Midlife Metamorphosis in Women:
Tackling Obesity During Aging and Menopause

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Disclosure

Consultant: Protagonist Therapeutics

Stock Options: Eli Lilly; Novo Nordisk; Viking Therapeutics; Zura

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OBJECTIVES

1. Understand the biological and sociologic drivers of midlife weight gain.
2. Identify effective strategies for prevention and treatment of midlife weight gain in women.
3. Recognize sex differences in response to GLP-1RA backbone drugs

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PATIENT A.M. PRESENTING FOR ANNUAL VISIT

"I don't get it — I'm eating the same, moving the same, but somehow the weight just keeps creeping on. Meanwhile, my husband's over there eating whatever he wants, and his pants still fit just fine!"

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CHANGES IN MIDLFE

- Age 40-65 years old
- Coincides with the menopause transition -> decline in hormones
- …and many other changes in life
  - Decrease in physical activity
    - Rates of physical activity decrease each decade of life

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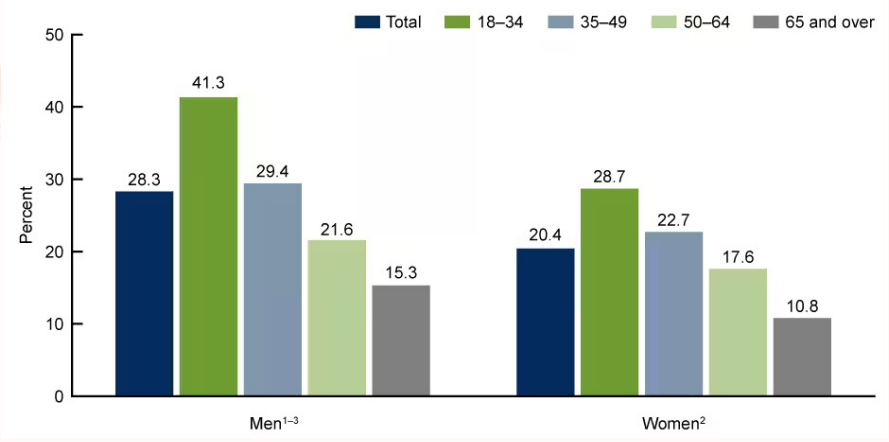
PERCENTAGE OF ADULTS 18+ WHO MEET CDC PHYSICAL ACTIVITY GUIDELINES (2020)



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Elgaddal N, et al. Physical activity among adults aged 18 and over: United States, 2020. NCHS Data Brief, no. 443. Hyattsville, MD: National Center for Health Statistics; 2022

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    - Rates of physical activity decrease each decade of life
    - **Moving from urban center to suburban/rural settings leads to less activity[1]**
    - **Busier lives: Increased child and eldercare responsibilities intersecting with peak professional development[2]**

1. Blackwell DL et al. State Variation in Meeting the 2008 Federal Guidelines for Both Aerobic and Muscle-Strengthening Activities Through Leisure-Time Physical Activity Among Adults Aged 18–64: United States, 2010–2015. *MMWR Morb Mortal Wkly Rep.* 2019;68(23):513-518.
2. Gordon JR, et al. *Women at Midlife and Beyond: A Glimpse into the Future*. Chestnut Hill, MA: Boston College Center for Work & Family; 2003. Available at: https://www.bc.edu/content/dam/files/centers/cwf/research/publications/researchreports/Women%20at%20Midlife%20and%20Beyond

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    - Moving from urban center to suburban/rural settings leads to less activity
    - Busier lives: Increased child and eldercare responsibilities intersecting with peak professional development
  - **Improvements in nutrition**

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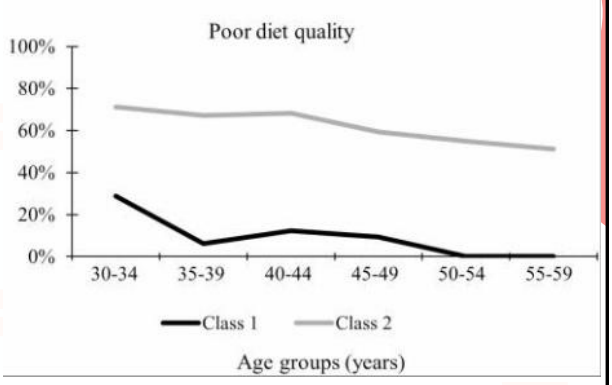
BALTIMORE LONGITUDINAL STUDY OF AGING



