

Interactions of exercise and diet in health prevention

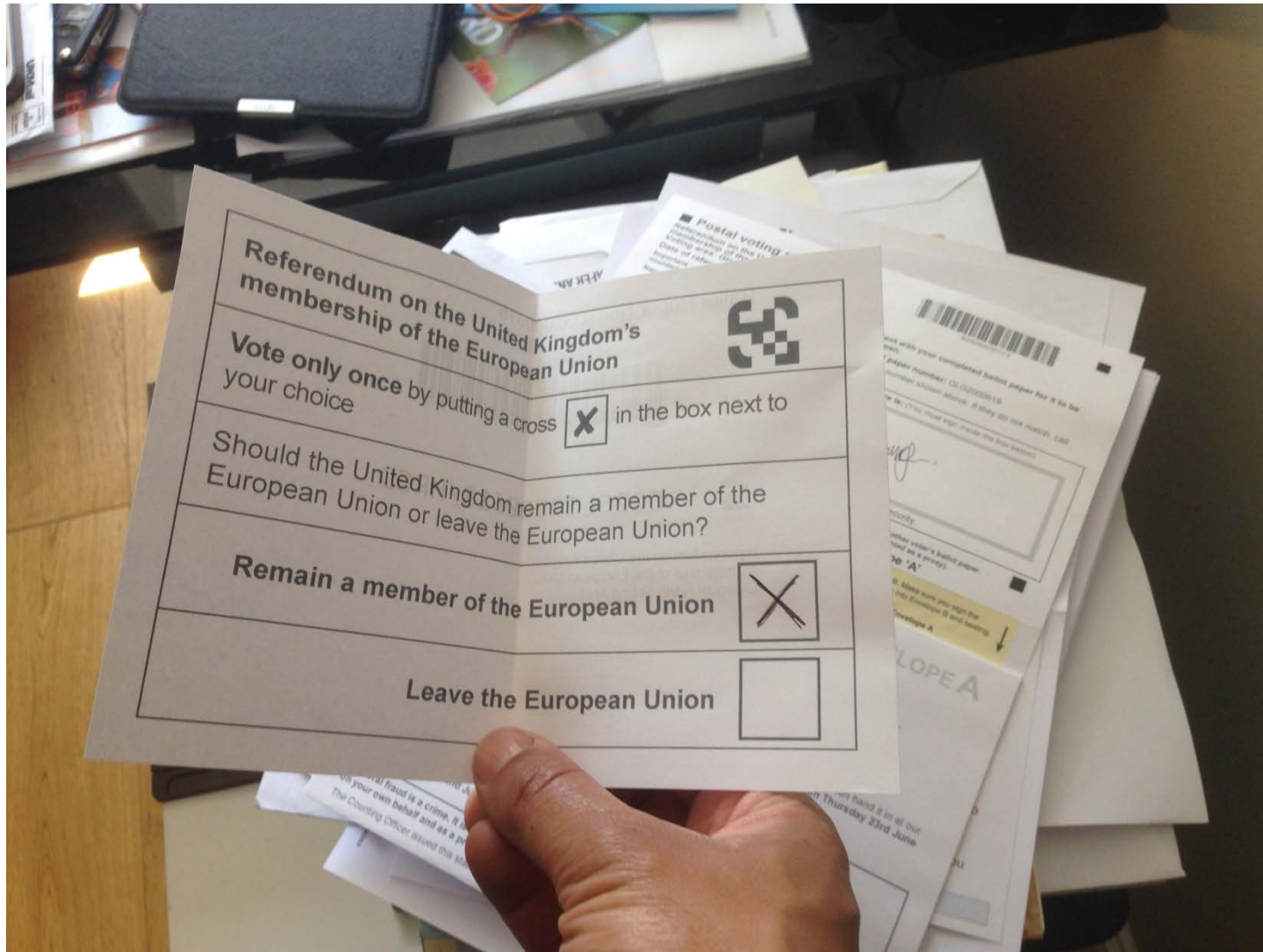
Dr Jason Gill

Institute of Cardiovascular and Medical Sciences
University of Glasgow



- **Physical activity and health outcomes – does one size fit all?**
- **Physical activity and postprandial lipoprotein metabolism**
- **Physical activity, dietary intake and energy balance**





Global burden of physical inactivity

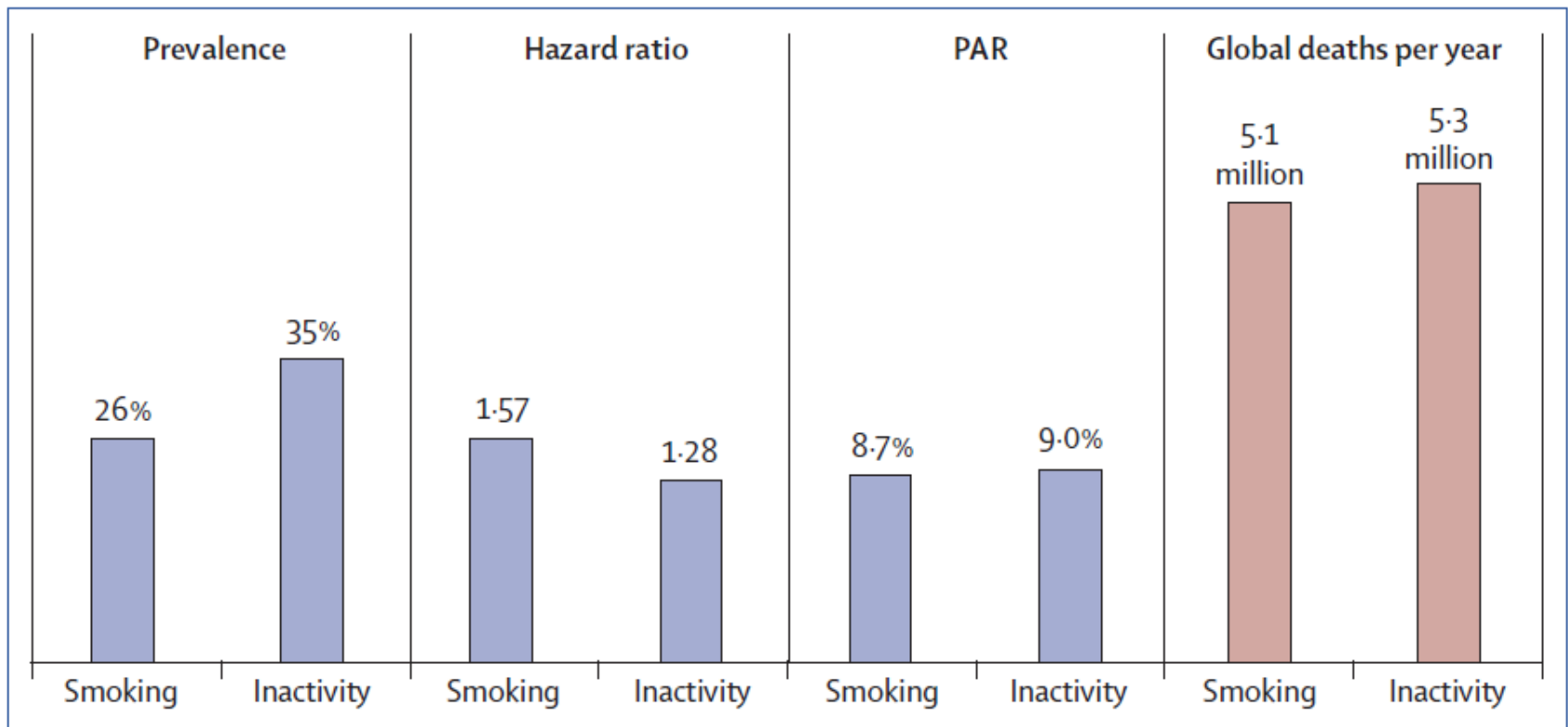


Figure: Comparison of global burden between smoking and physical inactivity

Prevalence of smoking, population attributable risk (PAR), and global deaths for smoking were obtained from WHO.⁷ Hazard ratio for all-cause mortality of smoking was obtained from meta-analysis studies.^{8,9} All inactivity data were obtained from Lee and colleagues.⁵

A brief history of physical activity guidelines (for adults)



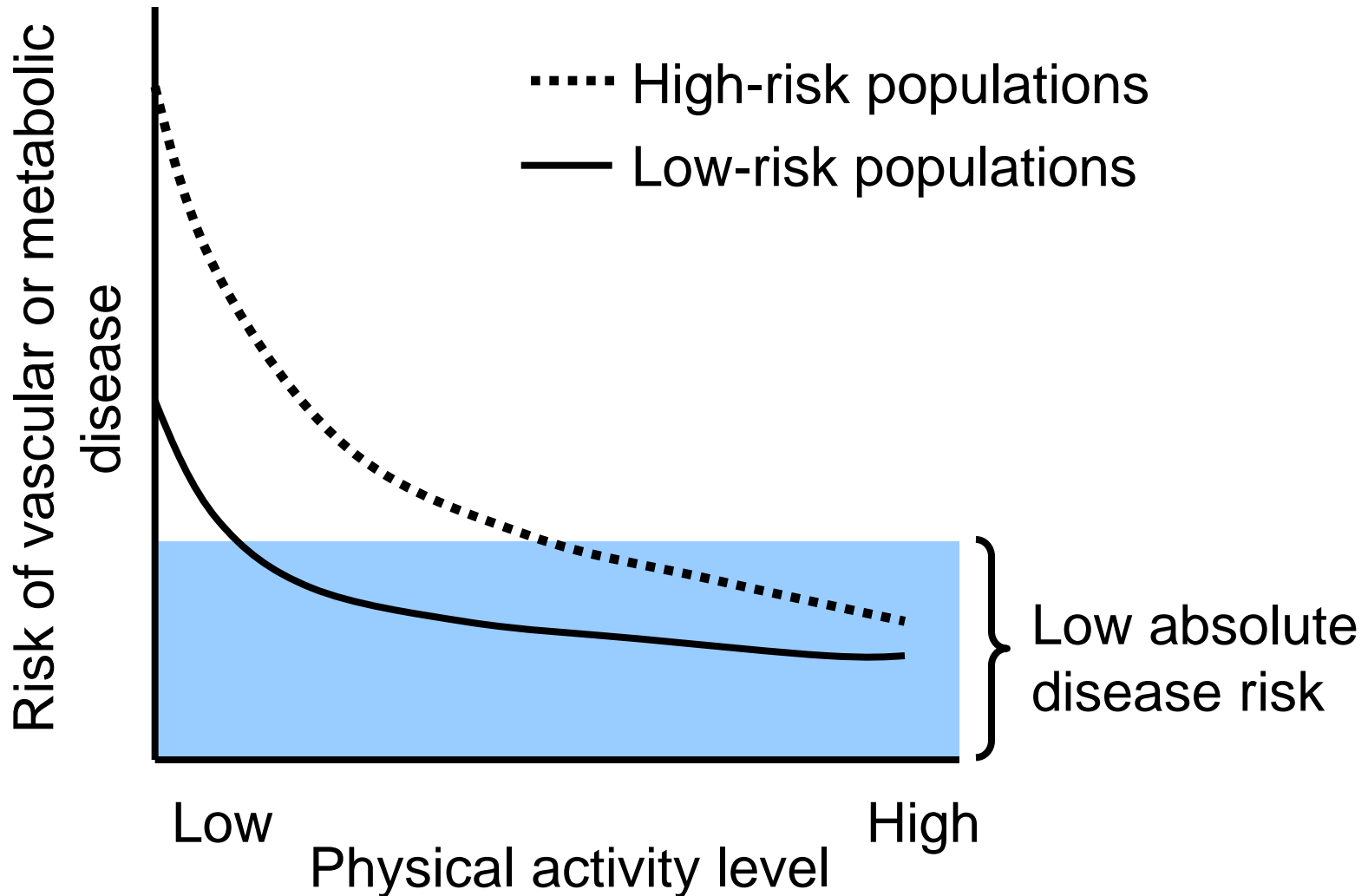
2011

- **150 minutes of moderate or 75 minutes of vigorous physical activity per week in bouts of at least 10 minutes**
- **Muscle strengthening activities 2 x per week**
- **Minimise the amount of time spent sedentary (sitting)**

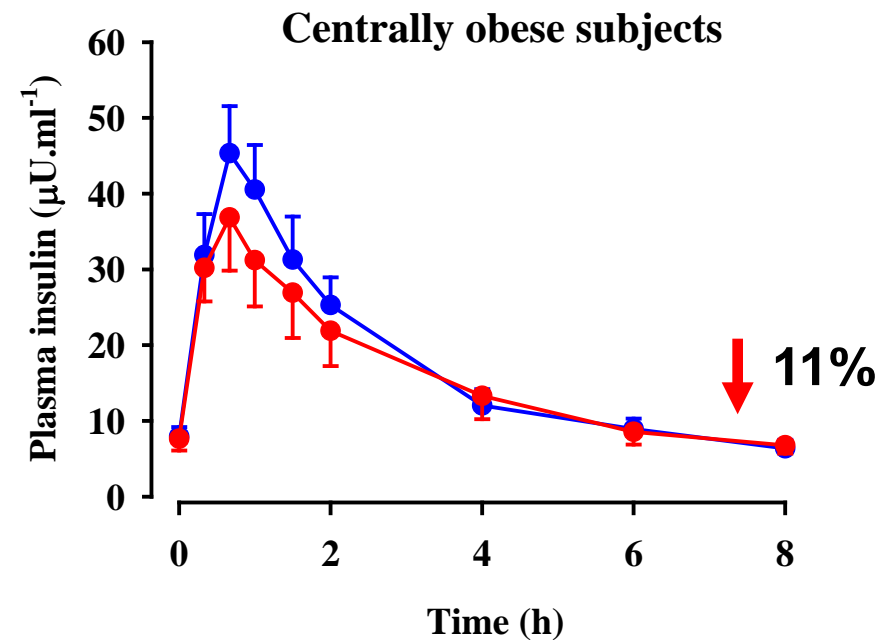
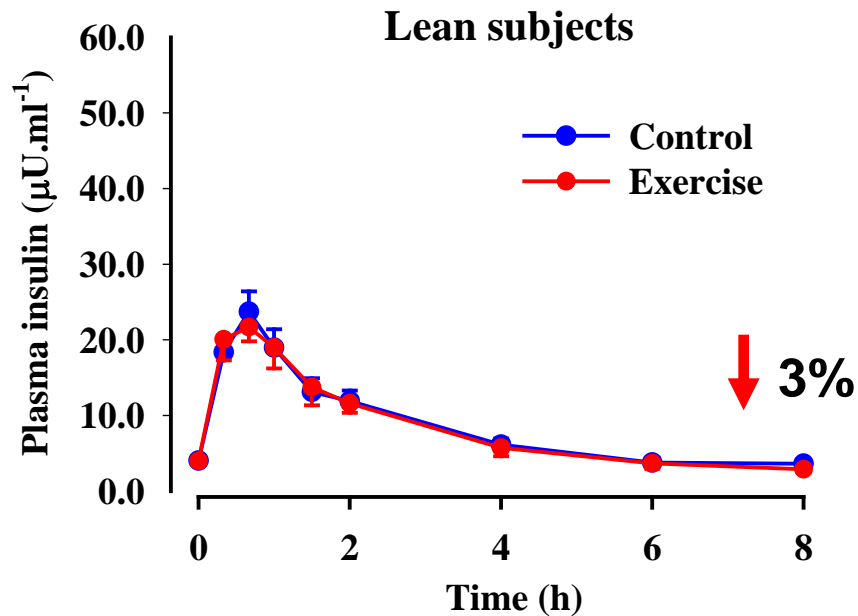
Physical activity and health outcomes: does one size fit all?



