

# 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.

# People living with obesity

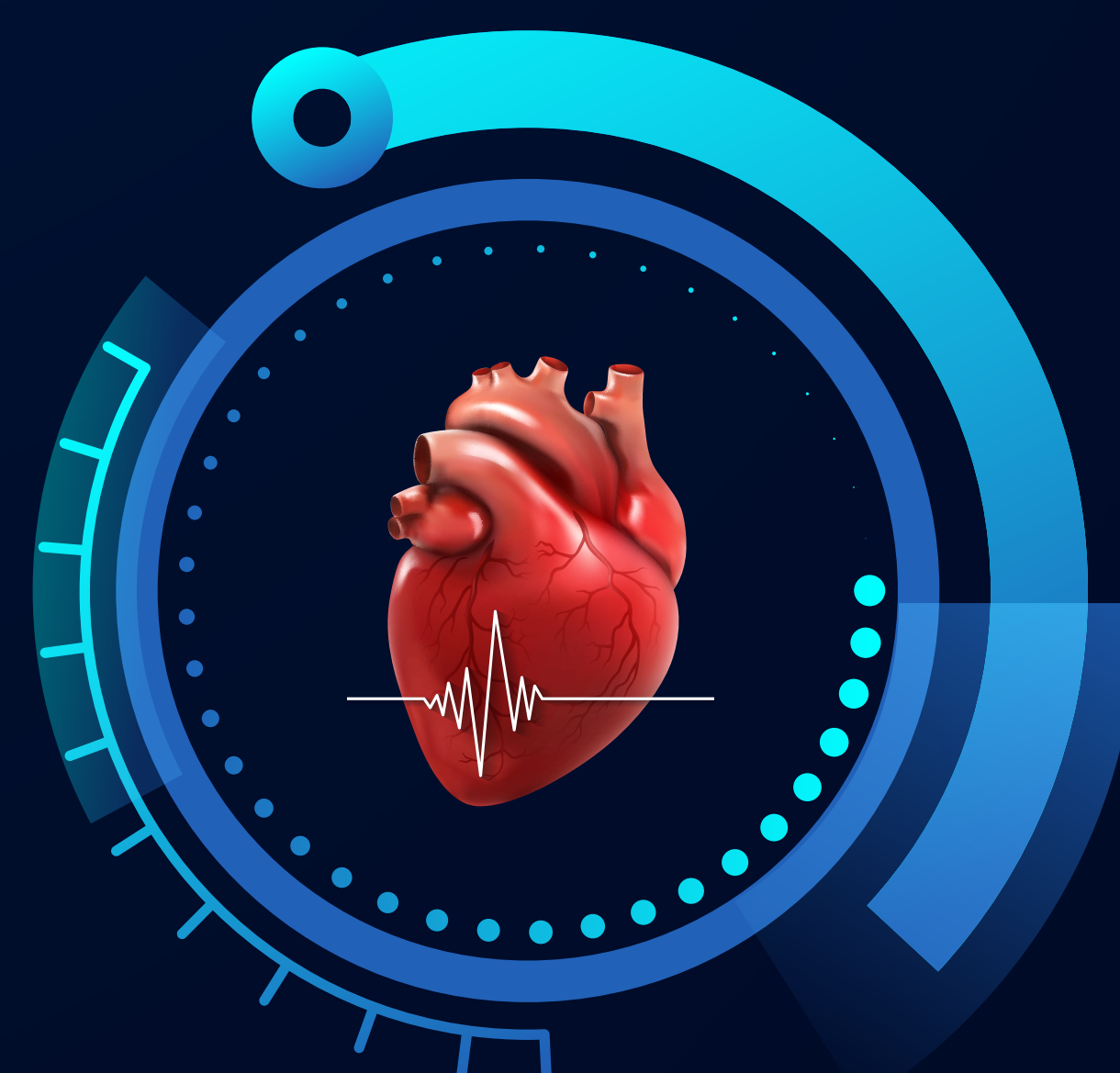
are at an increased risk for several health complications.



Cardiovascular outcomes



Heart failure HFpEF



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

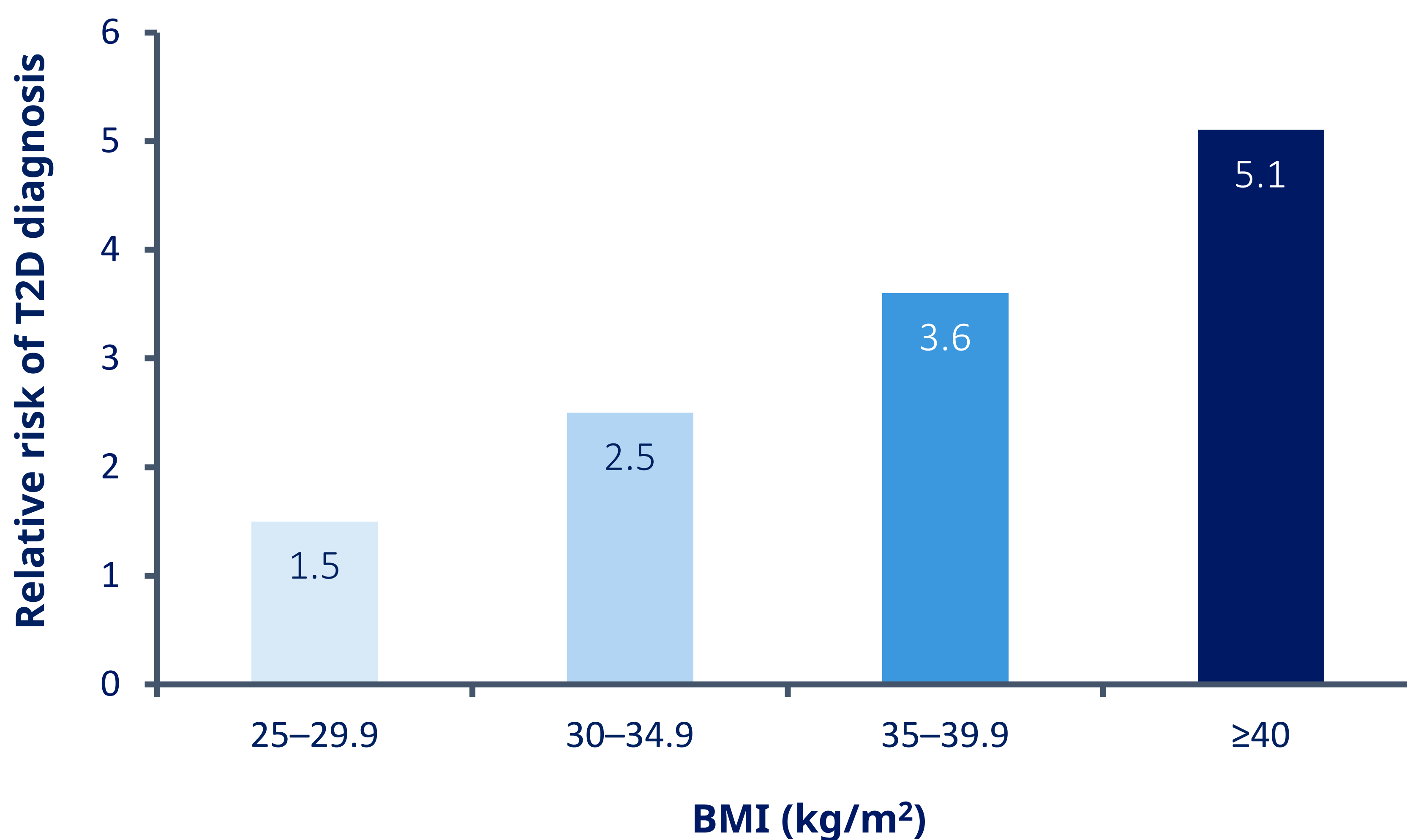


People living with obesity are at an increased risk for several health complications.

