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Non-interventional weight changes affect systolic blood pressure in normotensive individuals

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Abstract

The association between obesity and hypertension is well established. Weight loss has been shown to reduce blood pressure (BP) among hypertensive patients. Nevertheless, the effect of weight changes on BP in normotensive individuals is less clear. The author explored the association between non-interventional weight alterations and BP changes in a large cohort of normotensive adults. This is a retrospective analysis of normotensive individuals, between 2010 and 2018. All weight changes were non-interventional. Body mass index (BMI) and BP were measured annually. Patients were divided according to the change in BMI between visits: reduction of more than 5% ("large reduction"), between 2.5% and 5% ("moderate reduction"), reduction of <2.5% or elevation of <2.5% ("unchanged"), elevation between 2.5% and 5% ("moderate increase"), and elevation of more than 5% ("large increase"). The primary outcome was the change in systolic BP (SBP) between the visits. The final analysis included 8723 individuals. 20% of the patients reduced their BMI by at least 2.5% and 24.5% increased their BMI by more than 2.5%. "High reduction" inferred an absolute decrease of 3.6 mmHg in SBP, while "large increase" resulted in an absolute increase of 1.9 mmHg in SBP. The proportion of individuals with at least 10 mmHg decrease in SBP progressively declined according to the relative decrease in BMI, and the proportion of patients with at least 10 mmHg increase in SBP progressively increased. This effect was more pronounced in individuals with higher baseline SBP. Among normotensive adults, modest non-interventional weight changes may have significant effects on SBP.

1 | INTRODUCTION

The global epidemic of overweight and obesity is undeniably intensifying over the past four decades,[1] with the prevalence of obesity doubling worldwide,[2] particularly in developing countries.[3] Excess body weight is independently associated with an increasing burden of cardiovascular risk factors, including development of

hypertension (HTN), type 2 diabetes mellitus (DM-2), ischemic heart disease (IHD), dyslipidemia, chronic kidney disease (CKD), stroke, several malignancies, nonalcoholic fatty liver disease, and obstructive sleep apnea.[4–8] HTN is one of the clearest risk factors for IHD and cerebrovascular disease, both of which are leading causes of deaths in the US.[9,10] The risk of HTN is significantly greater among

individuals with obesity,[11,12] and the association between overweight and HTN has been routinely confirmed in epidemiological studies.[13–16] Moreover, obesity strongly correlates with treatment-resistant HTN.[17] There are several suggested mechanisms underlying the pathophysiological association between obesity and development of HTN, including insulin resistance, oxidative stress, inflammation, endothelial dysfunction, adipokine dysregulation and upregulation of the renin-angiotensin aldosterone system (RAAS), and the sympathetic nervous system.[18–21]

Many studies have previously shown that weight loss, even when modest, may have a significant impact of BP reduction.[6,22–26] These findings are consistent regardless of whether weight reduction was diet driven,[27,28] or induced by metabolic surgeries.[29–31] Nevertheless, while the relationship between weight loss and BP reduction among hypertensive patients is well established, data from dedicated studies, regarding the effect of weight loss on BP in normotensive individuals, are limited and somewhat conflicting[22,32–35]

In this study, we aim to explore the association between non-interventional weight alterations and BP changes in a large cohort of normotensive patients.

2 | METHODS

2.1 | Study population

The Chaim Sheba Medical Center Institute for Medical Screening performs approximately 10 000 annual examinations. The data source for this study is a computerized database established in 2000, to which all data are recorded. All participants are asymptomatic men and women examined annually at the Chaim Sheba Medical Center Institute for Medical Screening. All participants were outpatients referred by their insurance company and/or their employer between 2000 and 2018. The annual examination includes filling a standard questionnaire regarding demographic characteristics, a complete medical history, lifestyle and health-related habits, and any unusual medical events which occurred since the previous encounter. The height and weight of all participants, wearing light clothing without shoes, were measured and recorded at each visit. Patients underwent a thorough physical examination. Blood pressure and heart rate were measured by a trained nurse with an appropriate arm cuff and an automated sphygmomanometer ("Welch-Allyn" Vital Signs Monitor—Tiger-Medical, Irvington, NJ, USA). Blood pressure was measured twice, 1 min apart, in the seated position, after 3 min of rest. The average of the 2 measurements was recorded. The cuff was adjusted for arm size, and all BP measurements were obtained as a single measurement. The body mass index (BMI) was calculated as weight in Kg divided by the squared height in meters. Patients did not receive any special instructions or given any suggestions for particular weight reduction regimens, beyond general lifestyle recommendation, such as smoking cessation and physical activity, and therefore, all weight changes were patient-driven and not driven by an intervention program.

The study was approved by the Chaim Sheba Medical Center ethical Helsinki board. Data were recorded anonymously. No individual consent was obtained.

