Obesity will change the cardiovascular game

Prof. dr. Naveed Sattar

Obesity will change the cardiovascular game!

University of Glasgow

School of Cardiovascular & Metabolic Health

Naveed Sattar
Professor of Metabolic Medicine

British Heart Foundation

Duality of Interest Declaration

Consulting/speaker honoraria:

Abbott Laboratories, Afimmune, Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Hanmi Pharmaceuticals, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, Roche Diagnostics, Sanofi

Grant: AstraZeneca, Boehringer Ingelheim, Novartis, Roche Diagnostics

Options 2⁰ prevention expanded

BUT where is obesity?

Patients with or at high risk for ASCVD

Despite contemporary evidence-based therapies*, residual risk of ASCVD events persists

	Residual cholesterol risk	Residual inflammatory risk	Residual thrombotic risk	Residual triglyceride risk	Residual Lp(a) risk	Residual diabetes risk
Critical biomarker	LDL-C ≥ 100 mg/dL	hsCRP ≥ 2 mg/L	No simple biomarker	TG ≥ 150 mg/dL	Lp(a) ≥ 50 mg/dL	HbA_{1c} fasting glucose
Potential intervention	Targeted LDL/Apo B reduction	Targeted inflammation reduction	Targeted antithrombotic reduction	Targeted triglyceride reduction	Targeted Lp(a) reduction	SGLT2is GLP-1RAs
Randomised trial evidence	IMPROVE-IT FOURIER SPIRE ODYSSEY	CANTOS COLCOT LoDoCo2 **ZEUS**	PEGASUS COMPASS THEMIS	REDUCE-IT PROMINENT	Planned	EMPA-REG CANVAS DECLARE CREDENCE LEADER SUSTAIN-6 REWIND

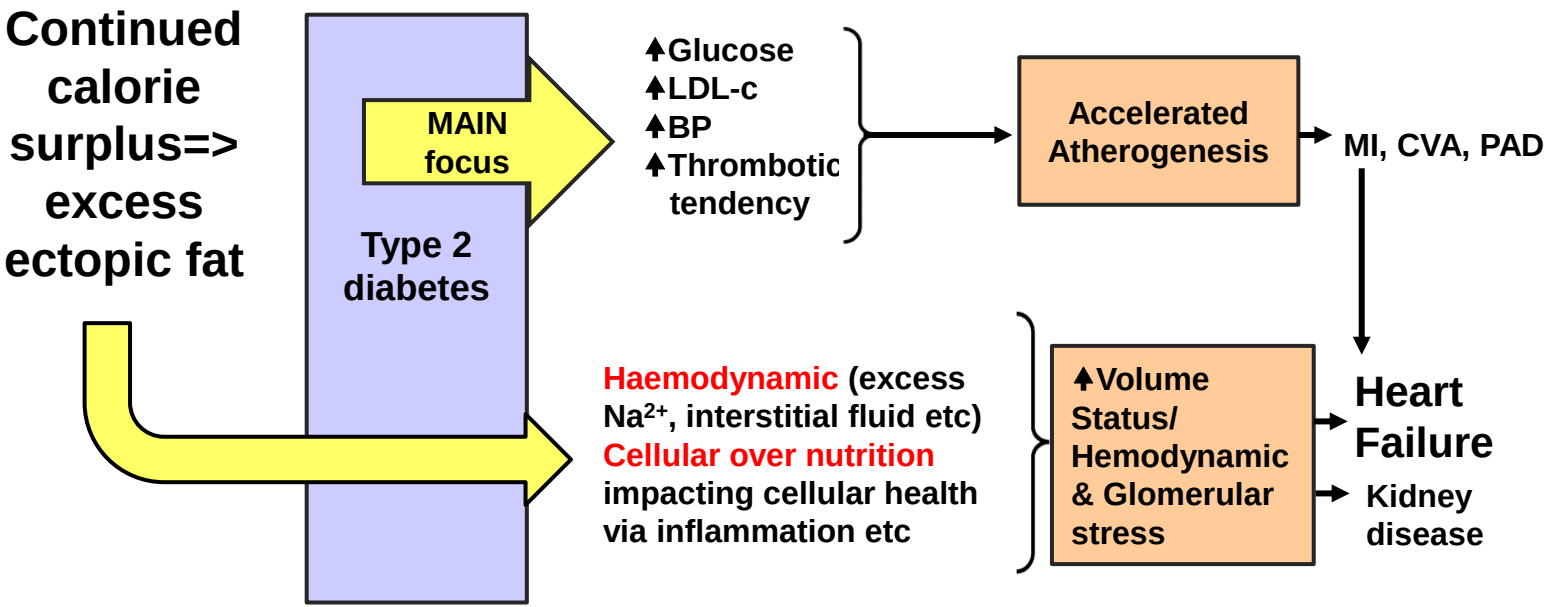
LDL-c main issue

GLP-1RA /SGLT2i

Why not bothered about weight loss?

- The evidence base is poor and don’t believe obesity is causal for outcomes that matter to me
- And, do not believe we can change weight much or for long enough?
- Too busy with more clever interventions?

Higher BMI over years



Sattar et al ©, adapted from *Sattar N, McGuire D (2018) Circulation – In press Diabetes Care*