## Obesity is a significant risk factor for type 2 diabetes

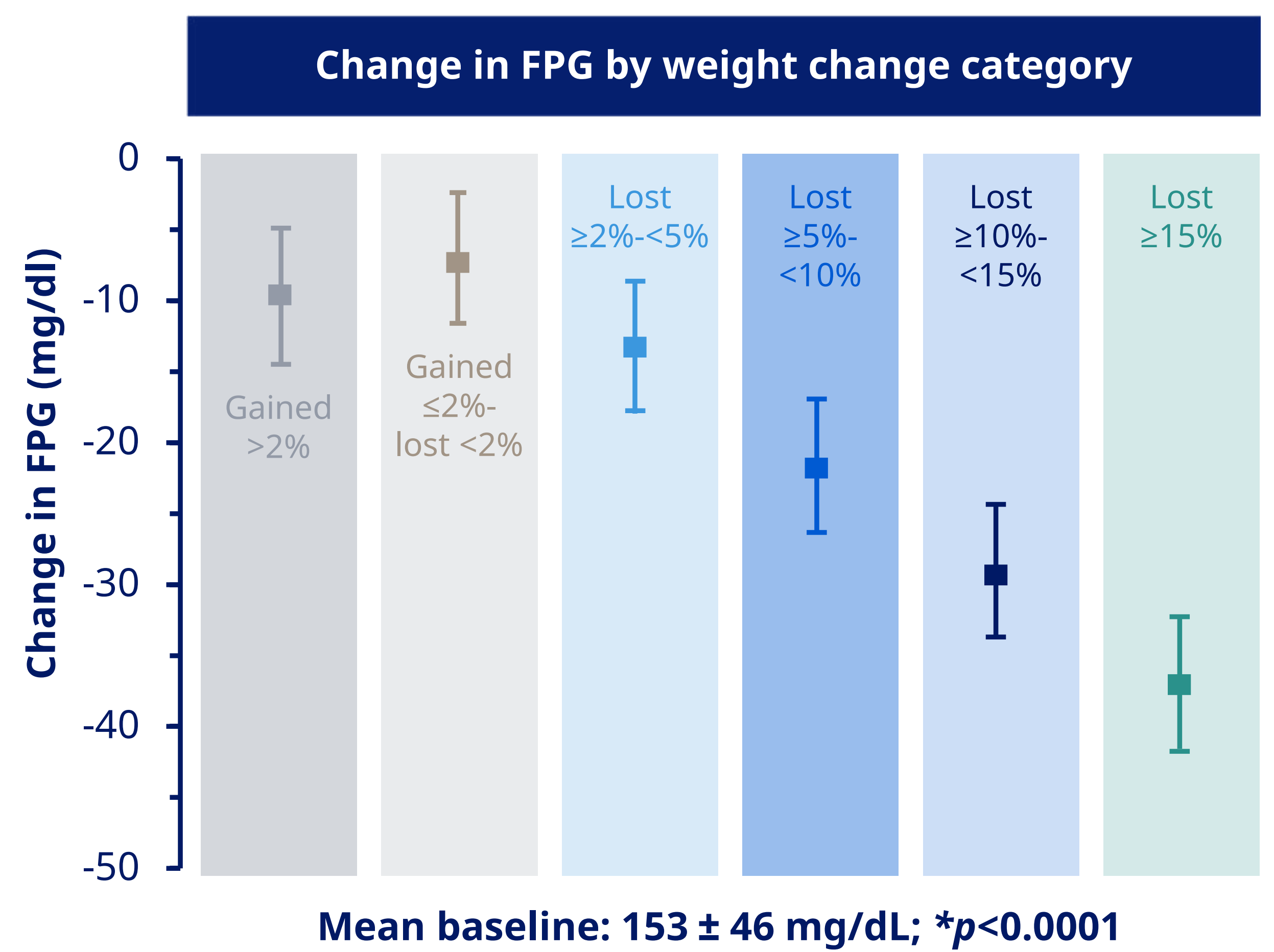
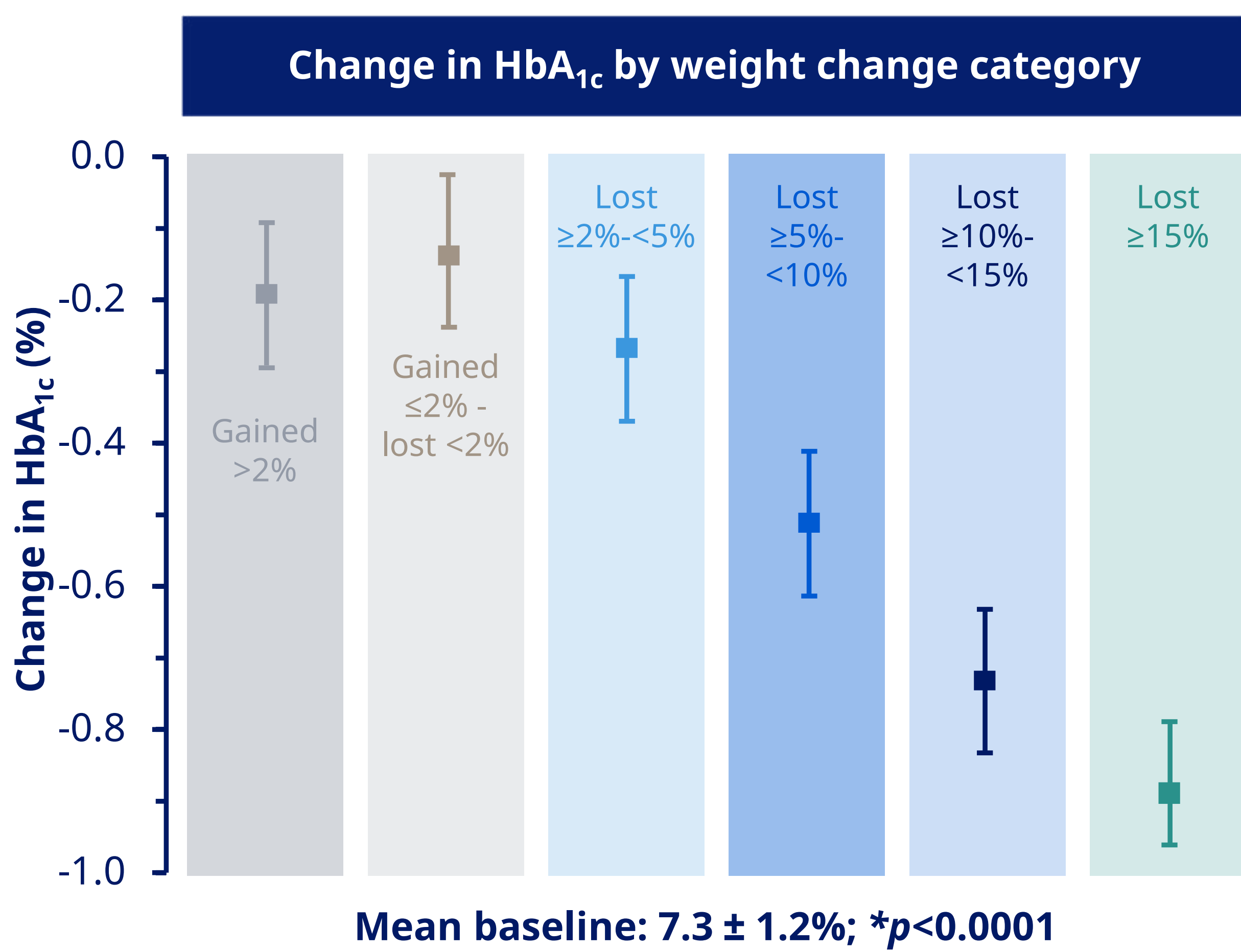
Prevalence of T2D increases with higher BMI<sup>1</sup>

### 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>

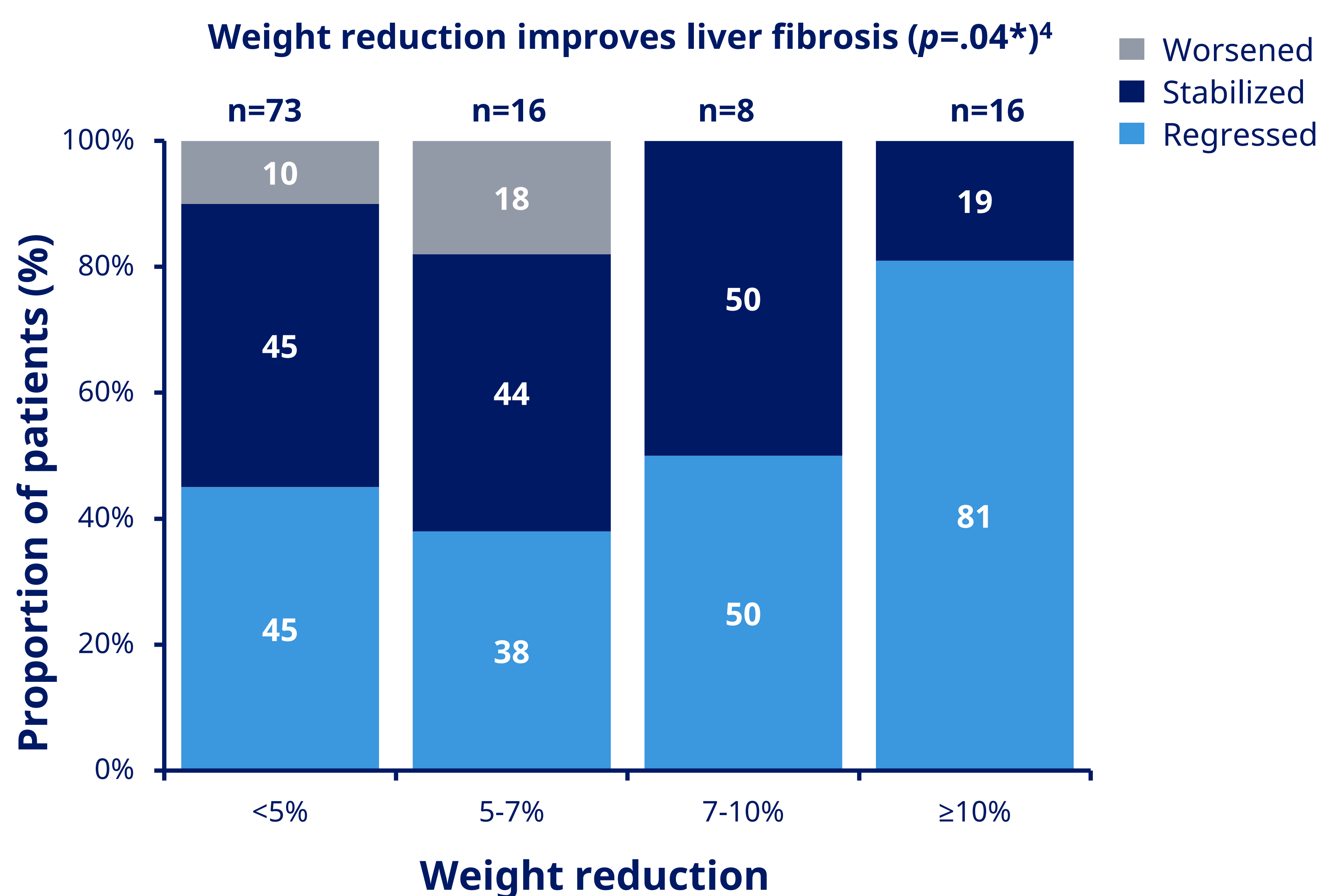
**Weight loss reduced hepatic steatosis and incident MASLD in patients with overweight/obesity and T2D<sup>2</sup>**



**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 c2 test for trend stratified by age older than 55 years, sex, BMI 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.

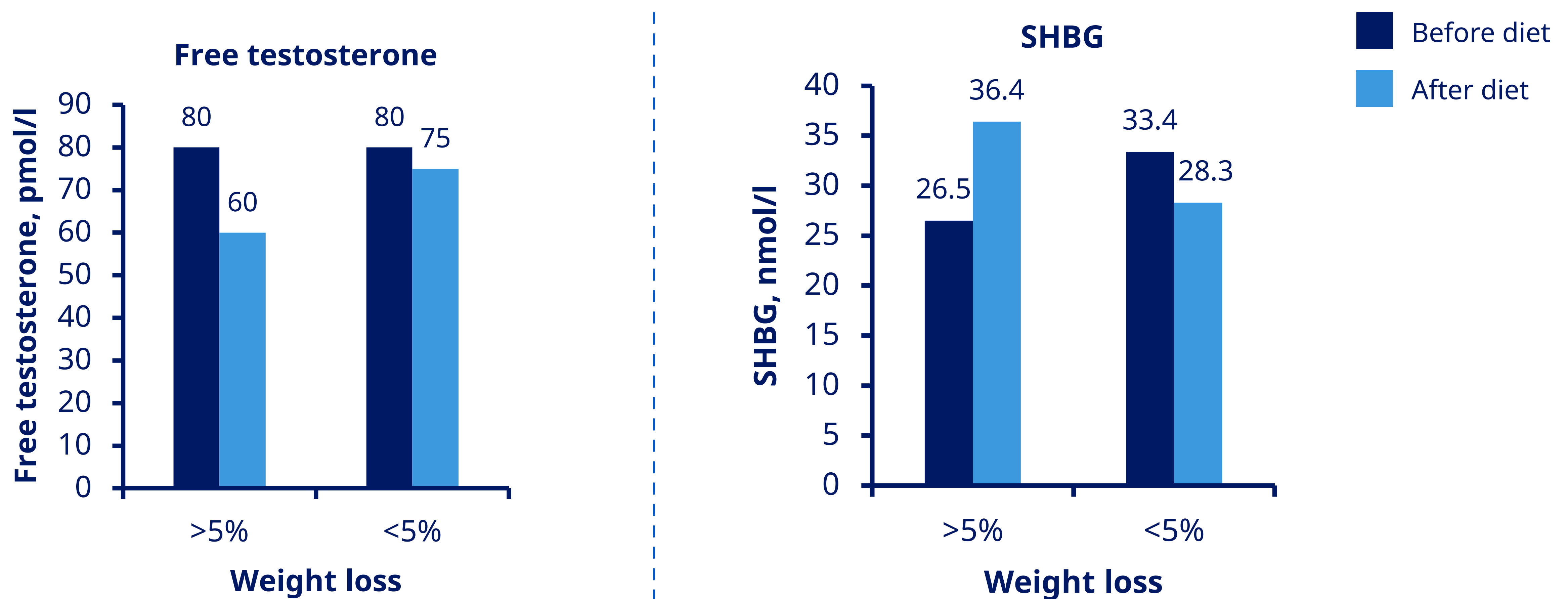


People living with obesity are at an increased risk for several health complications.

