Sex Differences in the Effects of Weight Reduction on Future Blood Pressure Elevation in a Mildly Obese Middle-Aged Population

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Background: The effectiveness of weight loss (WL) in preventing blood pressure (BP) elevation is common knowledge; however, the effect of sex differences is not known.

Methods and Results: Health checkup data from Kagoshima Kouseiren Medical Healthcare Center for middle-aged participants (40–49 years old) with mild obesity (body mass index [BMI] 25.0–29.9 kg/m²) who had examination data for 2 follow-up time-points (after 3 and 10 years) were analyzed. Propensity score (PS) matching using data from the first examination was used to match participants with a decrease in BMI ≥ 1.0 kg/m² at 3 years (WL group) with those with a BMI decrease <1.0 kg/m² or weight gain (non-WL group). BP values were compared after 3 and 10 years between the 2 groups, as was the prevalence of hypertension after 10 years. PS matching resulted in 232 men and 160 women in each group. Among women, systolic BP (SBP) and hypertension prevalence after 10 years were significantly lower in the WL than non-WL group (P<0.01 and P<0.05, respectively). There were no significant differences in SBP and hypertension prevalence after 10 years in men in the 2 groups.

Conclusions: There were sex differences in the effectiveness of WL in preventing future BP elevation in mildly obese middle-aged participants: WL prevented future BP elevation and hypertension onset in women, but not in men.

Key Words: Blood pressure elevation; Obesity; Sex difference; Weight loss
BP in middle-aged individuals. It is not always easy to assume the success of significant WL in daily clinical practice because even slight WL requires a strong will. In the present study we analyzed the health checkup data for a general Japanese population with the aim of investigating whether there were sex differences in the degree of BP increase and the prevalence of hypertension in the future following slight WL in middle-aged obese participants.

**Methods**

**Study Population**

Data from annual health checkups at Kagoshima Kouseiren Medical Healthcare Center (Kagoshima, Japan), collected from January 2001 through December 2015, were analyzed retrospectively. First, individuals who were aged in their 40s (age 40–49 years) and had had a health checkup at least once from 2001 to 2005 were identified. Among these individuals, those who underwent health examinations after both 3 years (range 2–4 years) and 10 years (range 9–11 years) were selected for inclusion in this study. To include only mildly obese individuals (BMI 25.0–29.9 kg/m²), subjects with a baseline BMI <25 and ≥30 kg/m² were excluded. Individuals with missing variable measurements used for the matching of baseline characteristics or statistical analyses were also excluded, as were those with cancer and endocrine diseases, which may affect body weight or BP. Moreover, participants who were receiving medical treatment at baseline for hypertension, dyslipidemia, or diabetes were also excluded. The remaining individuals were included in the analysis.

This study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Ethics Committees of the Graduate School of Medical and Dental Sciences, Kagoshima University.
Data Collection
Body height and weight were measured by trained personnel using standard anthropometric techniques, and BMI was calculated as weight (kg) divided by height squared (m²). Information on cigarette smoking and alcohol consumption was obtained from self-administered questionnaires, and subjects were classified as follows: smoker, smoking currently; non-smoker, never smoked or past smoker; chance drinker, drinking ≤10 days/month; and usual drinker, drinking >10 days/month. Data regarding diseases and current medications for hypertension, diabetes mellitus, and dyslipidemia were obtained using self-administered questionnaires. BP was measured after the participants had sat quietly for 5 min. Blood samples were obtained from the patient after overnight fasting. Serum triglyceride (TG), low-density lipoprotein cholesterol, blood glucose (BG), and creatinine concentrations were determined using standard laboratory procedures. The estimated glomerular filtration rate (eGFR) was determined according to the new Japanese coefficient for the modified isotope dilution mass spectrometry-traceable Modification of Diet in Renal Disease study equation¹³ as follows:

\[ \text{eGFR} = 194 \times \text{SCr}^{-1.094} \times \text{Age}^{-0.287} \text{ (for males)} \]
\[ \text{eGFR} = 194 \times \text{SCr}^{-0.867} \times \text{Age}^{-0.287} \times 0.739 \text{ (for females)} \]

where SCr is the serum creatinine concentration.

