

# People living with **obesity**

are at an increased risk for  
several health complications.



To know more about obesity related complications, please tap on the organs.



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Cardiovascular  
outcomes



Heart failure  
HFpEF



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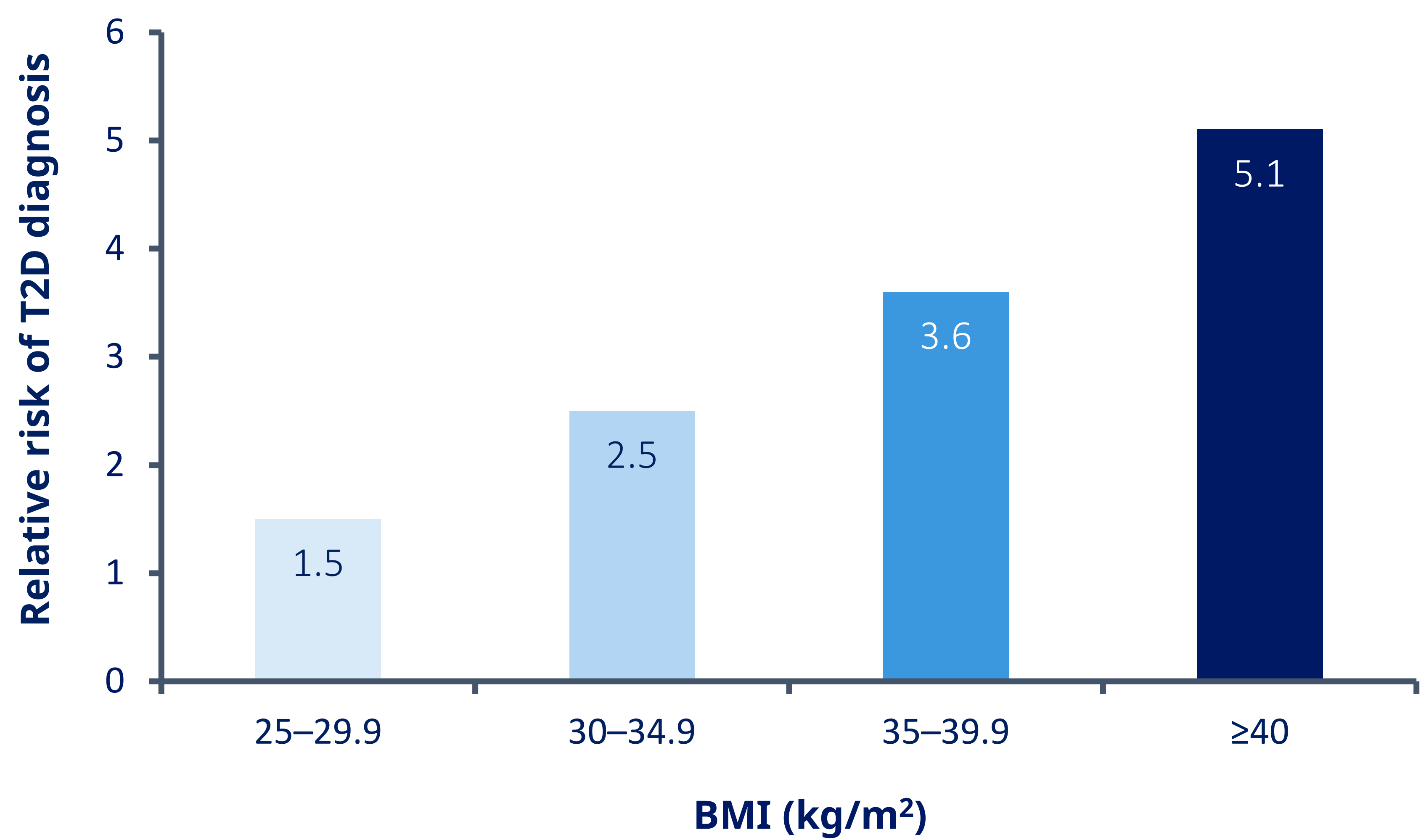


People living with obesity are at an increased risk for several health complications.

Obesity is a significant risk factor for type 2 diabetes

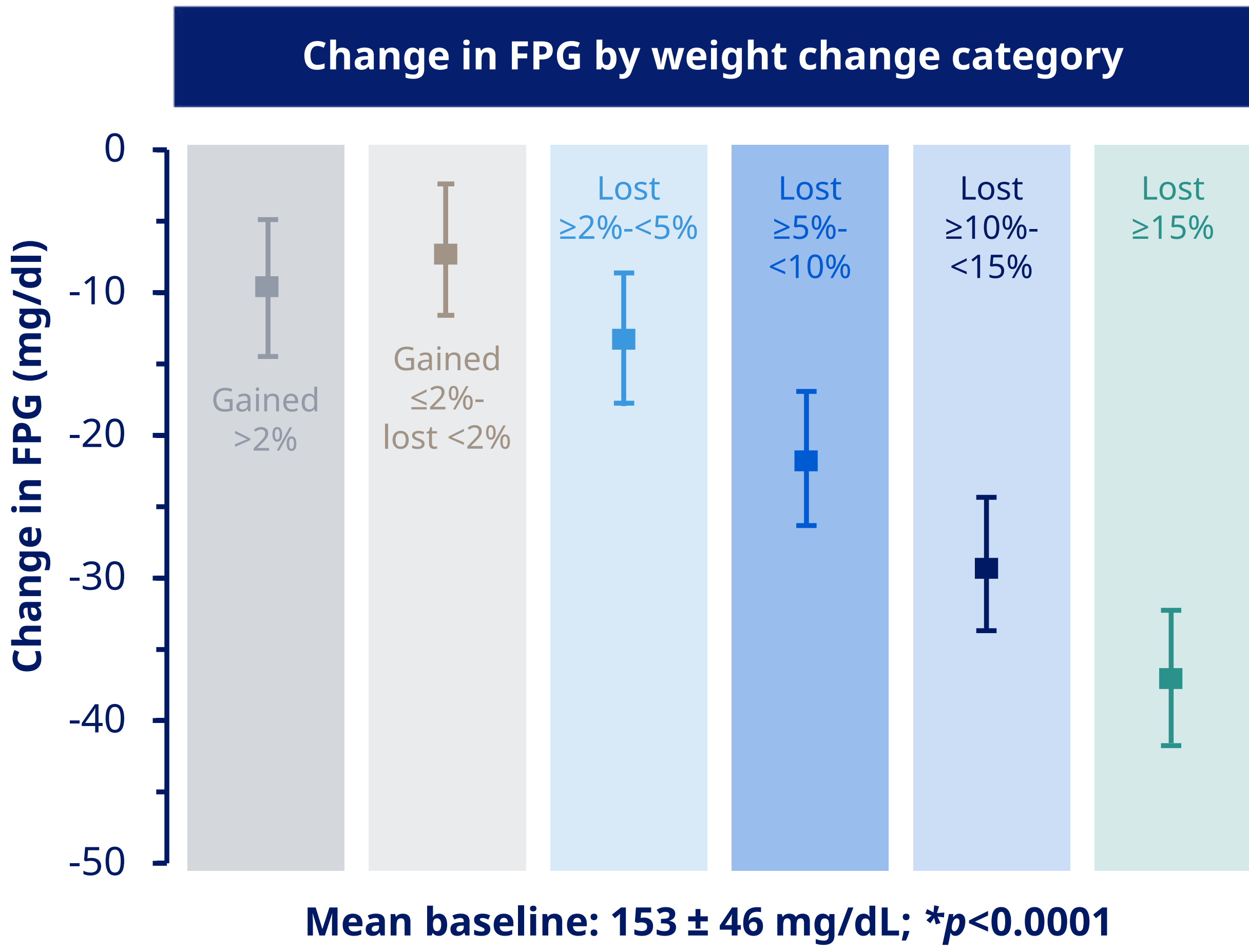
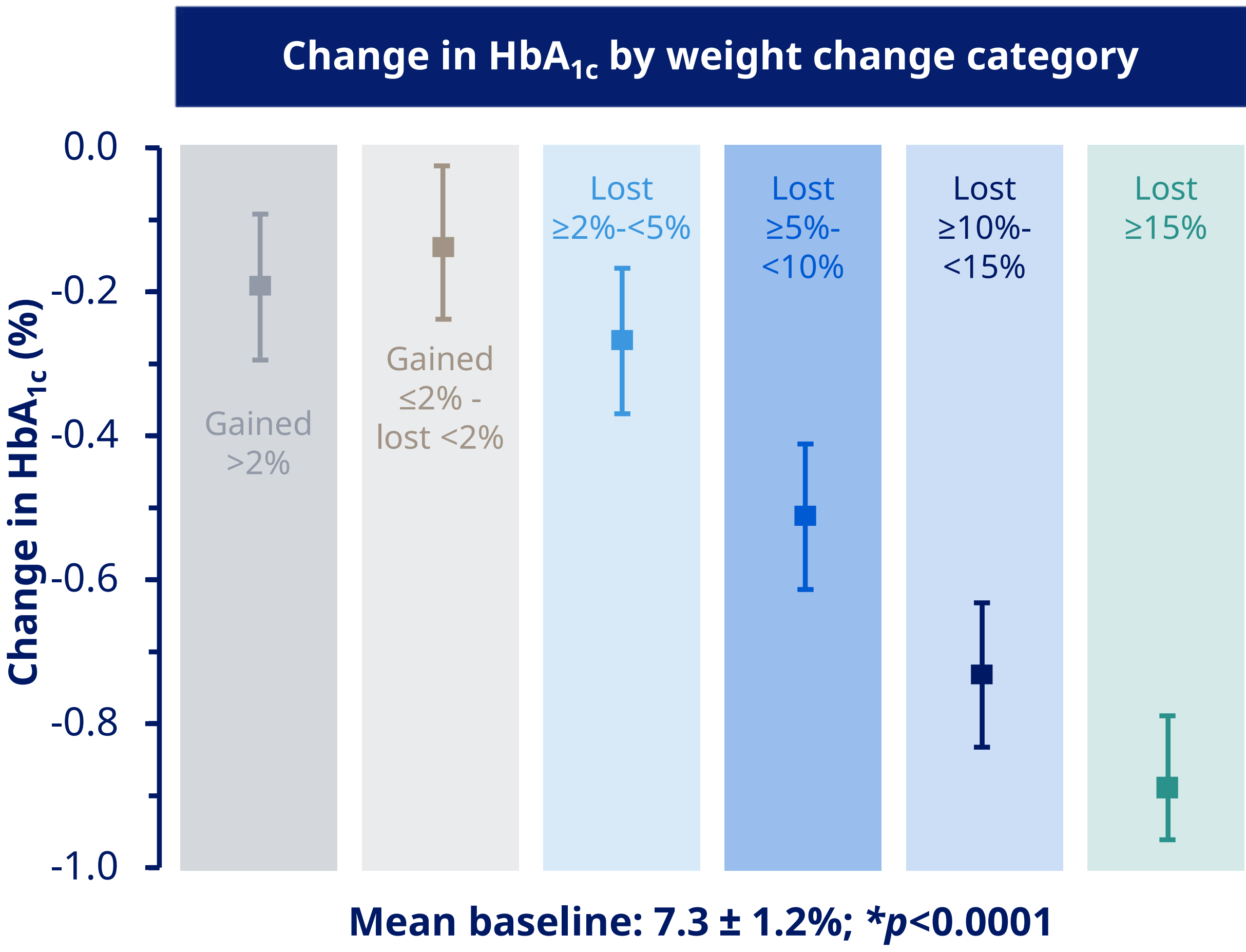
Prevalence of T2D increases with higher BMI<sup>1</sup>

Risk of Type 2 diabetes  
Relative to normal BMI (18.5–24.9 kg/m<sup>2</sup>)



ADA recommends the inclusion of weight management goals for achievement and maintenance of glycemic control in patients with type 2 diabetes and obesity<sup>2</sup>.