How much physical activity do people need to do?

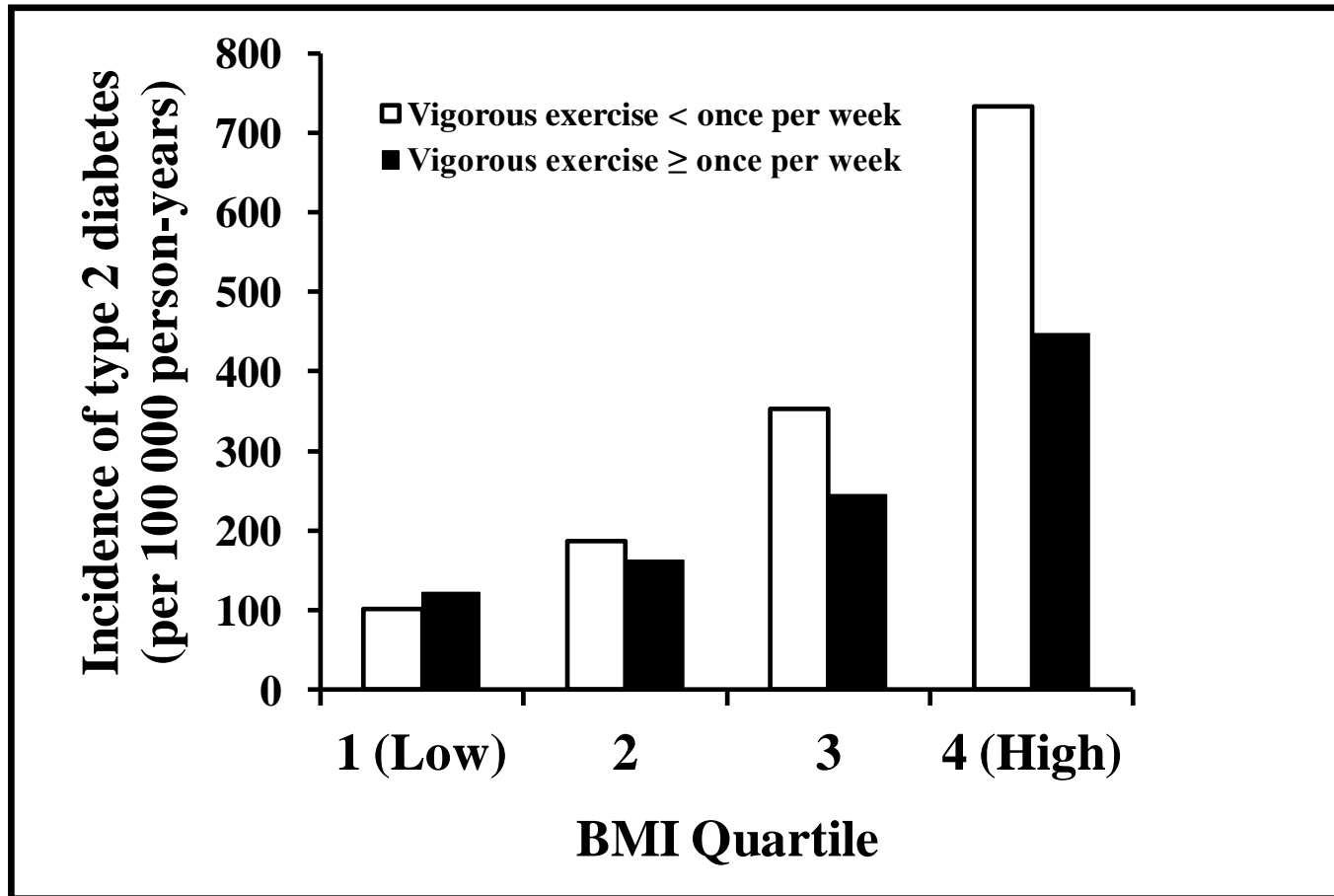


Moderate exercise and insulin responses in lean and obese men



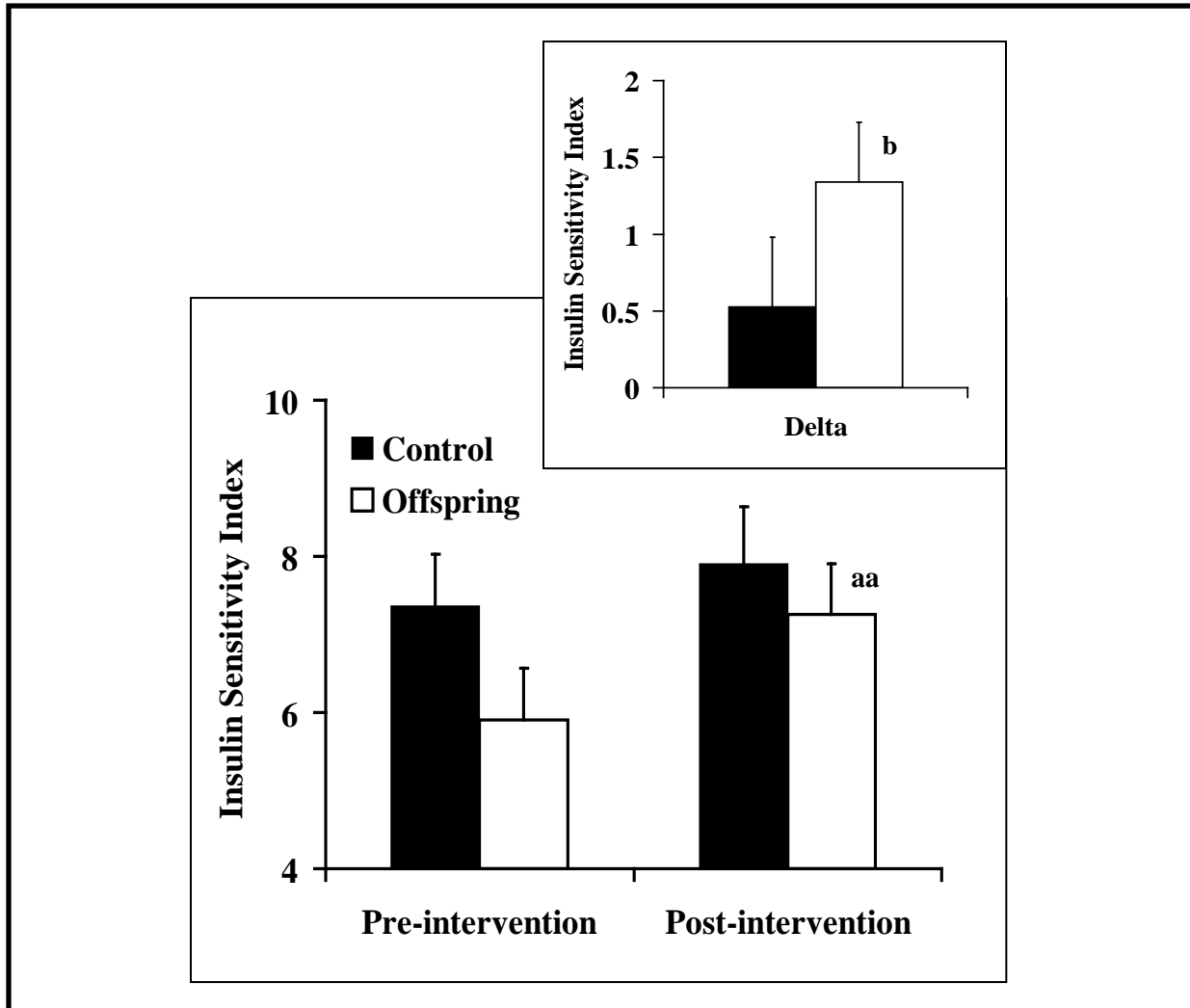


Vigorous exercise, BMI and diabetes incidence in the Physicians' Health Study

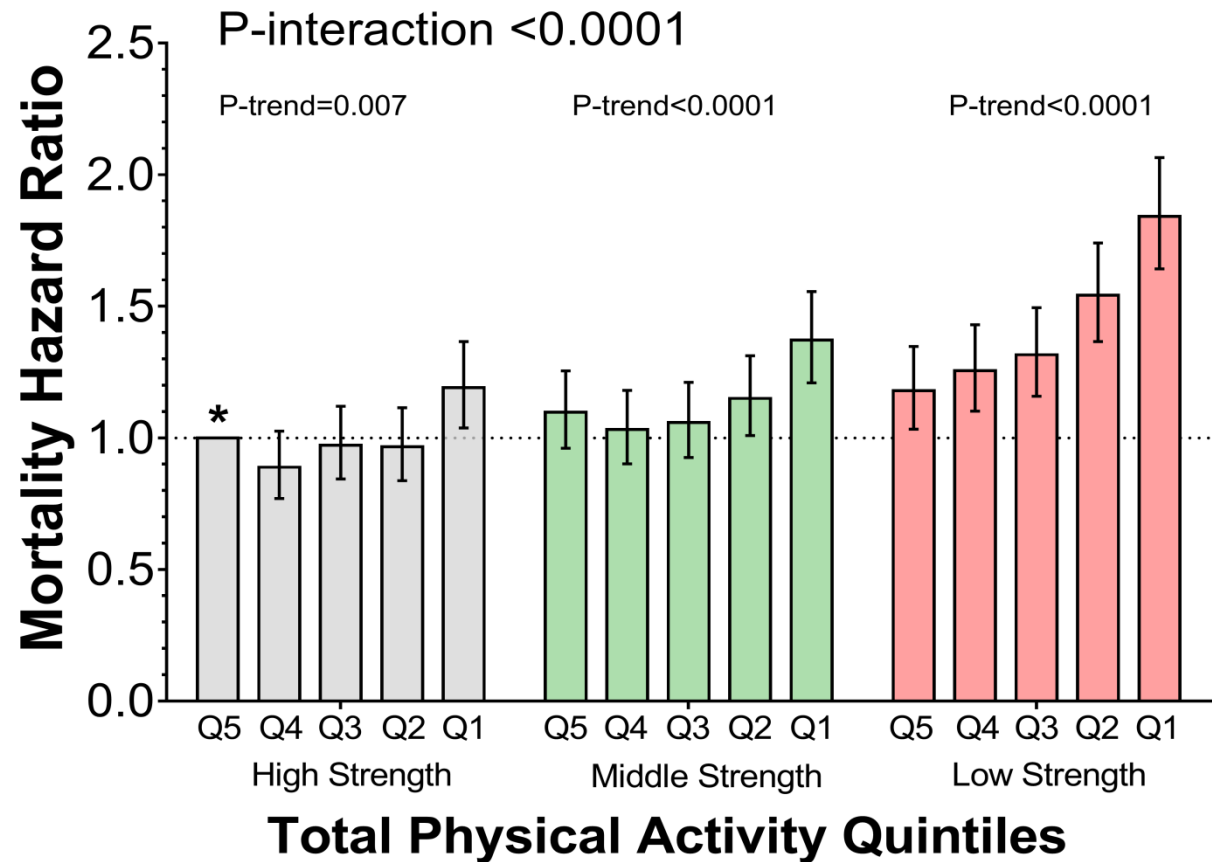




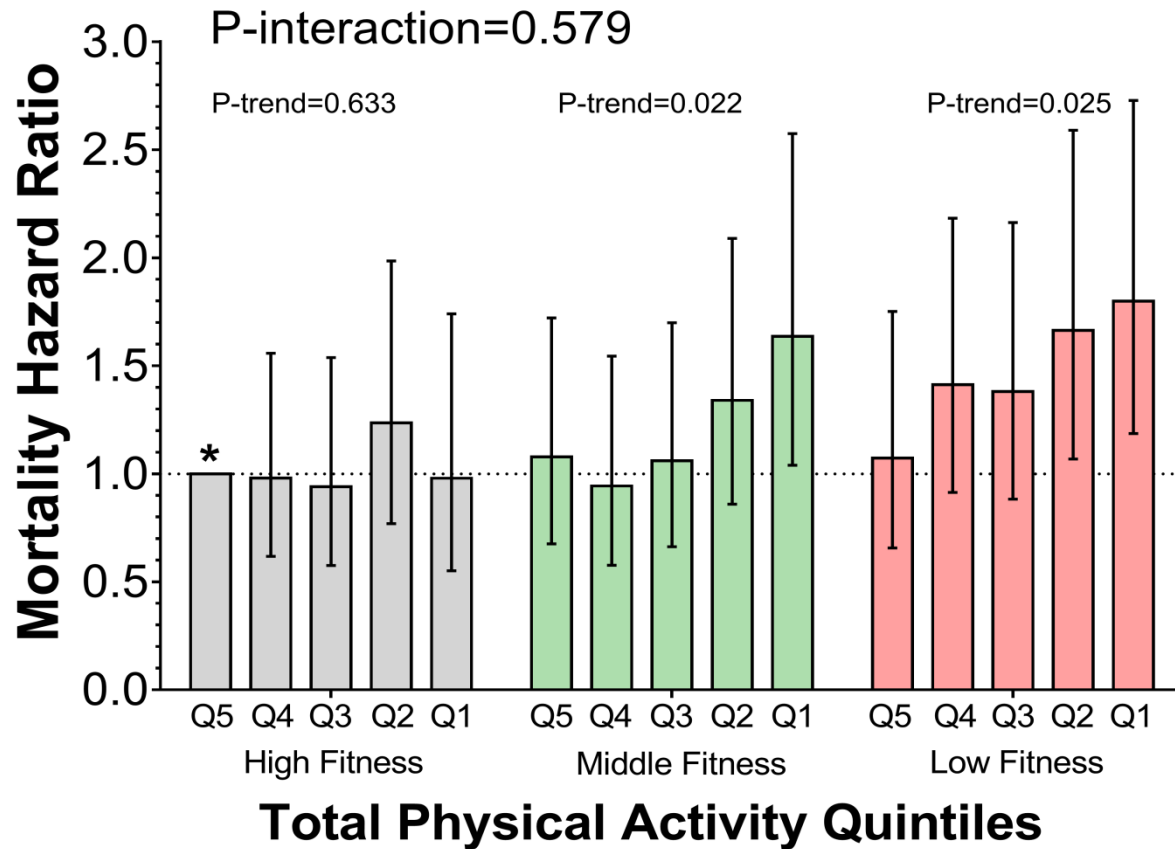
Change in insulin sensitivity following a 7-week exercise intervention in women with and without a family history of diabetes



