COVID-19 and obesity: research, risks and realities

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This webinar is organised and funded by Sanofi.
MAT-GB-2000655 – June 2020

British Heart Foundation

Duality of Interest Declaration

Consulted for:

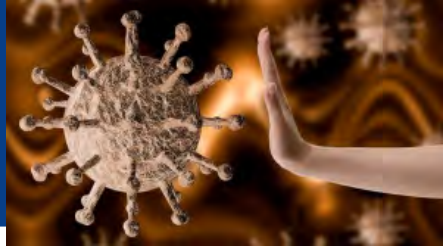
Amgen, AstraZeneca,

Boehringer Ingelheim, Eli Lilly,

Novo Nordisk, Pfizer, Sanofi

Grant: Boehringer Ingelheim

Introduction



- **COVID-19 Pandemic: >450K deaths**
  - Infectivity >> other coronaviruses, if mortality=1%, then many die
  - UK hospital ITU mortality >50% initially, down to ~25%

- **Country differences:**
  - Lockdown timing vs. inherent susceptibility
  - Some nations more primed against coronaviruses?

WHO COVID-19 Database accessed 7 June 2020
OpenSAFELY Collaborative. Accessed via medrxiv.org May 2020

Top thoughts

AGE

BIGGEST RISK FACTOR

Male sex

~1.2 to 2.0

Blacks and South Asians

(UK: lower mortality, reversed)

Deprivation (social distancing?) Risks higher

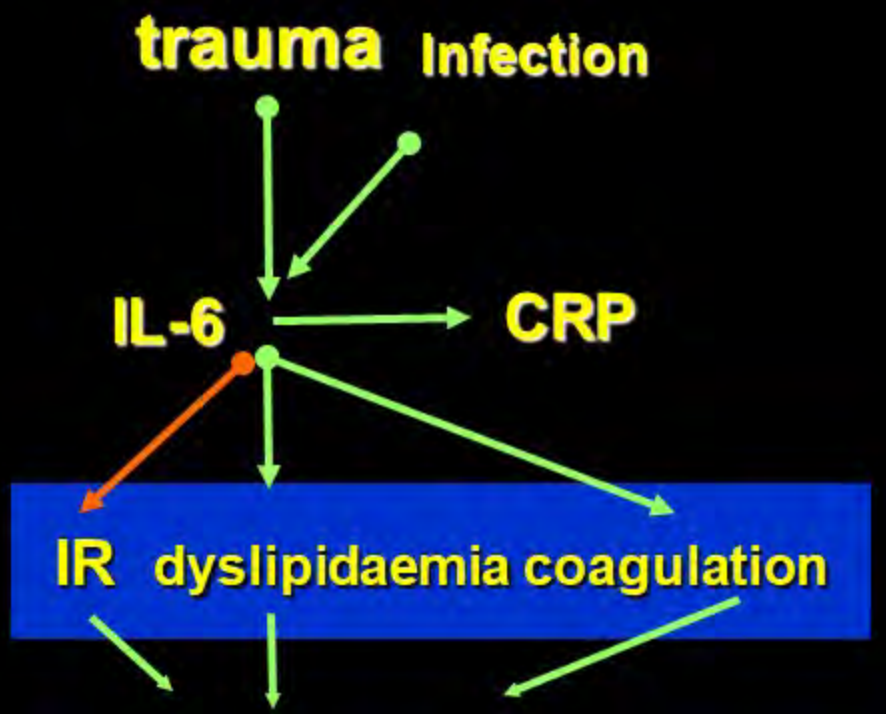
Prior HF, Stroke, CHD, renal dysfunction,

Obesity (multiple mechanisms)

Diabetes T1 and T2

- **COVID-19 – hyperimmune response (cytokine storm) stresses many organs beyond lungs**
- Even blunt Rx anti-inflammatory lessens mortality risks
  - Dexamethasone
- **Thrombosis** – **microvasculature** hit
- **Cardiometabolic** related deaths
  - More **diabetes** than expected
  - **Obesity / renal dysfunction /ethnicity**

Metabolic effects of acute inflammation



"Functional pleiotropy"

Outline

- **Evidence for obesity as relevant to COVID-19**
- Possible explanations – confounding?
- Causation? Multiple pathways make sense
- Implications for care / PH policy?

OpenSAFELY:
factors associated with
COVID-19-related
hospital death
in the linked
EHRs
of 17 million
adult NHS patients

https://www.medrxiv.org/content/10.1101/2020.05.06.20092999v1

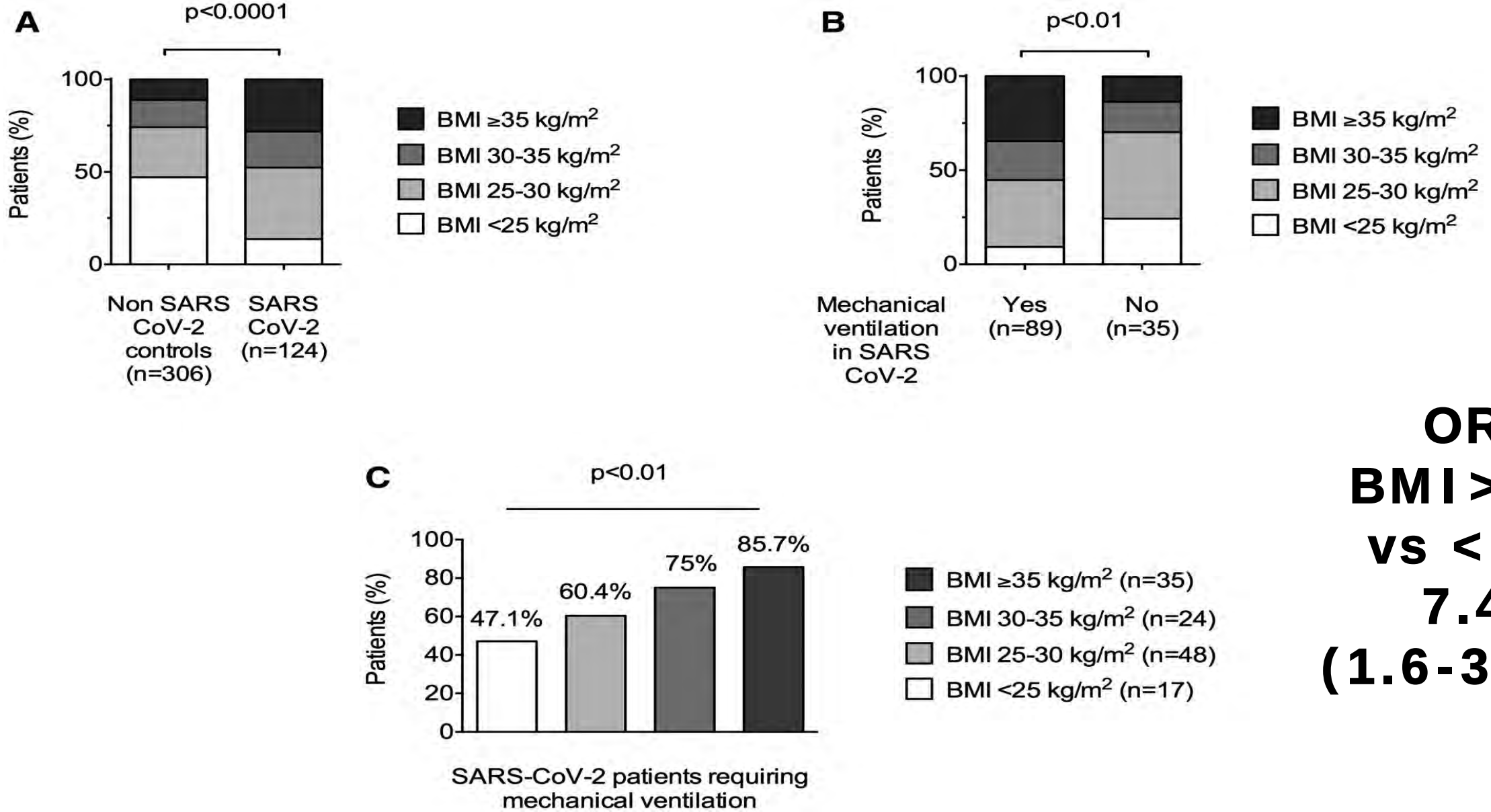
Sex		
Female	1.00 (ref)	1.00 (ref)
Male	2.24 (2.12-2.36)	1.99 (1.88-2.10)
BMI		
Not obese	1.00 (ref)	1.00 (ref)
Obese class I (30-34.9kg/m^2)	1.57 (1.47-1.68)	1.27 (1.18-1.36)
Obese class II (35-39.9kg/m^2)	2.01 (1.82-2.21)	1.56 (1.41-1.73)
Obese class III (≥40 kg/m^2)	2.97 (2.62-3.38)	2.27 (1.99-2.58)
Smoking		
Never	1.00 (ref)	1.00 (ref)
Ex-smoker	1.80 (1.70-1.90)	1.25 (1.18-1.33)
Current	1.25 (1.12-1.40)	0.88 (0.79-0.99)
Ethnicity*		
White	1.00 (ref)	1.00 (ref)
Mixed	1.83 (1.33-2.51)	1.64 (1.19-2.26)
Asian or Asian British	1.95 (1.73-2.18)	1.62 (1.43-1.82)
Black	2.17 (1.84-2.57)	1.71 (1.44-2.02)
Other	1.34 (1.03-1.74)	1.33 (1.03-1.73)

Other reports

- **In New York , in those < 60 years and with BMI <30 Kg/m2, risk for critical care was:**
  - **1.8 times** if BMI 30-34 Kg/m^2
  - **3.6 times** if >35 Kg/m^2

Lighter et al (2020) Clinical Infectious Diseases

Retrospective cohort 124 ITU patients France Simonnet et al (2020) Obesity

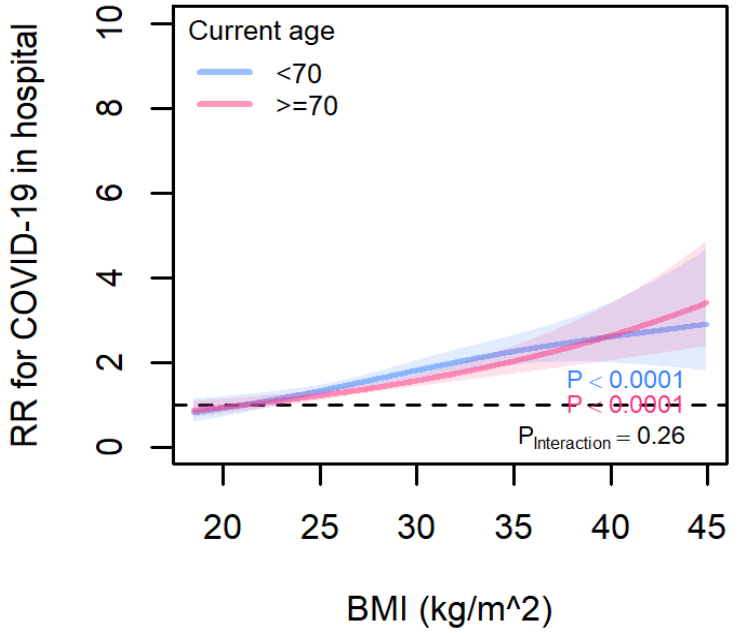


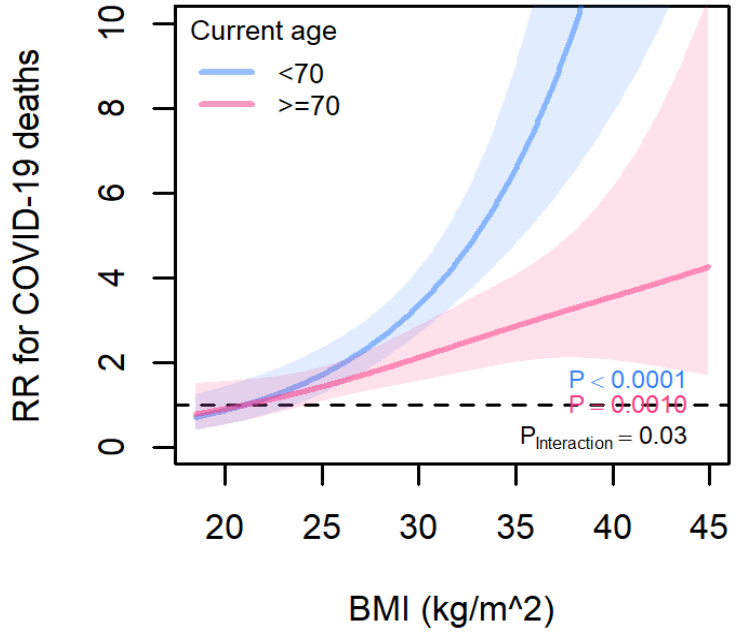
OR BMI > 35 vs < 25 7.4 (1.6-33.1)

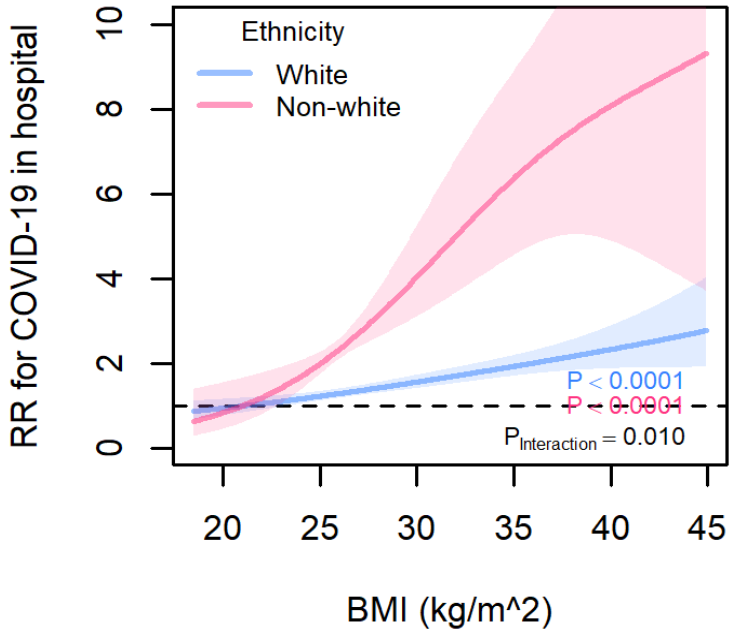
Preliminary data from UK biobank – needs confirmed as more data emerge

