THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

GLP-1 Receptor Agonists Effect in Older Adults

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RCCN Nutrition in Aging and Biology

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Funding Source + Disclosures

- National Institute on Health
  - R01-AG-077163, R01-AG-067416, R41-AG-071290, R42-AG-071290, R01-AG-058615, U01-AG-071450, UG1-HD-107692
- Patents:
  - 11,857,837B: Instrumented Resistance Exercise Device; 17/335,986 : Remote-Sensing, Bluetooth-enabled, Resistance Exercise Band
  - Provisional Patent Application: Geriatric Functional Assessment System Using Passive Wearable Sensing + Deep Learning
- Societies:
  - KAER Toolkit + Obesity Interest Group Convener (GSA), Program + Chair-Elect Clinical Science Committees (TOS), Member, Sarcopenic Obesity Global Leadership Initiative + Global Leadership Initiative for Sarcopenia
- Equity:
  - SynchroHealth LLC, remote monitoring startup
- Consultant:
  - Regeneron, MEDCorp

FDA-approved Rx for use in older adults

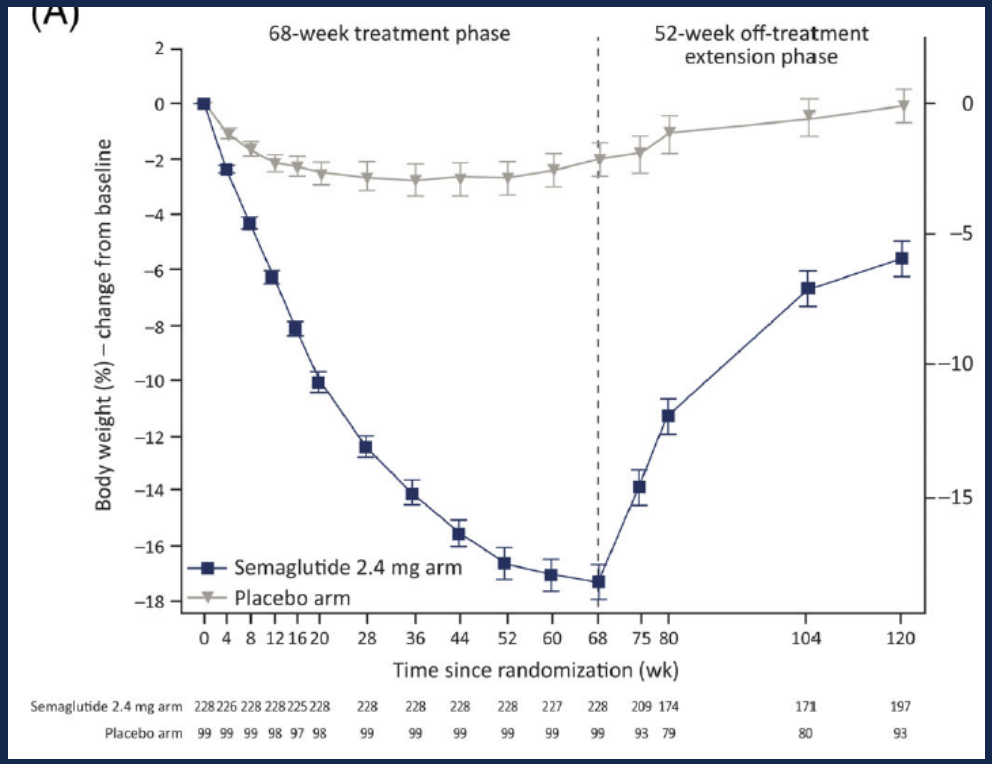
- AACE/ACE guidelines (2016): insufficient evidence
- ACG guidelines (2022): No discussion on prescribing Rx for older adults
- Phentermine/Topiramate, Liraglutide, Bupropion-naltrexone, Orlistat (Xenical)
  - 0–7% age >65 years, <1% age >75 years
- Semaglutide
  - STEP 1: n=744 (23.6%) >65 years; 3.2% >75 years
  - STEP 2: n=788 (48.0%) >65 years; 9.6% >75 years
  - SELECT: n=8803 (30.2%) >65 years; 8.0% >75 years
- Tirzepatide:
  - SURMOUNT-1: 6% age >65 years
  - SURMOUNT-2: n=165/938 (18%) age >65 years

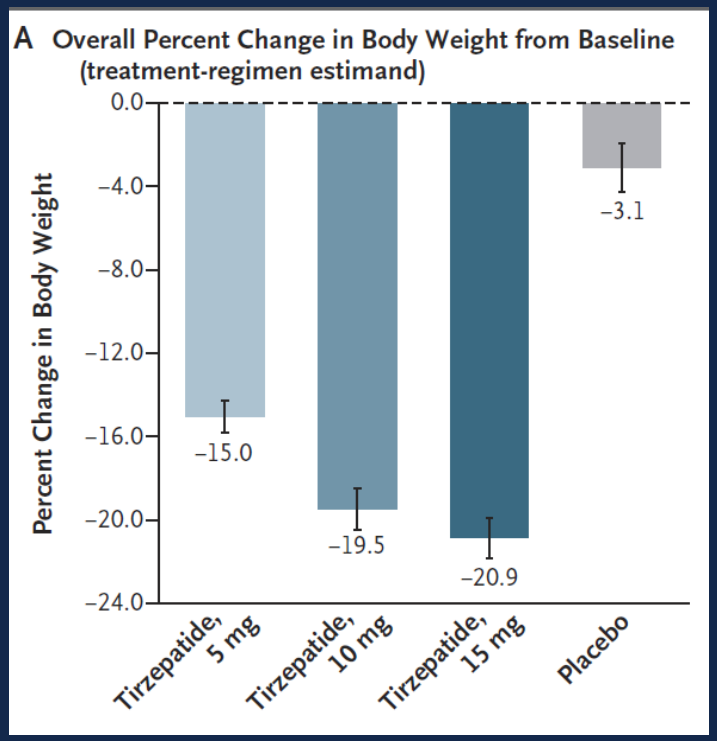
Studies	SURPASS-1 N=478	SURPASS-2 N=1878	SURPASS-3 N=1437	SURPASS-4 N=1995	SURPASS-5 N=475
Age (years)	54.1 ± 11.9	56.6 ± 10.4	57.4 ± 10.0	63.6 ± 8.6	60.6 ± 9.9

- Short-term safety + efficacy is similar compared to younger adults

Hollander P *Diab Care* 2013, Boye KS *Diabetes Ther* 2023
Garvey WT *Lancet* 2023, drugs@FDA, Lincoff *NEJM* 2023
Grunvald E *Gastroenterology 2022,* Kiyosue A *Diabetes Obes Metab* 2023