Grip-strength, physical activity and risk of mortality in UK Biobank

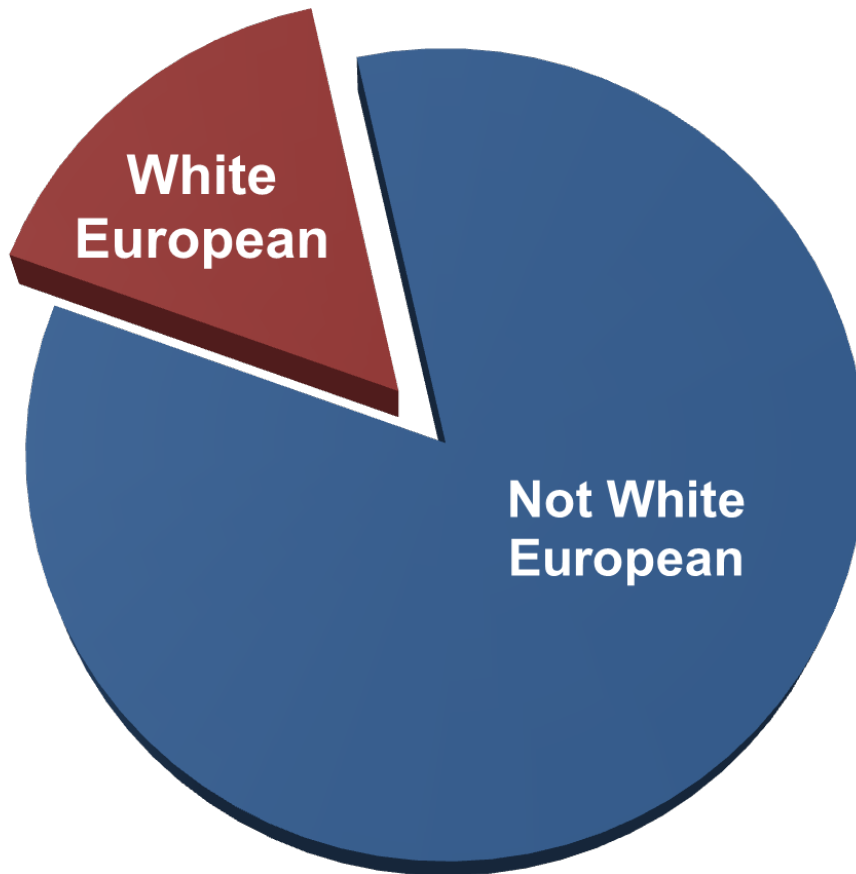


Fitness, physical activity and risk of mortality in UK Biobank



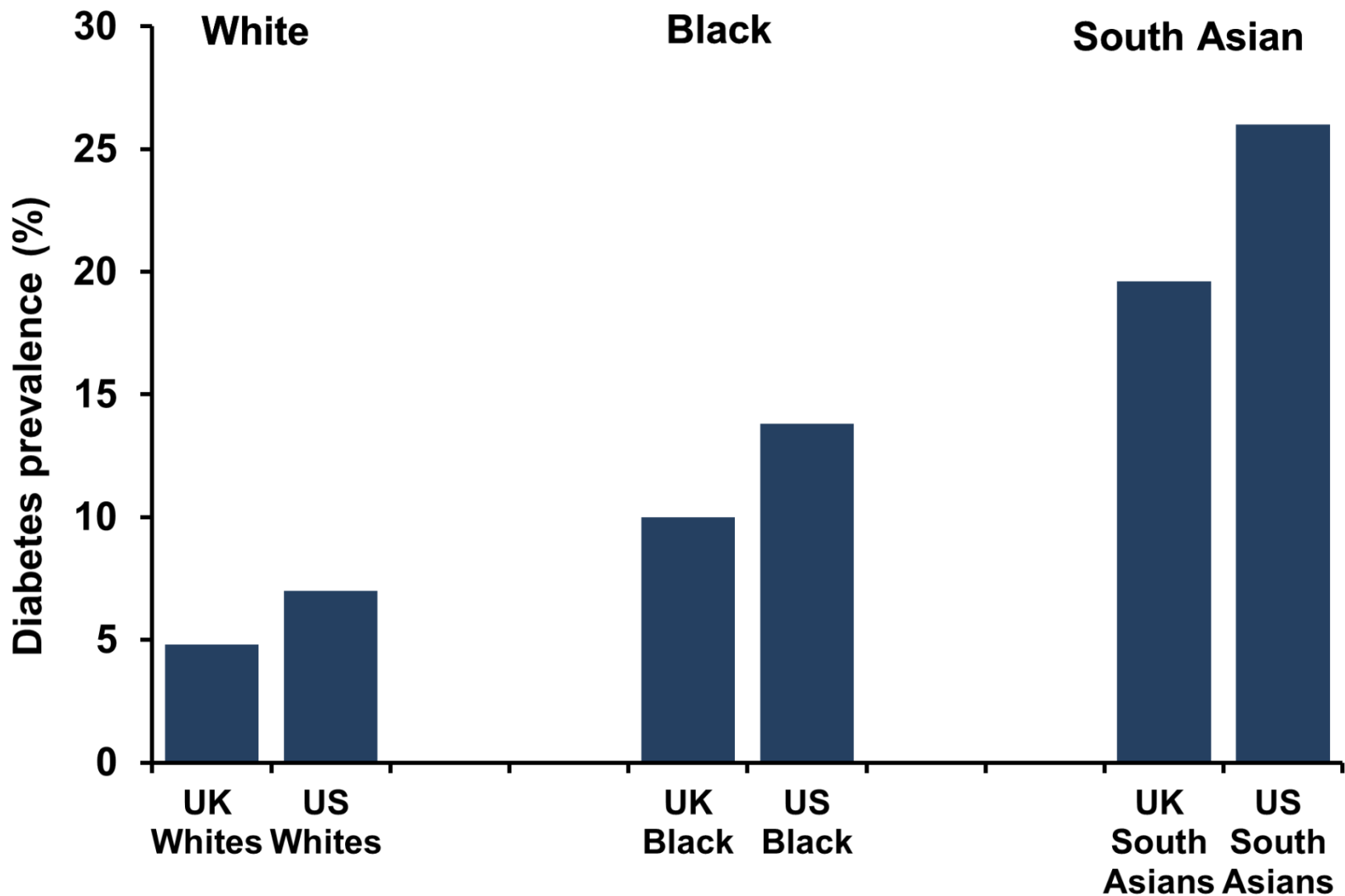
(n = 76,702)