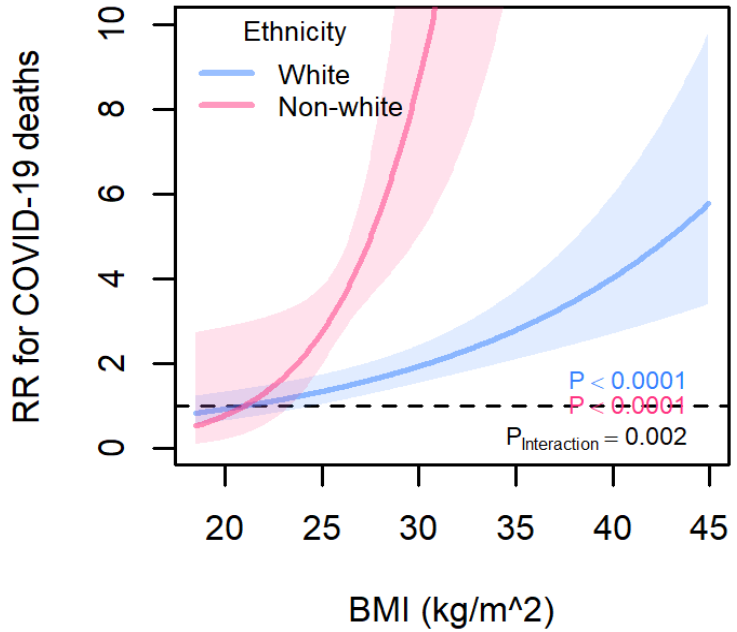
Sattar et al (submitted)

https://www.medrxiv.org/content/10.1101/2020.06.05.20122226v2









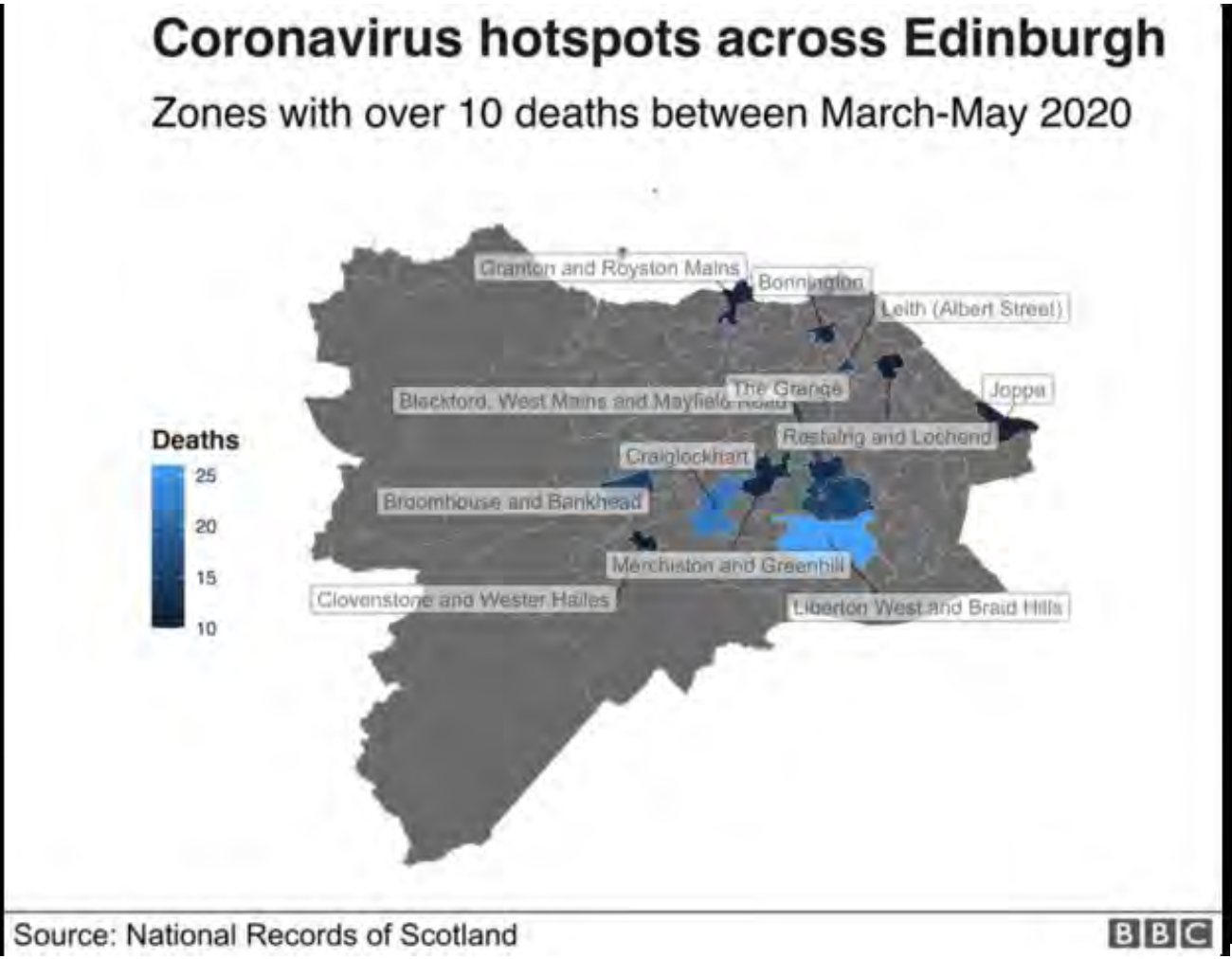
Outline

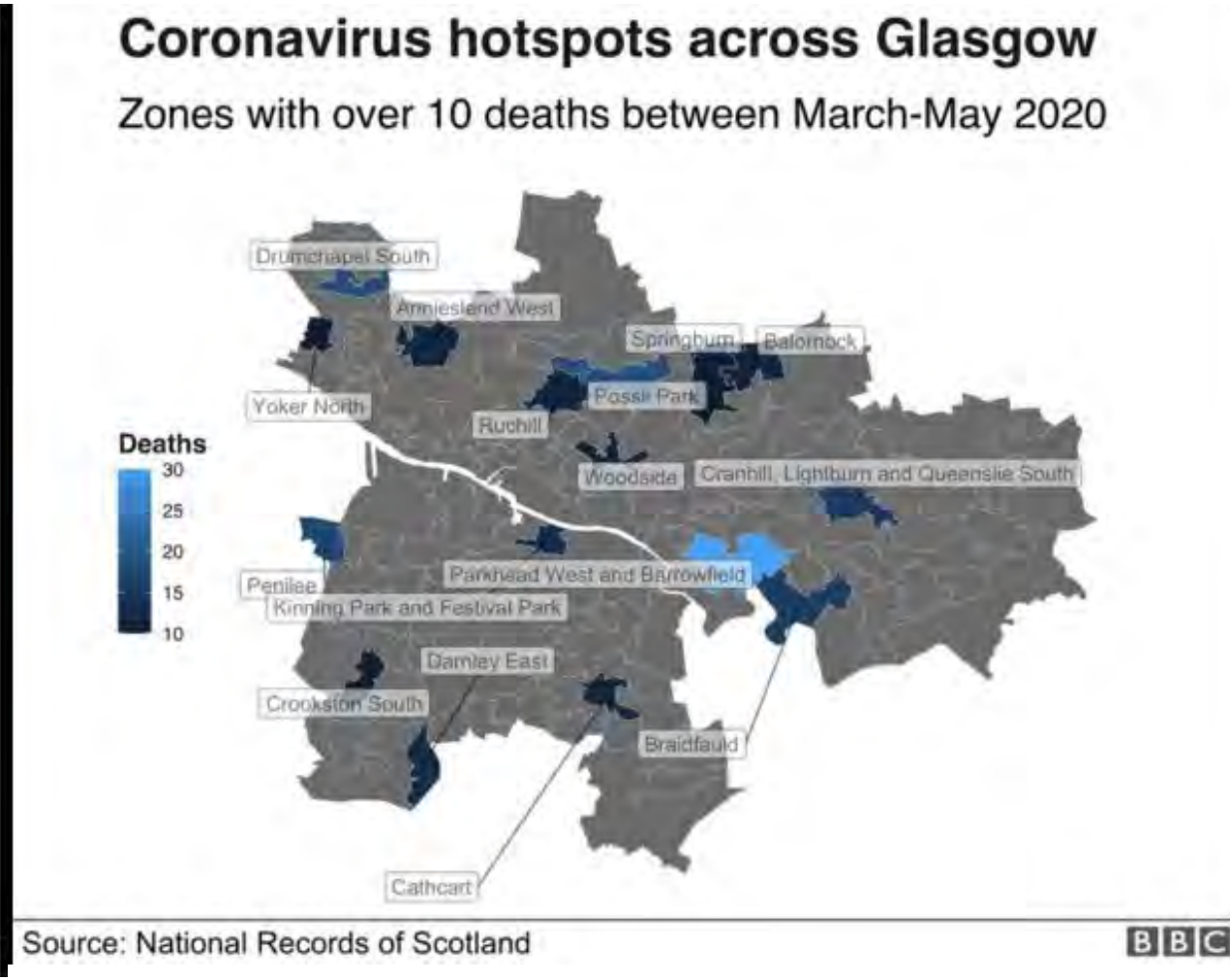
- Evidence for obesity as relevant to COVID-19
- **Possible explanations – confounding?**
- **Causation? Multiple pathways make sense**
- Implications for care / PH policy?

Confounding: Obesity and deprivation

Obesity leads to more infection in first place and so mores chances to develop severe outcomes?

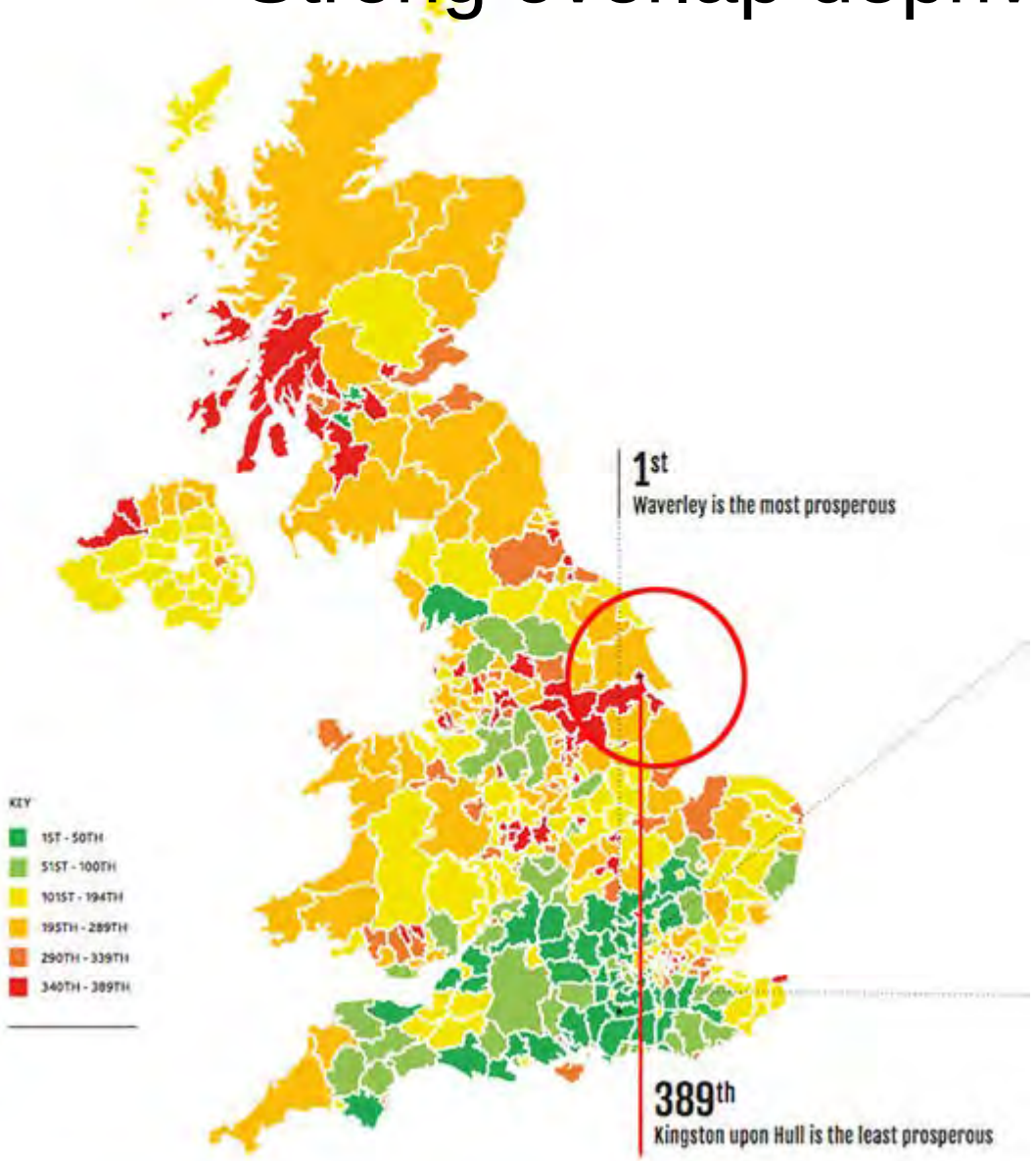
- Less physical distancing?
- Smaller houses / rooms
- Flats / tenements
- More time indoors
- Other reasons

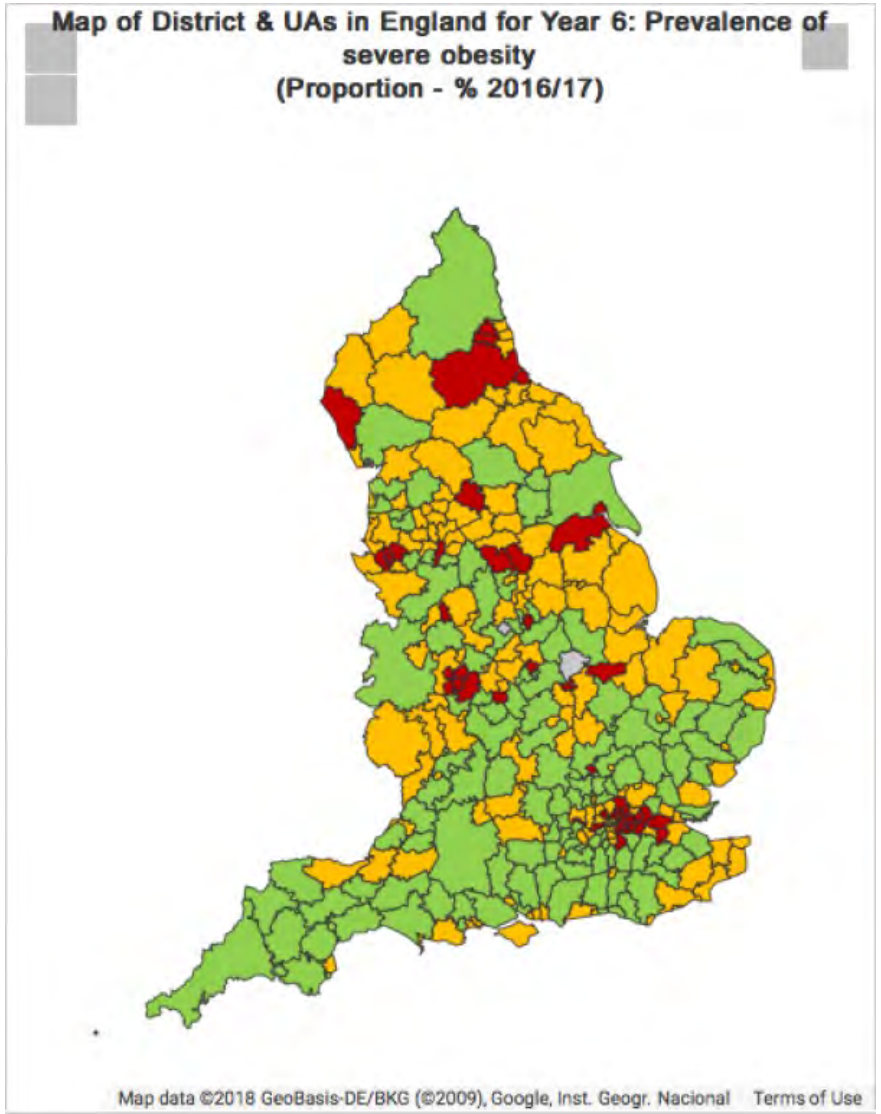




Poorer areas

Strong overlap deprivation and obesity in the UK





Causation: Medical Complications of Obesity

Stroke

Idiopathic intracranial hypertension

Cataracts

Pulmonary disease
abnormal function
obstructive sleep apnea
hypoventilation syndrome

Coronary heart disease

Pancreatitis

Diabetes

Dyslipidemia

Hypertension

Nonalcoholic fatty liver disease
steatosis
steatohepatitis
cirrhosis

Gynecologic abnormalities
abnormal menses/ infertility
polycystic ovarian syndrome
Numerous pregnancy comps.