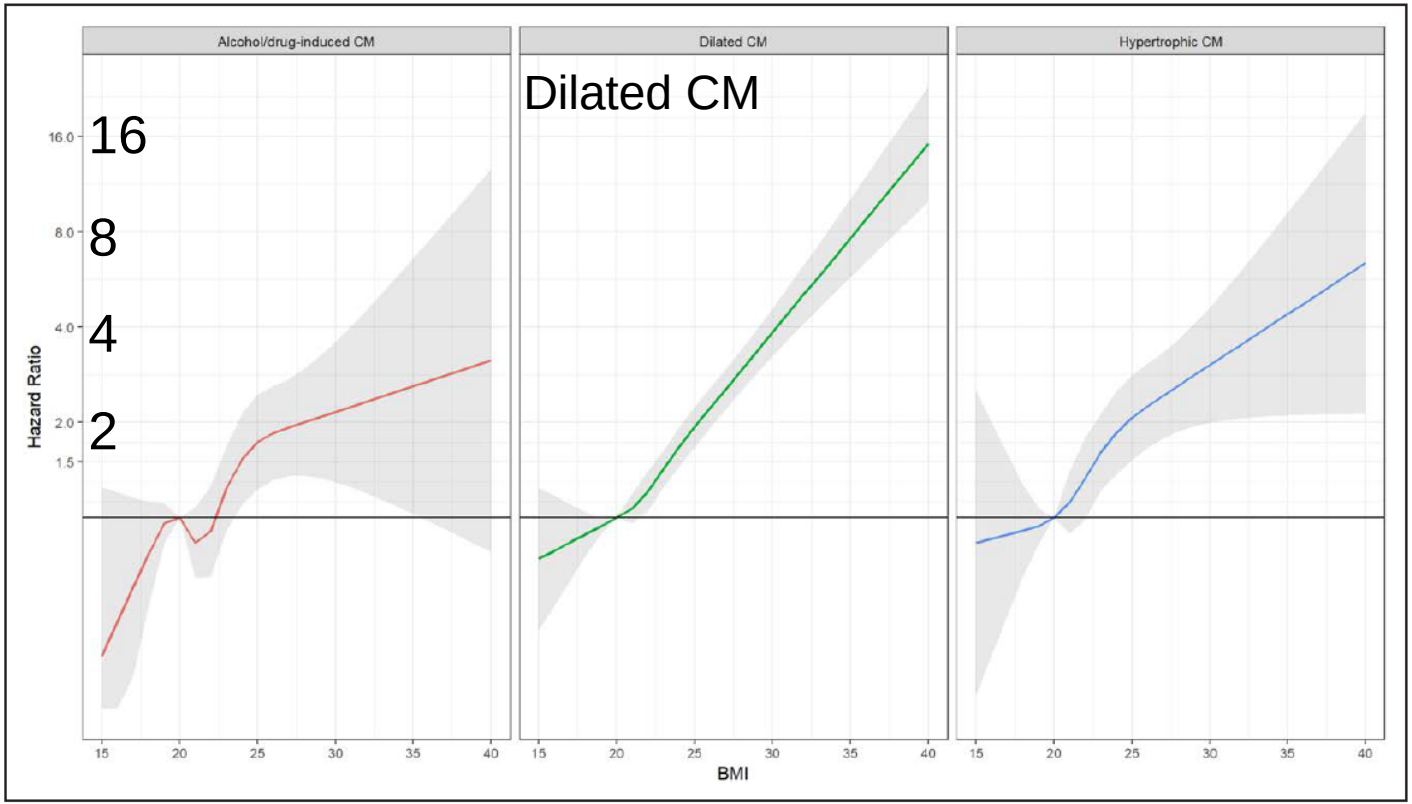
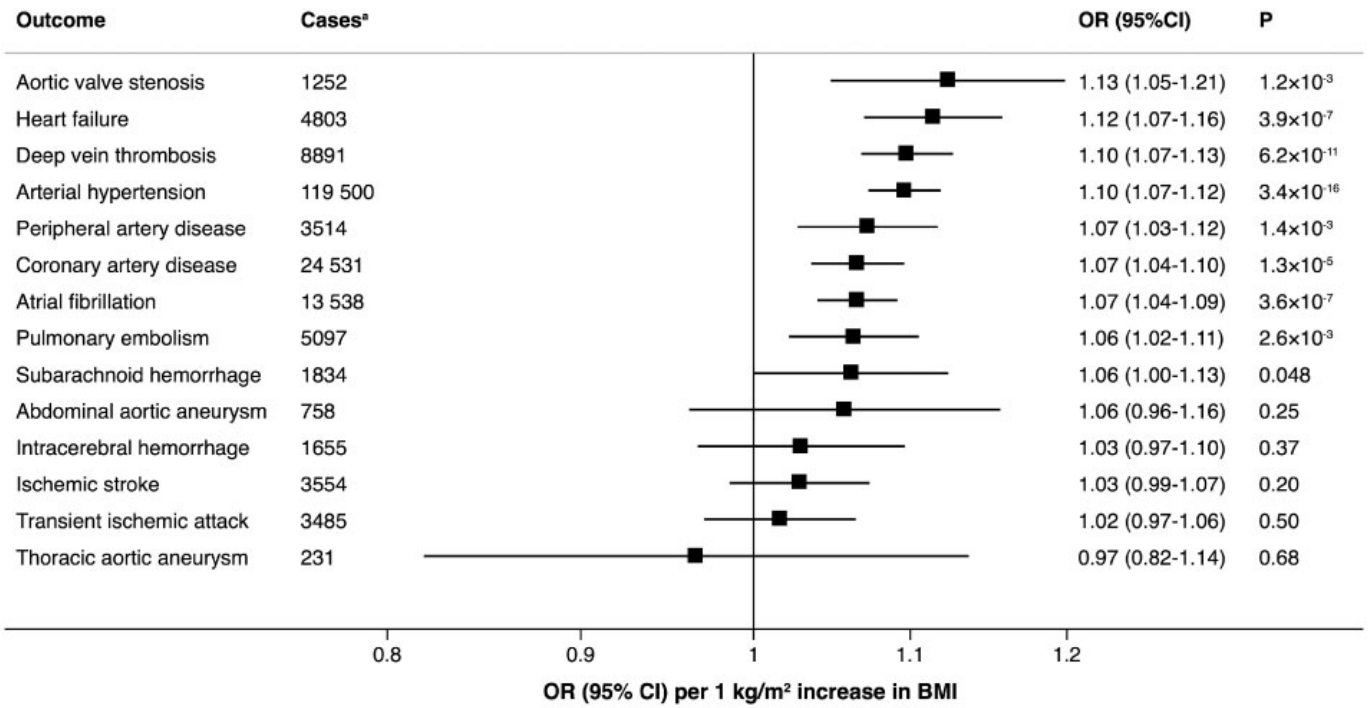
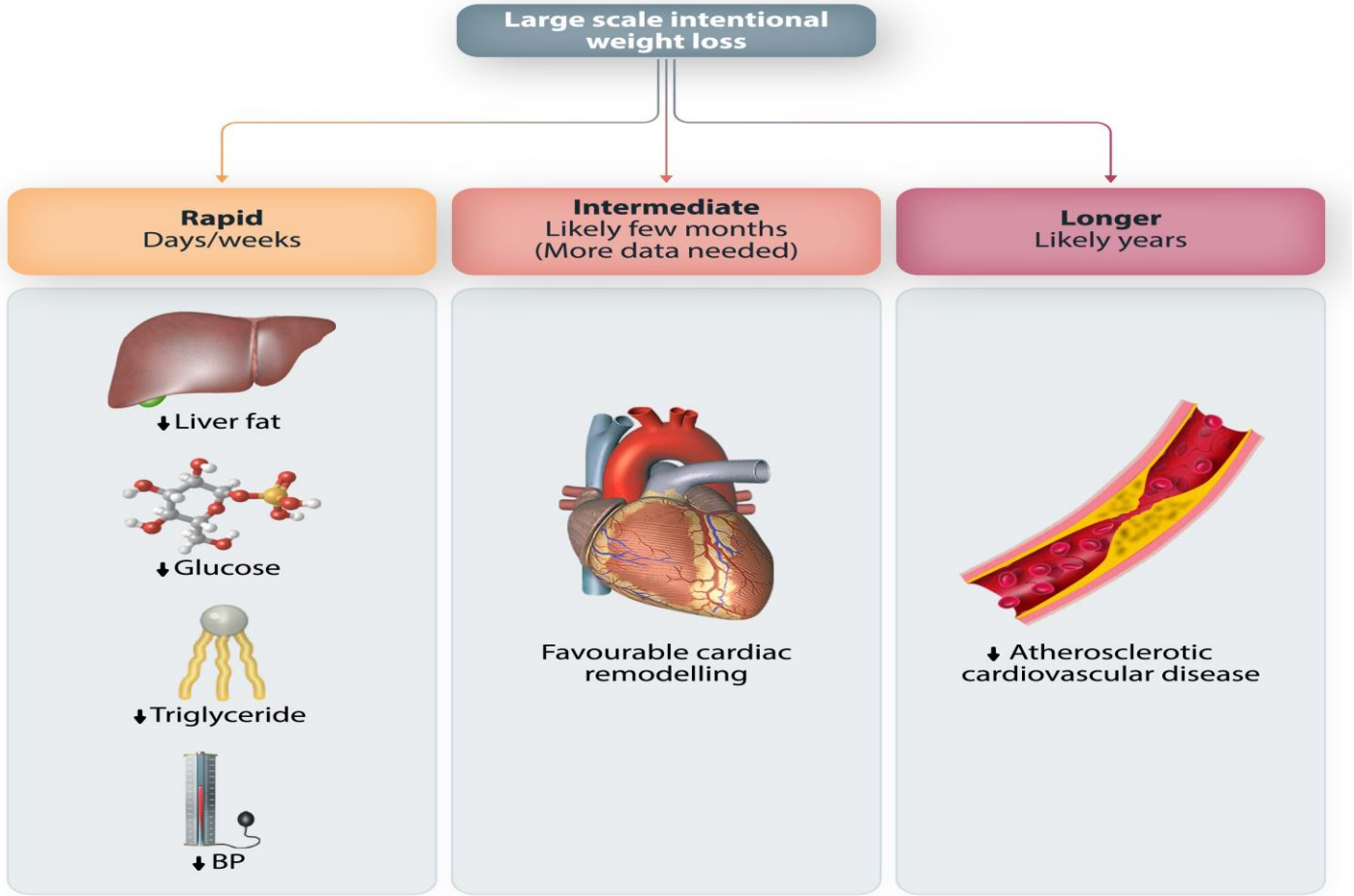


