Title Page

Title

Factors alleviating metabolic syndrome via diet-induced weight loss with or without exercise in overweight Japanese women

Short running title

Metabolic syndrome and weight loss

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Abstract

Objective: Although a 5%–10% loss in the baseline weight has been associated with improvement in obesity-related disorders, only a few studies have explored the factors to alleviate metabolic syndrome (MS). This study aimed to determine the factors that alter MS components in overweight Japanese women.

Methods: Between 1999 and 2006, 323 Japanese women aged 24–67 with body mass indices of 25–40 kg/m^2 and the presence of at least 1 component of MS were recruited from Ibaraki and Chiba. The participants were enrolled in a 3-month weight-loss program with a low-calorie diet with or without exercise. The factors to alleviate MS components were explored using classification and regression tree (CART) analyses.

Results: Of the 323 participants, 309 completed the weight-loss program and were included in the analyses. The CART analyses revealed that a weight reduction of 8.1% in baseline body weight was sufficient to improve at least 1 component of MS. Similarly, classification trees were generated for improvement in abdominal obesity (essential factor: ≥13.0% weight loss), hypertension (essential factor: baseline age, ≤41.5 years), and hyperglycemia (essential factor: ≥13.2% weight loss).

Conclusion: These results suggest that moderate weight loss of 8%–13% contributes to improving the MS components in overweight Japanese women.

Key words: metabolic diseases; intervention; diet; nutrition; exercise

Introduction

Metabolic syndrome (MS) is characterized by inter-related risk factors (Grundy et al., 2005) that increase susceptibility to cardiovascular diseases (Lakka et al., 2002; Hu et al., 2004), type 2 diabetes (Laaksonen et al., 2002; Lorenzo et al., 2003), and all-cause mortality (Lakka et al., 2002; Hu et al., 2004). Weight loss by caloric restriction combined with exercise is commonly employed for the management of MS. Recent systematic reviews have reported that moderate weight loss (5%–10% of the initial body weight) is associated with improvement in obesity-related cardiovascular and metabolic abnormalities (Aucott et al., 2004, 2005; Poobalan et al., 2004) and all-cause mortality (Poobalan et al., 2007). However, only a few studies have explored the factors that are necessary to alleviate MS.

In Japan, MS is acknowledged as a major public health concern that has been addressed by developing country-specific diagnostic criteria and guidelines (Fujita, 2008). The definition of MS in Japan differs from those of the World Health Organization (Alberti and Zimmet, 1998), the National Cholesterol Education Program (NCEP) (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001), and International Diabetes Federation (IDF) (Alberti et al., 2005). In the Japanese definition (The Examination Committee of Criteria for "Metabolic Syndrome" in Japan, 2005), abdominal obesity accompanies any 2 of the following features: dyslipidemia (triglycerides ≥ 150 mg/dL and/or high-density lipoprotein cholesterol < 40 mg/dL), hypertension (systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg), and hyperglycemia (fasting plasma glucose ≥ 110 mg/dL). Abdominal obesity is assessed by measuring the visceral fat area (VFA) by computed tomography (CT). VFA ≥ 100 cm^2 indicates the risk of obesity-related disorders (dyslipidemia, hypertension, and hyperglycemia) and corresponds to a waist circumference of ≥85 cm in men and ≥90 cm in women (The Examination Committee of Criteria for 'Obesity Disease' in Japan, Japan Society for the Study of Obesity, 2002). Although the IDF acknowledged specific cut-offs for different genders and ethnicities (Alberti et al., 2005), the Japanese movement towards country-specific diagnostic criteria for MS is controversial (Banerjee and Misra, 2007; Fujita, 2008). Here, however, we used the Japanese criteria in response to the Japanese national-level movement.

We aimed to determine the factors alleviating MS components in overweight Japanese women who underwent a 3-month weight-loss intervention consisting of a low-calorie diet with or without exercise, using classification and regression tree (CART) analyses (Bartali et al., 2008; Gu et al., 2006; Miyaki et al., 2002). Menopausal status, age, degree of obesity at baseline, percentage weight loss from baseline, and adding exercise to low-calorie diet were the potential contributory factors for alleviating MS through weight loss.

Methods

Participants

In 1999–2006, we recruited 563 Japanese women in Ibaraki and Chiba through advertisements in local newspapers for a 3-month weight-loss program. Of these, 323 women (age, 24–67 years; BMI, 25–40 kg/m^2) who had at least 1 component of MS were selected (Fig. 1). Of these, 124 were postmenopausal and 199 premenopausal. Menopause is defined as the absence of menses for at least 12 months. This study conformed to the Helsinki Declaration principles and was approved by the Review Board of the University of Tsukuba. The participants provided informed written consent.