Gall bladder disease

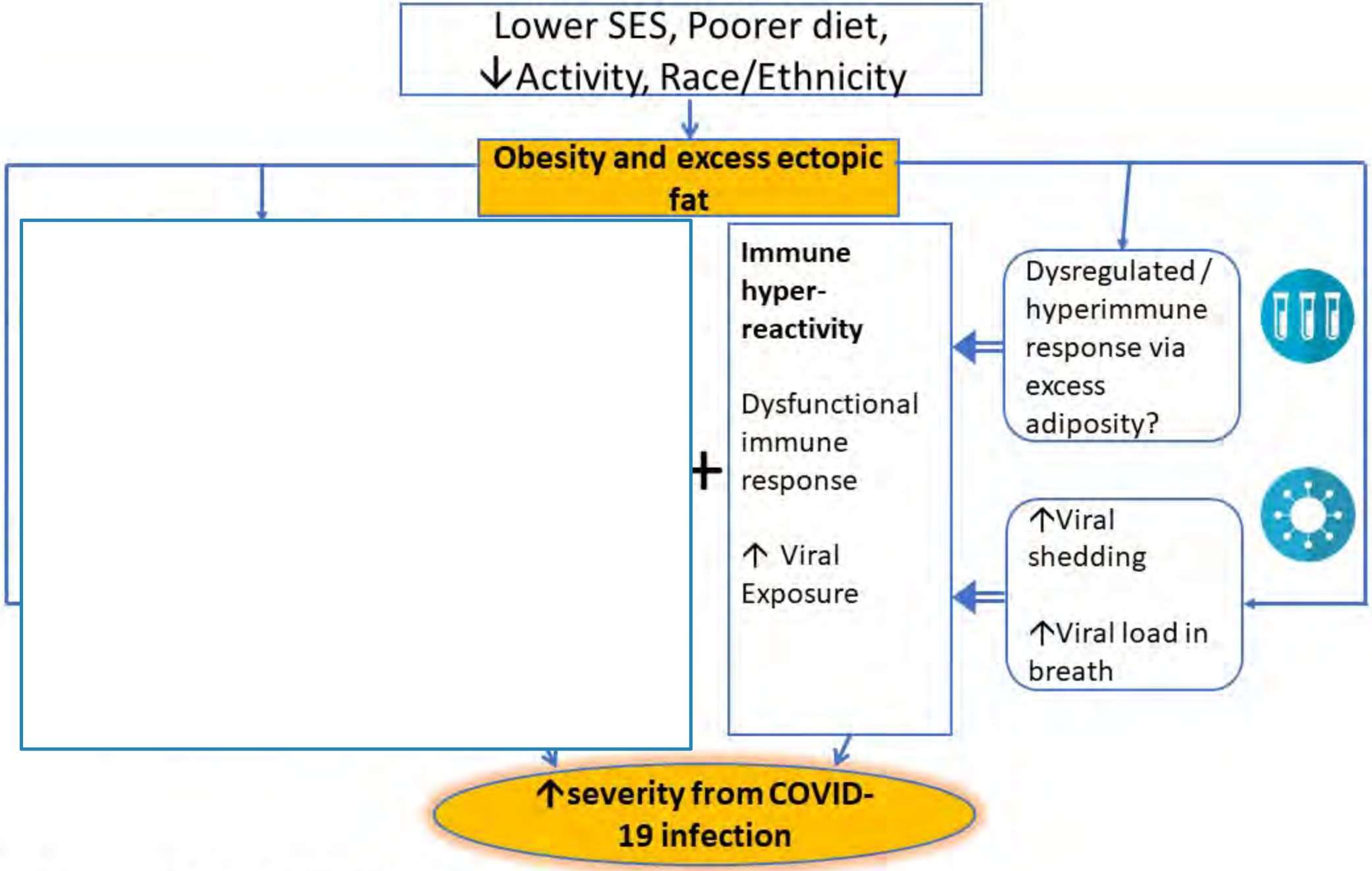
Cancer
breast, uterus, cervix, prostate, kidney
colon, esophagus, pancreas, liver

Osteoarthritis

Skin

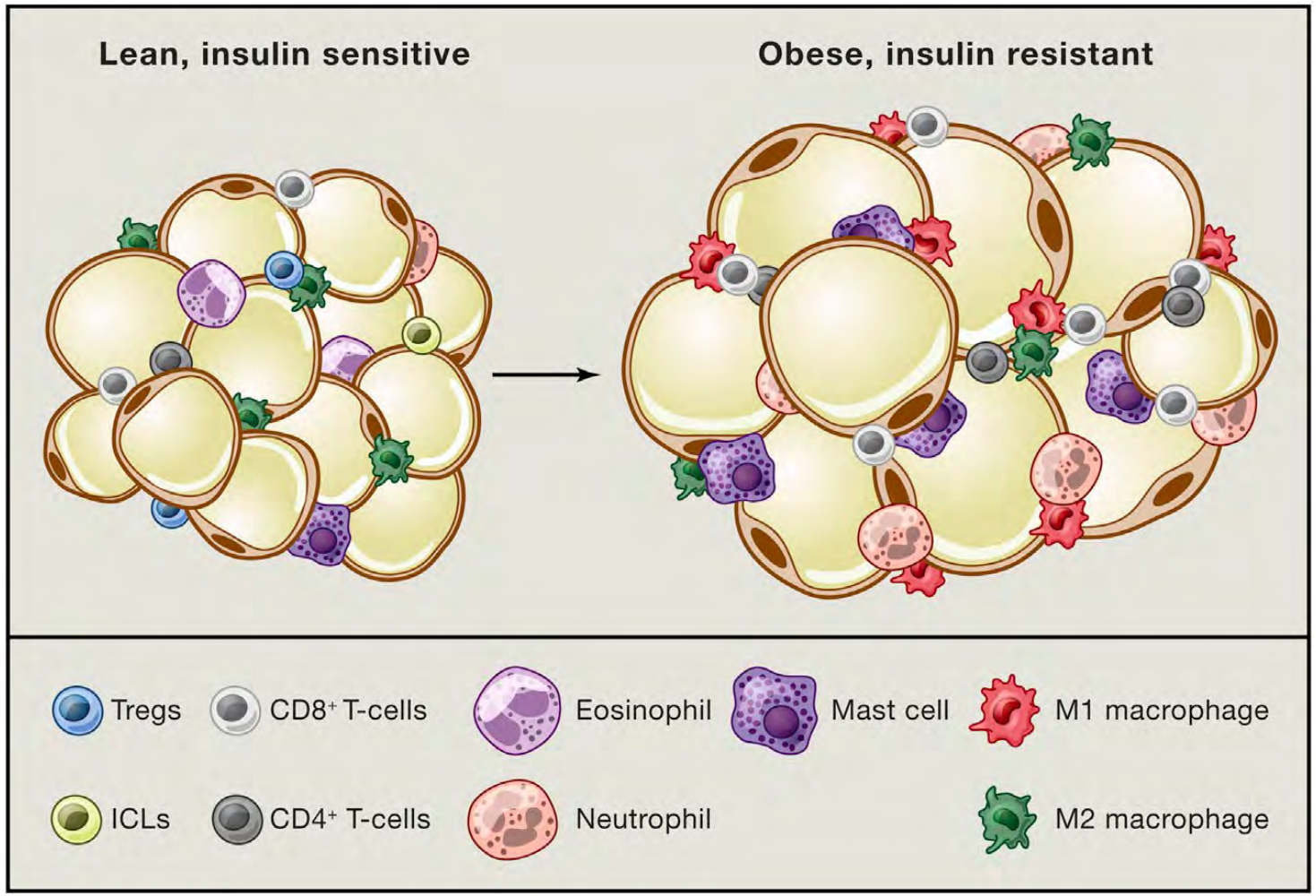
Phlebitis
venous stasis

Gout



Sattar, McInnes, McMurray (2020) Circulation

Adipose tissue – an immunological organ?



Putative mechanisms?

- Source of systemic and local inflammatory cytokines and adipokines
- Resetting the immunologic rheostat
- Inflammatory lipid source e.g. FFA?
- Altered microbiome / GI permeability?
- Neuroendocrine factors??

- Causality v association unclear.

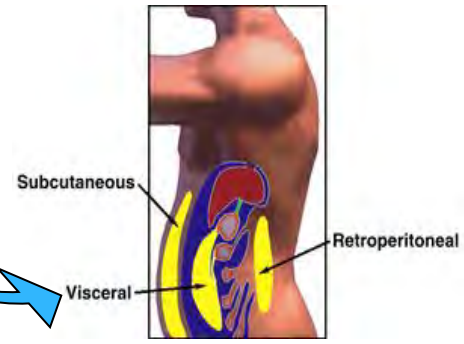
Rosen and Spiegelman *Cell* 156, 20 (2014)

Diabetes – disease of ectopic fat

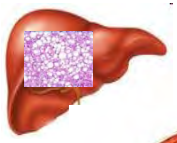
Sattar and Gill
(2014) BMC Medicine

Excess calories

Subcutaneous stores overwhelmed (genes / Sex FHx, ethnicity, ageing)



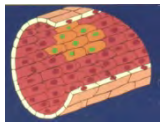
FAT
'Spill over'



Hepatic lipid Accumulation
higher TG /lower HDL-c

muscle

pancreatic beta cell



Perivascular fat ⇒
Endothelial dysfunction
+ fluid gain Higher BP

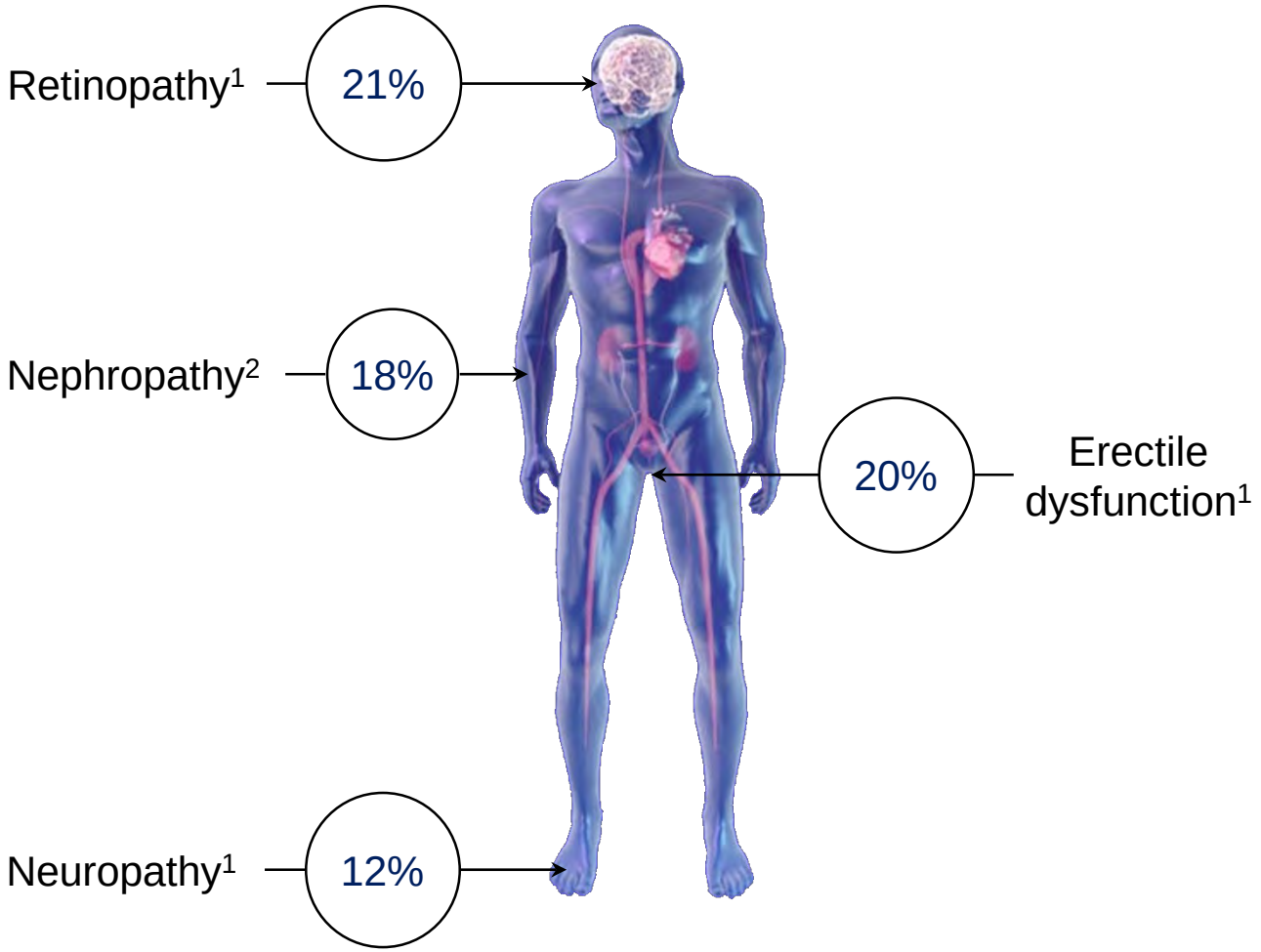
Insulin resistance

HIGH SUGAR LEVELS

(if susceptible)

