Current review of intervention studies on obesity and the role of physical activity in weight control

Yoshio Nakata^{1*} and Hiroyuki Sasai^{1,2}

¹ Faculty of Medicine, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan

² Japan Society for the Promotion of Science, Kojimachi Business Center Building, 5-3-1 Kojimachi, Chiyoda-ku, Tokyo 102-0083, Japan

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Abstract Obesity is a major public health problem, both globally and in Japan. A nationwide approach targeting metabolic syndrome has routinely been conducted in Japan since April 2008; however, the obesity statistics have not improved. Promotion of physical activity is one anti-obesity strategy. Numerous observational studies have revealed inverse associations between obesity and physical activity; however, these results have not always been conducted as randomized controlled trials (RCTs) that can provide the highest level of evidence. Therefore, this review looks at RCTs in the field of obesity and physical activity worldwide. The Diabetes Prevention Program and the Look AHEAD study are representative RCTs in this field. A guideline for the management of overweight and obesity among U.S. adults has recently been updated using a systematic review of good- or fair-quality RCTs, but a comprehensive, systematic review of RCTs in Japan has not yet been undertaken. This review seeks to fill this gap. Overall, we only found 10 RCTs that met the three inclusion criteria ([1] intervention study on obesity, [2] overweight or obese Japanese participants, and [3] RCT) and did not meet the exclusion criterion (study protocol without results). Based on our review results, it is strongly suggested that more RCTs in this field be conducted in Japan.

Keywords : randomized controlled trial, intervention studies, evidence, weight loss, diet, exercise

Introduction

Obesity is a major public health problem, both globally and domestically. It is a risk factor for cancer¹⁾, cardiovascular disease²⁾, coronary heart disease^{3,4)}, and diabetes⁴⁾. Furthermore, obesity is associated with increased mortality⁵⁾. In Japan, people typically have a lower body mass index (BMI) than people in other high-income countries; however, the mean BMI of men increased from 22.1 kg/m² to 23.5 kg/m² and that of women increased from 21.3 kg/m² to 23.3 kg/m² between 1980 and 2008⁶⁾. A nationwide health screening and intervention program specifically targeting metabolic syndrome⁷⁾ has been routinely conducted in Japan since April 2008; however, the obesity statistics have not improved⁸⁾.

Promotion of physical activity is one anti-obesity strategy. The American College of Sports Medicine Position Stand⁹⁾ recommends a minimum of 150 min/week of moderate-intensity physical activity to prevent significant weight gain and reduce associated chronic disease risk factors. According to the position stand, cross-sectional and prospective studies have indicated that weight maintenance after weight loss has improved with a reported

physical activity level of >250 min/week; however, no evidence from well-designed randomized controlled trials (RCTs) exists to judge the effectiveness of physical activity for the prevention of weight regain after weight loss.

Here, cross-sectional and prospective studies are categorized as observational studies. Observational studies aim to show an association between Exposure X and Outcome Y. On the other hand, an intervention study aims to demonstrate the causality of Exposure X (operated by an intervention) with Outcome Y. Such studies include the one-arm (single-arm) trial, non-RCT, and RCT. There are sometimes discrepancies between observational and intervention studies. In general, RCT is a study design that can provide the highest level of evidence (Fig. 1).

Taking the aforementioned topic as an example, observational studies indicate that physical activity (Exposure X) is associated with weight maintenance after weight loss (Outcome Y). For instance, the National Weight Control Registry (NWCR)¹⁰⁾ is the largest longitudinal prospective study of individuals who reported to be successful in long-term weight loss maintenance. The participants must have lost a minimum of 13.6 kg (30 lb) and must have maintained that weight loss for at least 1 year. An NWCR-based report¹⁰⁾ showed that the amount of physical activity was 2,621 ± 2,252 kcal/week; thus, over-

*Correspondence: nakata@md.tsukuba.ac.jp

Fig. 1 Level of evidence.

all NWCR participants were extremely physically active.