Weight reduction significantly reduces levels of HbA<sub>1c</sub> and FPG in patients with T2D<sup>3</sup>



Summary

- Modest and sustained weight reduction has been shown to significantly improve glycemic control.
- Effective obesity management can have a positive impact on the treatment of type 2 diabetes.

ADA, American Diabetes Association; BMI, body mass index; HbA<sub>1c</sub>, glycated hemoglobin; FPG, fasting plasma glucose; T2D, type 2 diabetes.  
\*p-values are strength of association of improvement with magnitude of weight loss.  
1. Ganz ML et al. *Diabetol Metab Syndr*. 2014;6:50. 2. American Diabetes Association (ADA). *Diabetes Care* 2023; 46(Suppl. 1): S140–S157 doi: <https://doi.org/10.2337/dc23-S009>; 3. Wing et al. *Diabetes Care* 2011;34:1481–6.





People living with obesity are at an increased risk for several health complications.

## Obesity is associated with an increased risk of metabolic dysfunction-associated steatotic liver disease

Obesity is associated with a **3.5-fold** increased risk of developing MASLD, compared with normal weight<sup>1</sup>

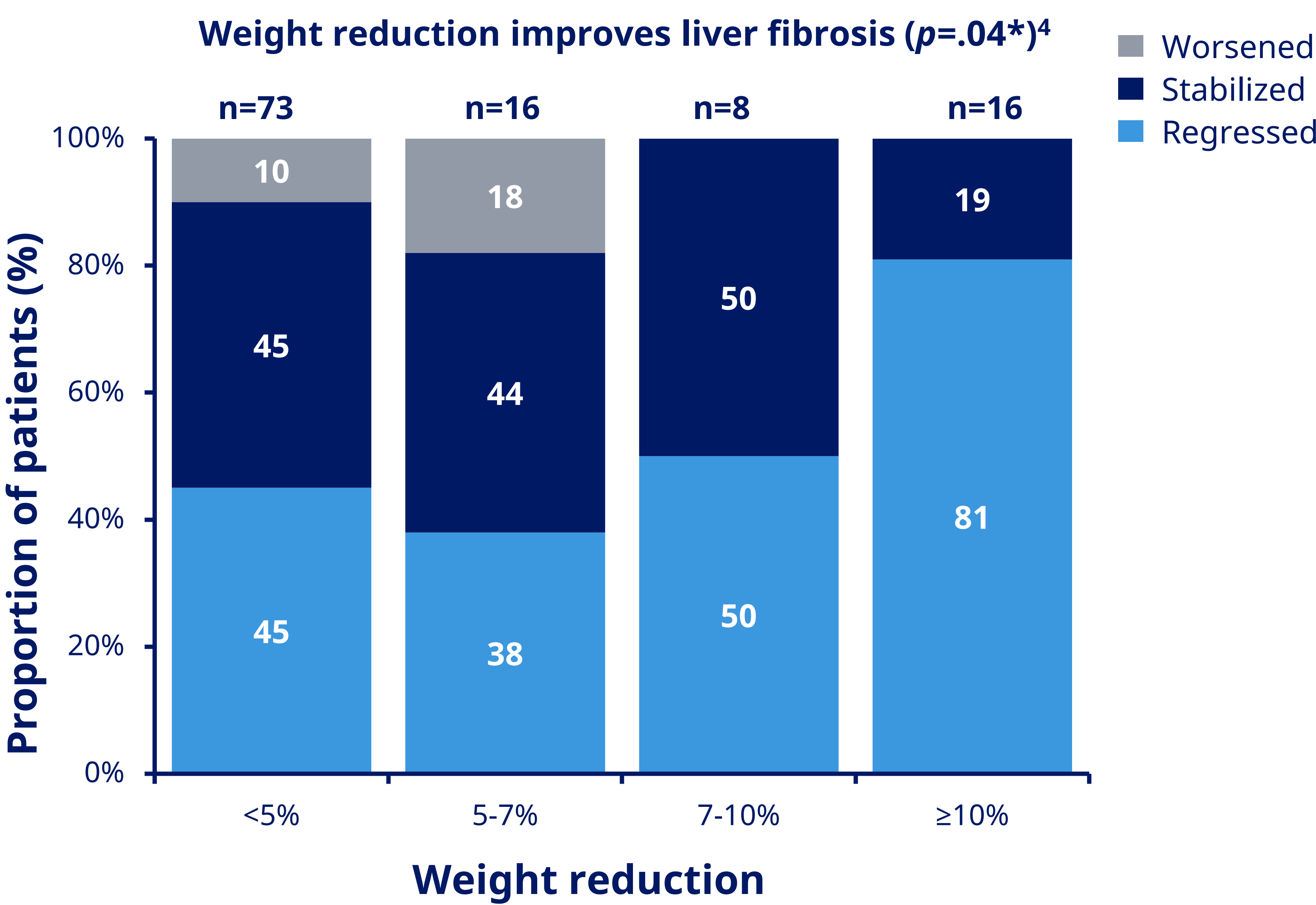
**Weight loss reduced hepatic steatosis and incident MASLD in patients with overweight/obesity and T2D<sup>2</sup>**



**Weight reduction with lifestyle intervention improved liver histology in patients with overweight/obesity and biopsy-proven MASH<sup>3,4</sup>**



According to AASLD, weight reduction of 3% to 5% can improve steatosis, while a weight reduction of 7% to 10% is recommended to improve most of the histopathological features of MASH<sup>5</sup>.



### Summary

- Obesity can lead to 3.5-fold increased risk of developing MASLD compared with normal weight.
- Effective weight management can reduce liver fat, resolve inflammation and improve scarring in patients with MASH.

\*P values for the Mantel-Haenszel  $\chi^2$  test for trend stratified by age older than 55 years, sex, BMI  $\geq 35$ , type 2 diabetes, medication of diabetes/hyperlipidemia, and baseline fibrosis score.  
AASLD, American Association for the Study of Liver Diseases; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; T2D, type 2 diabetes.  
1. Li L et al. *Obes Rev* 2016;7:510–9; 2. Lazo et al. *Diabetes Care* 2010;33:2156–63; 3. Promrat et al. *Hepatology* 2010;51:121–9; 4. Vilar-Gomez. *Gastroenterology* 2015;149:367–378; 5. Bahirwani R et al. *Clin Liver Dis (Hoboken)*. 2022;19(6):222-226.



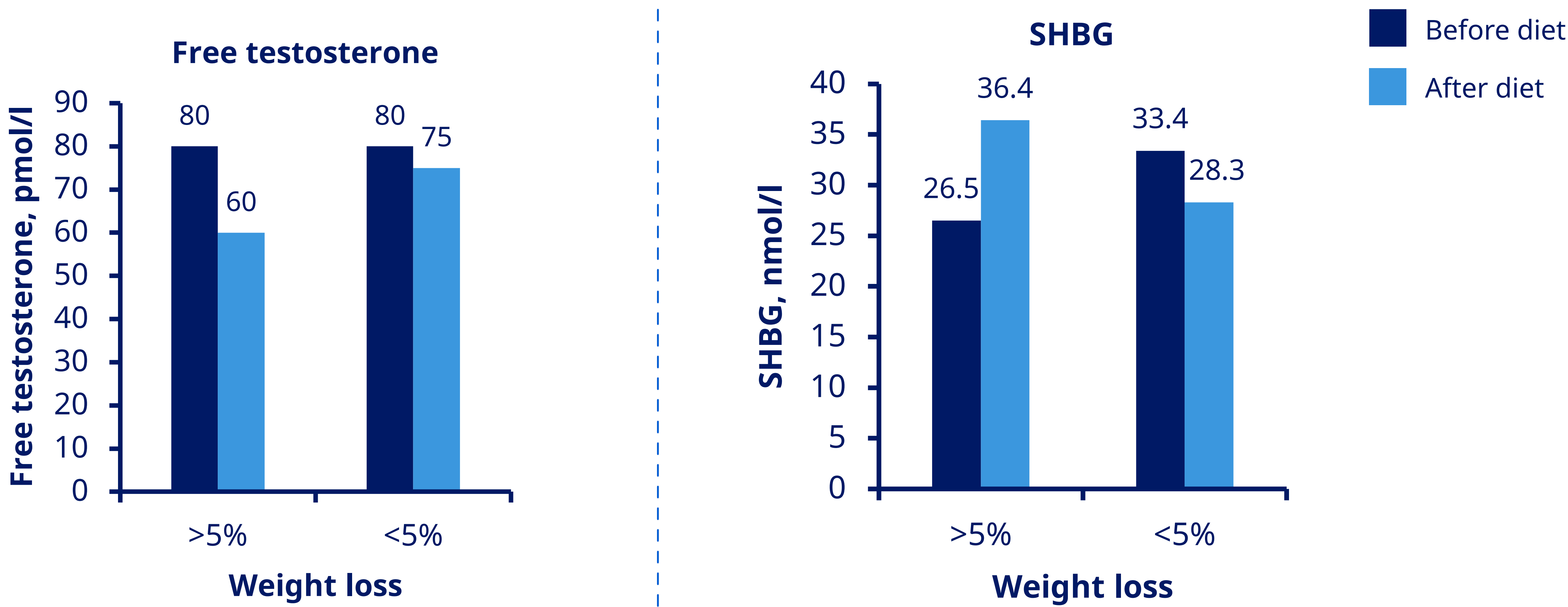


People living with obesity are at an increased risk for several health complications.

