The role of menopause hormone therapy in modulating tirzepatide-associated weight loss in postmenopausal women with overweight or obesity: a retrospective cohort study

Regina Castaneda, Dima Bechenati, Elif Tama, Rene Rivera Gutierrez, Maria A Espinosa, Jose Villamarin, Tamim I Rajjo, Andres Acosta, Stephanie Faubion, Chrisandra Shufelt, Maria D Hurtado Andrade

Lancet Obstet Gynaecol Womens Health 2026; 2: e118–28

Published Online January 22, 2026 https://doi.org/10.1016/S3050-5038(25)00145-1

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Division of Endocrinology, Diabetes and Metabolism, Mayo Clinic, Jacksonville, FL, USA (R Castaneda MD, R Rivera Gutierrez MD, M D Hurtado Andrade MD); **Precision Medicine for Obesity Program, Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA** (R Castaneda MD, R Rivera Gutierrez MD, M A Espinosa MD, J Villamarin MD, A Acosta MD, M D Hurtado Andrade MD); **Department of Family Medicine, Mayo Clinic, Rochester, MN, USA** (D Bechenati MD, T I Rajjo MD); **Division of Internal Medicine, Wayne State University, Henry Ford Rochester Hospital, Rochester, MI, USA** (E Tama MD); **Division of General Internal Medicine, Mayo Clinic, Jacksonville, FL, USA** (Prof S Faubion MD, Prof C Shufelt MD); **Center for Women's Health, Mayo Clinic, Rochester, MN, USA** (Prof S Faubion MD, Prof C Shufelt MD)

Correspondence to: Dr Maria Daniela Hurtado Andrade, Division of Endocrinology, Diabetes and Metabolism, Mayo Clinic, Jacksonville, FL 32224, USA **hurtado.mariadaniela@mayo.edu**

Summary

Background The risk of developing obesity increases during the menopause transition, contributing to elevated cardiometabolic risk in women in midlife. Tirzepatide is the most effective obesity medication to date. Data on its efficacy in postmenopausal women and the potential modifying effect of menopause hormone therapy remain scarce. This study aimed to evaluate whether use of hormone therapy enhances weight loss and cardiometabolic response to tirzepatide in postmenopausal women with overweight or obesity.

Methods We conducted a retrospective cohort study of data from the Mayo Clinic Health System on postmenopausal women with overweight or obesity treated with tirzepatide for ≥12 months. Women included were patients with overweight (BMI ≥27 kg/m²) in the presence of an adiposity-related comorbidity or with obesity (BMI ≥30 kg/m²) irrespective of the presence of adiposity-related comorbidities and prescribed tirzepatide for weight management. Electronic health record data were extracted at baseline (±14 days from tirzepatide initiation) and at subsequent follow-up visits at months 3 (±30 days), 6 (±30), 9 (±30), 12 (±45), 15 (±45), and last follow-up. Women using systemic hormone therapy were propensity score matched (1:2) to non-users based on age, BMI, age at and type of menopause, previous obesity medication use, and diabetes status. The primary endpoint was the percentage of total bodyweight change at last follow-up. Secondary outcomes included percentage of total bodyweight change at predefined intervals, categorical weight loss thresholds, and changes in cardiometabolic parameters.

Findings Between June 3, 2022, and May 25, 2024, 15 639 female individuals were identified and 120 were included. 40 postmenopausal women using hormone therapy were matched to 80 not using hormone therapy. Mean age was 56·4 years (SD 6·4) and 113 (94%) of 120 were White. The hormone therapy group lost more of their percentage bodyweight at last follow-up than the no hormone therapy group (–19·2% [SD 9·9, SE 1·6] *vs* –14·0% [SD 8·0, SE 0·9]; mean difference –5·2%, 95% CI 1·90–8·54, p=0·0023), with a higher proportion of women in the hormone therapy group reaching a total percentage bodyweight change of ≥20%, ≥25%, and ≥30%. Both groups had improvements in glycaemia, blood pressure, and concentration of liver enzymes, with additional reductions in diastolic pressure, and concentrations of triglycerides and aspartate aminotransferase in women using hormone therapy.

Interpretation In postmenopausal women with overweight or obesity, concurrent use of hormone therapy was associated with greater weight loss and improved cardiometabolic outcomes during tirzepatide treatment. These findings suggest that hormone therapy might enhance the therapeutic effects of tirzepatide in this population. Prospective, randomised controlled trials with clinical (eg, weight loss) and mechanistic endpoints (eg, measurement of energy balance components) are needed to substantiate these observations, establish causality, and inform clinical decision making.

Funding National Institutes of Health and Mayo Clinic Center for Women's Health Research.

Introduction

During midlife (age 40–65 years), obesity prevalence rises by nearly 30% in women, from 37% among those aged 20–39 years to 47% in those aged 40 years and older.[1] Although chronological ageing drives much of this weight gain, menopause amplifies the effect as the decrease in oestrogen accelerates lean mass loss, compounding the age-related decline in muscle and resting energy expenditure.[2,3] At the same time, physical activity declines, with only 7% of women in midlife consistently meeting the United States Preventive Services Task Force exercise guidelines.[4] Furthermore, the presence of menopausal vasomotor symptoms, which affect 70–80% of women during menopause, also contribute to weight gain. Vasomotor symptoms are associated with disrupted sleep that can lead to alterations in appetite-regulating hormones, promoting increased food intake and weight gain.[5] The hormonal shifts of the menopause transition

Research in context

Evidence before this study

We searched PubMed in April, 2025, for articles published in the previous 5 years, without language restrictions, using the search terms "glucagon-like peptide-1 receptor agonist", "GLP-1RA", "menopause", 'hormone therapy", "oestrogen", "obesity", "overweight", "tirzepatide", "semaglutide", and "weight loss". Postmenopausal women constitute a vulnerable and understudied population in obesity pharmacotherapy research. Declining oestrogen concentrations contribute to detrimental physiological changes, including increased central adiposity, reduced energy expenditure, and impaired fat oxidation, exacerbating age-related weight gain, and increasing cardiovascular disease risk. Menopause hormone therapy offers established clinical benefits in postmenopausal women, including reduced vasomotor symptoms and improvements in insulin sensitivity, adaptive thermogenesis, lipid profiles, abdominal fat distribution, and cardiovascular disease risk. These effects suggest that combining hormone therapy and obesity treatments might have potential synergistic benefits in postmenopausal women with excess adiposity. Previous research shows greater weight loss with semaglutide in individuals using hormone therapy. Although tirzepatide, the newest obesity medication approved by the US Food and Drug Administration shows meaningful weight loss and cardiometabolic improvements in phase 3 trials (SURMOUNT programme), the effect of reproductive stage and role of hormone therapy remain to be investigated.