Another study, the Nurses' Health Study II¹¹⁾, is an ongoing prospective study of 116,608 female nurses aged 25-42 years who responded to a mailed questionnaire in 1989. Follow-up questionnaires have been mailed biennially. One report based on this cohort study¹¹⁾ investigated the duration and type of activity required to prevent weight regain over 6 years among women who lost >5% of their baseline body weight (n=4,558). As a result, an increase of 30 min/day in total discretionary activity over 6 years was associated with less weight regain, particularly among overweight women. Increased jogging or running was associated with less weight regain than was increased brisk walking or other activities. Therefore, observational studies indicate that a high level of physical activity is important to maintain intentional weight loss.

However, no RCTs could demonstrate the causality of increasing physical activity (Exposure X operated by an intervention) with maintenance of weight loss (Outcome Y). A few previous studies tested this hypothesis^{12,13)}. One study¹²⁾ examined the effect of varying durations and intensities of exercise on weight loss in overweight women during a 24-month period. Two hundred one overweight and obese women were randomly assigned to one of 4 behavioral weight loss intervention groups based on physical activity energy expenditure (1,000 vs. 2,000 kcal/week) and intensity (moderate vs. vigorous). They were also told to reduce dietary intake to between 1,200 and 1,500 kcal/day. Consequently, weight loss did not differ among the 4 groups. This might have been the result of lack of adherence to the prescribed intensity during this study. In fact, a post-hoc analysis showed that individuals sustaining a loss of >10% of initial body weight at 24 months reported performing more physical activity (1,835 kcal/week or 275 min/week) compared to those who sustained a weight loss of less than 10% of initial body weight. Another study¹³⁾ examined the effects of different prescribed doses of physical activity on weight change. Two hundred seventy-eight overweight adults were randomly assigned to one of 3 groups: the self-help group (SELF); the MOD-

PA group, which was prescribed 150 min/week of physical activity; or the HIGH-PA group, which was prescribed 300 min/week of physical activity, without interventions promoting a reduction in energy intake. As a result, percent of weight change over 18 months did not differ among the 3 groups, despite the existence of significant differences in physical activity among the groups. A post-hoc analysis showed that individuals losing >3% of their baseline weight became significantly more physically active (18-month change: 161.9 ± 252.6 min/week) than those remaining within $\pm 3\%$ (78.2 ± 162.6 min/week) and those gaining >3% (74.7 ± 274.3 min/week) of their baseline weight. Therefore, intervention studies indicate that a prescribed physical activity intervention does not influence weight loss outcome; however, those who successfully sustain their weight loss are more physically active.

As just described, associations from observational studies are not always demonstrated by RCTs that can provide the highest level of evidence. Therefore, this review focused on RCTs in the field of obesity worldwide that included physical activity as a related factor. The other purpose was to systematically review RCTs conducted in Japan and show the current Japanese situation concerning the field of obesity and physical activity.

Narrative review of RCT worldwide

Diabetes Prevention Program. One representative RCT with lifestyle modification is the Diabetes Prevention Program (DPP)¹⁴⁾. This RCT was designed to compare the effectiveness on the onset of diabetes among a placebo control group, a group treated with metformin, and a group that received a lifestyle intervention. The study participants were 3,234 adults in the United States who were at high risk for developing type 2 diabetes and were randomly assigned to one of three groups (1082 to the placebo, 1073 to the metformin, and 1079 to the lifestyle group). The goals for the participants in the lifestyle intervention group were to achieve and maintain a weight loss of at least 7% of initial body weight through a healthy

low-calorie, low-fat diet, and to engage in physical activity of moderate intensity for at least 150 min/week.

The curriculum was composed of 16 lessons over 24 weeks covering diet, exercise, and behavioral modification. At the end of the curriculum, 50% of the participants in the lifestyle intervention group had achieved the goal of $\geq 7\%$ weight loss, and 74% had met the goal of ≥ 150 min/week of physical activity. Overall, the participants were followed for an average of 2.8 years. Participants assigned to the lifestyle intervention group had much greater weight loss and a greater increase in physical activity than did participants assigned to either the metformin or the placebo group. The average weight loss was 0.1, 2.1, and 5.6 kg in the placebo, metformin, and lifestyle intervention groups, respectively. Diabetes incidence was 58% lower in the lifestyle intervention group and 31% lower in the metformin group than in the placebo group, and it was 39% lower in the lifestyle intervention group than in the metformin group. Therefore, lifestyle intervention was demonstrated to reduce the incidence of diabetes much more than did metformin.