Poorer immunity

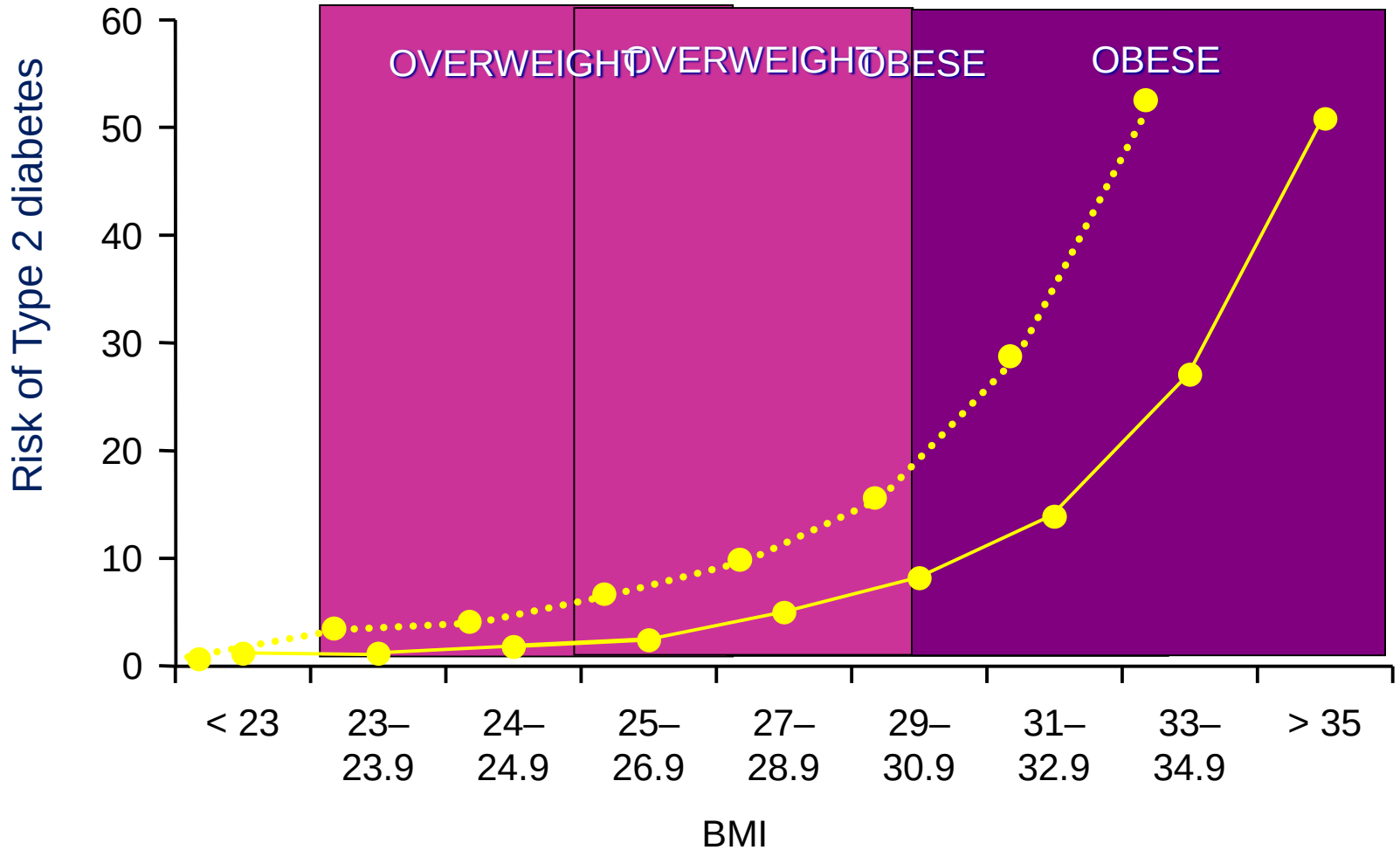
Type 2 diabetes – the microvascular burden at diagnosis a decade or so ago



T1 >T2
~3-fold excess
vs 2 fold mortality
COVID-19
(TLDE*2 papers
And SDRN)

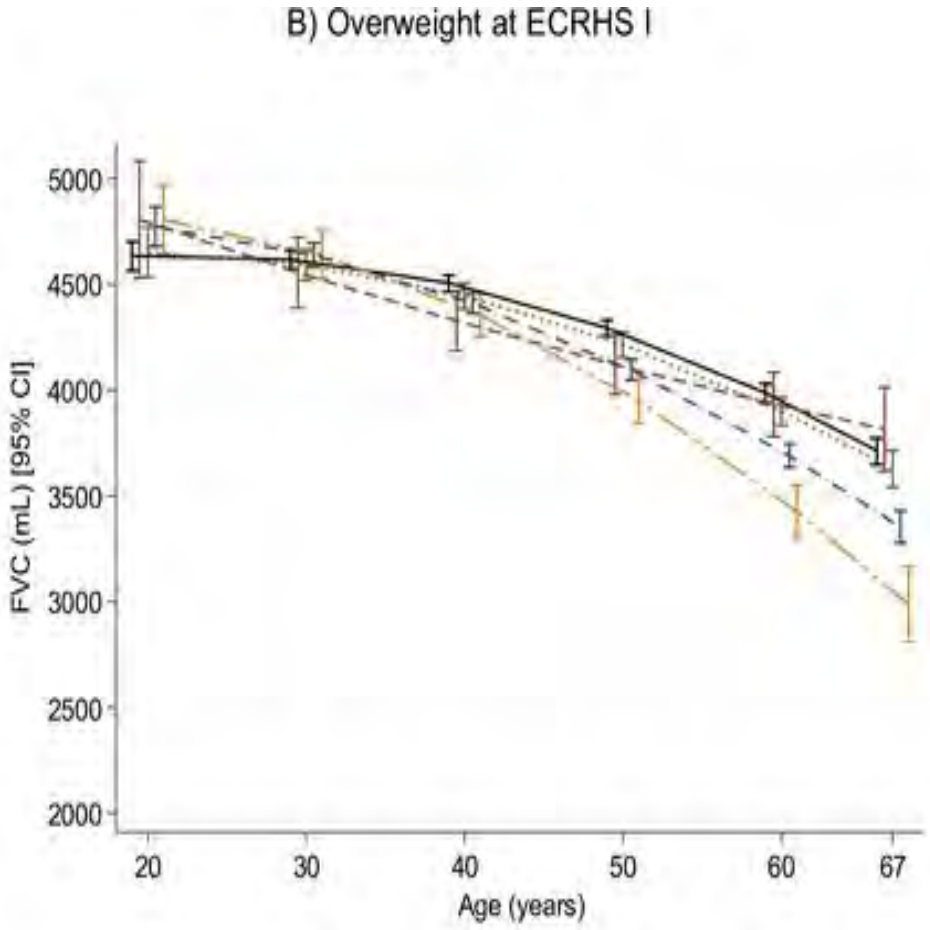
1. UKPDS Group. *Diabetes Res* 1990; **13**: 1–11.
2. The Hypertension in Diabetes Study Group. *J Hypertens* 1993; **11**: 309–317.

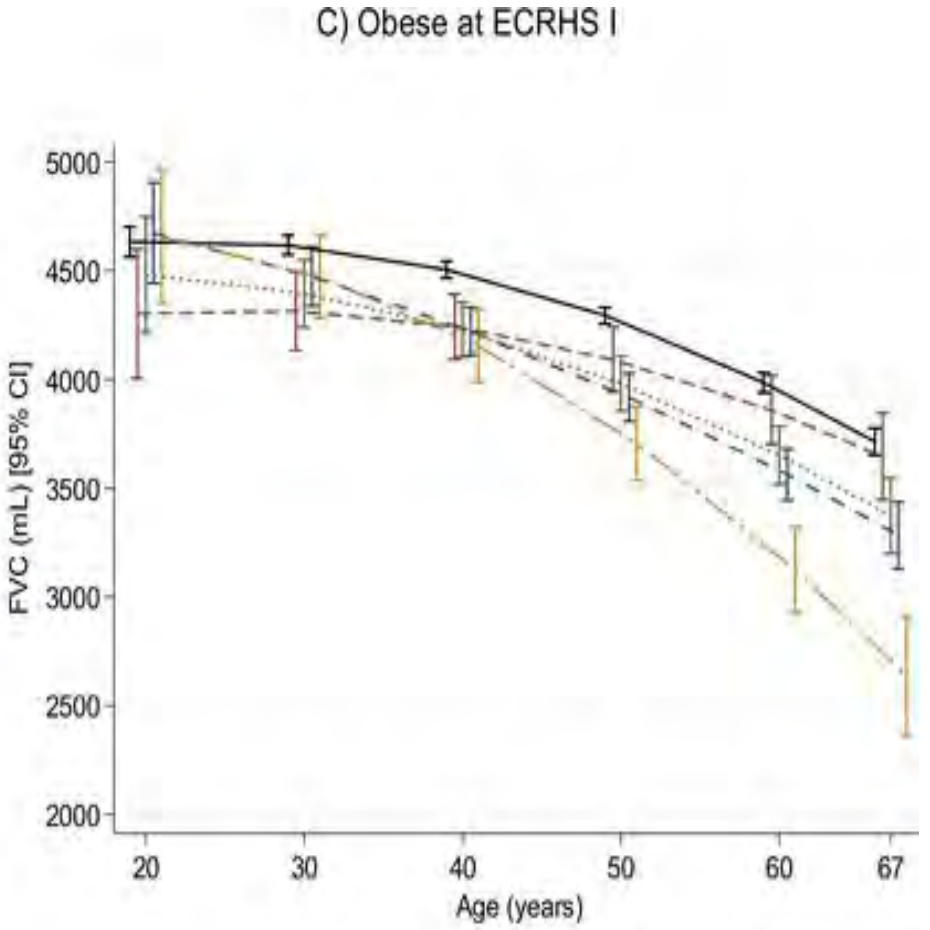
Obesity to diabetes link especially strong

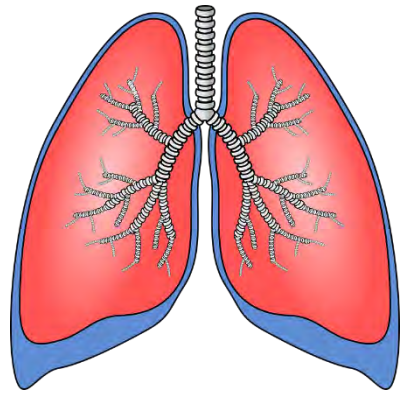


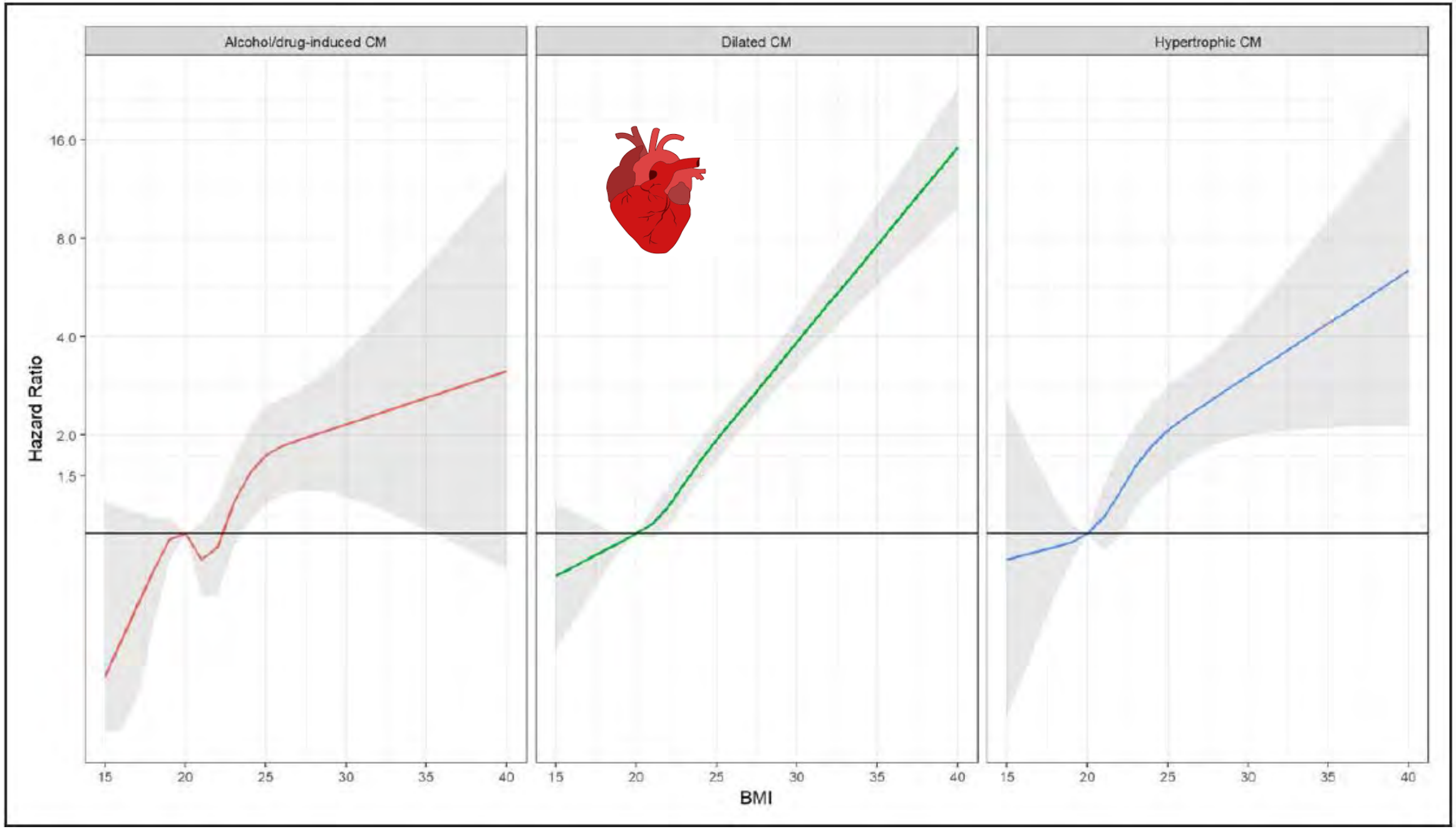
Chan JM *et al*. *Diabetes Care* 1994; **17**: 961–969.

