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Metabolic improvements during weight loss: The RNPC® cohort

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ABSTRACT

Background/Aim: Body weight loss is essential to lower risk factors for type 2 diabetes and cardiovascular diseases in overweight patients. Therefore, we examined the effectiveness of the Rééducation Nutritionnelle et Psycho-Comportementale (RNPC®) program, designed to improve metabolic parameters during weight loss, among different patient groups.

Methods: The RNPC® program, used in 54 French centers, starts with an energy-restricted 800–1000 kcaL/day high-protein, low-carbohydrate, and low-fat diet comprising real foods and meal replacement products. The 89% (n = 10,809) of the patients completing the ~15-week weight loss phase had a median 11% of initial body weight loss and was included in the study. The weight stabilization phases of the program were not included as metabolic risk markers were only sporadically measured in those phases.

Results: A total of 70.3% were obese and 30.3% classified as having the metabolic syndrome. Without differences in weight loss, improvements in fasting glucose were 0.1 mmoL/L (95% CI -0.2; -0.03, P < 0.05), 0.6 mmoL/L (95% CI -0.7; -0.5, P < 0.001), 3.0 mmoL/L (95% CI -3.6; -2.5, P < 0.001) and 2.0 mmoL/L (95% CI -3.1; -0.8, P < 0.05) for men with pretreatment fasting glucose of < 5.6, 5.6–6.9, ≥7.0, or receiving diabetic medication, respectively. Similarly, the largest improvements in triglycerides, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and alanine transaminase levels were found among male patients with the worst baseline level. Comparable results were obtained for females.

Conclusion: Weight loss during the RNPC® program is followed by overall metabolic improvement that is mainly driven by substantial improvements in specific metabolic risk markers among those with highest baseline values.

1. Introduction

Overweight and obesity are a global health problem and, with increasing body mass, the risk of coronary heart disease, ischemic stroke, non-alcoholic fatty liver disease (NAFLD), and type 2 diabetes grows steadily (Al-Dayyat et al., 2018; WHO, 2009). Several more or less efficient weight loss programs have been designed for achievement of weight loss (Gudzune et al., 2016). We recently presented the Rééducation Nutritionnelle et Psycho-Comportementale (RNPC®) program, as cost-effective and well tolerated for short-term body weight loss, where 89% of patients completed the ~15-week weight loss phase with a median weight loss of 11% of initial body weight, while consuming a high protein-low glycemic index (GI) diet (Thorning et al., 2018). The weight loss results obtained with the RNPC® program are similar to that reported from clinical research using very-low or low-calorie diets (Johansson et al., 2014). However, compared to low-calorie-diet formulae, the weight loss in the RNPC® program is achieved while continuing eating real foods and not solely meal replacements. The latter is expected to make the transition to weight maintenance easier and the potential reduction in metabolic risk markers to be maintained.

Metabolic syndrome is a disorder of energy use and storage that is characterized by the presence of three of the following five risk factors: abdominal obesity, high blood pressure, high blood glucose, high serum triglycerides and low high-density lipoprotein cholesterol (HDL-C) levels (Grundy et al., 2005). Weight loss of 5–10% is linked to clinically relevant reductions in metabolic syndrome risk factors, and greater weight losses have been shown to be associated with greater improvements in these risk factors (Wing et al., 2011). Furthermore,

Abbreviations: ALAT, Alanine transaminase; BMI, body mass index; CVD, cardiovascular disease; FPG, fasting plasma glucose; GI, glycemic index; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NAFLD, non-alcoholic fatty liver disease; RNPC®, Rééducation Nutritionnelle et Psycho-Comportementale; WC, waist circumference

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remission of type 2 diabetes was achieved among 34% of participants losing ≥5–10 kg, 57% of participants losing ≥10–15 kg, and 86% of participants losing ≥15 kg or more in a 12-month open-label, cluster-randomized trial at 49 primary care practices in Scotland (Lean et al., 2017). Recently, it was furthermore found that obese subjects with the metabolic syndrome have an 11-fold higher risk of type 2 diabetes compared to obese subjects without components of the metabolic syndrome, insulin resistance, fatty liver and inflammation (Sung et al., 2018). A moderate weight loss was shown to improve liver histology and cardio-metabolic profiles of subjects with NAFLD, and NAFLD is currently the most common chronic liver disease worldwide (Musso et al., 2012). Therefore, weight loss is crucial in disease management, not least among patients with the metabolic syndrome and NAFLD. However, it is largely unknown whether weight loss is achieved differently according to the number of metabolic risk factors and risk of NAFLD at baseline.

Therefore, the aim of the present study was to examine the metabolic improvements among the 89% of the overweight patients completing the weight loss phase of the RNPC® program (Thorning et al., 2018). This was investigated according to baseline levels of body weight and metabolic risk markers. Furthermore, reduction in body weight and waist circumference (WC) was investigated according to the number of metabolic risk factors and risk of NAFLD at baseline. We hypothesized that metabolic parameters improve during weight loss, but that the improvement is greatest in subjects with the worst baseline level of any given risk factor.

2. Materials and methods

2.1. Design

The RNPC® program is a novel ongoing weight loss program managed by 54 RNPC® centers distributed across France, and has previously been described in detail (Thorning et al., 2018). Initially, the patient determines a target weight loss in agreement with a dietician and a physician. The median duration of the weight loss phase previously reported was 111 days (IQR: 57; 182) in women and 92 days (IQR: 48; 157) in men.

2.2. Diet

The RNPC® weight loss diet is composed of daily intake of vegetables, animal proteins (from meat, fish, eggs or shellfish), and commercially available RNPC® meal supplements in the form of snacks (biscuits, cereal bars, bread, crackers, soups, omelets, drinks and desserts), which the patients can eat whenever they want. The diet targets an energy intake of 800 kcaL/day in women and 1000 kcaL/day in men, and a macronutrient composition of 60% proteins (1.5 g/kg for men and 1.2 g/kg for women), 25% low-GI carbohydrates, and 15% fats. The RNPC® meal supplements contribute to approximately 30% of the total energy intake in the diet. They were selected to support a high level of high-quality proteins (containing an average of 110 kcal, 15.8 g proteins, 2.4 g carbohydrates, 5.4 g fats and 2.3 g fibers, for an average serving size of 30 g) and these were fortified with vitamins and minerals in order to avoid deficiencies caused by a low energy intake. In addition, the products comply with the requirements specified by the European Food Safety Authority (EFSA, 2015).