From the DPP research group, various important findings were reported. In a 3.2-year follow-up, the impact on hypertension, dyslipidemia, and cardiovascular disease (CVD) events¹⁵⁾ were assessed, along with the effects on metabolic syndrome¹⁶⁾. Lifestyle intervention improved hypertension and dyslipidemia compared to the placebo and metformin; however, no differences in CVD events were observed among the three groups¹⁵⁾. Incidence of metabolic syndrome was reduced by 41% in the lifestyle group and by 17% in the metformin group compared with the placebo group¹⁶⁾. In a 10-year follow-up¹⁷⁾, participants in the lifestyle group returned to near their baseline weight, and there were no significant group differences in weight loss. However, diabetes incidence was reduced by 34% in the lifestyle group and by 18% in the metformin group compared with the placebo group.

Look AHEAD study. Look AHEAD (Action for Health in Diabetes)¹⁸⁻²¹⁾ was a National Institutes of Health (NIH)-funded clinical trial, conducted in 16 centers in the United States, that investigated the long-term (up to 13.5 years) effects of an intensive lifestyle intervention (ILI) delivered over 4 years in 5,145 overweight and obese individuals with type 2 diabetes. The participants who were 45-74 years of age and had a BMI ≥ 25 were randomized to one of 2 groups: the ILI group, which was designed to achieve and maintain weight loss through decreased caloric intake and increased physical activity, and a control group that was given diabetes support and education (DSE). The primary outcome was time to incidence of a major CVD event.

At 1 year, participants assigned to the ILI group lost an average of 8.6% of their initial body weight vs. 0.7% in the DSE group¹⁹⁾. Averaged across 4 years²⁰⁾, ILI could produce sustained weight loss (6.15% vs. 0.88%, in ILI

and DSE, respectively) and improvements in fitness, glycemic control, and CVD risk factors. At a median follow-up of 9.6 years²¹⁾, weight loss was greater in the ILI than the DSE group (6.0% vs. 3.5%, respectively), and improvements in most CVD risk factors were observed. However, the primary outcome, a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina during a maximum follow-up of 13.5 years, occurred in 403 ILI patients and 418 DSE patients. The hazard ratio was 0.95 (95% confidence interval, 0.83 to 1.09). As a result, the trial ended early on the basis of futility analysis.

Although there was no significant difference between the ILI and DSE groups in terms of cardiovascular morbidity and mortality, other benefits of the lifestyle intervention were identified. At 1 year, moderate weight loss reduced the incidence of urinary incontinence in women²²⁾ and men²³⁾. Sleep apnea was improved at 1 year²⁴⁾, and the effect persisted for 4 years²⁵⁾. At 4 years, the ILI group was significantly more likely to experience partial or complete remission of type 2 diabetes²⁶⁾. At 8 years, ILI showed long-term benefits on mobility function: better scores of physical performance battery, faster 20-m and 400-m walk speeds²⁷⁾, and a reduced incidence of very high-risk chronic kidney disease²⁸⁾. ILI reduced the risk of developing depression and preserved physical health-related quality of life over the observation period for a median of 9.6 years²⁹⁾. In addition, ILI participants had fewer hospitalizations, fewer medications, and lower healthcare costs, compared to DSE over 10 years³⁰⁾. Therefore, the importance of ILI cannot be denied.