Figure. Association between body mass index (BMI) at conscription and risk for cardiomyopathy (CM).
The model was adjusted for age, conscription year (as a spline with knots at 5%, 35%, 65%, and 95%, ie, 1971, 1982, 1992, and 2004), test center, and baseline comorbidities (diabetes mellitus, hypertension, congenital heart disease), systolic blood pressure, diastolic blood pressure, cardiorespiratory fitness, muscle strength, parental education, and alcohol or substance use disorder (n=773 679). BMI was restricted to BMI between 15 and 40 kg/m² and modeled as a restricted cubic spline with knots at 5%, 35%, 65%, and 95% (ie, 18.0, 20.5, 22.4, and 27.5 kg/m²), with BMI of 20 kg/m² as reference. The unadjusted model is presented in Figure II in the online-only Data Supplement.

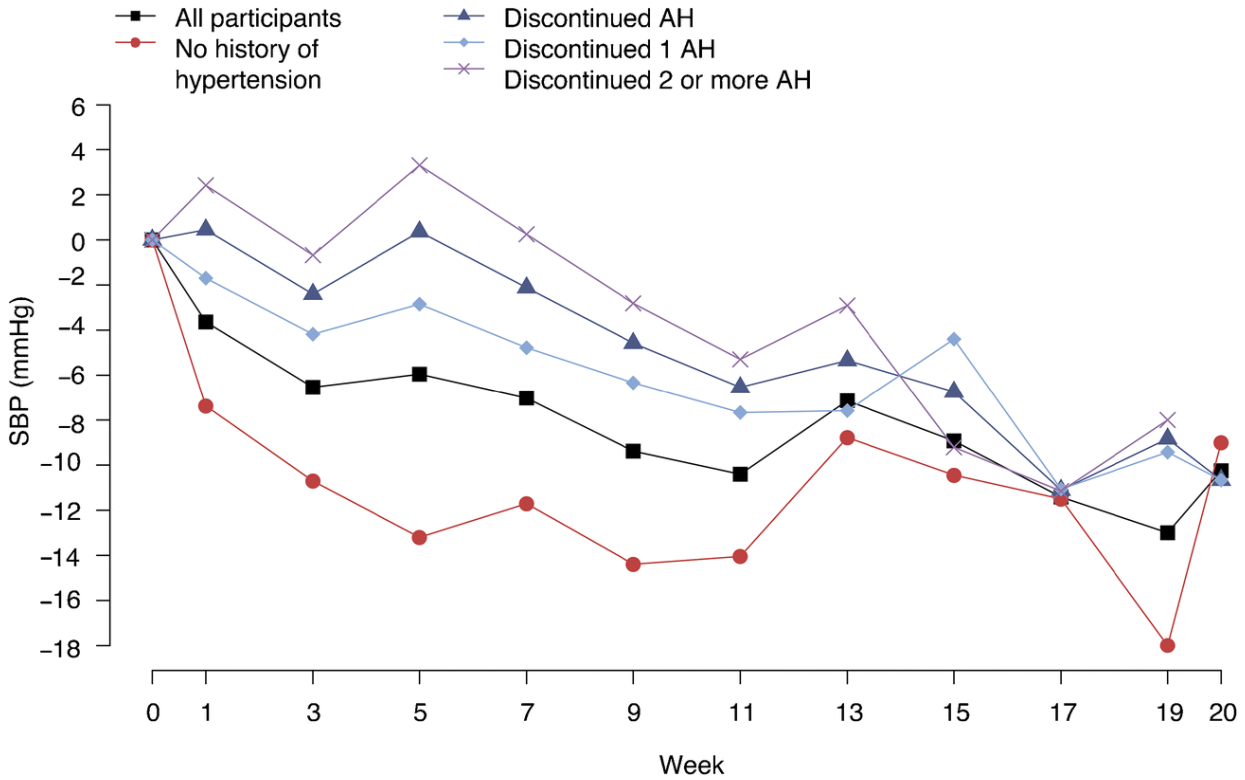
Robertson et al (2019) Circulation Higher BMI adolescence vs midlife CM risks

Genetically higher BMI and CVD outcomes Larsson et al (2019) EHJ



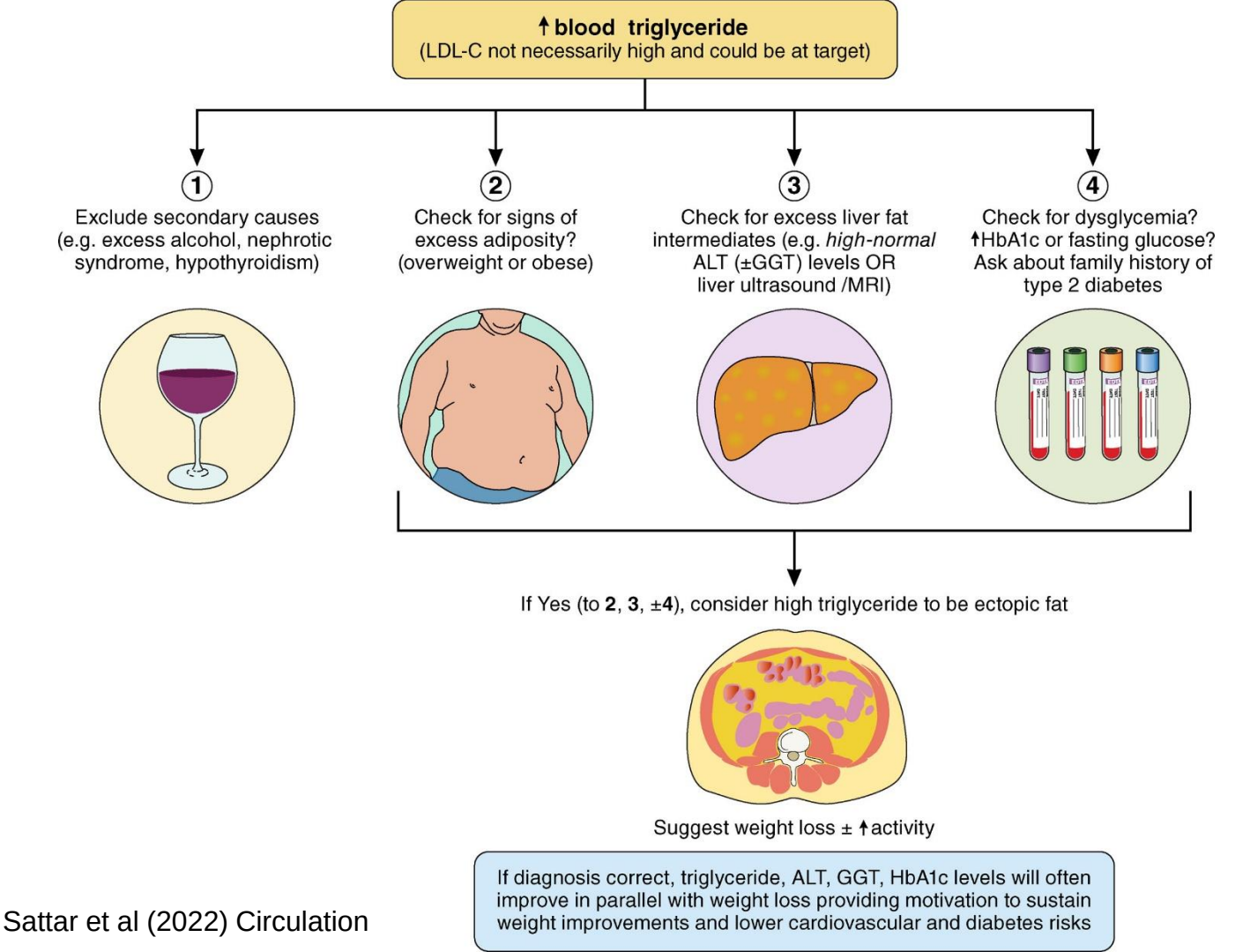


Sattar et al (2023) Cardiovascular Research



SBP down 8-10mmHg after low cal diet in T2DM with ~12kg weight loss
Including in those who stop AH meds!!!