Celis-Morales et al (2016) European Heart Journal



**Five-sixths of
the World's
population is
not of White
European origin.**

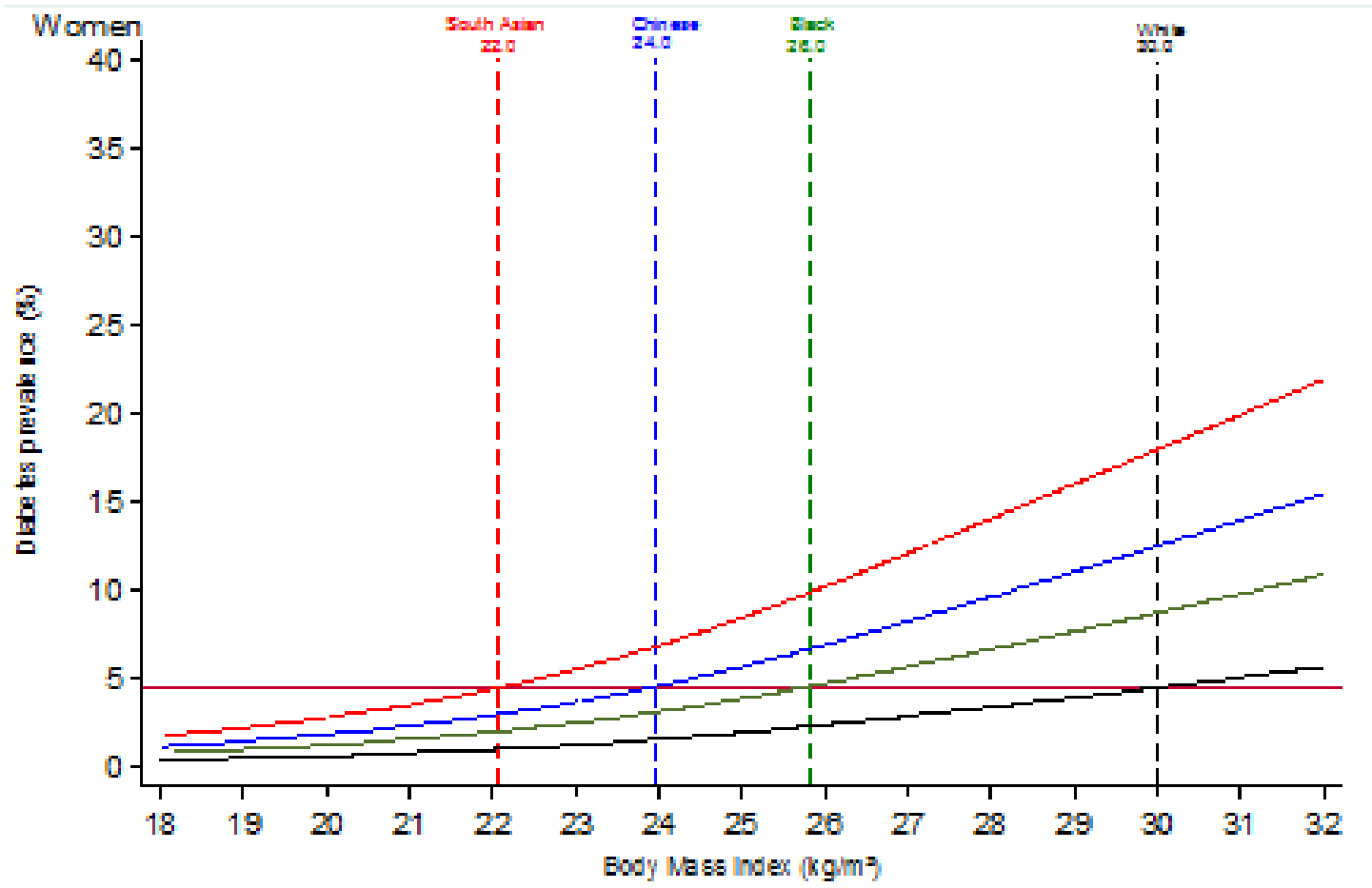
Ethnicity and diabetes risk





Ethnicity, BMI and diabetes prevalence in UK Biobank

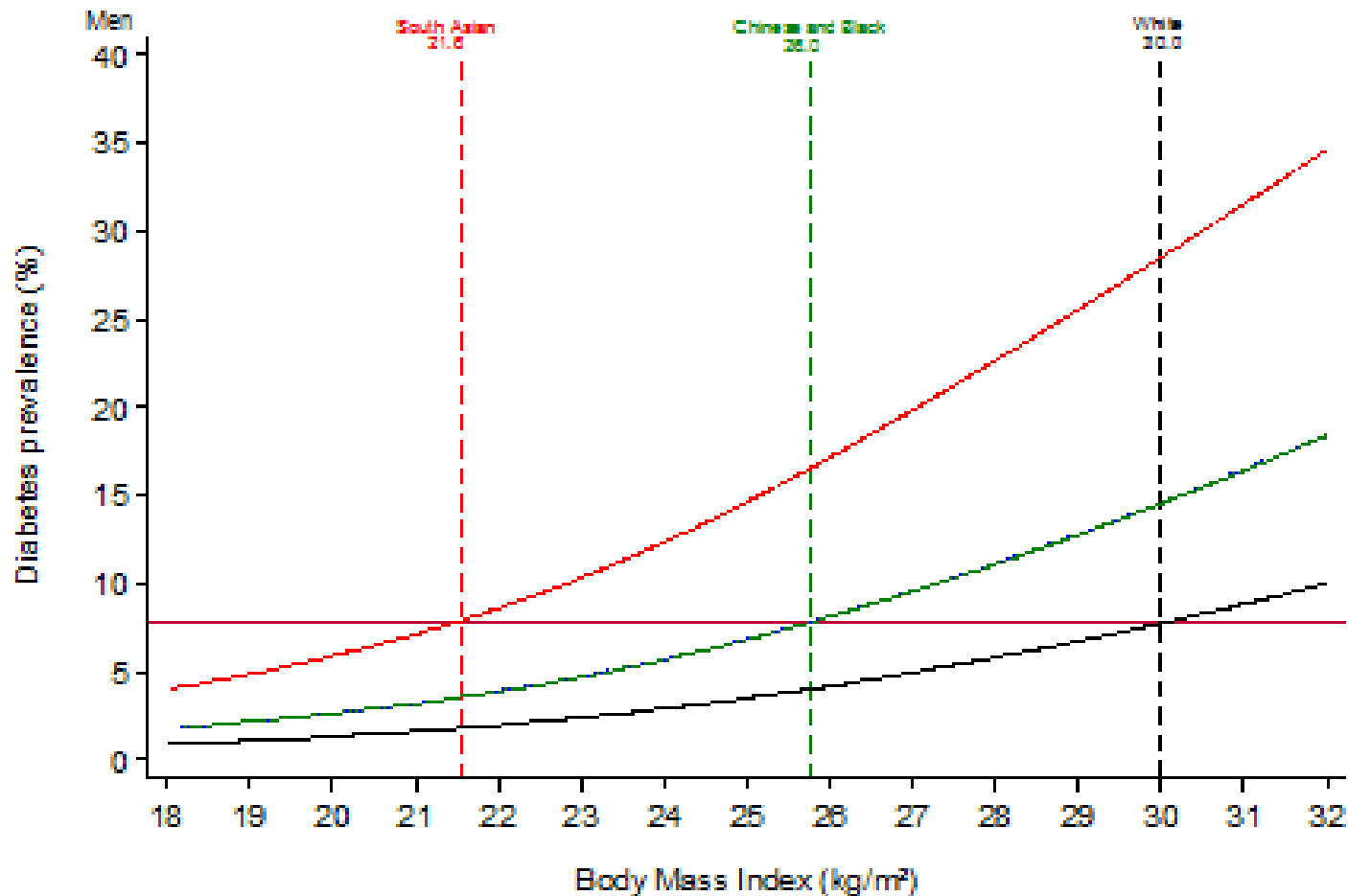
A



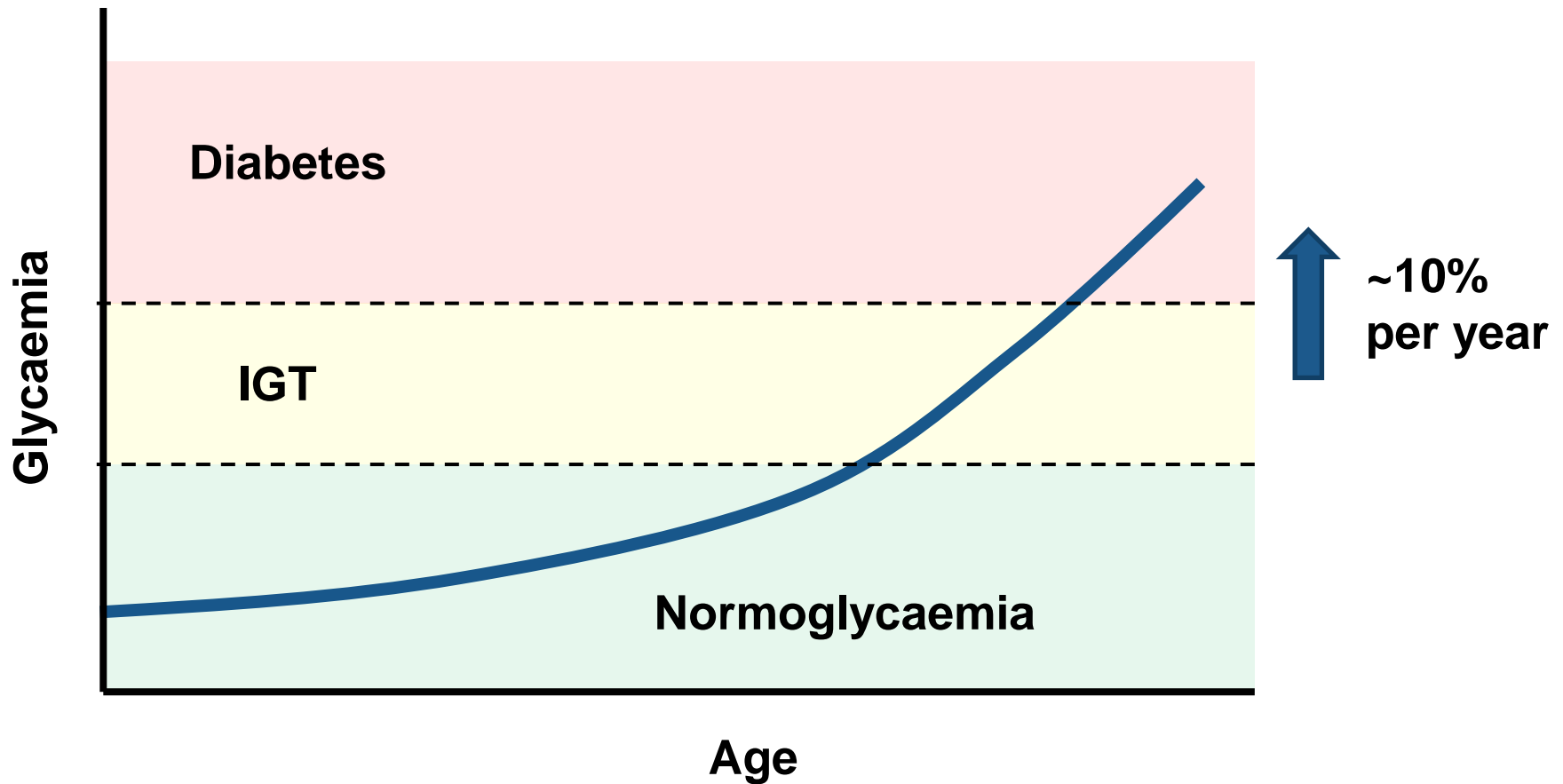


Ethnicity, BMI and diabetes prevalence in UK Biobank

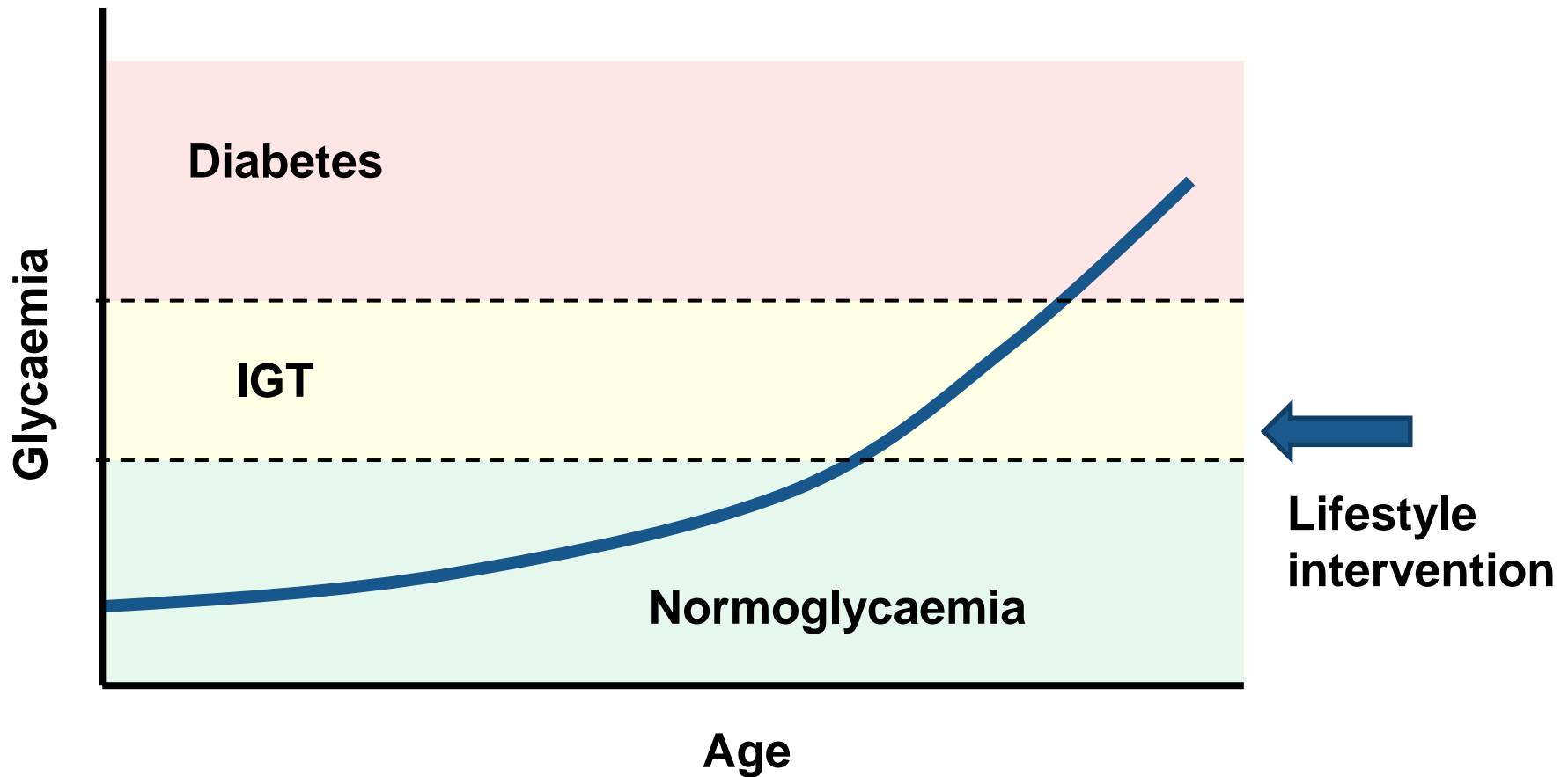
B



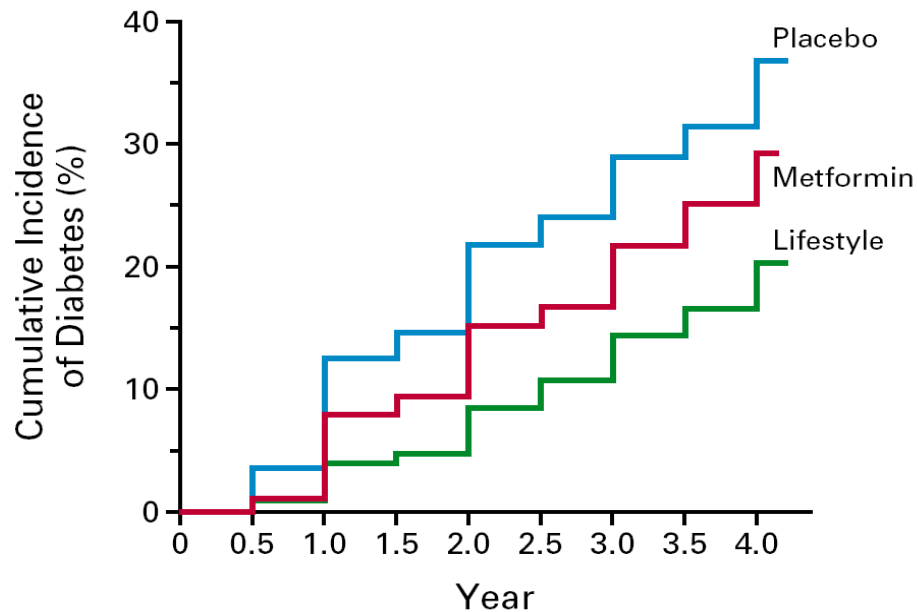
