributing to these favorable results? In her review of technology-based weight loss interventions Anna Khaylis [3] concluded that 5 key components are required for effective weight loss: self-monitoring, counselor feedback and communication, social support, a structured program, and the use of an individually tailored program. These 5 components are indeed elements of the intervention used in our study, in particular in the ABC group. Self-monitoring is carried out using the screen of the Aipermotion instrument. Counselor feedback was provided by mail (ABC) or by telephone (4S). A kind of

social support was ensured by the ABC letters showing the weight loss curves of the other patients, thus introducing group dynamics. The program was structured in terms of goals for diet and activity, with regular feedback. Finally, individual tailoring was ensured by specific reactions of the carers to the nutritional and physical data transmitted to them via the Internet.

The weight reductions were associated with relevant benefits in blood pressure and in biochemical parameters. The most pronounced effect was the improvement in parameters known to be associated with insulin resistance. This finding strengthens our belief that the 2 combined intervention measures used in this study, namely, a low-calorie diet replacing high-GI carbohydrates with low-GI carbohydrates plus an increase in moderate physical activity, reinforce each other in reducing insulin resistance. The number of patients with a baseline pathological HOMA index decreased from 18 to 4 after 12 months in the ABC group (-78%) and from 13 to 5 in the 4S group (-61%). The overall improvements are also reflected in the satisfying proportion of patients in whom a diagnosis of metabolic syndrome was no longer applicable (Fig. 4).

The finding that even the control group lost 3.7 kg ("original" in Table 4) warrants discussion, in particular because this was accompanied by a 33% reduction in the occurrence of metabolic syndrome in this group (Fig. 4). Three points may be considered. The first is that we believe that the instruction given to all 3 intervention groups, namely, the recommendations concerning the Magdeburg Dual Diet and optimized physical exercise, was quite effective. Secondly, this instruction was given at a time at which the participants became concerned about health risks detected in their initial physical and blood examinations. The third point concerns a potential selection bias. The control group had the highest rate of dropouts (36%) as opposed to 16% and 18% in the other 2 groups. It is probable that the lost cases were those with the smallest weight losses. This assumption is supported by the intention-to-treat assessment using the LOCF and BOCF protocols (Table 4), which yielded weight losses of 3.0 and 2.5 kg instead of 3.7 kg from the "original" evaluation for the control group. It may be therefore concluded that the results for the control subjects who completed the study overestimate the true effects.

This study also compared 2 methods of communication between the carers and the patients. The results show clearly that weekly information letters are better than monthly telephone calls. This was not expected at the outset, because communication by mail occurred entirely without personal contact for a whole year, whereas the monthly telephone calls allowed about 20 minutes of personal attention each time. We believe that 3 aspects contribute to the better effect in the ABC group. First, the feedback was more frequent: weekly instead of monthly. Second, a letter provides written documentation of the patient's data, in particular of his or her progress and of the carers' motivating responses. Finally, an element of group dynamics was

introduced by displaying the weight loss curves of other patients in the given group.

One important question in all weight reduction programs is the dropout rate. In this study the rates after 1 year were 18% in the ABC group and 17% in the 4S group. A recent study of 772 participants using a conventional weight reduction program known worldwide [32] reported a 12-month dropout rate of 39%, which is more than twice as high. This satisfactory adherence to the program most probably reflects an important advantage of telemonitoring, namely, that the patients do not lose time by visiting their carers.

A second major question relating to weight reduction concerns rebound weight gain. In many studies weight loss reaches a maximum after about 6 months and is then followed by a steady weight gain [33,34]. Such weight gain was observed in our study only in the control group after 8 months (Fig. 3). Groups ABC and 4S showed additional—although small—increases in weight loss (Figs. 2 and 3). One major reason for the frequent failure to maintain an achieved weight loss is that intake and storage of nutritional energy is one of the most important selfpreservation instincts. Continuous suppression of this instinct, particularly when one is confronted with a wealth of calorie-rich food and powerful advertisements for its consumption, requires more willpower than many individuals can exert. In contrast, increasing and maintaining physical activity may in the long run be easier, especially when one is rewarded by daily readings of personal achievement in combination with regular positive feedback from a respected carer.

# STRENGTHS, LIMITATIONS, AND CONCLUSION

The strengths of this study are sufficiently large group sizes, duration of the intervention, and an elaborate intent-to-treat evaluation of the data. A limitation is that the data for dropouts can only be estimated, as in many other weight loss studies. Overestimation (e.g., in the LOCF procedure) is probable, as is underestimation (e.g., in BOCF). In addition, there was a certain imbalance in baseline weight caused by a higher proportion of men in the ABC group. This may have only partly been balanced by reporting parameters that are less dependent of the baseline weight such as relative weight loss and lowering of BMI. A further limitation of this study is that it does not allow one to decide which of the telemonitoring components is more effective: physical activity or nutrition. Finally, more work is needed to test the long-term effects of this new treatment strategy.

Taken together, the results show that telemonitoring of nutrition and physical activity without intermittent face-to-face counseling can yield satisfactory weight loss, in particular when communication with the patients is by weekly letters as in the ABC group. In association with weight loss, there were relevant improvements in symptoms of metabolic syndrome.

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