Semaglutide + Tirzepatide





Mean age 48 years

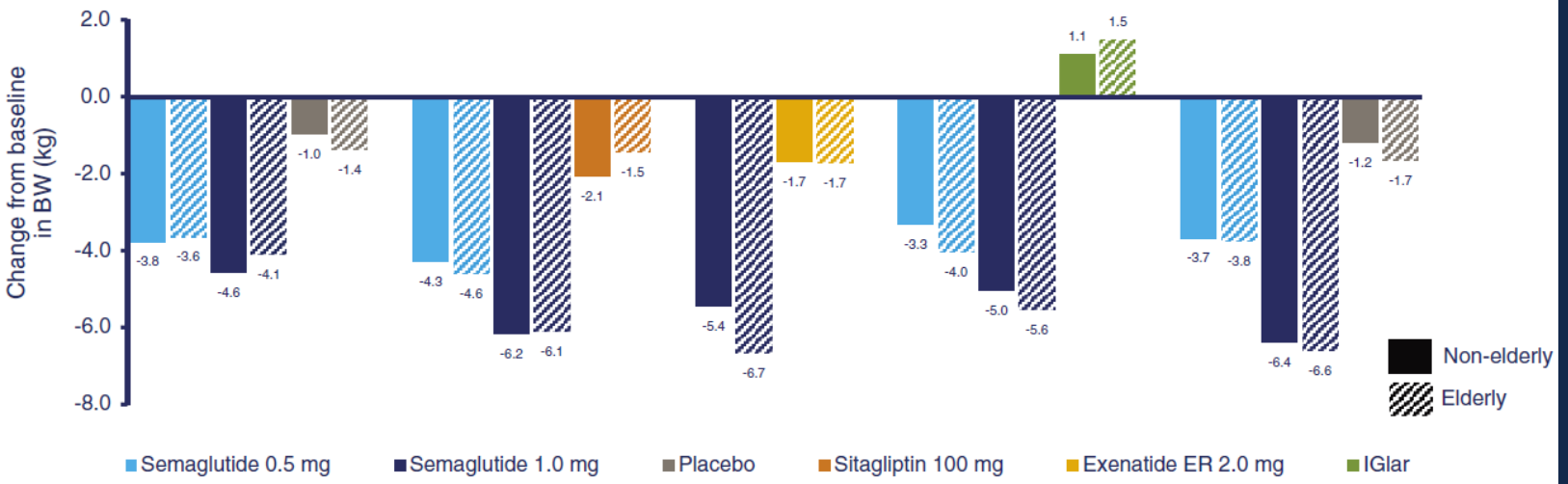
Mean age 46 years

Wilding JPH *Diab Obes Met* 2022
Jastreboff AM *NEJM* 2023

SUSTAIN Trials
≥ 65 vs. < 65 years

(B)

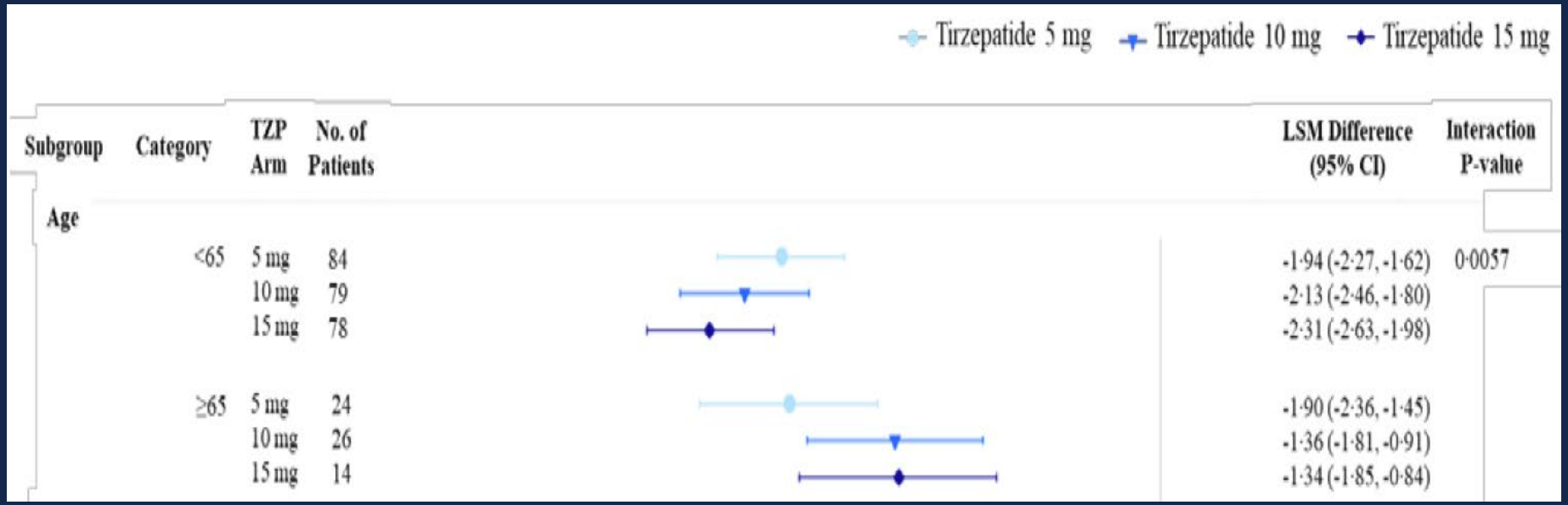
	SUSTAIN 1: semaglutide vs placebo	SUSTAIN 2: semaglutide vs sitagliptin	SUSTAIN 3: semaglutide vs exenatide ER	SUSTAIN 4: semaglutide vs IGlar	SUSTAIN 5: semaglutide add-on to insulin vs placebo
Treatment duration (weeks):	30	56	56	30	30
No. of patients:	387	1,225	809	1,082	396
Baseline BW (kg):	90.8 | 85.8 | 99.4 | 83.1 | 92.0 | 76.2	90.8 | 86.2 | 90.6 | 83.2 | 91.2 | 81.4	98.1 | 89.6 | 97.8 | 88.6	94.6 | 91.0 | 93.9 | 94.4 | 93.8 | 88.5	94.5 | 88.7 | 94.3 | 86.2 | 92.7 | 84.8