Added value of this study

This is the first study to evaluate the effect of hormone therapy on weight loss outcomes during tirzepatide treatment in postmenopausal women with overweight or obesity. It underscores the need for proactive cardiometabolic risk management in postmenopausal women, as menopause significantly elevates cardiovascular disease risk due to substantial physiological changes. This study suggests that hormone therapy enhances the therapeutic effect of tirzepatide, supporting its potential role as an adjunct to obesity pharmacotherapy in women with excess adiposity who also have a clinical indication for hormone therapy, such as vasomotor symptoms.

Implications of all the available evidence

The findings emphasise the importance of personalised obesity management strategies that account for menopausal status and vasomotor symptom burden. Combining hormone therapy with obesity medications might provide dual benefits, improving weight-related outcomes and cardiometabolic health. Although the retrospective design limits causal inference, the results provide compelling evidence to support the integration of hormone therapy into comprehensive obesity treatment plans for postmenopausal women when clinically appropriate. Prospective trials with mechanistic endpoints are needed to substantiate these findings and elucidate the underlying mechanisms driving the observed effects.

also promote a redistribution of body fat from a gynoid (hip and thigh) pattern to an android (abdominal) pattern, accounting for a 6% annual increase in visceral fat compared with a 1% increase in the premenopausal stage.[6]

These changes in weight and fat distribution markedly increase the risk for cardiometabolic dysregulation leading to type 2 diabetes, dyslipidaemia, hypertension, gastro-oesophageal reflux disease, metabolic dysfunction-associated liver disease, obstructive sleep apnoea, and cardiovascular disease. Notably, the incidence of cardiovascular disease in women rises more steeply than men during midlife, eventually matching or exceeding that of men after menopause.[7] Menopause itself, through adverse effects on lipid metabolism, body composition, and vascular function, is now recognised as an independent risk factor for cardiovascular disease.[8] Consequently, the American Heart Association recommends vigilant monitoring and management of cardiovascular risk in perimenopausal and postmenopausal women.[4] Although early intervention strategies, including lifestyle modifications and possibly menopause hormone therapy, might be beneficial in reducing this risk, women with overweight or obesity often require more intensive interventions, with excess adiposity remaining a primary therapeutic target for reducing cardiovascular disease risk.

The field of obesity pharmacotherapy is rapidly evolving, with newer agents offering enhanced efficacy and broader health benefits. For example, the GLP-1 receptor agonist semaglutide decreases cardiovascular disease events in individuals with established cardiovascular disease.[9] Despite the evidence supporting the benefits of obesity medications, data on the effect of reproductive stage and hormone therapy are scarce. Our previous work showed that postmenopausal women using hormone therapy had superior weight loss outcomes in response to semaglutide compared with non-users.[10] These data suggest that hormone therapy might potentiate semaglutide-induced weight loss in this group, potentially via oestrogen's effects on visceral fat reduction and lean mass preservation.[11,12]

Tirzepatide, a novel dual GLP-1 and glucose-dependent insulinotropic polypeptide receptor agonist, has emerged as a promising therapeutic agent for the treatment of overweight and obesity.[13] Clinical trials have placed tirzepatide as the most effective obesity medication available, while also improving glycaemic control and other cardiometabolic parameters.[13–15] This cohort study was designed to compare the weight loss response to tirzepatide in postmenopausal women with and without concurrent hormone therapy use. We hypothesised that, among postmenopausal women using tirzepatide for the treatment of overweight or

obesity, those receiving hormone therapy had a superior weight loss response compared with those not receiving hormone therapy.

Methods

Study design and population

This retrospective cohort study analysed electronic health records from the Mayo Clinic Health System by comparing weight loss and cardiometabolic parameters outcomes in postmenopausal women using tirzepatide for weight management by hormone therapy use (users *vs* non-users). Individuals included in this study were women based on self-reported sex assigned at birth, with overweight (BMI ≥27 kg/m²) in the presence of an adiposity-related comorbidity or obesity (BMI ≥30 kg/m²) irrespective of the presence of adiposity-related comorbidities, prescribed tirzepatide treatment between June, 2022, and May, 2024, and treated for ≥12 months. We excluded women with less than 12 months of tirzepatide use, previous bariatric surgery, concurrent use of other obesity medications (including compounded products), inconsistent medication use, pregnancy, active malignancy, or medical conditions that affect weight loss outcomes (eg, uncontrolled hypothyroidism). Menopausal status was confirmed by either natural cessation of menses for ≥12 months without other underlying causes or by bilateral oophorectomy (surgical menopause). In women without a date of last menstrual period (ie, post-hysterectomy or with endometrial ablation), a documented follicle-stimulating hormone level greater than 50 IU/L was used to confirm menopausal status. The hormone therapy group included women using continuous systemic transdermal or oral oestrogen (oestradiol or conjugated oestrogens) with or without progestogen (based on the presence or absence of uterus) for at least 12 months concurrently with tirzepatide treatment. To reduce confounding, we used 1:2 nearest-neighbour propensity score matching without replacement. Propensity scores were estimated using logistic regression, with covariates including age, baseline BMI, age at menopause, type of menopause (natural *vs* surgical), previous use of obesity medications, and type 2 diabetes status. Each woman in the hormone therapy group was matched to two women without hormone therapy use. The no hormone therapy group had never received systemic hormone therapy. This study was approved by the Mayo Clinic Institutional Review Board, who waived the informed consent requirements due to minimal risk and the retrospective nature of the study (IRB 17–001068). The study adhered to STROBE guidelines.