Diabetes risk progression



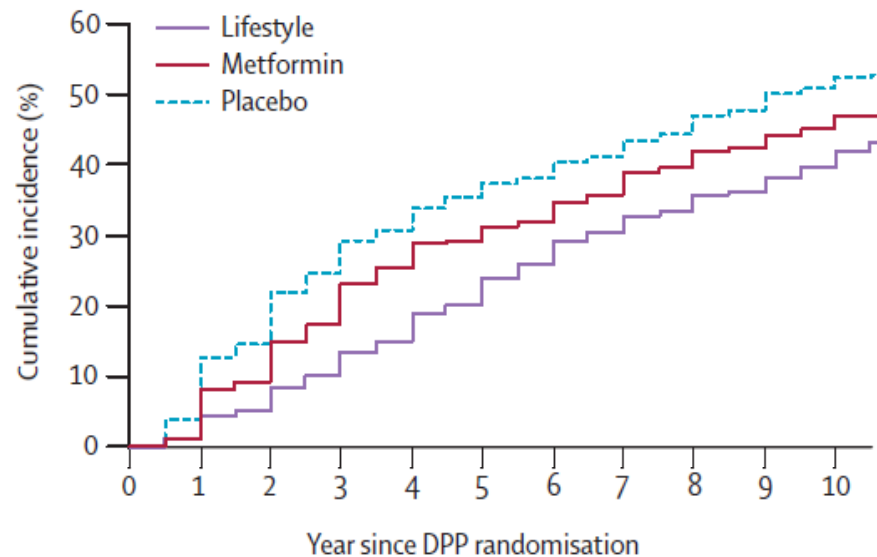
Diabetes risk progression



Long-term follow-up in US Diabetes Prevention Program



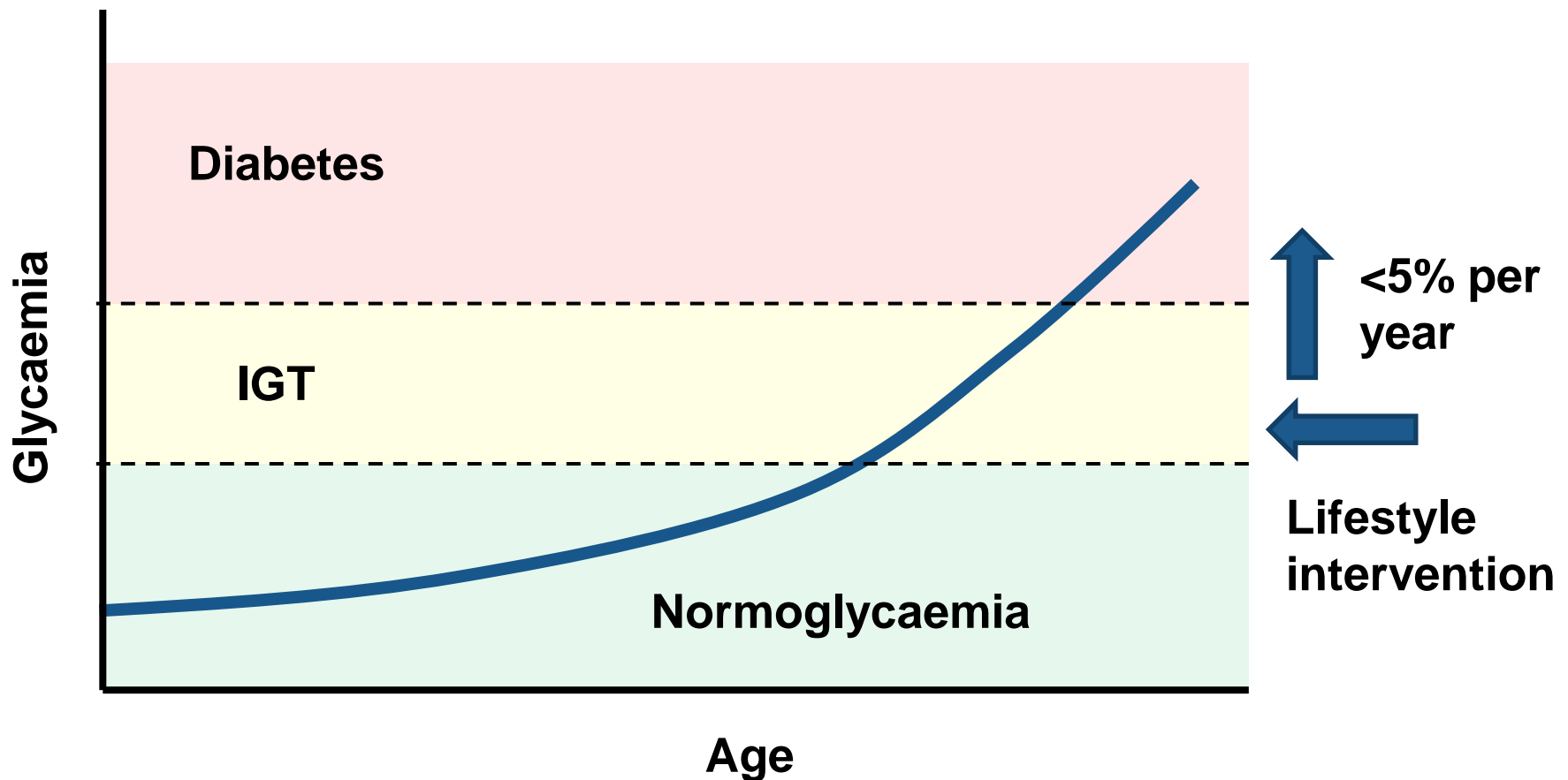
Knowler et al. NEJM 2002; 346:393-403



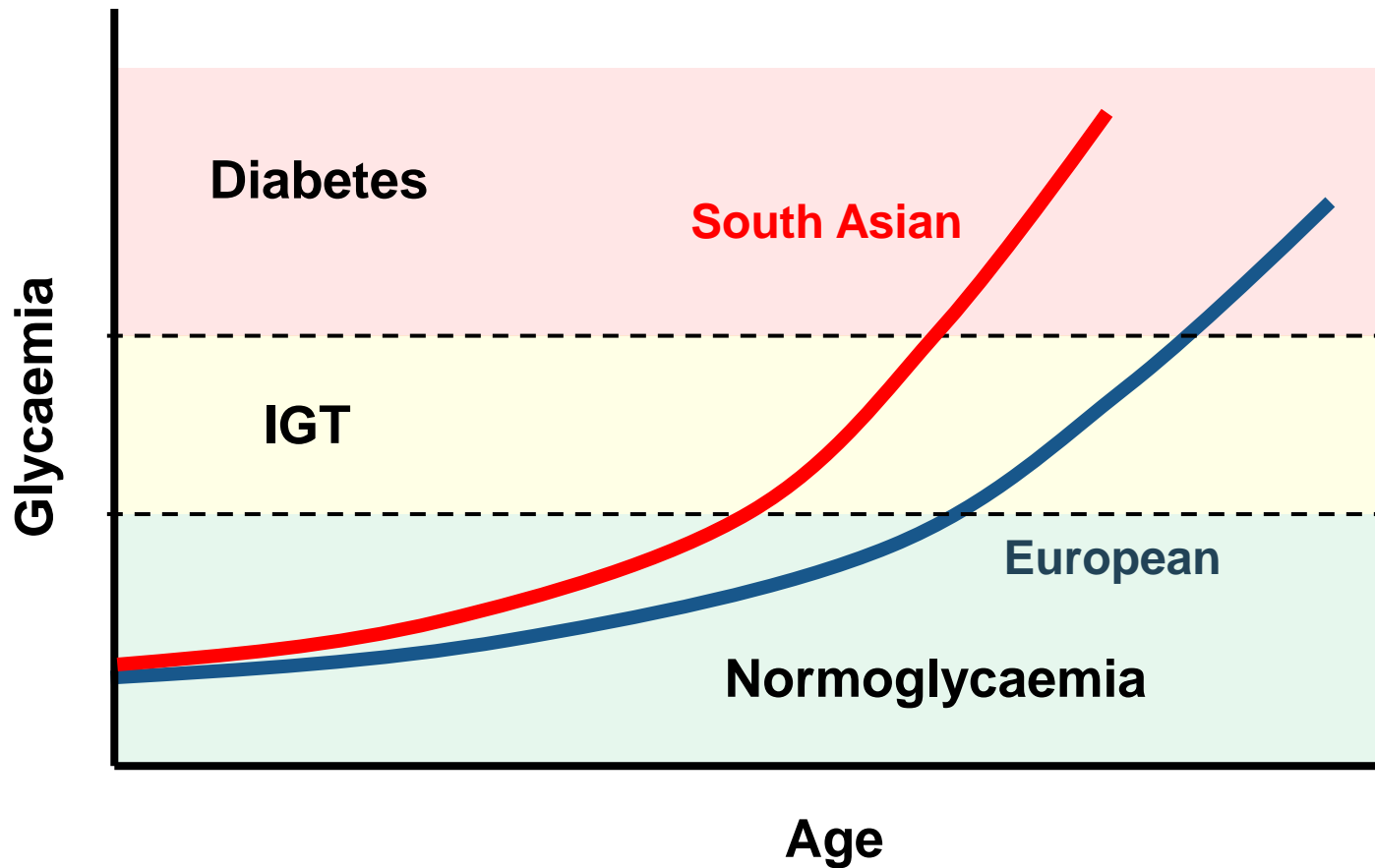
Knowler et al. Lancet 2009; 374:1677-86

Diabetes risk progression

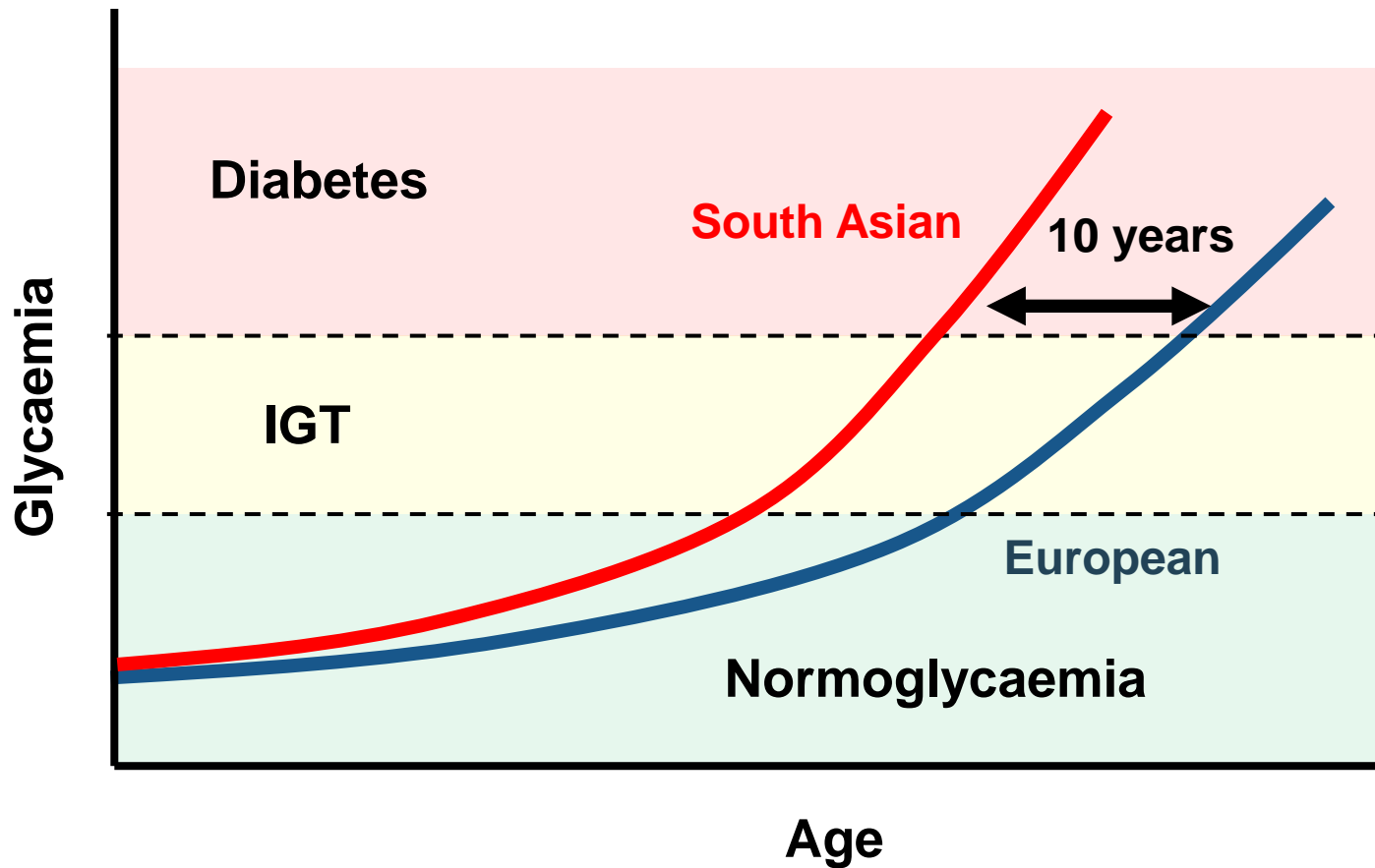
Lifestyle reduces absolute diabetes incidence by
~5-7 cases per 100 in patients with IGT