Weight gain >more rapid decline lung function – Peralta et al (2019) Thorax



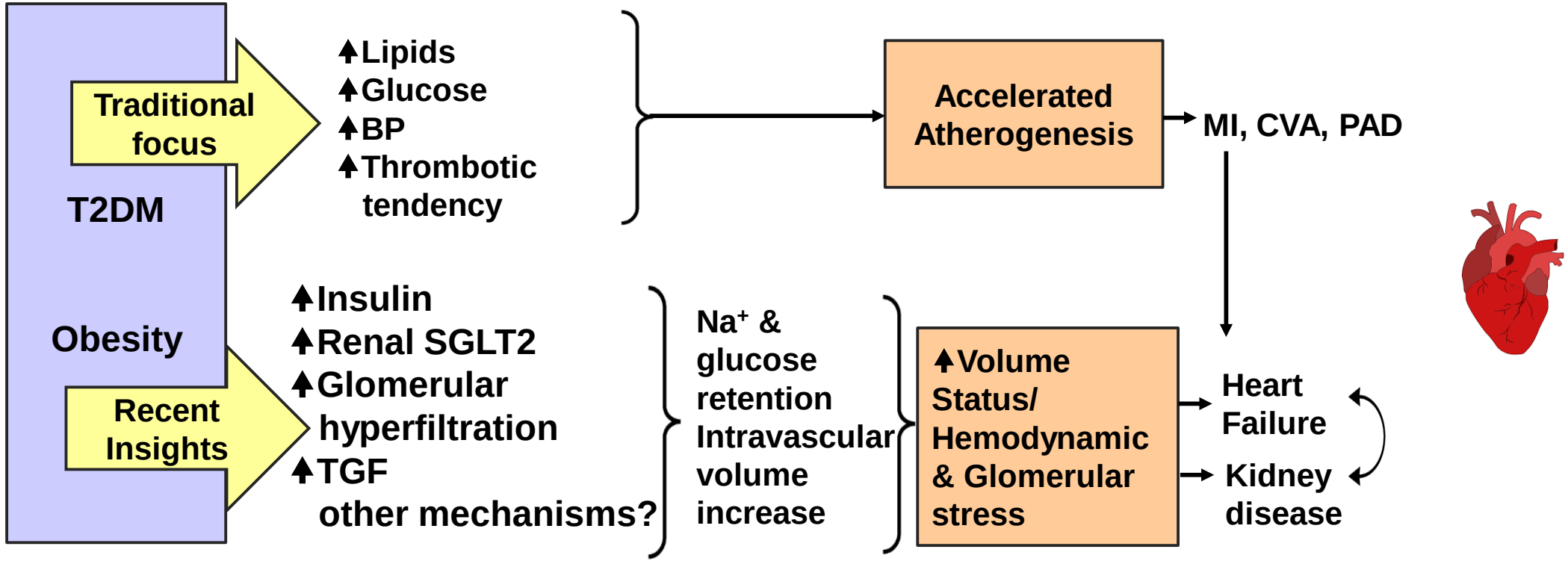






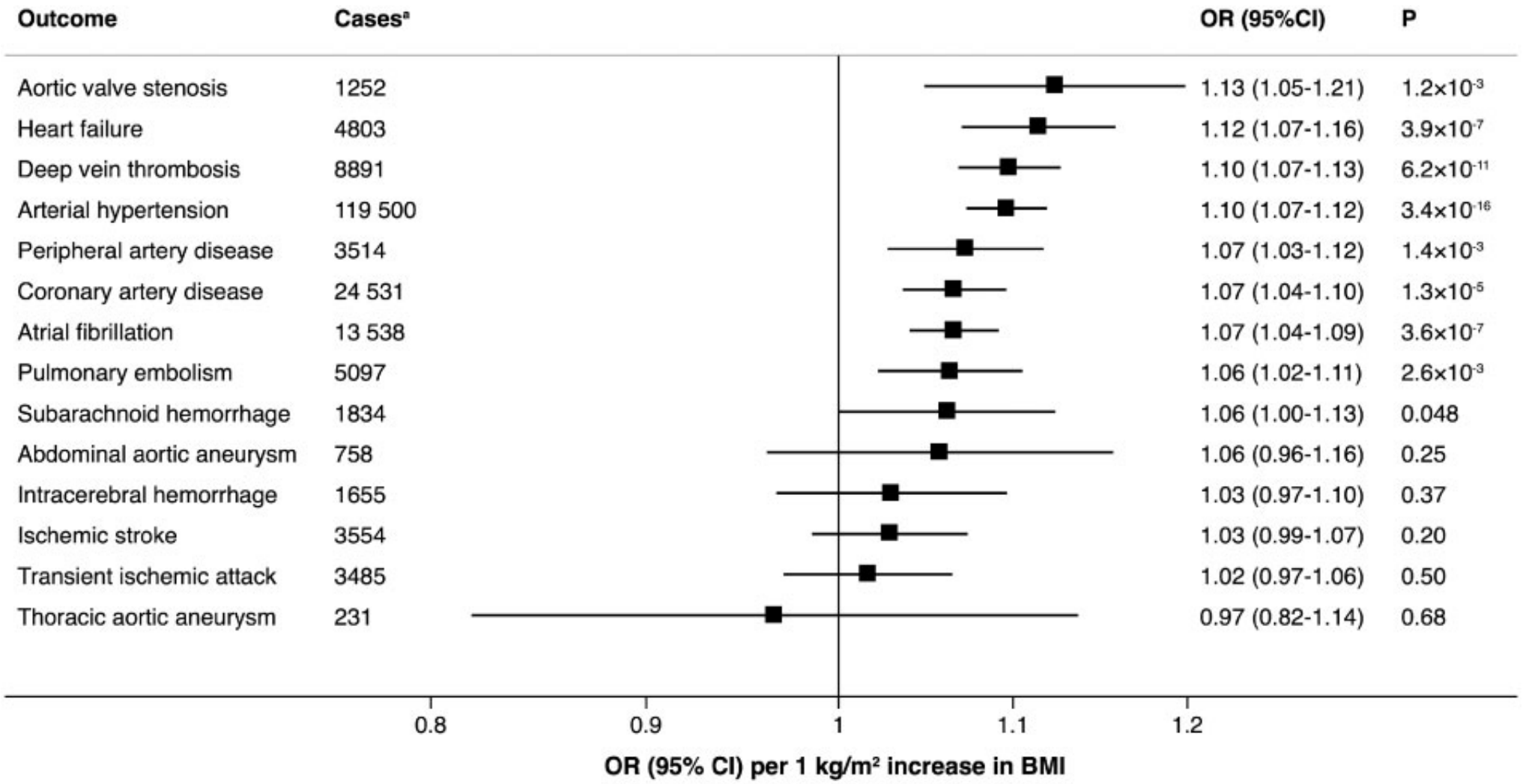
Robertson et al (2019) Circulation Higher BMI adolescence vs midlife CM risks

Diabetes / obesity accelerate atherogenic pathways and cause haemodynamic stress

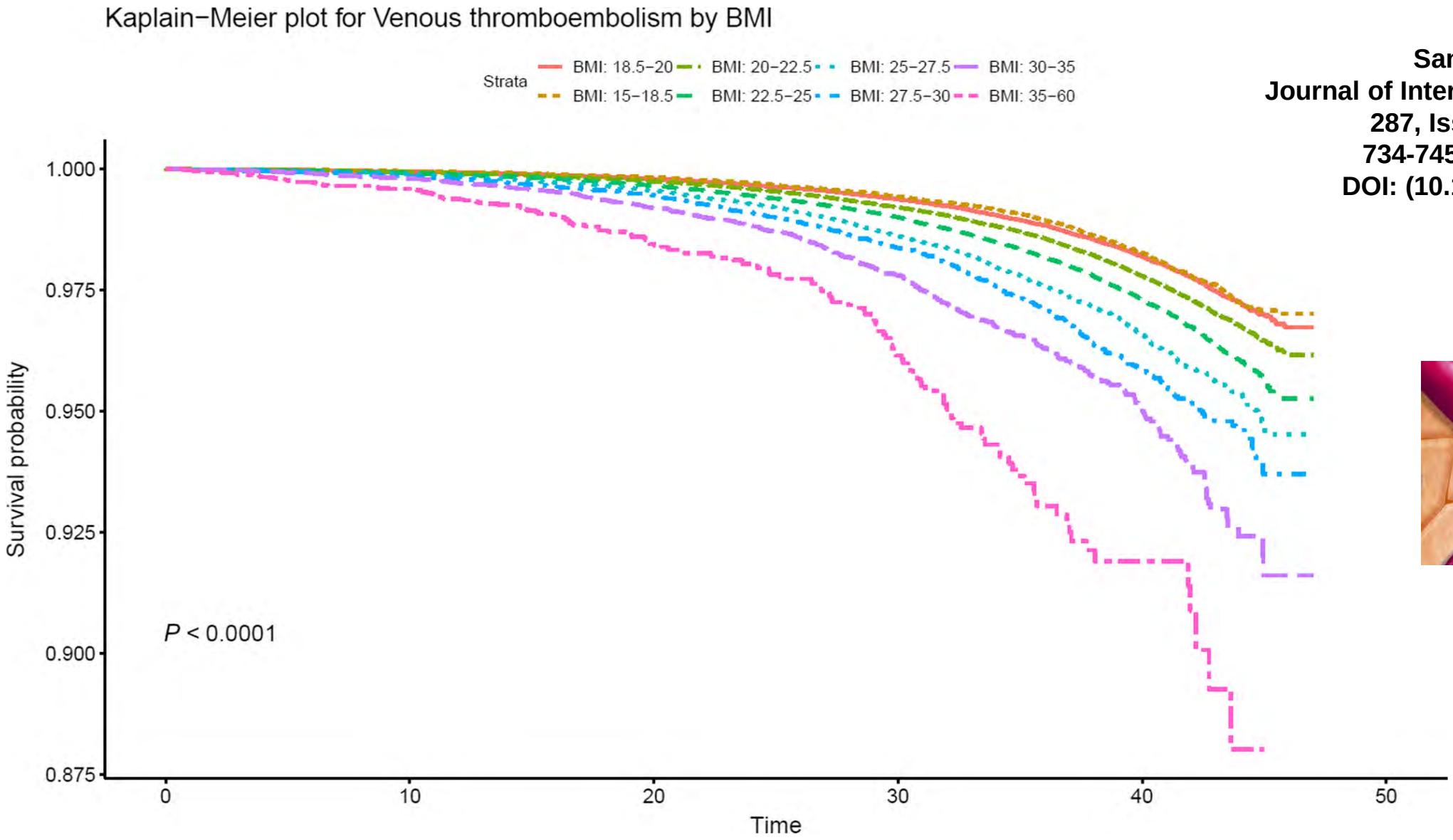


Sattar N, McGuire D. (2018) Circulation

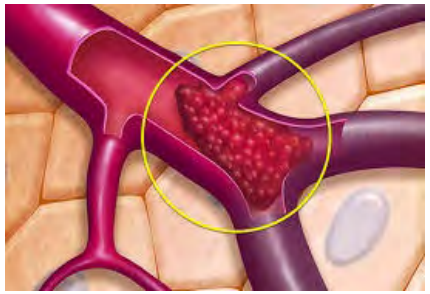
Genetically higher BMI and CVD outcomes
Larsson et al (2019) EHJ

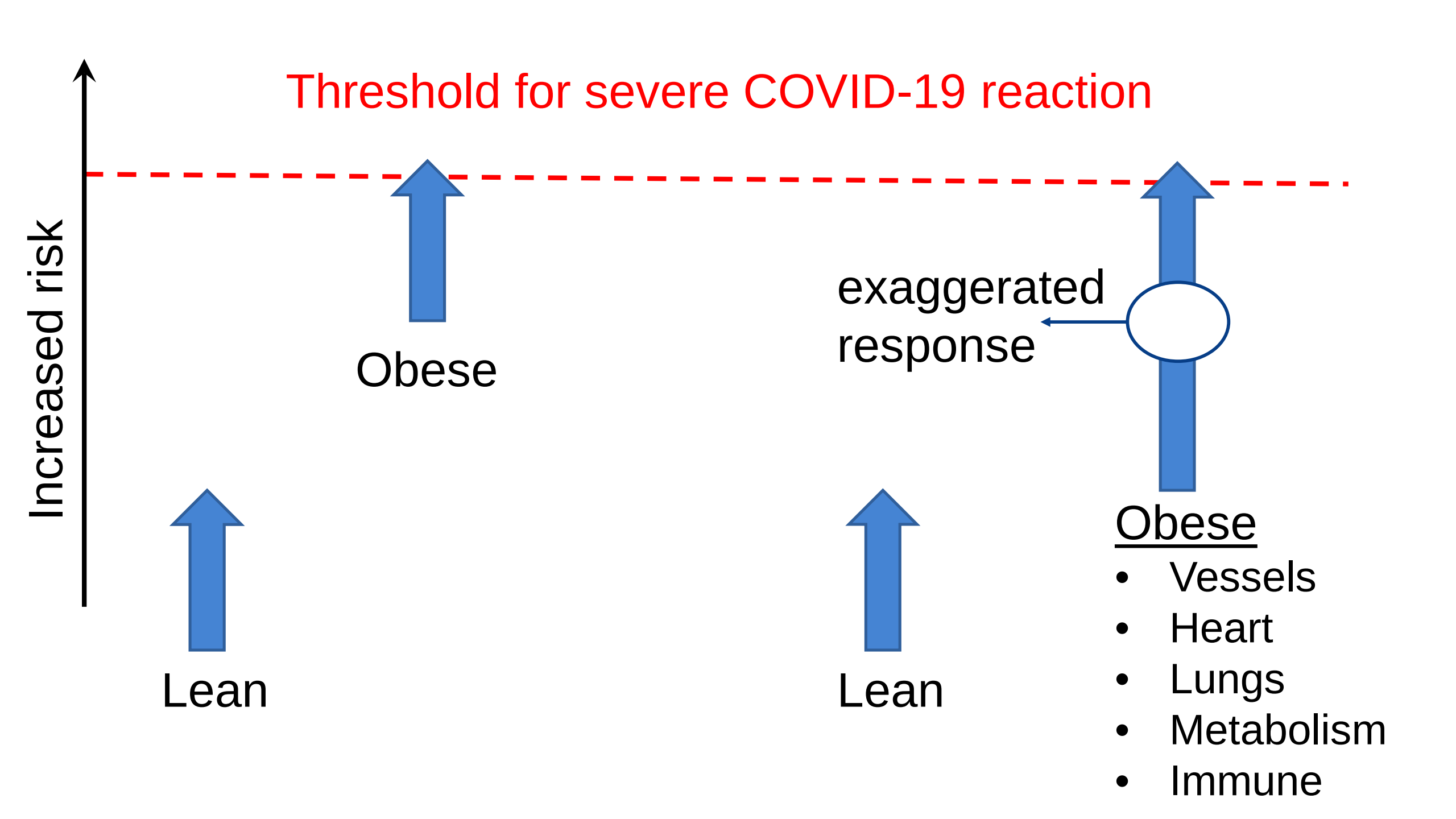


Obesity in adolescent men increases the risk of venous thromboembolism in adult life



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




Threshold for severe COVID-19 reaction
Increased risk
Obese
exaggerated
response
Lean
Lean
Obese
• Vessels
• Heart
• Lungs
• Metabolism
• Immune