Data collection

Data were extracted from electronic health records at baseline (±14 days from tirzepatide initiation) and at subsequent follow-up visits at months 3 (±30 days), 6 (±30 days), 9 (±30 days), 12 (±45 days), 15 (±45 days), and last follow-up. Broader follow-up windows were applied at later timepoints to address the inherent variability in clinical follow-up and improve data completeness. Although this approach might reduce temporal precision, it reflects a pragmatic balance that supports robust sample sizes and minimises missing data, without substantially compromising the overall integrity of outcome assessment. Baseline and last follow-up weights were available for all participants; therefore, no imputation was required. Data included demographics (ie, age, race, relationship status, highest level of education, and financial strain), anthropometric measures (ie, weight, height, and BMI), vital signs (ie, blood pressure), laboratory parameters, and smoking history. In addition to blood pressure, additional cardiometabolic parameters included glycated haemoglobin (HbA_{1c}), fasting glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lipids (total cholesterol, triglycerides, LDL cholesterol, and HDL cholesterol). Medical history data included the following adiposity-related comorbidities: dyslipidaemia, hypertension, type 2 diabetes, gastro-oesophageal reflux disease, metabolic dysfunction-associated liver disease, obstructive sleep apnoea, depression, and anxiety. Additionally, the history of malignancies (excluding non-melanoma skin cancer) and major cardiovascular events (eg, myocardial infarction) were recorded. Atherosclerotic cardiovascular disease risk scores were calculated at baseline using the ASCVD Risk Estimator Plus from the American College of Cardiology.[16] Data on the use of weight-gain-promoting medication during tirzepatide treatment, as well as previous use of obesity medication, were collected. Weight-gain-promoting medications included systemic corticosteroids, opioids, β blockers, insulin, sulfonylureas, thiazolidinediones, anticonvulsants (eg, pregabalin), antipsychotics (eg, olanzapine and quetiapine), and antidepressants (eg, amitriptyline). Weight trajectory at 1 year before tirzepatide initiation was collected, including percentage weight change and categorical threshold of ≥5% change. The maximum tirzepatide dose achieved was recorded and categorised as low (2·5 mg, 5 mg, or 7·5 mg) or high (10 mg, 12·5 mg, or 15 mg), consistent with the available subcutaneous weekly dosing options. Additionally, collected data on menopause included age at onset, type (natural or surgical, with surgical defined as bilateral oophorectomy with or without hysterectomy), and hormone therapy use details for women using hormone therapy (oestradiol delivery method; ie, oral or transdermal, concomitant progesterone use, and doses of oestradiol and progesterone), and duration of hormone therapy before tirzepatide initiation. Medication adherence for both hormone therapy and tirzepatide was assessed through detailed chart review, including documentation of prescription refills, patient-reported use, and clinician notes during follow-up visits.

Outcomes

The primary endpoint was the percentage of total bodyweight lost at the last available follow-up after tirzepatide initiation and stratified by hormone therapy use. Percentage of total change in bodyweight was calculated with the formula: percentage of total bodyweight change=100×([weight at follow-up− baseline weight] / baseline weight). Secondary endpoints included percentage change in total bodyweight at months 3, 6, 9, 12, and 15 by hormone therapy use, proportion of women meeting weight loss thresholds (≥5%, ≥10%, ≥15%, ≥20%, ≥25%, and ≥30%) at the last follow-up by hormone therapy use, and changes in cardiometabolic parameters from baseline to last follow-up by hormone therapy use. We conducted additional sensitivity analyses that were outside the scope of the study and, therefore, are not reported here.

Statistical analysis

Data normality was assessed using the Shapiro–Wilk test. Continuous variables with normal distribution are presented as mean (SD), and non-normally distributed variables as median (IQR). Group comparisons were conducted using independent *t* tests for normally distributed continuous variables and Fisher's exact tests for categorical variables. For non-normally distributed continuous variables, Wilcoxon signed-rank test was used for within-group comparisons, and Mann–Whitney *U* test for between-group comparisons. All statistical tests were two-tailed, with a significance level of p less than 0·05. Analyses were performed using BlueSky Statistics (version 10.3.7) and R (version 4.4.2), and figures were created with GraphPad Prism (version 10.4.2).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between June 3, 2022, and May 25, 2024, 15 639 female patients with an active tirzepatide prescription were identified. 15 380 had at least one exclusion criterion. Of the 259 women fulfilling the inclusion criteria, 120 were included. 40 postmenopausal women using hormone therapy were matched to 80 not using hormone therapy (figure 1). The mean age was 56·4 years (SD 6·4), and most women were White (113 [94%] of 120). As a result of the propensity score matching used, there was no significant difference in age distribution between the hormone therapy and no hormone therapy groups. Race distribution was similar between the two groups. Sociodemographic factors, including relationship status, highest level of education, and financial strain, were similar between groups. Most patients were married or with a partner, had a college degree as their highest level of education, and reported no history of financial strain. The average BMI for the entire cohort was 33·6 kg/m² (SD 5·4), with most patients classified as having obesity class I.

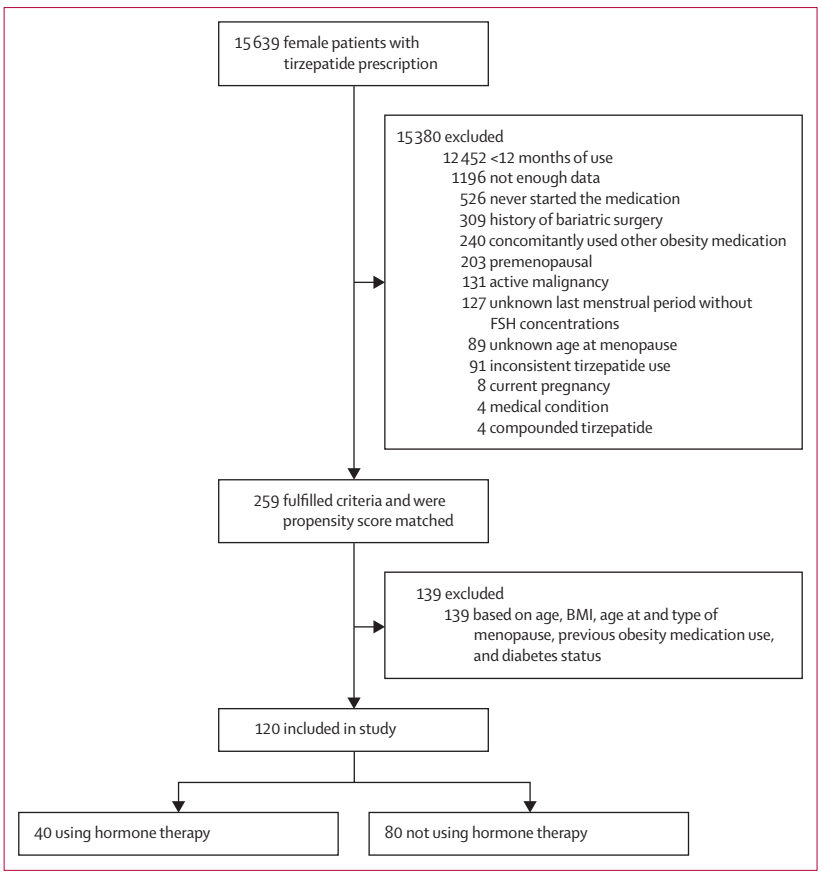

Figure 1: **Study flowchart**
FSH=follicle-stimulating hormone.

Adiposity-related comorbidities did not differ significantly between the groups. The most prevalent adiposity-related comorbidities were dyslipidaemia, hypertension, and type 2 diabetes. The prevalence of major cardiovascular events was rare, reported in only two women in the no hormone therapy group. This low event rate was further reflected by a significantly higher 10-year ASCVD Risk Score in the no hormone therapy group than in the hormone therapy group. There was no significant difference in statin use between groups. 79 (66%) of 120 patients were never smokers, 38 (32%) were former smokers, and only three (3%) were current smokers. Although active smokers were only present in the no hormone therapy group, no significant differences in smoking status were observed between the groups. 18 (15%) of 120 women included had a history of malignancy other than non-melanoma skin cancer, with no significant difference by hormone therapy status (table). The most common malignancy was breast cancer, observed exclusively in the no hormone therapy group, as expected. Other reported cancers included lymphoma,

cervical, thyroid, bladder, and ovarian cancers, all of which were in remission at the time of tirzepatide initiation. Baseline cardiometabolic parameters, including blood pressure, glucose concentration, HbA_{1c} concentration, lipid profile, and liver enzymes, were also similar between the groups.