2.3. Measurements and calculations

Body weight was measured at baseline and after the weight loss period by the dieticians using a calibrated weight scale (Beurer BG42, Ulm, Germany). Height was measured to the nearest cm at baseline using a height gauge. Body mass index (BMI) was calculated with the formula: body weight [kg]/(height [m])^2. WC was measured to the nearest cm at the natural waist. However, for patients with abdominal adiposity with no visible natural waist, the measurement was taken at the level midway between the lowest rib and the iliac crest, approximately 2–5 cm above the navel.

A 12-h fasting blood sample was drawn at baseline and after the weight loss phase. The blood samples were analyzed for plasma glucose, hemoglobin A1c (HbA1c), HDL-C, low-density lipoprotein cholesterol (LDL-C), total cholesterol, triglycerides, and alanine transaminase (ALAT). The physicians were encouraged to prescribe these blood analyses. Methods used for blood sample analyses were all validated according to the general requirements defined by the NF EN ISO 15189 and NF EN ISO/IEC 17025 standards for routine blood sample analysis. All data was entered in MySQL 5.7 database, and the database was managed by the IT consultant company Oriolis (Villeurbanne, France).

There were no exclusion criteria based on medications or medical conditions; however, protein intake was reduced among patients with poor renal function according to the recommendations from the Haute Autorité de Santé. The only exclusion criterion was pregnancy. Furthermore, we excluded patients with an age < 18 years and a baseline BMI < 25 or WC < 80 cm for women and < 94 cm for men from the current analyses. Finally, patients sometimes repeat the program; however, the current analysis only included the first weight loss phase for each patient.

2.4. Specific patient groups

Body composition was analyzed by categorizing WC and BMI. WC (cm) was classified into low or high: women < 88 & men < 102 or women ≥88 & men ≥102, and BMI (kg/m^2) was classified as following: < 30, ≥30- < 35, ≥35- < 40, ≥40- < 45, or ≥45. Classification of the metabolic syndrome, was defined according to the "AHA/NHLBI statement" (Grundy et al., 2005), i.e. having ≥3 of the following 5 risk factors: WC (men > 102 cm; women > 88 cm); triglycerides (≥1.7 mmoL/L); HDL-C (men < 1.03 mmoL/L; women < 1.30 mmoL/L), fasting plasma glucose (FPG) ≥5.6 mmoL/L; the use of hypertension drugs (as blood pressure was not measured). To further analyze metabolic risk parameters, FPG, HbA1c, total and LDL-C were divided into categories. FPG was stratified into three groups not receiving diabetic treatment (< 5.6, 5.6–6.9, and ≥7.0 mmoL/L) and one group receiving diabetic treatment (Grundy et al., 2005). HbA1c (%) was also stratified into three groups not receiving diabetic treatment (< 5.7, ≥5.7–6.4, and ≥6.5%) and one group receiving diabetic treatment (Sherwani et al., 2016). Total cholesterol (mmol/L) was stratified into < 5.2, ≥5.2- < 6.2, and ≥6.2 (mmol/L), and LDL-C was divided into < 2.6, ≥2.6- < 3.4, ≥3.4- < 4.2, and ≥4.2 (mmol/L) (Independent Panel to Revi, 2002).

As a proxy for liver health, ALAT was stratified into high (women < 20 & men < 30) or low (women ≥20 & men ≥30) levels. High risk of NAFLD was defined as having the metabolic syndrome and high ALAT-levels (Yki-Järvinen, 2016). Furthermore, another group having the metabolic syndrome, but with low ALAT-levels, was defined as having lower risk of NAFLD.

2.5. Statistical methods

Baseline characteristics were summarized as mean ± standard deviation (SD), median (interquartile range [IQR]), or as proportions (%). Differences in baseline characteristics between genders were assessed using two-sample t-tests (variables possibly transformed before analysis) or Pearson's chi-squared tests. Metabolic risk factors before and after the weight loss phase, according to the stratified risk group at baseline, was reported as median (IQR) as several were non-normally distributed. Changes in these metabolic outcomes during the weight loss phase were reported as means (95% CI) and tested using a paired sample *t*-test, as changes in biological data are often normally distributed even though the pre- and post-values are not (Fay and Gerow, 2012). Differences in body weight change according to baseline values

Table 1
Baseline characteristics among the 10,809 patients completing the weight loss phase of the RNPC® program stratified by gender.

	n	Women	n	Men	P-value
Age (years)	8121	53.6 ± 14.1	2686	55.8 ± 13.2	< 0.001
Height (cm)	8078	163 ± 6	2668	176 ± 7	< 0.001
Body weight (kg)	8123	84.7 (76.0; 96.0)	2686	105.0 (95.1; 117.1)	< 0.001
Body mass index (kg/m[b])	8078	32.1 (28.9; 36.1)	2668	34.1 (31.1; 37.4)	< 0.001
Metabolic syndrome	5200	26.8%	1673	41.2%	< 0.001
Medication					
Type 2 diabetes	8122	1.5%	2686	3.5%	< 0.001
Hypertension	8122	6.1%	2686	9.8%	< 0.001
Metabolic measures					
Waist circumference (cm)	8099	103 (95; 113)	2676	116 (109; 125)	< 0.001
Total-C (mmol/L)	5492	5.46 (4.79; 6.19)	1807	5.23 (4.51; 6.01)	< 0.001
HDL-C (mmol/L)	5414[a]	1.45 (1.24; 1.71)	1790	1.17 (1.01; 1.37)	< 0.001
LDL-C (mmol/L)	5393	3.34 (2.77; 3.99)	1757[b]	3.24 (2.56; 3.94)	< 0.001
Triglyceride (mmol/L)	5486[c]	1.20 (0.88; 1.66)	1809	1.57 (1.15; 2.26)	< 0.001
Fasting glucose (mmol/L)	5466	5.33 (4.94; 5.77)	1774	5.72 (5.27; 6.38)	< 0.001
HbA1c (%)	2011[d]	5.7 (5.3; 6.1)	849[e]	5.9 (5.6; 6.7)	< 0.001
ALAT (UI/L)	4425	22 (16; 30)	1466	35 (25; 50)	< 0.001

Abbreviations: ALAT = Alanine aminotransferase, C = Cholesterol, HbA1c = Hemoglobin A1c, HDL = High density lipoprotein, LDL = Low density lipoprotein.
Data are presented as proportions (%), mean ± SD or median (IQR) and analyzed by two sample t-tests (numerical data; possibly transformed before analysis) or chi^2-tests (categorical data).