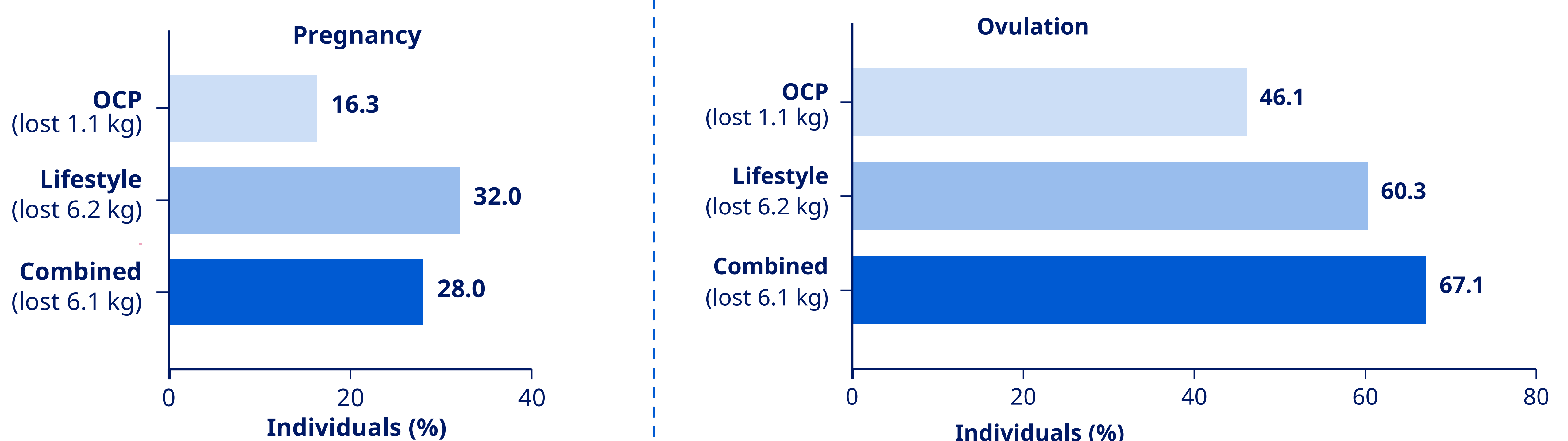
## Obesity is linked with the development of polycystic ovary syndrome

- 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.

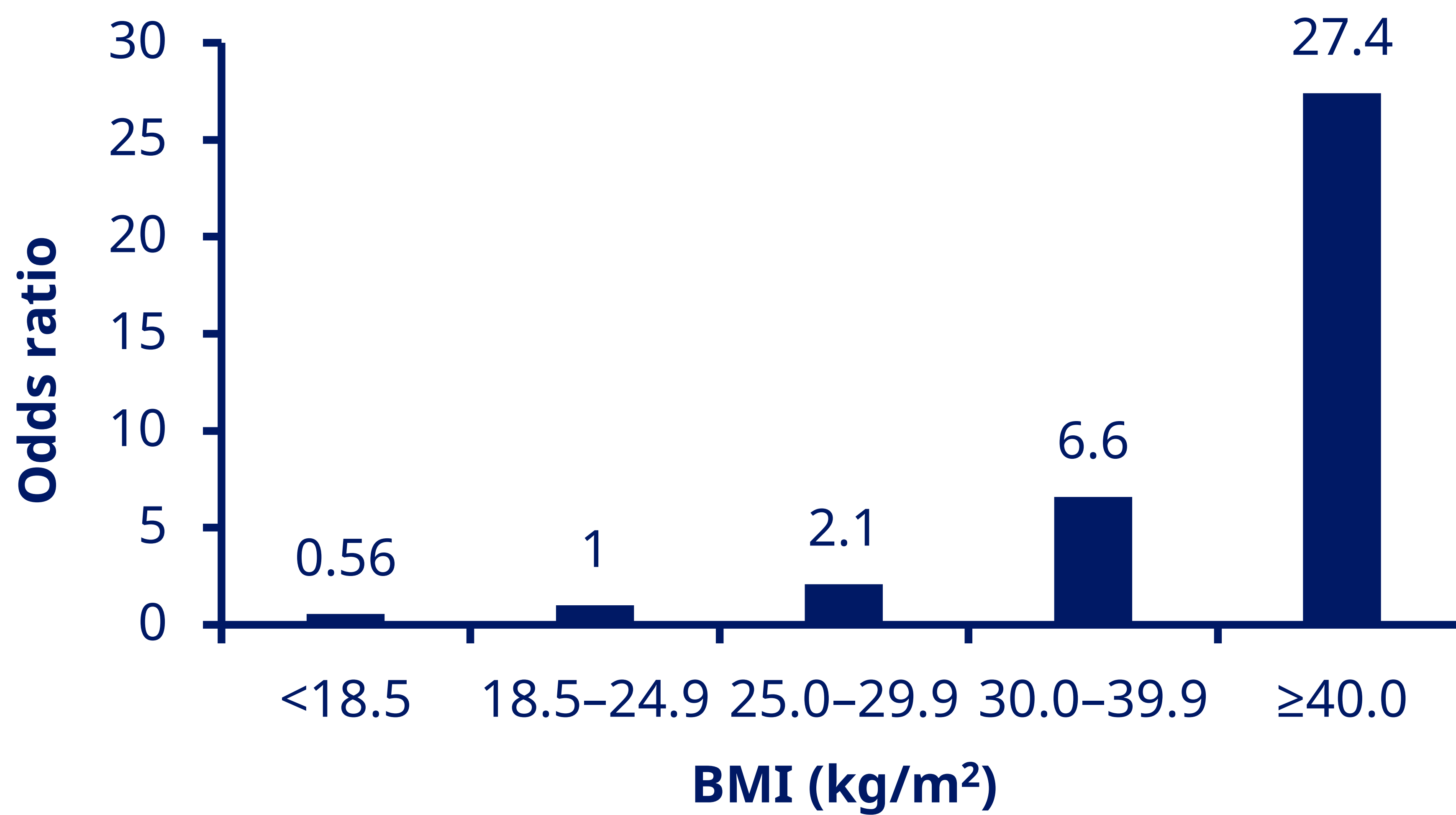


People living with obesity are at an increased risk for several health complications.