Research procedures

We implemented 2 weight-loss programs: (i) a low-calorie diet alone (group D, *n* = 118) and (ii) a diet-plus-exercise program (group DE, *n* = 205). Participants were assigned to either program according to their personal preferences. Assays and measurements were performed before and after the 3-month intervention. An explorative approach was used to determine the factors alleviating MS and its components.

Measurements

Anthropometric variables. Body weight was measured to the nearest 0.1 kg using a digital scale (TBF-551; Tanita, Tokyo, Japan), and height to the nearest 0.1 cm on a wall-mounted stadiometer (YG-200; Yagami, Nagoya, Japan). Body mass index (BMI) was calculated as (body weight)/(height)^2 (kg/m^2). Waist circumference was measured at the umbilicus level to the nearest 0.1 cm using flexible plastic tape when the subjects were standing.

VFA by CT. VFA was measured at the umbilicus level by CT (SCT-6800TX; Shimadzu, Tokyo, Japan) when the subjects were supine, and calculated using the FatScan software (N2system, Osaka, Japan) (Yoshizumi et al., 1999).

Blood pressure and biochemical blood assay. Blood pressure was measured using a manual sphygmomanometer (SM-100; Ars, Tokyo, Japan) in the seated position after a 20-minute rest period. Approximately 10 mL blood was drawn from each subject after overnight fasting.

Fresh samples were used for the enzymatic analysis of triglycerides, and the fasting plasma glucose was assayed using glucose oxidase. Serum high-density lipoprotein cholesterol was measured using heparin-manganese precipitation.

MS components. The Japanese criteria (The Examination Committee of Criteria for "Metabolic Syndrome" in Japan, 2005) were used to evaluate the prevalence of MS and its components. The number of MS components (0–4) was also counted.

Intervention

Dietary protocol. All participants were instructed to restrict their energy intake to approximately 1200 kcal/d. The energy intake per meal (3 times per day) was 80 kcal each from eggs and/or dairy products; meat, fish, and/or soybean products; and vegetables and fruits, and 160 kcal from carbohydrates and oils. They maintained a daily food diary during the 3-month intervention and attended group-based 90-minute weekly lectures on low-calorie diets, where dieticians encouraged weight loss through nutrition education and dietary behavior modification.

Exercise protocol. In addition to dieting, group DE participants performed 3 aerobic exercise sessions (bench stepping and/or walking) every week in a fitness room and/or outdoors. The exercise intensity was set such that it raised the subjects' heart rate to 40%–85% of the heart rate at their $\dot{V}O_2max$, which was determined during a graded exercise test using a cycling ergometer at the baseline, or from 9 (very light) to 17 (very hard) on the Borg scale (Borg, 1973). The exercise intensity was gradually increased during the intervention. The average energy expenditure was approximately 150 kcal/d (Okura et al., 2003).

Statistical analyses

Baseline characteristics and changes during the intervention period were recorded separately for groups D and DE. Values are represented as means ± standard deviation. Paired *t* tests were used to analyze differences between the quantitative variables before and after the intervention. Differences in the prevalence of MS and its components were analyzed using McNemar's tests, and those in the number of MS components using Wilcoxon signed-rank tests.

CART analyses were used to explore the successive binary divergences of the explanatory variables (menopausal status, baseline age, baseline BMI, weight-loss program, and percentage weight loss) to identify the subgroups on the basis of their homogeneity in representing an improvement in MS and its components. CARTs are binary classification trees constructed by iteratively splitting the subsets of the dataset using all the explanatory variables to create 2 subgroups. Each explanatory variable is evaluated to identify the optimum cutoff point (continuous variables) or groupings (nominal variables) based on the improvement score (calculated by the Gini criterion function) at each branch point, and the variable with the best improvement is selected for the split. The process is repeated recursively until one of the following stopping rules is triggered: the maximum tree depth is reached (2 in this study) or no more splits can be produced because all terminal subgroups satisfy 1 or more of the following conditions: (a) no significant explanatory variable is left to split the subgroup, (b) the number of cases in the terminal subgroup is less than the minimum split number (30 in this study), and (c) if an upper subgroup were to be split, the number of cases in 1 or more lower subgroup would be less than the minimum number of cases (15 in this study). At each branch point, P values were represented from chi-square tests. Fisher's exact tests were performed for the branch points in which the expected value for at least 1 of the 2×2 cells was less than 5 (P' value).

Data were analyzed using SPSS statistical software (version 16.0J; SPSS, Chicago, IL), with the statistical significance set at 5%.