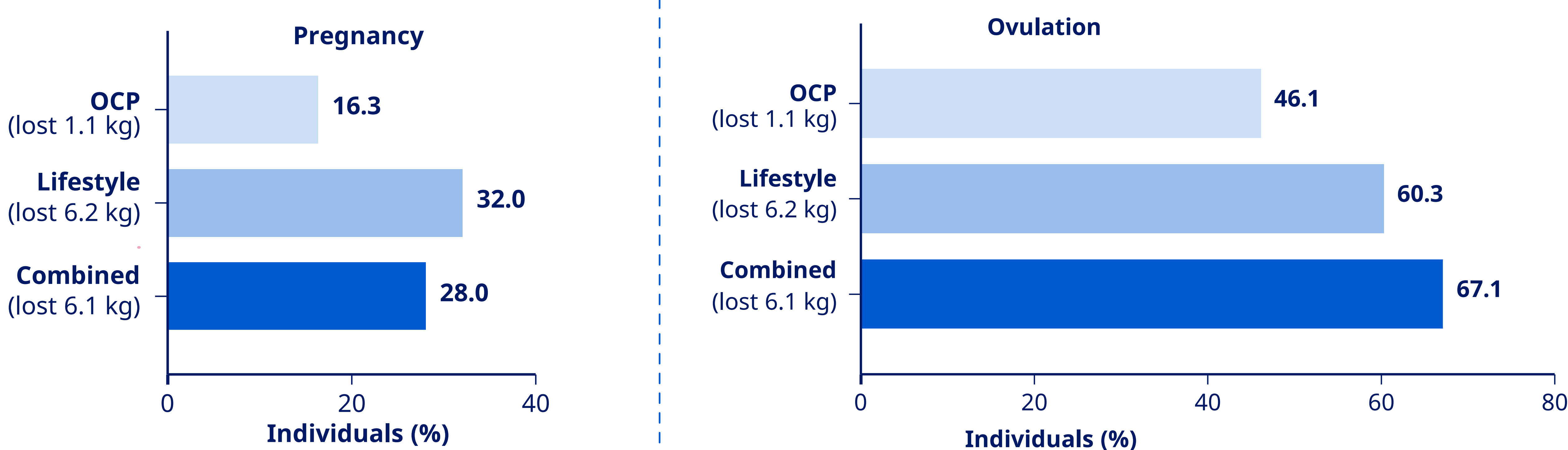
## Obesity is linked with the development of polycystic ovary syndrome

- In the United States, approximately 80% of women with PCOS have overweight or obesity<sup>1</sup>.
- Elevated BMI at age 18 is predictor of ovulatory infertility<sup>2</sup>.
- Relative risks of infertility were significantly elevated above BMI of 23.9<sup>2</sup>.
- ASRM/ESHRE recommends weight management as the first-line therapy in overweight women with PCOS attempting to conceive<sup>3</sup>.

### Weight reduction improves clinical and biochemical parameters in women with obesity and PCOS<sup>4</sup>



### Weight reduction improves fertility in women with obesity and PCOS<sup>5</sup>



### Summary

- The prevalence of PCOS is higher in women with obesity.
- Weight reduction is associated with improvement in the abnormalities related to PCOS.

ASRM, American Society for Reproductive Medicine; ESHRE, European Society of Human Reproduction and Embryology; BMI, body mass index; PCOS, polycystic ovary syndrome; SHBG, sex hormone binding globulin; OCP, oral contraceptives.  
1. Sam S. *Obes Manag* 2007;3(2):69-73; 2. Rich-Edwards et al. *Am J Obstet Gynecol* 1994;171(1):171-7; 3. Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. *Fertil Steril*. 2008;89(3):505-22; 4. Tolino et al. *Eur J Obstet Gynecol Reprod Biol* 2005; 119(1): 87-93; 5. Legro et al. *J Clin Endocrinol Metab* 2015;100:4048-58.



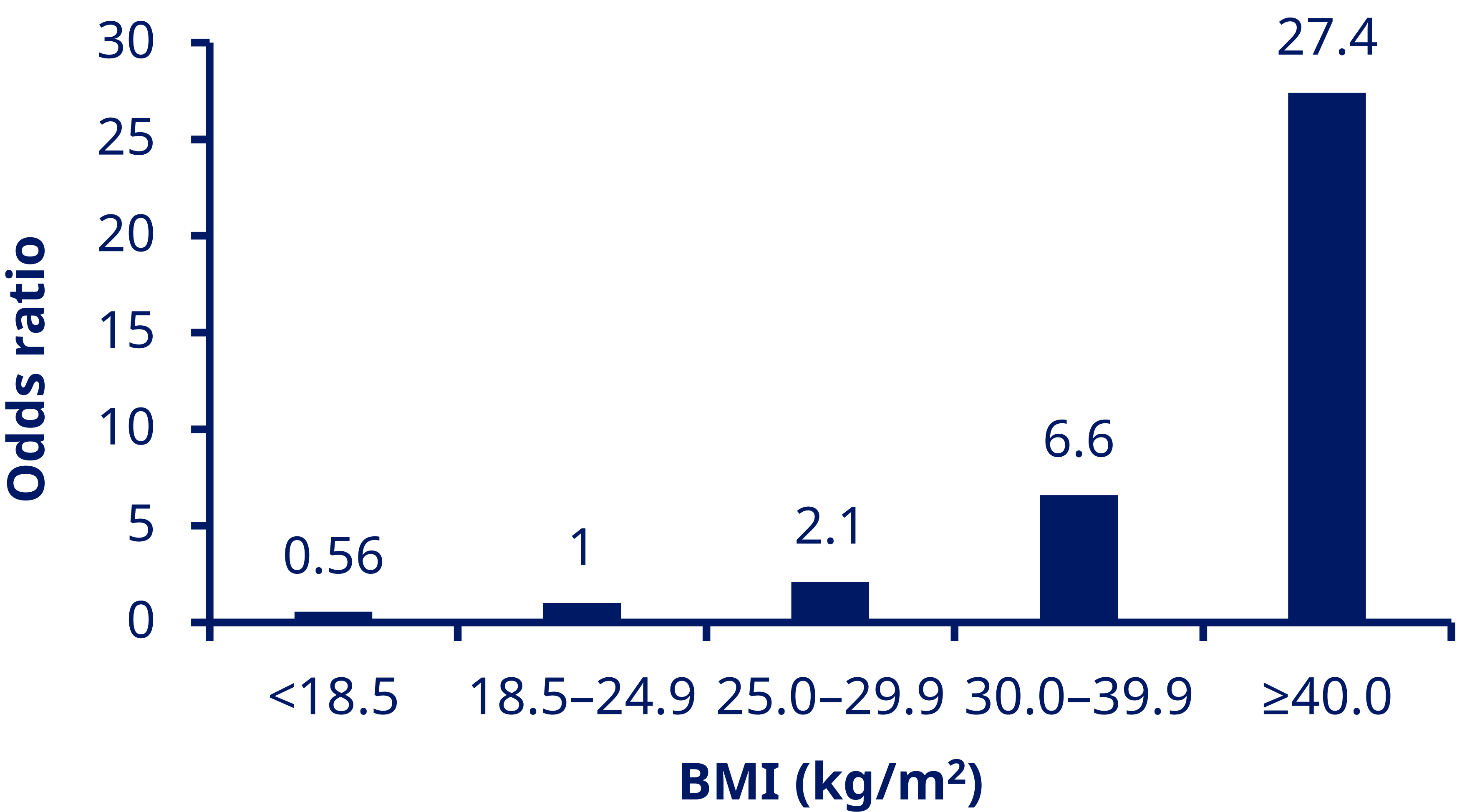


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## Obstructive sleep apnea is associated with obesity

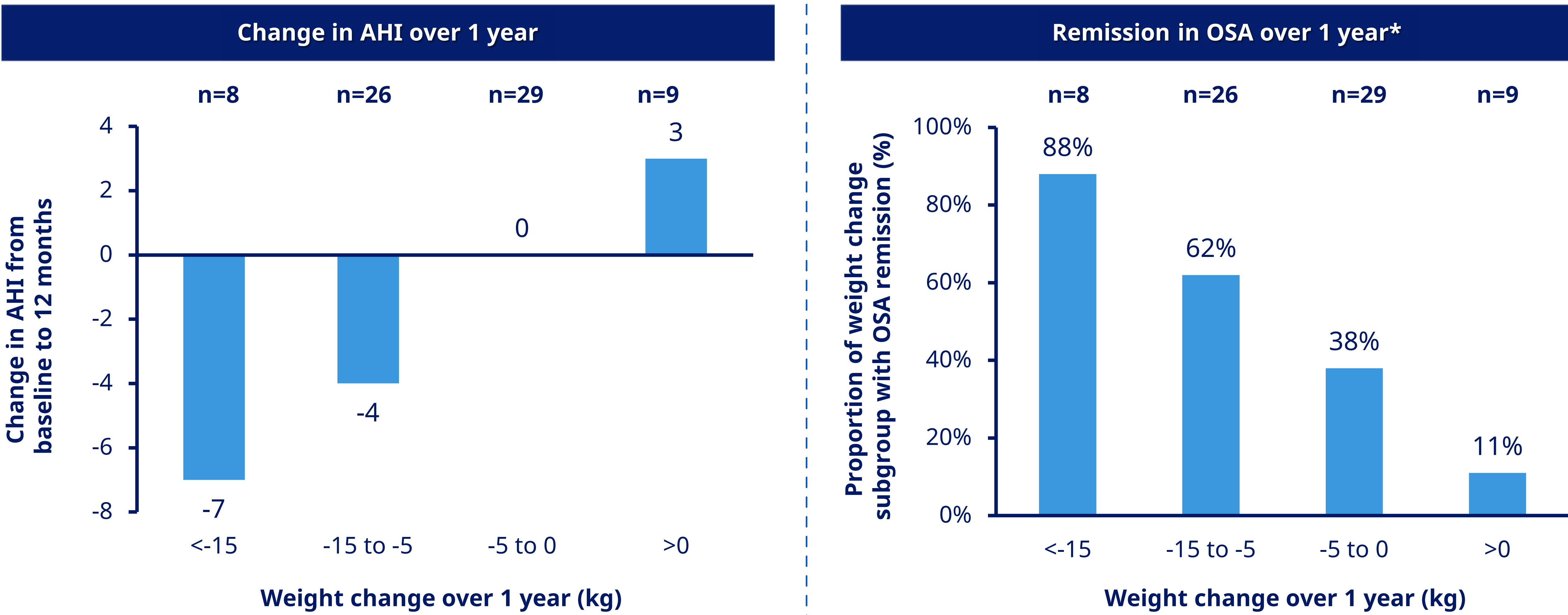
>80% of adult patients with OSA have overweight and >50% have obesity<sup>1</sup>

### Patients with overweight/obesity have higher risk of OSA<sup>2</sup>



ACP and AASM recommends weight reduction for patients with obesity/overweight to manage OSA<sup>3,4</sup>.

### Weight reduction is associated with reduced AHI and increased remission in adults with mild OSA<sup>5</sup>



## Summary

- Patients with overweight/obesity have higher risk of OSA than people with normal BMI.
- In adults with mild OSA, weight reduction achieved through a VLCD program showed better improvement in AHI than adults in the control group.

OSA, obstructive sleep apnea; BMI, body mass index; ACP, American College of Physicians; AASM, American Academy of Sleep Medicine; AHI, apnea-hypopnea index; VLCD, very low-calorie diet.  
\*Remission defined as AHI <5.  
1. Almendros et al. *Int J Obes* 2020; 2. Wall H et al. *Prim Care Respir J.* 2012;21(4):371-376; 3. Qaseem et al. *Ann Intern Med* 2013;159:471-483; 4. AASM Clinical Guideline for the Evaluation, Management and Long-term Care of Obstructive Sleep Apnea in Adults. Available [http://www.aasmnet.org/Resources/clinicalguidelines/OSA\\_Adults.pdf](http://www.aasmnet.org/Resources/clinicalguidelines/OSA_Adults.pdf); 5. Tuomilehto et al. *Am J Respir Crit Care Med* 2009;179:320-7.