[a] Excluded two observations of 25.9 mmoL/L.
[b] Excluded one observation of 259 mmoL/L.
[c] Excluded one observation of 98.3 mmoL/L.
[d] Excluded two observations (50% and 54%).
[e] Excluded two observations (41% and 55%).

of the metabolic markers were tested using one-way analysis of variance (ANOVA) with *post hoc* group-wise comparisons when overall significance were reached. Completion rate and changes in body size and waist circumference during the weight loss phase according to the number of metabolic risk factors and/or risk of NAFLD at baseline were also reported as proportions (%) or means (95% CI) and analyzed by Chi-square test or one-way ANOVA with *post hoc* group-wise comparisons when overall significance between groups were reached. The level of significance was set at $P < 0.05$, with no adjustment for multiple testing, and statistical analyses were conducted using STATA/SE 14.1 (Houston, USA).

3. Results

Baseline characteristics of the 10,809 patients are shown in Table 1. A total of 30.3% of the patients had metabolic syndrome with 70.3% of the entire patient group being obese, 33% being severely obese (BMI > 35), and 11.7% being morbidly obese (BMI > 40). Men were older, heavier, more medicated, more likely to have the metabolic syndrome, and had higher levels of triglycerides, FPG, HbA1c and ALAT compared to women, whereas women had higher cholesterol levels compared to men (all $P < 0.001$).

The reductions in BMI during the weight loss phase were larger for patients with the highest baseline values. A mean BMI reduction of 2.1 units (95% CI 2.0; 2.2, $P < 0.001$) was observed for men and 2.4 (95% CI 2.3; 2.4, $P < 0.001$) for women when having baseline BMI < 30, and 6.3 units (95% CI 5.5; 7.0, $P < 0.001$) for men and 6.4 (95% CI 5.9; 6.9, $P < 0.001$) for women, when having baseline BMI of ≥45 (Table 2). Similarly, WC reductions were larger for patients with the highest baseline values. A mean WC reduction of 7.7 cm (95% CI 8.4; 7.1, $P < 0.001$) was observed for men with baseline WC < 102 cm, and 6.8 cm (95% CI 7.2; 6.5, $P < 0.001$) for women when having baseline WC < 88 cm, whereas men having baseline WC ≥ 102 reduced WC by 12 cm (95% CI 12.3; 11.7, $P < 0.001$), and women having a baseline WC ≥ 88 had a reduction of 10.8 cm (95% CI 11.0; 10.6, $P < 0.001$) (Table 2).

Men having normal FPG experienced only a very small reduction in FPG of 0.1 (0.03; 0.2, $P < 0.05$) mmol/L, and no difference was observed for women. Among patients with impaired fasting glucose, a reduction of 0.6 mmoL/L (95% CI 0.5; 0.7, $P < 0.001$) was observed for both men and women. However, the largest improvements were observed among subjects with the highest FPG levels at baseline (≥7.0 mmoL/L) with a reduction of 3.0 mmoL/L (95% CI -3.6; -2.5, $P < 0.001$) for men and 2.4 mmoL/L (95% CI -2.8; 1.9, $P < 0.001$) for women (Table 3). Similar patterns were observed for HbA1c. Also, patients on type 2 diabetes medication improved their FPG and HbA1c additionally after losing weight. Similarly, largest improvements in specific risk markers were found among patients with the worst baseline level of the particular risk marker. This was true for triglycerides (≥1.7 mmoL/L), total cholesterol (≥6.2 mmoL/L), LDL-C (≥4.2 mmoL/L), ALAT (women ≥ 20 & men ≥ 30 UI/L), and HDL-C (women < 1.30 & men < 1.03 mmoL/L). At the same time, lowering of HDL-C was observed among those with the highest baseline levels. Weight loss was not found to be higher among those patients that had the worst baseline level of the particular risk marker (even though they improved their risk marker the most) with the only exceptions being HDL-C (women only) and ALAT. On the contrary, patients with the worst baseline level of HbAlc, total cholesterol and LDL-C lost less weight (despite improving the most in metabolic health) (Supplementary Table 1).

No overall difference in completion rate was observed according to the number of risk factors for the metabolic syndrome ($P = 0.057$). Patients with no risk factors for the metabolic syndrome experienced the least improvements in body weight, BMI and WC compared to patients with one to four risk factors, and patients with one risk factor had lower improvements compared to those with two to four risk factors (except relative weight loss among subjects with three risk factors). Overall, patients with two to four risk factors responded the same, while those with five risk factors tended to lose relatively less body weight (Table 4).

Subjects defined as having high and low risk of NAFLD did not differ in percentage of body weight loss or BMI units lost (Table 5); however, mean ALAT level was reduced by 5.5 (95% CI 0.4; 10.6, $P = 0.036$) more among women with high basal ALAT and the metabolic syndrome compared to those having high basal ALAT without the metabolic syndrome (Table 3).

Table 2
Changes in waist circumference and BMI during the weight loss phase of the RNPC® program according to baseline values stratified by gender.