Results

A total of 309 participants completed the study (n = 115 and n = 194 in groups D and DE, respectively). Three participants from group D and 11 from group DE withdrew from the respective programs. Table 1 presents the baseline characteristics and changes that occurred during the 3-month weight-loss intervention in the 309 participants. The average weight loss was 11.9% ± 4.2%. The prevalence of MS and its components significantly decreased in both the groups.

The CART analysis results are shown in Figs 2–5. The first table of Fig. 2 shows that weight loss alleviated at least 1 component of MS in 225 of the 309 participants (72.8%). The best factor to alleviate at least 1 component of MS was ≥8.1% weight loss. At least 1 component of MS was improved in 199 of the 250 participants with ≥8.1% weight loss (79.6%) and in only 26 of the 59 participants (44.1%) with <8.1% weight loss. The baseline BMI (cutoff: 25.85 kg/m^2) was used to subdivide the ≥8.1% weight loss group. At least 1 component of MS was improved in 37 of the 40 participants with a baseline BMI of ≤25.85 kg/m^2 (92.5%) and in 162 of the 210 participants with a BMI of >25.85 kg/m^2 (77.1%).

Fig. 3 shows the classification tree demonstrating the improvement in abdominal obesity. The first table indicates that 203 women had abdominal obesity at baseline, which was alleviated through weight loss in 117 (57.6%). The weight loss (cutoff: 13.0%) was the best factor for division. Abdominal obesity was improved in 65 of the 82 participants with ≥13.0% weight loss (79.3%) and in 52 of the 121 participants with <13.0% weight loss (43.0%). In the subgroup exhibiting ≥13.0% weight loss, the baseline age (cutoff: 52.5 years) was the best factor for further division, exhibiting reduced abdominal obesity in 41 of 42 (97.6%) vs. 24 of 40 (60.0%) participants in the ≤52.5- and >52.5-year groups, respectively. Further, in the subgroup exhibiting <13.0% weight loss, the baseline BMI (cutoff: 26.89 kg/m^2) was the best factor for the subdivision: exhibiting reduced abdominal obesity in 24 of 31 (77.4%) vs. 28 of 90 (31.1%) in the ≤26.89 kg/m^2 and >26.89 kg/m^2 groups, respectively.

Fig. 4 shows the classification tree demonstrating improvement in hypertension. The first table shows that 240 participants had hypertension at baseline, which was alleviated via weight loss in 113 participants (47.1%). The baseline age (cutoff: 41.5 years) was the best factor for alleviating hypertension. Hypertension was alleviated in 26 of the 35 participants below 41.5

years (74.3%) and in 87 of the 205 participants over 41.5 years (42.4%). In the >41.5-year group, hypertension was reduced in 23 of the 79 participants who followed the diet without exercise (29.1%) and in 64 of the 126 who followed the diet plus exercise (50.8%).

Fig. 5 shows the classification tree for improvement in hyperglycemia. The first table shows that 57 participants had baseline hyperglycemia, which was alleviated through weight loss in 34 participants (59.6%). The weight loss (cutoff: 13.2%) was the best factor for alleviating hyperglycemia. Hyperglycemia was alleviated in 14 of the 15 participants with ≥13.2% weight loss (93.3%) and in 20 of the 42 participants with <13.2% weight loss (47.6%).

All classifications were statistically significant by chi-square or Fisher's exact tests. No classification trees were generated for MS alleviation (69 participants had baseline MS that was alleviated by weight loss in 59 (85.5%)) and dyslipidemia (83 participants had baseline dyslipidemia that was alleviated by weight loss in 67 (80.7%)).

Discussion

We used the CART algorithm to determine the factors alleviating the MS components in overweight Japanese women who participated in a 3-month weight-loss program that included a low-calorie diet with or without exercise. The best factor that alleviated at least 1 component of MS was 8.1% weight loss, which is similar to values reported in recent systematic reviews (5%–10%) for improvement in obesity-related cardiovascular and metabolic abnormalities and all-cause mortality (Aucott et al., 2004, 2005; Poobalan et al., 2004, 2007). Further, recent clinical trials employing NCEP criteria determined that 7%–8% weight loss reduced the prevalence of MS in obese men and women (Phelan et al., 2007) and MS development in men and women with impaired glucose tolerance (Orchard et al., 2005). Therefore, our findings are reasonable and could be set as the target value for improving MS.

Greater weight reduction was required for improving abdominal obesity (≥13.0%) and hyperglycemia (≥13.2%). Participants aged ≤41.5 years were the best candidates for alleviating hypertension, and for those aged >41.5 years, exercise combined with a low-calorie diet contributed to alleviating hypertension. Relatively higher weight loss is required for overweight Japanese women in order to improve abdominal obesity or hyperglycemia. For improving hypertension through weight loss, the importance of exercise becomes clinically evident in the case of women aged >41.5 years. Thus, the CART analyses present a possible strategy for the management of metabolic risk factors, especially for group planning purposes, that is, it provides a target weight-loss value under each baseline condition. The additional chi-square and Fisher's exact tests revealed that all the classifications were statistically significant indicating that our classification efficiently categorizes overweight Japanese women into more or less improved groups in as distinct a manner as possible.