## Obstructive sleep apnea is associated with obesity

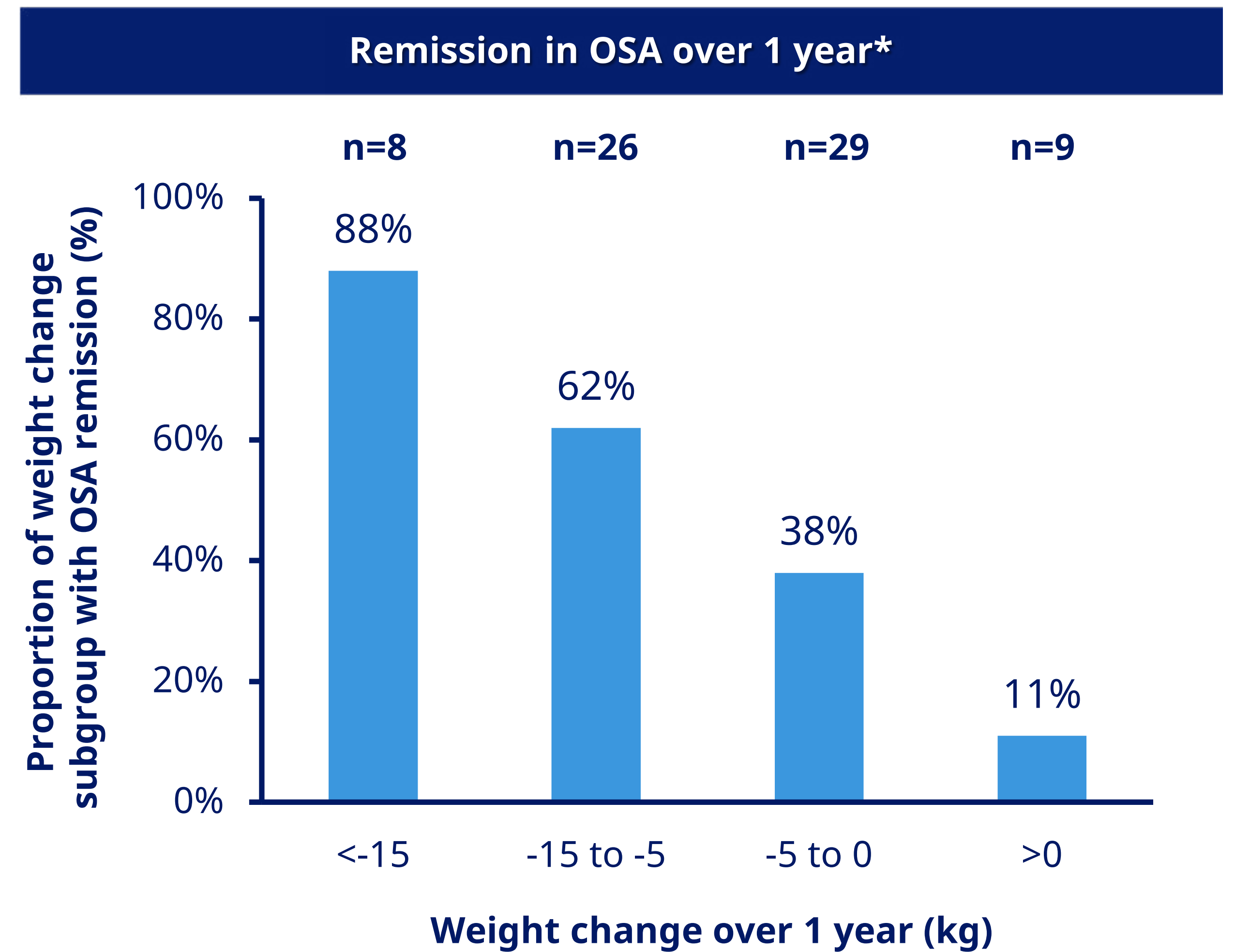
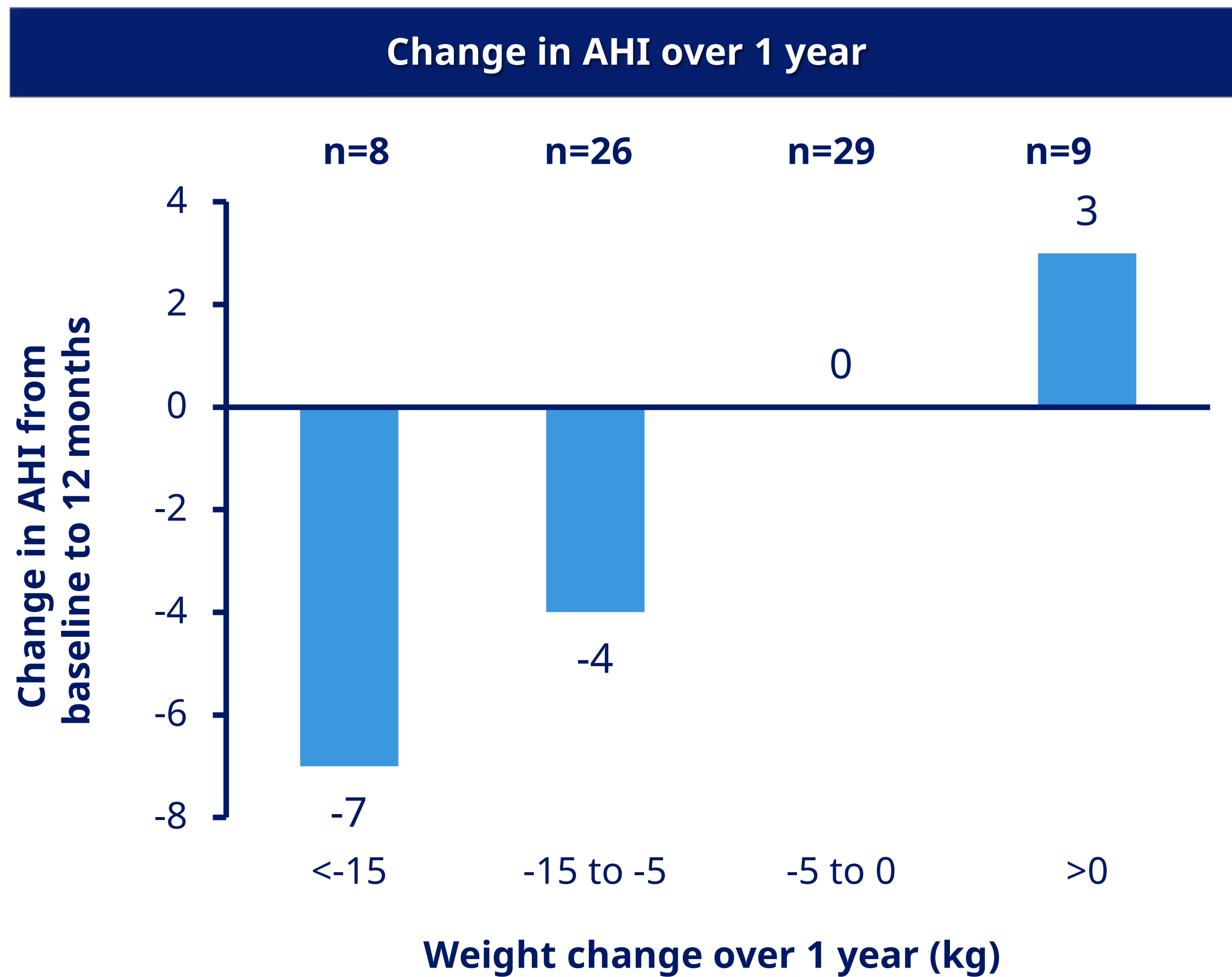
>80% of adult patients with OSA have overweight and >50% have obesity<sup>1</sup>

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.

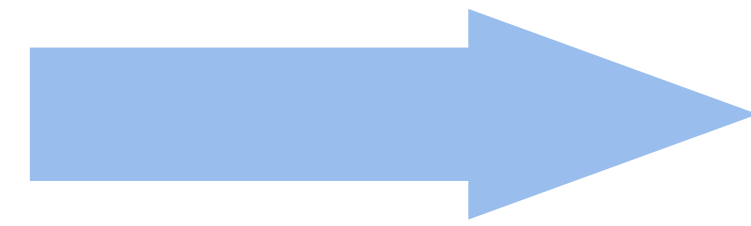


People living with obesity are at an increased risk for several health complications.

## 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

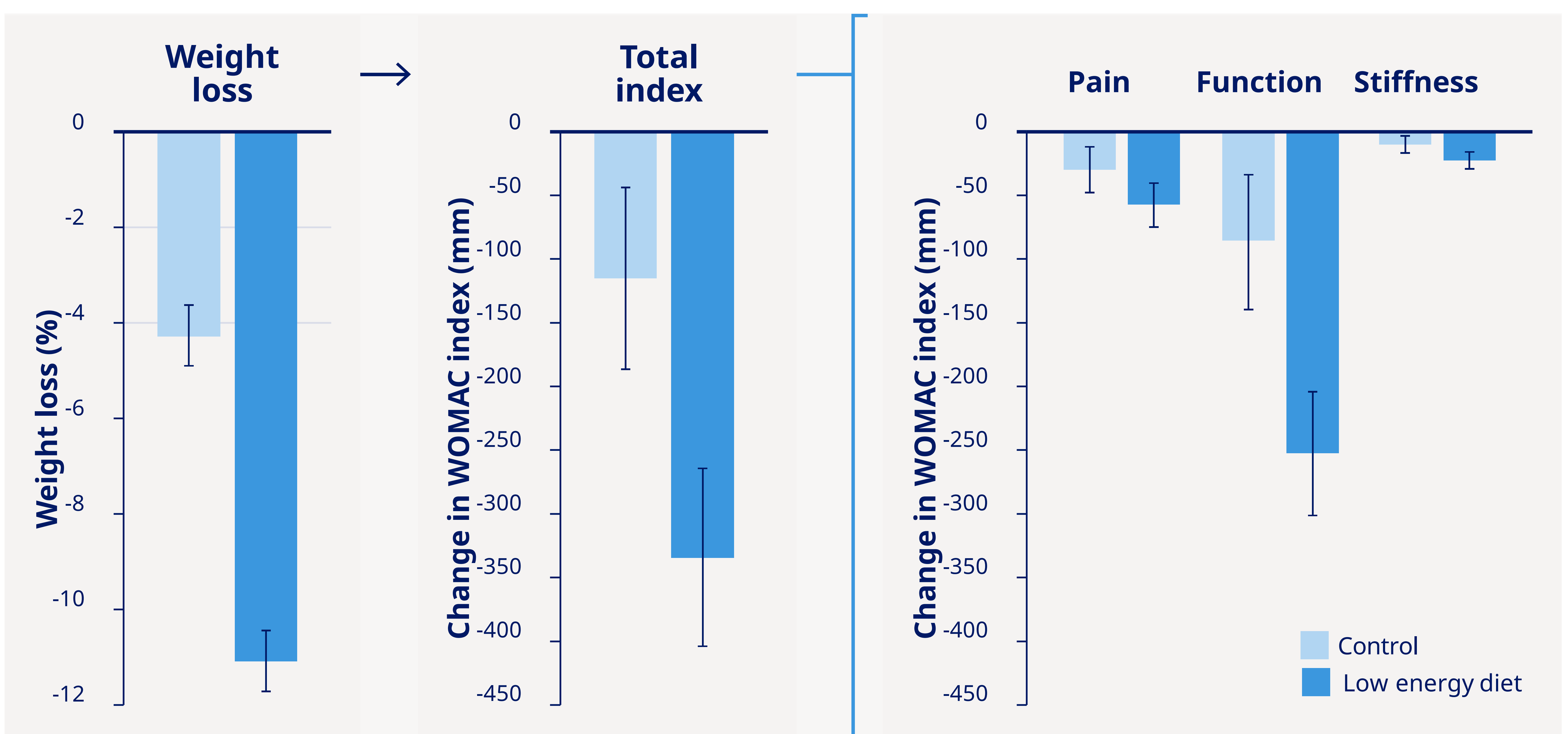


**35%**  
increase in risk of  
**knee OA**  
[95% CI, 1.18-1.53, p<0.001]



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.

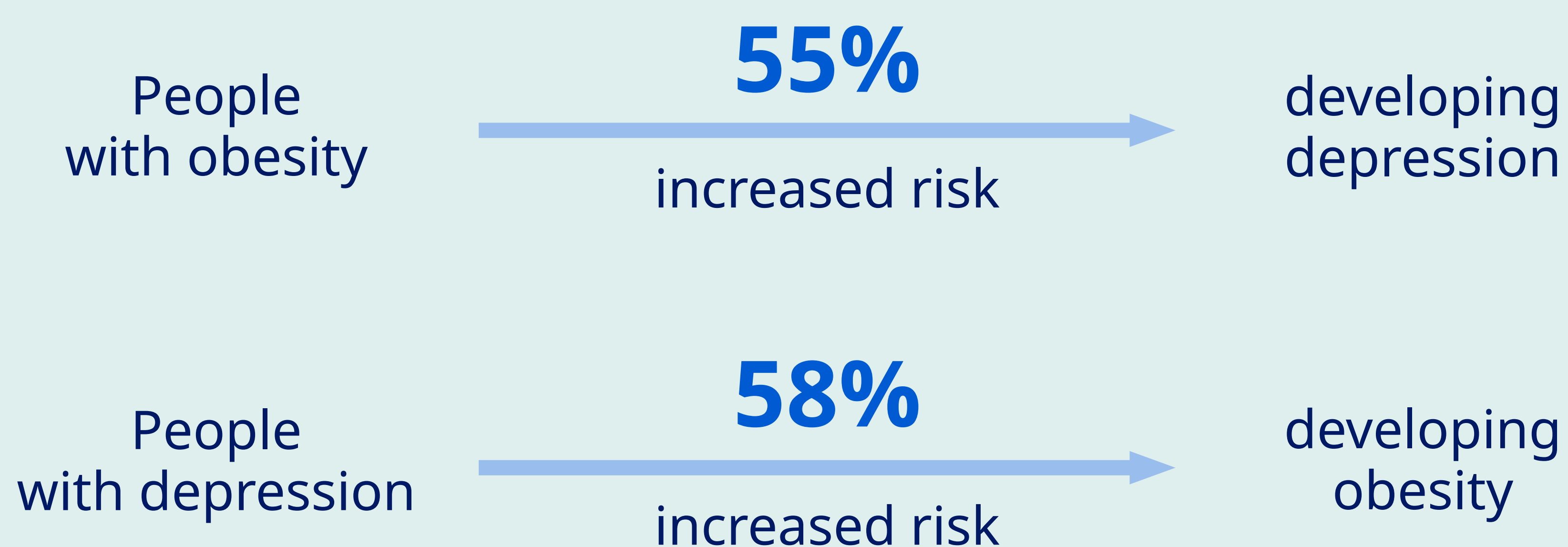


People living with obesity are at an increased risk for several health complications.