	Men				Women			
	n	Before Median (IQR)	After Median (IQR)	Δ(After-Before) Mean (95%CI)	n	Before Median (IQR)	After Median (IQR)	Δ(After-Before) Mean (95%CI)
Body size								
WC (cm)	2643	116 (109; 125)	105 (98; 113)	−11.7 (−12.0;-11.4)**	8031	103 (95; 113)	93 (86; 101)	−10.5 (−10.7;-10.4)**
W < 88 & M < 102	195	99 (97; 100)	91 (88; 94)	−7.7 (−8.4;-7.1)**	505	85 (83; 86)	78 (75; 81)	−6.8 (−7.2;-6.5)**
W ≥ 88 & M ≥ 102	2448	118 (111; 126)	106 (99; 114)	−12.0 (−12.3;-11.7)**	7626	104 (97; 113)	94 (87; 102)	−10.8 (−11.0;-10.6)**
BMI (kg/m^2)	2668	34.1 (31.1; 37.4)	30.2 (27.8; 33.2)	−3.7 (−3.8;-3.6)**	8078	32.1 (28.9; 36.1)	28.6 (25.9; 32.2)	−3.5 (−3.5;-3.4)**
< 30	432	28.6 (27.8; 29.4)	26.4 (25.4; 27.4)	−2.1 (−2.2;-2.0)**	2762	27.9 (26.7; 29.0)	25.3 (24.3; 26.5)	−2.4 (−2.4;-2.3)**
≥30- < 35	1119	32.5 (31.3; 33.8)	29.1 (27.9; 30.6)	−3.3 (−3.4;-3.2)**	2885	32.4 (31.2; 33.6)	29.0 (27.4; 30.6)	−3.4 (−3.5;-3.3)**
≥35- < 40	740	36.9 (35.9; 38.2)	32.7 (30.7; 34.8)	−4.3 (−4.5;-4.2)**	1551	37.0 (36.0; 38.3)	33.1 (30.9; 35.1)	−4.3 (−4.4;-4.2)**
≥ 40- < 45	278	41.7 (40.9; 43.0)	36.6 (34.2; 38.9)	−5.4 (−5.8;-5.1)**	596	41.8 (40.8; 43.1)	37.1 (34.0; 39.4)	−5.5 (−5.8;-5.2)**
≥ 45	99	47.8 (46.2; 49.8)	42.2 (40.0; 45.6)	−6.3 (−7.0;-5.5)**	284	47.6 (46.0; 50.1)	42.2 (38.6; 45.6)	−6.4 (−6.9;-5.9)**

Abbreviations BMI = Body mass index, WC = Waist circumference.
Analyzed by paired sample *t*-test.
**P < 0.001.

4. Discussion

As hypothesized, we found overall improvements in most metabolic parameters as a response to the high protein-low GI-diet during the RNPC® weight loss phase. Furthermore, we observed these metabolic improvements to occur mainly, and in some instances exclusively, among those with the worst baseline values of the particular metabolic parameter. At the same time, we found the RNPC® weight loss phase to result in larger weight losses in patients with larger initial BMI and no difference in weight loss dependent on the risk of NAFLD. Furthermore, weight loss was approximately the same among subjects having at least one metabolic risk factor. Although, a tendency of lower weight loss was found for subjects having five risk factors and among subjects with the highest levels of cholesterols, as well as among those receiving diabetes medications.

The metabolic improvements experienced during weight loss may alter the progression of diseases associated with the metabolic syndrome, such as type 2 diabetes, cardiovascular diseases (CVD), and NAFLD. Among the patients with impaired fasting glucose, FPG levels improved as a result of the weight loss intervention. For prediabetics, diabetics and patients treated with diabetes medication, respectively, FPG dropped to 5.6 mmoL/L (IQR: 5.2; 5.9), 6.1 mmoL/L (IQR: 5.6; 6.6), and 5.7 mmoL/L (IQR: 5.1; 6.3) for men, and 5.6 mmoL/L (IQR: 5.2; 5.9), 6.1 mmoL/L (IQR: 5.6; 7.0), and 6.2 mmoL/L (IQR: 5.6; 7.3) for women, bringing the FPG closer to the normal range. Sustaining the weight loss may be of importance to avoid developing type 2 diabetes, as the risk of the disease can be reduced by 30%–60% by weight losses of 2.5 kg–5.5 kg at ≥2 years (Jensen et al., 2014). Weight loss interventions can also reduce the risk of cardiovascular mortality by 7% in subjects with obesity, as shown in a recent systemic review (eight trials, 134 events; risk ratio 0.93, 95% CI 0.67 to 1.31) (Ma et al., 2017). Besides impaired glucose metabolism, dyslipidemia is a known risk factor for CVD, and lowering LDL-C is the primary target of lipid-lowering therapy (Miller, 2018). In the RNPC® program, the largest reductions in LDL-C were seen among the patients who had the largest initial values, but also patients with less critical values improved their LDL-C level to a minor extend. This indicates that the weight loss intervention improved dyslipidemia among the affected patients, and their CVD risk is therefore expected to be reduced compared to baseline (Ference et al., 2017).

Larger weight losses in patients with higher initial BMI may partly be explained by the fact that patients had different weight loss goals, which has also influenced the duration of the weight loss period. In weight loss trials with fixed duration, a larger absolute weight loss if often observed among patients with the largest BMI, but this might especially be true in this study, because patients had defined individual weight loss goals based on their initial body weight. However, a larger weight loss per se did not seem to drive the differences in metabolic improvements observed between those with high and low metabolic risk at baseline.

Strengths of the current study was the free-living set-up in which we were able to test real-life efficacy of the novel RNPC® weight loss program in a very large sample size. It is unknown if the high-protein, low-carbohydrate, and low-fat diet composition was a causal factor in improving the metabolic parameters or if it was solely driven by caloric restriction. Nevertheless, the satiating, high-protein diet, including real foods, was likely to play a vital role to ensure the high completion rate of 89% and thereby indirectly enhancing weight loss.