Talegawkar SA, et alDietary Pattern Trajectories in Middle Age and Physical Function in Older Age. J Gerontol A Biol Sci Med Sci. 2021 Feb 25;76(3):513-519. doi: 10.1093/gerona/glaa287. PMID: 33216872; PMCID: PMC7907482.

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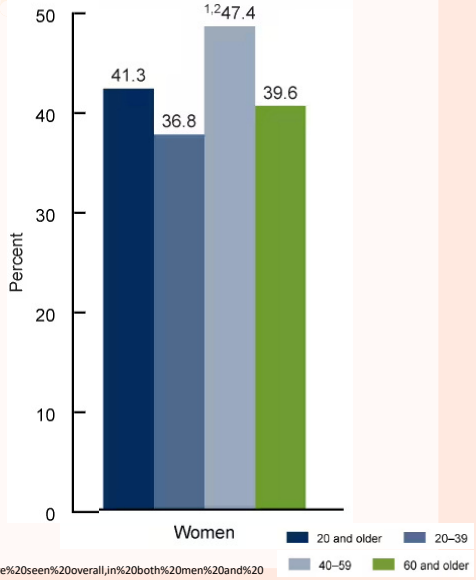
WEIGHT GAIN FOR WOMEN

Not isolated to midlife, or to women

- US adults gain 0.5-1.0 kg/year
- Highest rate of weight gain during mid-30's

Summative effect -> higher rates of overweight/obesity, peaking during midlife

Prevalence of Obesity in Adults: US 2021-2023 (CDC)



https://www.cdc.gov/nchs/products/databriefs/db508.htm#:~:text=No%20significant%20differences%20between%20men%20and%20women%20were%20seen%20overall,in%20both%20men%20and%20women.

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WEIGHT GAIN FOR WOMEN

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Outcome	Age categories					F	P
	36–39 years	40–49 years	50–59 years	60–69 years	70–79 years		
Women only ($n = 7108$)							
10-year weight gain (kg)	$9.0^{a} \pm 0.7$	$7.7^{a} \pm 0.5$	$5.9^{b} \pm 0.6$	$3.3^{c} \pm 0.6$	$1.8^{d} \pm 0.5$	30.2	<0.0001
10-year weight gain (%)	$14.5^{a} \pm 0.9$	$12.8^{a} \pm 0.7$	$10.1^{b} \pm 0.8$	$6.5^{c} \pm 0.8$	$3.7^{d} \pm 0.6$	46.4	<0.0001
Men only ($n = 6694$)							
10-year weight gain (kg)	$6.5^{a} \pm 0.7$	$5.0^{b} \pm 0.4$	$2.7^{c} \pm 0.4$	$0.9^{d} \pm 0.5$	$-1.1^{e} \pm 0.5$	33.7	<0.0001
10-year weight gain (%)	$8.5^{a} \pm 0.7$	$6.8^{b} \pm 0.5$	$3.9^{c} \pm 0.4$	$1.7^{d} \pm 0.5$	$-0.6^{e} \pm 0.5$	45.2	<0.0001

Tucker LA, et al. 10-Year Weight Gain in 13,802 US Adults: The Role of Age, Sex, and Race. *J Obes*. 2022;2022:7652408.