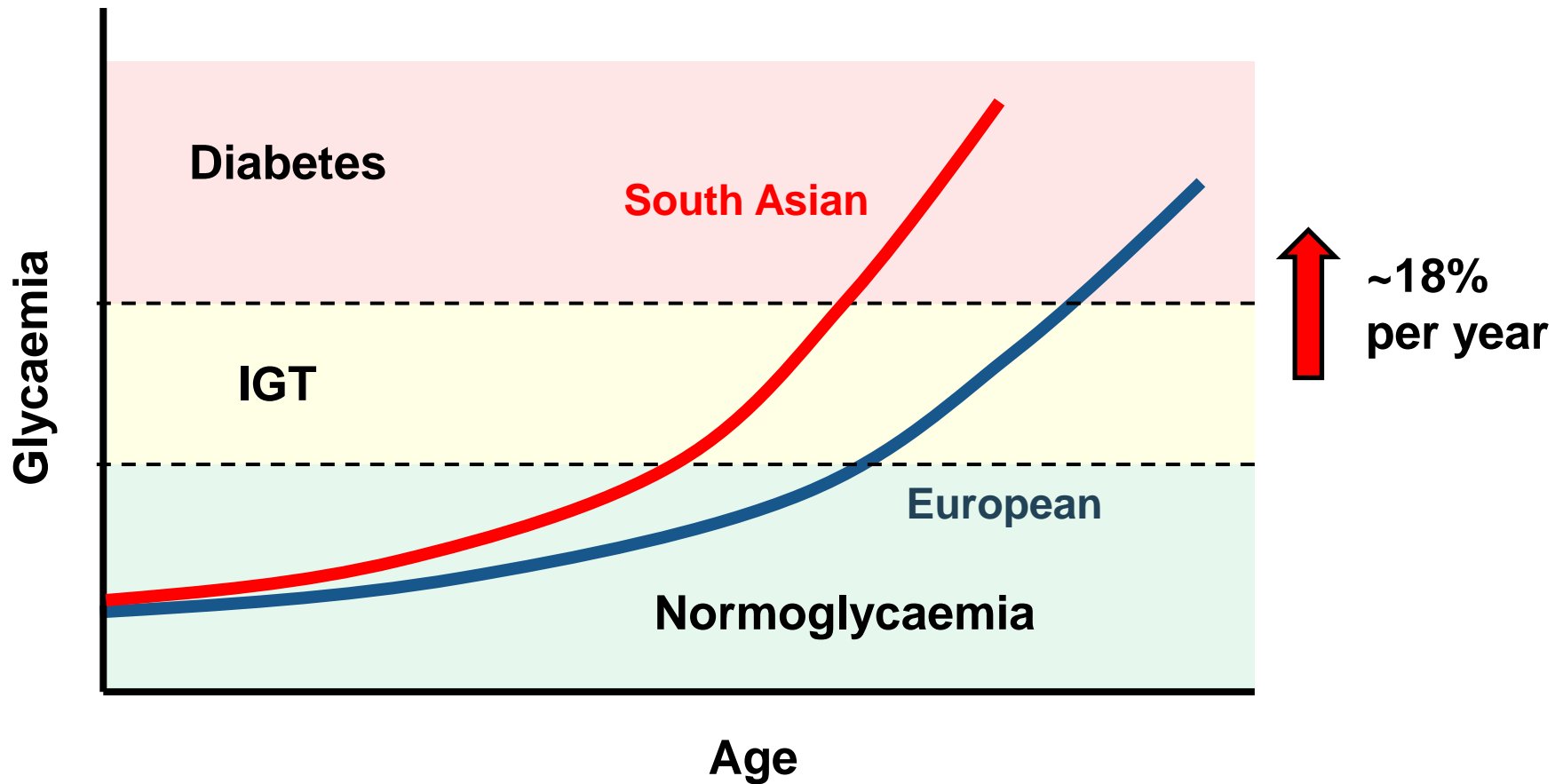
Diabetes risk progression



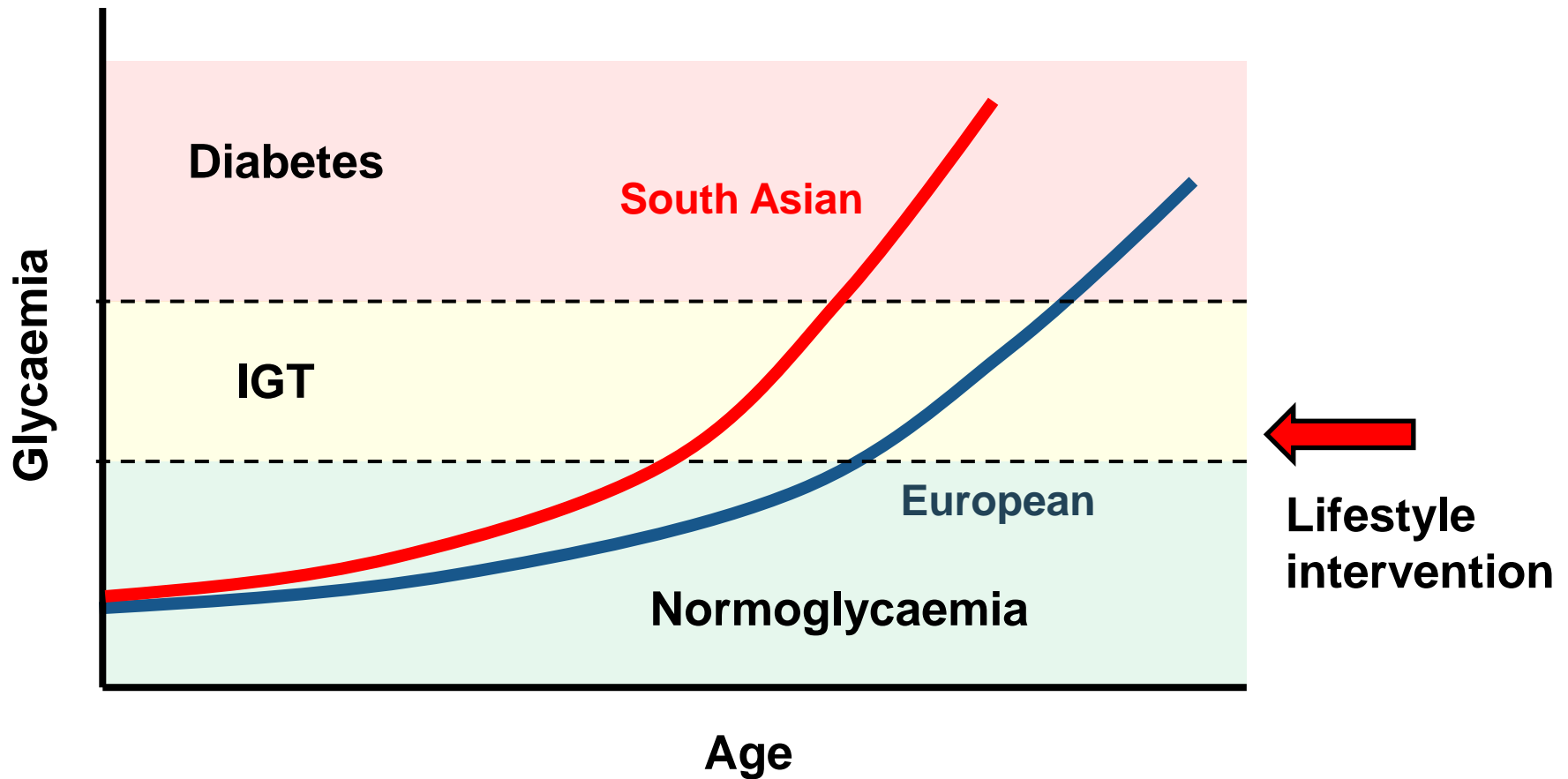
Diabetes risk progression



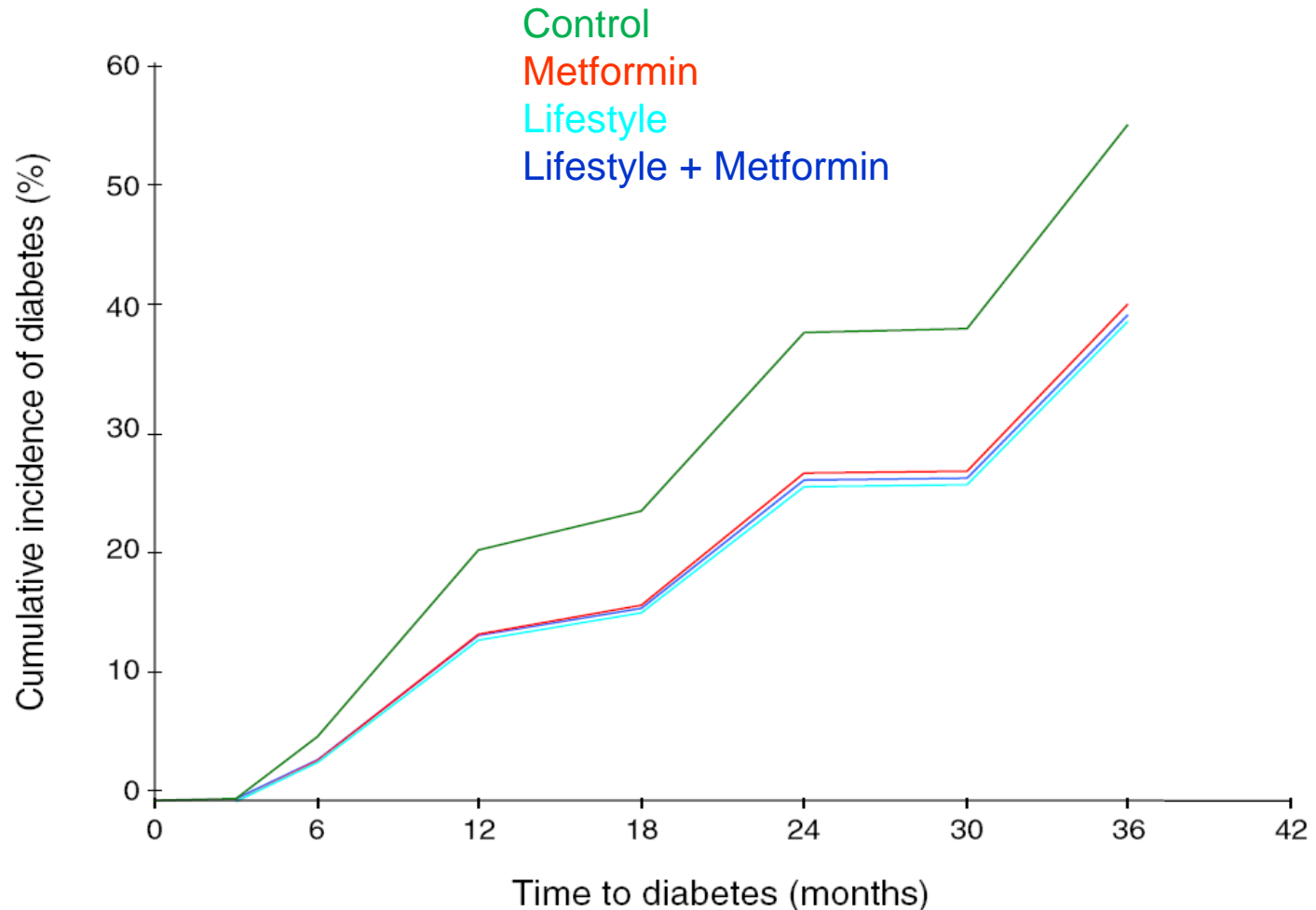
Diabetes risk progression



Diabetes risk progression

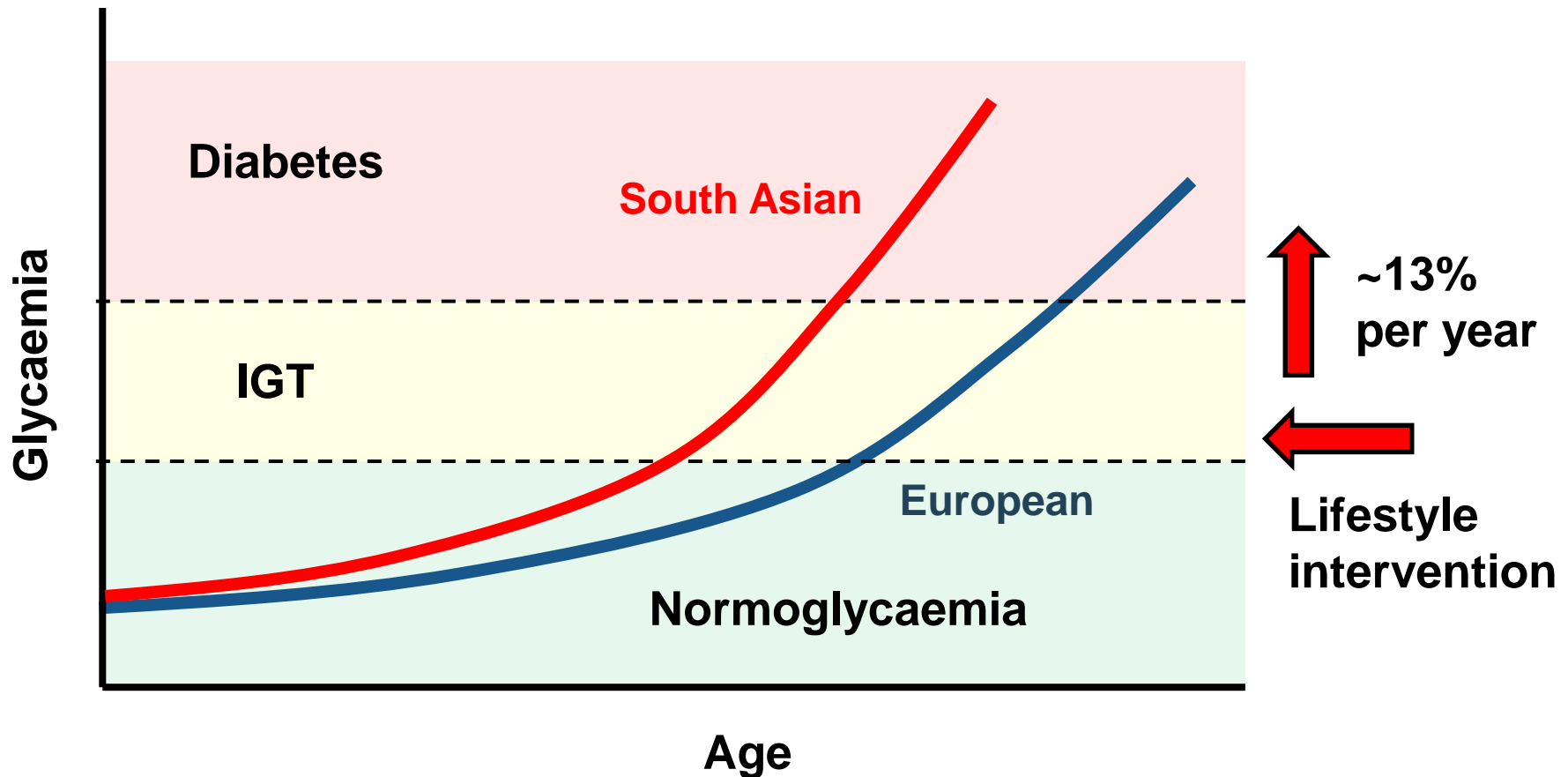


The Indian Diabetes Prevention Programme



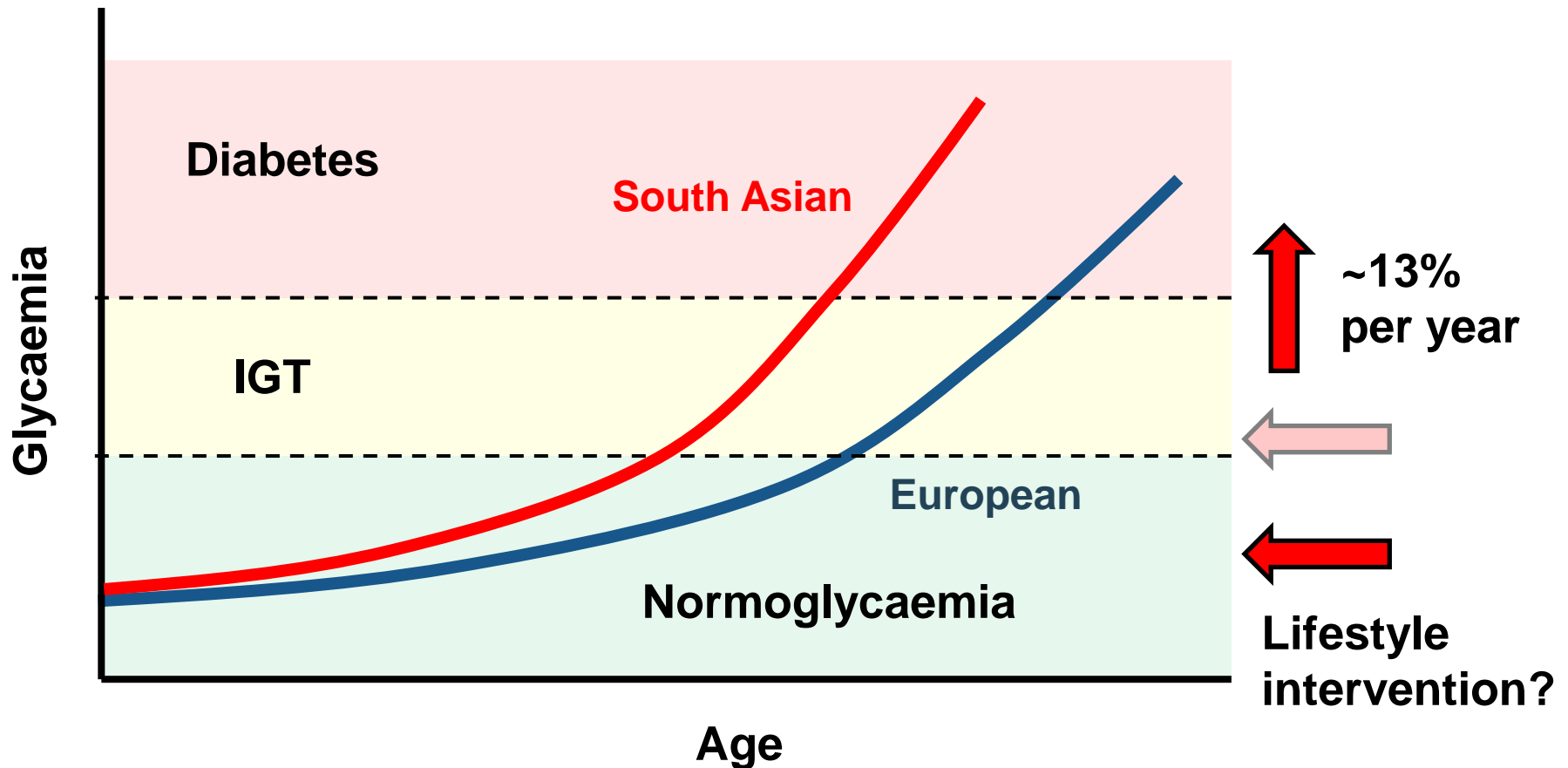
Diabetes risk progression

**Lifestyle reduces absolute diabetes incidence by
~5 cases per 100 in patients with IGT**

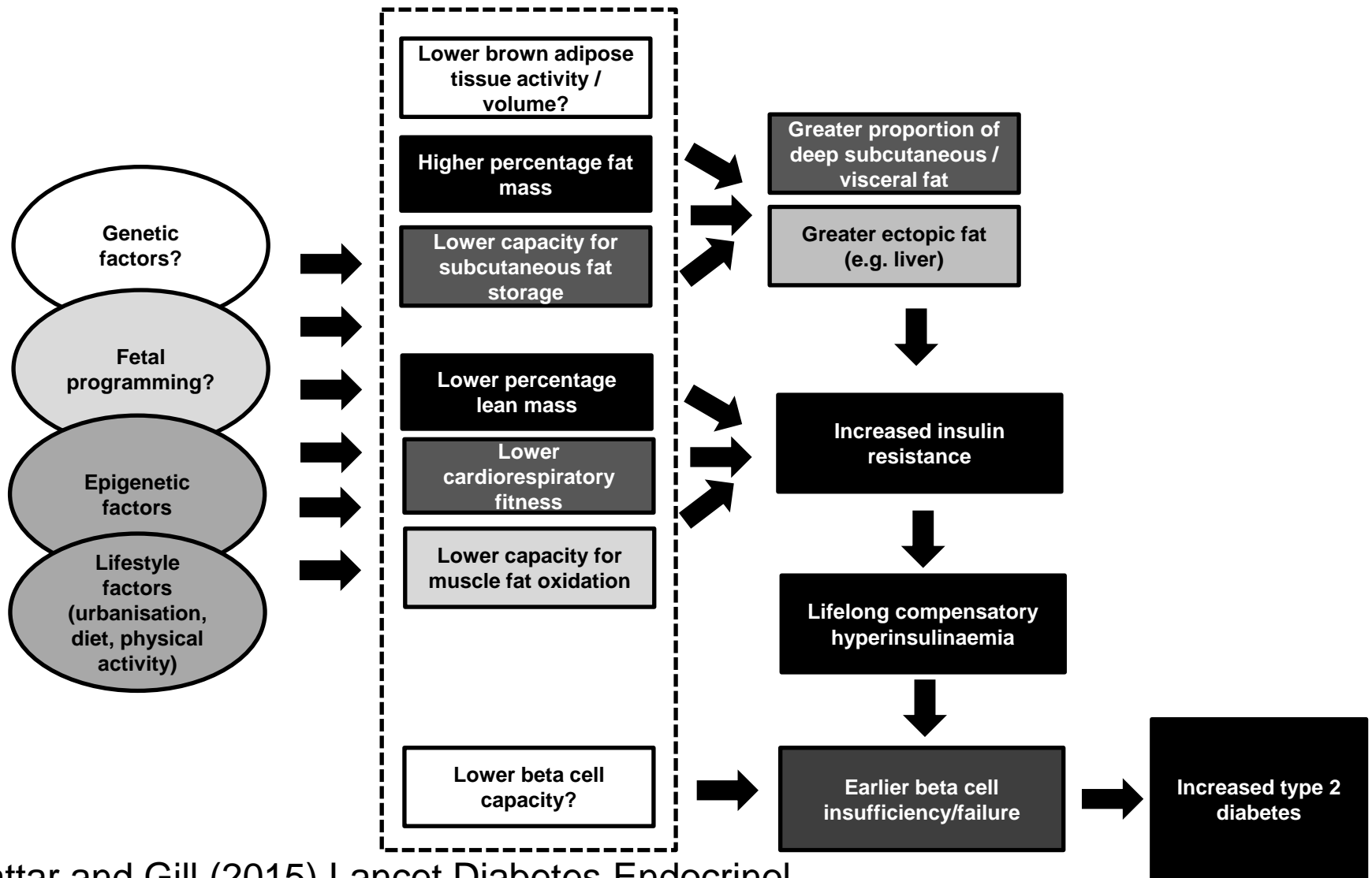


Diabetes risk progression

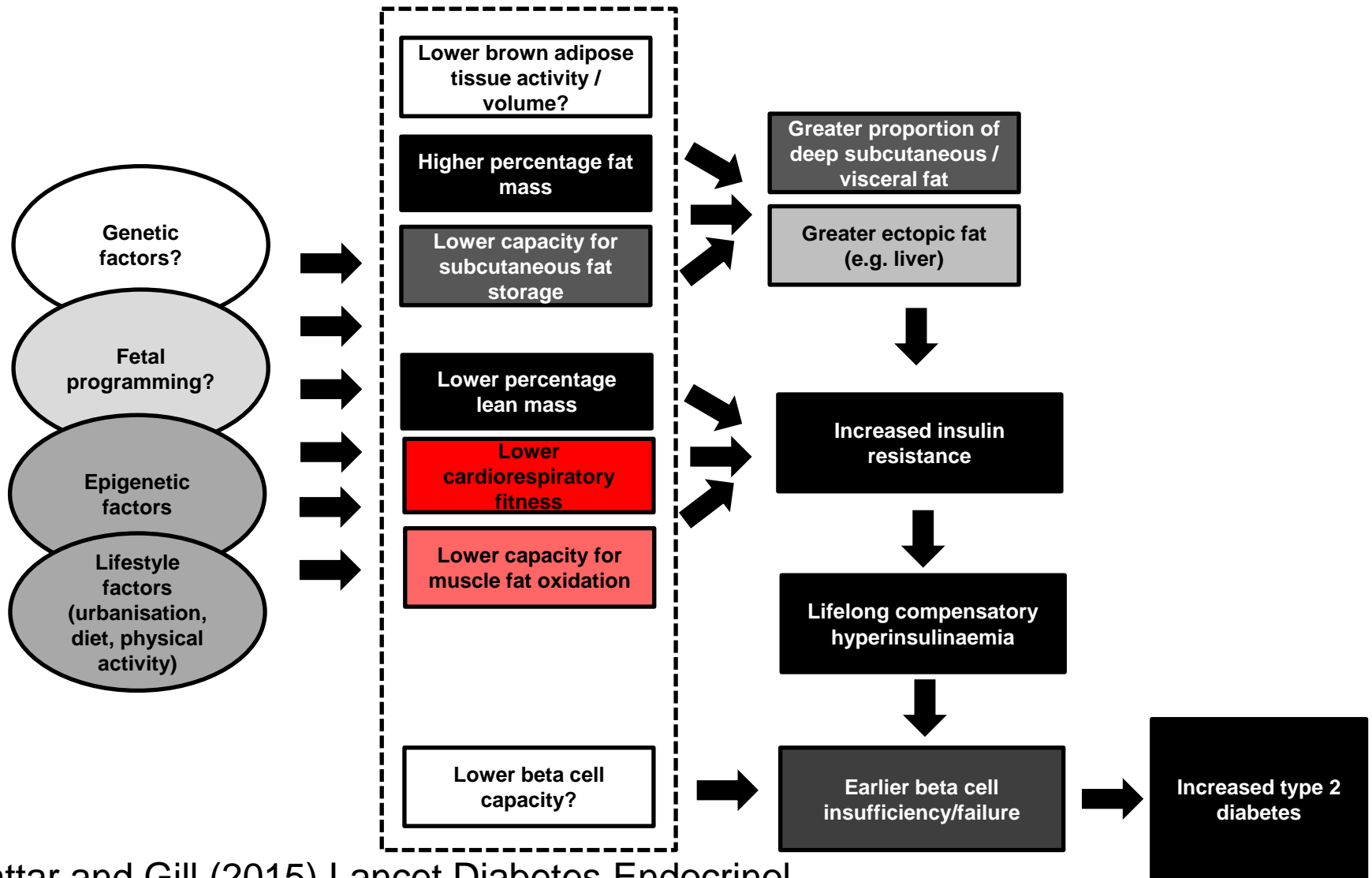
**BUT absolute progression rate still much higher.
Should we target South Asians for earlier intervention?**



Hypothesised mechanisms for South Asians' increased diabetes risk



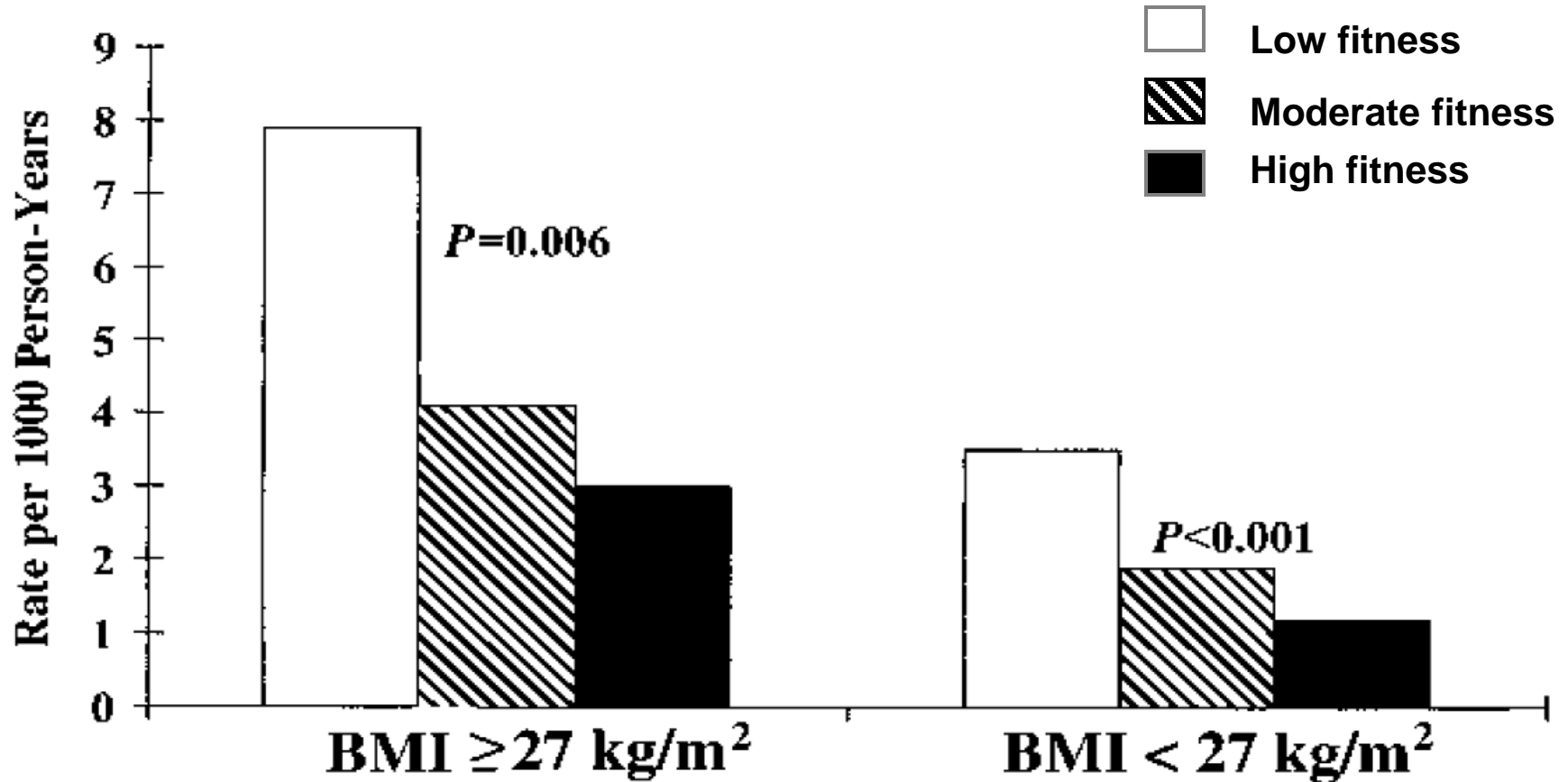
Hypothesised mechanisms for South Asians' increased diabetes risk



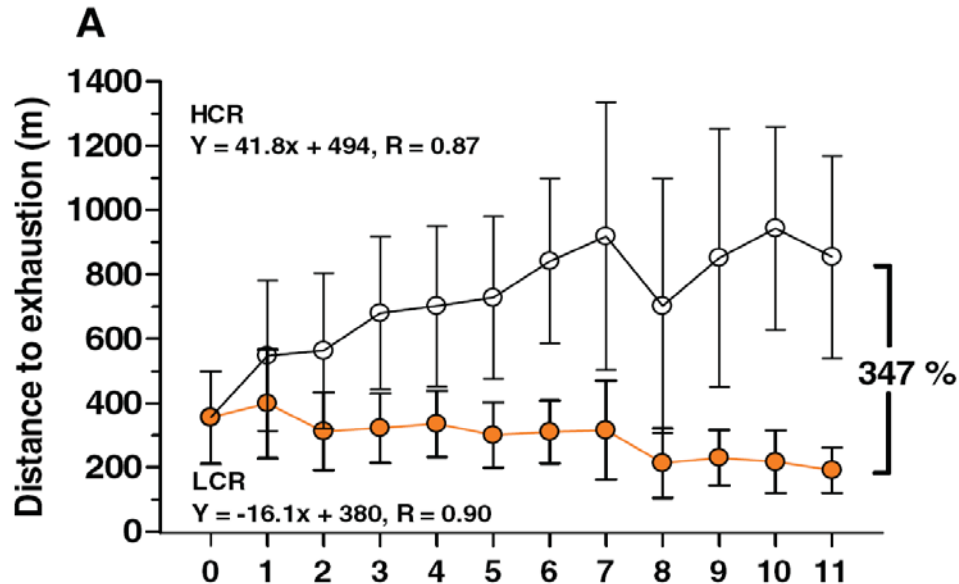
Adiposity, fitness and insulin resistance in South Asian and European men

	South Asians (n = 20)	Europeans (n = 19)	P (unadjusted)	P (adjusted for age, BMI and fat mass)
Age (years)	26.9 ± 3.9	24.5 ± 5.5	0.12	
BMI (kg.m ⁻²)	23.6 ± 2.9	22.6 ± 2.7	0.31	