Obesity lowers vit D levels

Diabetes & Metabolic Syndrome: Clinical Research & Reviews 14 (2020) 561–565

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

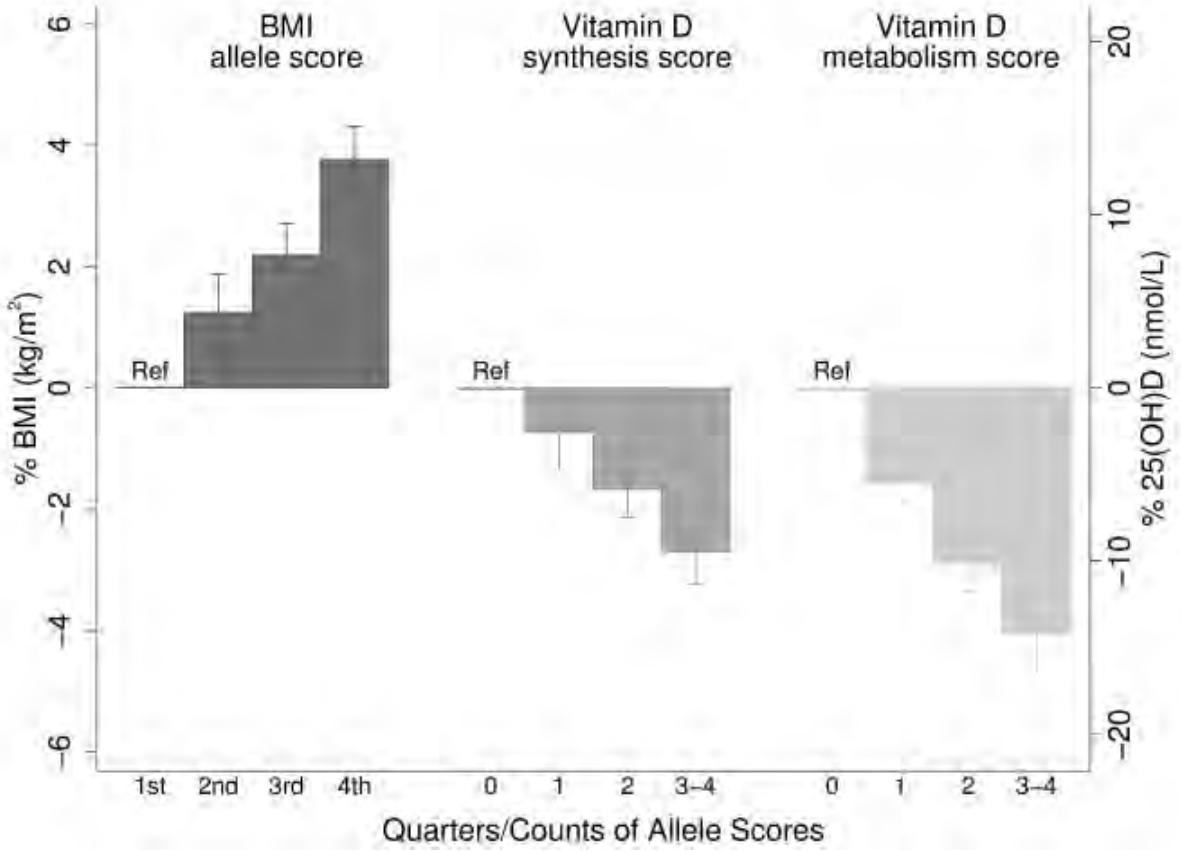
Vitamin D concentrations and COVID-19 infection in UK Biobank

Claire E. Hastie [a], Daniel F. Mackay [a], Frederick Ho [a], Carlos A. Celis-Morales [a, b], Srinivasa Vittal Katikireddi [a], Claire L. Niedzwiedz [a], Bhautesh D. Jani [a], Paul Welsh [b], Frances S. Mair [a], Stuart R. Gray [b], Catherine A. O'Donnell [a], Jason MR. Gill [b], Naveed Sattar [b, 1, **], Jill P. Pell [a, *, 1]

[a] Institute of Health and Wellbeing, University of Glasgow, 1 Lilybank Gardens, Glasgow, G12 8RZ, UK
[b] Institute of Cardiovascular and Medical Sciences, University of Glasgow, BHF Glasgow Cardiovascular Research Centre, 126 University Place, Glasgow, G12 8TA, UK

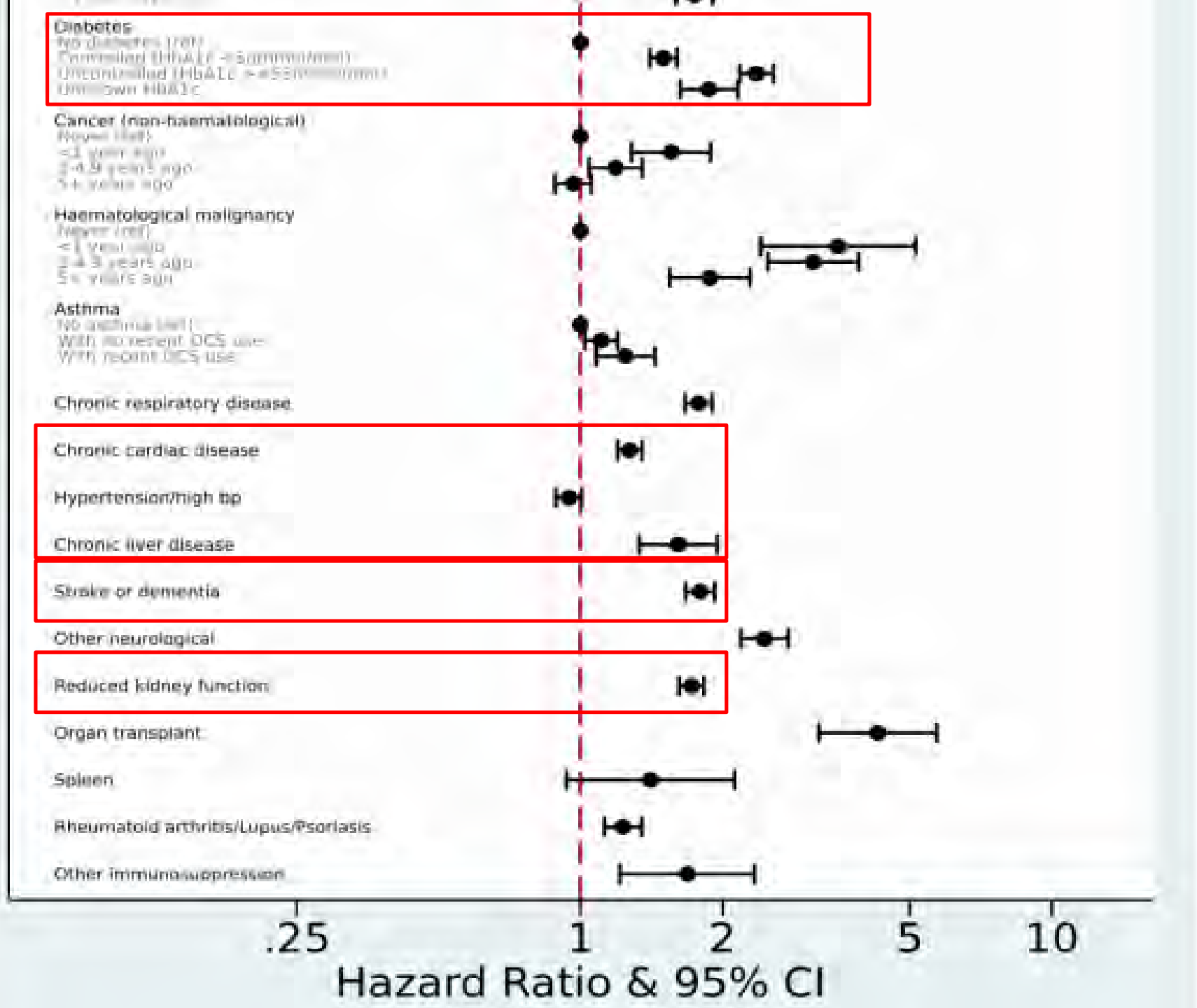
No evidence vitamin D levels linked to:

- future infection risk
- explain higher ethnicity risks



Vimaleswaran et al (2013) PLOS Med

"Population level interventions to reduce BMI are expected to decrease the prevalence of vitamin D deficiency".



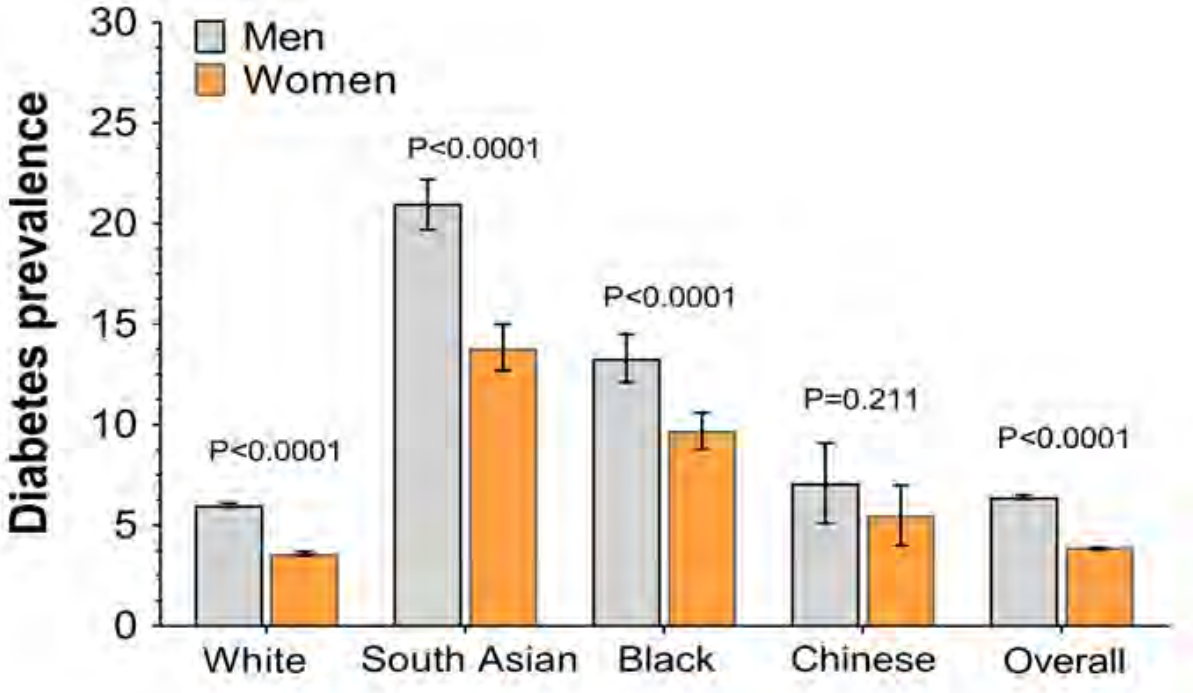
OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients.

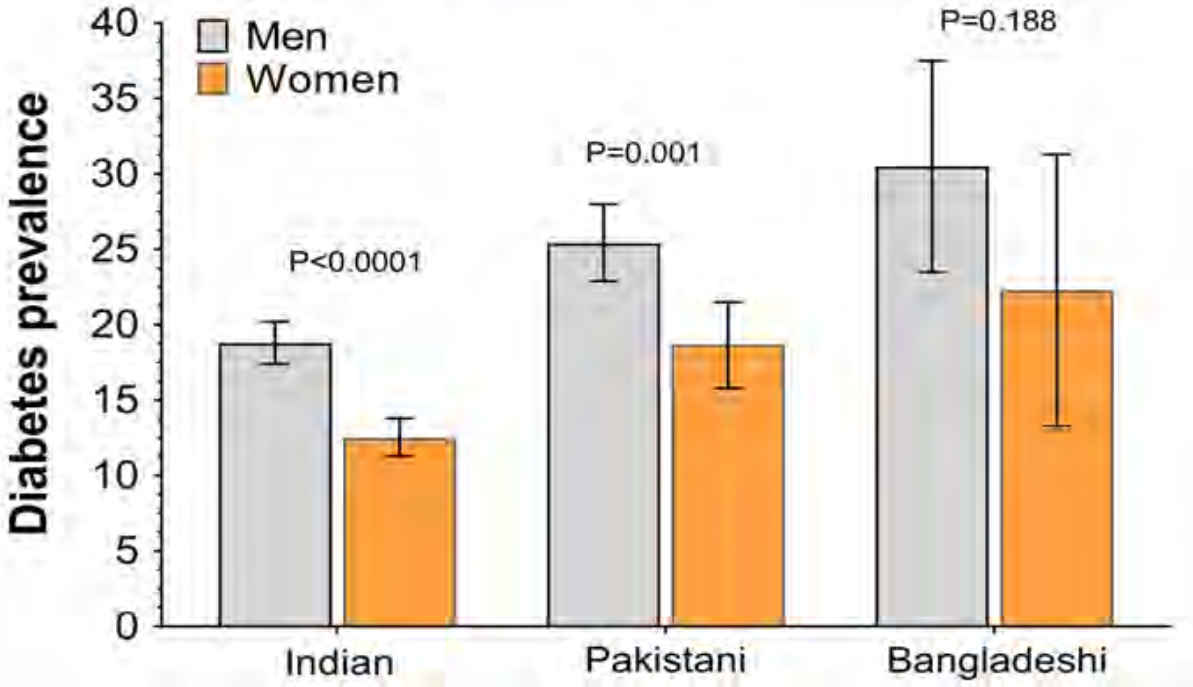
Can we link excess fatness to excess male or ethnicity risks?