Other representative RCTs. The abovementioned RCTs were conducted on a very long-term basis. Most RCTs were not so long in duration. The Dose-Response to Exercise in postmenopausal Women (DREW) trial was a representative RCT that examined the effects of 50%, 100%, and 150% of the NIH Consensus Panel physical activity recommendations (4, 8, and 12 kcal/kg per week in energy expenditure, respectively), compared to a no-exercise control group, on cardiorespiratory fitness in sedentary, overweight, or obese postmenopausal women with elevated blood pressure³¹⁾. Four hundred sixty-four participants were randomly assigned to 1 of the 4 groups during a 6-month study period. After adjusting for covariates, the exercise intervention groups increased their peak $\dot{V}O_2$ by 4.2%, 6.0%, and 8.2% in the 4, 8, and 12 kcal/kg per week groups, respectively, compared to the control group. Although there were no significant differences between the groups for body weight and other health outcomes, the DREW study demonstrated a graded dose-response change in fitness across levels of exercise training in overweight and obese women.

Another recent, good-quality RCT was a one-year intensive lifestyle intervention study consisting of diet and physical activity for severely obese adults (BMI >35)³²⁾.

This study recruited 130 participants and assigned them into 2 intervention groups. One group had a diet and physical activity intervention for the entire 12 months (initial-activity group). The other had the identical dietary intervention, but with a physical activity intervention that was delayed for 6 months (delayed-activity group). At 6 months, both intervention groups had lost a significant amount of body weight, but the initial-activity group lost significantly more weight in the first 6 months compared to the delayed-activity group (10.9 kg vs. 8.2 kg). At 12 months, weight loss was similar for the 2 groups (12.1 kg vs. 9.9 kg), and no significant difference was observed.

Recently, an updated guideline for the management of overweight and obesity in adults was published by the American College of Cardiology, the American Heart Association Task Force on Practice Guidelines, and the Obesity Society³³). According to the guideline, the principle components of an effective comprehensive lifestyle intervention include: [1] the prescription of a moderately reduced-calorie diet; [2] a program of increased physical activity; and [3] the use of behavioral strategies to facilitate adherence to diet and physical activity recommendations. The comprehensive lifestyle intervention is designed to induce an energy deficit of ≥ 500 kcal/day. This deficit is often achieved by prescribing an energy intake of 1,200 to 1,500 kcal/day for women and 1,500 to 1,800 kcal/day for men and by prescribing increased physical activity (such as brisk walking) for ≥ 150 min/week, which is equal to ≥ 30 min/day most days of the week. Higher levels of physical activity, approximately 200-300 min/week, are also recommended to maintain lost weight or minimize weight regain in the long term (>1 year). The behavioral strategies include regular self-monitoring of food intake, physical activity, and body weight. The strength of evidence for these strategies was reported to be high from a systematic review of good- or fair-quality RCTs.

Current review of RCTs in Japan

A systematic review was conducted to summarize RCTs on obesity and physical activity in Japan. Published studies up to August 2015 were identified from PubMed. The search terms used included (“obes*” OR “overweight” OR “over weight” OR “weight loss” OR “weight reduction” OR “weight maintenance” OR “weight control”) AND (“randomized controlled trial” OR “randomized trial” OR “clinical trial” OR “randomised controlled trial” OR “randomised trial”) in the title and abstract, and (“physical activity” OR “exercise” OR “physical training” OR “fitness” OR “physical performance” OR “physical capability”) among all fields. The initial search identified 1,654 articles. In the second search, (Japan*) was added to the search terms for the search of all fields. The second search identified only 28 articles. The authors (YN and HS) independently assessed the eligibility of the studies

for inclusion according to the following criteria: [1] intervention study on obesity, [2] overweight or obese Japanese participants, and [3] RCT. In addition, study protocols without results that were identified were excluded. Eighteen articles were excluded, and the remaining 10 articles³⁴⁻⁴³) are summarized in Table 1.