Total fat mass (kg)	18.4 ± 5.3	13.6 ± 5.2	0.007	
VO₂max (ml.kg⁻¹.min⁻¹)	40.6 ± 6.6	52.4 ± 5.7	< 0.0005	0.001
VO₂max (ml.kg⁻¹ fat-free mass.min⁻¹)	54.1 ± 6.6	64.3 ± 5.8	< 0.0005	0.001
Fasting glucose (mmol.l ⁻¹)	5.14 ± 0.47	5.24 ± 0.52	0.53	0.94
Fasting insulin (mU.l⁻¹)	6.56 ± 3.53	5.39 ± 4.20	0.11	0.023
2 hour insulin (mU.l⁻¹)	46.6 ± 29.6	27.5 ± 5.3	0.017	0.043
Insulin sensitivity index	5.89 ± 2.93	7.96 ± 3.49	0.048	0.012

Fitness, BMI and risk of type 2 diabetes: The Aerobics Center Longitudinal Study



Artificial selection for fitness and insulin sensitivity



Breeding rats for low fitness makes them insulin resistant

	LCR	HCR	% Difference LCR vs. HCR	<i>P</i> value
Random glucose (mg/dl)	86 ± 6	75 ± 12	15%	0.036
Fasting glucose (mg/dl)	110 ± 9	92 ± 5	20%	0.0007
Insulin (pM)	684 ± 195	296 ± 172	131%	0.002
C-peptide (pM)	1590 ± 938	1077 ± 565	48%	0.061
C-peptide/insulin	2.4 ± 0.4	3.8 ± 1.2	-58%	0.013
Visceral adiposity/body weight (%)	1.55 ± 0.39	0.95 ± 0.32	63%	0.005
Triglycerides (mg/dl)	67 ± 24	25 ± 4	168%	0.013
Free fatty acids (meq/l)	0.64 ± 0.22	0.33 ± 0.04	94%	0.031

Does lower fitness in South Asians simply reflect lower physical activity levels?