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BEYOND THE SCALE – MALADAPTIVE BODY COMPOSITION CHANGES

- Fat mass increases throughout adulthood for women
- Faster rate of fat mass accumulation for women 45-75 yo
- When stratifying by menopausal status:
  - Peri- and post-menopausal women absolute fat mass > premenopausal women
    - More concerning: larger amounts of central fat deposition

Greendale GA, et al. Changes in body composition and weight during the menopause transition. *JCI Insight*. 2019;4(5):e124865

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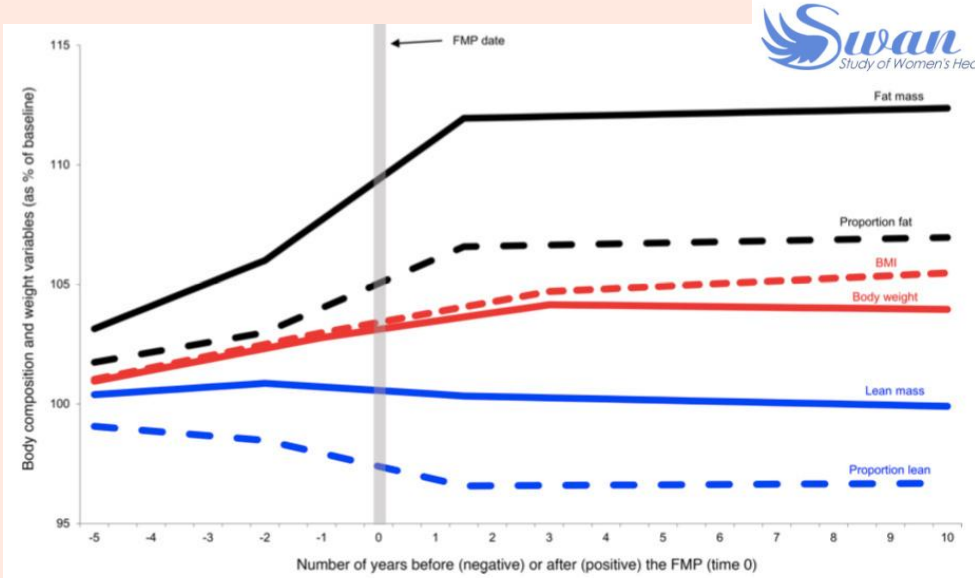

Figure 2. Model-predicted trajectories of body composition and body weight outcomes relative to the time prior to or after the FMP, SWAN. Values shown are for an average study participant (i.e., with each model covariate set at its analysis sample mean). Covariates were age at FMP, race, SWAN study site, and HT use.

Greendale GA, et al. Changes in body composition and weight during the menopause transition. *JCI Insight*. 2019;4(5):e124865

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WHAT'S THE CAUSE?

Aging vs Hormonal Changes of Menopause

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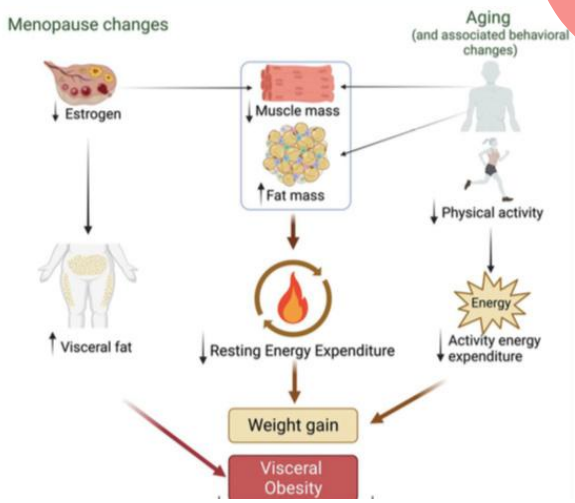
EFFECTS OF AGING

1. BMR decreases -> Decrease in TEE

- Likely due to decrease in muscle mass
- Begins at 30 yo
- Accelerates with menopause

2. No change in diet/exercise (or decrease in exercise)

- ~7% of adults meet recommended activity guidelines
- Decrease in activity with age
- 1+2 = weight gain



Hurtado MD, et al. Weight Gain in Midlife Women. Curr Obes Rep. 2024 Jun;13(2):352-363. doi: 10.1007/s13679-024-00555-2. Epub 2024 Feb 28.

