

# Change in Cardiometabolic Risk Factors Associated With Magnitude of Weight Regain 3 Years After a 1-Year Intensive Lifestyle Intervention in Type 2 Diabetes Mellitus: The Look AHEAD Trial

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**Background**—Weight regain after weight loss is common. The impact on cardiometabolic risk factors is not well established.

**Methods and Results**—Publicly available data were analyzed from participants of the Look AHEAD (Action for Health in Diabetes) trial with  $\geq 3\%$  initial weight loss ( $n=1561$ ) during a 1-year intensive lifestyle intervention and with year 4 follow-up data. Participants who regained (regainers) or maintained (maintainers) weight loss were defined with 5 dichotomized cut points (0%, 25%, 50%, 75%, and 100%) of percentage weight loss regained (weight change from years 1–4 as percentage of first year weight loss). Change in cardiometabolic risk factors after initial weight loss was compared in maintainers and regainers, after controlling for demographics, medications, and baseline and year 1 change in body mass index. The effect was assessed separately in participants with  $<10\%$  and  $\geq 10\%$  initial weight loss, and women and men. Maintainers exhibited significant improvements to the cardiometabolic risk factors assessed compared with regainers. No weight regain cut point maximized risk difference between maintainers and regainers across risk factors or sex/initial weight loss subgroups. For many risk factors, allowing more regain as part of maintenance (increasing cut point) diminished the cardiometabolic benefit among maintainers.

**Conclusions**—Maintaining weight loss was better than regain for all risk factors. No single cut point maximized the risk difference between maintainers and regainers. Maintainers who kept off  $\geq 75\%$  of weight lost had the greatest benefit. These findings emphasize the importance of intervention programs focusing not only on weight loss but weight loss maintenance, given the adverse consequences of the latter.

**Clinical Trial Registration**—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00017953. (*J Am Heart Assoc.* 2019;8:e010951. DOI: 10.1161/JAHA.118.010951.)

**Key Words:** cardiovascular disease risk factors • diabetes mellitus • lifestyle intervention • Look AHEAD (Action for Health in Diabetes) trial • obesity • weight loss • weight regain

Excess body weight is a major modifiable cause of morbidity and mortality.<sup>1</sup> Behavioral lifestyle weight loss interventions are an effective noninvasive strategy to achieve weight loss and improve cardiometabolic risk factors.<sup>2–5</sup> Although lifestyle interventions can produce substantial

weight loss and short-term health benefits,<sup>3,6</sup> their rate of recidivism is high.<sup>7,8</sup> Maintaining weight loss is beneficial for lowering the incidence of type 2 diabetes mellitus<sup>3</sup> and sustaining favorable cardiometabolic risk factors,<sup>5,9</sup> and weight regain is associated with deterioration of cardiometabolic benefits associated with weight loss.<sup>9,10</sup>

Few studies directly compare individuals with successful weight loss maintenance (maintainers) and individuals who regained weight (regainers). A challenge in comparing successful weight loss maintainers with regainers is the lack of a standard definition of successful weight loss maintenance.<sup>11,12</sup> One factor contributing to the wide range of methods used to define successful weight loss is that several approaches have been used to define successful weight loss maintenance over time.<sup>13</sup> In addition, several cut points have been used across studies to differentiate maintainers and regainers. We recently compared 3 different calculations and 8 cut points that have been used to differentiate maintainers and regainers.<sup>13</sup> Cut points derived from the different

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## Clinical Perspective

### What Is New?

- Few studies directly compare cardiometabolic risk between individuals with successful weight loss maintenance and individuals who regained weight.
- The findings from this study indicate that, generally, 3 years after weight loss, people who regain their weight lost had a deterioration of cardiometabolic risk factors, whereas individuals with successful weight loss maintenance have stabilization or further improvement.

### What Are the Clinical Implications?

- The relationship between cardiometabolic risk factors and weight regain varied by sex and risk factor: Men and women responded similarly to weight regain on the basis of fasting glucose and hemoglobin A1c concentrations, but differently on the basis of plasma lipid concentrations and blood pressure.
- No single cut point of percentage weight loss regained was identified to maximize risk difference between individuals with successful weight loss maintenance and individuals who regained weight, but maintaining 75% of weight loss was generally beneficial.
- The findings from this study emphasize the need to further investigate long-term impact of partial weight regain after a weight loss intervention given the challenge of keeping off all of weight lost.

percentages overlapped according to agreement statistics. Herein, we examined cut points derived from the percentage of weight loss that is regained. Limited evidence is available comparing different cut points to define weight regain at different magnitudes with respect to clinical end points.<sup>12,13</sup> Therefore, using data from the Look AHEAD (Action for Health in Diabetes) trial, the objectives of this study were to examine the difference between maintainers and regainers in cardiometabolic risk factor change from years 1 to 4 after the intensive lifestyle intervention on the basis of 5 different cut points for percentage weight loss maintained/regained and to identify a cut point differentiating maintainers and regainers that maximizes the risk difference between the 2 groups.

## Methods

### Population

A detailed description of the design and procedures from the Look AHEAD trial has been described elsewhere.<sup>14</sup> Briefly, the Look AHEAD trial was a 16-site multicenter, randomized, parallel, controlled clinical trial designed to assess the association between an intensive lifestyle intervention to promote

weight loss compared with standard care on cardiovascular disease risk in individuals with a body mass index >25 kg/m<sup>2</sup> (or >27 kg/m<sup>2</sup> if taking insulin) and a type 2 diabetes mellitus diagnosis. The 1-year intensive lifestyle intervention targeted ≈7% weight loss. Included were group support sessions, calorie and fat gram restrictions, and recommendations to use meal replacements and increase physical activity. The intervention was then altered to target weight maintenance. The 3-year maintenance phase included monthly group meetings and recommendations to use a single meal replacement per day and continue engaging in regular physical activity.