## Obesity and depression are common comorbidities

### Bidirectional association between obesity and depression

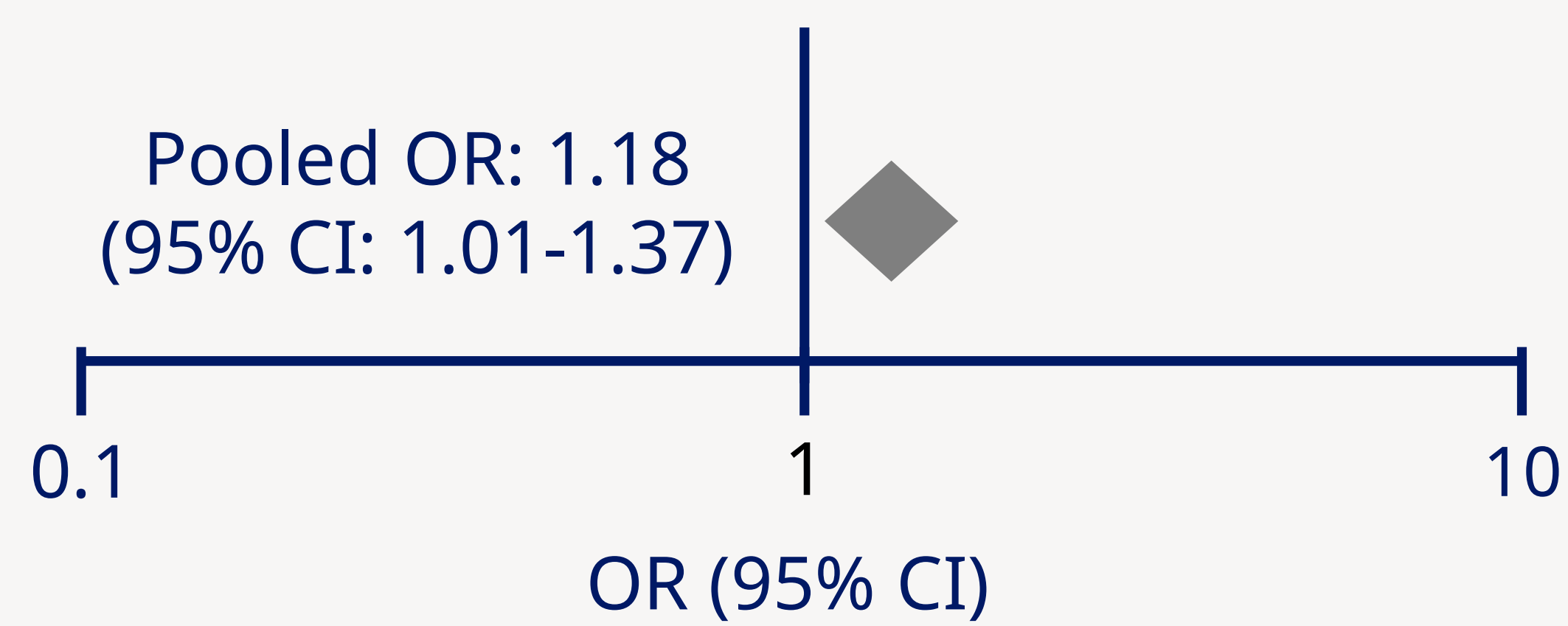
#### Meta-analysis of 15 longitudinal studies (n= 58,745)<sup>1</sup>



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

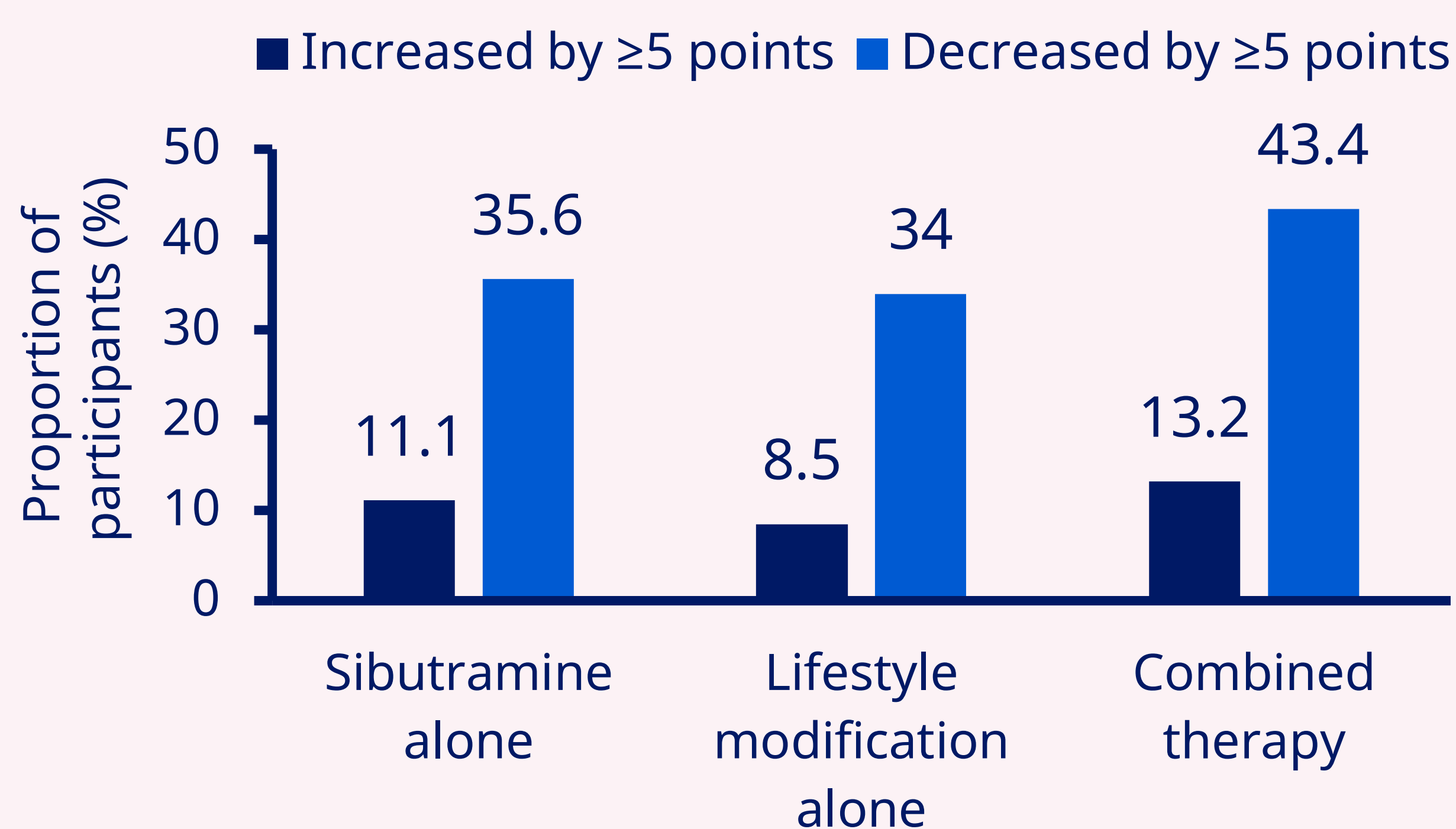
#### Meta-analysis of 17 epidemiological studies<sup>2</sup>

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.

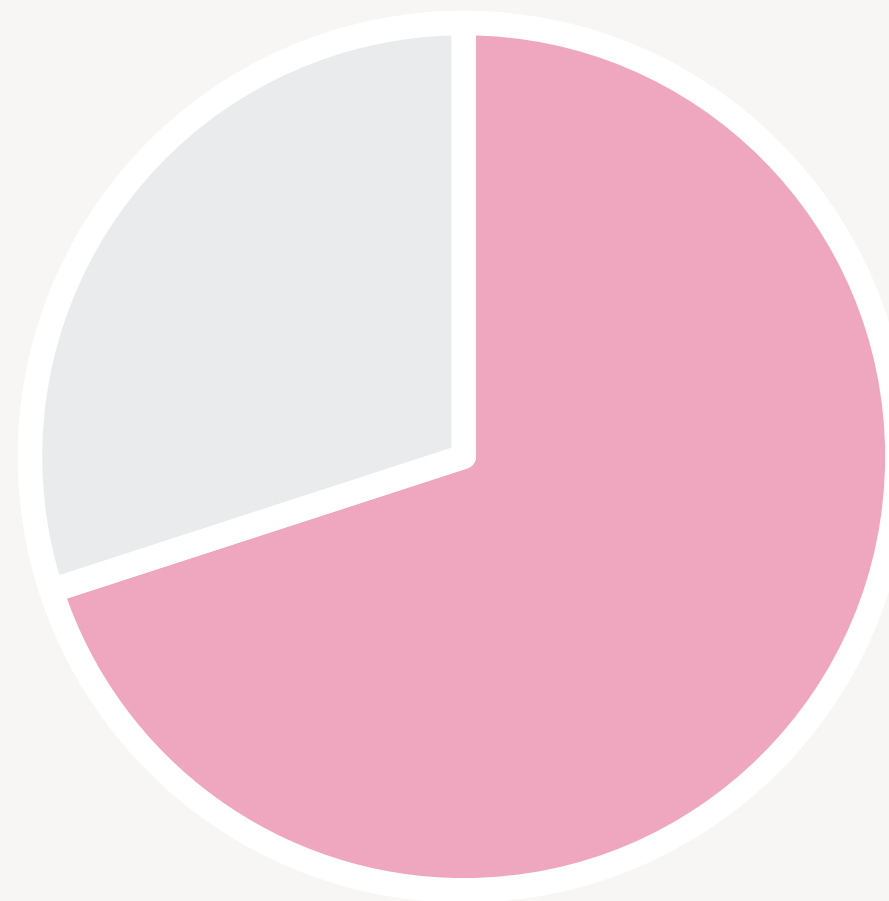




People living with obesity are at an increased risk for several health complications.