YES

Part of it

- Ectopic fat





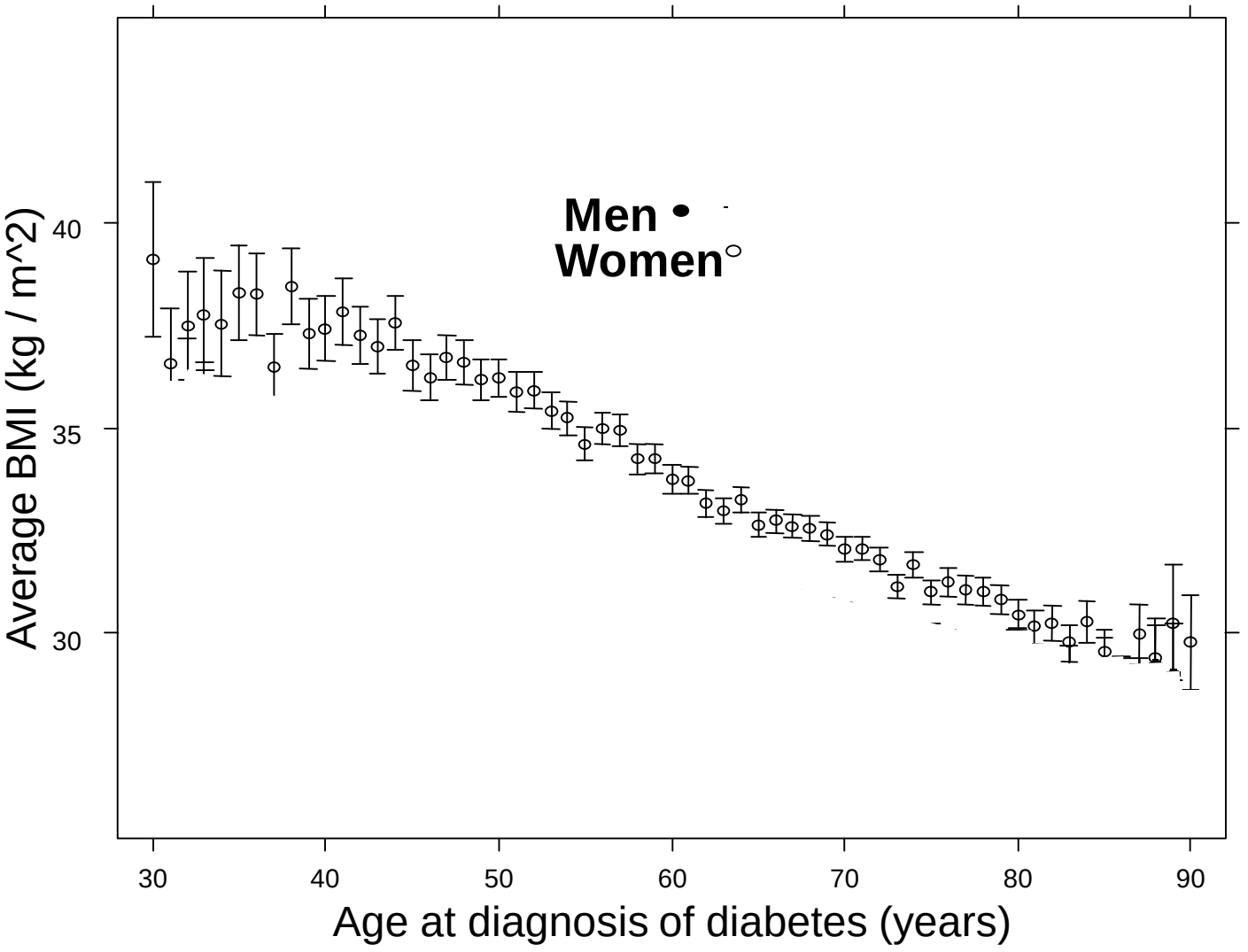
Ferguson LD.
Diabet Med. 2017

Men more DM

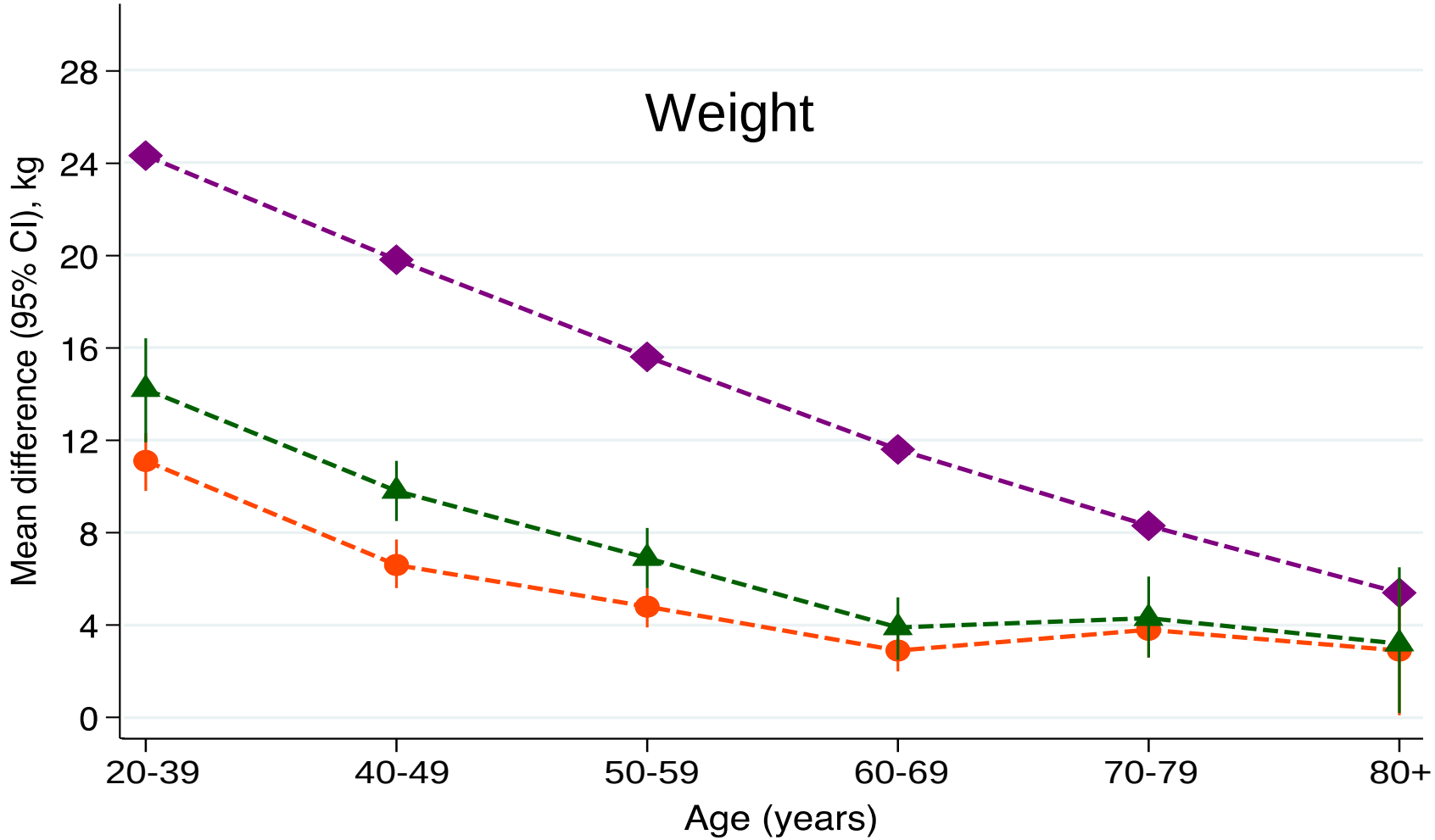
More CHD

More Liver disease

Men need to put on less weight to get diabetes



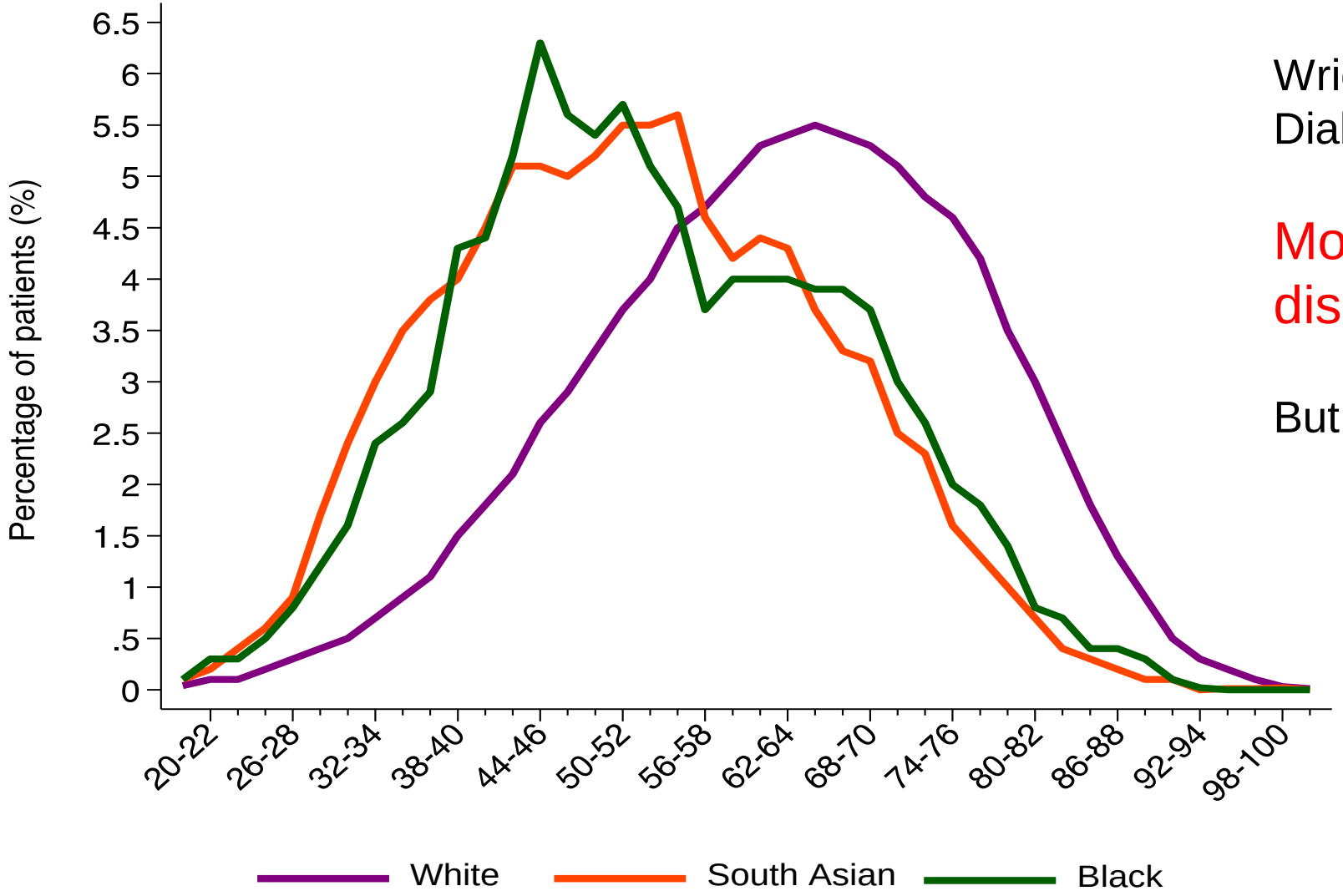
Logue et al (2012) Diabetologia



South Asians, Blacks less weight gain to develop diabetes

Wright et al…Sattar (2020) Diabetologia

South Asians, Blacks less develop diabetes ~10 years earlier



Wright et al (2020)
Diabetologia

More microvascular disease in non-whites

But usually LESS mortality

Outline

- Evidence for obesity as relevant to COVID-19
- Possible explanations – confounding?
- Causation? Multiple pathways make sense
- **Implications for care / PH policy?**
  - If obesity proven causal for excess risk
  - And any weight loss may help

Going forwards – improve PH messaging on obesity

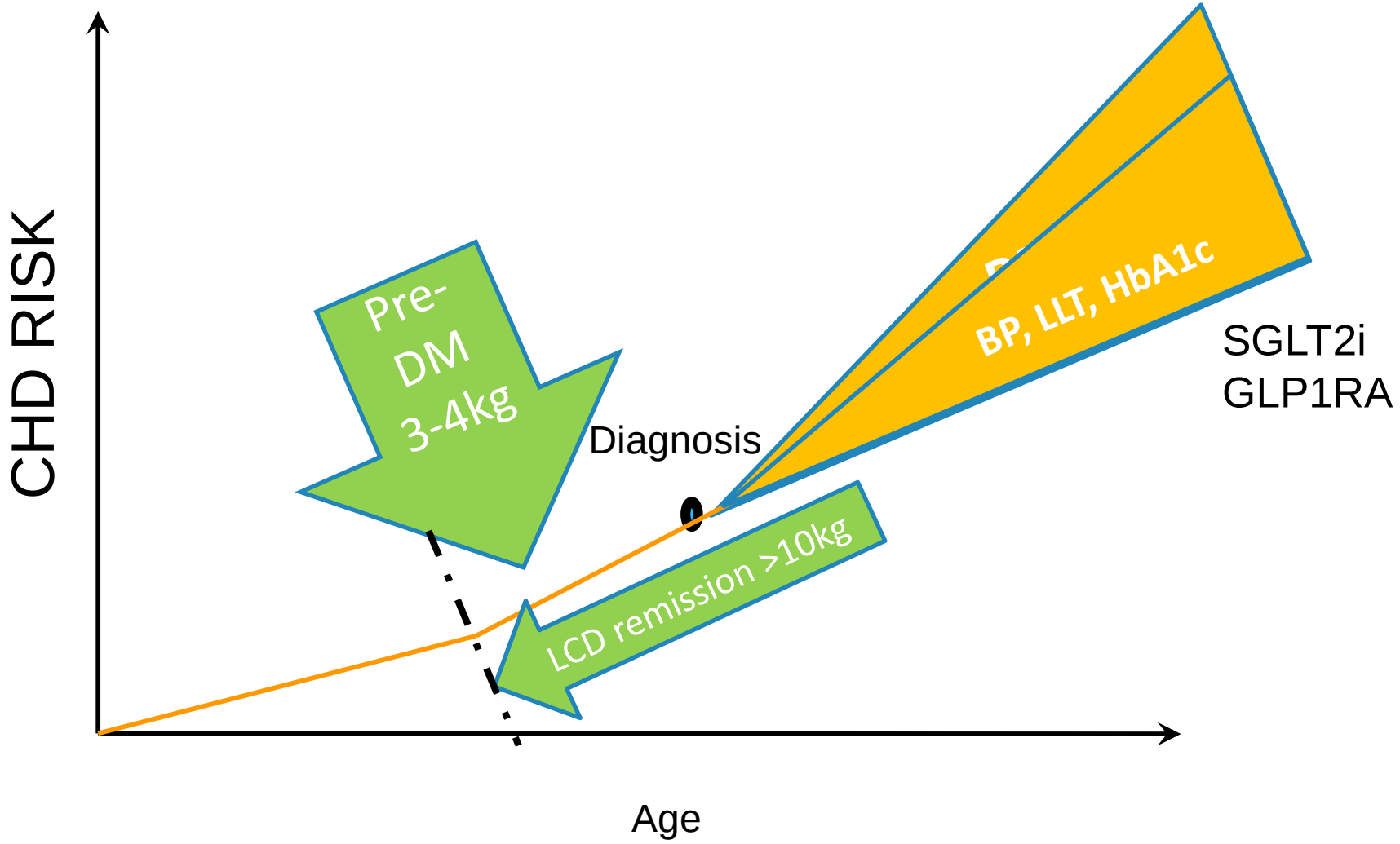
Improve public health messaging **to help** people improve lifestyle