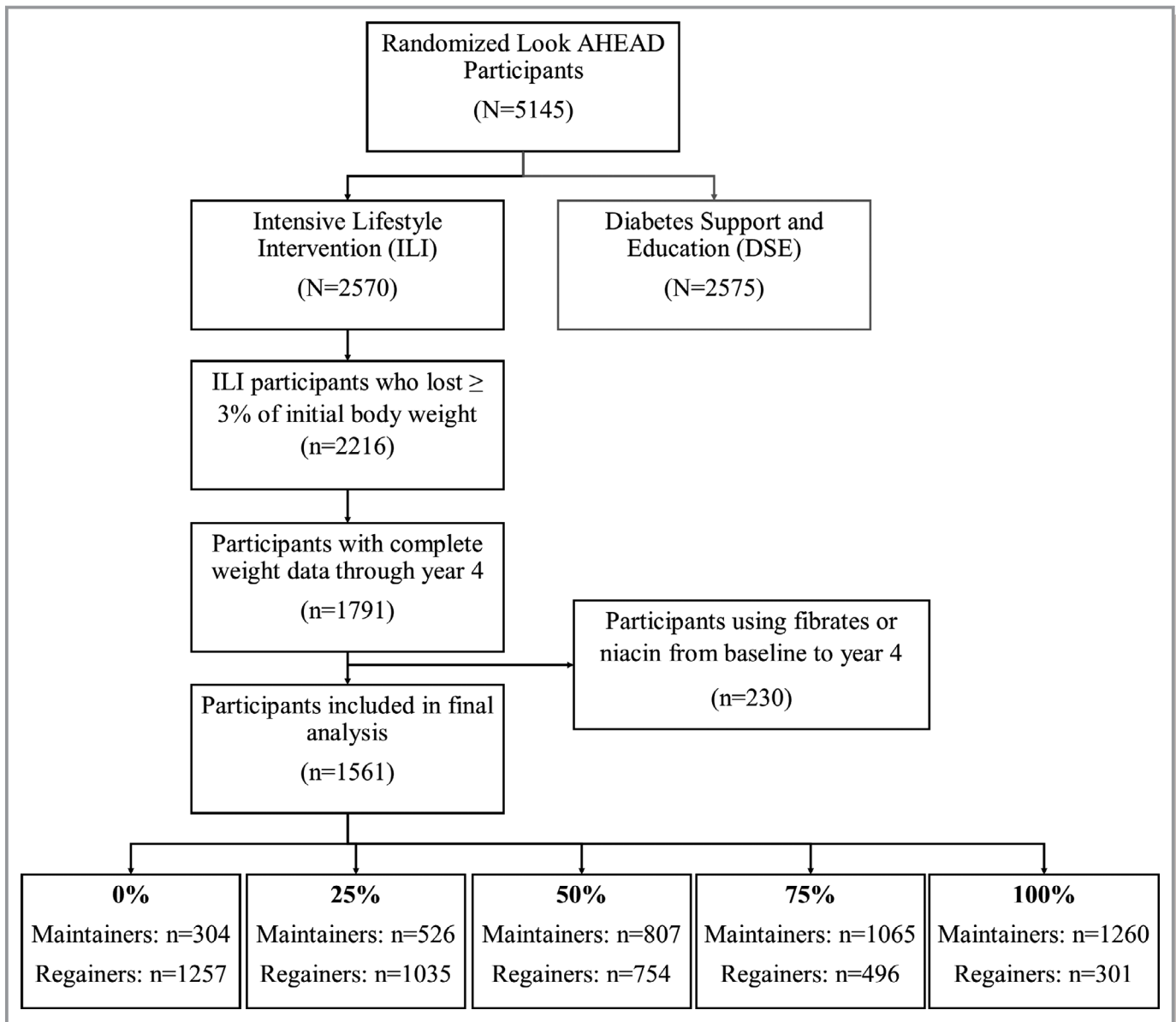
Analyses were conducted in the subset of participants from the publicly available data of the Look AHEAD trial who were assigned to the intensive lifestyle intervention group, lost ≥3% of initial body weight, and had follow-up data through the end of year 4 (n=1791). Anonymized data and materials have been made publicly available at the National Institute of Diabetes and Digestive Kidney Diseases Central Repository.<sup>15</sup> Individuals taking niacin or fibrates at any point from baseline to year 4 were excluded (n=230), leaving 1561 included participants (Figure 1).

### Cut Points to Define Maintainers and Regainers

The cut points for weight regain were calculated using body weight measurements from baseline, year 1, and year 4. Body weight was measured with a digital scale (model BWB-800; Tanita, Willowbrook, IL) by certified staff members. Weight change after the initial intensive lifestyle intervention (year 4 weight–year 1 weight) as a percentage of initial weight loss (initial weight–year 1 weight) was used to calculate percentage of weight loss regained.<sup>7,16–20</sup> From this calculation, maintainers versus regainers were defined using 5 different cut points, with weight regain increments increasing by 25%, from 0% regain to 100% regain. Zero percent is indicative of ≤0% regain as successful weight loss maintenance (maintainers), and any regain (>0%) is not successful maintenance (regainers). The same categorization applies for 25%, 50%, 75%, and 100%. All 1561 participants were included in each of the 5 models defining maintainers versus regainers with different regain cut points. Because of the small number of individuals who successfully maintained their weight loss or continued to lose weight, these individuals were analyzed together. Sample sizes of maintainers and regainers within each sex and initial weight loss subgroup can be found in Table 1.

### Statistical Analysis

Generalized linear models were used to assess the adjusted mean difference between maintainers and regainers in change after the initial intensive lifestyle intervention from years 1 to 4 in high-density lipoprotein (HDL) cholesterol, triglyceride,



**Figure 1.** Flow chart of included Look AHEAD (Action for Health in Diabetes) trial participants (n=1561) and participant breakdown by each categorization criterion. Maintainers indicates individuals with successful weight loss maintenance; regainers, individuals who regained weight.

fasting glucose, and percentage hemoglobin A1c (HbA1c) concentrations, systolic blood pressure, diastolic blood pressure, and waist circumference. The models also generated adjusted change from years 1 to 4 in maintainers and regainers separately. Models were run separately, defining maintainers versus regainers with 0%, 25%, 50%, 75%, and 100% weight loss regained. The relationships were examined separately for individuals with <10% and ≥10% weight loss in the first year and in men and women, on the basis of previous publications<sup>13,21</sup> and statistically significant interactions (data not shown). The adjusted model controlled for age, hormone replacement therapy (among women), race (white/black/other), baseline body mass index, percentage initial weight

loss in first year, baseline value of each outcome, change in first year of each outcome, use of thiazolidinediones, and outcome-specific medication use (lipid and for lipid outcomes, antihypertensive medication use for blood pressure, and diabetes mellitus medication use for fasting glucose, percentage HbA1c, and waist circumference). Medication use was categorized into 4 categories based on use from baseline to year 4: always on medication, never on medication, went on medication, and went off medication. Analyses were conducted using SAS, version 9.4 (SAS Institute Inc, Cary, NC).

This project has received Institutional Review Board exemption from the Tufts University Health Sciences Institutional Review Board.

**Table 1.** Sample Size in Each Maintainer and Regainer Group, According to Each Weight Regain Categorization Criterion

Weight Regain Criterion, %	<10% Initial Weight Loss (n=797)				≥10% Initial Weight Loss (n=764)			
	Men (n=296)		Women (n=501)		Men (n=325)		Women (n=439)	
	Maintainer	Regainer	Maintainer	Regainer	Maintainer	Regainer	Maintainer	Regainer
0	82 (28)	214 (72)	125 (25)	376 (75)	34 (10)	291 (90)	63 (14)	376 (86)
25	117 (40)	179 (60)	169 (34)	332 (64)	102 (31)	223 (69)	138 (31)	301 (69)
50	138 (47)	158 (53)	230 (46)	271 (54)	195 (60)	130 (40)	244 (56)	195 (44)
75	179 (60)	117 (40)	291 (58)	210 (42)	264 (81)	61 (19)	331 (75)	108 (25)
100	228 (77)	68 (23)	342 (68)	159 (32)	302 (93)	23 (7)	388 (88)	51 (12)

Data are given as number (percentage) of each group. Percentages are of maintainers and regainers within sex by each categorization criterion. Each row corresponds to the entire sample (n=1561). Maintainer indicates an individual with successful weight loss maintenance; regainer, an individual who regained weight.