Leslie et al (2021) Diabetologia



Sattar et al (2022) Circulation

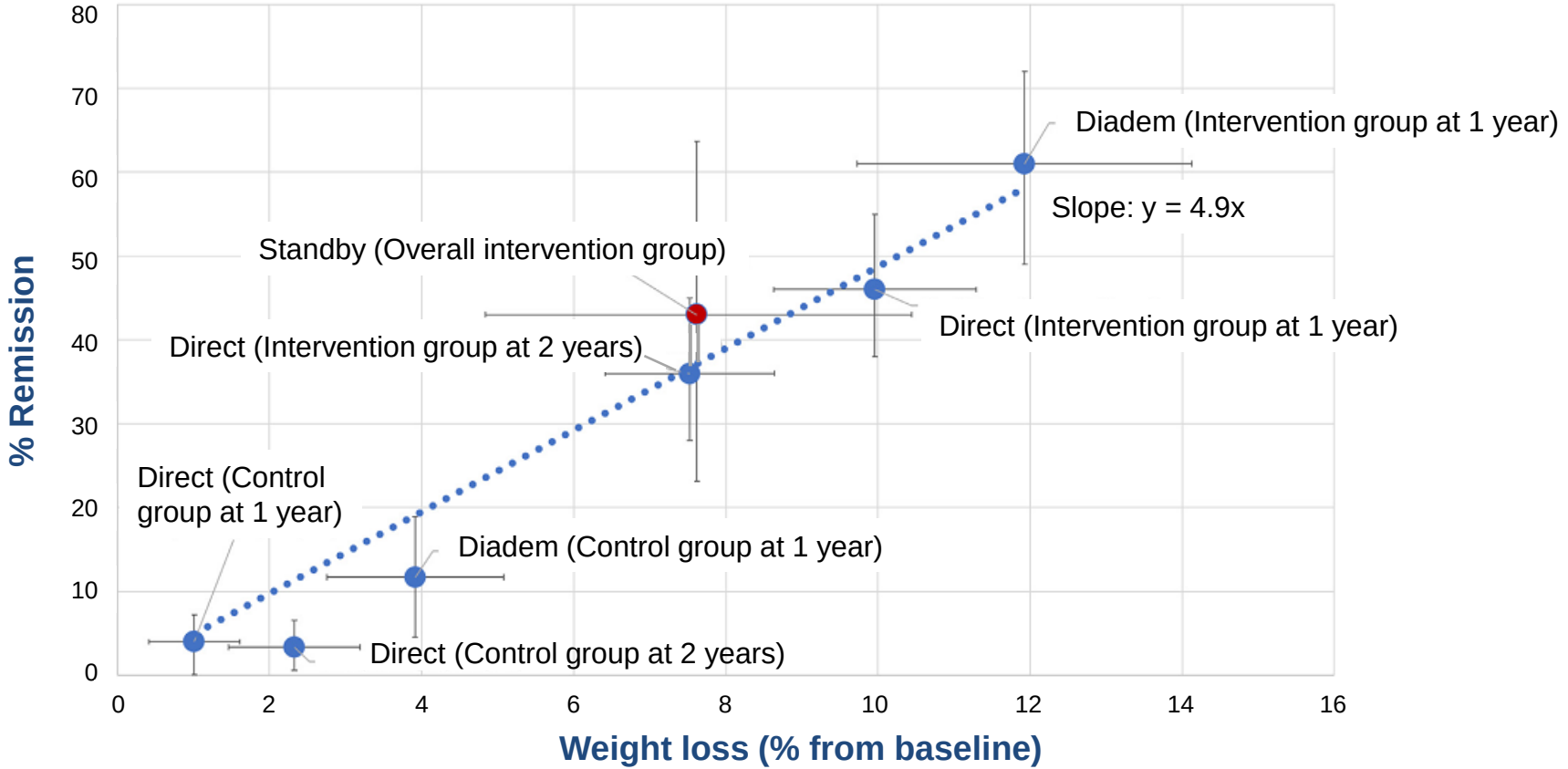
typically, 1.5 to 18 mmol/l

19kg weight gain

Lost once pandemic abated

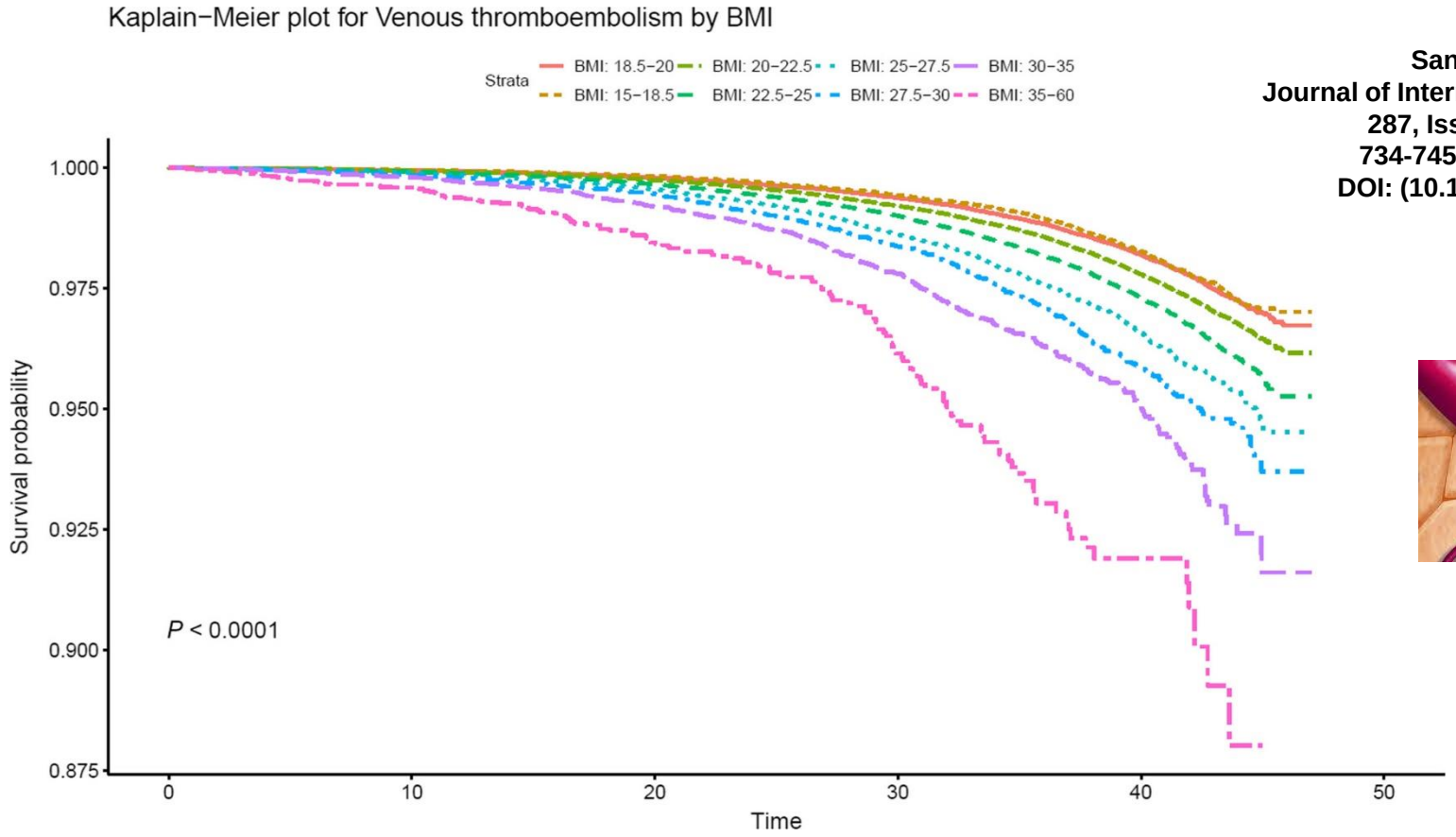
Trib back to 2mmol/l
ALT 81 to 22

Weight loss reverses diabetes in randomised trials (~5% remission per 1% wt loss EARLY T2D short to medium term)

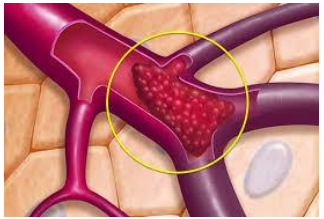


Sattar, Lean et al (2022) Lancet RH

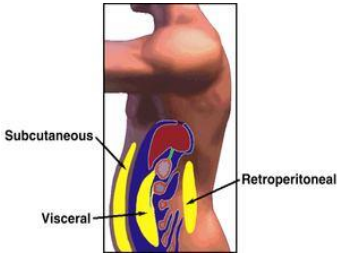
Obesity in adolescent men
↑ risk of VTE in adult life



Sandblad et al
Journal of Internal Medicine, Volume: 287, Issue: 6, Pages: 734-745 27 April 2020, DOI: (10.1111/joim.13044)



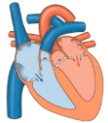