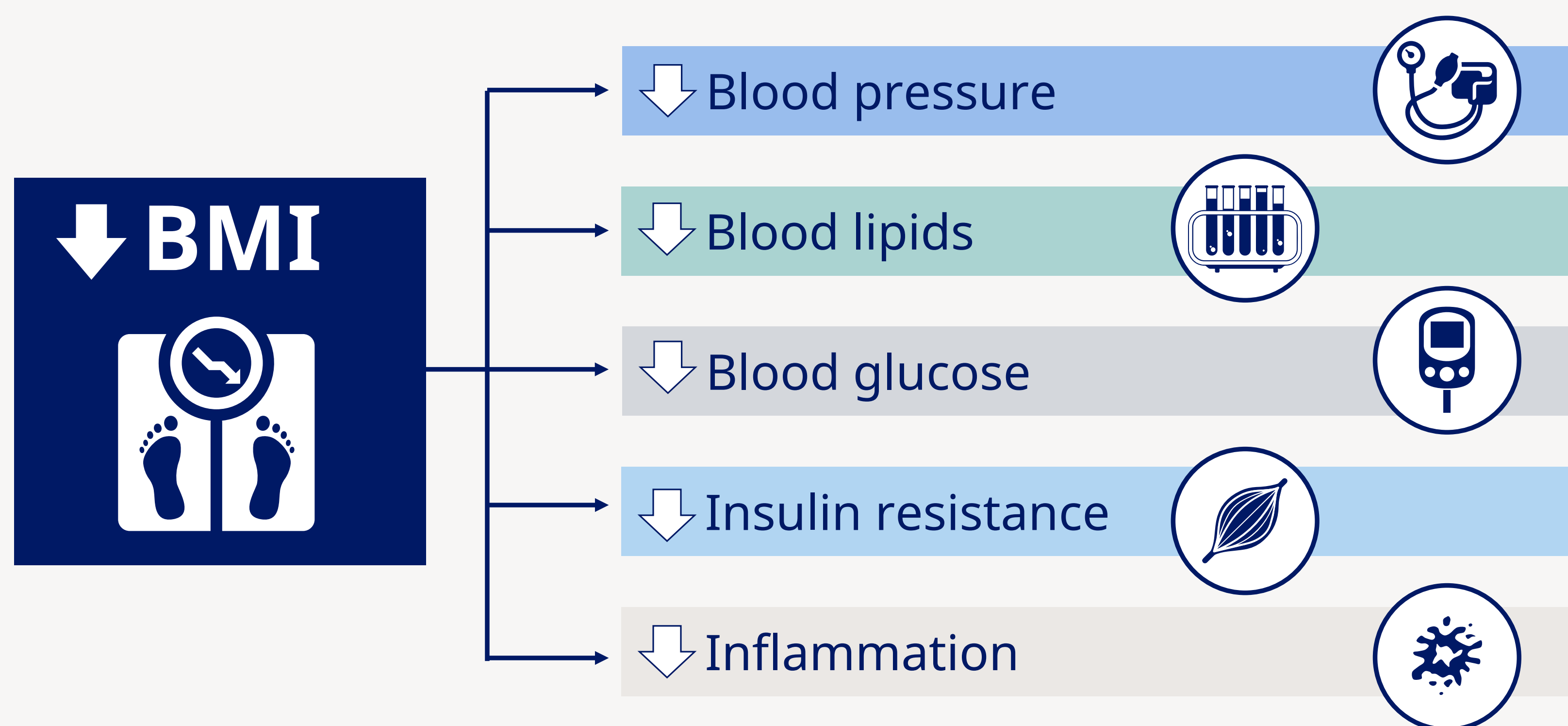
## Obesity is associated with increased cardiovascular morbidity and mortality

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



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.



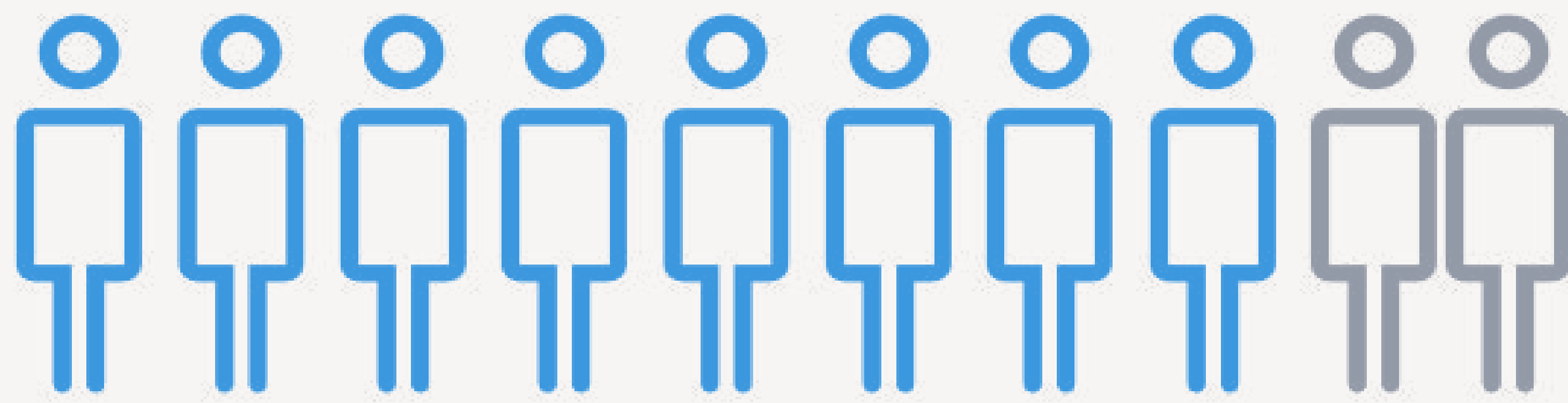
People living with obesity are at an increased risk for several health complications.

## 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

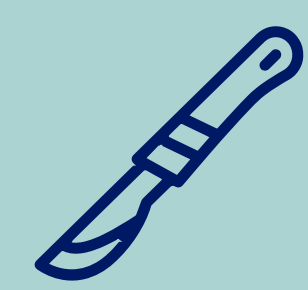
#### Lifestyle interventions



#### Pharmacotherapy



#### Bariatric surgery



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.



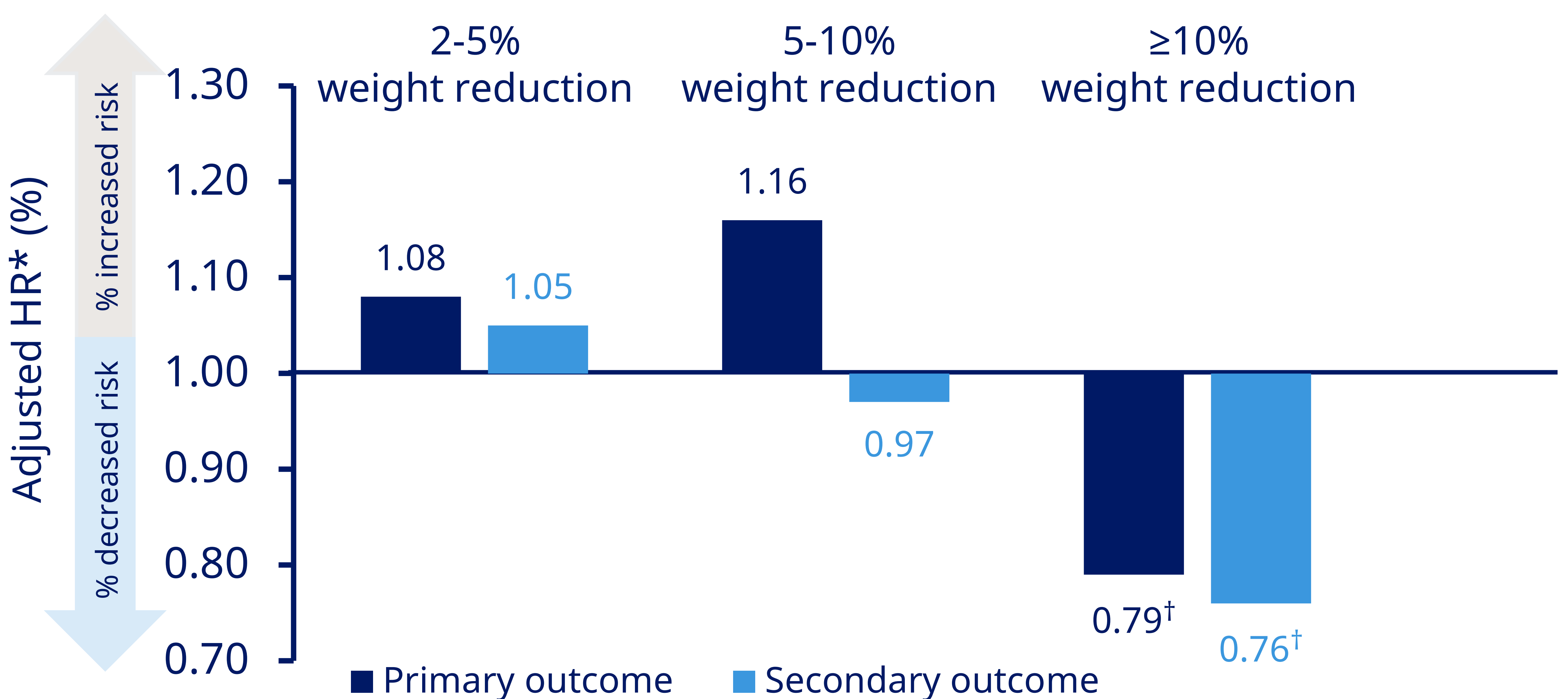
People living with obesity are at an increased risk for several health complications.