Sustainable increases in activity

Sustainable reductions in calorie intake

To potentially lessen chances of severe more severe SARS-CoV-2

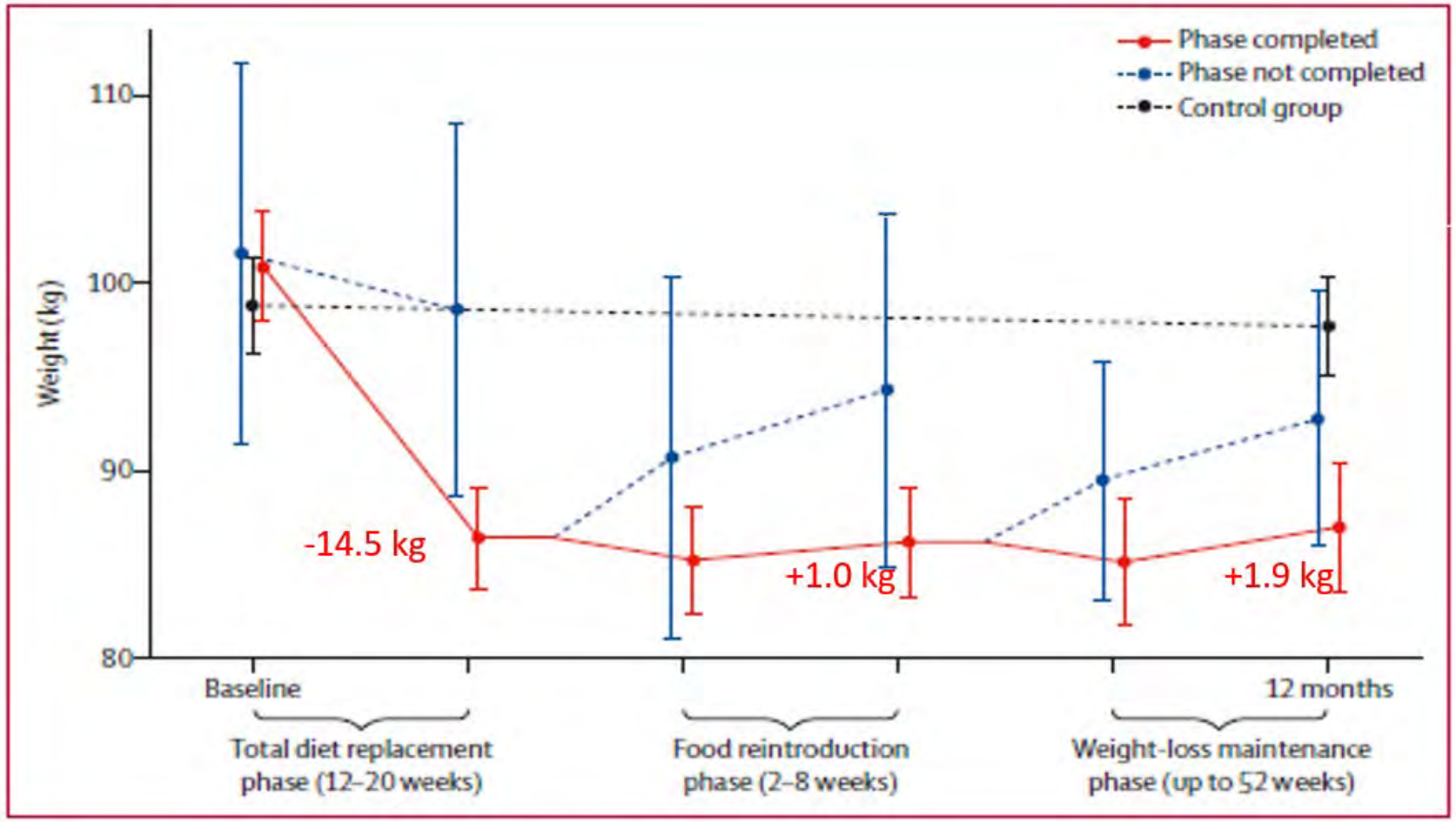
Lifestyle can delay diabetes, or reverse it



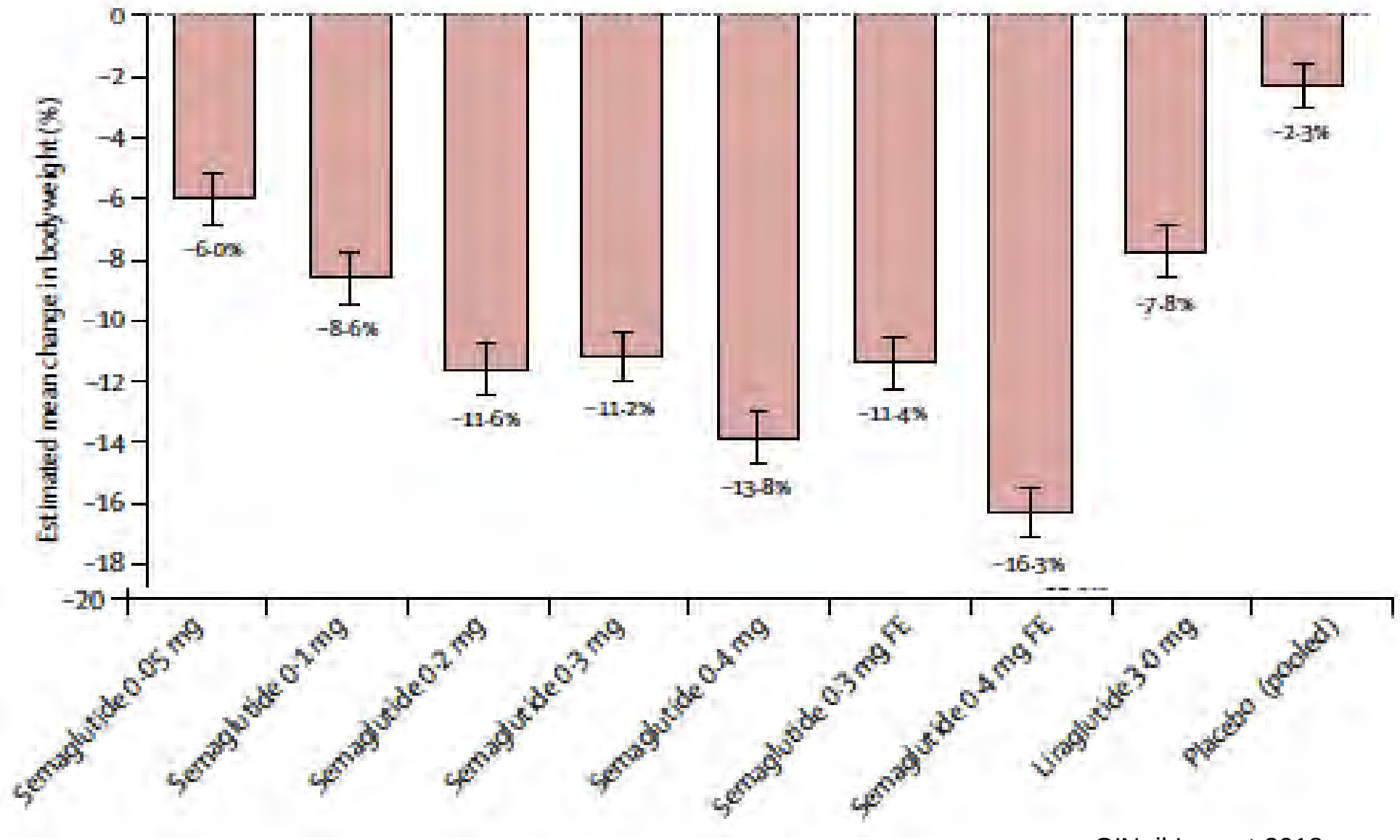
Sattar (2013) Diabetologia (studies support concept) DIRECT (Lean et al Lancet 2018)

Low calorie diets and diabetes remission

Lean et al (2018) DIRECT



Drugs that lessen appetite: Semaglutide expensive



O'Neil Lancet 2018

What resources now?

COMMERCIAL WEIGHT LOSS COMPANIES

ONLINE RESOURCES

COUCH TO 5K

BUT ALSO LOTS OF CONFUSION

Anderson et al. Int J Epidemiol. 2017

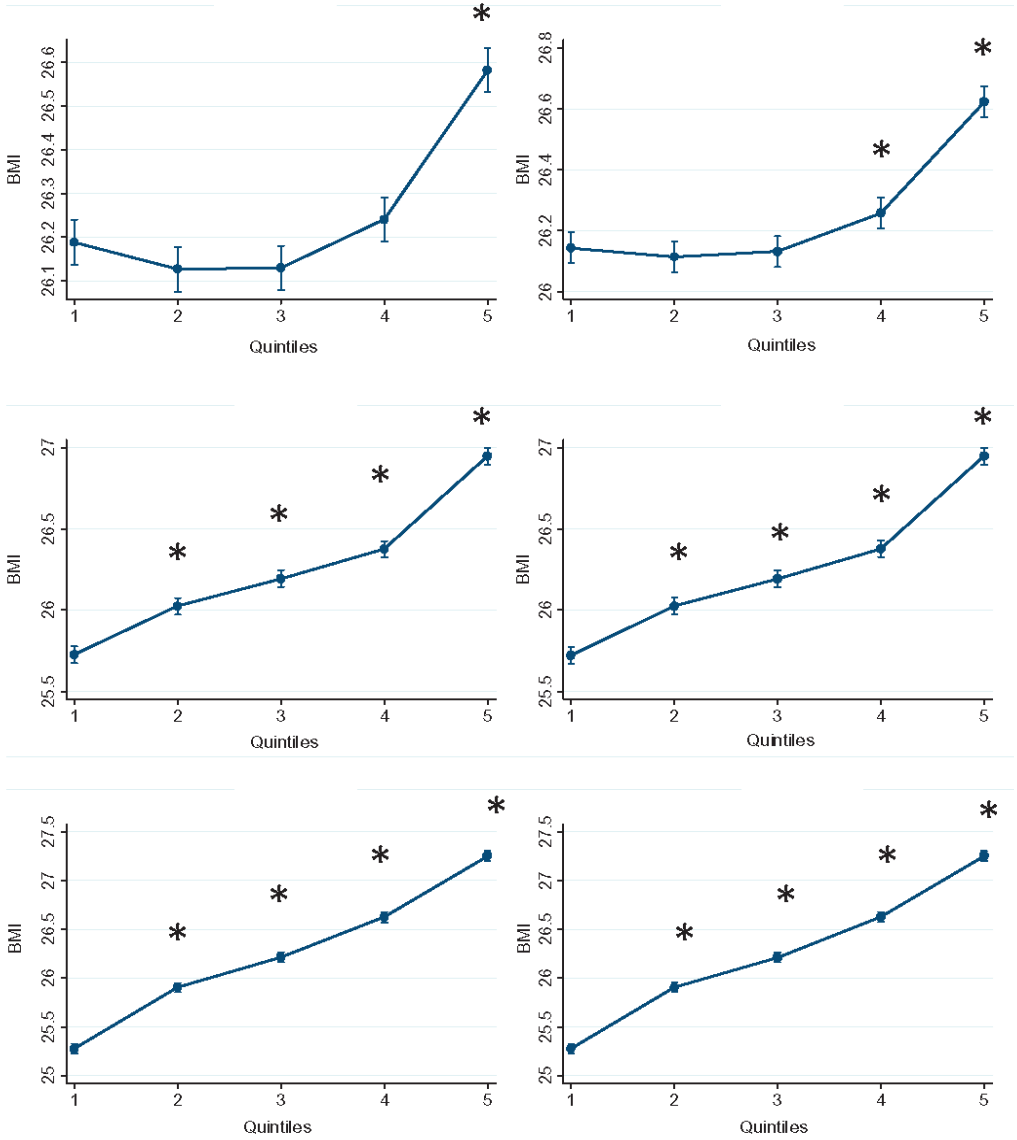
Adjusted for age, sex, ethnicity

Adjusted for age, sex, ethnicity and physical activity

Sugar

Starch

Fat



Further adjust for TOTAL ENERGY INTAKE?

Lifestyle advice:
if weight is up, or recent rapid weight gain, or if seeking advice →

Range of dietary options proven to work

- Simple written leaflet: self-explanatory range of options
- Encouraged to try one or more, and to not worry about failing (can retry)
- Warned some dietary changes can take time to embed (retraining palate proven concept)
- Advice given in supportive and non-judgemental manner
- Signposts to other, more-intensive options if simpler ones do not help

Goals:
either sustainable weight loss or slow or stop weight gain →

Activity

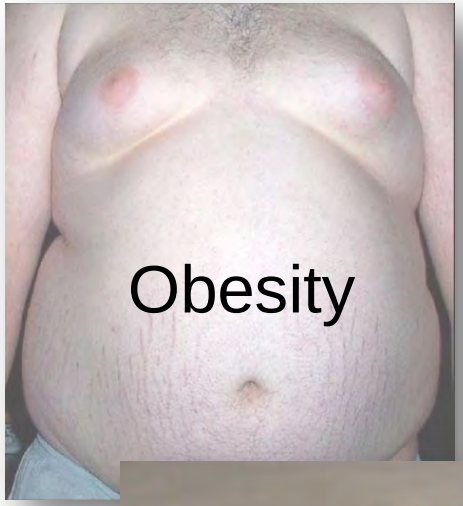
- Warned weight loss hard to achieve by activity alone
- Try simple steps first; e.g., ↑step count by 1,000 per day (i.e., extra 10 min walking)
- ↑activity in commute to work
- Find activities that give pleasure
- Tips for simple resistance exercises at home

Sattar et al (2020) Nature Medicine Campaign on simple evidence based messages

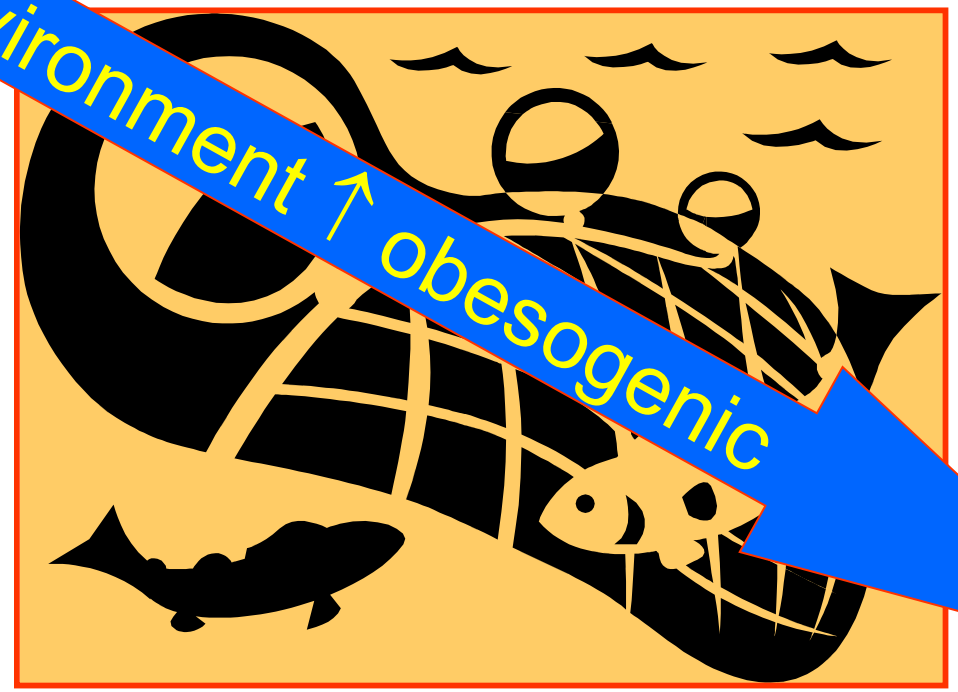
“1949”

“…an epidemic; under the right economic & social circumstances, obesity from overeating will be a dominant nutritional problem.”

Ancel Keys



Quality Education For All



Food, retail and catering Industry – HALF A STORY!

- “Increase healthy options”
- “Increase range of portion sizes”
- “Promoting fruits and vegetables”

- DECREASE LESS HEALTHY OPTIONS
- DECREASE LARGE PORTION SIZES
- DECREASE CONFECTIONERY OPTIONS

- At very least …? Level playing field……. And cost

COVID-19 severity /death and obesity (ectopic fat)

- **Link appears strong (obesity strong for cardiometabolic comorbidity)**
  - Partially explains risks – males, non-white, diabetes, and pathways (microvessels, thrombosis, inflammation, heart and lungs)
- **Can we lessen risks by weight loss? Possibly but other benefits**
  - Greater help for weight loss
  - Reduce deprivation: difficult as pandemic = more poverty
  - Economies back food industries (conflict)
  - <u>Need simple advice urgently</u>