Calories surfeit + salt (increased intake or reduced energy expenditure)



But other CV risk factors LDLc, smoking

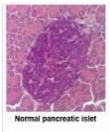
Excess total and ectopic weight

FAT
'Spill over'



Liver fat
higher triglyceride

muscle



pancreatic beta cell

Perivascular fat
Higher BP

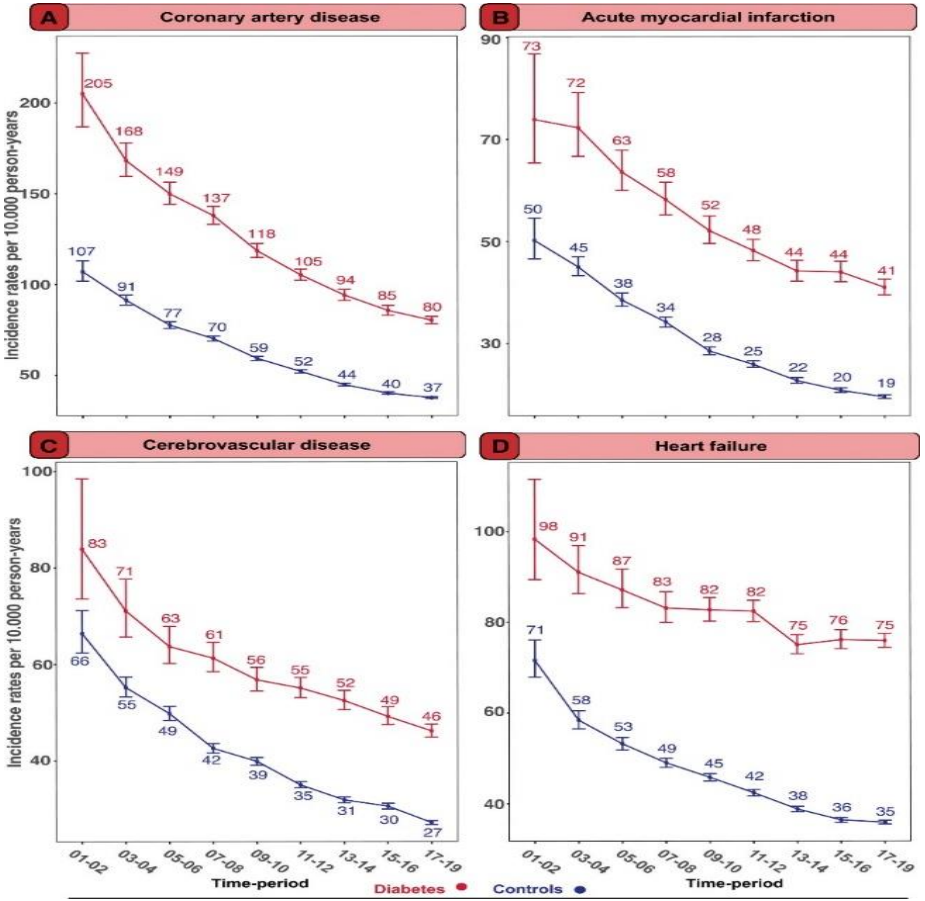
Greater Insulin resistance

Hyperglycaemia

(beta cell failure)

Adapted from Sattar and Gill (2014) BMC Medicine

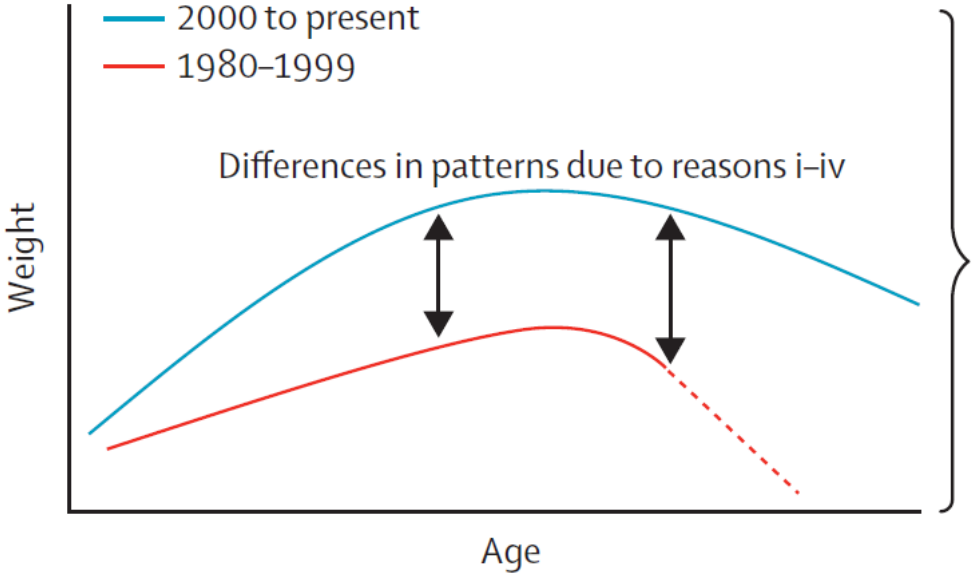
Change in CV risks in diabetes and general population in Sweden over the last two decades



Sattar, Rawshani et al (2023) Circulation

Treating chronic diseases without tackling excess adiposity promotes multimorbidity