The best quality RCT seemed to be the Zensharen Study for the Prevention of Lifestyle Diseases Group³⁸). This study was a multi-center RCT that recruited overweight individuals with impaired fasting glucose levels and investigated the effectiveness of lifestyle modification on type 2 diabetes incidence. Six hundred forty-one participants were randomly assigned into one of two groups: an intervention and a control group. All the participants were individually instructed to reduce their total energy intake and increase physical activity, aiming at a 5% loss of baseline weight through the help of nurses, dietitians, physical therapists, and physicians. Participants in the intervention group were invited to a series of follow-up visits and worked toward their goals by using self-monitoring sheets for recording body weight, pedometer counts, and how close they came to attaining their goals. Mean weight reduction during the first 12 months was 2.5 kg in the intervention group and 1.1 kg in the control group. The proportion of participants who achieved a 5% loss of baseline weight was significantly higher in the intervention group at 12, 24, and 36 months. In the overall analysis, the adjusted hazard ratio for type 2 diabetes in the intervention group was 0.56 (95% confidence interval, 0.36-0.87). This RCT demonstrated that lifestyle modifications could prevent type 2 diabetes incidence among overweight Japanese people with impaired fasting glucose levels.

Sapporo Fitness Club Trial³⁵) was an RCT that tested the effects of exercise at a fitness club on CVD risk factors. Participants were recruited based on the results from a database of the Sapporo Health Promotion Center, and 561 overweight Japanese with CVD risk factors were randomized into one of two groups - an intervention and control group - after lifestyle counseling. Participants in the intervention group received a membership to a fitness club (one of 5 designated clubs) for 6 months. Participants in the control group did not receive the membership for the first 6 months, but they could receive the same benefits in the second 6 months. The exercise group exercised at fitness clubs an average of 2.6 times per week. A significant between-group difference was observed in body weight loss (-1.88 kg and -0.28 kg, in intervention and control groups, respectively), and a marginally significant difference was observed in systolic blood pressure reduction (-8.30 mm Hg and -6.17 mm Hg, respectively). This RCT demonstrated that exercising at a fitness club improved CVD risk factors in overweight Japanese individuals with multiple CVD risk factors.

The Saku Control Obesity Program³⁹) was a 1-year lifestyle intervention for weight loss based on a behavioral

Table 1. Summary of randomized controlled trials on obesity and physical activity in Japan.

Study	Participants (sex, age, BMI)	Follow-up (months)	Intervention arms	Weight change (kg)
Adachi Y et al., 2007 ³⁴⁾	205 (F, 46 yr, 26.1)	7	1: computer tailored advice with self monitoring 2: computer tailored advice only 3: self-help booklet with self monitoring 4: self-help booklet only	1: -2.9 2: -2.2 3: -1.6 4: -1.4 (n=183)
Nishijima H et al., 2007 ³⁵⁾	561 (234M/327F, 67 yr, 26.4)	6	1: exercise 2-4 times/week at a fitness club 2: lifestyle-modification advice	1: -1.88 2: -0.28 (n=501)
Tanaka M et al., 2010 ³⁶⁾	51 (M, 46 yr, 26.2)	7	1: booklet and computer tailored advice 2: booklet only	1: -2.4 2: -1.6
Takada A et al., 2011 ³⁷⁾	97 (32M/65F, 46 yr, 25.7)	6	1: telephone and mail support 2: self help	1: -2.1 2: -0.6 (n=47, 4 months)
Saito T et al., 2011 ³⁸⁾	641 (143M/498F, 49 yr, 27.0)	36	1: frequent intervention at least 9 times for 36 months 2: lifestyle-modification advice	1: -2.5 2: -1.1 (12 months)
Nakade M et al., 2012 ³⁹⁾	235 (116M/119F, 54 yr, 30.6)	24	1: individual-based counseling and mail support 2: no support for 1 year	1: -4.5 2: -0.1 (n=226, 12 months)
Nanri A et al., 2012 ⁴⁰⁾	102 (M, 53 yr, 25.8)	6	1: lifestyle modification 4 times for 3 months 2: standard health guidance	1: -2.01 2: -0.28
Sakurai R et al., 2013 ⁴¹⁾	66 (15M/51F, 62 yr, 25.4)	3	1: exercise, diet, hot bathing 2: exercise, diet 3: hot bathing 4: health class	1: -2.4 2: -0.6 3: +0.9 4: +0.3
Nakata Y et al., 2014 ⁴²⁾	188 (43M/145F, 51 yr, 28.9)	30	1: group-based support for 6 months (9 times) 2: single lecture and educational materials (2 times) 3: single lecture (1 time)	1: -7.7 2: -4.7 3: -2.9 (6 months) ⁴⁴⁾
Tanaka S et al., 2014 ⁴³⁾	200 (M, 42 yr, 27.0)	6	1: dietary intervention and dairy delivery 2: dietary intervention	1: -3.3 2: -3.3 (n=125, 30 months)
				1: -1.1 2: -2.6