## Results

### Participant Characteristics

Depicted in Table 2 are participant characteristics, change in medication use from baseline to year 4, and baseline and year 1 values of cardiometabolic risk factor measures. When comparing the 2 initial weight loss subgroups (<10% and ≥10%), there were no significant differences on the basis of age, hormone replacement therapy use (among women), lipid medication use, and baseline HDL cholesterol, triglyceride, or fasting glucose concentrations for men or women (Table 1). In both men and women, participants with ≥10% initial weight loss had a significantly lower proportion of participants starting on diabetes mellitus medication (3.1% versus 7.5%) and a higher proportion stopping diabetes mellitus medication (16.7% versus 3.4%) from baseline to year 4 ( $P<0.0001$ ). In men only, losing ≥10% initial weight was associated with a significantly lower proportion starting antihypertensive medication (15.5% versus 7.4%) and a higher proportion stopping antihypertensive medication (7.1% versus 4.0%) from baseline to year 4 compared with those who lost <10% of initial weight ( $P=0.003$ ; Table 1). Among men, at baseline, those with <10% initial weight loss had significantly higher HbA1c concentrations and diastolic blood pressure than those with ≥10% initial weight loss. In contrast, there were no significant differences in baseline concentrations of cardiometabolic risk factors by initial weight loss group in women. At year 1, cardiometabolic risk factors were significantly more favorable for both sexes with ≥10% initial weight loss than <10% initial weight loss.

### Change in Cardiometabolic Risk Factors

#### Maintainers versus regainers

The adjusted mean difference between maintainers and regainers in change from years 1 to 4 in all cardiometabolic risk factors is shown in Figure 2. An inverse linear pattern between an increase in cut point of percentage of weight loss

regained and decrease in difference in cardiometabolic risk factors between maintainers and regainers was found for select risk factors and initial weight loss/sex subgroups. The linear pattern of improvement was observed in the following initial weight loss and sex subgroups: among men who lost <10% initial weight for HbA1c concentration and waist circumference (Figure 2), among women who lost <10% initial weight for systolic blood pressure, among men who lost ≥10% initial weight loss for HDL cholesterol and HbA1c concentrations and diastolic blood pressure, and among women who lost ≥10% initial weight for waist circumference and HbA1c concentration (Figure 2).

In some cardiometabolic risk factors, maintainers had significantly greater improvement in cardiometabolic risk factors than regainers across all or most cut points of percentage of weight lost regained, but not in a linear pattern. Significant improvements were observed for HDL cholesterol concentrations in women of both initial weight loss categories; triglyceride concentration among men of both initial weight loss categories and women who lost ≥10% initial weight; waist circumference and HbA1c concentration among women who lost <10% initial weight loss; waist circumference, triglyceride, fasting glucose, and HbA1c concentrations, and systolic blood pressure among men who lost ≥10% initial weight loss; and HDL, triglyceride, and fasting glucose concentrations and systolic blood pressure among women with ≥10% initial weight loss (Figure 2). There were no significant differences in fasting glucose concentration in women with <10% initial weight loss or diastolic blood pressure in men with <10% weight loss and women with ≥10% initial weight loss (Figure 2).

#### Change among maintainers

There were also significant changes among maintainers from years 1 to 4 in cardiometabolic risk factors using different cut points of percentage of weight lost regained (Figure 3). Maintainers had no significant change in cardiometabolic risk factors or significant improvement, according to the 0% and

**Table 2.** Characteristics of Participants by Initial Weight Loss and Sex

Characteristics	<10% Initial Weight Loss (n=797)		≥10% Initial Weight Loss (n=764)		P Value (Men)*	P Value (Women)†
	Men	Women	Men	Women		
No.	296	501	325	439	...	...
Age, mean±SD, y	60.3±6.8	57.9±6.6‡	60.5±6.7	58.6±7.0‡	0.7079	0.0927
Baseline BMI, mean±SD, kg/m <sup>2</sup>	35.3±6.2	35.8±6.1	35.1±5.5	36.7±6.0‡	0.7089	0.0163
Initial weight loss, median±IQR, %	6.2±3.5	6.5±3.3	14.6±7.2	13.8±5.8 <sup>  </sup>	<0.0001	<0.0001
Hormone replacement therapy, n (%)						
Yes	...	279 (55.8)	...	247 (57.2)	...	0.6727
No	...	221 (45.6)	...	185 (42.8)	...	...
Race, n (%)						
White	219 (74.0)	297 (59.3)‡	283 (87.1)	296 (67.4)‡	0.0002	<0.0001
Black	43 (14.5)	140 (27.9)	24 (7.4)	67 (15.3)	...	...
Other	34 (11.5)	64 (12.8)	18 (5.5)	76 (17.3)	...	...
Medication use						
Use of lipid medication from baseline to year 4, n (%)						
Always	137 (46.3)	206 (41.1)	167 (51.9)	167 (38.2)‡	0.1057	0.1225
Never	81 (27.4)	149 (29.7)	83 (25.8)	141 (32.3)	...	...
Went on	70 (23.7)	133 (26.6)	56 (17.4)	106 (24.3)	...	...
Went off	8 (2.7)	13 (2.6)	16 (5.0)	23 (5.3)	...	...
Use of diabetes mellitus medication from baseline to year 4, n (%)						
Always	238 (81.2)	388 (78.7)	223 (69.0)	314 (72.4)	<0.0001	<0.0001
Never	23 (7.9)	42 (8.5)	36 (11.2)	53 (12.2)	...	...
Went on	22 (7.5)	37 (7.5)	10 (3.1)	15 (3.5)	...	...
Went off	10 (3.4)	26 (5.3)	54 (16.7)	52 (12.0)	...	...
Use of antihypertensive medication from baseline to year 4, n (%)						
Always	197 (66.6)	354 (70.7)	216 (66.7)	303 (69.0)	0.0030	0.4462
Never	41 (13.9)	79 (15.8)	61 (18.8)	68 (15.5)	...	...
Went on	46 (15.5)	55 (11.0)	24 (7.4)	48 (10.9)	...	...
Went off	12 (4.0)	13 (2.6)	23 (7.1)	20 (4.6)	...	...
Cardiometabolic risk factors						
HDL cholesterol, mmol/L						
Baseline	1.02±0.25	1.24±0.32‡	1.02±0.23	1.24±0.32‡	0.8154	0.9238
Year 1	1.07±0.25	1.31±0.33‡	1.18±0.28	1.37±0.34‡	<0.0001	0.0160
Triglycerides, mmol/L						
Baseline	1.71±1.22	1.62±1.15	1.68±1.10	1.69±1.24	0.5564	0.4304
Year 1	1.46±1.01	1.56±1.02	1.08±0.65	1.33±0.83 <sup>  </sup>	<0.0001	<0.0001
Glucose, mmol/L						
Baseline	8.52±2.57	8.20±2.35	8.20±2.18	8.29±2.40	0.0952	0.5568
Year 1	7.22±1.94	7.17±2.03	6.65±1.47	6.55±1.65	<0.0001	<0.0001
HbA1c, %						
Baseline	7.3±1.1	7.2±1.1	7.0±1.1	7.1±1.1‡	0.0011	0.2415
Year 1	6.6±0.9	6.7±0.9	6.1±0.7	6.3±1.0‡	<0.0001	<0.0001