Warren M *Diabetes Obes Metab* 2018

Older Adults + Efficacy Outcomes

HbA1c at 40-weeks



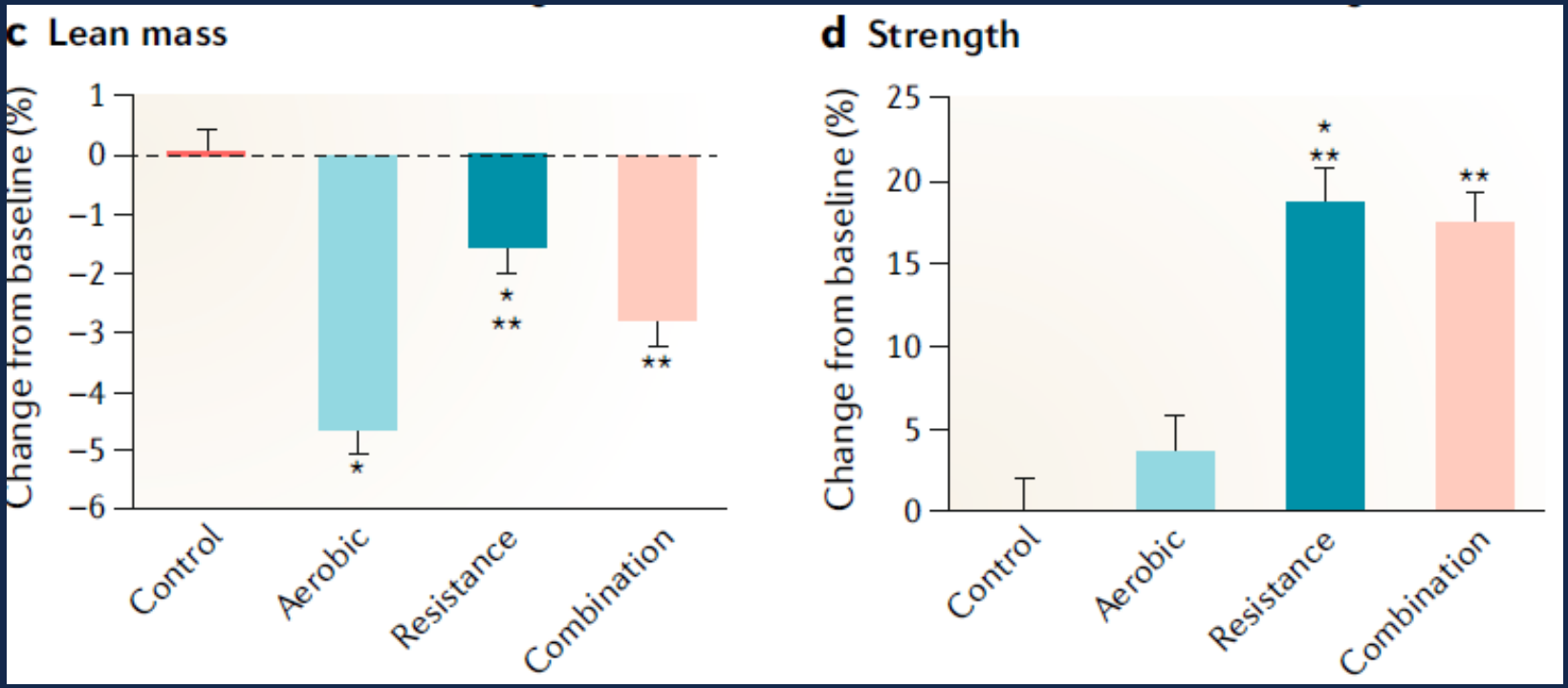
Subgroup	Category	TZP Arm	No. of Patients	LSM Difference (95% CI)	Interaction P-value
Age					
	<65	5 mg	84	-1·94 (-2·27, -1·62)	0·0057
		10 mg	79	-2·13 (-2·46, -1·80)	
		15 mg	78	-2·31 (-2·63, -1·98)	
	≥65	5 mg	24	-1·90 (-2·36, -1·45)	
		10 mg	26	-1·36 (-1·81, -0·91)	
		15 mg	14	-1·34 (-1·85, -0·84)	