Grouping and Baseline Matching
Participants were divided into 2 groups according to changes in BMI from baseline to the 3-year follow-up as follows: WL group, participants in whom BMI decreased ≥1.0 kg/m²; non-WL group, participants who gained weight or lost no more than 1.0 kg/m². Furthermore, propensity score (PS) matching was used to create a balanced distribution of baseline characteristics between the WL and non-WL groups. First, a logistic regression for WL was used to develop the PS for each participant. Variables such as age, BMI, smoking and drinking status, eGFR, systolic blood pressure (SBP), diastolic blood pressure (DBP), and hypertension (defined as SBP ≥140 mmHg and/or DBP ≥90 mmHg) at baseline were included for the calculation of the PS. A greedy nearest-neighbor matching algorithm with a caliper of width of 0.2SD of the logit of the PS was used. The balance of covariates between the WL and non-WL groups was assessed using absolute standardized differences, whereby an absolute standardized difference >0.1 represents meaningful imbalance. In order to keep the post-balancing assumptions at baseline, we did not exclude individuals who had cancer or endocrine disease in the follow-up period.

Statistical Analyses
Because the aim of this study was to investigate sex differences

| Table. Baseline Characteristics of the Participants by Sex |
|---------------------------------|
|                                | Before matching | After matching |
|                                | WL(+) | WL(-) | P-value | WL(+) | WL(-) | P-value | SD |
| Men No. subjects                | 251   | 1,256 |         | 232   | 232   |         |     |
| Age (years)                    | 44.0±2.8 | 44.1±2.8 | 0.49 | 43.9±2.7 | 43.8±2.8 | 0.67 | 0.04 |
| BMI (kg/m²)                    | 26.9±1.3 | 26.6±1.2 | <0.001 | 26.9±1.3 | 27.0±1.4 | 0.31 | 0.09 |
| SBP (mmHg)                     | 124.8±15.8 | 121.8±15.3 | <0.01 | 123.7±15.0 | 125.2±17.9 | 0.33 | 0.09 |
| DBP (mmHg)                     | 80.7±11.4 | 79.4±11.2 | 0.09 | 80.4±11.5 | 80.1±12.8 | 0.59 | 0.05 |
| TG (mg/dL)                     | 156.5 | [105, 235.6] | 0.65 | 153.5 | [110, 230.5] | 0.97 | 0.05 |
| LDL-C (mg/dL)                  | 126.3±42.9 | 123.2±39.3 | 0.27 | 126.2±42.8 | 125.1±47.1 | 0.79 | 0.02 |
| BG (mg/dL)                     | 104 | [95, 117.8] | <0.001 | 103 | [95, 116] | 0.79 | 0.08 |
| eGFR (mL/min/1.73 m²)          | 84.1±16.5 | 81.1±13.7 | <0.01 | 83.4±15.2 | 82.0±14.3 | 0.31 | 0.09 |
| Smoker                         | 128 (51.0) | 628 (50.0) | 0.77 | 119 (51.3) | 116 (50.0) | 0.78 | 0.02 |
| Usual drinker                  | 170 (67.7) | 818 (65.1) | 0.43 | 159 (68.5) | 156 (67.2) | 0.76 | 0.02 |
| Women No. subjects             | 184   | 804   |         | 160   | 160   |         |     |
| Age (years)                    | 45.0±2.7 | 44.7±2.8 | 0.22 | 45.1±2.7 | 45.0±2.7 | 0.62 | 0.05 |
| BMI (kg/m²)                    | 26.8±1.2 | 26.7±1.3 | 0.23 | 26.7±1.2 | 26.7±1.3 | 0.96 | <0.01 |
| SBP (mmHg)                     | 118.5±14.8 | 117.6±16.0 | 0.51 | 118.6±15.1 | 119.0±15.9 | 0.82 | 0.02 |
| DBP (mmHg)                     | 74.0±9.3 | 73.7±10.3 | 0.71 | 74.1±9.4 | 73.4±9.9 | 0.50 | 0.07 |
| TG (mg/dL)                     | 84 | [64, 119] | 0.29 | 86 | [66, 120] | 0.69 | 0.07 |
| LDL-C (mg/dL)                  | 124.2±29.9 | 123.4±30.8 | 0.74 | 124.4±29.8 | 126.7±32.0 | 0.52 | 0.07 |
| BG (mg/dL)                     | 97 | [90, 105] | <0.01 | 97 | [90, 103.75] | 0.46 | 0.05 |
| eGFR (mL/min/1.73 m²)          | 86.2±15.0 | 85.6±16.2 | 0.65 | 85.9±14.9 | 84.5±15.8 | 0.43 | 0.08 |
| Smoker                         | 9 (4.9) | 26 (3.2) | 0.27 | 7 (4.4) | 8 (5.0) | 0.79 | 0.02 |
| Usual drinker                  | 9 (4.9) | 52 (6.5) | 0.42 | 7 (4.4) | 4 (2.5) | 0.35 | 0.10 |