A weakness of our study is that the reductions in the metabolic risk markers may in part be transient, and it is likely that some of the markers will increase slightly with an increasing caloric intake in a weight maintenance period. As an example, triglyceride levels decrease in response to an acute dietary energy deficit (Bellou et al., 2013). It was not possible to investigate if the changes observed during weight loss were sustained, as blood samples were only sporadically measured during the weight maintenance period of the RNPC® program. Another

Table 3
Metabolic changes during the weight loss phase of the RNPC® program according to baseline values stratified by gender.

	Men				Women			
	n	Before Median (IQR)	After Median (IQR)	Δ(After-Before) Mean (95%CI)	n	Before Median (IQR)	After Median (IQR)	Δ(After-Before) Mean (95%CI)
Glucose metabolism								
FPG (mmol/L)	301	6.1 (5.6; 7.2)	5.6 (5.1; 6.0)	−1.2 (−1.4;-1.0)**	704	5.7 (5.2; 6.5)	5.4 (4.9; 5.8)	−0.6 (−0.7;-0.5)**
< 5.6[a]	77	5.3 (4.9; 5.5)	5.1 (4.7; 5.4)	−0.1 (−0.2;-0.03)*	302	5.1 (4.8; 5.3)	5.0 (4.7; 5.4)	−0.01 (−0.07; 0.05)
≥5.6–6.9[a]	131	6.1 (5.8; 6.4)	5.6 (5.2; 5.9)	−0.6 (−0.7;-0.5)**	279	6.0 (5.8; 6.4)	5.6 (5.2; 5.9)	−0.6 (−0.7;-0.5)**
≥7.0[a]	73	8.7 (7.7; 10.1)	6.1 (5.6; 6.6)	−3.0 (−3.6;-2.5)**	90	8.2 (7.4; 9.5)	6.1 (5.6; 7.0)	−2.4 (−2.8; 1.9)**
Diabetic treatment	20	7.2 (5.8; 9.4)	5.7 (5.1; 6.3)	−2.0 (−3.1;-0.8)*	33	7.7 (6.3; 8.5)	6.2 (5.6; 7.3)	−1.0 (−1.5;-0.5)**
HbAlc (%)	169	6.7 (6.1; 7.5)	5.7 (5.4; 6.2)	−1.0 (−1.2;-0.9)**	253[b]	6.4 (6.0; 7.0)	5.8 (5.5; 6.2)	−0.9 (−1.2;-0.5)**
< 5.7[a]	12	5.2 (5.2; 5,5)	5.2 (5.0; 5.4)	−0.1 (−0.3; 0.1)	40	5.5 (5.3; 5.6)	5.4 (5.2; 5.5)	−0.1 (−0.2;-0.02)*
≥5.7–6.4[a]	48	6.0 (5.8; 6.2)	5.6 (5.4; 5.9)	−0.4 (−0.5;-0.3)**	84	6.2 (6.0; 6.3)	5.7 (5.5; 6.0)	−0.4 (−0.5;-0.3)**
≥6.5[a]	69	7.4 (6.8; 8.3)	6.1 (5.6; 6.4)	−1.5 (−1.7;-1.2)**	94	7.1 (6.7; 7.9)	6.2 (5.8; 6.6)	−1.1 (−1.3;-1.0)**
Diabetic treatment	40	7.0 (6.5; 8.1)	5.8 (5.4; 6.2)	−1.2 (−1.5;-0.9)**	35[b]	6.6 (6.2; 7.4)	5.9 (5.6; 6.5)	−0.7 (−0.9;-0.5)**
Lipid metabolism								
Triglyceride (mmol/L)	315	1.9 (1.4; 2.7)	1.1 (0.8; 1.5)	−1.0 (−1.1;-0.9)**	686[c]	1.5 (1.1; 2.0)	1.0 (0.8; 1.3)	−0.5 (−0.6;-0.5)**
< 1.7	139	1.4 (1.1; 1.5)	0.9 (0.7; 1.2)	−0.3 (−0.4;-0.2)**	429	1.2 (1.0; 1.4)	0.9 (0.7; 1.1)	−0.2 (−0.3;-0.2)**
≥1.7	176	2.6 (2.1; 3.4)	1.3 (1.0; 1.7)	−1.6 (−1.8;-1.3)**	257[c]	2.2 (1.9; 2.6)	1.3 (1.1; 1.7)	−1.1 (−1.2;-0.9)**
Total-C (mmol/L)	310	5.2 (4.5; 6.0)	4.3 (3.6; 5.0)	−0.9 (−1.0;-0.8)**	677	5.5 (4.8; 6.3)	5.0 (4.3; 5.6)	−0.6 (−0.7;-0.5)
< 5.2	151	4.4 (3.9; 4.8)	3.8 (3.3; 4.4)	−0.5 (−0.6;-0.3)**	254	4.7 (4.3; 4.9)	4.3 (3.9; 4.8)	−0.2 (−0.3;-0.1)*
≥5.2- < 6.2	94	5.6 (5.4; 5.9)	4.7 (4.1; 5.1)	−0.9 (−1.2;-0.7)**	240	5.7 (5.4; 5.9)	5.1 (4.6; 5.6)	−0.6 (−0.7;-0.5)**
≥6.2	65	6.8 (6.5; 7.1)	5.0 (4.3; 5.7)	−1.8 (−2.1;-1.6)**	183	6.9 (6.5; 7.4)	5.8 (5.1; 6.4)	−1.3 (−1.5;-1.1)**
LDL-C (mmol/L)	292	3.1 (2.5; 3.9)	2.6 (2.0; 3.3)	−0.5 (−0.6;-0.4)**	653	3.4 (2.7; 4.1)	3.1 (2.5; 3.7)	−0.3 (−0.4;-0.2)
< 2.6	89	2.2 (1.9; 2.4)	1.9 (1.6; 2.2)	−0.2 (−0.3;-0.03)*	121	2.1 (1.9; 2.4)	2.1 (1.8; 2.6)	0.1 (0.01; 0.2)*
≥2.6- < 3.4	88	3.0 (2.8; 3.1)	2.6 (2.3; 3.1)	−0.3 (−0.5;-0.04)*	206	3.0 (2.8; 3.2)	2.8 (2.5; 3.3)	−0.05 (−0.2; 0.1)
≥3.4- < 4.2	63	3.7 (3.6; 3.9)	3.1 (2.7; 3.6)	−0.7 (−0.8;-0.5)**	189	3.8 (3.6; 4.0)	3.3 (2.9; 3.7)	−0.4 (−0.5;-0.3)**
≥4.2	52	4.6 (4.4; 5.0)	3.5 (2.8; 4.1)	−1.2 (−1.5;-1.0)**	137	4.7 (4.5; 5.2)	4.0 (3.5; 4.6)	−0.9 (−1.1;-0.7)**
HDL-C (mmol/L)	305	1.11 (0.96; 1.30)	1.11 (0.96; 1.27)	−0.004 (−0.03; 0.03)	660	1.40 (1.19; 1.63)	1.35 (1.14; 1.55)	−0.05 (−0.07;-0.03)**
W < 1.30 & M < 1.03	110	0.91 (0.83; 0.96)	0.93 (0.83; 1.09)	0.09 (0.05; 0.13)**	266	1.13 (1.04; 1.22)	1.14 (1.01; 1.27)	0.04 (0.01; 0.06)*
W ≥ 1.30 & M ≥ 1.03	195	1.22 (1.11; 1.37)	1.19 (1.06; 1.37)	−0.06 (−0.02;-0.10)*	394	1.58 (1.45; 1.79)	1.49 (1.32; 1.68)	−0.12 (−0.14;-0.09)**
Risk of NAFLD								
ALAT (UI/L)	224	42 (29; 59)	28 (20; 38)	−21 (−25;-16)**	515	26 (18; 38)	21 (16; 29)	−7 (−9;-5)**
W < 20 & M < 30	63	23 (20; 27)	21 (16; 26)	−1.2 (−2.9; 0.4)	149	16 (14; 18)	17 (13; 21)	2 (1; 3)**
W ≥ 20 & M ≥ 30	161	50 (38; 73)	32 (23; 43)	−28 (−34;-23)**	366	31 (25; 45)	24 (18; 32)	−11 (−13;-8)**
W ≥ 20 & M ≥ 30% MS	66	45 (37; 63)	31 (21; 39)	−28 (−36;-19)**	187	31 (25; 43)	24 (19; 31)	−9 (−12;-6)**
W ≥ 20 & M ≥ 30 + MS	73	54 (41; 84)	32 (26; 43)	−29 (−36;-21)**	139	33 (25; 48)	22 (17; 31)	−15 (−19;-10)**