2.2 | Inclusion and exclusion criteria

The complete database included 14 059 individuals with 2 consecutive annual clinic visits, which included measurements of BP, height, and weight. HTN diagnosis was made based on prior diagnosis or use of anti-hypertensive medications, including beta-blockers, alpha-blockers, and sodium-glucose co-transporter 2 (SGLT-2) inhibitors that are prescribed for other indications. Individuals were excluded if they were younger than 20 or no available age data ($n = 19$), if they had a diagnosis of HTN on visit 1 ($n = 5100$) or taking anti-hypertensive medications ($n = 213$), and if they had extreme BMI values (less than 15 kg/m^2 or more than 50 kg/m^2) ($n = 1$) or extreme systolic BP (SBP) values (less than 80 mmHg or more than 180 mmHg) ($n = 12$). Thus, the final study cohort comprised 8723 normotensive participants (Figure 1).

2.3 | Definitions and outcome measures

Elevated BP was defined as SBP > 120 mm/Hg and/or DBP > 80 mm/Hg. The primary outcome was the change in SBP between the first and second visit (visit 1 and visit 2, respectively).

Patients were divided according to the percent change in BMI between the visit 1 and visit 2: BMI reduction of more than 5% ("large reduction"), BMI reduction between 2.5% and 5% ("moderate reduction"), BMI reduction of <2.5% or elevation of <2.5% ("unchanged"), BMI elevation between 2.5% and 5% ("moderate increase"), and BMI elevation of more than 5% ("large increase").

Self-reported smoking status and physical activity level of participants were also obtained. Co-morbidities, including IHD, CKD, and DM, were recorded based on the electronic medical record system reports.

2.4 | Statistical analysis

Trends in characteristics for categorical variables were assessed using chi-square test. Linear regression or Kendall rank correlation coefficient was conducted as appropriate for normal/non-normal distributed continuous variables. A linear regression model was calculated to assess the relationship between baseline characteristics and SBP visit 2.

Logistic regression, presented as a forest plot, was calculated to assess the relationship between baseline characteristics and the outcome of visit 2 SBP increase of at least 10 mmHg (the 75th percentile of the absolute change in SBP). Subset analysis was performed for the subsets of gender, baseline SBP and baseline BMI and the year 2009, as it represents the median year of the cohort.
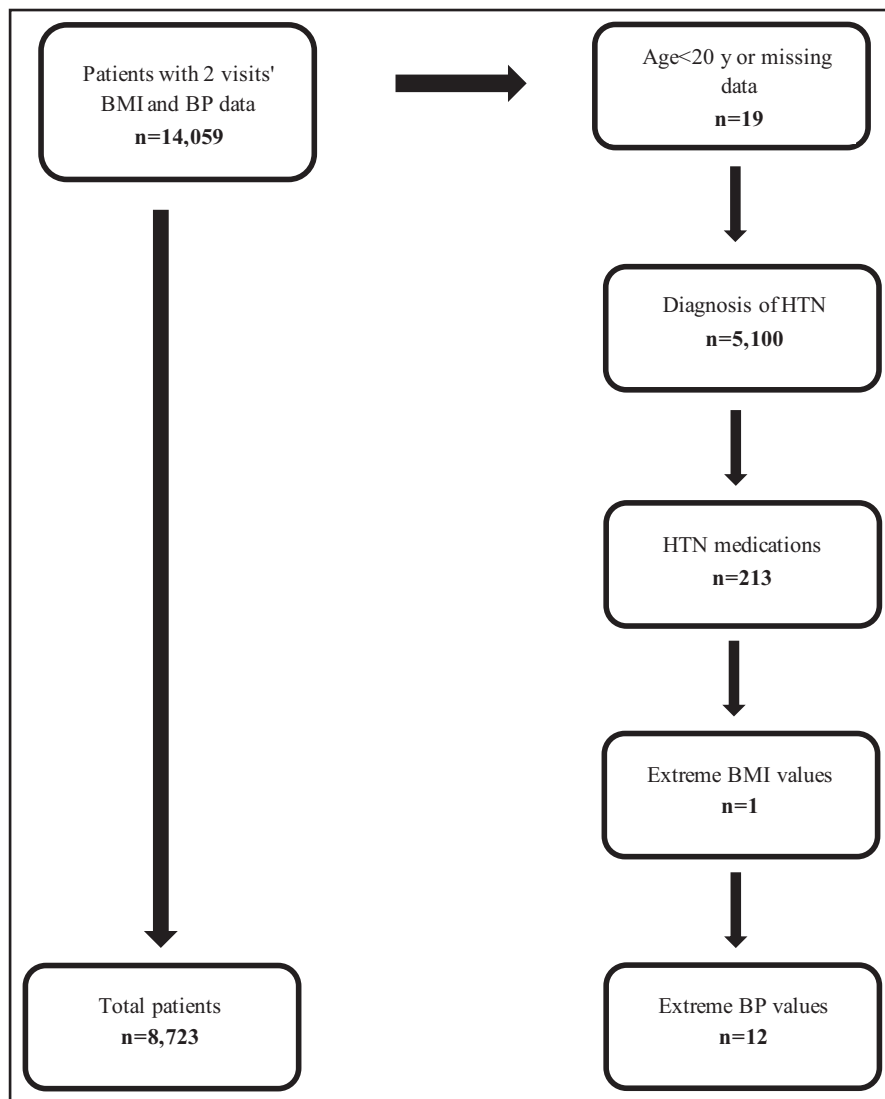
FIGURE 1 14 059 individuals with at least 2 consecutive clinic visits were screened. Individuals were excluded if they were younger than 20 or no available age data ($n = 19$), if they had a diagnosis of HTN in any visit ($n = 5100$) or taking anti-hypertensive medications ($n = 213$), and if they had extreme BMI values (<15 kg/m^2 or more than 50 kg/m^2) ($n = 1$) or extreme SBP values (less than 80 mmHg or more than 180 mmHg) ($n = 12$). The final study cohort comprised 8723 participants. *Abbreviations: BP, blood pressure; BMI, body mass index; HTN, hypertension