	Total cohort (n=120)	With hormone therapy (n=40)	Without hormone therapy (n=80)	p value
Age, years	56·4 (6·4)	55·7 (6·5)	56·7 (6·4)	0·44
Race				0·32
White	113 (94%)	38 (95%)	75 (94%)	..
Black	3 (3%)	2 (5%)	1 (1%)	..
Asian	2 (2%)	0	2 (3%)	..
Other	2 (2%)	0	2 (3%)	..
Relationship status				0·78
Married or with partner	98 (82%)	34 (85%)	64 (80%)	..
Divorced	12 (10%)	4 (10%)	8 (10%)	..
Single	9 (8%)	2 (5%)	7 (9%)	..
Widowed	1 (1%)	0	1 (1%)	..
Highest level of education				0·82
Lower than college	26 (22%)	9 (23%)	17 (21%)	..
College	61 (51%)	19 (48%)	42 (53%)	..
Higher than college	33 (28%)	12 (30%)	21 (26%)	..
Financial strain	87 (73%)	31 (78%)	56 (70%)	0·44
Baseline anthropometrics measures				
Weight, kg	90·9 (16·3)	92·9 (16·6)	89·9 (16·2)	0·33
BMI, kg/m²	33·6 (5·4)	34·2 (5·3)	33·3 (5·4)	0·35
Obesity category				0·41
Overweight (≥27 kg/m²)	28 (23%)	6 (15%)	22 (28%)	..
Obesity class I (≥30 kg/m²)	48 (40%)	18 (45%)	30 (38%)	..
Obesity class II (≥35 kg/m²)	33 (28%)	13 (33%)	20 (25%)	..
Obesity class III (≥40 kg/m²)	11 (9%)	3 (8%)	8 (10%)	..
Adiposity-related comorbidity				
Dyslipidaemia	90 (75%)	27 (68%)	63 (79%)	0·19
Hypertension	75 (63%)	24 (60%)	51 (64%)	0·69
Type 2 diabetes	64 (53%)	20 (50%)	44 (55%)	0·60
GERD	39 (33%)	15 (38%)	24 (30%)	0·42
MASLD	22 (18%)	4 (10%)	18 (23%)	0·13
OSA	28 (23%)	9 (23%)	19 (24%)	1·00
Anxiety	40 (33%)	16 (40%)	24 (30%)	0·31
Depression	43 (36%)	17 (43%)	26 (33%)	0·32
Previous major cardiovascular event	2 (2%)	0	2 (3%)	0·55
ASCVD Risk Score				
Lifetime	38·4% (13·8)	35·9% (14·7)	40·8% (12·6)	0·20
Current 10-year	5·2 (4·6)	3·0 (2·2)	6·6 (5·2)	0·0016
Statin use	64 (53%)	19 (47%)	45 (56%)	0·36
History of malignancy	18 (15%)	4 (10%)	14 (17%)	0·28
Breast cancer	9/18 (50%)	0	9/14 (64%)	..
Other	9/18 (50%)	4/4 (100%)	5/14 (36%)	..
Smoking history				0·73
Never smoker	79 (66%)	27 (68%)	52 (65%)	..
Former smoker	38 (32%)	13 (33%)	25 (31%)	..
Current smoker	3 (3%)	0	3 (4%)	..

(Table continues on next page)

Regarding weight trajectory 1 year before tirzepatide initiation, both groups showed modest weight changes, with no significant difference. Approximately a third of women in each group experienced a ≥5% weight change over the 1-year period. Nearly half of the cohort used weight-gain-promoting medications, and 65 (54%) women had a history of previous use of obesity medication, with no significant differences between groups. The maximum dose of tirzepatide achieved was variable, with the most frequently achieved dose being 15 mg weekly for both groups in almost a third of patients. The proportion of patients reaching low versus high doses did not differ significantly between the groups.

Menopause type and age were also similar between groups by design, with natural menopause being the most common type of menopause in the two groups. Among women on systemic hormone therapy, transdermal oestradiol was the most common oestrogen delivery method at doses ranging from 0·025 mg/day to 0·1 mg/day, followed by oral oestrogen with doses between 0·5 mg and 2 mg daily. Among women using oral oestrogen, the majority were using oestradiol and the rest conjugated oestrogen. All women in the hormone therapy group who had a uterus also used 100 mg oral progesterone daily.

The mean follow-up time for the entire cohort was 18 months (SD 5) and did not vary between groups, with 17 months (5) for the hormone therapy group and 18 months (5) for the no hormone therapy group (p=0·57). The mean percentage change in total bodyweight at last follow-up was significantly greater in the hormone therapy group than in the no hormone therapy group (–19·2% [SD 9·9, SE 1·6] *vs* –14·0% [SD 8·0, SE 0·9]; mean difference –5·2%, 95% CI 1·90–8·54, p=0·0023; figure 2A). At months 3, 6, 9, 12, and 15, the hormone therapy group had a numerically greater percentage reduction in total bodyweight than the no hormone therapy group. These differences only reached statistical significance at 15 months with a mean percentage change in total bodyweight of –18·7% (SD 10·4, SE 2·0) in the hormone therapy group and –13·7% (SD 8·9, SE 1·3) in the no hormone therapy group (mean difference –5·03%, 95% CI 0·54–9·53, p=0·029; figure 2B). At the last follow-up, a higher proportion of women in the hormone therapy group reached a total bodyweight loss of ≥20%, ≥25%, and ≥30% than in the no hormone therapy group (figure 2C); the proportion of women reaching a total percentage bodyweight loss of ≥20%, ≥25%, and ≥30% was approximately two-fold, nearly four-fold, and four-fold greater, respectively, in the hormone therapy group than in the no hormone therapy group. There was no significant difference in the proportion of women reaching categorical total percentage change in bodyweight of ≥5%, ≥10%, and ≥15% between the two groups at the last follow-up.

Overall, both groups showed improvements in cardiometabolic risk parameters (figure 3). Significant

reductions were observed in concentrations of fasting glucose, HbA_{1c}, HDL cholesterol, and ALT, and systolic blood pressure in both groups. When compared with the no hormone therapy group, the hormone therapy group had additional significant reductions in diastolic blood pressure, concentration of triglycerides, and AST concentration. Total cholesterol and LDL cholesterol concentrations remained stable in the hormone therapy group, whereas these concentrations increased, non-significantly, in the no hormone therapy group. Although HDL cholesterol concentration significantly increased in the no hormone therapy group, it remained stable in the hormone therapy group. When comparing the mean difference from baseline to the last follow-up between the two groups, no significant differences were observed for any cardiometabolic risk marker (figure 3).