## 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; † 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.



## Overview of CVOTs for anti-obesity medications

	SCOUT <sup>1</sup>	CRESCENDO <sup>2</sup>	LIGHT <sup>3</sup>	CONVENE <sup>4</sup>
<b>Intervention</b>	Sibutramine*	Rimonabant*	Naltrexone/ Bupropion	Naltrexone/ Bupropion
<b>Primary Outcome</b>	3P-MACE + resuscitated cardiac arrest	3P-MACE	3P-MACE	3P-MACE
<b>Trial status</b>	<b>Completed</b>	<b>Terminated prematurely</b> <i>(Increased psychiatric and GI AEs)</i>	<b>Terminated prematurely</b> <i>(Study integrity compromised)</i>	<b>Terminated prematurely</b> <i>(Selling of US rights)</i>
<b>HR (95% CI) for primary outcome</b>	<b>1.16</b> (1.03–1.31); P=0.02	<b>0.97</b> (0.84–1.12); P=0.68	<b>0.88</b> (0.57–1.34); <i>50% interim analysis</i>	No data available
<b>Weight change in treatment (vs. control) group</b>	–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>
<b>Intervention</b>	Lorcaserin*	Semaglutide 2.4 mg	Tirzepatide	Naltrexone/ Bupropion
<b>Primary Outcome</b>	1. 3P-MACE (safety outcome) 2. MACE+ (efficacy outcome)	3P-MACE	5P-MACE	3P-MACE
<b>Trial status</b>	<b>Completed</b>	<b>Completed</b>	<b>Estimated completion: October 2027</b>	<b>Estimated completion: July 2029</b>
<b>HR (95% CI) for primary outcome</b>	<b>3P-MACE: 0.99</b> (0.85–1.14); P<0.001 for noninferiority <b>MACE+: 0.97</b> (0.87–1.07); P=0.55 for superiority	<b>0.80</b> (0.72–0.90); P<0.111	N/A	N/A
<b>Weight change in treatment (vs. control) group</b>	–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.



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



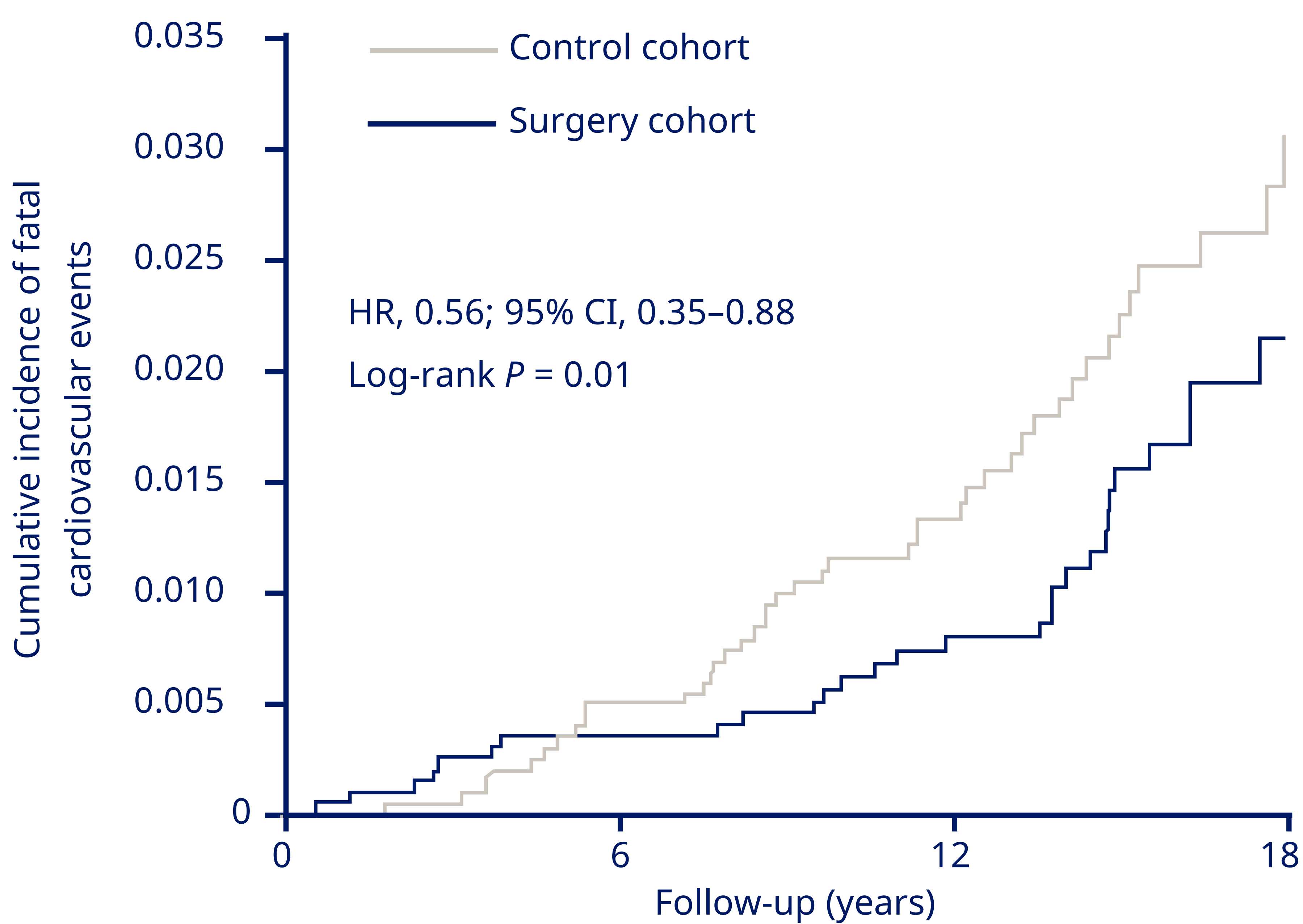
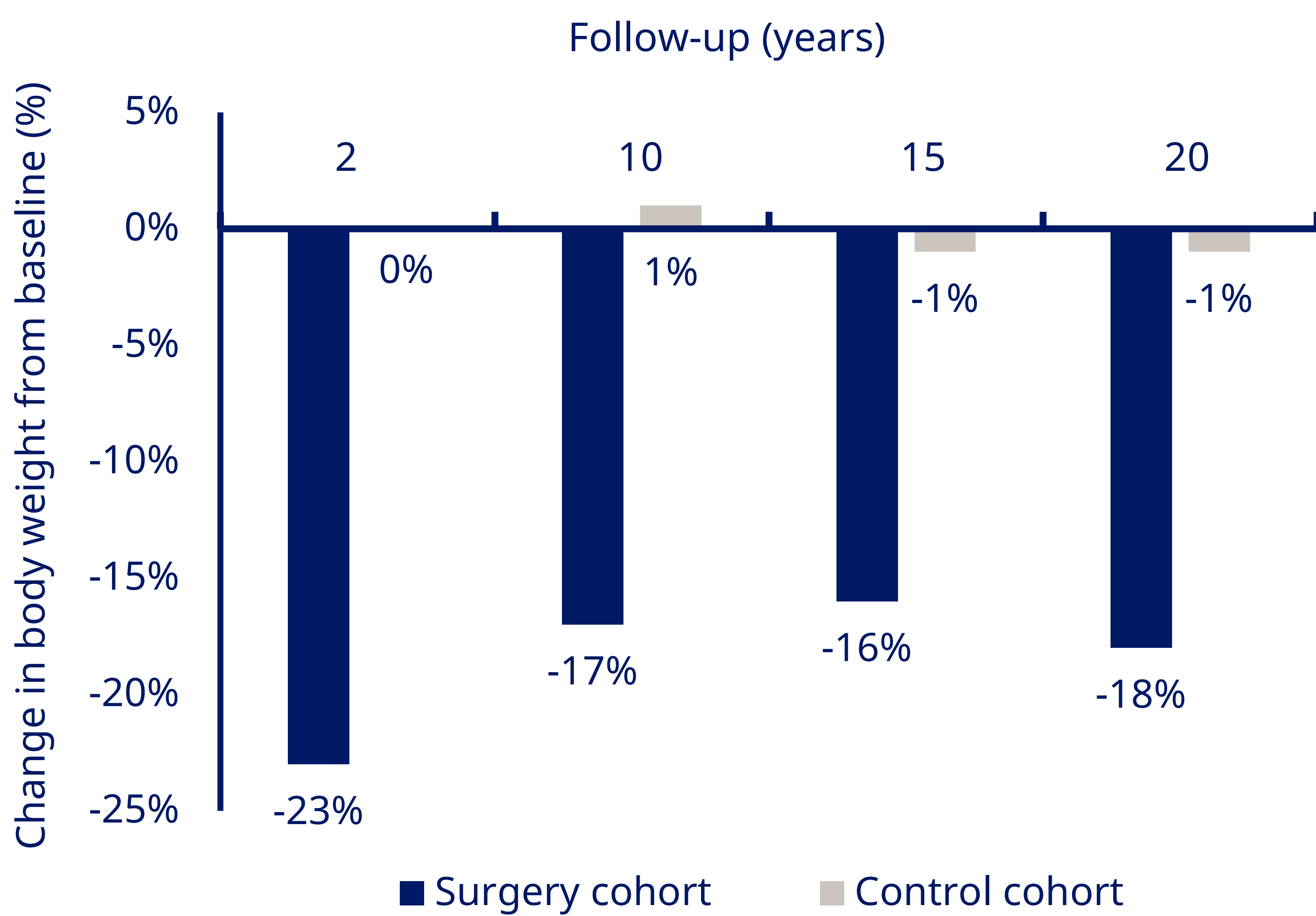
## Adults who received metabolic and bariatric surgery had fewer fatal CV events than matched controls

### Population (N=4047):

Patients with obesity

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

Participants who underwent bariatric surgery (N=2,010) matched with participants with BMI  $\geq 34$  kg/m<sup>2</sup> (N=2,037)