TABLE 1 Baseline characteristics

	Overall	Large reduction	Moderate reduction	Unchanged	Moderate increase	Large increase	p for trend
n	8723	773	909	4904	1261	876	
Age, mean (SD)	48 (9.9)	48 (10.2)	48 (10.1)	49 (9.9)	48 (9.6)	46 (9.8)	.001
Gender, male (%)	5815 (66.7)	486 (62.9)	595 (65.5)	3412 (69.6)	830 (65.8)	492 (56.2)	.005
BMI, mean (kg/m^2)	25.2 (3.5)	27.3 (4.3)	25.7 (3.4)	25.1 (3.3)	24.8 (3.30)	24.5 (3.63)	<.001
BMI categories (%)							
<25 kg/m^2	4362 (50)	235 (30.4)	395 (43.5)	2493 (50.8)	719 (57)	520 (59.4)	<.001
25–29 kg/m^2	3559 (40.8)	370 (47.9)	411 (45.2)	2025 (41.3)	461 (36.6)	292 (33.3)	<.001
30–34 kg/m^2	702 (8)	131 (16.9)	92 (10.1)	354 (7.2)	68 (5.4)	57 (6.5)	<.001
≥35 kg/m^2	100 (1.1)	37 (4.8)	11 (1.2)	32 (0.7)	13 (1)	7 (0.8)	<.001
Current smoker (%)	1388 (15.9)	128 (16.6)	137 (15.1)	717 (14.6)	214 (17)	192 (21.9)	.001
DM (%)	167 (1.9)	18 (2.3)	21 (2.3)	91 (1.9)	22 (1.8)	15 (1.7)	.216
IHD (%)	136 (1.6)	13 (1.7)	14 (1.5)	80 (1.6)	19 (1.5)	10 (1.1)	.396
CKD (%)	37 (0.4)	4 (0.5)	4 (0.4)	21 (0.4)	3 (0.2)	5 (0.6)	.818

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; DM, diabetes mellitus; IHD, ischemic heart disease.

All analyses were performed using R software (R Development Core Team, version 4.0.0, Vienna, Austria). A 2-sided p-value < .05 was used for statistical significance.

3 | RESULTS

Our final analysis included 8723 patients, of whom 66.7% were male (Table 1). Baseline demographic and clinical characteristics according to the pre-specified groups of BMI change are presented in Table 1. Half of our cohort had normal weight, with a BMI of <25 kg/m^2, and 90.8% had a BMI of <30 kg/m^2 (Table 1). Overall, for the entire cohort, there was no significant change in mean BMI between visits (Table 2). However, 20% of the patients reduced their BMI by at least 2.5% and 24.5% increased their BMI by more than 2.5% (Table 2).

Patients in the "large reduction" and "moderate reduction" groups were slightly overweight and had higher initial SBP (Table 2), while in the other groups mean BMI was normal (Table 2). Patients in the "large increase" group were younger and less likely to be female, compared with other BMI change groups (Table 2).

Mean baseline BP for all patients was 117.6/75 mmHg (Table 2). Compared with visit 1, patients in the pre-specified "high reduction" group had an absolute mean SBP decrease of 3.6 mmHg on visit 2, with a mean percent decrease of 2.3% (Table 2) (Figure 2). Compared

with visit 1, patients in the "large increase" group had an absolute mean SBP increase of 1.9 mmHg on visit 2, with a mean percent increase of 2.4% (Table 2) (Figure 2). We observed similar findings regarding DBP changes (Table 2) (Figure S1).