Side-effects were reported in 47 (39%) of 120 women overall, with no significant difference between those receiving hormone therapy (13 [32%] of 40) and those not (34 [43%] of 80; p=0·29). Gastrointestinal symptoms were the most commonly reported side-effects, occurring in 34 (43%) 80 women without hormone therapy treatment and 12 (30%) of 40 with hormone therapy treatment (p=0·18). Other side-effects in the full cohort included headache (five [4%] of 120 women), hypoglycaemia (four [3%]), fatigue (one [1%]), and urticaria (one [1%]), with no significant differences between groups.

	Total cohort (n=120)	With hormone therapy (n=40)	Without hormone therapy (n=80)	p value
(Continued from previous page)				
Baseline laboratories and vital signs				
Systolic blood pressure, mm Hg	126·1 (14·2)	124·9 (13·0)	126·7 (14·7)	0·50
Diastolic blood pressure, mm Hg	79·5 (8·7)	80·8 (7·6)	78·8 (9·1)	0·22
Fasting glucose, mg/dL	123·1 (51·2)	125·8 (69·2)	121·6 (39·3)	0·79
HbA_{1c}	6·5% (1·5)	6·7% (1·7)	6·7% (1·3)	0·93
Triglycerides, mg/dL	147·4 (82·5)	150·7 (81·4)	145·5 (83·8)	0·77
Total cholesterol, mg/dL	187·0 (44·0)	194·0 (39·8)	183·0 (46·1)	0·24
LDL cholesterol, mg/dL	103·9 (38·6)	108·1 (38·9)	101·6 (38·6)	0·46
HDL cholesterol, mg/dL	56·3 (16·6)	59·2 (17·8)	54·7 (15·8)	0·25
AST, U/L	26·2 (12·1)	26·5 (8·7)	27·2 (14·5)	0·79
ALT, U/L	27·4 (20·7)	33·0 (20·5)	30·1 (18·9)	0·58
Weight trajectory before treatment				
1-year weight change	–0·1% (7·1)	1·6% (8·2)	–0·9% (6·3)	0·11
≥5% 1-year weight change	33 (28%)	12 (30%)	21 (26%)	0·75
Weight-gain-promoting medication use	57 (48%)	18 (45%)	39 (49%)	0·70
Previous obesity medication	65 (54%)	21 (53%)	44 (55%)	0·80
Tirzepatide dosing (weekly subcutaneously)				0·24
2·5 mg	4 (3%)	1 (3%)	4 (5%)	..
5 mg	10 (8%)	1 (3%)	9 (11%)	..
7·5 mg	31 (26%)	9 (23%)	19 (24%)	..
10 mg	24 (20%)	9 (23%)	15 (19%)	..
12·5 mg	16 (13%)	8 (20%)	9 (11%)	..
15 mg	35 (29%)	12 (30%)	12 (15%)	..
Tirzepatide low *vs* high dose				0·18
Low dose (≤7·5 mg)	43 (36%)	11 (28%)	32 (40%)	..
High dose (≥10 mg)	77 (64%)	29 (73%)	48 (60%)	..
Type of menopause				0·42
Natural	75 (63%)	23 (58%)	52 (65%)	..
Surgical*	45 (38%)	17 (43%)	28 (35%)	..
Age at menopause, years	49 (5·4)	48·5 (4·9)	49·2 (5·6)	0·47
Oestrogen delivery				
Transdermal oestradiol	..	27 (68%)	..	..
Oral	..	13 (33%)	..	..
Oral oestradiol		10/13 (76%)		..
Conjugated oestrogens	..	3/13 (24%)	..	..
Progesterone use	..	17 (43%)	..	..
Hormone therapy use duration, years	..	4·5 (4·9)	..	..

Continuous variables are reported as mean (SD) with corresponding *t* test p values and qualitative variables are shown as n (%) with Fisher's exact test p values. Percentages might not total 100 due to rounding. GERD=gastro-oesophageal reflux disease. MASLD=metabolic-associated liver disease. OSA=obstructive sleep apnoea. HbA_{1c}=glycated haemoglobin. AST=aspartate aminotransferase. ALT=alanine aminotransferase. *Surgical menopause is defined as history of bilateral oophorectomy.

Table: **Demographic and clinical characteristics**

Discussion

This retrospective cohort study is the first study to investigate the effect of menopause hormone therapy on weight loss and cardiometabolic parameters in postmenopausal women using tirzepatide for weight management. After 15 months of treatment, women using hormone therapy experienced a 35% greater total bodyweight loss than those not using hormone therapy. Furthermore, a significantly higher proportion of women in the hormone therapy group had clinically meaningful total bodyweight loss thresholds of ≥20%, ≥25%, and ≥30%. This research expands the evidence base for tirzepatide's efficacy in weight reduction among postmenopausal women with overweight and obesity—a group at high cardiometabolic risk. This study also provides novel insights into the potential enhancing effect of hormone therapy on the therapeutic effects of GLP-1 receptor agonist-based medications.

The enhanced weight loss response to tirzepatide in people using hormone therapy aligns with our previous findings in postmenopausal women using semaglutide for obesity treatment, whereby those using hormone therapy showed a 32% greater weight loss after 12 months.[10] The total bodyweight loss observed in the current study's hormone therapy group is similar to results from the pivotal tirzepatide phase 3 trial, the SURMOUNT-1 trial, which reported approximately 20% total bodyweight loss after 18 months at the highest dose of tirzepatide in a cohort comprised of men and women.[13] However, the total bodyweight loss in the hormone therapy group is lower than the 24% reported in a cohort of women only (post-hoc analyses of all phase 3 trials of the SURMOUNT programme).[17] The suboptimal weight loss observed in the no hormone therapy group, compared with outcomes reported in