Unless indicated otherwise, data are given as the mean ± SD, median [interquartile range], or n (%). BG, blood glucose; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SD, standardized difference; TG, triglyceride; WL, weight loss.
Men (Pre-matching) | Men (Post-matching)
---|---
Baseline | 26.6±1.2 | 26.0±1.4 | 26.6±1.9 | 26.8±1.5 | 26.8±1.2 | 26.5±1.8
3 year after | 26.9±1.3 | 25.2±1.5 | 25.5±1.8 | 26.9±1.3 | 25.2±1.4 | 25.5±1.8
10 year after | <0.001 | <0.001 | <0.001 | 0.31 | <0.001 | <0.001

Women (Pre-matching) | Women (Post-matching)
---|---
Baseline | 26.7±1.3 | 25.9±1.2 | 25.3±2.0 | 26.7±1.3 | 24.9±1.4 | 25.3±1.9
3 year after | 26.8±1.2 | 24.9±1.4 | 25.3±2.0 | 26.7±1.3 | 24.9±1.4 | 25.3±1.9
10 year after | 0.23 | <0.001 | <0.001 | 0.96 | <0.001 | <0.001

**Figure 2.** Changes in the body mass index (BMI) of participants before and after propensity score matching at baseline. The BMI at baseline and after 3 and 10 years was stratified according to weight loss (WL). Solid lines indicate changes in BMI in the WL group, whereas dashed lines indicate changes in BMI in the non-WL group. Data are presented for each sex separately and for participants before and after matching at baseline. Data are the mean±SD.

Changes in BMI, BP, and the Prevalence of Hypertension

Changes in BMI from baseline to follow-up in the WL and non-WL groups for participants before and after PS matching are shown in Figure 2. For participants both before and after matching, BMI after 3 years was significantly lower in the WL than non-WL group, and this significant difference persisted even after 10 years among both men and women.

Changes in BP from baseline to the 10-year follow-up in the WL and non-WL groups are shown in Figure 3. In the male population before matching, DBP after 3 years was significantly lower in the WL than non-WL group (79.1±11.1 vs. 81.7±11.0 mmHg, respectively; *P*<0.001),
Effect of Weight Reduction on BP Elevation

whereas there was no significant difference in SBP between the 2 groups. After 10 years, neither SBP nor DBP differed significantly between the WL and non-WL groups. In the male population after matching, the results were similar to those before matching, except that SBP after 3 years was significantly lower in the WL than non-WL group (121.8±15.2 vs. 127.1±18.0 mmHg, respectively; P<0.001).

In the female population before matching, DBP after 3 years was significantly lower in the WL than non-WL group (73.2±10.3 vs. 76.2±10.8 mmHg, respectively; P<0.001), whereas there was no significant difference in SBP. After 10 years, both SBP and DBP were significantly lower in the WL than non-WL group (SBP: 125.1±16.4 vs. 128.3±18.5 mmHg, respectively [P<0.05]; DBP: 76.8±10.0 vs. 79.2±11.0 mmHg, respectively [P<0.01]). In the female population after matching, SBP after 10 years was significantly lower in the WL than non-WL group (124.8±16.3 vs. 130.3±19.0 mmHg, respectively; P<0.01), but there was no significant difference in DBP after 10 years between the 2 groups.

Figure 4 shows the prevalence of hypertension at the 10-year follow-up in the WL and non-WL groups. In the analysis of the male population before and after matching, there were no significant differences in the prevalence of hypertension between the groups. However, a significant difference was found in the prevalence of hypertension between women in the WL and non-WL groups after matching (35.0% vs. 48.1%, respectively; P<0.05), but not before PS matching.

Figure 3. Changes in systolic and diastolic blood pressure (SBP and DBP, respectively) in participants before and after baseline matching. SBP and DBP at baseline and after 3 and 10 years were stratified according to weight loss (WL). Solid lines indicate changes in blood pressure in the WL group, whereas dashed lines indicate changes in blood pressure in the non-WL group. Data are presented for each sex separately and for participants before and after matching at baseline. Data are the mean±SD.
In this study, subjects were divided into WL and non-WL groups according to changes in BMI from baseline to 3 years. Ten years after the baseline measurements, both men and women in the WL group maintained significantly lower BMI than those in the non-WL group. Focusing on BP after 10 years, SBP and the prevalence of hypertension were significantly lower in women in the WL than non-WL group; in men, no differences were observed between the 2 groups. In middle-aged (40 s) individuals with mild obesity, we observed sex differences in the long-term effects of slight WL on BP.