Continued



Table 2. Continued

Characteristics	<10% Initial Weight Loss (n=797)		≥10% Initial Weight Loss (n=764)		P Value (Men)*	P Value (Women)†
	Men	Women	Men	Women		
Waist circumference, cm						
Baseline	118.4±14.9	109.3±13.6‡	118.4±13.4	110.4±12.9‡	0.9854	0.1845
Year 1	112.1±14.3	103.1±12.1‡	103.8±13.1	98.5±12.4‡	<0.0001	<0.0001
Systolic BP, mm Hg						
Baseline	129.9±16.5	127.4±17.1‡	127.7±16.0	129.7±18.6	0.0961	0.0516
Year 1	122.7±16.4	122.4±17.7	117.6±16.7	120.1±18.9‡	0.0001	0.0548
Diastolic BP, mm Hg						
Baseline	74.3±8.9	68.5±9.5‡	72.1±8.8	67.3±9.6‡	0.0036	0.0537
Year 1	70.3±9.1	66.2±9.6‡	67.5±8.9	63.9±9.2‡	0.0001	0.0002

BMI indicates body mass index; BP, blood pressure; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IQR, interquartile range.

\*Comparison of mean±SD, according to Student *t* test, or proportions, according to Pearson's  $\chi^2$  test, between <10% and ≥10% initial weight loss groups among men.

†Comparison of mean±SD, according to Student *t* test, or proportions, according to Pearson's  $\chi^2$  test, between <10% and ≥10% initial weight loss groups among women.

‡*P*<0.05 for comparison of mean±SD, according to Student *t* test, or proportions, according to Pearson's  $\chi^2$  test, between men and women within weight loss group.

§*P*<0.05 for comparison between median±IQR of men and women within weight loss group, according to Mann-Whitney *U* test.

25% cut points of weight regain, for all cardiometabolic risk factors in all initial weight loss and sex subgroups. Among women with <10% initial weight loss, maintainers had no significant change in cardiometabolic risk factors or significant improvement across all percentage cut points of weight regain.

Maintainers had significant improvement or no change in cardiometabolic risk factors across most cut points of weight loss regained (Figure 3). Among men who lost ≥10% initial weight, maintainers had no significant change or significant improvement to all cardiometabolic risk factors using all cut points, except for triglyceride concentrations when the 75% and 100% cut points were used and waist circumference when the 50%, 75%, and 100% cut points were used (Figure 3). Among women who lost ≥10% initial weight, maintainers had no significant change or significant improvement to all cardiometabolic risk factors, except waist circumference using the 75% and 100% cut points and systolic blood pressure using the 50%, 75%, and 100% cut points (Figure 3).

Maintainers had a significant deterioration in cardiometabolic risk factors when using the 75% and 100% cut points for select risk factors within initial weight loss and sex subgroups. Maintainers, according to the 75% and 100% cut points, had a significant increase in HbA1c concentration and systolic blood pressure among men who lost <10% initial weight, triglyceride concentrations and waist circumference among men who lost ≥10% initial weight, and systolic blood pressure and waist circumference among women who lost ≥10% initial weight (Figure 3).

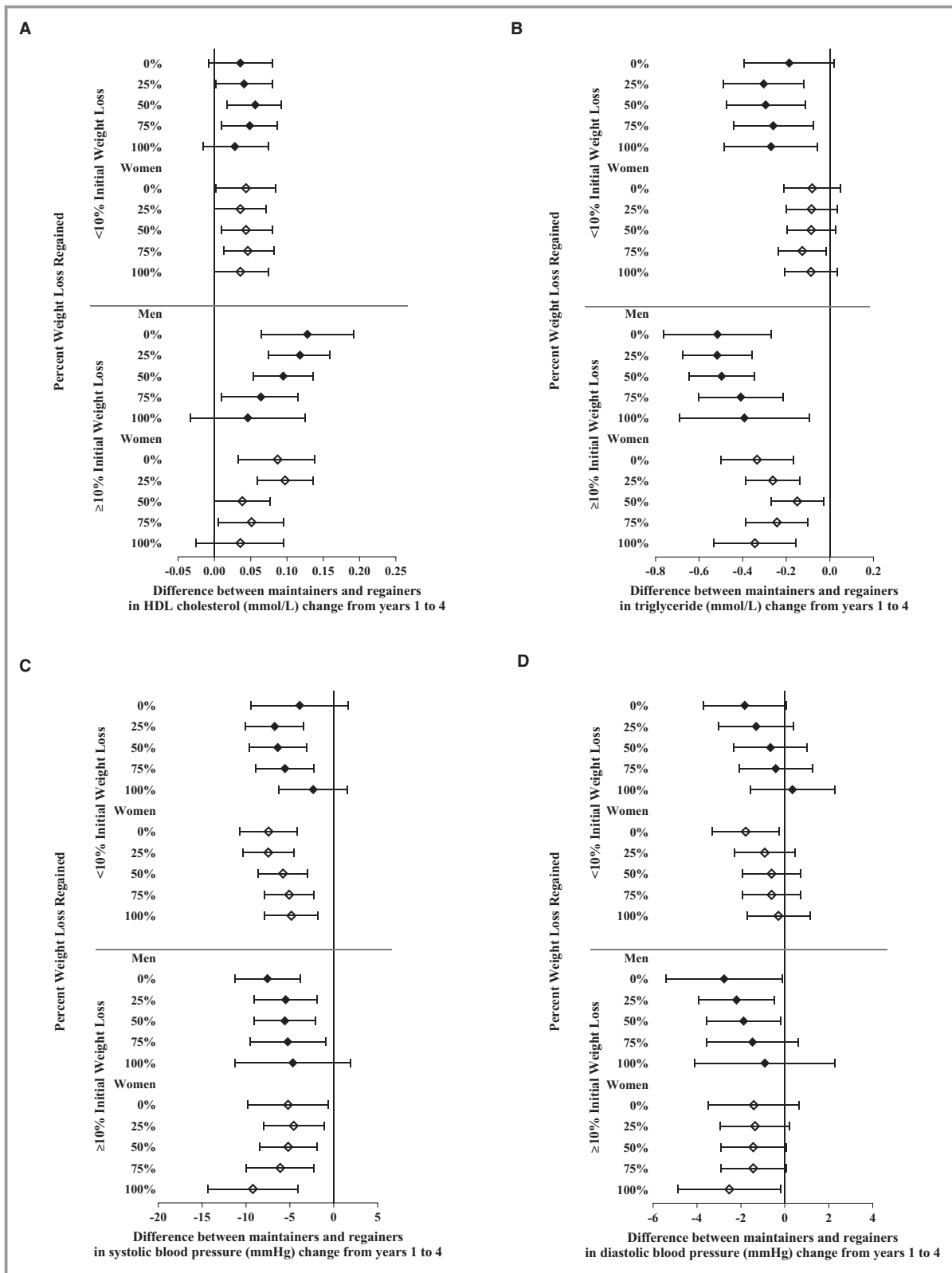
### Change among regainers

There were also significant changes among regainers from years 1 to 4 in cardiometabolic risk factors across different

cut points of percentage of weight lost regained (Figure 4). When examining change in cardiometabolic risk factors from years 1 to 4 among regainers, a positive linear pattern was found in select risk factors and initial weight loss/sex subgroups between larger percentage of weight loss regained cut point and change in cardiometabolic risk factors in regainers. The positive linear pattern among regainers was observed among men with ≥10% initial weight loss for triglyceride and fasting glucose concentrations, systolic blood pressure, and waist circumference (Figure 4). In addition, the linear pattern was seen in regainers among women with ≥10% initial weight loss for fasting glucose and HbA1c concentrations, systolic blood pressure, and waist circumference (Figure 4).