Abbreviations: ALAT = Alanine aminotransferase, FPG = Fasting plasma glucose, HbA1c = Hemoglobin A1c, HDL = High density lipoprotein, LDL = Low density lipoprotein, MS = Metabolic syndrome, NAFLD = Non-alcoholic fatty liver disease.
Analyzed by paired sample *t*-test.
*P < 0.05; **P < 0.001.
[a] Does not include those being treated with diabetes medicine.
[b] Excluded one observation with a follow-up value of 54%.
[c] Excluded one observation with a follow-up value of 214 mmoL/L.

weakness of the study is that the metabolic markers were not measured in all patients. At baseline, 6,873 subjects (64%) had a measure of all five metabolic risk markers in the metabolic syndrome score. However, only about 1,000 subjects (≈9%) had their different metabolic risk markers measured before and after the weight loss period. Therefore, our results showing changes in metabolic risk markers may not be representable for the entire population enrolled in the weight loss program. It is also a limitation that blood pressure was not measured in the

Table 4
Changes (After-Before) in body weight and metabolic parameters according to the number of metabolic syndrome conditions[a] at baseline (n = 6,873).

	No risk factor (n = 243)	One risk factor (n = 2,243)	Two risk factors (n = 2,302)	Three risk factors (n = 1,407)	Four risk factors (n = 575)	Five risk factors (n = 103)	P-value
Completion (%)	92.0	90.4	89.7	89.5	86.5	88.8	0.057[c]
BW (kg)	−6.4 (−7.3;-5.6)[a]	−9.2 (−9.5;-8.9)[b]	−10.7 (−11.0;-10.4)[c]	−10.7 (−11.0;-10.3)[c]	−11.2 (−11.8;-10.7)[c]	−10.4 (−11.8;-9.1)[bc]	< 0.001[d]
BW (%)	−8.5 (−9.3;-7.7)[a]	−10.3 (−10.6;-10.1)[b]	−11.1 (−11.4;-10.9)[c]	−10.7 (−11.1;-10.4)[bc]	−11.0 (−11.6;-10.5)[c]	−9.8 (−11.0;-8.6)[ab]	< 0.001[d]
BMI (kg/m[b])	−2.4 (−2.7;-2.1)[a]	−3.4 (−3.5;-3.3)[b]	−3.9 (−4.0;-3.8)[cd]	−3.8 (−4.0;-3.7)[c]	−4.1 (−4.3;-3.9)[d]	−3.7 (−4.2;-3.2)[bcd]	< 0.001[d]
WC (cm)[b]	−7.4 (−8.3;-6.5)[a]	−10.4 (−10.7;-10.2)[b]	−11.6 (−11.8;-11.3)[c]	−11.2 (−11.6;-10.9)[c]	−11.6 (−12.1;-11.0)[c]	−10.8 (−12.2;-9.5)[bc]	< 0.001[d]

Abbreviations: BMI = Body mass index, BW = Body weight, WC = Waist circumference.
Data are presented as mean (95% CI) or proportions (%).
[a] Risk factors for the metabolic syndrome are as following: Waist circumference (men > 102 cm; women > 88 cm); Triglycerides (≥1.7 mmoL/L); HDL cholesterol (men < 1.03 mmoL/L; women < 1.30 mmoL/L), Fasting glucose ≥5.6 mmoL/L; The use of hypertension drugs.
[b] A total of 54 patients is omitted from this analysis, as they did not have a measured waist circumference.
[c] Chi-square test.
[d] One-way ANOVA. Different superscript letters in a row (a,b,c,d) indicate significant differences (P < 0.05).