Older adult outcomes < than younger individuals and NOT dose-dependent

Rosenstock J *Lancet* 2021

Weight-Loss Induced Lean Mass

Lifestyle Interventions – older adults with obesity

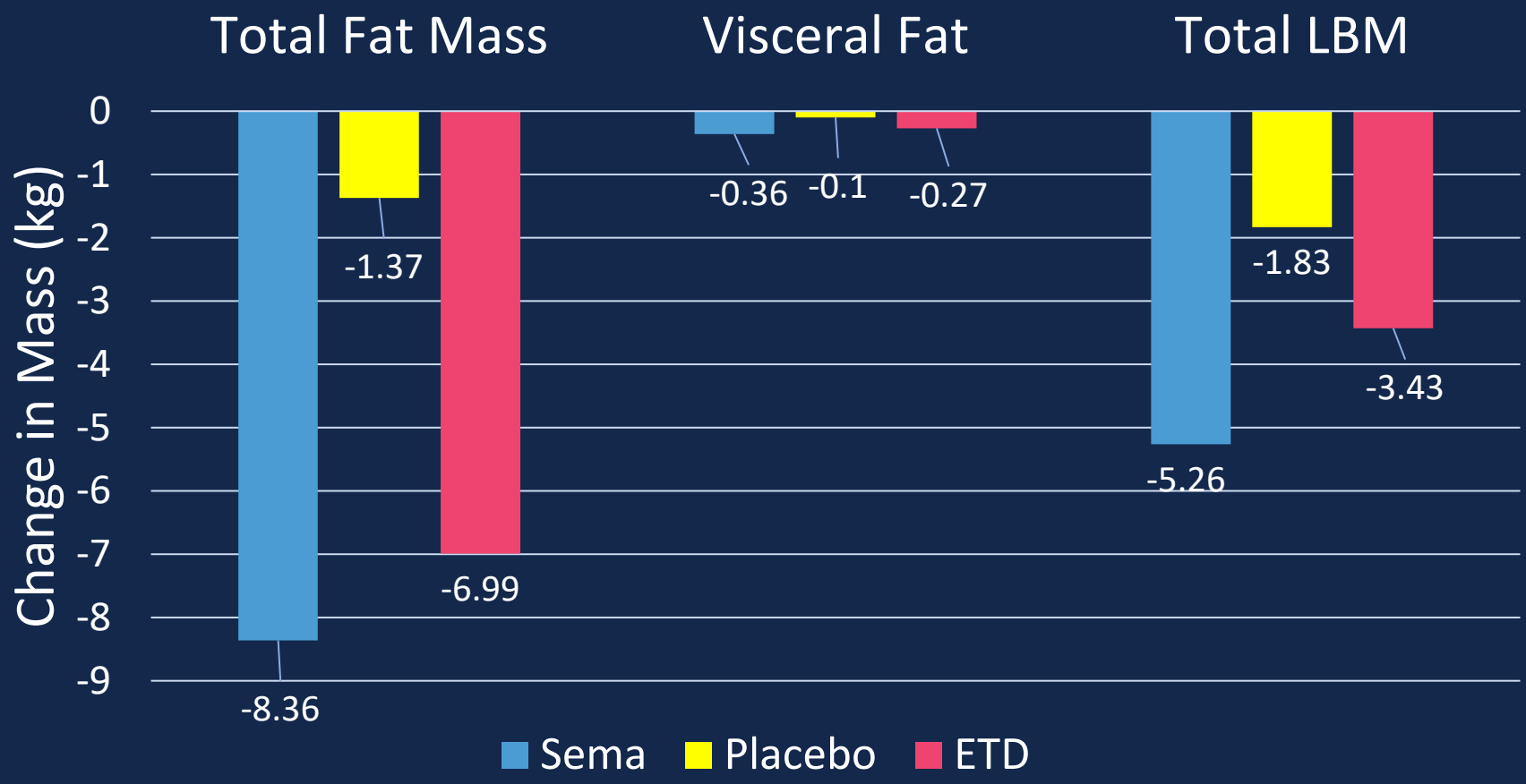


Combination Aerobic/Resistance/Diet led to reductions in Lean Mass but improved strength