In some cardiometabolic risk factors, regainers had a significant deterioration from years 1 to 4 using all or most cut points of percentage of weight lost regained but not in a linear pattern. Among men and women with <10% initial weight loss, regainers had a significant increase in HbA1c concentration, systolic blood pressure, and waist circumference across all or most cut points of weight regain (Figure 4). Women with <10% initial weight loss who were regainers also had a significant increase in fasting glucose concentration using all cut points, except 100% regain. Among men and women with ≥10% initial weight loss, regainers also had a significant increase in HbA1c concentrations using the different percentage of weight regained cut points (Figure 4).

For some cardiometabolic risk factors and in select initial weight loss and sex subgroups, regainers had significant adverse changes to cardiometabolic risk from years 1 to 4 but only using certain cut points of percentage of weight regained. Among men with <10% initial weight loss, regainers



**Figure 2.** Difference in change from years 1 to 4 between individuals with successful weight loss maintenance (maintainers) and individuals who regained weight (regainers) in high-density lipoprotein (HDL) cholesterol (A), triglyceride (B), systolic blood pressure (C), diastolic blood pressure (D), waist circumference (E), fasting glucose (F), and hemoglobin A1C (HbA1c) (G). Differences are reported by initial weight loss and sex subgroups.

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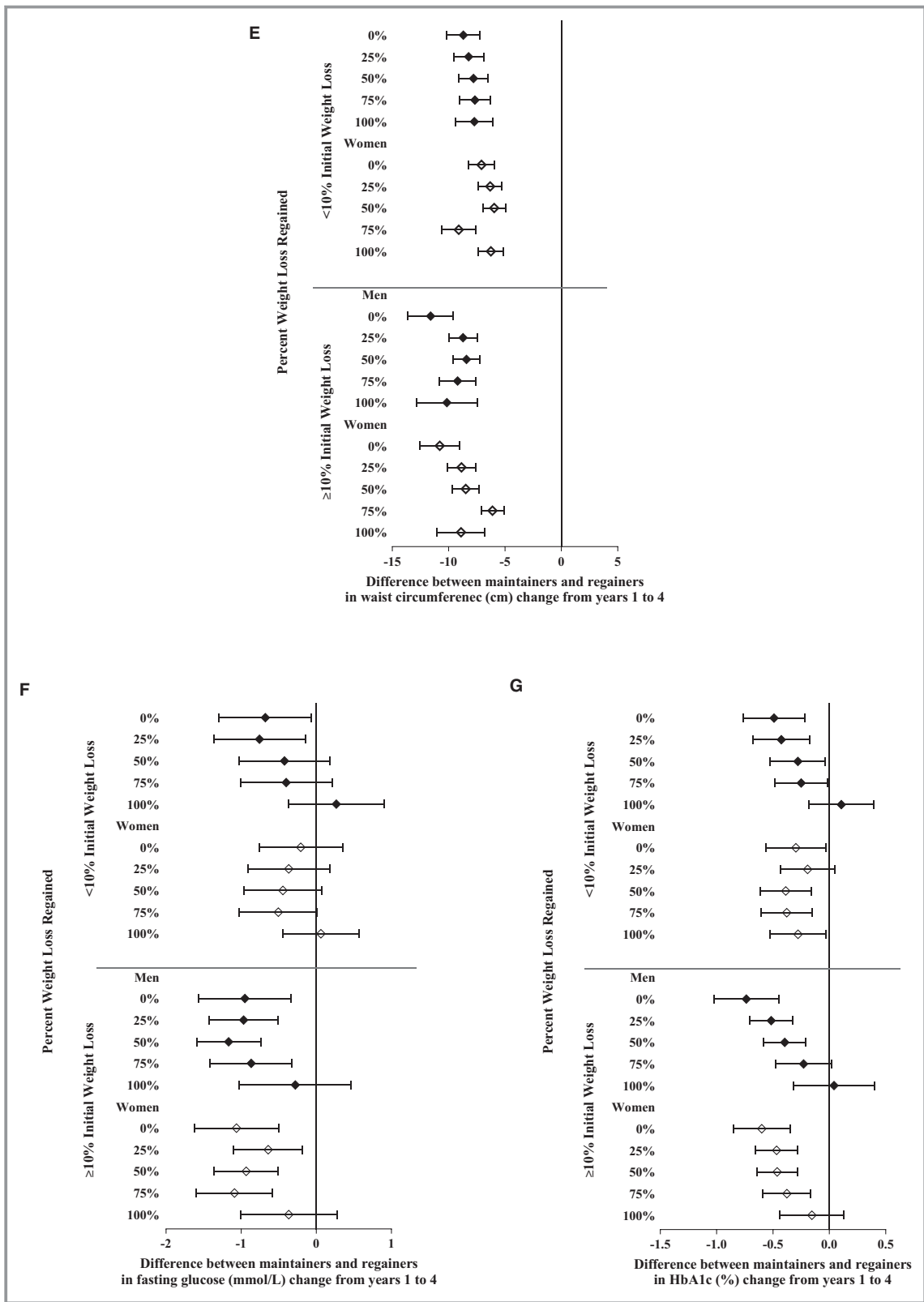
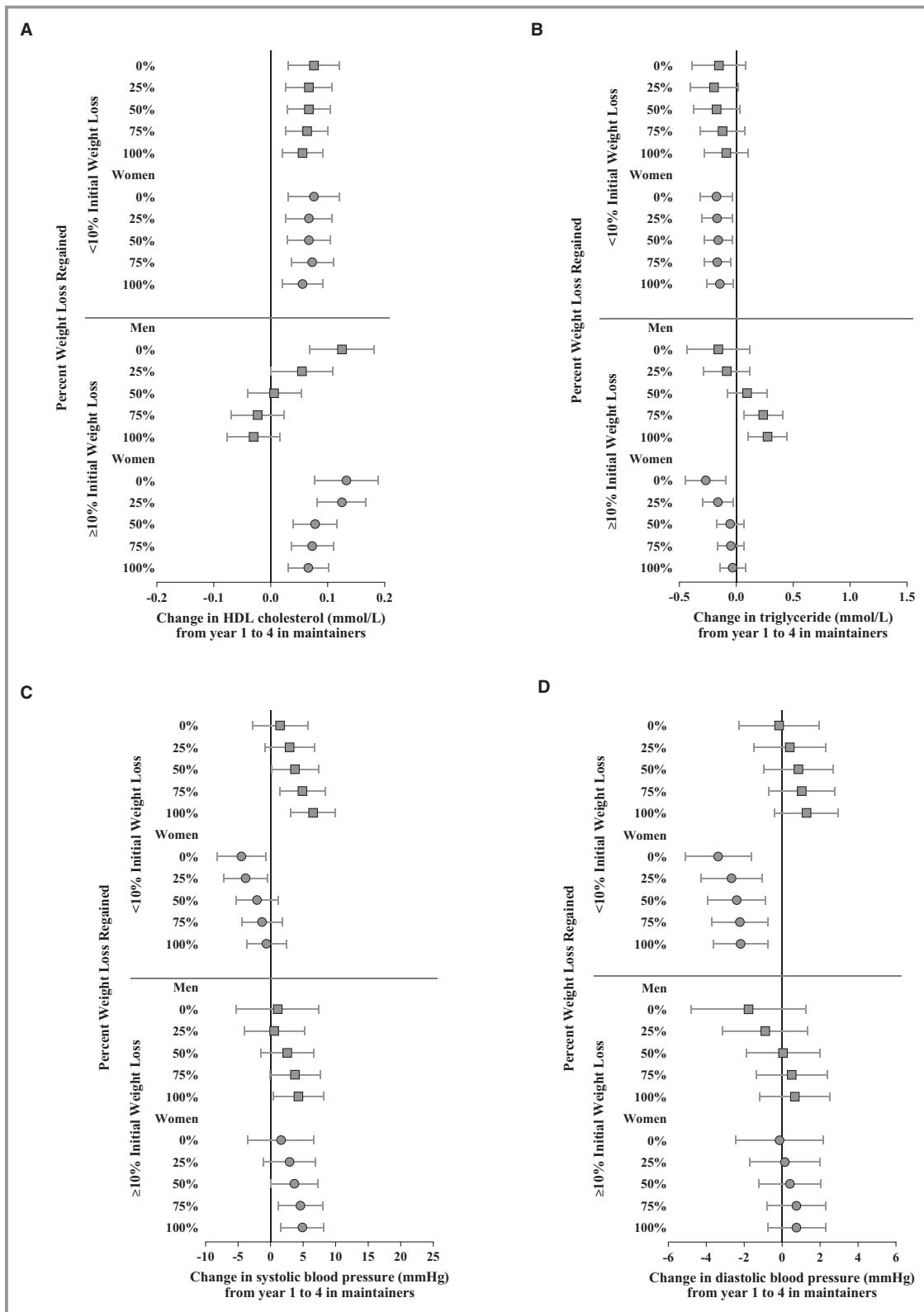