There are many reports regarding the association between obesity and hypertension. Visceral adiposity, an overactivated renin-angiotensin-aldosterone system, sympathetic nervous system enhancement, the presence of sodium retention, insulin resistance and hyperinsulinemia, and the involvement of sleep apnea syndrome have been reported as causes for the development of hypertension due to obesity. It has also been reported that BP decreases according to WL. A previous report showed that a 2.4 kg/m² decrease in BMI by dietary therapy resulted in a 10 mmHg decrease in SBP. In a study conducted in the Japanese population, WL ≥3% resulted in a significant decrease in BP. It is well recognized that diet is useful for suppressing hypertension in both men and women. Although previous studies reported the effects of suppressing BP by WL with a relatively short follow-up after WL, evidence for the long-term benefits of WL is lacking. Thus, the present study is novel because it revealed the effects of WL on BP with a relatively long-term follow-up period.

In the Japanese population, BP and the prevalence of hypertension consistently increase with age in both men and women. BMI and the prevalence of obesity have clear sex differences by age. In women, the prevalence of obesity is low for those in their 30 s and 40 s, but begins to increase markedly after menopause and peaks in women in their 60 s. In men, the prevalence of obesity increases from a young age and peaks in those in their 40 s, gradually decreasing thereafter. When focusing on the same age, men and women may have different pathophysiology and lifestyles regarding obesity.

In the analysis of the male population before PS matching, BMI, SBP, and BG were significantly higher in the WL than non-WL group. These participants may be more motivated to lose weight due to concerns about future health problems. At the 3-year follow-up, both SBP and DBP were slightly decreased in the WL group and slightly increased in the non-WL group relative to baseline. At the 10-year follow-up, there were no significant differences in SBP and DBP between the 2 groups. In the analysis of the female population both before and after PS matching, SBP was significantly lower in the WL than non-WL group after 10 years.

In this study the favorable effects of WL on BP persisted...
in women but disappeared in men after 10 years. Considering that differences in BMI still existed after 10 years, the result in men was surprising. There are several possibilities for this sex difference. BP is affected by several cardiovascular risk factors. In men, various cardiovascular risk factors begin to worsen starting at the age of 30 years. In contrast, in women, the metabolic cardiovascular risks are suppressed by the effects of estrogen until menopause, and lifestyle-related cardiovascular risks, including smoking and alcohol consumption, were fewer in women than in men. There is a possibility that the contribution of obesity to increases in BP is relatively larger in women because they have fewer cardiovascular risk factors than men. In general, when focusing on a particular cardiovascular risk, the effect of risk is often stronger in women. BP increases after menopause in women, therefore, the correction of obesity during perimenopause is important for preventing future BP increases in women. Furthermore, sex differences have been reported in vascular endothelial function and arterial stiffness. Vascular endothelial function evaluated by flow-mediated dilation starts to decrease at 30–40 years of age in men, whereas the decrease is observed in women in their mid-50s. Arterial stiffness evaluated by brachial-ankle pulse wave velocity (baPWV) showed a linear increase with age in men, whereas in women the degree of increase in baPWV was lower than in men and was not high with age until around 50 years. To prevent future increases in BP, WL around the age of 40 years may be too late in men. Earlier interventions may be necessary.

The present study has several limitations. First, the data were not collected prospectively; therefore, the results need to be verified in further prospective observational studies. Second, the participants were limited to those who underwent health checkups at a single facility in Japan. Furthermore, there is the potential of selection bias because the subjects in this study tended to have a deep interest in their health. Third, we did not collect any information on the actions taken for WL, such as dietary restrictions, exercise habits, oral medical treatment, surgery, and lifestyle improvement. However, because most oral and surgical treatments are not performed in Japan, most of the participants seem to have lost weight due to lifestyle improvements. Fourth, confounding factors related to BP, such as salt intake, vegetable and fruit consumption, exercise habits, stress, and sleep time, were not measured. Information on menopause in women, which may affect BP, was also not available. Finally, we did not consider indicators such as waist circumference or fat mass.

In conclusion, there were sex differences in the effectiveness of WL to prevent future increases in BP in mildly obese, middle-aged, Japanese participants. WL could prevent future BP increases and the onset of hypertension in women, but not in men.

Acknowledgments
The authors are grateful to the medical staff at Kagoshima Kouseiren Medical Health Care Center for support with data collection.

Sources of Funding
This study did not receive any specific funding.

Disclosures
M.O. is a member of Circulation Reports’ Editorial Team. The other authors declare that they have no conflicts of interest.

IRB Information
This study was approved by the Institutional Ethics Committees of the Graduate School of Medical and Dental Sciences, Kagoshima University (No. 170130(520)).

Data Availability
The deidentified participant data will not be shared.

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