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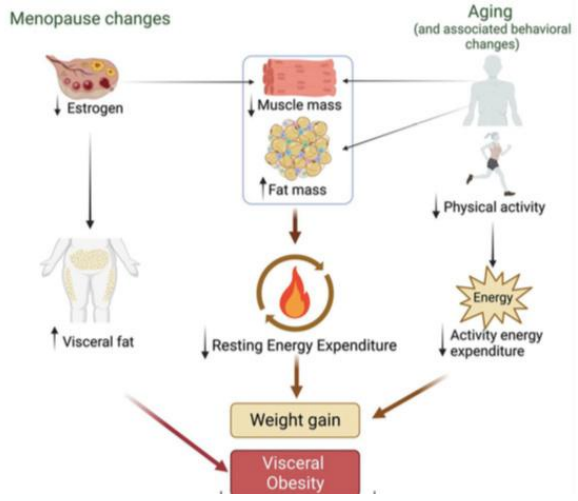
EFFECTS OF HORMONAL CHANGES

1. Loss of Estrogen

- Increased degradation
- Decreased maintenance + regeneration/repair

2.Loss of Androgens (DHEAS) -> less muscle

1+2 = less muscle, decrease BMR



3. Vasomotor Symptoms -> higher rates of weight gain

- a/w: less physical activity, poor sleep quality

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Hurtado MD, et al. Weight Gain in Midlife Women. Curr Obes Rep. 2024 Jun;13(2):352-363. doi: 10.1007/s13679-024-00555-2. Epub 2024 Feb 28.

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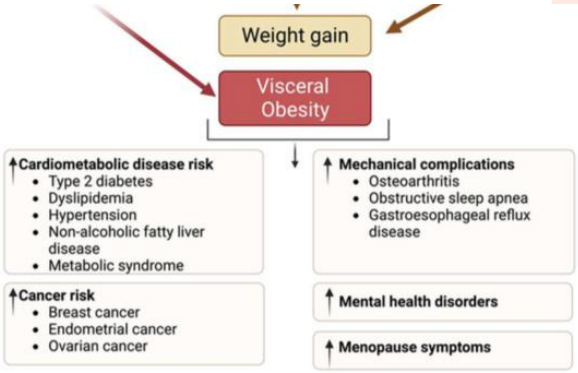
CLINICAL CONSEQUENCES OF MIDLIFE WEIGHT GAIN

Weight gain and maladaptive body composition changes play a role in cardiac risk in postmenopausal women vs premenopausal women

CVD is the #1 cause of death in postmenopausal women.

Risk factor modification is key!



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WEIGHT MANAGEMENT FOR WOMEN IN MIDLIFE

1. Prevention
2. Menopause management
3. Treating Obesity

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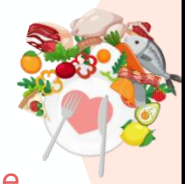
WEIGHT MANAGEMENT FOR WOMEN IN MIDLIFE: PREVENTION

- Educate women starting at a young age about importance of exercise
- Screen annually for activity levels and nutrition habits
- Counsel women to engage in anaerobic and aerobic exercise, adequate protein intake
- Discuss signs/symptoms of perimenopause



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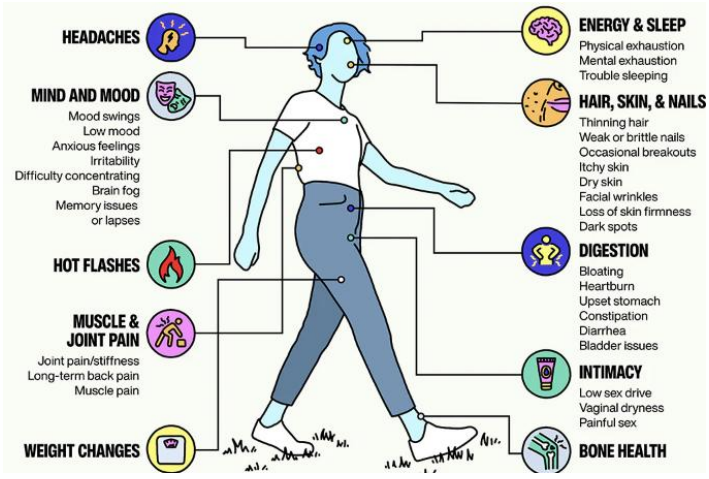
SIGNS/SYMPTOMS OF PERIMENOPAUSE