Figure 2. Continued





**Figure 3.** Change from years 1 to 4 among individuals with successful weight loss maintenance (maintainers) in high-density lipoprotein (HDL) cholesterol (A), triglyceride (B), systolic blood pressure (C), diastolic blood pressure (D), waist circumference (E), fasting glucose (F), and hemoglobin A1c (HbA1c) (G). Differences are reported by initial weight loss and sex subgroups.

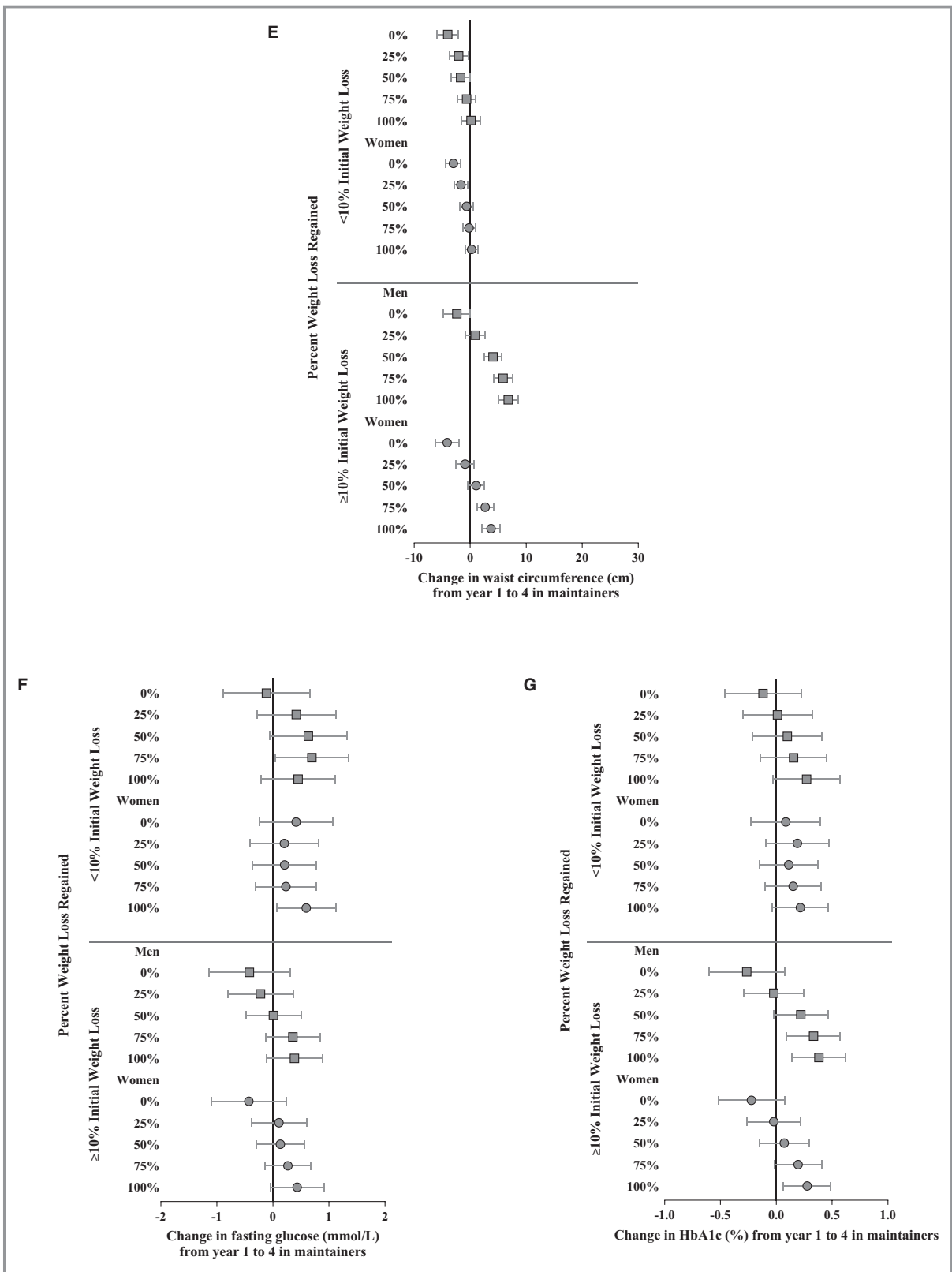
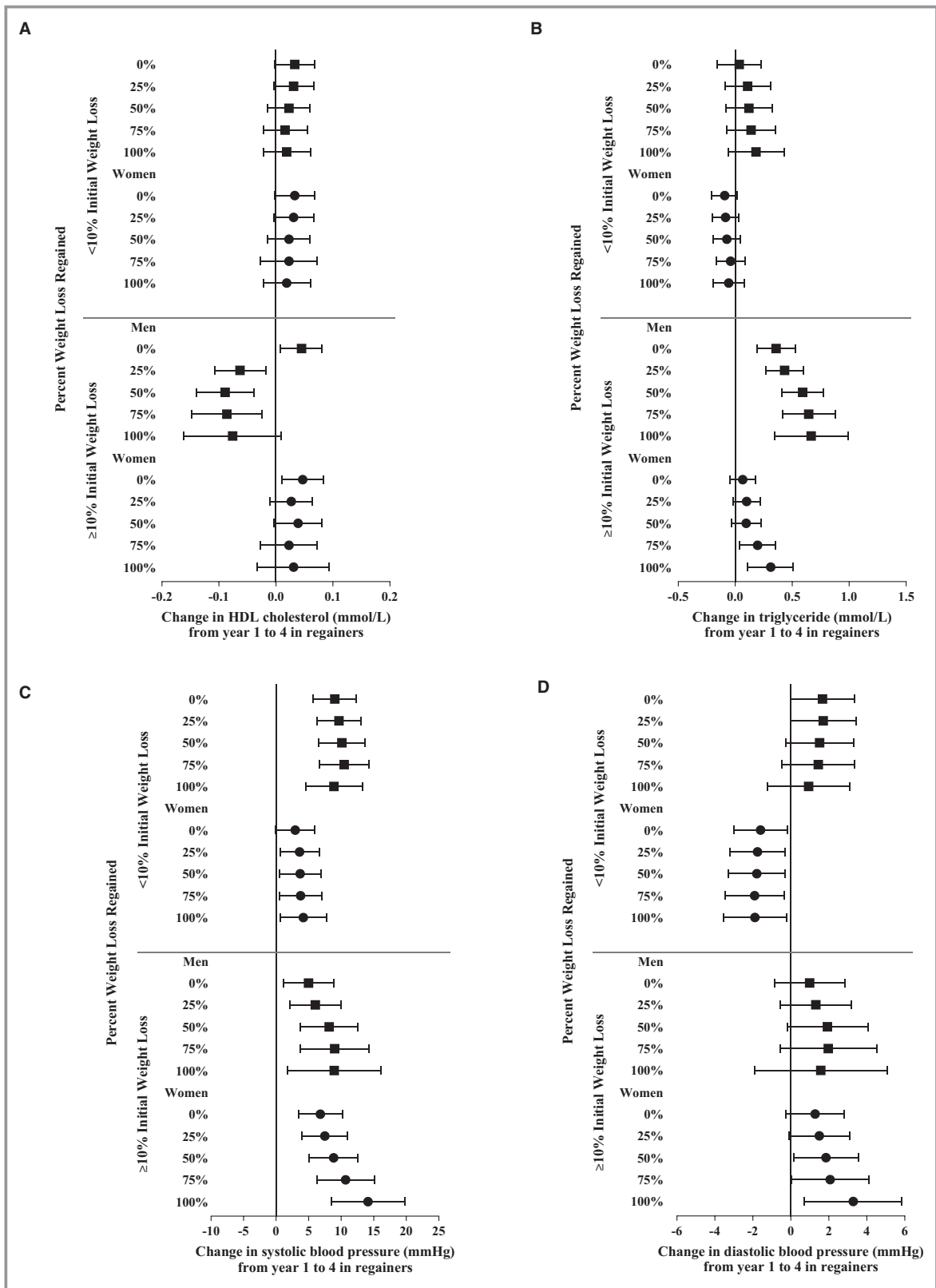