Naveed Sattar, John J V McMurray, Iain B McInnes, Vanita R Aroda, Mike E J Lean



Presence of excess adiposity for longer and later in life
Excess adiposity present for longer and later in life in more people with one condition

Greater risks of second, third, and subsequent comorbidities and symptoms due to effects of excess adiposity that are :
- Metabolic
- Physical
- Haemodynamic
- Inflammatory
- Cellular

Solution

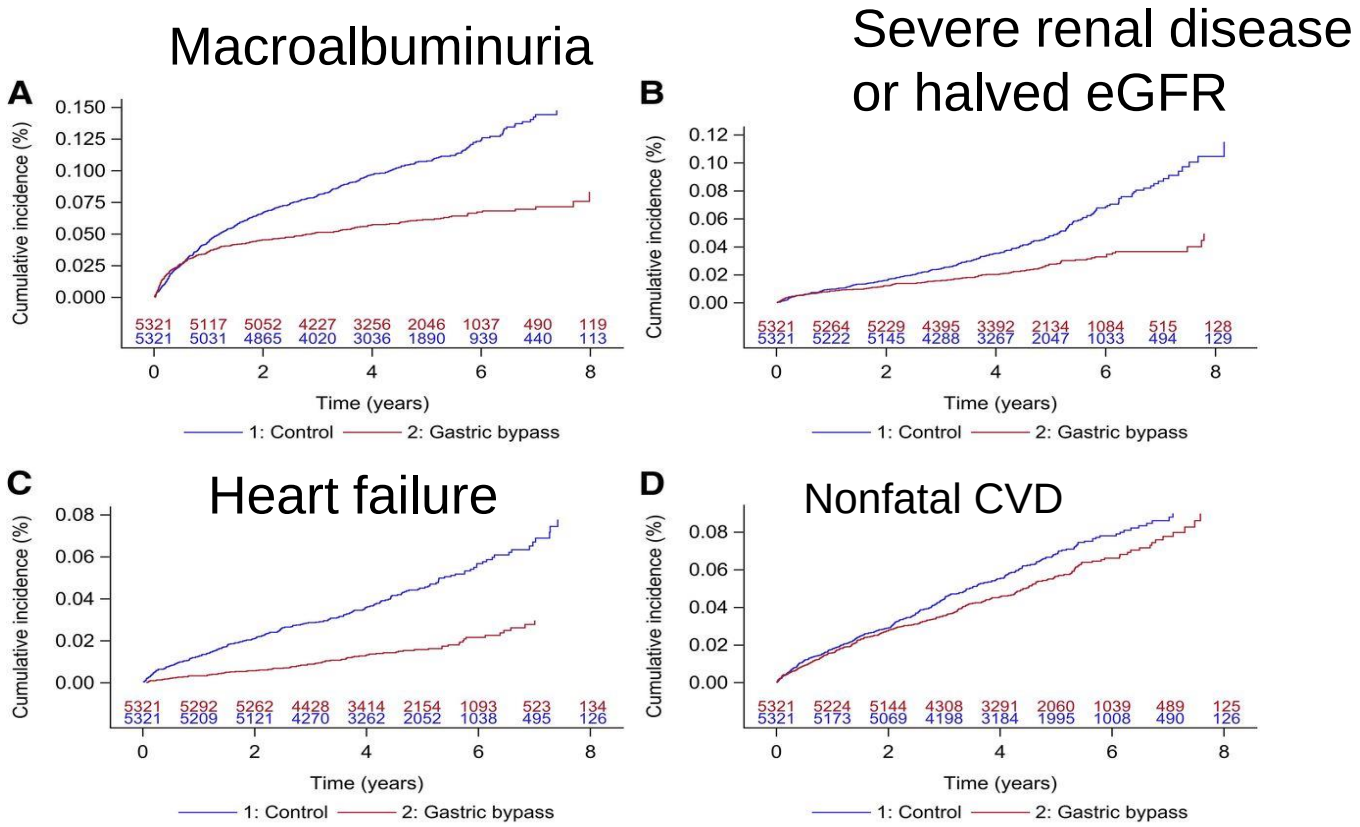
Target weight management much earlier in many chronic conditions and upscale preventive policies

Sattar et al (2022) Lancet D/E

Evidence for weight loss and CV outcomes?

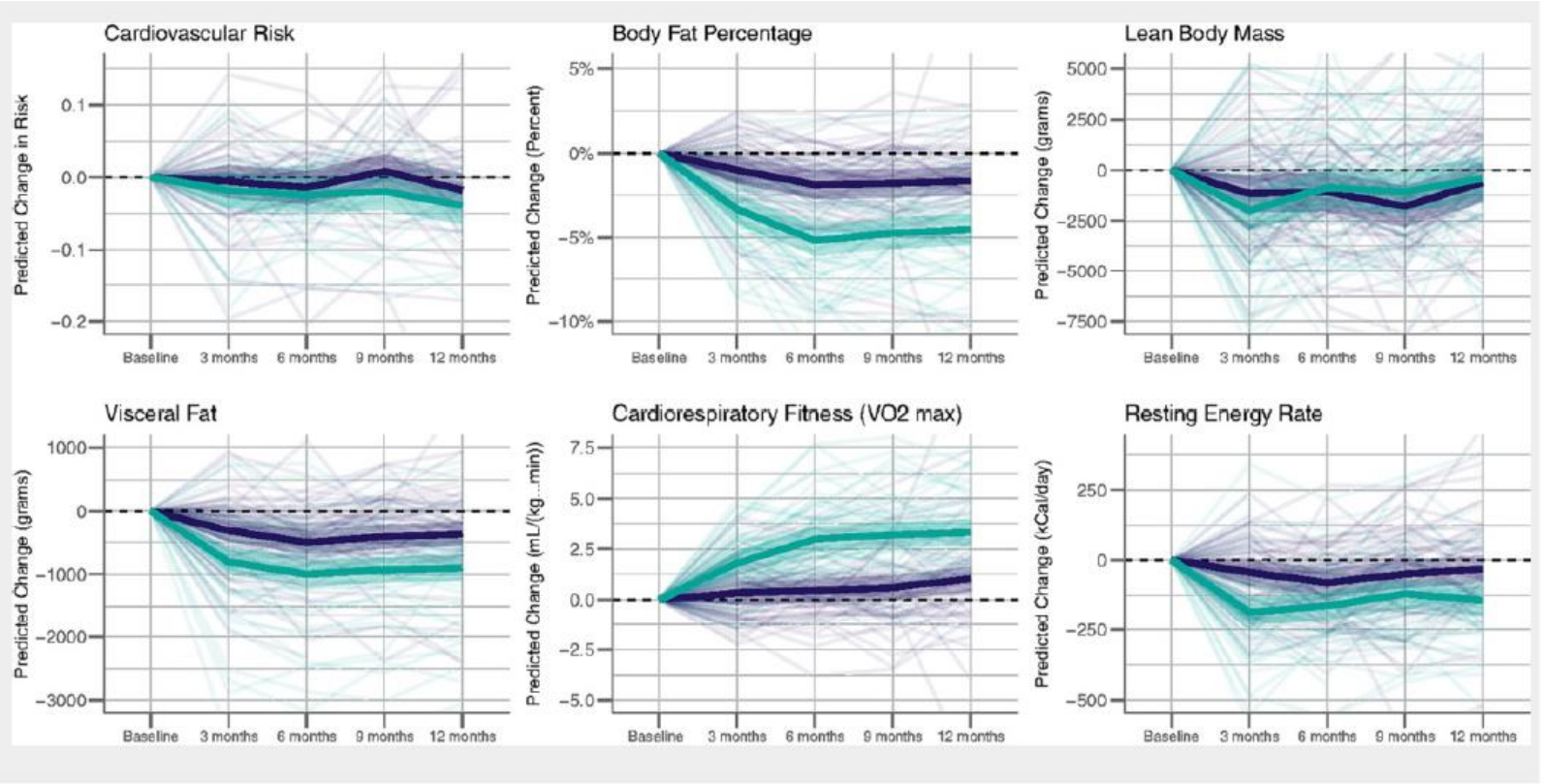
1. Risk factors: BP, DM, trigs, YES
2. Surrogate evidence – observational, surgery, biomarkers, other types? Yes
3. Trial outcomes?