Study limitations and strengths

Although this study aimed to determine the factors alleviating MS in overweight Japanese women, no classification tree was generated for this because of low prevalence (total prevalence, 22%) and small available datasets (n = 69). Classification trees were generated for the alleviation of at least 1 component of MS and for improving abdominal obesity, hypertension, and hyperglycemia individually. However, these findings are limited to this group of overweight Japanese women who participated in a 3-month low-calorie-diet weight-loss program with or without exercise. Therefore, the results of this study may not be generalized.

Since the CART algorithm was originally designed for large sample sizes, a larger sample size would result in more diverse classification trees. Sufficiently large samples would be divided into a training sample and a testing sample from which the classification tree is generated, and on which the tree is tested for cross-validation, respectively. Our sample size was sufficiently large to apply CART analyses to determine the factors alleviating MS in overweight Japanese women, but it was insufficient to divide into training and testing samples. Further studies with larger sample sizes are required.

Exercise combined with low-calorie diet efficiently alleviated hypertension in a subgroup of women aged >41.5 years. However, this outcome is probably biased because the participants were non-randomly assigned to groups D and DE. The wide range of exercise intensities, which was prescribed, also hinders the generalization of the relationship. Further, it is possible that the CART algorithm might have oversimplified the relationship between weight loss and medical co-morbidity. The present study does not deny the possibility of an improvement in hypertension with the weight-loss regimen in patients over 41.5 years.

Numerous algorithms exist for predicting continuous or categorical variables from a set of continuous and/or categorical factors. However, CART has 2 advantages over alternative techniques. First, it is very simple to interpret the results. It is easier to evaluate a few logical if-then conditions than to compute classification scores for each possible group. Second, CART analysis is nonparametric and nonlinear, and is particularly well suited to identify a hierarchical order of potentially complex interactions between a set of continuous and/or categorical variables. Since few attempts have been made to explore the conditions for alleviating MS, our findings appear important.

Conclusion

Our interventional study comprising a 3-month weight-loss program with a low-calorie diet with or without exercise suggests that moderate weight loss of 8–13% helps in reducing MS components in overweight Japanese women. Baseline conditions (age and BMI) could also be important factors. However, further studies using an ideal study design are required to confirm these findings.

Conflict of interest statement

There are no conflicts of interest.

Acknowledgments

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Figure legends

Fig. 1. Flow diagram of the participants (Ibaraki and Chiba, Japan: years 1999–2006).

Fig. 2. Classification tree of participants for decreasing at least 1 component of metabolic syndrome. The participants in category 0 continued to exhibit the same number of the components, while those in category 1 exhibited a decreased number of the components (Ibaraki and Chiba, Japan: years 1999–2006).

Fig. 3. Classification tree of participants for improvement in abdominal obesity. The participants in category 0 continued to exhibit abdominal obesity, while those in category 1 showed reduced abdominal obesity (Ibaraki and Chiba, Japan: years 1999–2006).

Fig. 4. Classification tree of participants for improvement in hypertension. The participants in category 0 continued to exhibit hypertension, while those in category 1 showed an improvement in hypertension (Ibaraki and Chiba, Japan: years 1999–2006).

Fig. 5. Classification tree of participants for improvement in hyperglycemia. The participants in category 0 continued to exhibit hyperglycemia, while those in category 1 showed improvement in hyperglycemia (Ibaraki and Chiba, Japan: years 1999–2006).

Table 1

Descriptive characteristics of subjects at baseline and after intervention. (Ibaraki and Chiba, Japan: years 1999-2006)