The proportion of patients with at least 10 mmHg decrease in SBP progressively declined according to the relative change in BMI (38.7%, 33%, 29.1%, 27.2%, 24.5% for "large reduction," "moderate reduction," "unchanged," "moderate increase," and "large increase," respectively, p <.01) (Figure 3). The proportion of patients with at least 10 mmHg increase in SBP progressively increased according to the relative change in BMI (21.2%, 24.2%, 28.7%, 33%, 34% for "large reduction," "moderate reduction," "unchanged," "moderate increase," and "large increase," respectively, p <.01) (Figure 3). A similar association pattern was observed regardless of baseline BMI (patients with BMI < 25 kg/m^2 vs. those with BMI ≥ 25 kg/m^2) (Figure S2A,B) and baseline SBP (patients with SBP < 120 mmHg vs. those with SBP ≥ 120 mmHg) (Figure S3A,B). Notably, in patients with baseline SBP higher than 120 mmHg, the weight loss effect was more pronounced. Compared with those with baseline SBP of less than 120 mmHg, a larger proportion of patients decreased their SBP by more than 10 mmHg, and a lower proportion increased their SBP by more than 10 mmHg, (Table 2).

A multiple linear regression was calculated to predict SBP in visit 2 based on SBP in visit 1, age, BMI at visit 1, BMI percent change

TABLE 2 Blood pressure and body mass index

	Overall	Large reduction	Moderate reduction	Unchanged	Moderate increase	Large increase	P for trend
n	8723	773	909	4904	1261	876	
SBP, visit 1, mean (mmHg) (SD)	117.6 (13.2)	119.8 (13.9)	117.9 (13.1)	117.8 (13.1)	116.4 (12.7)	115.9 (13.3)	<.001
SBP, visit 2, mean (mmHg) (SD)	117.4 (13.1)	116.2 (12.7)	116.5 (12.9)	117.7 (13)	117.6 (13.1)	117.8 (13.9)	.003
Absolute SBP change, mean (mmHg) (SD)	−0.2 (13.3)	−3.6 (13.8)	−1.4 (13.2)	−0.1 (13.2)	1.2 (12.9)	1.9 (13.8)	<.001
Percent SBP change, mean (mmHg) (SD)	0.5 (11.3)	−2.3 (11.2)	−0.5 (11.4)	0.5 (11.2)	1.6 (11.2)	2.4 (12)	<.001
DBP, visit 1, mean (mmHg) (SD)	75 (8.9)	76.4 (9.1)	75.3 (8.8)	75 (8.9)	74.6 (8.8)	73.8 (9)	<.001
DBP, visit 2, mean (mmHg) (SD)	74.5 (9.2)	73.5 (8.9)	73.8 (8.8)	74.5 (9.1)	74.9 (9.2)	74.8 (9.9)	<.001
Absolute DBP change, mean (mmHg) (SD)	−0.5 (9.9)	−2.9 (10.1)	−1.4 (10.2)	−0.5 (9.7)	0.4 (9.8)	1.1 (10.3)	<.001
Percent DBP change, mean (mmHg) (SD)	0.2 (13.7)	−2.9 (13.8)	−0.9 (14.3)	0.2 (13.3)	1.3 (13.7)	2.3 (14.7)	<.001
BMI, visit 1, mean (kg/m^2) (SD)	25.2 (3.5)	27.3 (4.3)	25.7 (3.4)	25.1 (3.3)	24.8 (3.30)	24.5 (3.63)	<.001
BMI, visit 2, mean (kg/m^2) (SD)	25.3 (3.4)	24.9 (3.5)	24.8 (3.3)	25.1 (3.3)	25.7 (3.4)	26.4 (3.9)	<.001
absolute BMI change, mean (kg/m^2) (SD)	0 (1.2)	−2.4 (1.7)	−0.9 (0.2)	0 (0.3)	0.9 (0.2)	1.9 (0.9)	<.001
Percent BMI change, mean (kg/m^2) (SD)	0.2 (4.5)	−8.5 (4)	−3.6 (0.7)	0.1 (1.2)	3.6 (0.7)	8.1 (4.1)	<.001