Villareal DT *NEJM* 2017
Batsis JA *Nat Rev Endocrin* 2018

Semaglutide + Body Composition

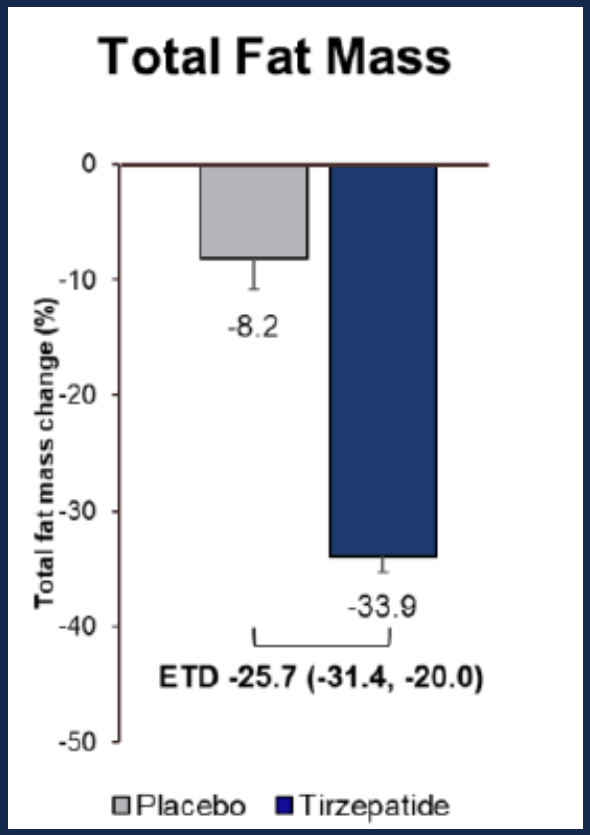
STEP-1 Substudy

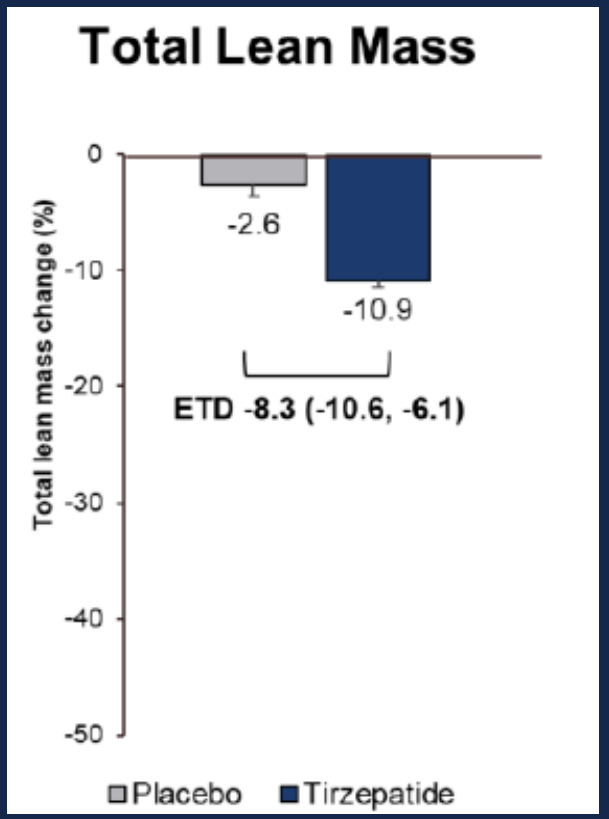


Wilding J *NEJM* 2021

SURMOUNT-1 – DEXA assessment

6% of participants aged ≥65 years

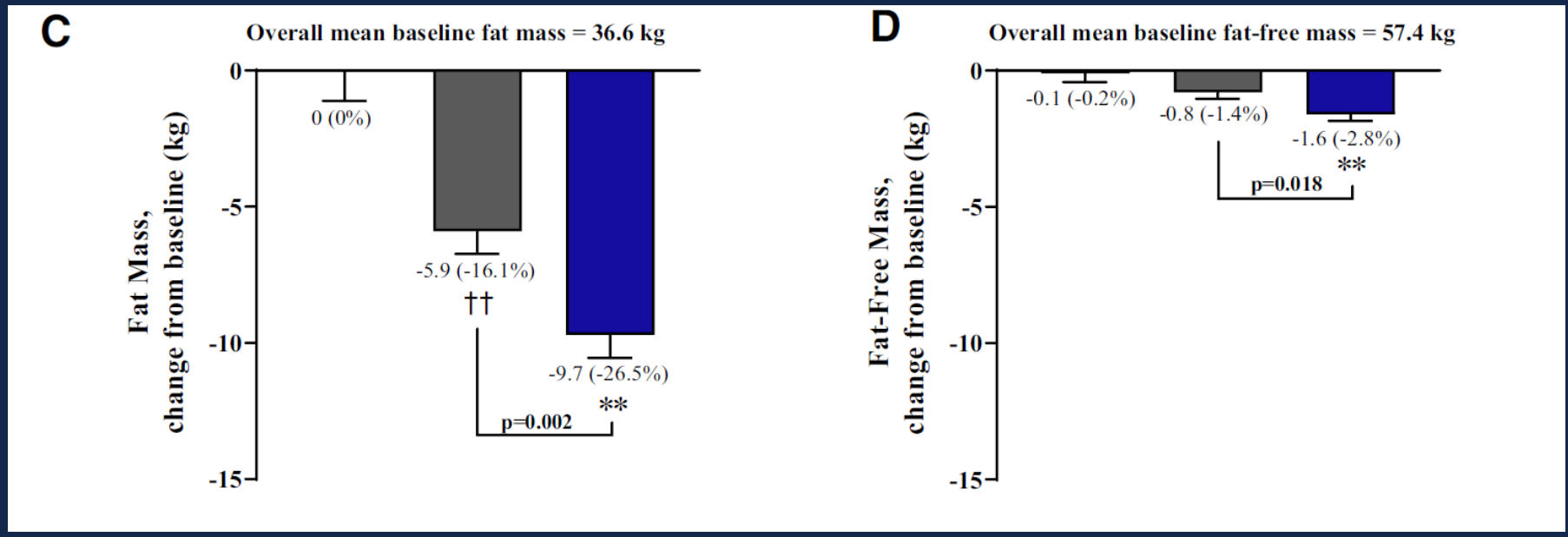




Absolute segmentation not discussed: ~24%

Jastreboff AM *NEJM* 2022

Semaglutide vs. Tirzepatide vs. Placebo
28-week trial, mean age 62



Semaglutide ~11.9% + Tirzepatide 14.2% of weight loss is fat-free mass (Bod-Pod)

Heise T *Diabetes Care 2023*

Tirzepatide in Older Adults
Subanalysis of East Asian SURPASS

	Tirzepatide 5 mg				Tirzepatide 10 mg				Tirzepatide 15 mg			
BMI (kg/m^2)	<25		≥25		<25		≥25		<25		≥25	
Age (year)	≤65	>65	≤65	>65	≤65	>65	≤65	>65	≤65	>65	≤65	>65
N	67	31	206	68	64	39	207	61	61	39	222	52
D/C due to AE	7 (10.4)	6 (19.4)	6 (2.9)	6 (8.8)	5 (7.8)	8 (20.5)	14 (6.8)	6 (9.8)	9 (14.8)	12 (30.8)	13 (5.9)	8 (15.4)

Side Effects in Older Adults are dose-dependent

Kiyosue A *Diab Obes Met* 2023

Adverse Effects of AOM

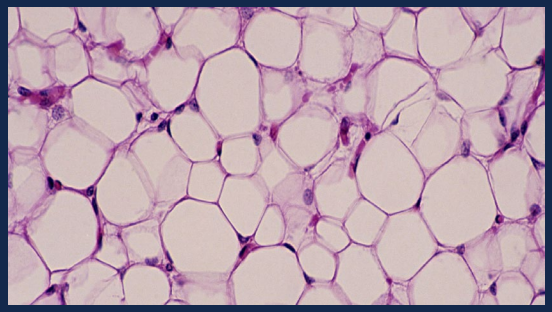
Generic Name	Absolute Contraindications	Side-Effects (>10%) & Major Risks in Older Adults
Phentermine/ Topiramate	Glaucoma, MAOI hyperthyroidism	**Constipation** headache, **xerostomia**
Phentermine	Glaucoma, Heart failure, **CAD,** Hyperthyroidism, **Arrhythmias**	**Renal insufficiency**, Reduced exercise tolerance
Orlistat	Malabsorption, cholestasis	**Fecal urgency**, Flatulence, **Steatorrhea**
Buproprion/ naltrexone	HTN, Seizures, Hepatic impairment	**More sensitive to CNS effects, Renal insufficiency**, Headache, **Constipation**, N/V
Liraglutide	Angioedema, MEN-2, MTC	**Constipation, Diarrhea, Hypoglycemia,** Palpitations, N/V
Semaglutide & Tirzepatide	MEN-2, MTC	**Nausea (>20%), Diarrhea (>17%), Vomiting (~10%), Dyspepsia (~8%)**

De Mesquita YLL *Int J Obes* 2023

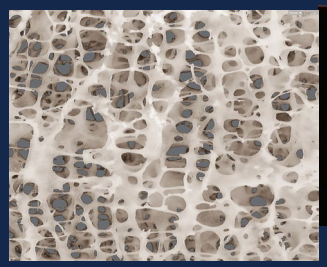
Is all Weight Loss the Same?