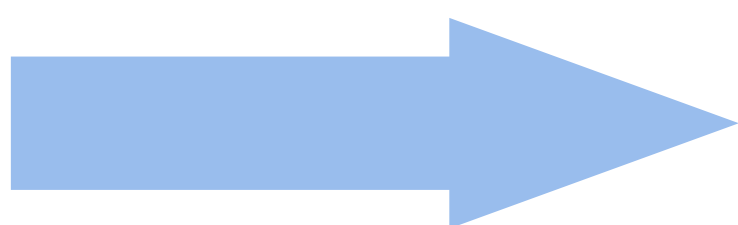


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## Obesity increases the risk of knee osteoarthritis

Prevalence of knee OA increases with higher BMI<sup>1</sup>

5 kg/m<sup>2</sup>  
increase in BMI

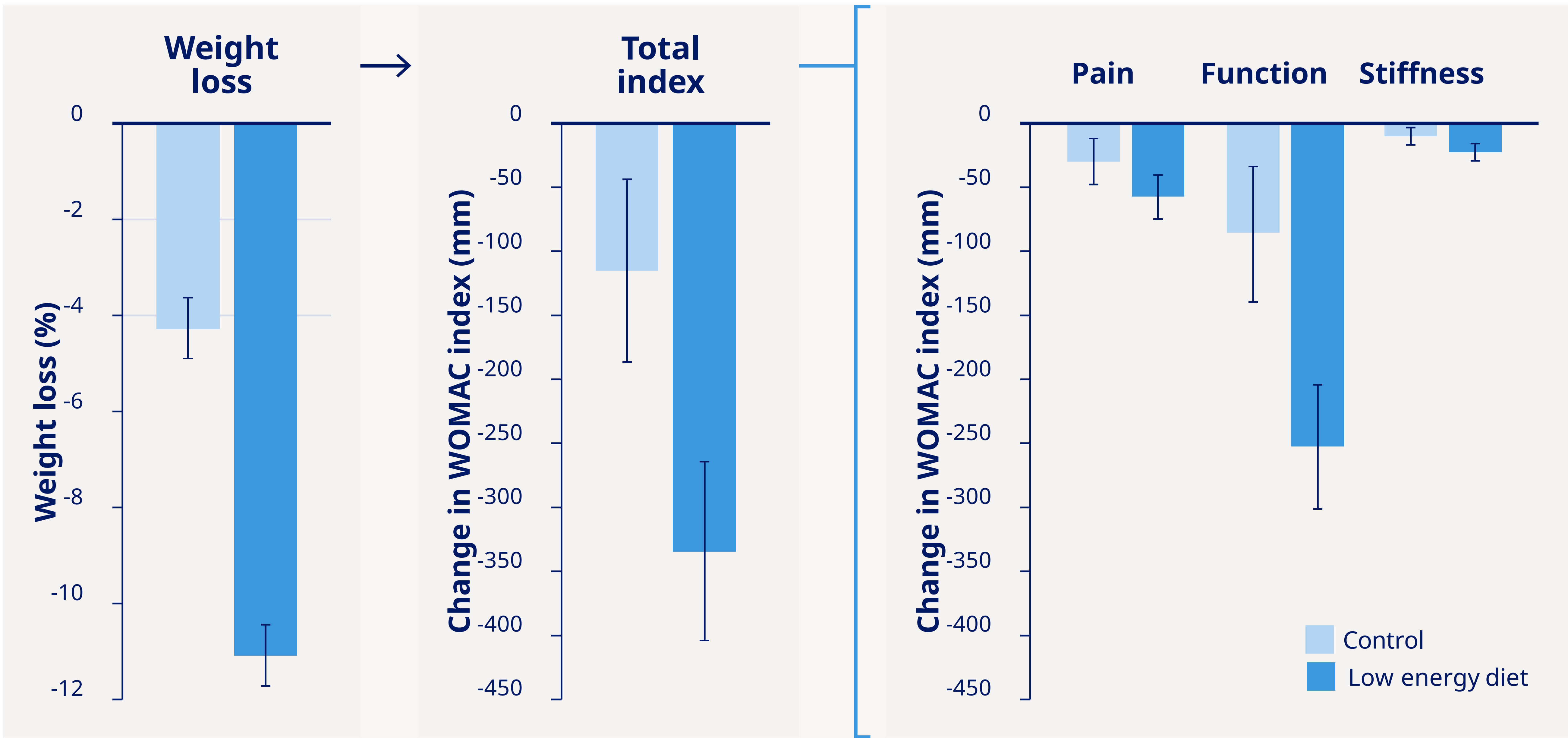


35%  
increase in risk of  
knee OA  
[95% CI, 1.18-1.53, p<0.001]



ACR guidelines recommend weight reduction for patients with obesity/overweight to manage knee OA<sup>2</sup>.

Weight reduction from low-energy diet is associated with improved functional status



≥10% reduction in body weight was associated with improvements in functional status (28% improvement in OA) comparable to knee joint replacement<sup>3,4</sup>

### Summary

- Overweight and obesity are associated with higher risks of knee OA.
- In overweight patients with knee OA, ≥10% reduction in body weight was associated with improvements in functional status.

BMI; body mass index; OA, osteoarthritis; ACR, American College of Rheumatology; WOMAC, Western Ontario and McMaster University Osteoarthritis index.  
1. Zheng et al. *BMJ Open* 2015; 5(12): e007568; 2. Shumnalieva R et al. *Life (Basel)*. 2023 Jul 28;13(8):1650; 3. Christensen et al. *Osteoarthritis Cartilage* 2005;13:20–7; 4. Bachmeier et al. *Osteoarthritis Cartilage* 2001;9:137–46.



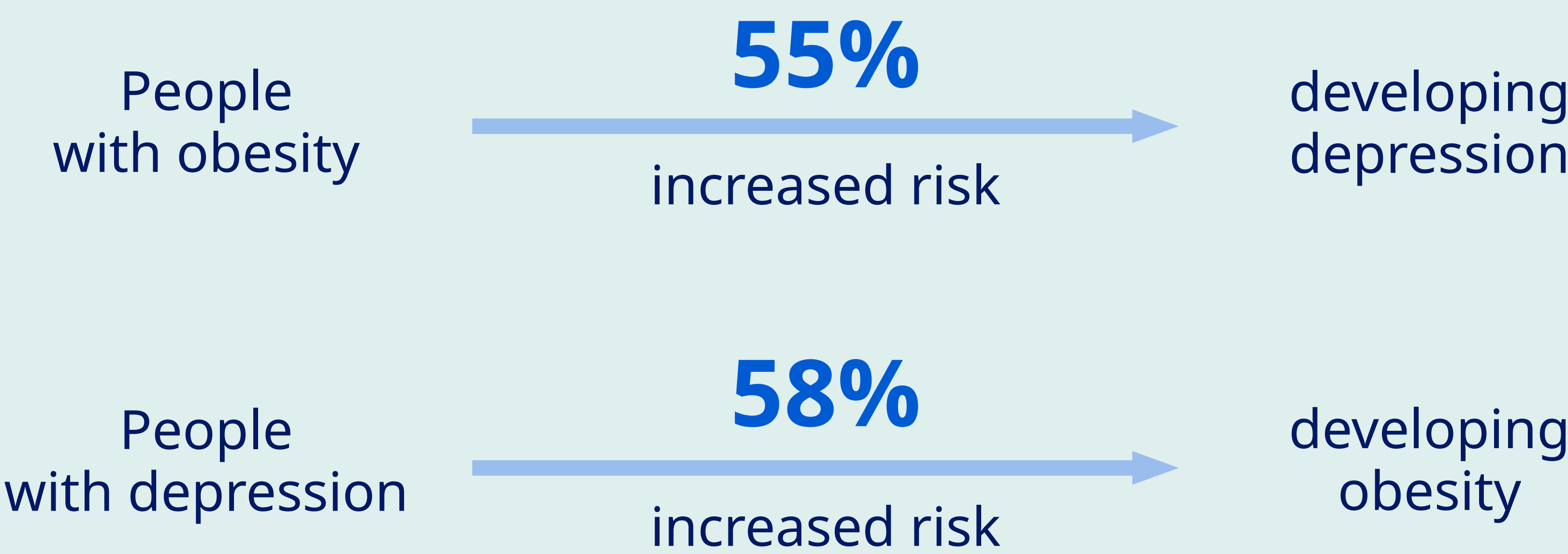


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## Obesity and depression are common comorbidities

### Bidirectional association between obesity and depression

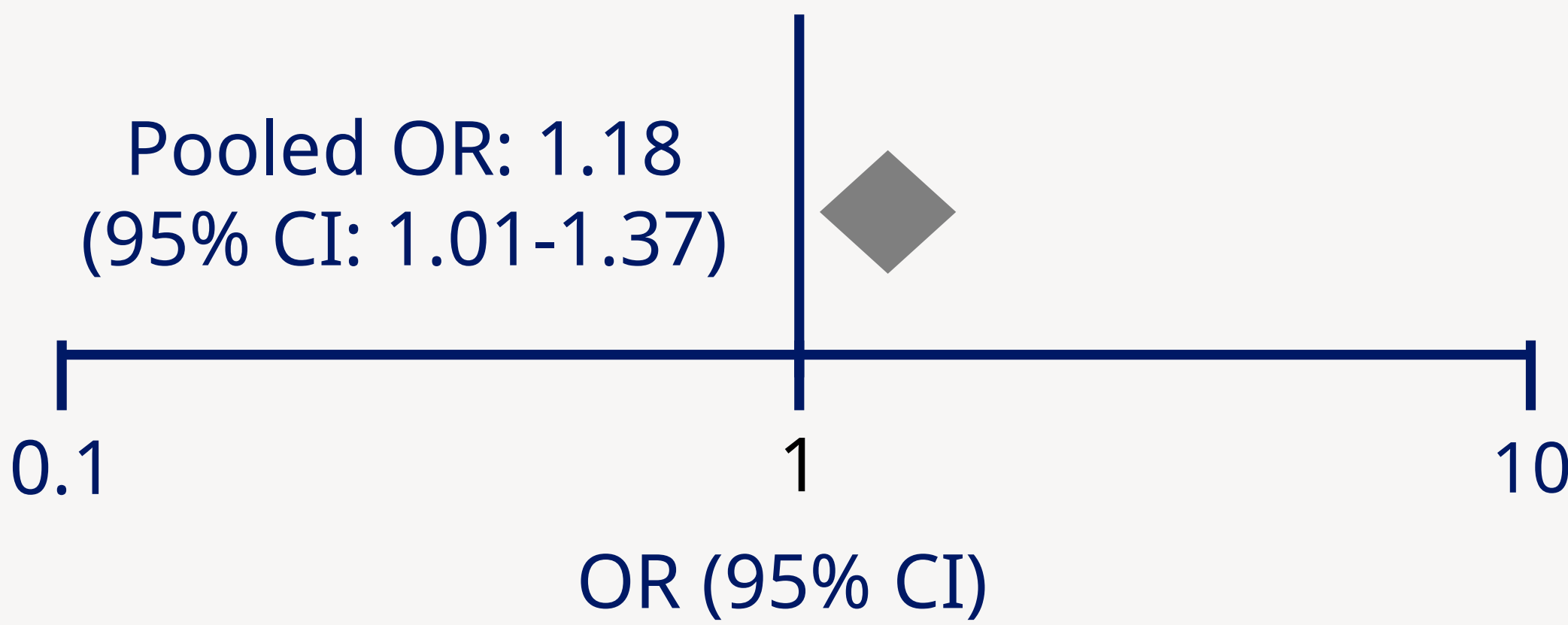
#### Meta-analysis of 15 longitudinal studies (n= 58,745)<sup>1</sup>