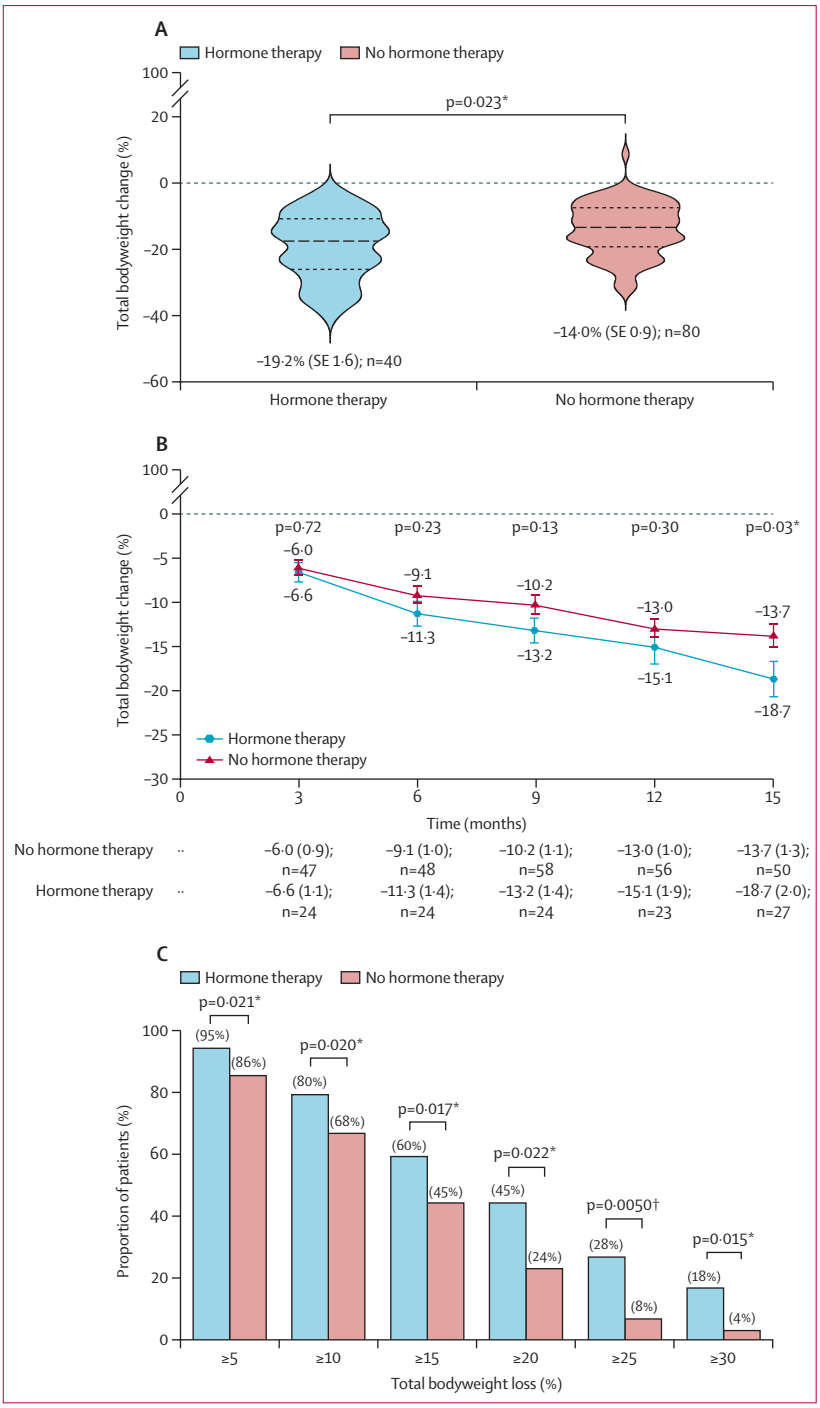

Figure 2: **Tirzepatide weight loss outcomes by hormone therapy group**
(A) Total change in bodyweight at the last follow-up for postmenopausal women with and without hormone therapy. Violin plots represent median (IQR) with mean (SE) reported below each group. p value reflects comparison using an independent *t* test. (B) Trajectories of total change in bodyweight for women in the hormone therapy group and no hormone therapy group at months 3, 6, 9, 12, and 15. Error bars indicate standard error. Group comparisons at each timepoint were performed using independent *t* tests. (C) Proportion of women in the hormone therapy group and no hormone therapy group reaching a total percentage of total bodyweight loss of ≥5%, ≥10%, ≥15%, ≥20%, ≥25%, and ≥30% at the last follow up. Fisher's exact test was used to compare the proportions between groups. *p<0·05. †p<0·001.

pivotal phase 3 clinical trials, underscores the potential benefit of hormone therapy in postmenopausal women with obesity seeking weight loss treatments. Our study is the first study to report data on the effect of hormone therapy on weight loss response to tirzepatide. Although a 2025 study found no significant effect of menopausal status on tirzepatide's efficacy, it did not assess the role of hormone therapy, leaving this potential effect unexplored.[18] Notably, the differential weight loss response among women using and not using hormone therapy in our study was not explained by differences in factors that can affect weight loss among the two groups, such as age, baseline weight or BMI, type 2 diabetes status, weight trajectory before use of tirzepatide, maximum tirzepatide dose achieved, prevalence of weight-gain-promoting medication use, or previous use of obesity medications. Previous use of obesity medications might be particularly relevant as it could reflect previous weight loss attempts, which are known to trigger compensatory reductions in energy expenditure and increases in appetite (also known as metabolic adaptations), which impair subsequent attempts.

Both groups showed improvements in cardiometabolic parameters, consistent with the phase 3 SURMOUNT trials.[13–15] However, the hormone therapy group showed additional significant reductions in diastolic blood pressure and concentrations of triglycerides and AST. Although these improvements probably stem from the greater weight loss in this group, hormone therapy might also exert independent beneficial effects due to the well-established physiological actions of oestrogen on glucose and lipid metabolism, liver function, vascular health, and its favourable effect on mitigating visceral fat deposition.[19,20] The increase in HDL cholesterol in the no hormone therapy group, although seemingly beneficial, might not reflect true cardiovascular protection. An increase in HDL cholesterol during menopause has been linked to subclinical atherosclerotic progression, suggesting potential lipoprotein dysfunction.[21] By contrast, the stable HDL cholesterol concentrations in the hormone therapy group, coupled with reductions in total cholesterol and LDL cholesterol, suggest a more favourable lipid profile and improved cardiovascular protection.