Loss of Weight

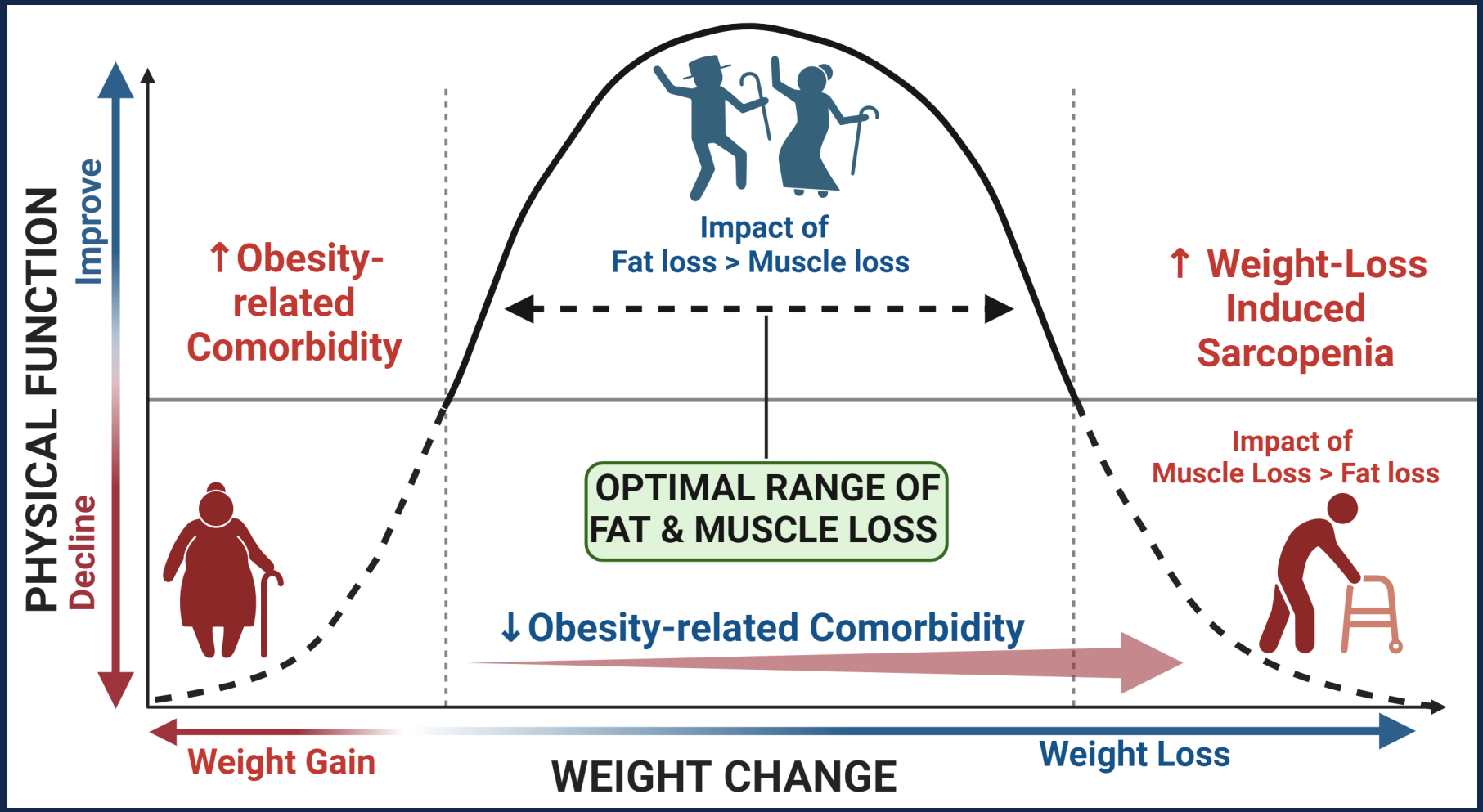
Fat-Mass



Fat-Free Mass

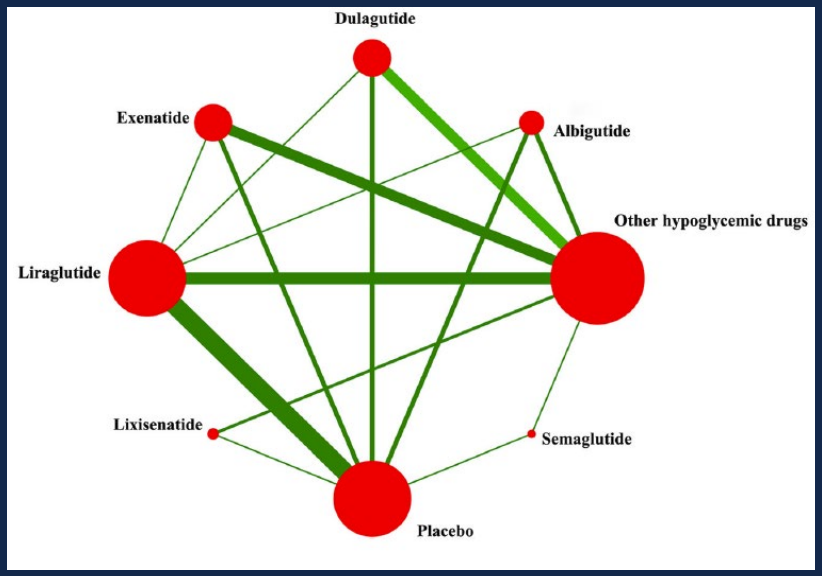


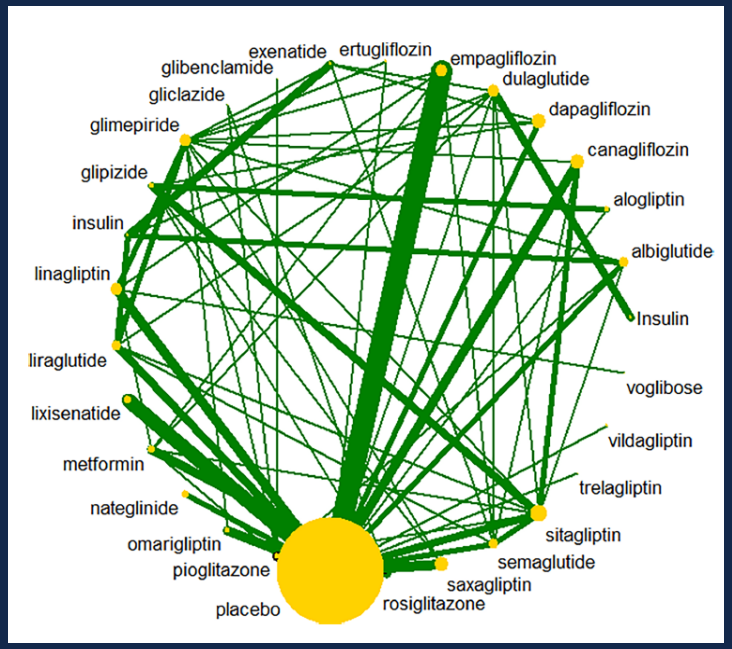
Balancing Fat + Muscle



GLP-1 + Fracture Risk

Network meta-analysis