### Risk of depression is elevated in people with obesity

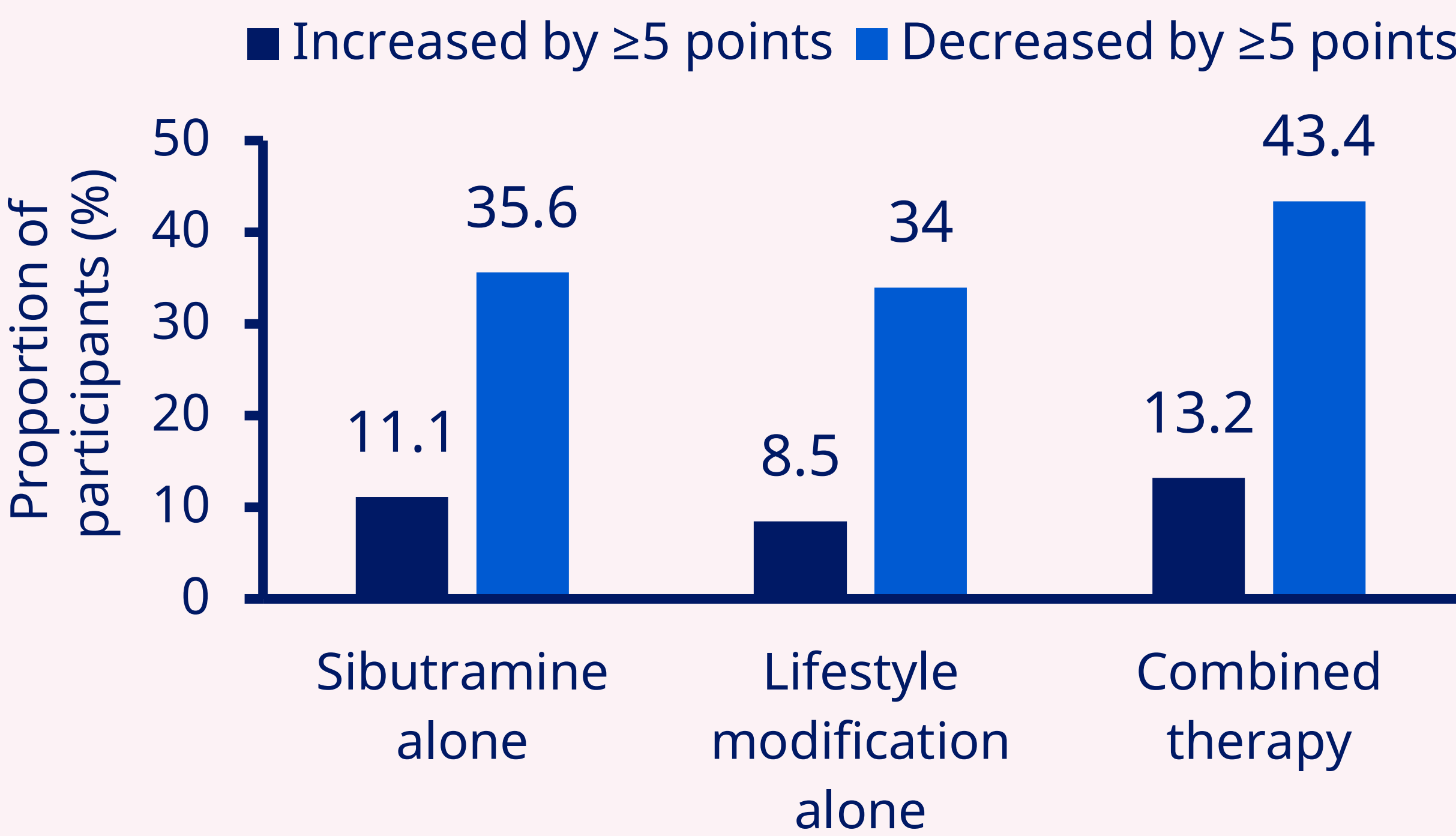
#### Meta-analysis of 17 epidemiological studies<sup>2</sup>

Odds of depression in individuals with obesity are **18%** higher than in individuals with normal weight



### Weight reduction may improve symptoms of depression

In a meta-analysis of 31 RCTs, symptoms of depression were reduced by lifestyle and medication interventions<sup>3</sup>



In a 1-year randomized trial of lifestyle modification and/or sibutramine therapy, mean depression scores\* decreased across groups ( $p<0.001$ )<sup>4</sup>. While some patients experienced increased symptoms, reductions were approximately 3 times more common<sup>4</sup>

### Summary

- People with obesity have a higher risk of developing depression than people with normal weight.
- Mean reductions in symptoms of depression are observed across multiple studies of obesity interventions.

\*Beck Depression Inventory-II.  
RCT, randomized controlled trial ; CI, confidence interval; OR odds ratio  
1. Luppino et al. Arch Gen Psychiatry 2010;67:220–9; 2. de Wit et al. Psychiatry Res 2010;178:230–5; 3. Fabricatore et al. Int J Obes (Lond) 2011;35:1363–76; 4. Faulconbridge et al. Obesity (Silver Spring) 2009;17:1009–16.

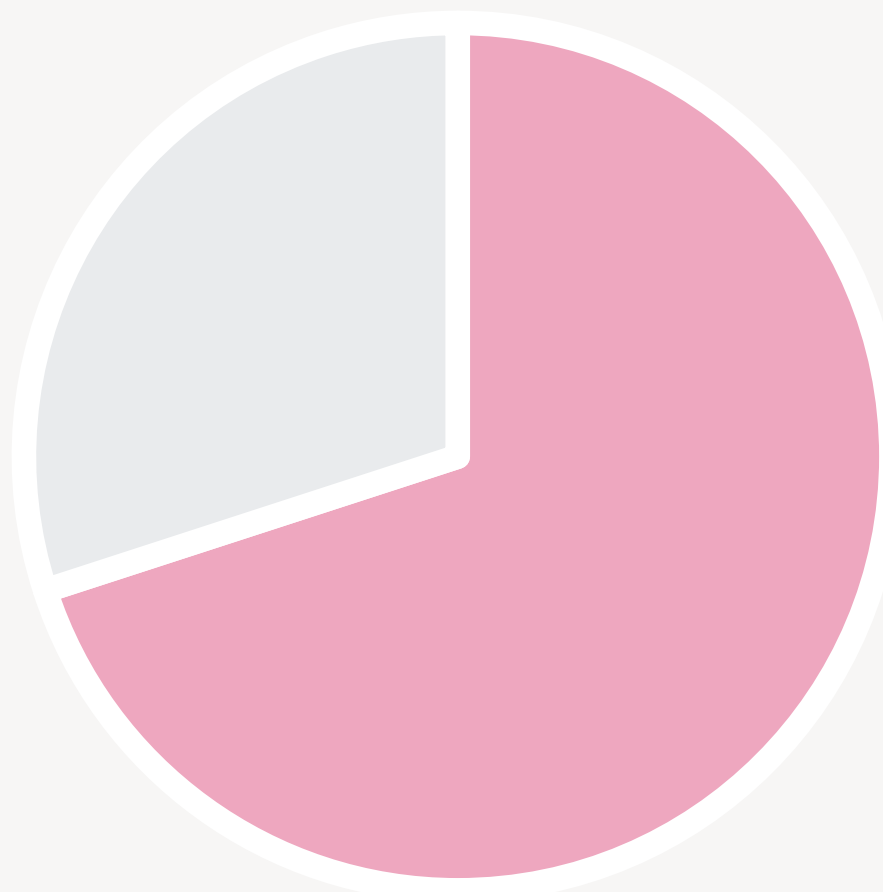




People living with obesity are at an increased risk for several health complications.

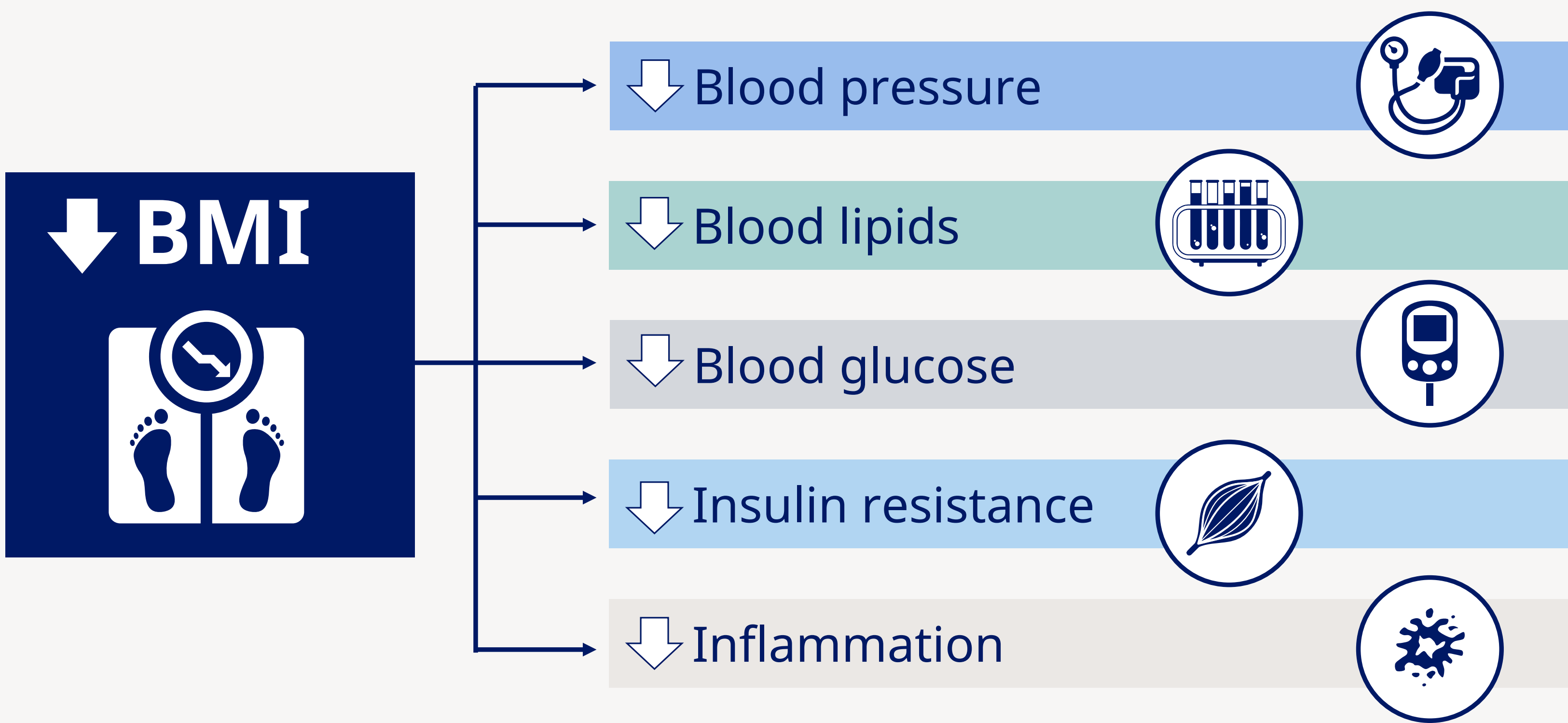
# Obesity is associated with increased cardiovascular morbidity and mortality

Obesity carries a high risk of cardiovascular death<sup>1,2</sup>



70% of deaths related to overweight/obesity are due to CVD<sup>1</sup>

Weight reduction is associated with improvement of CV risk factors<sup>3,4</sup>



Weight reduction through lifestyle interventions, pharmacotherapy and bariatric surgery may improve CV risk factors and/or outcomes

Lifestyle interventions

Pharmacotherapy

Bariatric surgery

For more details: tap on the above circles

## Summary

- People with overweight or obesity have a high risk of CV events and mortality.
- Intentional weight reduction in PwO is associated with improvement of CV risk factors.