This research has substantial clinical implications. Menopause triggers profound shifts in physiology and metabolism that, in the presence of obesity, dramatically increase cardiovascular disease risk in women.[7,22] Our study suggests that combining menopause hormone therapy with obesity medications in postmenopausal women with excess adiposity might enhance their clinical benefits. Although, the observational design limits causal inference, improved weight loss and cardiometabolic outcomes in women using hormone therapy and treated with tirzepatide could reflect oestrogen's physiological effects, including improved body composition with reduced visceral fat, improved adaptive thermogenesis, and increased insulin sensitivity.[12]

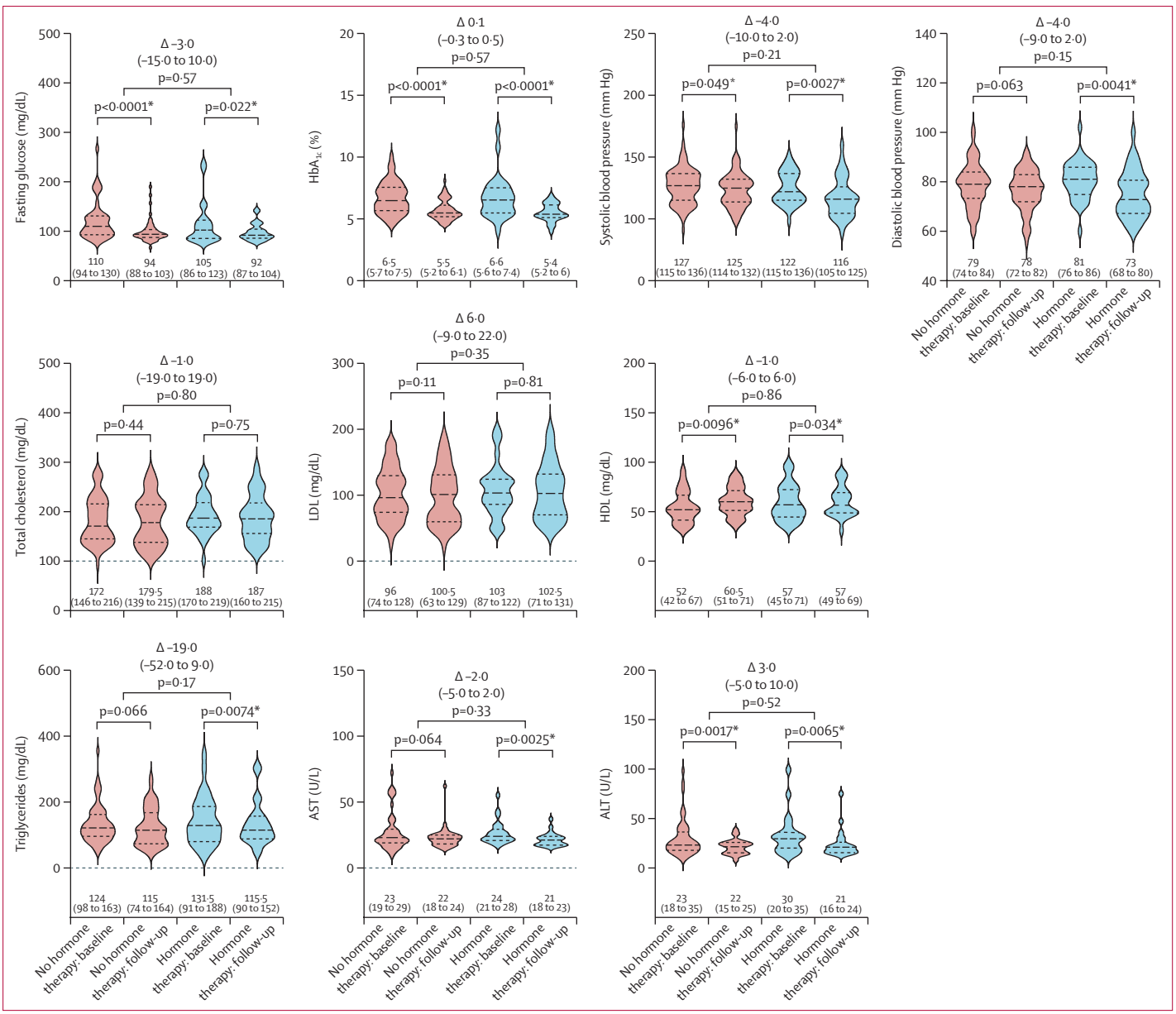

Figure 3: **Tirzepatide cardiovascular outcomes by hormone therapy group**

Cardiometabolic parameters change from baseline to last follow-up for women with and without hormone therapy. Violin plots are constructed using median (IQR). The Wilcoxon signed-rank test was used to evaluate differences in laboratory values from baseline to last follow-up within a group. A Mann–Whitney *U* test was used for between-group comparisons. ALT=alanine aminotransferase. AST=aspartate aminotransferase. HbA_{1c}=glycated haemoglobin. *p<0·05.

Remarkably, it has been established that women have a more pronounced response to GLP-1-based medications than men. This effect might be explained, at least in part, by preclinical evidence from rodent models showing that oestrogen can modulate and enhance the appetite-suppressing effects of endogenous and exogenous GLP-1, amplify the reward-reducing properties of endogenous GLP-1, and reduce food-motivated behaviour.[23] Additional advantages of hormone therapy, including vasomotor symptoms alleviation, improved sleep quality, and greater emotional wellbeing, can foster greater adherence to diet and exercise, further amplifying weight loss outcomes in response to tirzepatide.[24]

One important consideration for the differential weight loss outcomes in response to tirzepatide between people using and not using hormone therapy is the potential role of healthy-user effect. Healthy-user effect is a well-recognised phenomenon in observational research and has particularly affected studies involving users of hormone therapy, whereby individuals who choose to use certain therapies are also more likely to engage in other health-promoting behaviours that independently

improve outcomes. Previous studies have shown that users of hormone therapy tend to have more favourable psychological, demographic, and behavioural profiles, which can confound observed outcomes. For instance, compared with non-users, users of hormone therapy are more likely to have lower waist-to-hip ratios, undergo regular physical examinations, use calcium supplements, have a lower prevalence of diabetes, and use prescription medications more frequently.[25] In our cohort, and supporting the hypothesis of heightened health consciousness, the more favourable 10-year ASCVD Risk Score profile observed among users of hormone therapy might reflect greater health awareness, health-care access, and overall healthier baseline behaviours in this group. This heightened health consciousness might contribute to greater adherence to lifestyle interventions, such as diet and physical activity, potentially amplifying the weight loss effects beyond the pharmacological actions of tirzepatide.

Despite its well-established efficacy in treating the highly prevalent vasomotor symptoms of menopause, hormone therapy remains substantially under-prescribed. This underuse is driven by multiple factors, including patient anxiety, often shaped by media coverage and outdated studies, provider hesitancy, poor familiarity with current guidelines, negative societal perceptions, and a growing preference for non-hormonal alternatives.[26] Although concerns about breast cancer and thrombotic risk persist, obesity is associated with increased risk of some cancers and cardiovascular disease.[27] Therefore, the potential benefits of greater weight loss and cardiometabolic improvements should be weighed against the risks of hormone therapy.