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.
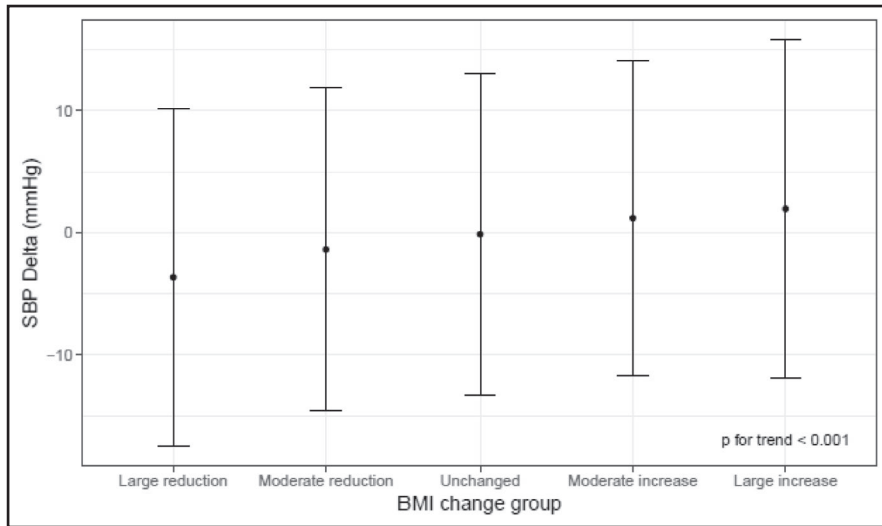
FIGURE 2 Systolic blood pressure changes between visits, according to the pre-specified BMI change group. Black dots represent mean SBP changes. Bars represent SD. *Abbreviations: SBP, systolic blood pressure; BMI, body mass index
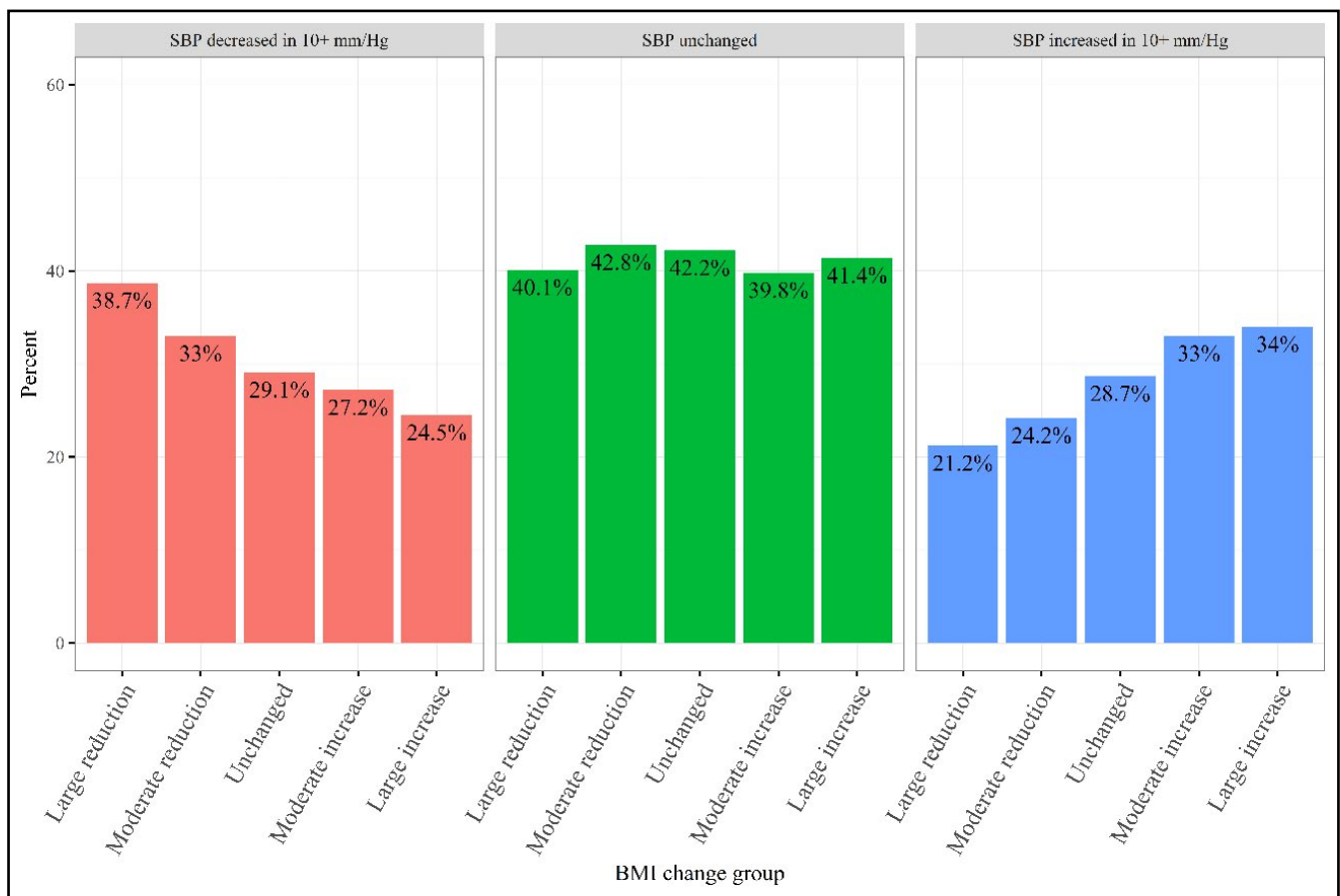