BMI, body mass index; CV, cardiovascular; CVD, cardiovascular disease; PwO, people with obesity.  
1. GBD 2015 Obesity Collaborators. N Engl J Med 2017;377:13–27; 2. Powell-Wiley TM, et al. Circulation 2021;143:e984–e1010; 3. Burke GL et al. Arch Intern Med 2008;168:928–35; 4. Ayer J et al. Eur Heart J 2015;36:1371–6.





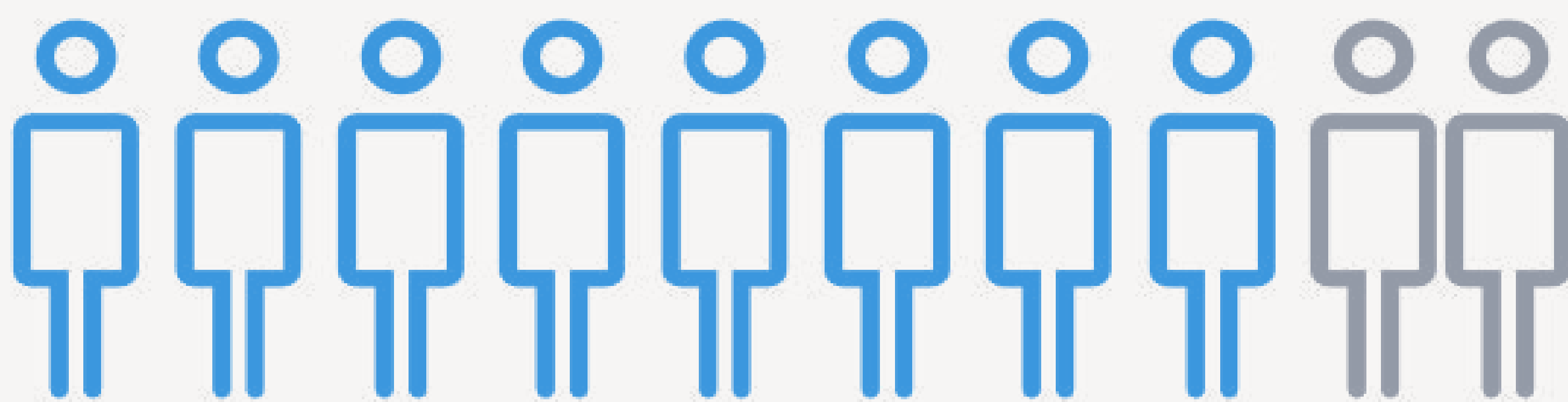
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## Obesity is a major risk factor for incident heart failure

### Prevalence of HF increases with higher BMI

- Risk of HF increases by **41%** for every **5 kg/m<sup>2</sup>** higher BMI<sup>1</sup>
- Higher BMI is more strongly associated with risk of **HFpEF** than **HFrEF**<sup>2</sup>

Up to 80% of patients with HFpEF have overweight/obesity<sup>3</sup>



Weight reduction through lifestyle interventions, pharmacotherapy and bariatric surgery may have a beneficial impact on HFpEF



For more details: tap on the above circles

### Summary

- Excess adiposity increases the risk of developing HF, particularly for HF with preserved ejection fraction.
- Weight reduction can have a beneficial impact on reducing the development of HF in patients with obesity and improving function in patients with obesity and HFpEF.

HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.  
1. Aune D et al. Circulation. 2016;133(7):639-649; 2. Chrysant SG et al. Hosp Pract (1995). 2019;47(2):67-72; 3. Haass M et al. Circulation 2011;4:324–331.





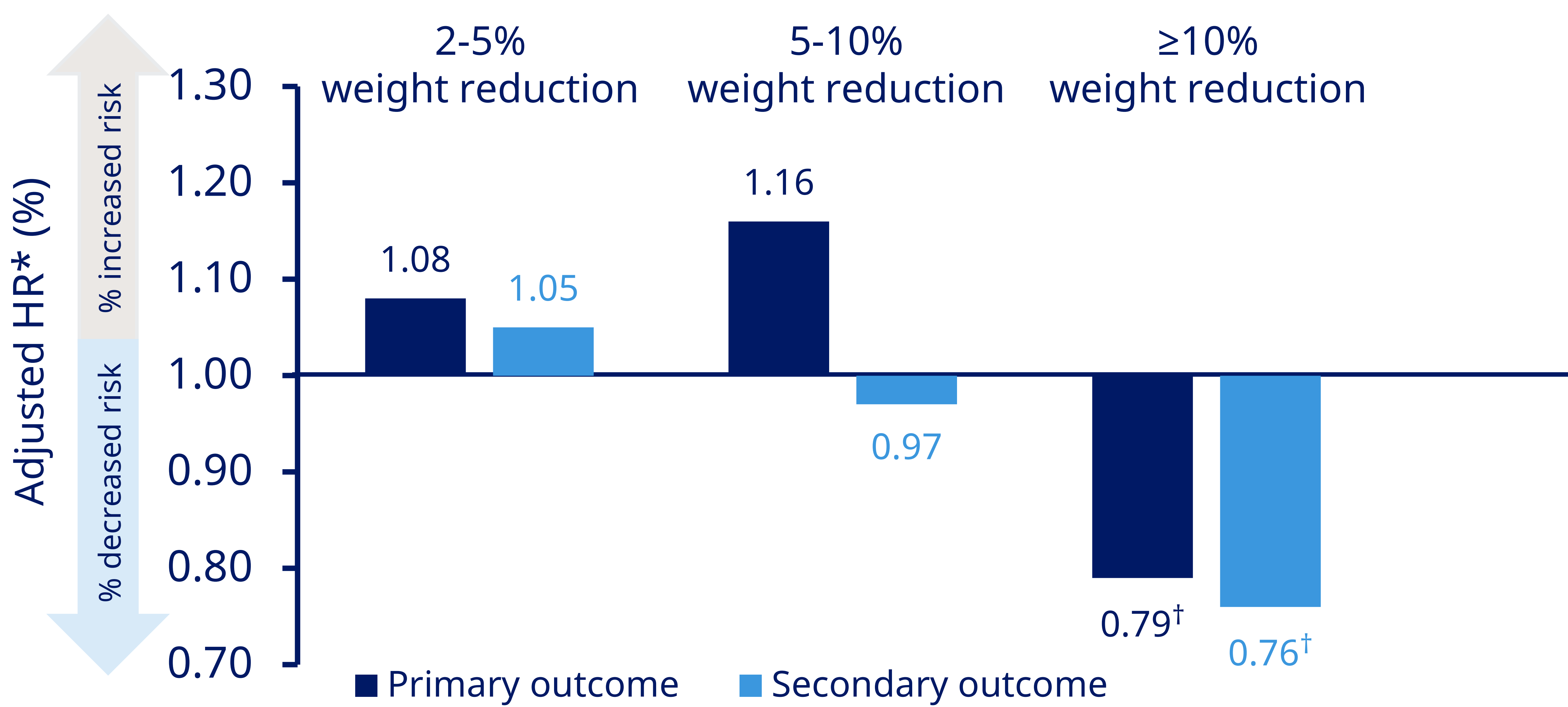
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## Outcomes associated with weight reduction Look AHEAD study population

In the Look AHEAD trial, participants in ILI group had greater weight reduction than participants in DSE group<sup>1</sup>.

Although the primary outcome did not differ across treatment groups, a post-hoc analysis found significantly reduced CV risk in those with  $\geq 10\%$  weight reduction<sup>2</sup>.



### Primary outcome

Composite of the occurrence of death from CV causes, non-fatal acute MI, stroke or admission to hospital for angina

### Secondary outcome

Primary endpoint plus coronary artery bypass grafting, carotid endarterectomy, percutaneous coronary intervention, admission to hospital for congestive heart failure, peripheral vascular disease and total mortality

\*Adjusted hazard ratio; adjusted for sex, age, baseline weight (weight change models), baseline fitness (fitness change models), CVD history, insulin use, diabetes duration, smoking status, LDL, SBP, DBP; <sup>†</sup>  $p < 0.05$   
CV, cardiovascular; DSE, diabetes support and education; HR, hazard ratio; ILI, intensive lifestyle intervention; MI, myocardial infarction; T2D, type 2 diabetes.  
1. Look AHEAD Research Group. Obesity (Silver Spring). 2014 Jan;22(1):5-13; 2. Look AHEAD Research Group. Lancet Diabetes Endocrinol. 2016; 4(11): 913-21. 2. Look AHEAD Research Group. Lancet Diabetes Endocrinol. 2016; 4(11): 913-21.





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## Overview of CVOTs for anti-obesity medications

	SCOUT <sup>1</sup>	CRESCENDO <sup>2</sup>	LIGHT <sup>3</sup>	CONVENE <sup>4</sup>
Intervention	Sibutramine*	Rimonabant*	Naltrexone/ Bupropion	Naltrexone/ Bupropion
Primary Outcome	3P-MACE + resuscitated cardiac arrest	3P-MACE	3P-MACE	3P-MACE
Trial status	Completed	Terminated prematurely <i>(Increased psychiatric and GI AEs)</i>	Terminated prematurely <i>(Study integrity compromised)</i>	Terminated prematurely <i>(Selling of US rights)</i>
HR (95% CI) for primary outcome	1.16 <i>(1.03–1.31); P=0.02</i>	0.97 <i>(0.84–1.12); P=0.68</i>	0.88 <i>(0.57–1.34); 50% interim analysis</i>	No data available
Weight change in treatment (vs. control) group	–1.7 kg (vs +0.7 kg) at 12 months	N/A	–3.6% (vs –1.1%) at trial end	No data available

	CAMELLIA-TIMI <sup>5</sup>	SELECT <sup>6</sup>	SURMOUNT-MMO <sup>7</sup>	NB-CVOT3 <sup>8</sup>
Intervention	Lorcaserin*	Semaglutide 2.4 mg	Tirzepatide	Naltrexone/ Bupropion
Primary Outcome	1. 3P-MACE (safety outcome) 2. MACE+ (efficacy outcome)	3P-MACE	5P-MACE	3P-MACE
Trial status	Completed	Completed	Estimated completion: October 2027	Estimated completion: July 2029
HR (95% CI) for primary outcome	3P-MACE: 0.99 <i>(0.85–1.14); P&lt;0.001 for noninferiority</i> MACE+: 0.97 <i>(0.87–1.07); P=0.55 for superiority</i>	0.80 <i>(0.72–0.90); P&lt;0.111</i>	N/A	N/A
Weight change in treatment (vs. control) group	–4.0 kg (vs –2.1 kg) at 40 months	–9.4% (vs –0.9%) at 104 weeks	N/A	N/A

- HR for primary outcome <1 and intervention is significant for superiority compared to control arm
- HR for primary outcome <1 and intervention is either significant for noninferiority or non-significant for superiority compared to control arm
- HR for primary outcome >1 and intervention is significant for inferiority compared to control arm

\*The following drugs have been withdrawn by the FDA: Rimonabant (2008), Sibutramine (2010), and Lorcaserin (2020). † Abbreviations: 3P-MACE, composite of CV death, non-fatal MI and non-fatal stroke; 5P-MACE, composite of all-cause death, non-fatal MI, non-fatal stroke, coronary revascularization or HF events; MACE+, composite of MI, stroke, CV death, and hospitalization due to unstable angina, HF or any coronary revascularization. CI, confidence interval; CV, cardiovascular; CVOT, cardiovascular outcome trial; GI, gastrointestinal; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction; T2D, type 2 diabetes. 1. James WPT et al. N Engl J Med 2010;363:905–17; 2. Topol EJ et al. Lancet 2010;376:517–23; 3. Nissen SE et al. JAMA 2016;315:990–1004; 4. <https://clinicaltrials.gov/ct2/show/NCT02638129>. Accessed November 2022; 5. Bohula EA et al. NEJM 2018;379:1107–17; 6. Lincoff AM et al. N Engl J Med. Nov 11, 2023. Advanced online publication. DOI: 10.1056/NEJ-Moa2307563; 7. <https://clinicaltrials.gov/ct2/show/NCT05556512>. Accessed November 2022; 8. <https://clinicaltrials.gov/study/NCT06098079>. Accessed November 2023.