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Hanna C. What are the Main Symptoms of Perimenopause and Menopause? Versalie. Published September 22, 2023. https://www.versalie.com/blogs/learn/symptoms-perimenopause-menopause

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WEIGHT MANAGEMENT FOR WOMEN IN MIDLIFE: MENOPAUSE TREATMENT

Traditional: focus on symptom management

- Lifestyle change
- Medications, like SSRIs/SNRIs, gabapentin

Hormone Therapy

- Estrogen therapy (for women without a uterus)
- Estrogen + progestin (for women with a uterus to prevent endometrial hyperplasia)

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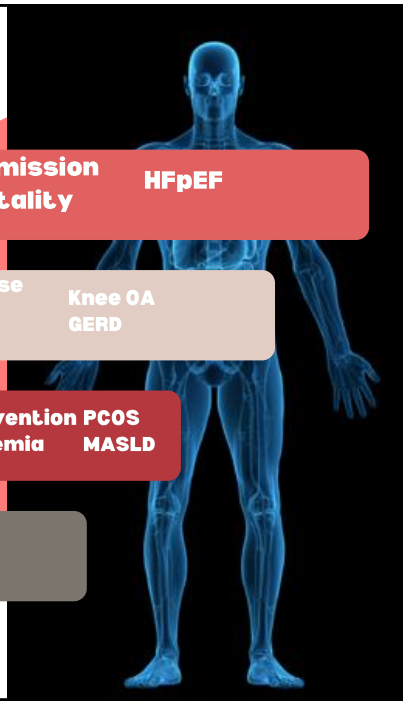
TREATING OBESITY WHAT IS THE GOAL?

- **Improving health, NOT for size conformity**
  - **Should NOT assume excess weight = unhealthy**
- **Modest weight loss can improve health**
- **Don't fixate on BMI targets for treatment**
- **Chronic disease management**



Garvey WT et al. Endocr Pract 2016;22(Suppl. 3):1–203; 2
Look AHEAD Research Group. Lancet Diabetes Endocrinol 2016;4:913–21;
Lean ME et al. Lancet 2018;391:541–51; 4. Benraoune F and Litwin SE. Curr Opin Cardiol 2011;26:555–61.

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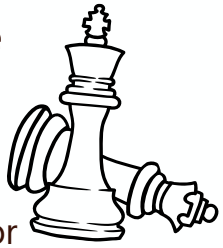
WEIGHT MANAGEMENT FOR WOMEN IN MIDLIFE: TREATING OBESITY



- Treating obesity is like pulling out the queen in a game of chess — with one strategic move, you take down multiple threats at once, not just one at a time like the rest.
- Same considerations – lifestyle change, medications for weight loss
- Women have higher rates of weight loss with GLP1-RA backbone drugs than men

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Weight Loss Associated with Semaglutide 2.4 mg Based on Sex (STEP-HFpEF)

	Women (n = 570)		Men (n = 575)	
	Semaglutide 2.4 mg (n = 277)	Placebo (n = 293)	Semaglutide 2.4 mg (n = 296)	Placebo (n = 279)
Change in body weight at 52 wks, %	n = 257 −12.6 (−13.5 to −11.7)	n = 268 −3.0 (−3.9 to −2.1)	n = 275 −10.2 (−11.1 to −9.3)	n = 252 −3.0 (−4.0 to −2.1)

Kosiborod MN, et al. Semaglutide in patients with heart failure with preserved ejection fraction and obesity. *N Engl J Med*. 2023;389(12):1069-1084.