Hormone therapy's capacity to augment weight loss and enhance cardiometabolic health alongside obesity medications warrant careful consideration when both interventions are indicated (ie, in women with obesity and vasomotor symptoms). Moreover, the direct cardio-protective effects of oestrogen further support tailoring obesity treatment to optimise weight reduction and mitigate long-term cardiovascular disease risk in this population.[28] Nevertheless, it is imperative to consider these potential benefits on an individualised basis and consider the associated risks of hormone therapy, including venous thromboembolism, stroke, and its contraindication in patients with known breast cancer or a history of the disease.[29]

This retrospective study, although offering valuable insights into the potential enhancing impact of hormone therapy on tirzepatide's therapeutic effect in postmenopausal women with obesity, has limitations inherent to its design. The observational nature of this study limits causal inference and is susceptible to confounders, biases related to data collection, and missing information. Specifically: (1) although propensity score matching addressed several key confounders (eg, diabetes status, previous obesity medication use, age, and baseline BMI), complete control over all potential confounders was not possible; (2) the small sample size might have limited the detection of differences at specific timepoints; (3) retrospective data collection inherently limits the precision of medication start and stop dates, as well as adherence; (4) incomplete documentation of weight history, age at obesity onset, and previous successful weight loss attempts limits our ability to account for important factors that might influence treatment response and long-term weight outcomes, potentially confounding the interpretation of observed effects; (5) although all women received lifestyle intervention advice, the absence of detailed records on diet and physical activity limits our ability to assess the contribution of lifestyle behaviours to the observed weight loss outcomes; and (6) although missing data limited the comprehensiveness of the allostatic load assessment (a cumulative physiological stress measure linked to adverse health outcomes and weight loss effectiveness), analysis of available components (eg, financial strain, education, adiposity-related comorbidities, use of weight-gain-promoting medications, and cardiometabolic parameters) showed no significant differences between groups.[30] Additionally, the disproportionately high prevalence of women without a uterus in our cohort, particularly among those using hormone therapy, probably reflects a combination of factors, including high rates of surgical menopause, referral bias at our tertiary care centre, and clinical practice patterns favouring oestrogen-only hormone therapy in women without a uterus.[31] The higher rate of hysterectomy in our cohort than the general population represents a selection bias and further limits the generalisability of our findings to the broader population of postmenopausal women. Furthermore, several factors might have contributed to an overestimation of the weight loss response among hormone therapy users. Healthy-user bias, as mentioned above, warrants further investigation through controlled studies. Additionally, the inclusion criterion requiring at least 1 year of treatment introduces a potential selection bias, as individuals who discontinued therapy early due to side-effects or absence of efficacy were excluded. Finally, the cohort was composed predominantly of non-Hispanic White individuals, which limits the generalisability of our findings to more diverse populations. Given known racial and ethnic differences in obesity prevalence, hormone therapy use, and treatment response, future prospective studies should include more racially and ethnically diverse populations to ensure broader applicability of the results.

There is a crucial need for prospective, randomised controlled trials with larger and more diverse cohorts to validate these findings and determine the true efficacy of tirzepatide in postmenopausal women receiving menopause hormone therapy. To disentangle behavioural effects from pharmacological efficacy, future prospective studies should include menopausal women with vasomotor symptoms that are randomly assigned to

hormone-based and non-hormone-based therapies in combination with GLP-1 agents. Importantly, studies should include systematic collection of lifestyle data, assessments of body composition, and comprehensive evaluations of energy balance components, including satiation, satiety, hunger, and energy expenditure, as well as vasomotor symptom burden. These measures will help elucidate the potential mechanisms underlying the differential weight loss responses observed between hormone therapy users and non-users. Additionally, exploring whether hormone therapy enhances the effects of tirzepatide on metabolic comorbidities, such as hypertension, type 2 diabetes, and metabolic dysfunction-associated liver disease, might provide valuable clinical insights and inform more targeted treatment approaches. To fully elucidate underlying mechanisms, these trials should include mechanistic endpoints focused on changes in insulin sensitivity, adipose tissue biology, inflammation, and hepatic metabolism. This comprehensive approach will help to optimise treatment strategies, refine patient selection, and advance the development of individualised therapies for women with obesity.

This retrospective cohort study shows a significant association between hormone therapy use and greater weight loss in postmenopausal women with overweight and obesity treated with tirzepatide. Women in the hormone therapy group lost 35% more bodyweight than those in the no hormone therapy group and showed notable improvements in key cardiometabolic parameters, supporting a potential enhancing effect of hormone therapy on tirzepatide's therapeutic effect. These findings have important clinical implications, as the menopause transition is associated with increased cardiovascular risk, particularly in women with obesity. The combined use of hormone therapy and tirzepatide might offer substantial benefits in this high-risk population, especially when hormone therapy is indicated for the management of menopausal symptoms. However, the use of hormone therapy, including the type, dose, and route of administration, should be evaluated in the context of its potential risks, including thromboembolic events, breast cancer, and stroke. Notably, these risks differ based on individual characteristics such as age, time since menopause, and underlying comorbidities. The potential benefits of combined therapy should therefore be weighed against the potential risks in a personalised, shared, decision-making process. Although this study shows a strong association, it does not establish causality. The results provide a compelling rationale for larger prospective trials to substantiate these findings, clarify underlying mechanisms, and determine the broader use of this approach in optimising weight management and improving cardiometabolic health in postmenopausal women with overweight or obesity. More broadly, these findings underscore the importance of individualised treatment strategies that thoughtfully integrate hormone therapy with emerging anti-obesity pharmacotherapies.

Contributors

RC, DB, ET, SF, CS, and MDHA contributed to the study design. RC, DB, RRG, MAE, and JV collected the data. RC and DH prepared the first draft of the manuscript and performed the statistical analyses. All authors had complete access to all study data. RC and MDHA directly accessed and verified the underlying data reported in the manuscript. MDHA is the guarantor of this work and, as such, takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors reviewed, edited, and approved the final version of the manuscript for submission.

Declaration of interests

MDHA is an advisor for Novo Nordisk and receives research funding from the National Institutes of Health (K12-AR084222), the Mayo Clinic Center for Women's Health Research, and Phenomix Sciences. AA has research technologies licensed by Gila Therapeutics and Phenomix Sciences from the University of Florida and Mayo Clinic and receives research funding from the National Institutes of Health, Vivus Pharmaceuticals, Novo Nordisk, Apollo Endosurgery, Satiogen Pharmaceuticals, Spatz Medical, Rhythm Pharmaceuticals, Regeneron, and Boehringer Ingelheim. SF is a consultant for Era Women's Health Platform, delivers continuing medical education lectures for PriMed, AiCME, MedAll, and Medscape, and serves on the scientific advisory board for Weight Watchers. CS is an advisor for Bayer Pharmaceuticals. All other authors declare no competing interests.

Data sharing

De-identified individual patient data and data dictionary will be made available with publication on request. Data will be shared for the purpose of conducting scientific analyses related to the study. Requests should be directed to the corresponding author at hurtado.mariadaniela@mayo.edu.

Acknowledgments

This study was supported by the National Institutes of Health (K12-AR084222) and the Mayo Clinic Center for Women's Health Research, which provided protected research time for MDHA.

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