FIGURE 3 Systolic blood pressure changes according to the pre-specified BMI change. Bars from left to right represent percent of patients with at least 10 mmHg decrease in SBP from visit 1 to visit 2, of those whose SBP was unchanged (ie, a −10 to 10 mmHg change from visit 1 to visit 2), and of those with at least 10 mmHg increase in SBP from visit 1 to visit 2. *Abbreviations: BMI, body mass index; SBP, systolic blood pressure

and year of admission (2009 + vs. <2009), with logarithmic transformation on SBP (Table 3). A significant regression equation was found [$F_{(58717)} = 736$, $p < .001$], with an adjusted R squared of 0.3. Patients' predicted SBP in visit 2, is equal to: 2.67 + 0.39(log(SBP visit 1)) + 0.03(BMI % change) + 0.01(AGE) + 0.03(BMI visit 1) −0.01(year 2009+) where SBP is measured in mmHg (with logarithmic transformation), age is measured in years- per 5 years, BMI is measured as kg/m^2 per 5 units, and years are coded as "2009+"=1, "<2009"=0. Patients' log(SBP) in visit 2 increased 0.39% for each 1% increase in SBP in visit 1, 3.05% for each 10% increase in BMI percent change,

	B (95% CI)	p
log(SBP), visit 1	0.39 (0.37–0.41)	<.001
BMI percent change (per 10%)	0.03 (0.02–0.03)	<.001
Age at visit 1 (per 5 years)	0.01 (0.01–0.01)	<.001
BMI at visit 1 (per 5 units)	0.03 (0.03–0.03)	<.001

Note: Model was adjusted to visit 1 systolic blood pressure, body mass index change (absolute and percent change), visit 1 age and the year 2009.

Abbreviations: BMI, body mass index; SBP, systolic blood pressure.

1.01% for each 5 years in age, 3.05% for each 5 kg/m^2 BMI at visit 1, and patients who admitted later than 2009 had a lower SBP (–1%) than those examined before 2009 (Table 3).

Among patients who were defined as overweight on visit 1 (BMI ≥ 25 kg/m^2), we found that compared with the reference group ("large reduction") the OR for an at least 10 mmHg increase in SBP was 0.96 (0.7–1.3, p =.79), 1.43 (1.1–1.8, p =.005), 1.62 (1.2–2.2, p =.002), 2.24 (1.6–3.1, p <.001), for "moderate reduction," "unchanged," "moderate increase," and "large increase," respectively (Figure 4A). Male gender was found to be significantly associated with a 45% increased risk for an at least 10 mmHg in SBP elevation (OR 1.45, 1.2–1.8, p <.001) (Figure 4A). In addition, older age inferred a 24% increased risk for SBP elevation for every 5-year age increase (OR 1.24, 1.2–1.3, p <.001) (Figure 4A). A similar yet somewhat attenuated association pattern was also observed among patients who were defined as normal weight at visit 1 (BMI < 25 kg/m^2). We found that compared with the reference group ("large reduction") the OR for an at least 10 mmHg increase in SBP was 1.28 (0.9–1.9, p =.25), 1.4 (1.0–2.0, p =.06), 1.8 (1.2–2.6, p =.003), 1.7 (1.1–2.5, p =.01) for "moderate reduction," "unchanged," "moderate increase," and "large increase," respectively) (Figure 4B). In normal-weight patients, male gender inferred a 100% increased risk for a 10 mmHg or more elevation in SBP (OR 2.0, 1.8–2.4, p <.001) (Figure 4B).

4 | DISCUSSION

We present data supporting a significant association between non-interventional weight changes and alterations in SBP among annually examined normotensive individuals. SBP decline was more pronounced in those who lost at least 5% of their BMI, and SBP increase was more prevalent in those who gained weight, even if only modest. Patients who lost the most weight had higher baseline BMI and SBP compared with those whose weight did not change or increased. Our findings were consistent regardless of baseline BMI and SBP, albeit the weight loss effect was much more evident in those with higher baseline SBP values. Additionally, male gender and older age infer a higher risk for increase in SBP, both in normal-weight and overweight individuals.

The positive relationship between overweight, obesity, and elevated BP has been long reported, dating back to the early 1920s.[13]

These early findings were later extensively supported by numerous epidemiological studies.[11,12,14–16] There are robust data to support the beneficial role of weight loss on BP reduction among hypertensive patients.[1,22–27,29–31,36–38] Notably, in contrast to previous studies, any weight loss in our cohort was patient-driven and non-interventional.