	Low-calorie diet (*n* = 115)			**Low-calorie diet plus exercise (*n* = 194)**		
	Baseline	**After**	***P***	**Baseline**	**After**	***P***
Age (years)	49.5 ± 8.4			49.9 ± 8.7		
Body mass index (kg/m^2)	28.9 ± 2.9	26.0 ± 3.0	<0.001	28.5 ± 2.6	24.9 ± 2.6	<0.001
Waist circumference (cm)	97.7 ± 7.7	91.0 ± 7.8	<0.001	97.6 ± 7.6	88.3 ± 7.6	<0.001
Visceral fat area (cm^2)	123 ± 51	93 ± 43	<0.001	113 ± 40	75 ± 31	<0.001
Systolic blood pressure (mmHg)	141 ± 21	128 ± 18	<0.001	137 ± 17	123 ± 15	<0.001
Diastolic blood pressure (mmHg)	87 ± 11	81 ± 11	<0.001	85 ± 10	76 ± 10	<0.001
Triglycerides (mg/dL)	122 ± 64	90 ± 41	<0.001	130 ± 102	75 ± 34	<0.001
High-density lipoprotein cholesterol (mg/dL)	59 ± 16	59 ± 14	not significant	62 ± 13	63 ± 12	not significant
Fasting plasma glucose (mg/dL)	99 ± 17	94 ± 14	<0.001	104 ± 27	92 ± 14	<0.001
Number of metabolic syndrome components	1.9 ± 0.8	1.2 ± 0.9	<0.001	1.9 ± 0.9	0.7 ± 0.8	<0.001
Number (%) of subjects with						
Abdominal obesity	78 (67.8)	45 (39.1)	<0.001	125 (64.4)	42 (21.6)	<0.001
Dyslipidemia	32 (27.8)	16 (13.9)	<0.01	51 (26.3)	9 (4.6)	<0.001
Hypertension	92 (80.0)	61 (53.0)	<0.001	148 (76.3)	69 (35.6)	<0.001
Hyperglycemia	21 (18.3)	11 (9.6)	<0.05	36 (18.6)	15 (7.7)	<0.001
Metabolic syndrome	28 (24.3)	7 (6.1)	<0.001	41 (21.1)	4 (2.1)	<0.001

Values are mean ± standard deviation. Using the Japanese criteria of metabolic syndrome, prevalence of metabolic syndrome and its components were evaluated: (i) abdominal obesity (visceral fat area ≥ 100 cm^2 and/or waist circumference ≥ 90 cm), (ii) dyslipidemia (triglycerides ≥ 150 mg/dL and/or high-density lipoprotein cholesterol < 40 mg/dL), (iii) hypertension (systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg), and (iv) hyperglycemia (fasting plasma glucose ≥ 110 mg/dL). Metabolic syndrome was defined as having abdominal obesity along with any two of the (ii) to (iv). Number of the metabolic syndrome components (0-4) was also counted.

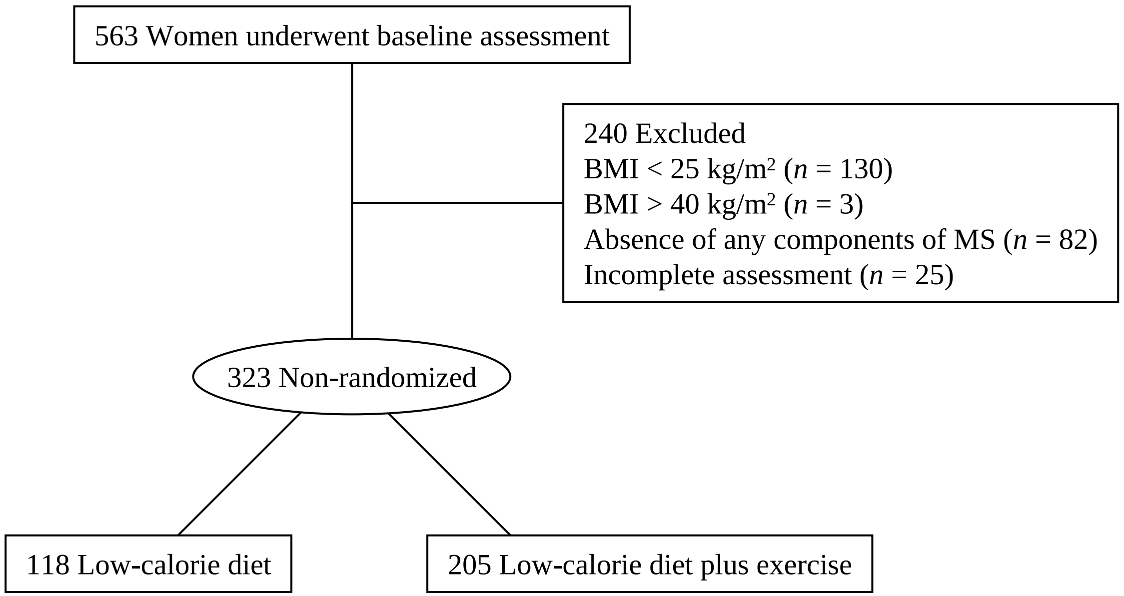
563 Women underwent baseline assessment
240 Excluded
BMI < 25 kg/m2 (n = 130)
BMI > 40 kg/m2 (n = 3)
Absence of any components of MS (n = 82)
Incomplete assessment (n = 25)
323 Non-randomized
118 Low-calorie diet
205 Low-calorie diet plus exercise