2b. Intentional weight loss bariatric surgery: not randomised – but give optimism?



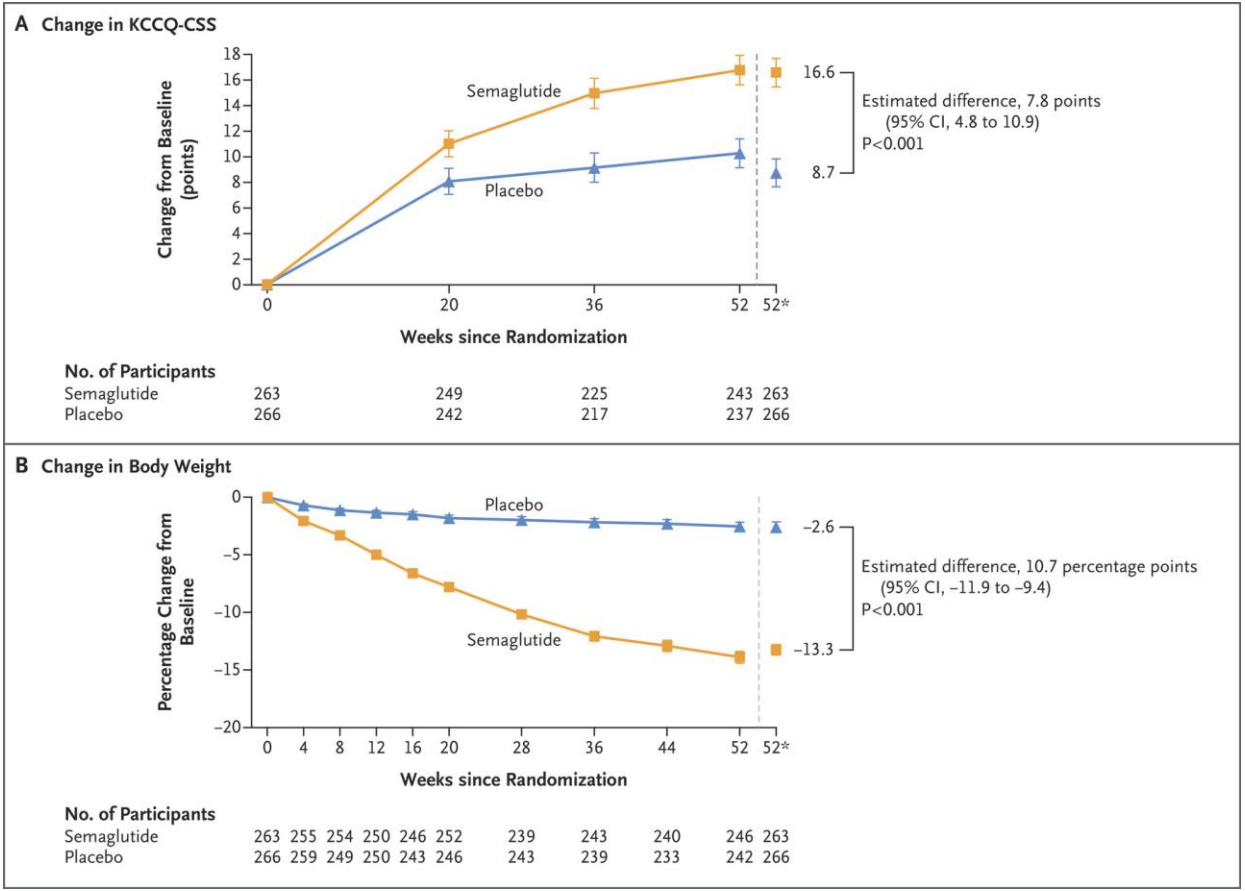
Liakopoulos et al (2020) Diabetes Care

Proteomic marker changes with 10% weight loss suggest rapid improvement in CR Fitness and 20% lower CV outcomes



Sattar et al (2023) Diabetes Care

STEP HFpEF



- 10.7 % weight loss – 7.8 KCCQ improvements
- REDUCTION in NT-proBNP
- 6 min walk test improved

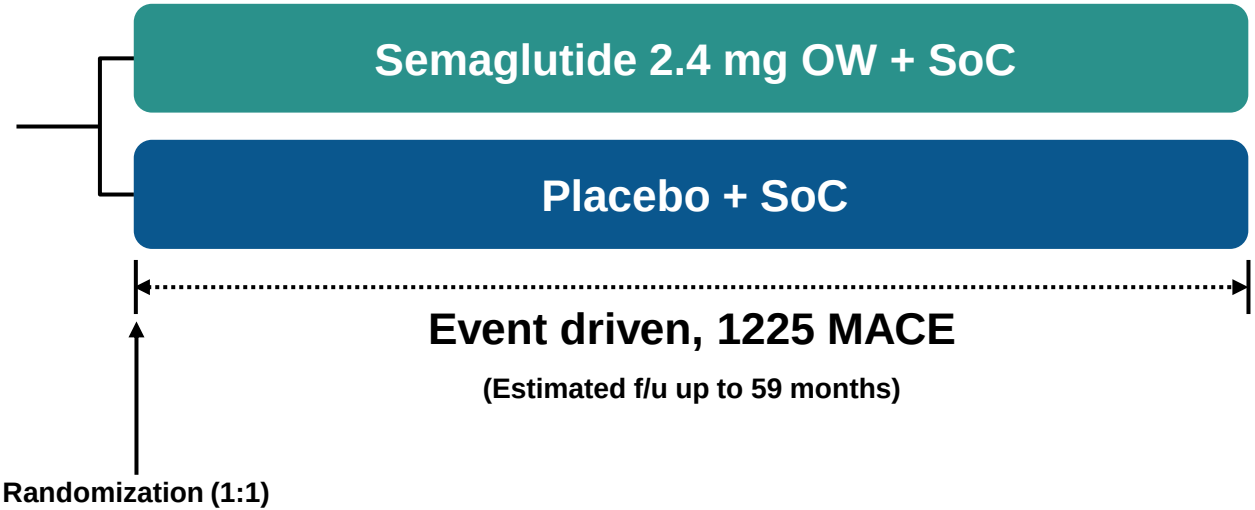
- How much weight loss vs direct effects of Semaglutide?