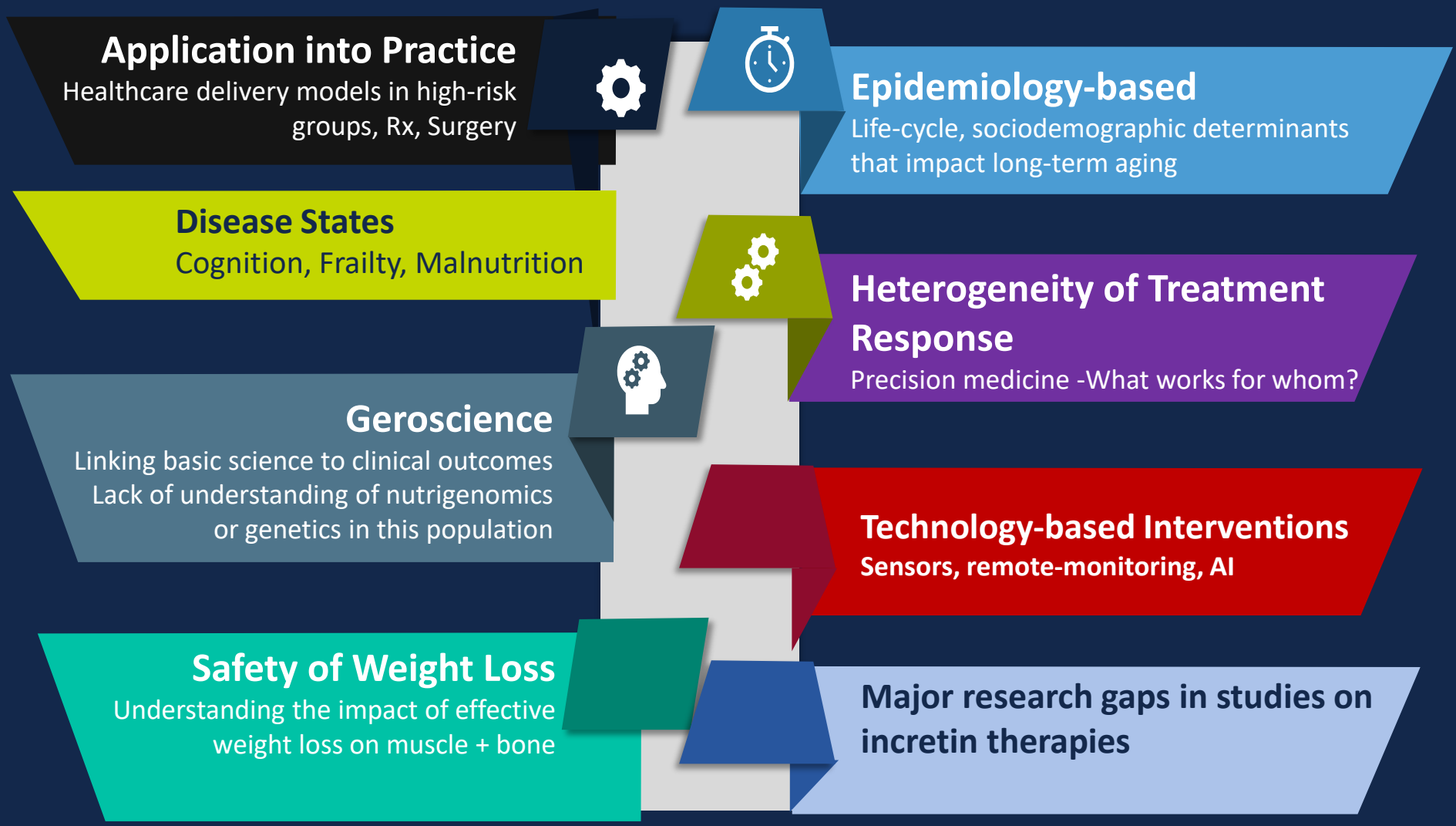


Exenatide 0.17 (0.03,0.67)
Dulaglutide 1.04%
Liraglutide 1.39%
Semaglutide 18.72%

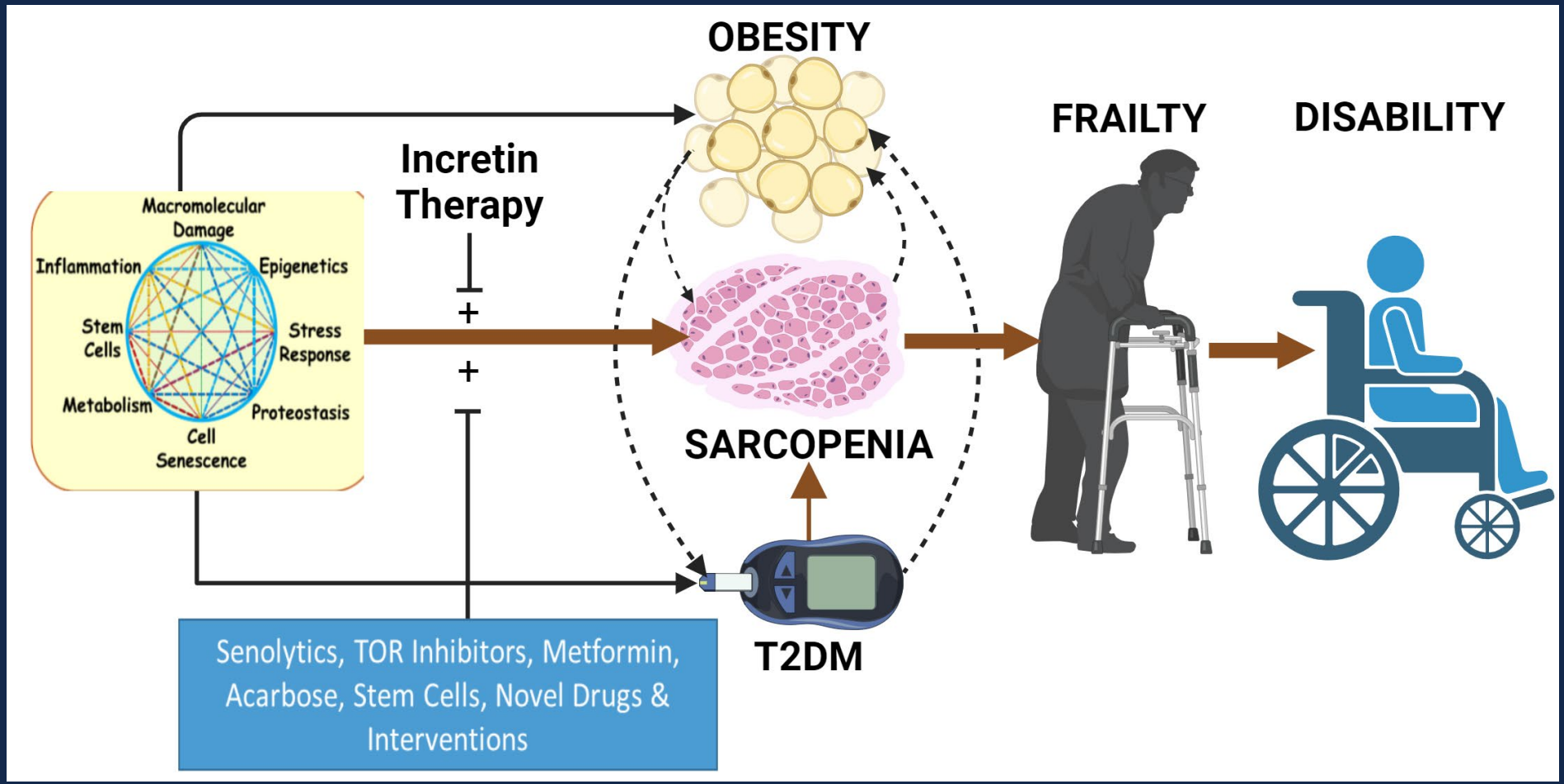
Incretins led to reduced fracture risk but <u>not</u> statistically significant