Figure 1

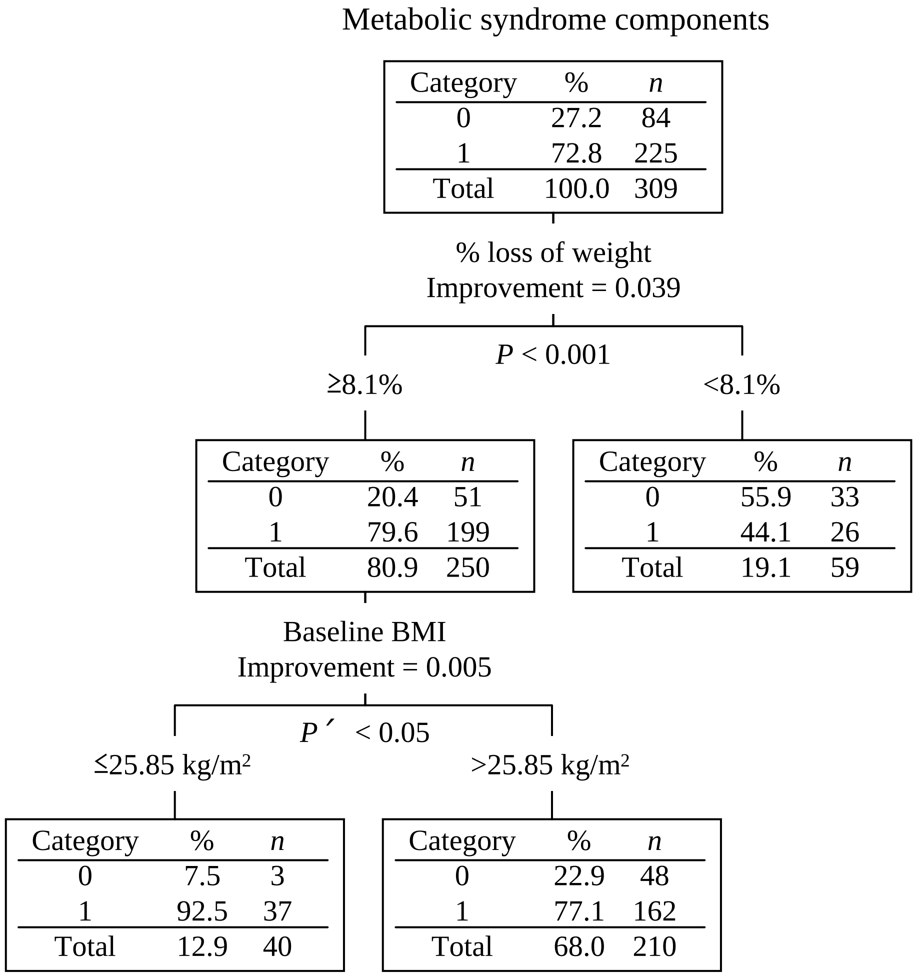
Metabolic syndrome components
Category % n
0 27.2 84
1 72.8 225
Total 100.0 309
% loss of weight
Improvement = 0.039
P < 0.001
≥8.1%
<8.1%
Category % n
0 20.4 51
1 79.6 199
Total 80.9 250
Category % n
0 55.9 33
1 44.1 26
Total 19.1 59
Baseline BMI
Improvement = 0.005
P´ < 0.05
≤25.85 kg/m2
>25.85 kg/m2
Category % n
0 7.5 3
1 92.5 37
Total 12.9 40
Category % n
0 22.9 48
1 77.1 162
Total 68.0 210