Figure 3. Continued



**Figure 4.** Change from years 1 to 4 among individuals who regained weight (regainers) in high-density lipoprotein (HDL) cholesterol (A), triglyceride (B), systolic blood pressure (C), diastolic blood pressure (D), waist circumference (E), fasting glucose (F), and hemoglobin A1c (HbA1c) (G). Differences are reported by initial weight loss and sex subgroups.

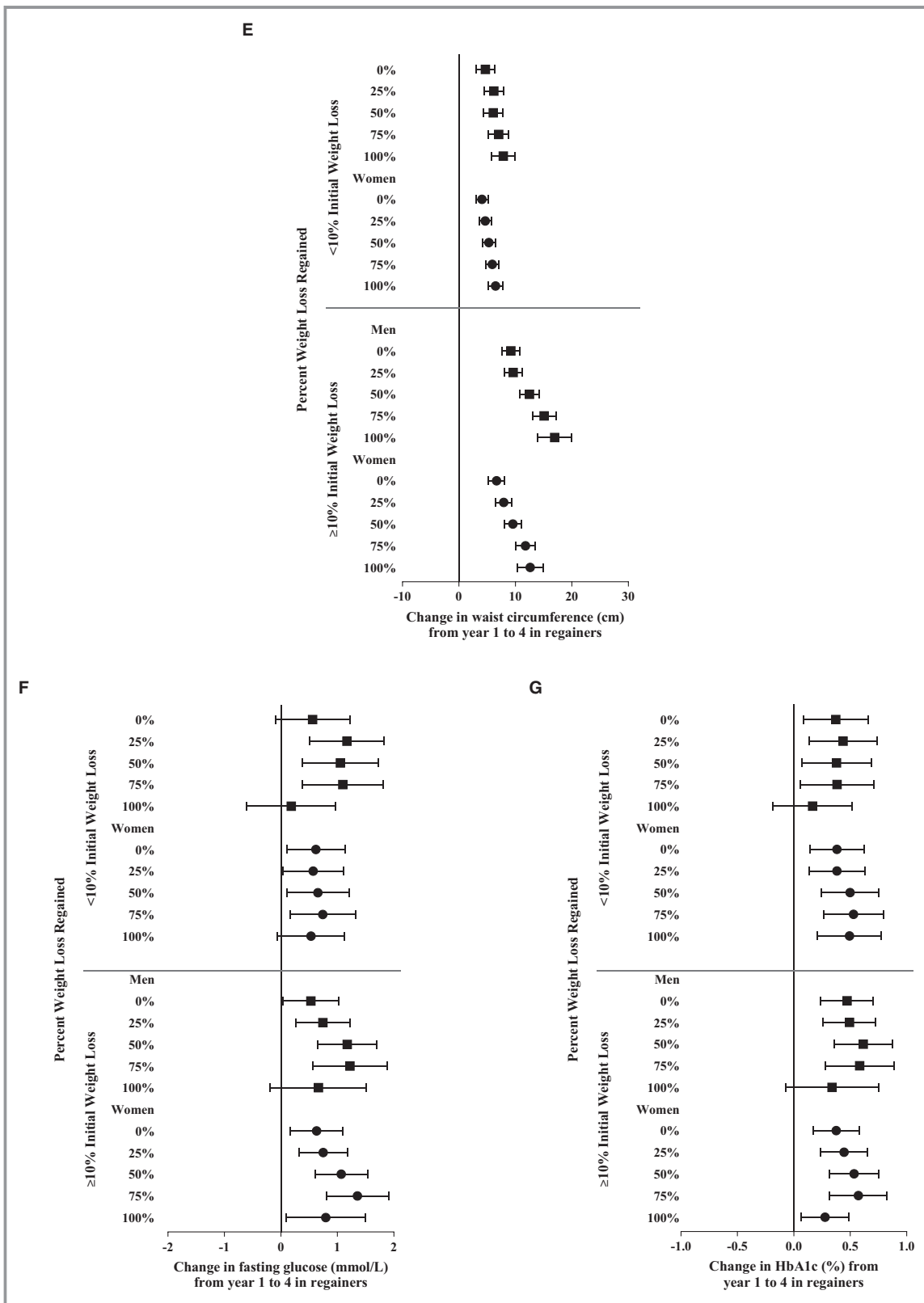


Figure 4. Continued

had a significant increase of fasting glucose using the 25%, 50%, and 75% cut points (Figure 4). Among men with  $\geq 10\%$  initial weight loss, regainers had a significant increase in HDL cholesterol when defined by 0% of weight loss regained but had a significant decrease in HDL cholesterol when all other percentages of regain cut points were used (Figure 4). Among women with  $\geq 10\%$  initial weight loss, regainers had a significant increase to HDL cholesterol only when using the 0% cut point. Regainers also had a significant increase in triglyceride concentrations only when using 0%, 25%, or 50% cut points of percentage of weight regained and diastolic blood pressure, according to the cut points of 50%, 75%, or 100% (Figure 4).