Table 5
Changes (After-Before) in weight and metabolic parameters in patients with and without the metabolic syndrome as well as with low and high ALAT at baseline (n = 5,465).

	No metabolic syndrome[a]; Low ALAT[b] (n = 1,689)	No metabolic syndrome[a]; High ALAT [b] (n = 2,164)	Metabolic syndrome[a]; Low ALAT[b] (n = 475)	Metabolic Syndrome[a]; High ALAT[b] (n = 1,137) High risk of NAFLD[c]	P-value
Completion (%)	89.9	91.3	89.0	89.5	0.18[e]
BW (kg)	−9.5 (−9.8;-9.1)[a]	−10.4 (−10.7;-10.1)[b]	−10.9 (−11.5;-10.2)[bc]	−11.2 (−11.6;-10.8)[c]	< 0.001[f]
BW (%)	−10.5 (−10.8;-10.2)[a]	−11.1 (−11.4;-10.8)[b]	−10.9 (−11.5;-10.3)[ab]	−11.1 (−11.5;-10.7)[b]	0.012[f]
BMI (kg/m^2)	−3.4 (−3.6;-3.3)[a]	−3.8 (−3.9;-3.7)[b]	−3.9 (−4.1;-3.7)[bc]	−4.1 (−4.2;-3.9)[c]	< 0.001[f]
WC (cm)[d]	−10.7 (−11.1;-10.4)[a]	−11.4 (−11.7;-11.1)[b]	−11.4 (−12.0;-10.7)[ab]	−11.7 (−12.1;-11.3)[b]	0.002[f]

Abbreviations: ALAT = Alanine aminotransferase, BMI = Body mass index, BW = Body weight, NAFLD = Non-alcoholic fatty liver disease, WC = Waist circumference. Data are presented as mean (95% CI) or proportions (%).

[a] The metabolic syndrome is defined as having ≥3 of the following 5 risk factors: Waist circumference (men > 102 cm; women > 88 cm); Triglycerides (≥1.7 mmoL/L); HDL cholesterol (men < 1.03 mmoL/L; women < 1.30 mmoL/L), Fasting glucose ≥5.6 mmoL/L; The use of hypertension drugs.

[b] High ALAT: ≥20 UI/L for women and ≥30 UI/L for men; Low ALAT: < 20 UI/L for women and < 30 UI/L for men.

[c] The risk of having NAFLD is defined as high when classified as having the metabolic syndrome while having high level of ALAT.

[d] A total of 36 patients is omitted from this analysis, as they did not have a measured waist circumference.

[e] Chi-square test.

[f] One-way ANOVA. Different superscripts in a row (a,b,c) indicate significant differences (P < 0.05).

study, and thus only information about hypertension treatment was available, which has previously been shown not to cover all subjects with hypertension (Appleton et al., 2013). Nonetheless, it could be speculated that this CVD risk marker would also improve in the RNPC® program, as there is a dose–response relationship between the amount of weight loss achieved and the lowering of blood pressure (Jensen et al., 2014). Furthermore, some of the effects observed could be the result of regression towards the mean (Morton and Torgerson, 2003). In general, we observed the largest improvements in metabolic risk markers among the patient groups with the largest baseline values. At the same time, we also observed patients with normal/high HDL-C levels at baseline to reduce HDL-C during the weight loss, as well as women with low ALAT at baseline to slightly increase ALAT levels. It is difficult to quantify, but it would therefore be expected that a minor part of our findings are not explained by metabolic improvements but due to regression towards the mean (Morton and Torgerson, 2003). However, mild increases in ALAT (women only) (Gasteyger et al., 2008) and reductions in HDL (Aicher et al., 2012) are commonly seen during weigh loss programs, and are probably transient and without consequences to cardiovascular health.

Lifestyle and dietary intervention for six months is the recommended choice to treat obesity (Van Gaal and Dirinck, 2016), and a greater weight loss will result in larger improvements in metabolic risk factors and diabetes remission (Wing et al., 2011; Lean et al., 2017). Therefore, successful weight loss programs, such as the RNPC®, are an important tool for physicians. Only when this approach has failed, pharmacological treatments can be introduced to patients, but such an addition is costly for healthcare systems and can be associated with side-effects (Van Gaal and Dirinck, 2016). Improving dietary weight loss intervention programs and their maintenance phase further is therefore of importance. In the maintenance phase, where energy intake is gradually increased, a discussion about whether the additional calories should come from carbohydrates or fat is of high relevance (Ludwig et al., 2018). In the maintenance phase in the RNPC program, the target of macronutrient composition is 25% proteins, 45% carbohydrates and 30% fats, but is designed individually by a dietician, and very-low carbohydrate diet approaches, such as a ketogenic diet, may be considered for some patients to improve their appetite regulation and satiety (Ludwig et al., 2018) Recent scientific discoveries within personalized nutrition (Ordovas et al., 2018; Zeevi et al., 2015; Lean et al., 2018) and biomarkers (e.g. FPG and gut microbiota-based dietary advice) (Hjorth et al., 2017a, 2017b, 2018) may help answer this question about macronutrient composition, and thus further enhance compliance and improve the outcomes of future weight loss programs.

In conclusion, the substantial short-term weight loss during the RNPC® program is followed by overall metabolic improvement that is mainly driven by substantial improvements in specific metabolic risk markers among patients with highest baseline values. Furthermore, the RNPC® weight loss program seems to work equally well regardless of metabolic risk at baseline with the exception of patients treated with diabetes medication and patients with high cholesterol levels.

Statement of ethics

The data used in the present manuscript was originally collected as part of clinical practice. Therefore, no protocol has been approved by any institute committee on human research, and patients were not asked to give their informed content. However, according to French law we are allowed to use the data for research as the data has been anonymized.