Figure 2

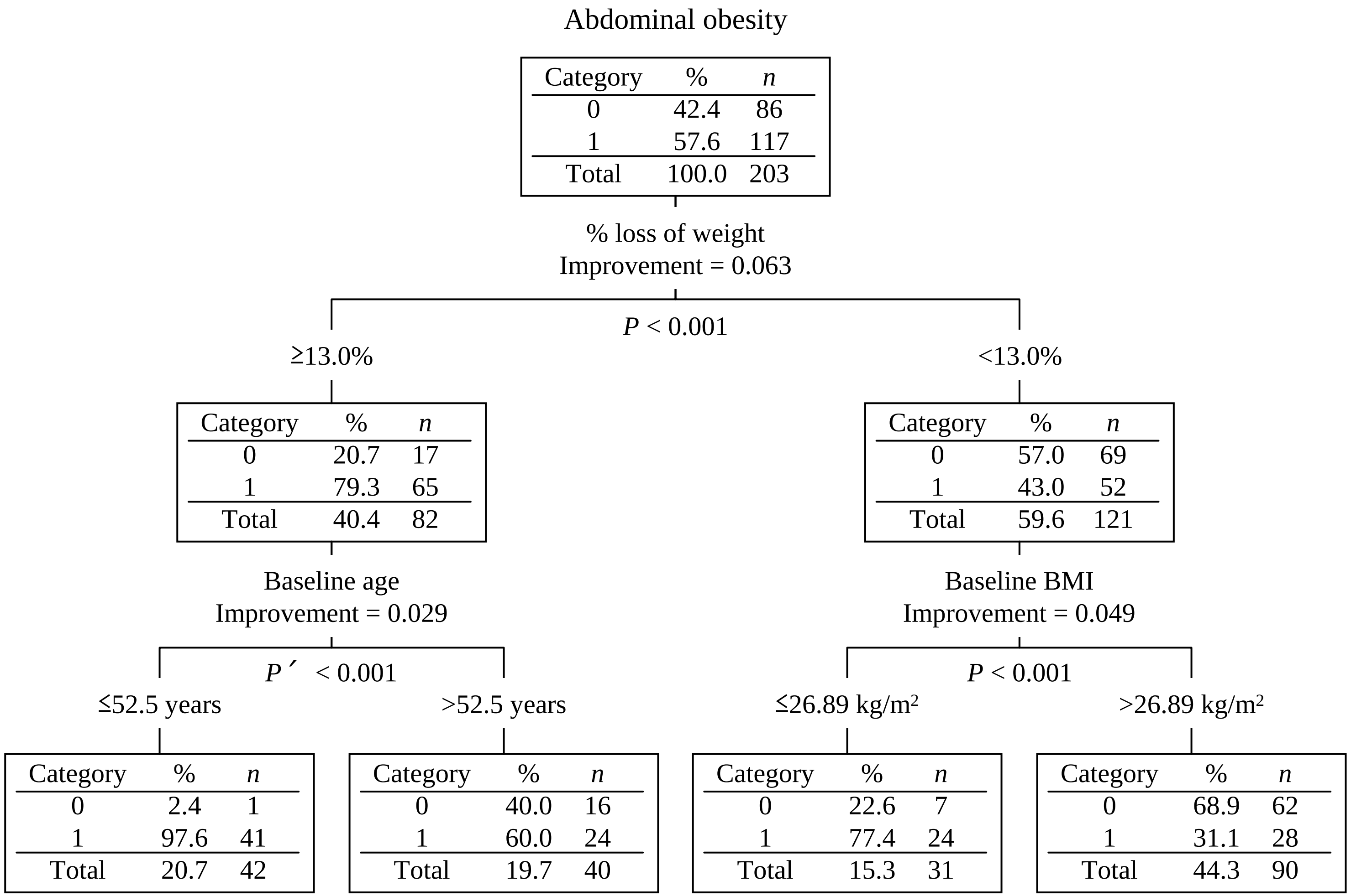
Abdominal obesity
Category % n
0 42.4 86
1 57.6 117
Total 100.0 203
% loss of weight
Improvement = 0.063
P < 0.001
≥13.0%
<13.0%
Category % n
0 20.7 17
1 79.3 65
Total 40.4 82
Category % n
0 57.0 69
1 43.0 52
Total 59.6 121
Baseline age
Improvement = 0.029
P´ < 0.001
Baseline BMI
Improvement = 0.049
P < 0.001
≤52.5 years
>52.5 years
≤26.89 kg/m2
>26.89 kg/m2
Category % n
0 2.4 1
1 97.6 41
Total 20.7 42
Category % n
0 40.0 16
1 60.0 24
Total 19.7 40
Category % n
0 22.6 7
1 77.4 24
Total 15.3 31
Category % n
0 68.9 62
1 31.1 28
Total 44.3 90