Hard to properly quantify BUT weight loss likely key

Kosiborod MN et al. 2023. NEJM

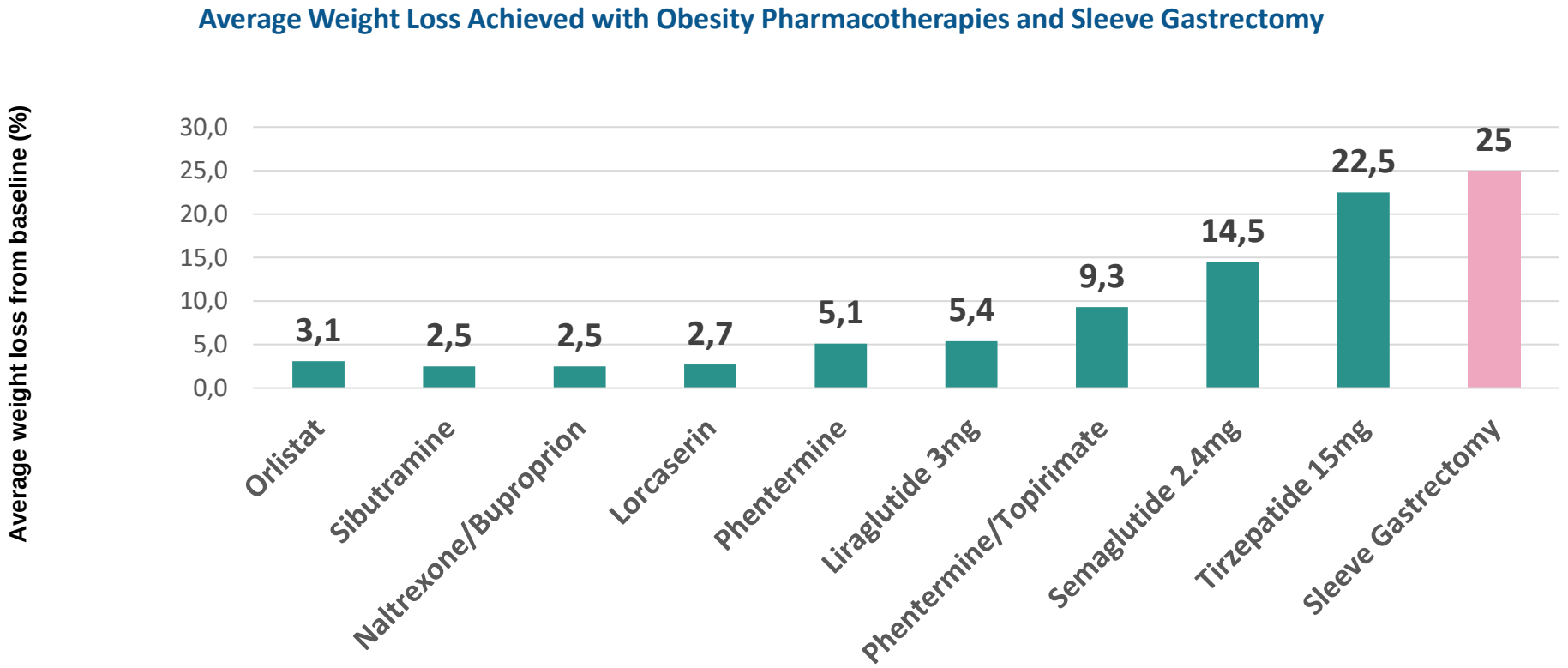
SELECT trial

- N=17,500
- Age ≥45 years
  - BMI ≥27 kg/m^2
  - HbA1c <6.5%
  - Prior MI, stroke or PAD



1º outcome: CV death/MI/stroke – 20% lower
Not positive in hierarchal outcomes BUT nominal
Lower all cause mortality, HF & weight loss 8.5kg & improved QOL and less SAE than with placebo

SELECT trials Lincoff et al (2023) NEJM



SURMOUNT MMO; SYNCHRONISE, others

Weight loss drugs become competitive in 2^0 prevention

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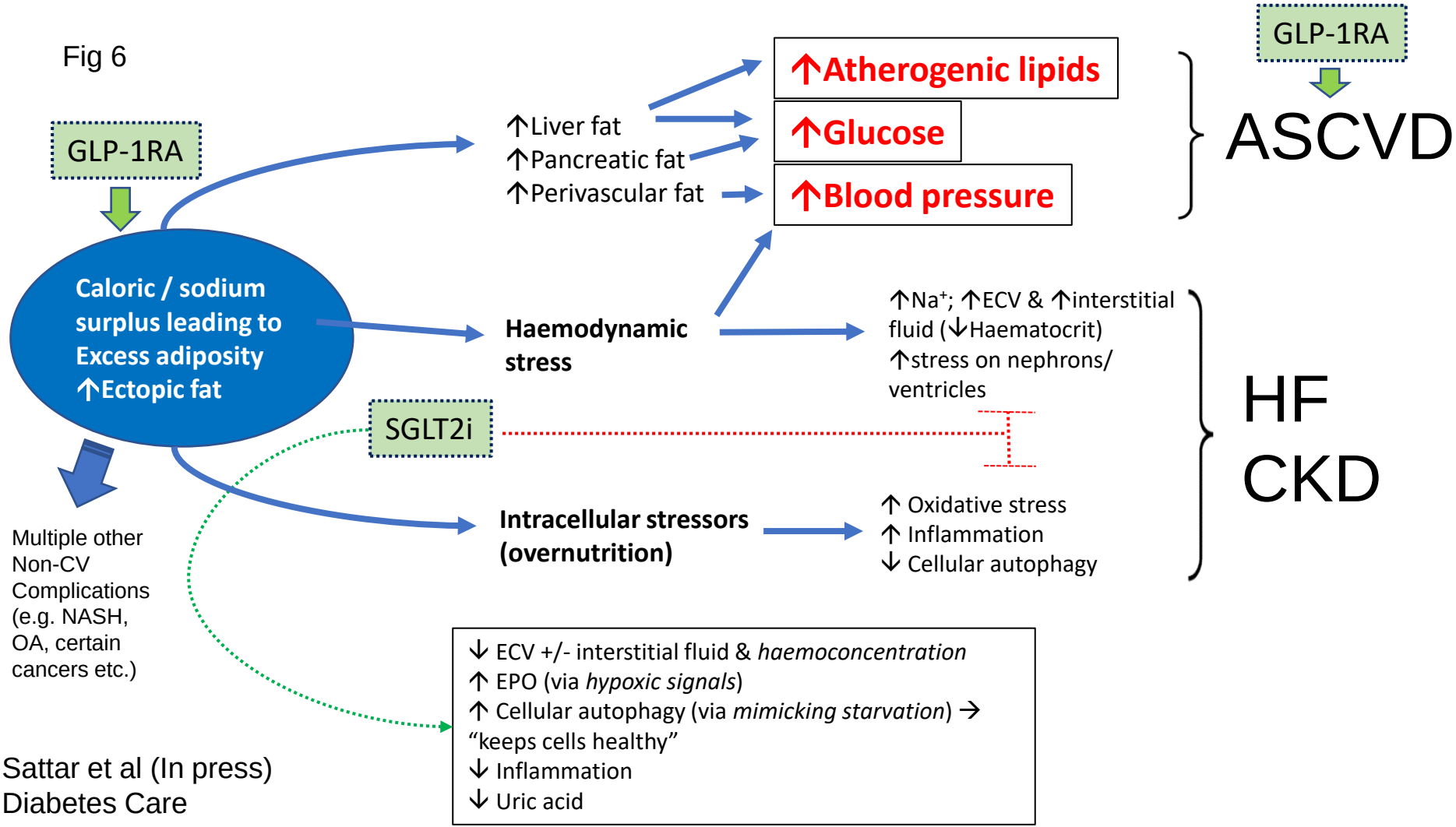
LDL-c main issue

GLP-1RA /SGLT2i

Fig 6



Sattar et al (In press)
Diabetes Care

So what might patients want?

- Improvements in downstream biomarkers e.g. LDLc – but don't feel different?
- Or weight loss from agents that lower MACE risks
- Less multimorbidity, better QOL? Yes
- HEALTH COSTS: Reduced?
- But train cardiologists to prescribe GLP-1RA? Access to drugs, compete with other areas of medicine?

Final summary & thank you!

- Excess adiposity important risk factor for ASCVD (but takes time) and HF (somewhat missed)
  - *Previously underestimated*
- Need to treat xs weight more and PREVENT obesity
- Multiple benefits likely in 2^0 prevention

- Delight to collaborate with Dutch colleagues