Zhang YS *Osteoporos Int* 2018
Zhang YS *Front Endocrine* 2021

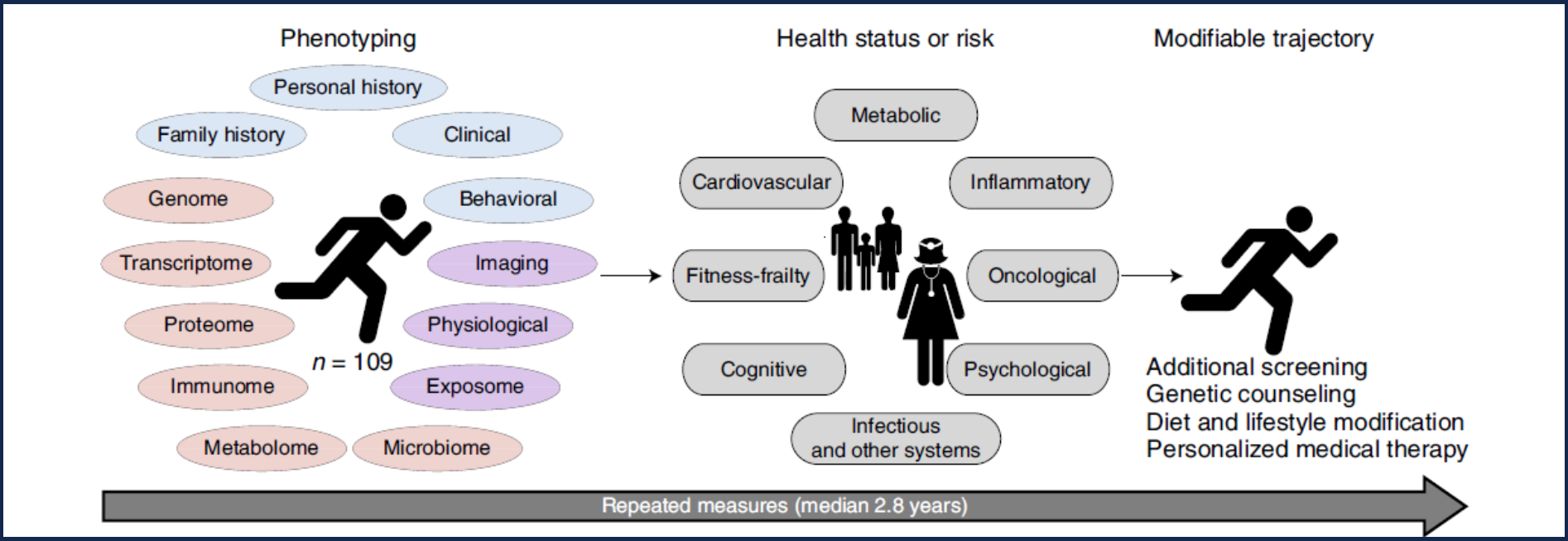
Future Research Efforts & Gaps?



How should we treat obesity?



Phenotyping using Artificial Intelligence

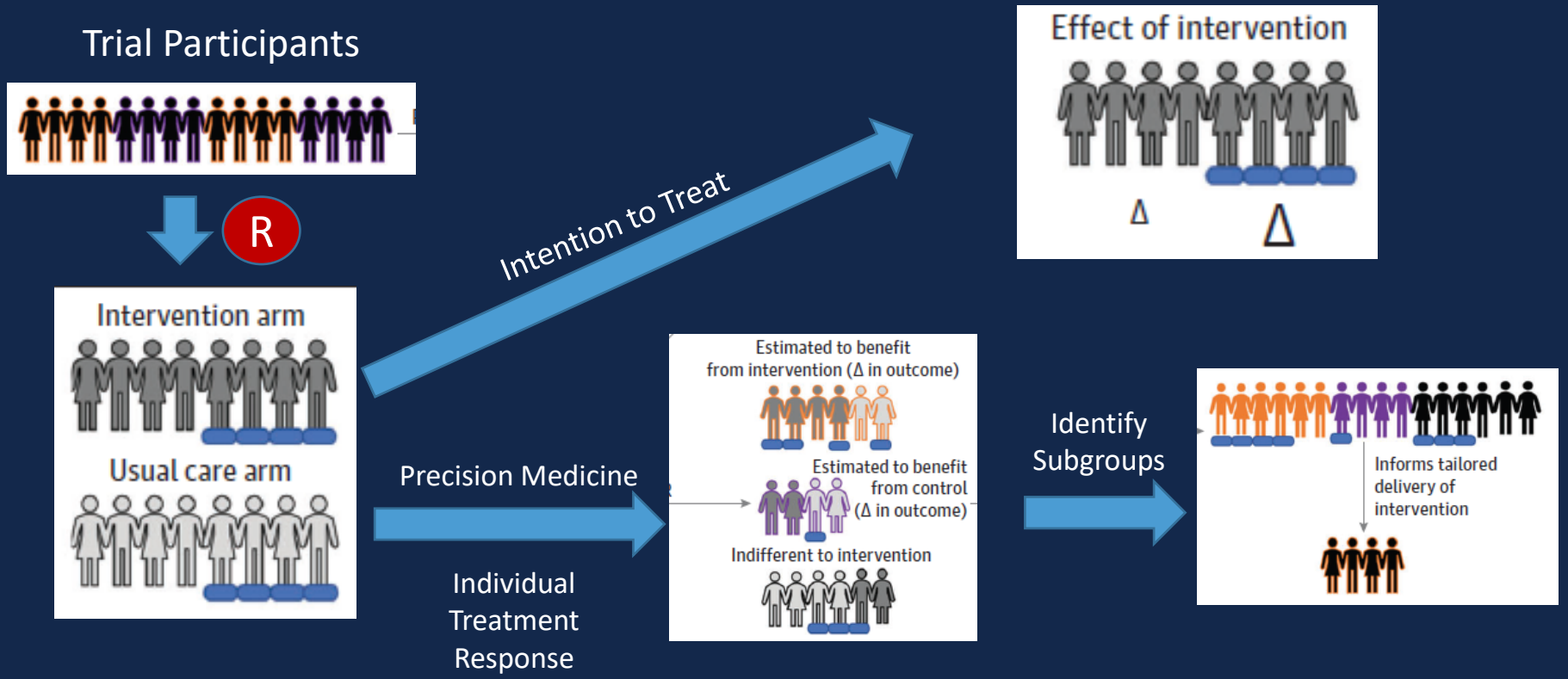


- Incorporate multiple streams of data sources
- Cluster subjects + extract latent factors into different clusters

Rose S *Nat Med* 2019

Using novel trial design + analytics to maximize treatment response

- Clinical Trial Designs that individualize approaches
- Trials of biological hallmarks of aging



Thank you - Questions?

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