Figure 3

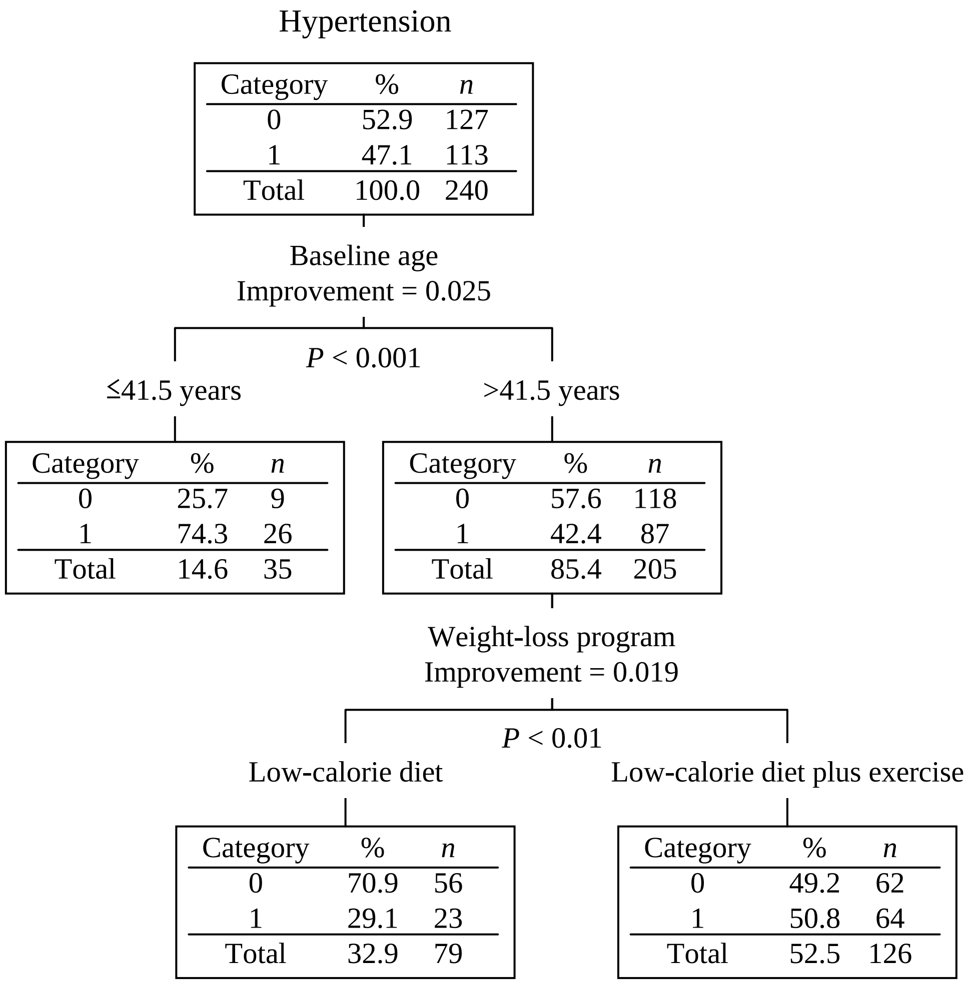
Hypertension
Category % n
0 52.9 127
1 47.1 113
Total 100.0 240
Baseline age
Improvement = 0.025
P < 0.001
≤41.5 years
>41.5 years
Category % n
0 25.7 9
1 74.3 26
Total 14.6 35
Category % n
0 57.6 118
1 42.4 87
Total 85.4 205
Weight-loss program
Improvement = 0.019
P < 0.01
Low-calorie diet
Low-calorie diet plus exercise
Category % n
0 70.9 56
1 29.1 23
Total 32.9 79
Category % n
0 49.2 62
1 50.8 64
Total 52.5 126

Figure 4

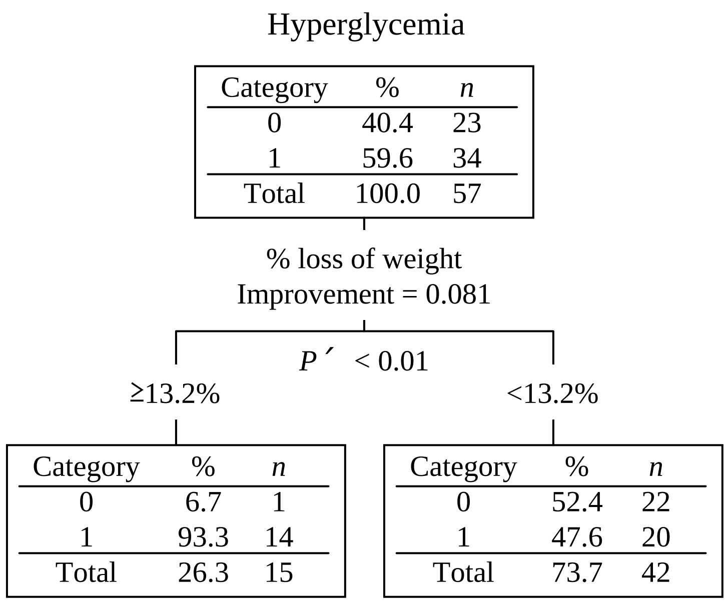
Hyperglycemia
Category % n
0 40.4 23
1 59.6 34
Total 100.0 57
% loss of weight
Improvement = 0.081
P´ < 0.01
≥13.2%
<13.2%
Category % n
0 6.7 1
1 93.3 14
Total 26.3 15
Category % n
0 52.4 22
1 47.6 20
Total 73.7 42

Figure 5