BMI, body mass index; M, male; F, female.

approach. Participants were recruited at the Saku Health Dock Center in Nagano Prefecture, and 235 overweight and obese adults were randomly assigned to one of two groups: an intervention or a wait-list control group. Participants in the intervention group received an initial 30-min individual counseling session at baseline, followed up by 20-min group sessions concerning effective exercise provided by registered dietitians and exercise instructors at 1, 3, 6, and 9 months. During the months between the 5 face-to-face sessions, the participants recorded their progress for the previous month and their new plans for the following month, and mailed their records to the dietitians. The dietitians checked these and sent back comments to each participant. One year later, results showed that the intervention group lost significantly more weight than the control group (-5.0 kg vs. +0.1 kg for men, and -3.9 kg vs. -0.2 kg for women, respectively). And, at a 1-year follow-up to the intervention period, it was seen that the intervention group maintained significantly lower weight. This RCT demonstrated that the behavioral approach led to weight loss and maintenance of weight loss through diet and behavior modification.

Nakata et al. focused on providing educational materials (textbooks, notebooks, and a pedometer) and implementing group-based support as effective individual components of a weight loss program^{42,44}. Participants were recruited through newspaper advertisements, and 188 overweight and obese adults were randomly assigned into one of three groups: control group, moderate intervention group, or intensive intervention group. All participants received an initial motivational lecture. The energy intake goals were 1,200 and 1,600 kcal/day for women and men, respectively, and the increased energy expenditure goal was 1,000 kcal/week. Participants in the moderate and intensive intervention groups also received the educational materials and a lecture on how to use them. Only participants in the intensive intervention group received group-based support at weeks 2, 4, 6, 10, 14, 18, and 22, during which a trained staff member gave lectures and two other staff members reviewed participants' notebooks and advised them on their diet and other lifestyle-related factors.

During the 6-month intervention period, the participants in the control, moderate, and intensive intervention groups reduced their weight by 2.9, 4.7, and 7.7 kg, respectively. All differences between groups were significant⁴⁴. A follow-up exam 2 years later showed the amount of weight lost in the moderate and intensive intervention groups to be the same (3.3 kg)⁴². Secondary analysis using the data of those who completed the study (n=100) revealed that the participants in the highest quartile of percentage of weight lost significantly increased their step counts and moderate-to-vigorous physical activity compared to the lowest quartile group⁴². This RCT demonstrated that group-based support was an effective component of a weight loss program, but the effect seemed to disappear within 2 years. In addition, it was suggested that increas-

ing physical activity is a crucial factor for successful weight loss maintenance.

The other studies found in our literature review focused on computer tailored advice^{34,36}, telephone and mail support³⁷, tailor-made lifestyle modification⁴⁰, hot bathing⁴¹ and dairy delivery⁴³. Although all RCTs provided valuable findings, RCTs in this specific field in Japan were quite limited. For instance, no RCTs compared diet plus exercise with diet only. Our research group published related articles⁴⁵⁻⁴⁷, but these studies were not RCTs. As a result, no RCTs in Japan were found to be eligible for a recent systematic review⁴⁸ comparing the efficacy of diet plus exercise with diet only.

Conclusions

The RCT is a study design that can provide an extraordinarily high level of evidence. There are many RCTs in the world, and good quality ones are utilized for making guidelines or systematic reviews. Regrettably, RCTs in the field of obesity and physical activity in Japan are quite limited. Ideally, Japanese national guidelines should be based on RCTs conducted in Japan. Accordingly, it is strongly suggested that more RCTs in this field be conducted in Japan.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this article.

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