For select cut points and cardiometabolic risk factors, weight regain was associated with significant improvement to cardiometabolic risk. As noted previously, men and women with  $\geq 10\%$  initial weight loss, defined as regainers according to the 0% cut point, had a significant increase to HDL cholesterol concentrations. Among women with  $< 10\%$  initial weight loss, regainers had significant decreases to diastolic blood pressure using 50%, 75%, and 100% cut points (Figure 4).

Some cardiometabolic risk factors were unaffected by weight regain. HDL cholesterol and triglyceride concentrations were not significantly different from years 1 to 4 in regainers using any cut points of weight regain. Diastolic blood pressure was not significantly changed in regainers using any cut point among men of all weight losses (Figure 4).

## Discussion

The findings from this study indicate that overall, 3 years after weight loss, people with type 2 diabetes mellitus who regain their weight lost had a deterioration of cardiometabolic risk factors, whereas maintainers have stabilization or further improvement. We sought to identify a weight regain cut point across both sex and both initial weight loss subgroups that maximized the cardiometabolic risk difference between maintainers and regainers but found none. The relationships varied by risk factor, sex, and initial weight loss subgroup. Among those who lost  $\geq 10\%$  initial weight, the results across most risk factors indicated maximal risk factor reduction among maintainers who successfully maintained 100% of the lost weight (0% regain cut point). Successfully maintaining most ( $\geq 75\%$ ) of the weight loss (25% regain cut point) was also associated with significant maintenance of improved risk factors or no significant change across all outcomes. Several risk factors exhibited a linear pattern across increasing percentage of weight loss regained cut points, whereas others showed that maintaining any amount of weight loss was significantly better than regaining weight loss across cut points, but the association did not change across cut points.

Men and women responded similarly to weight regain when assessed on the basis of fasting glucose and HbA1c concentrations, but differently on the basis of plasma lipid concentrations and blood pressure.

High rates of weight regain across lifestyle intervention programs raise the question of whether weight regain could have adverse effects on cardiometabolic risk factors after the initial weight intensive loss intervention period ended.<sup>7,8</sup> This study suggests that the answer to that question is dependent on the definition used for successful weight loss maintenance, the relative amount of weight regain, and sex. Five cut point definitions were examined, and a range of cardiometabolic risk factors was evaluated. The findings of this and prior studies support the benefit of losing weight and maintaining 100% of the loss for lowering cardiometabolic risk.<sup>3,21,22</sup> However, a recent investigation comparing different criteria used to define maintainers and regainers highlighted the limitation of using the strict 0% regain cut point.<sup>13</sup> The strict cut point dramatically reduces the proportion of participants classified as maintainers who can be used to evaluate the outcomes. Because regaining  $< 25\%$  of weight lost was also beneficial across risk factors among maintainers, this cut point may be a more useful criterion to evaluate cardiometabolic risk factors and weight loss maintenance.

The pattern in which the association between postintervention change in cardiometabolic risk factors and maintaining weight or regaining weight was different by risk factor, sex, and initial weight loss subgroup. Across most risk factors, changes in association with increasing cut points of weight regain were more likely to be linear among those who lost  $\geq 10\%$  initial weight loss, indicating a larger benefit of keeping off more weight for those who lost the most weight; for those who lost  $< 10\%$  initial weight, keeping it off is better than regaining, but it appears the degree of maintaining the weight loss has little impact on cardiometabolic risk factors. Among those with  $< 10\%$  initial weight loss, the linear pattern with increasing cut points was significant for waist circumference and fasting glucose and HbA1c concentrations, but not for lipid concentrations or blood pressure. For most of the results, waist circumference and HbA1c concentrations showed a similar pattern of associations across initial weight loss and sex subgroups. This is likely because of an association between waist circumference and insulin resistance.<sup>23,24</sup> As expected, men had a significantly larger waist circumference than women at baseline and year 1. However, there was no significant difference in the change in waist circumference over time between men and women during the initial weight loss or weight maintenance periods. Hence, it is unlikely that sex differences in waist circumference were drivers of the sex differences observed in this study.

A limitation of this study is that the effect of weight loss and regain on the incidence of cardiovascular disease

outcomes could not be examined. Change in cardiometabolic risk factors cannot be extrapolated to long-term disease outcomes. Although the Look AHEAD trial is currently the largest lifestyle intervention trial in individuals with type 2 diabetes mellitus, the generalizability of these findings is limited to this subgroup. In addition, the evaluation of weight regain using body weight measurements may not reflect body fat distribution. However, body weight and waist circumference are highly correlated in the Look AHEAD trial cohort, as reported previously<sup>25</sup> and confirmed in the data set used for the analyses presented. Despite this correlation, in the future, it may be valuable to conduct a similar investigation using waist circumference rather than body weight. Strengths of the study are that the Look AHEAD trial resulted in a wide range of successful weight loss maintenance and magnitudes of weight regain patterns. In addition, the Look AHEAD trial was of sufficient size to allow for analyses by sex.

In conclusion, after a successful 1-year intensive lifestyle-induced weight loss intervention that resulted in beneficial changes in cardiometabolic risk factors in patients with type 2 diabetes mellitus, subsequent weight regain resulted in a deterioration of these benefits, whereas weight maintenance resulted in no significant change or significant improvement to risk factors. Responses varied across cardiometabolic risk factors, and across initial weight loss and sex subgroups. No single cut point of percentage weight loss regained was identified to maximize the risk difference between maintainers and regainers. Among maintainers, maintaining all the weight lost was the most beneficial across all risk factors, but maintaining 75% of the weight loss was also beneficial. The findings from this study emphasize the need to further investigate long-term impact of partial weight regain after a weight loss intervention given the challenge of keeping off all of weight lost.

## Author Contributions

Dr Lichtenstein, Dr Huggins, and S. E. Berger: designed research; S. E. Berger, Dr Huggins, Dr McCaffery, and Dr Jacques: conducted research; S. E. Berger: analyzed data; S. E. Berger and Dr Lichtenstein: wrote the article; Dr Lichtenstein, Dr Huggins, Dr McCaffery, Dr Jacques, and S. E. Berger: had primary responsibility for final content. All authors read and approved the final article.

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## Disclosures

None.

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