A 5% weight loss from baseline is generally accepted as clinically meaningful,[39] as reflected by professional society guidelines recommendations.[40] Specifically, SBP reduction begins with a 2%–5% weight loss, while improvement in DBP begins with 5%–10% weight reduction.[41] In our study, we found that a reduction of at least 5% in BMI was associated with the most significant decrease in SBP. While we found a relatively small 3.6 mmHg decline in SBP, one cannot overestimate the significance of BP reduction, even if only modest. It has been shown that a reduction of 12 mmHg in SBP will reduce incident mortality by 9%–11%,[42] and a reduction of 5.5 mmHg in SBP results in an estimated 15% decline in coronary heart disease and a 27% reduction in stroke.[43] Our study population is unique as it consists of true normotensive patients, even by new and more stringent professional society guidelines.[44] Thus, any attempts to significantly reduce SBP are expected to be somewhat limited and attenuated. Indeed, we have found that the effect of weight changes on alterations in SBP was much more pronounced among those with higher baseline SBP. There are limited and conflicting clinical data regarding the effects of weight loss on BP in normotensive patients, as most studies were conducted among hypertensive patients. Several studies have also included patients who were previously defined as non-hypertensive.[33–35] In a meta-analysis comparing subgroups on the basis of initial BP levels, there was no difference in SBP response between hypertensive and normotensive patients (defined as less than 140/90 mmHg).[22] In another meta-analysis including patients with a mean BP of 129/79 mmHg, a 0.4 units reduction in BMI was associated with 3.8 mmHg in SBP.[45] Contrarily, in a multicenter randomized controlled trial including patients with SBP of less than 140 mmHg and an elevated DBP, no significant difference in SBP visit-to-visit variability was found.[32] Additionally, in a small study of twelve normotensive patients (mean 24-h BP of 119/65 mmHg), there was no change in 24-h BP 6 weeks after bariatric surgery.[34] Of note, according to recent American society guidelines, most of the patients enrolled in these aforementioned studies would currently not be defined as true normotensive.[44] Multiple pathophysiological mechanisms underlie the relationship between overweight, obesity, and the development of HTN.[18–20] Of particular, significance is the combination of enhanced sympathetic nervous system activity and upregulation of the RAAS, which causes impaired natriuresis, increased renal sodium reabsorption, and extracellular volume expansion,[46] both in hypertensive as well as in normotensive obese individuals.[47] Weight loss corresponds to a decline in the activity of both RAAS and sympathetic nervous system, consequently resulting in BP reduction.[48,49] These findings may partially account for the modest improvement in SBP observed in our study, even among true normotensive patients,

(A) Multivariable model for 10mmHg increase in SBP: Overweight patients

	OR (95% CI)
SBP at visit 1 (per 10mmHg)	0.39 (0.36,0.42)
Moderate reduction (vs. Large reduction)	0.94 (0.68,1.29)
Unchanged (vs. Large reduction)	1.4 (1.1,1.8)
Moderate increase (vs. Large reduction)	1.58 (1.17,2.14)
Large increase (vs. Large reduction)	2.22 (1.6,3.09)
Age at visit 1 (per 5 years)	1.23 (1.18,1.28)
Male	1.45 (1.21,1.75)
DM at visit 1	1.74 (1.12,2.68)
IHD at visit 1	1.32 (0.79,2.16)
CKD at visit 1	0.83 (0.27,2.24)