Disclosure statement & funding sources

AA is consultant for Groupe Éthique et Santé, and chairman of their scientific advisory board. He is consultant or member of advisory boards for Dutch Beer Institute, NL, Feast Kitchen A/S, DK, McCain Foods Limited, USA, Nestlé Research Center, Switzerland, Weight Watchers, USA; Gelesis, USA, BioCare Copenhagen, Zaluvida, Switzerland, Basic Research, USA, Beachbody, USA, Novo Nordisk, DK, Saniona, DK, & Scandinavian Airlines System, DK. Current research is in part funded by grants from Arla Foods, DK, Danish Dairy Research Council, & Gelesis, USA. AA is co-author of a number of diet/cookery books, including personalized nutrition for weight loss, published in several languages. He is co-owner and member of the Board of the consultancy company Dentacom Aps, co-founder and co-owner of UCPH spin-out companies Mobile Fitness A/S, Flaxslim ApS, and Personalized Weight Management Research Consortium ApS (Gluco-diet.dk). MFH reports grants from Groupe Éthique et Santé and Gelesis (USA) during the conduct of the study. In addition, MFH is co-inventor on a pending provisional patent application on the use of biomarkers for prediction of weight-loss responses (with University of Copenhagen & Gelesis, USA), he is co-author of 2 diet/cookery books regarding personalized nutrition for weight loss, and co-owner of UCPH spin-out company “Personalized Weight Management Research Consortium ApS (Gluco-diet.dk)”. OF is employed at the Groupe Éthique et Santé. RL is CEO and founder of Groupe Éthique et Santé, and TKT and LC reports grants from Groupe Éthique et Santé during the conduct of the study.

Author contributions

MFH, RL, and AA conceived the idea of the current analysis. MFH analyzed the data and LC and MFH wrote the first draft of the paper. All

authors have reviewed the manuscript critically and approved the final manuscript. LC had primary responsibility for the final content.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.obmed.2019.100085.

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Supplementary Material

Supplementary table 1: Differences (After-Before) in body weight change during the weight loss phase of the RNPC® program according to baseline values of metabolic markers stratified by gender

	Men		Women		All	
	n	Overall P-value and mean (95%CI)	n	Overall P-value and mean (95%CI)	n	Overall P-value and mean (95%CI)
Glucose metabolism						
FPG (mmol/L)	301	P=0.40	704	P=0.06	1005	P=0.11
<5.6[1]	77	REF	302	REF	379	REF
≥5.6-6.9[1]	131	-0.6 (-3.0;1.7)	279	-0.8 (-2.1;0.6)	410	-0.9 (-2.1;0.2)
≥7.0[1]	73	-0.6 (-3.3;2.1)	90	0.7 (-1.3;2.6)	163	-0.3 (-1.8;1.2)
Diabetic treatment	20	2.7 (-1.4;6.9)	33	1.7 (-1.3;4.7)	53	1.8 (-0.6;4.2)
HbAlc (%)	169	P=0.03	253[2]	P=0.02	422[2]	P=0.002
<5.7[1]	12	REF[ab]	40	REF[a]	52	REF[a]
≥5.7-6.4[1]	48	-1.5 (-6.7;3.8)[a]	84	0.4 (-2.7;3.4)[a]	132	-0.4 (-3.0;2.2)[a]
≥6.5[1]	69	1.6 (-3.4;6.7)[b]	94	3.5 (0.5;6.5)[b]	163	2.6 (0.02;5.1)[b]
Diabetic treatment	40	3.6 (-1.7;8.9)[b]	35[2]	2.9 (-0.7;6.6)[ab]	75[2]	3.1 (0.2;5.9)[b]
Lipid metabolism						
Triglyceride (mmol/L)	315	P=0.50	686[3]	P=0.54	1001[3]	P=0.62
<1.7	139	REF	429	REF	568	REF
≥1.7	176	0.6 (-1.2;2.5)	257[3]	0.4 (-0.9;1.6)	433[3]	0.3 (-0.8;1.3)
Total-C (mmol/L)	310	P=0.43	677	P=0.01	987	P=0.003
<5.2	151	REF	254	REF[a]	405	REF[a]
≥5.2-<6.2	94	-0.1 (-2.3;2.0)	240	0.4 (-1.1;1.8)[b]	334	0.3 (-0.9;1.5)[b]
≥6.2	65	1.4 (-1.0;3.9)	183	2.2 (0.7;3.8)[b]	248	2.1 (0.8;3.4)[b]
LDL-C (mmol/L)	292	P=0.84	653	P=0.03	945	P=0.04
<2.6	89	REF	121	REF[ab]	210	REF[ab]
≥2.6-<3.4	88	0.5 (-2.0;3.0)	206	-1.4 (-3.2;0.5)[a]	294	-0.6 (-2.0;0.9)[a]
≥3.4-<4.2	63	0.4 (-2.3;3.1)	189	-0.04 (-1.9;1.8)[ab]	252	0.4 (-1.1;1.9)[ab]
≥4.2	52	1.3 (-1.5;4.2)	137	1.3 (-0.7;3.2)[b]	189	1.6 (-0.02;3.2)[b]
HDL-C (mmol/L)	305	P=0.76	660	P=0.008	965	P=0.06
W<1.30 & M<1.03	110	REF	266	REF	376	REF
W≥1.30 & M≥1.03	195	-0.3 (-2.3;1.7)	394	1.7 (0.4;3.0)	589	1.0 (-0.02;2.1)
Risk of NAFLD						
ALAT (UI/L)	224	P=0.46	515	P=0.04	739	P=0.04
W<20 & M<30	63	REF	149	REF	212	REF
W≥20 & M≥30	161	-1.0 (-3.5;1.6)	366	-1.6 (-3.2;-0.05)	527	-1.4 (-2.8;-0.1)

Abbreviations: ALAT=Alanine aminotransferase, FPG=Fasting plasma glucose, HbA1c=Hemoglobin A1c, HDL=High density lipoprotein, LDL=Low density lipoprotein, MS=Metabolic syndrome, NAFLD=Non-alcoholic fatty liver disease, REF=Reference

Tested by one-way analysis of variance (ANOVA) with post hoc t-tests when P<0.05

[1]Does not include those being treated with diabetes medicine.

[2]Excluded one observation with a follow-up value of 54%

Supplementary Material

[3]Excluded one observation with a follow-up value of 214 mmol/L