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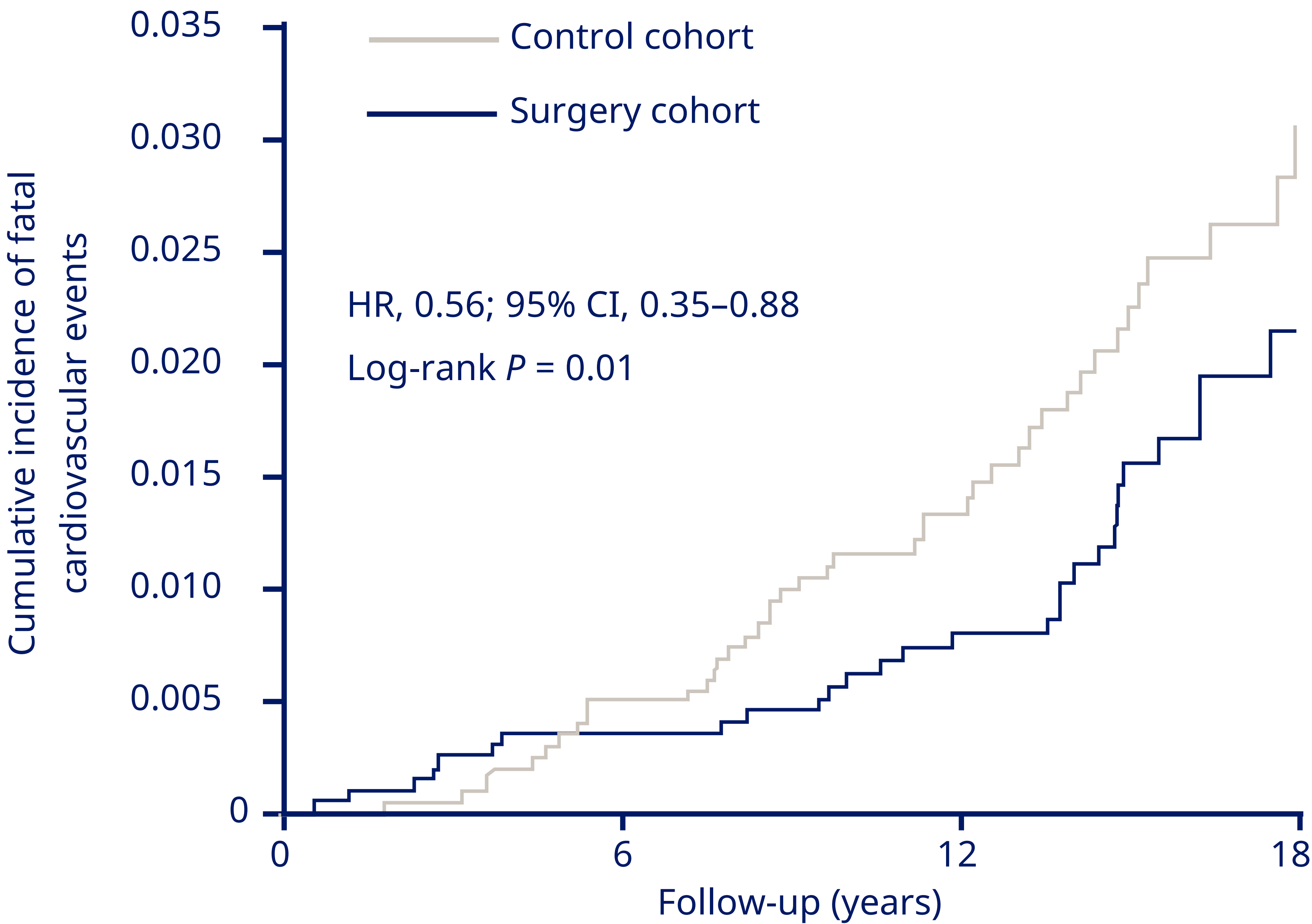
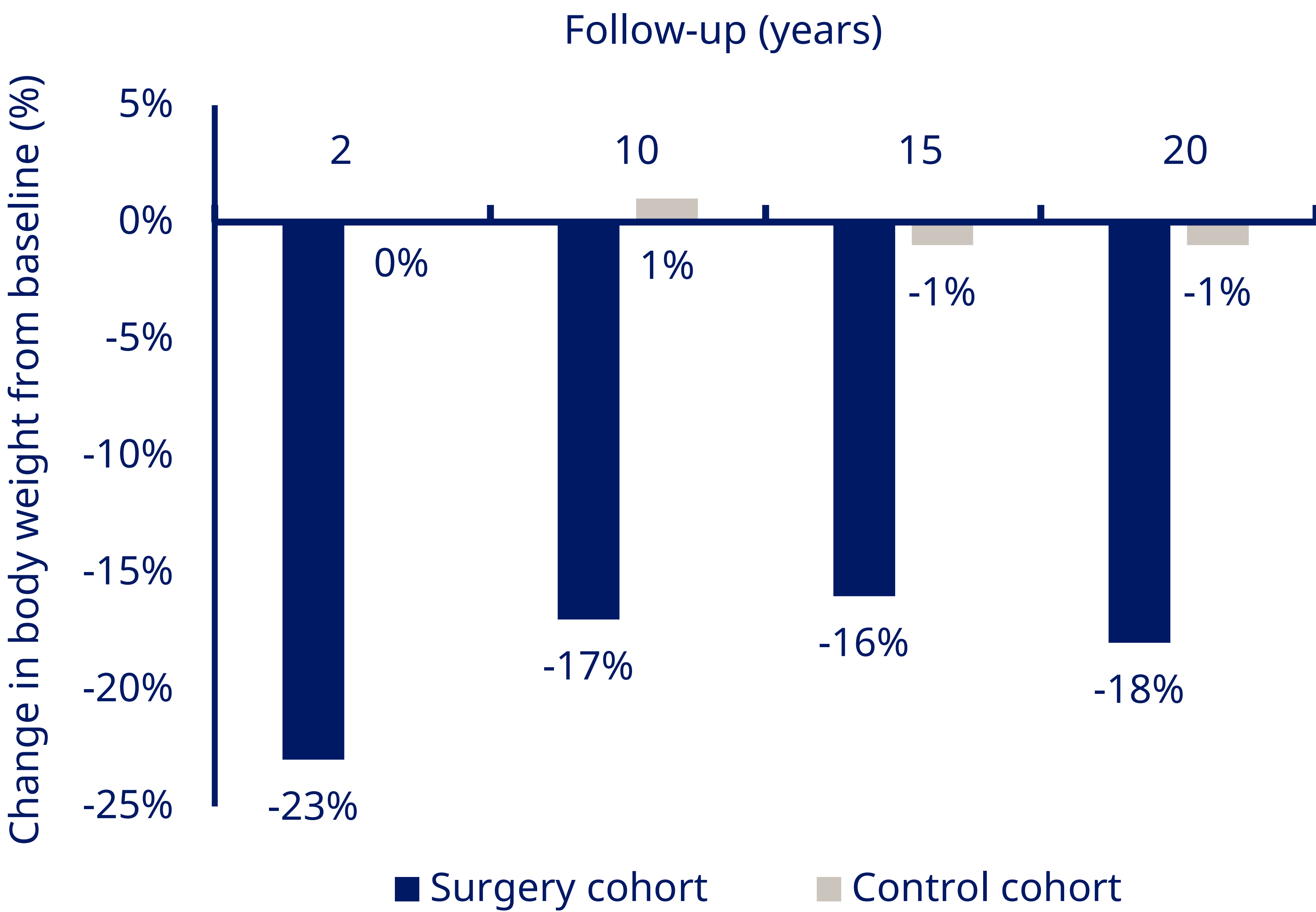
## Adults who received metabolic and bariatric surgery had fewer fatal CV events than matched controls

**Population (N=4047):**

Patients with obesity

**Non-randomized, prospective, controlled study:**

Participants who underwent bariatric surgery (N=2,010) matched with participants with BMI ≥34 kg/m² (N=2,037)