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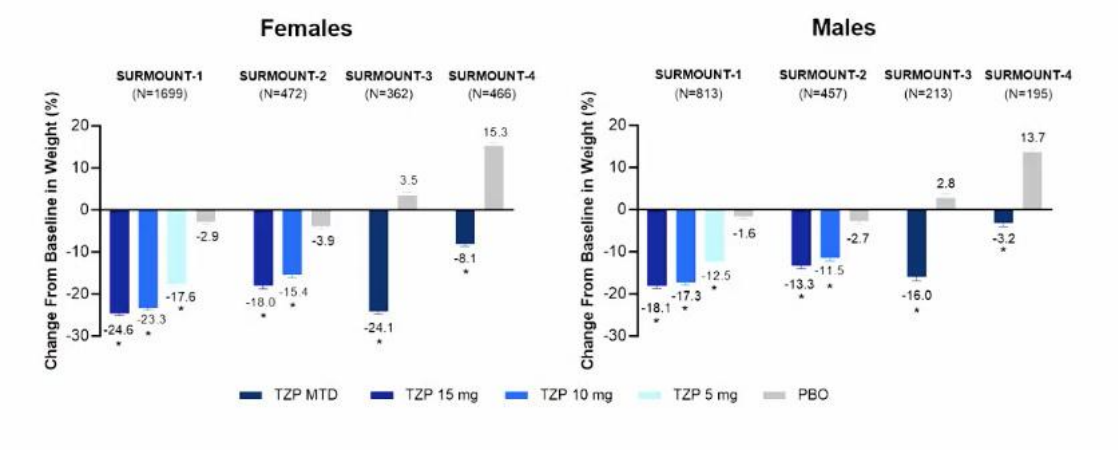
Weight Loss Associated with Tirzepatide Based on Sex



Garcia, LE. Body Weight Reduction with Tirzepatide by Sex: a Subgroup Analysis of SURMOUNT Clinical Trials. 60th Annual Meeting, European Association for the Studies of Diabetes. 2025.

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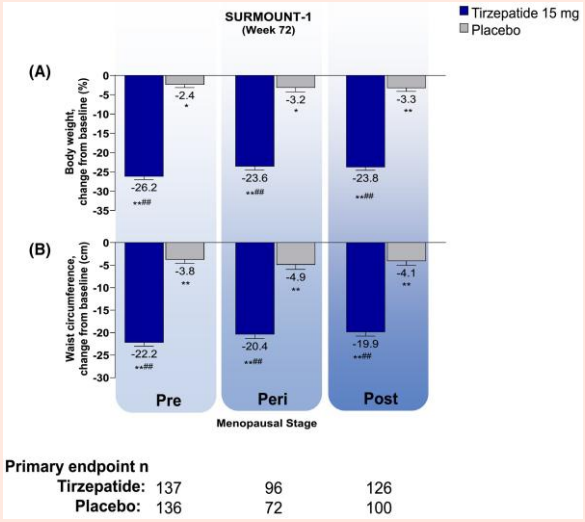
Weight Loss in Women Based on Reproductive Stage



Tchang BG, et al. Body weight reduction in women treated with tirzepatide by reproductive stage: a post hoc analysis from the SURMOUNT program. Obesity.

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CLINICAL TAKEAWAYS

1. **Prioritize Early Prevention** – Educate and empower younger female patients to focus on strength training and maintaining activity levels to mitigate future weight gain and body composition changes.
2. **Screen for Lifestyle Changes** – Routinely assess activity levels and dietary habits in midlife patients
   - Shifts in energy balance can significantly impact weight gain during this stage.
3. **Consider Hormone Therapy (HT) When Appropriate** – For symptomatic menopausal women, HT can be a valuable tool in managing weight and metabolic health, provided it is used safely and within clinical guidelines.
4. **Screen Regularly for Weight Changes in Midlife**
   - Earlier recognition and intervention can prevent significant maladaptive body composition changes + weight gain -> reduce risk of developing obesity + cardiometabolic disease, mechanical disease, cancer (breast, endometrial, ovarian)
5. For patients with obesity - **Use a comprehensive obesity management approach**
   - Combine lifestyle, behavioral, and pharmacological interventions, including GLP-1 RA backbone medications
     - Have shown greater weight loss efficacy in women, tirzepatide improves waist circumference
     - Premenopausal women have marginally more weight loss than postmenopausal women

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