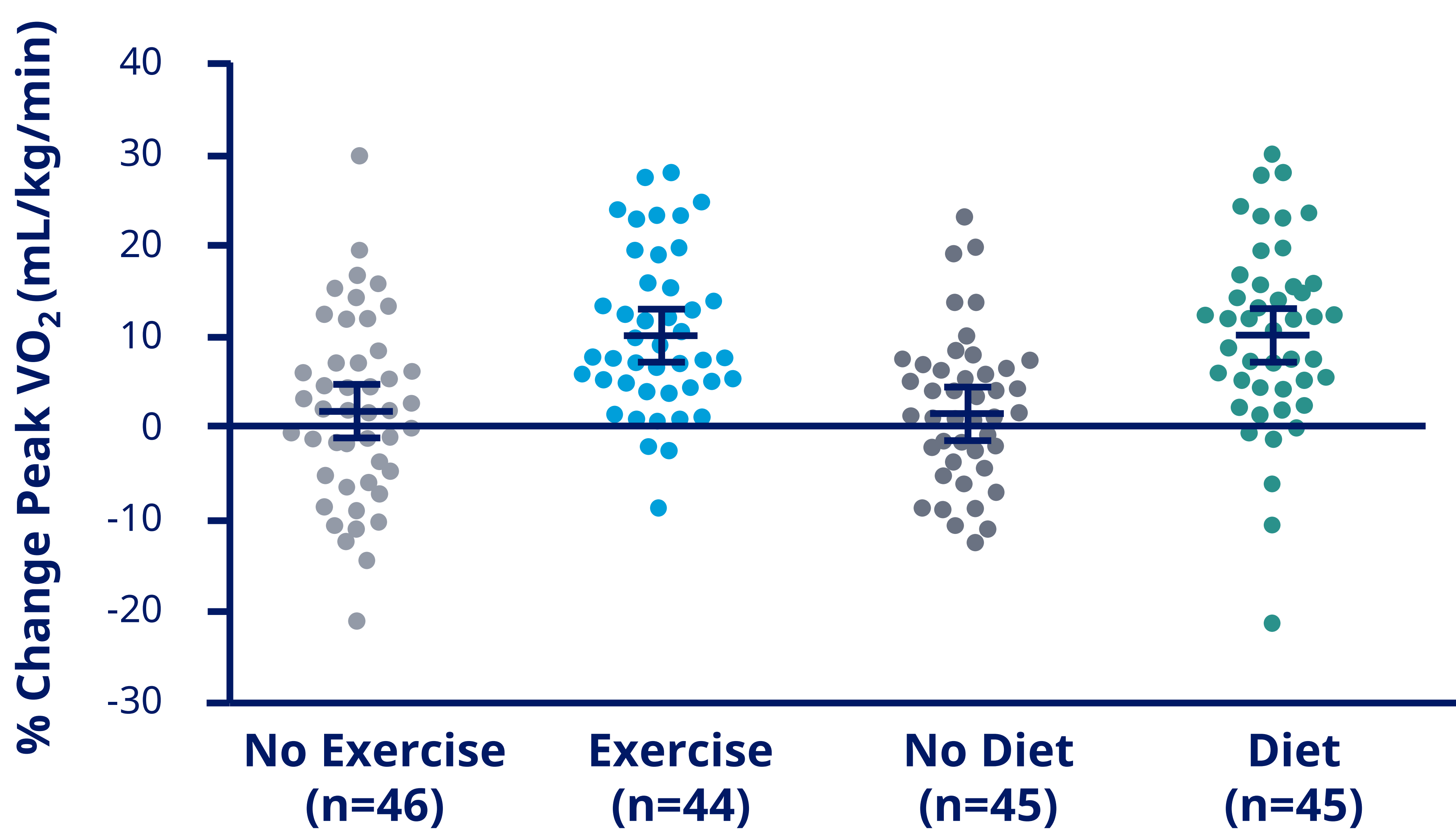
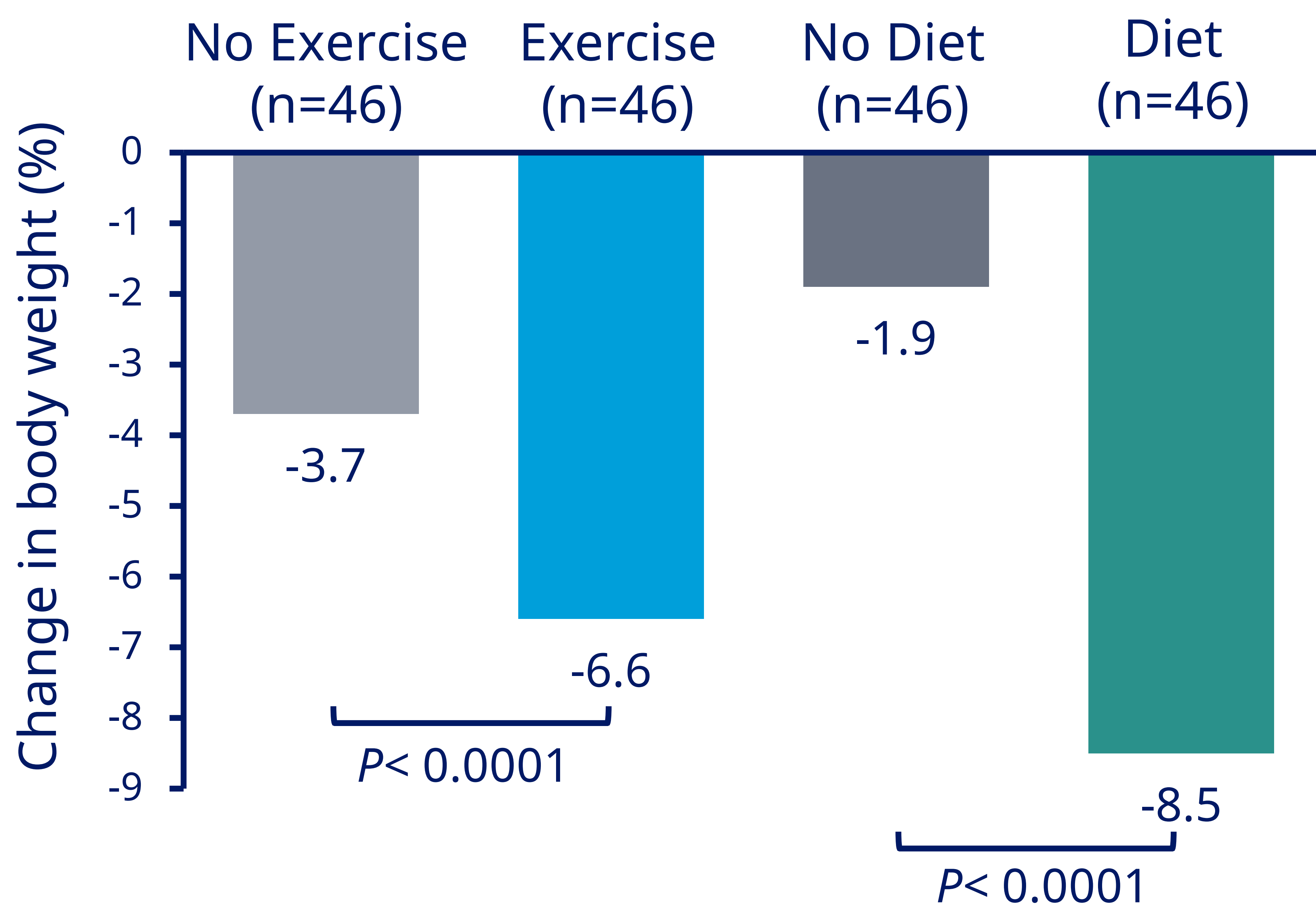


People living with obesity are at an increased risk for several health complications.



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

**Caloric restriction and/or exercise** resulted in weight reduction and improved peak  $VO_2$ <sup>1</sup>



HFpEF, heart failure with preserved ejection fraction;  $VO_2$ , oxygen uptake.  
1. Kitzman et al. JAMA 2016;315:36-46.



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



## Anti-obesity medications in HFpEF trials

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

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

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

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.

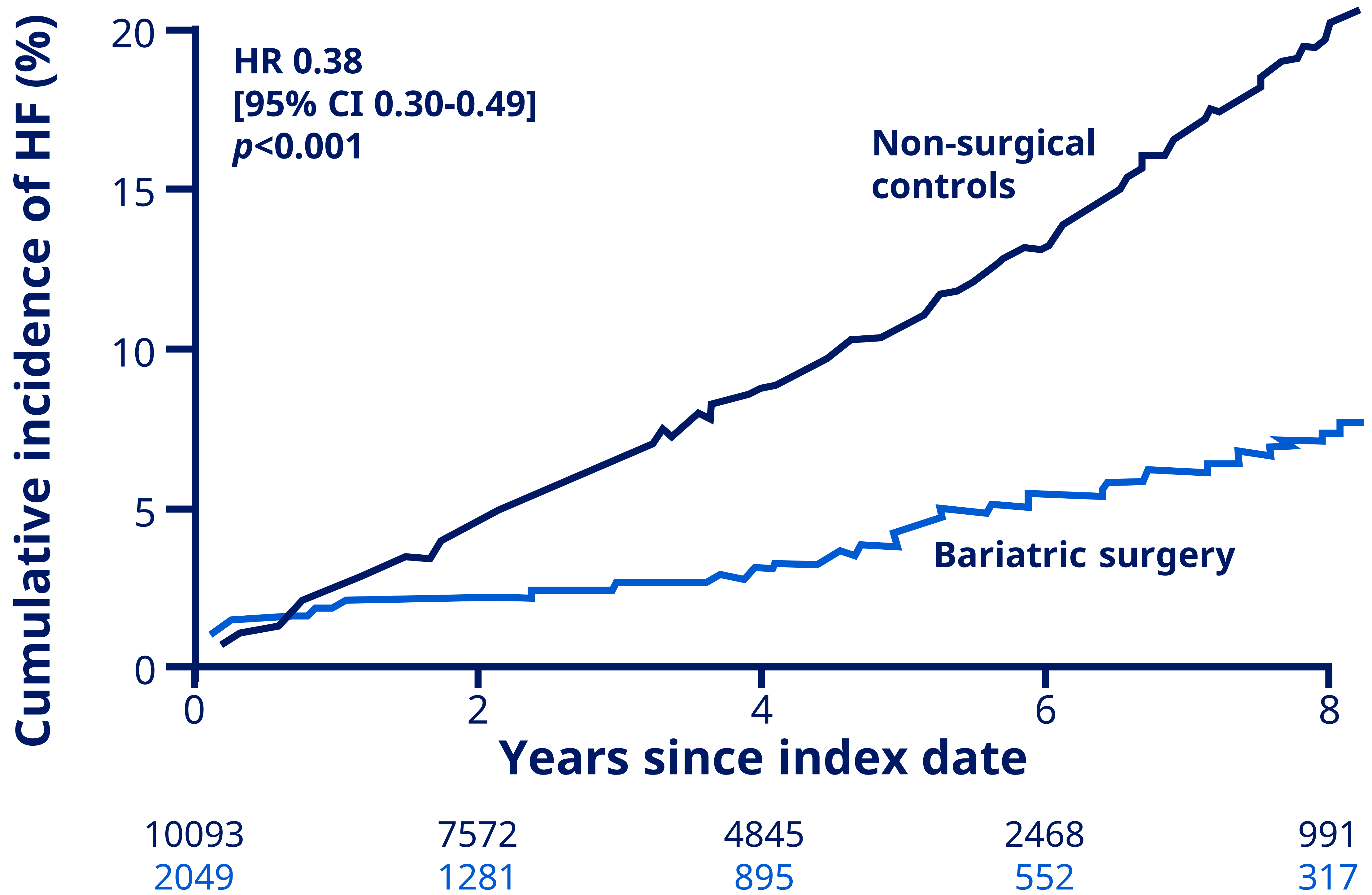
1. Kosiborod MN et al. *N Engl J Med.* 2023;10.1056/NEJMoa2306963. doi:10.1056/NEJMoa2306963; 2. Novo Nordisk A/S. NCT04916470. Available at: <https://clinicaltrials.gov/ct2/show/NCT04916470> (accessed May 2022); 3. Eli Lilly and Company. NCT04847557. Available at: <https://clinicaltrials.gov/ct2/show/NCT04847557> (accessed May 2022).



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



## 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