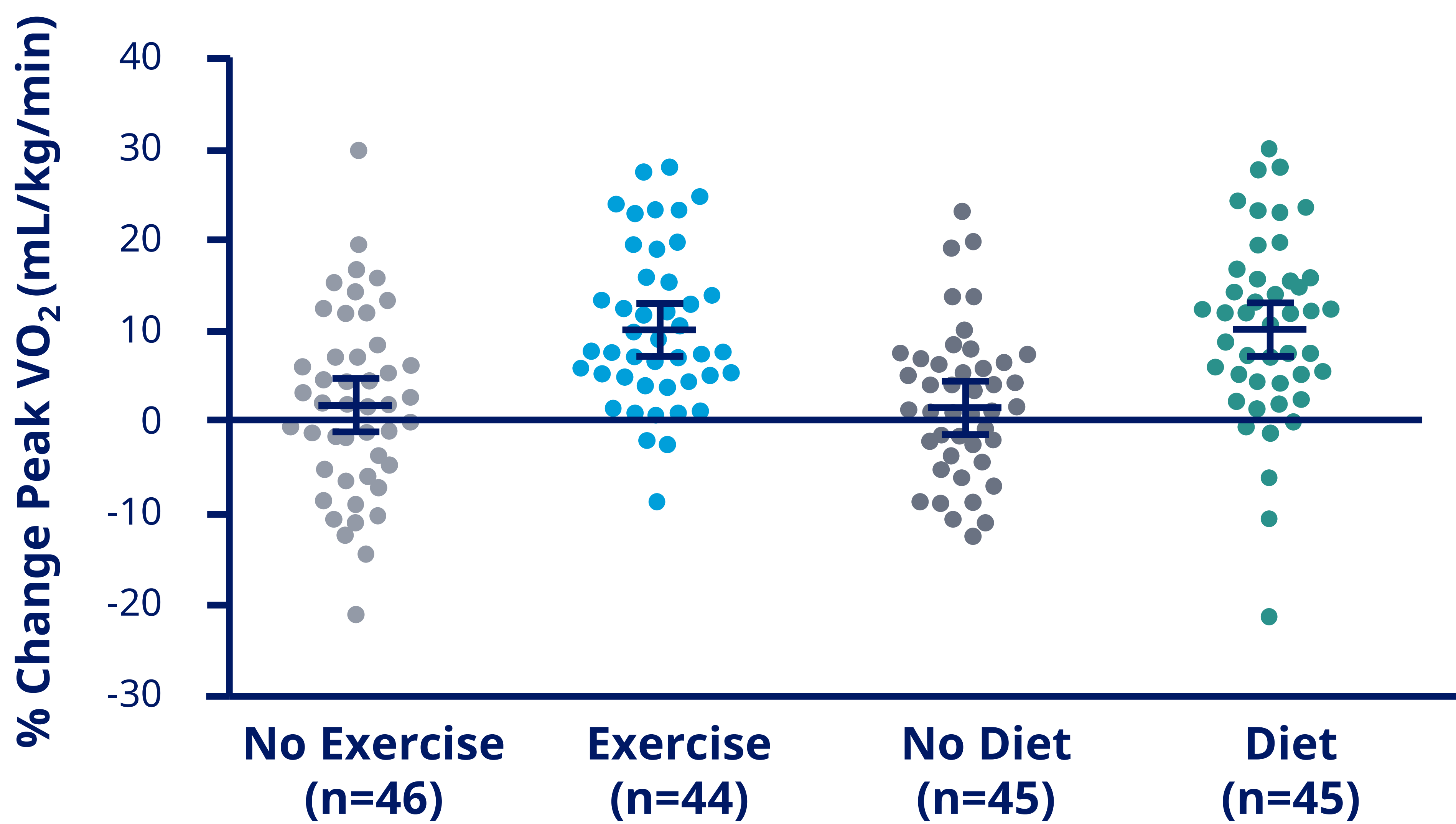
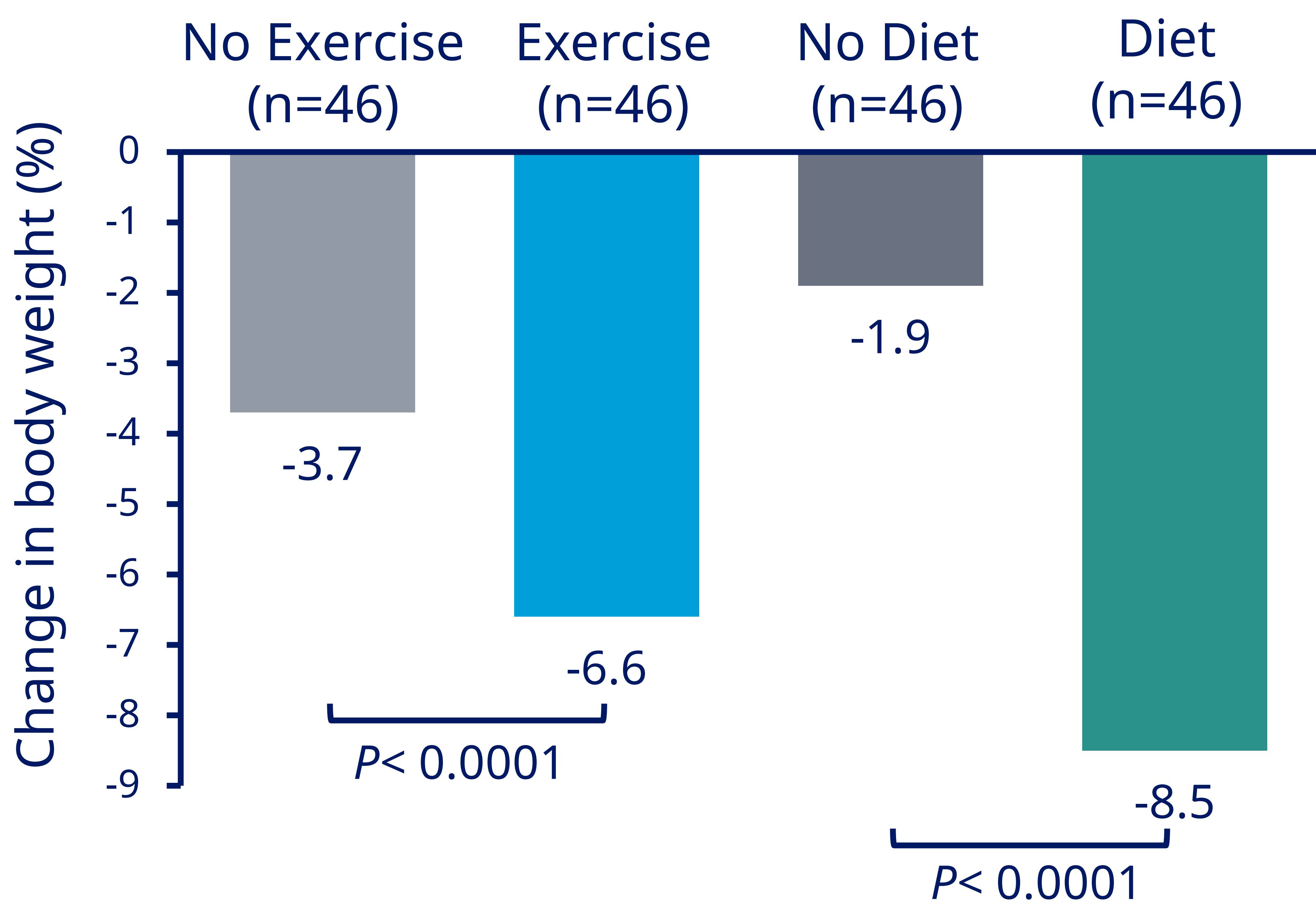


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## Beneficial impact of weight reduction in patients with obesity and HFpEF

**Caloric restriction and/or exercise**  
resulted in weight reduction and improved peak  $\text{VO}_2$ <sup>1</sup>



HFpEF, heart failure with preserved ejection fraction;  $\text{VO}_2$ , oxygen uptake.  
1. Kitzman et al. JAMA 2016;315:36–46.





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## Anti-obesity medications in HFpEF trials

	STEP HFpEF <sup>1</sup>
Intervention	Semaglutide 2.4 mg
Primary Outcome	Change from baseline to week 52 in: KCCQ-CSS Body weight
Trial status	Completed

	STEP HFpEF-DM <sup>2</sup>
Intervention	Semaglutide 2.4 mg
Primary Outcome	Change from baseline to week 52 in: KCCQ-CSS Body weight
Trial status	Completed

	SUMMIT <sup>3</sup>
Intervention	Tirzepatide
Primary Outcome	Hierarchical composite of all-cause mortality, HF events, 6MWD or KCCQ-CSS  Change from baseline to week 52 in 6MWD
Trial status	Estimated completion: July 2024

6MWD, 6-minute walk distance; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; DM, diabetes mellitus.  
1. Kosiborod MN et al. *N Engl J Med.* 2023;10.1056/NEJMoa2306963. doi:10.1056/NEJMoa2306963; 2. Novo Nordisk A/S. NCT04916470. Available at: <https://clinicaltrials.gov/ct2/show/NCT04916470> (accessed May 2022); 3. Eli Lilly and Company. NCT04847557. Available at: <https://clinicaltrials.gov/ct2/show/NCT04847557> (accessed May 2022).

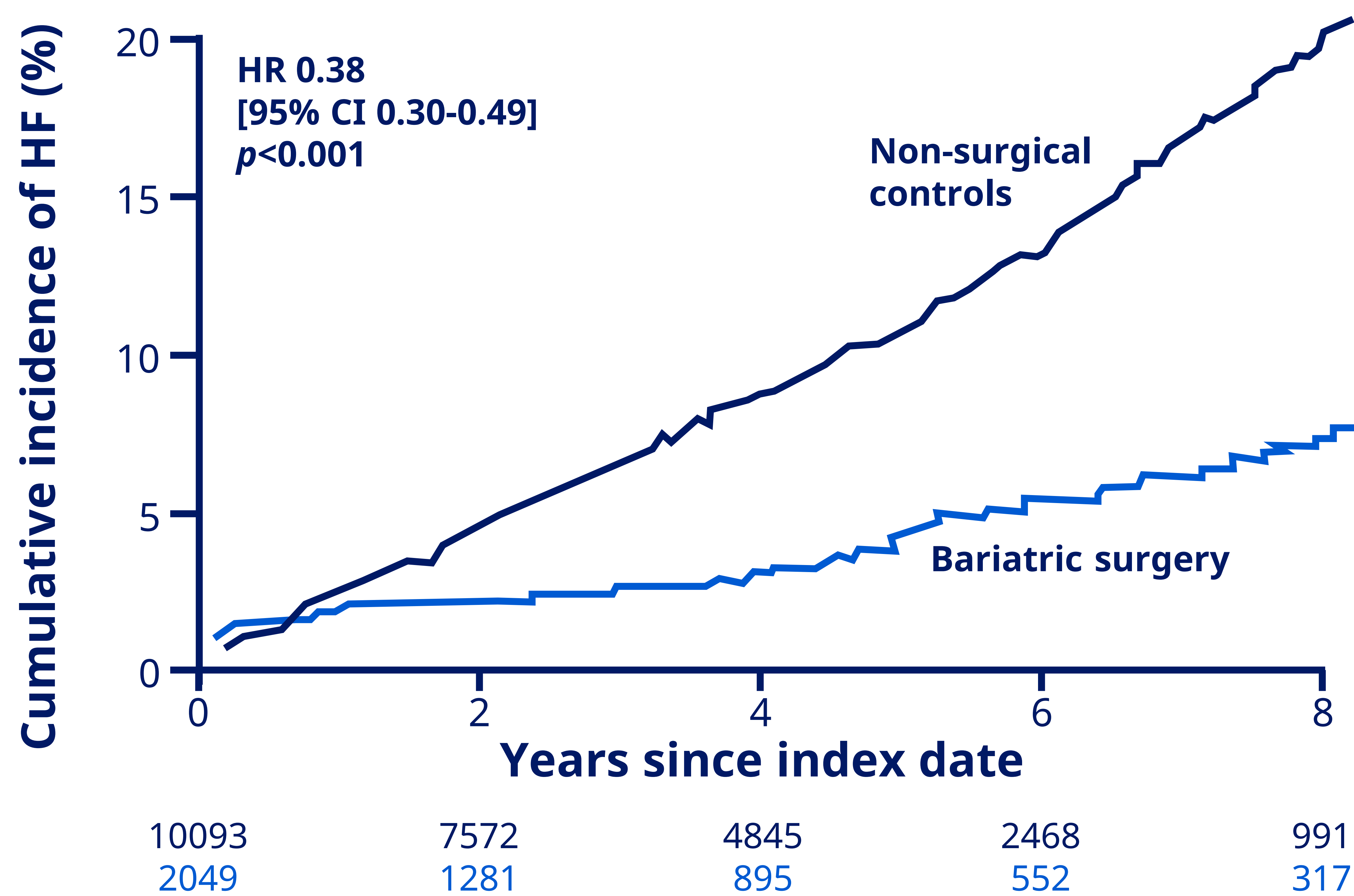




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## Bariatric surgery reduced the development of heart failure in patients with obesity and T2D



**Bariatric surgery** is associated with decreased risk of developing heart failure in patients with diabetes and obesity (BMI  $\geq 30$  kg/m<sup>2</sup>)

Mean weight loss = 14.7% at the end of 8 years