(B) Multivariable model for 10mmHg increase in SBP: Normal-weight patients

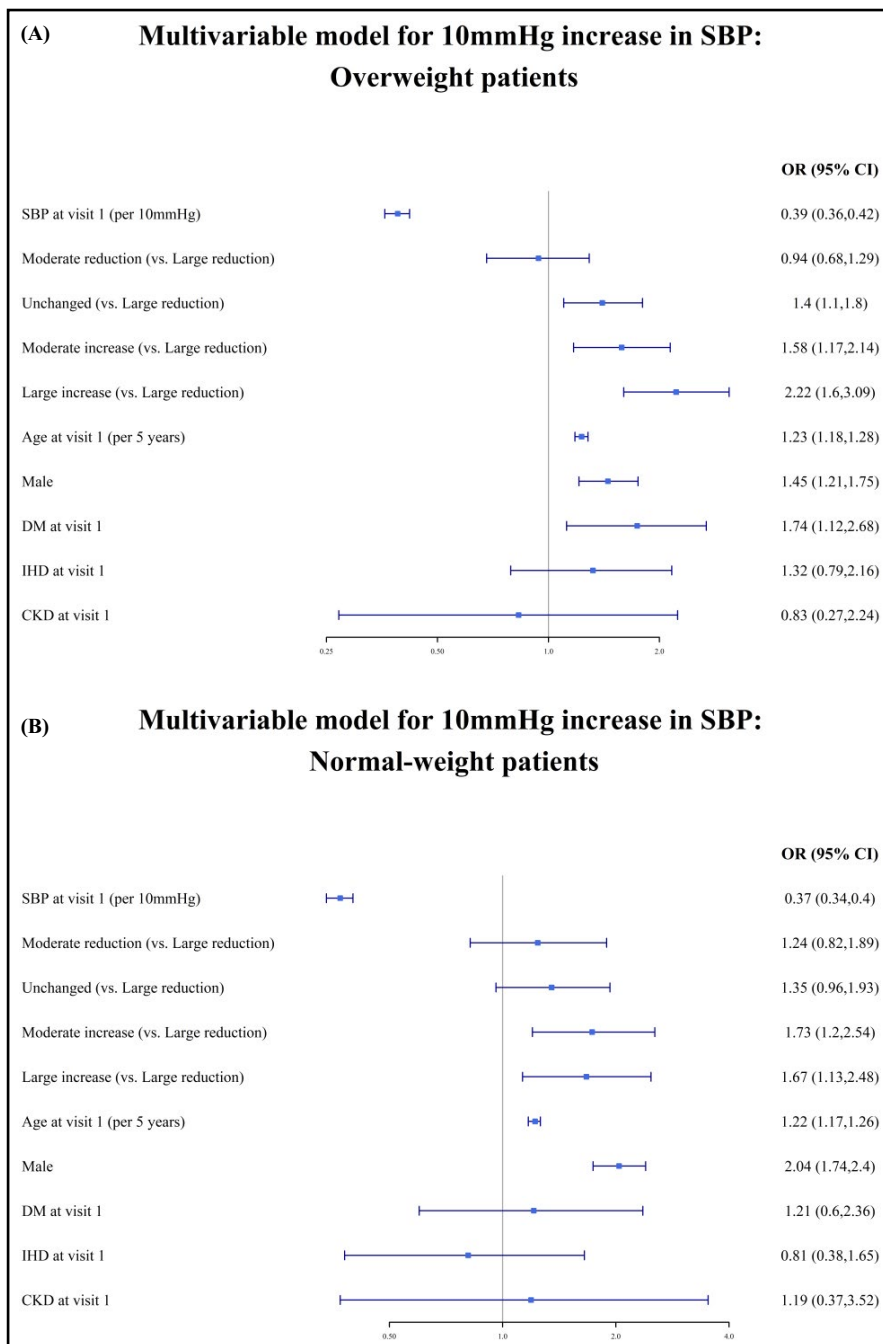|	OR (95% CI)
SBP at visit 1 (per 10mmHg)	0.37 (0.34,0.4)
Moderate reduction (vs. Large reduction)	1.24 (0.82,1.89)
Unchanged (vs. Large reduction)	1.35 (0.96,1.93)
Moderate increase (vs. Large reduction)	1.73 (1.2,2.54)
Large increase (vs. Large reduction)	1.67 (1.13,2.48)
Age at visit 1 (per 5 years)	1.22 (1.17,1.26)
Male	2.04 (1.74,2.4)
DM at visit 1	1.21 (0.6,2.36)
IHD at visit 1	0.81 (0.38,1.65)
CKD at visit 1	1.19 (0.37,3.52)

FIGURE 4 Logistic regression, presented as a forest plot, to assess the relationship between baseline characteristics and increase of at least 10 mmHg in SBP on visit 2, in overweight (A) and normal-weight (B) individuals. * Abbreviations: SBP, systolic blood pressure

and for the enhanced SBP lowering affect observed in those with higher SBP values.

Our study has several limitations. First, this is a retrospective analysis with all of its inherent biases. Second, we do not have information regarding the weight loss methods employed for each BMI change group nor do we have data regarding medication use in the interim between clinic visits. However, we aimed to mitigate the potential bias by excluding patients who initiated any medications that affect blood pressure or that influence weight. Finally, while we have information regarding BMI values, we do not have data regarding waist or hip circumference.

In conclusion, our data show that modest non-interventional weight changes may have significant effects on SBP, even among true normotensive and slightly overweight individuals. These findings are of paramount importance as normotensive patients constitute a large component of the adult population.[50] This demographic allows for very large-scale weight loss intervention programs, with possible considerable implications on public health.

CONFLICT OF INTEREST

All authors of the manuscript "Non-interventional weight changes affect systolic blood pressure in normotensive individuals" have taken care to ensure the integrity of their work and their scientific reputation. There are no financial or other relationships that might lead to a conflict of interest.

AUTHOR CONTRIBUTION

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by GS, TO, RK, and EG. The first draft of the manuscript was written by GS and AL; and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.