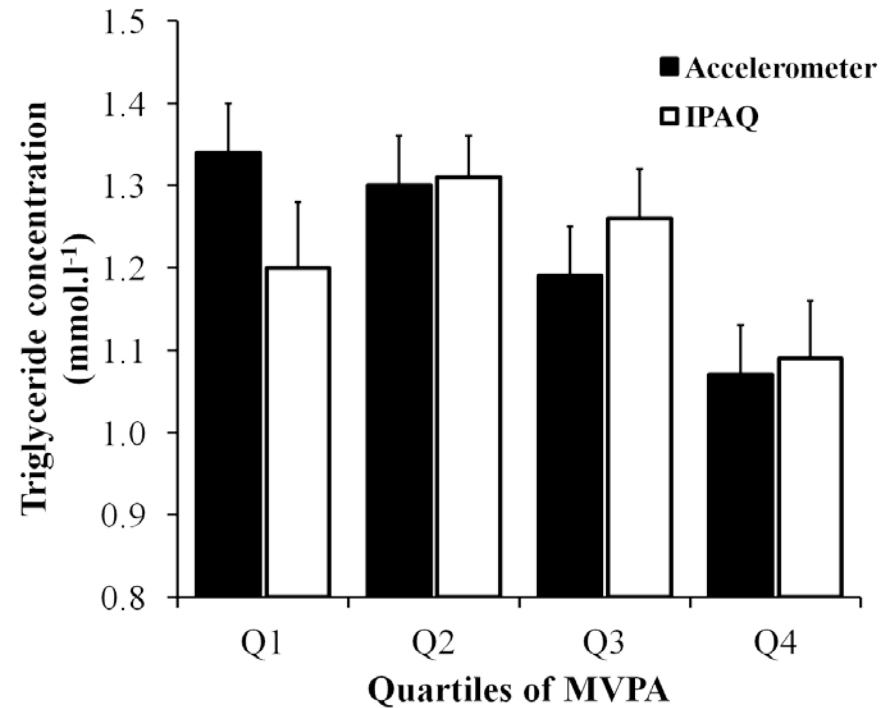
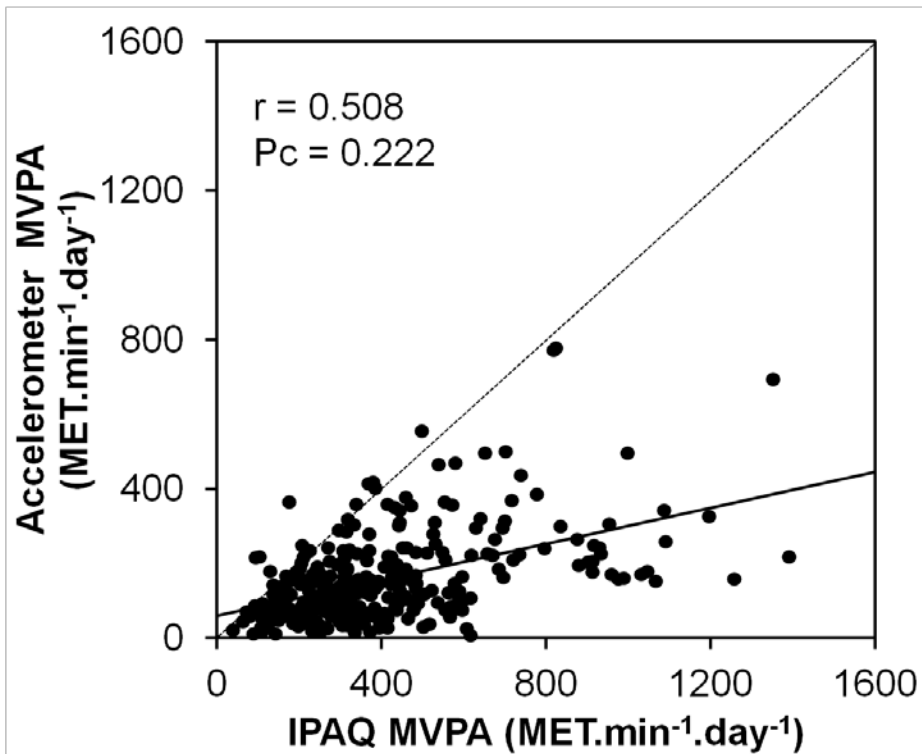
How physically active are South Asians in the United Kingdom? A literature review

C. M. Fischbacher, S. Hunt and L. Alexander

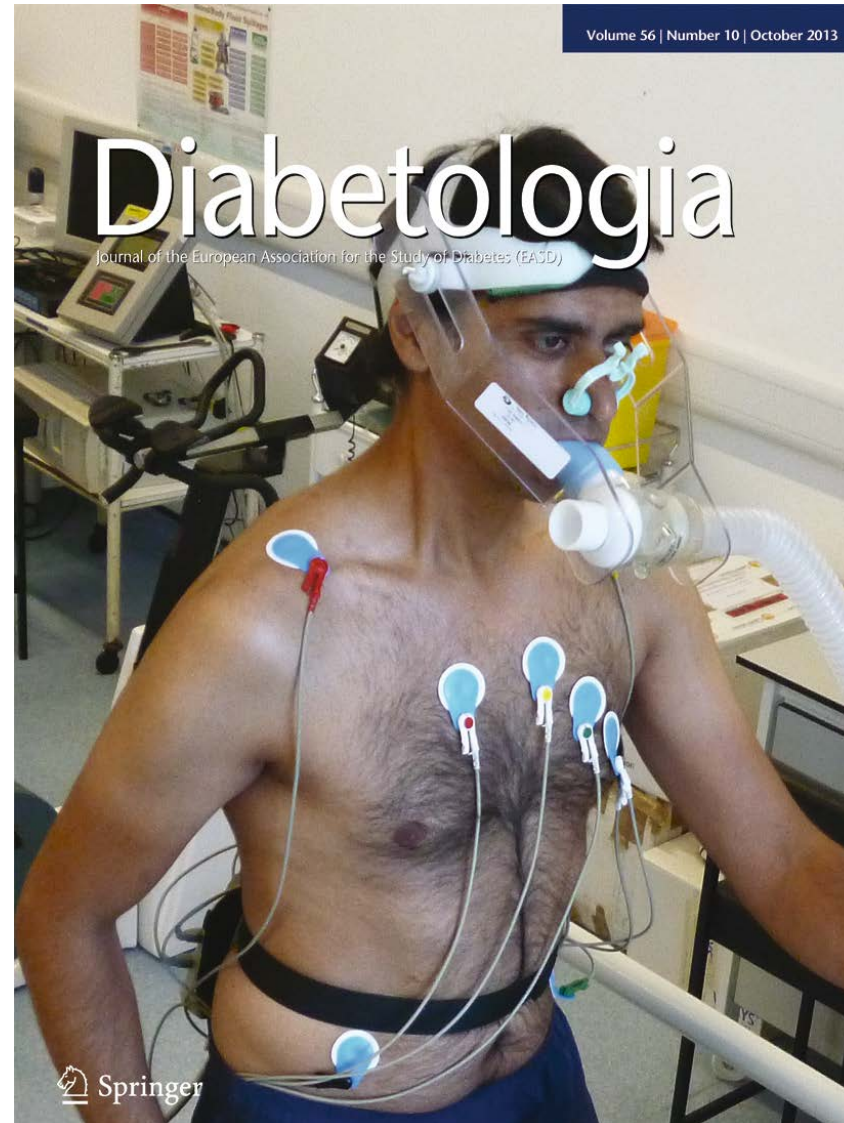
Results We identified 12 studies in adults and five in children. Various methods were used to assess physical activity and fitness, but all the studies reported lower levels among South Asian groups. The differences were substantial, particularly among women and older people. For example, the Health Survey for England found that Indian, Pakistani and Bangladeshi men were 14, 30 and 45 per cent less likely than the general population to meet current guidelines for physical activity. Limited information was provided about translation and adaptation of questionnaires.

Conclusions Levels of physical activity were lower in all South Asian groups than the general population and patterns of activity differed. No studies used validated measures. Insufficient attention has been paid to issues of cross-cultural equivalence. With these caveats, low levels of physical activity among UK South Asian ethnic groups may contribute to their increased risk of diabetes and CHD. Closer attention to validity, translation and adaptation is necessary to monitor changes and assess the effectiveness of interventions to increase physical activity.

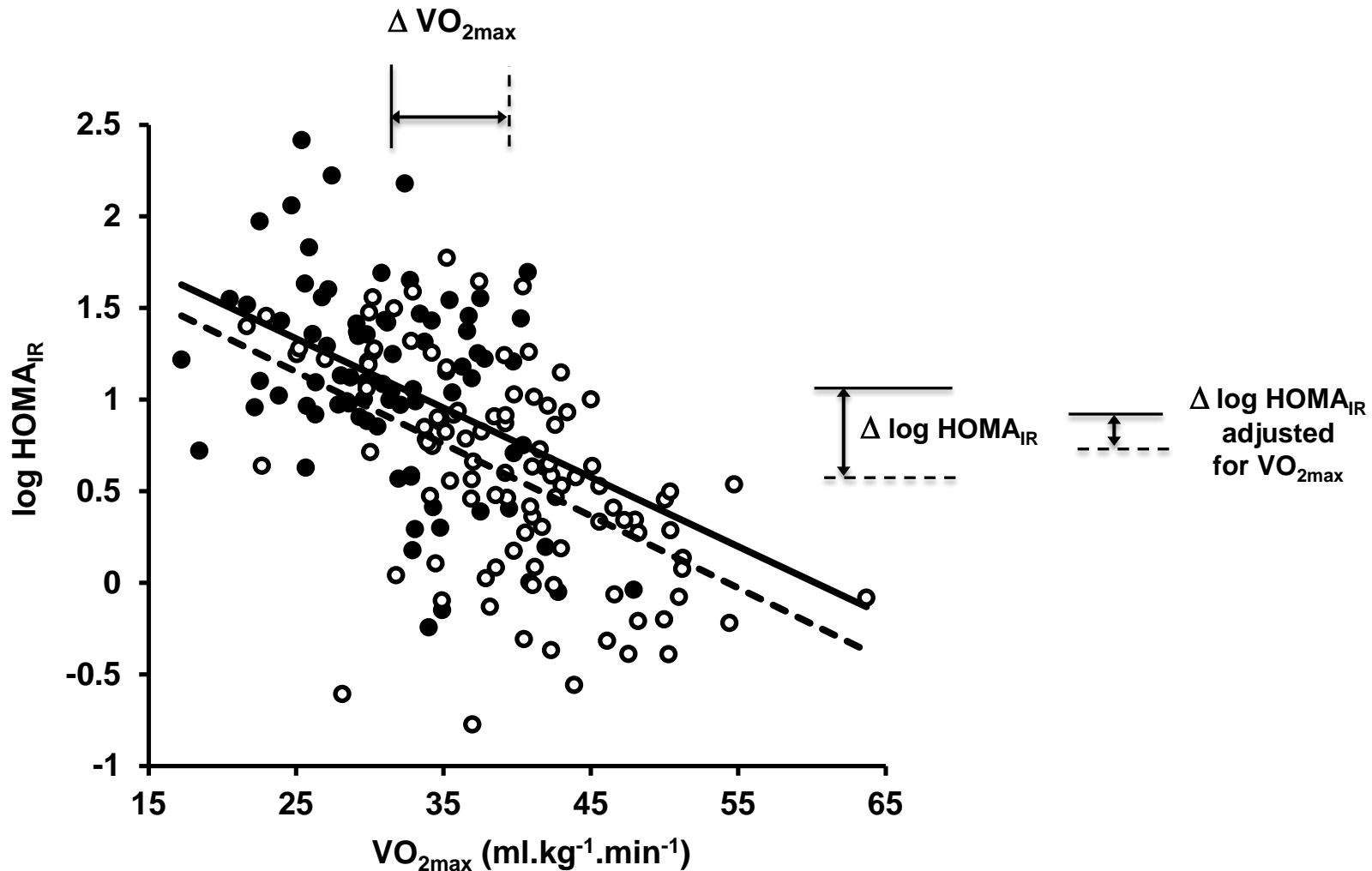
Self-reported vs objective physical activity measurement



Can lower fitness explain increased insulin resistance in South Asians?

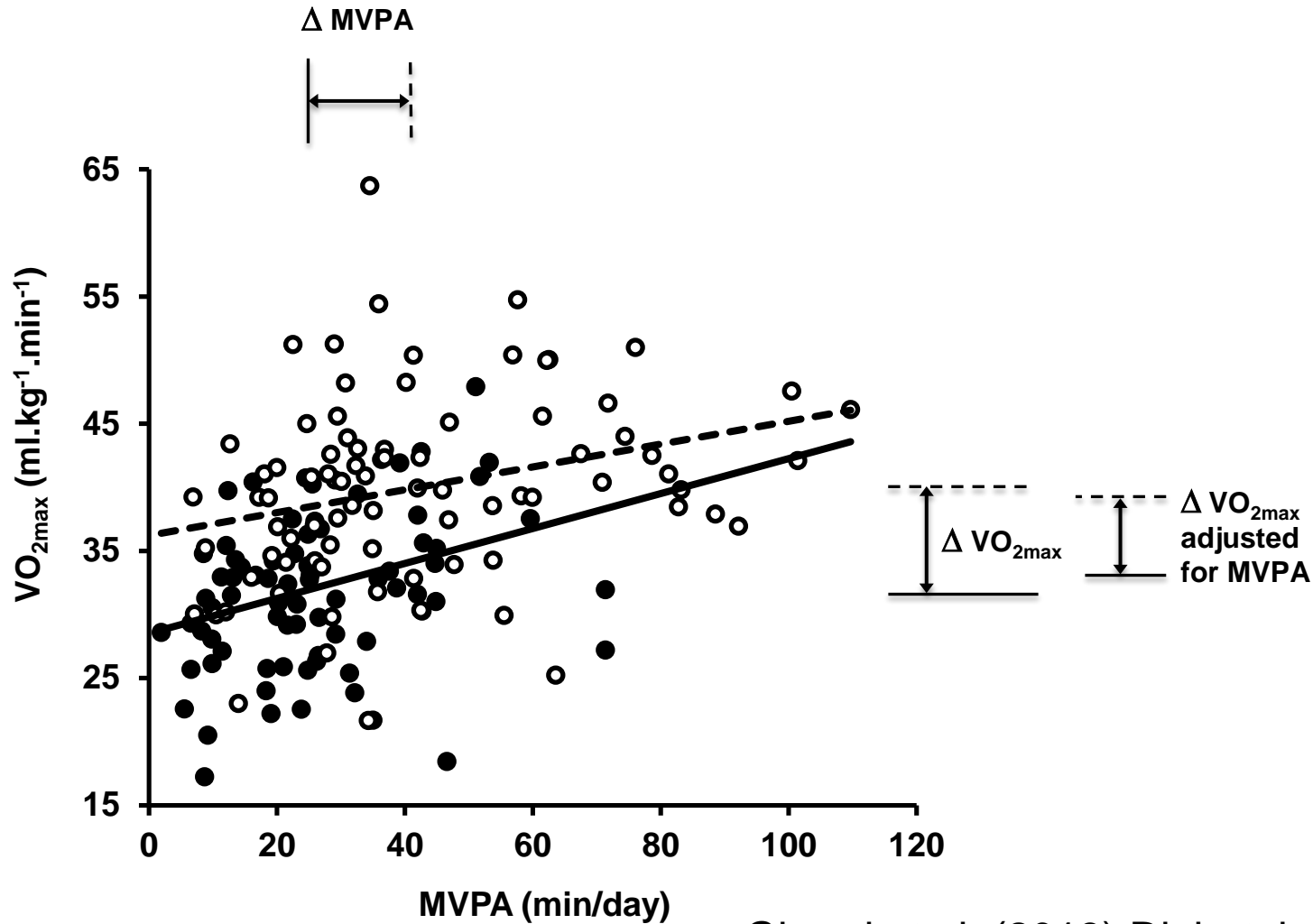


Relationship between fitness and HOMA in European and South Asian men

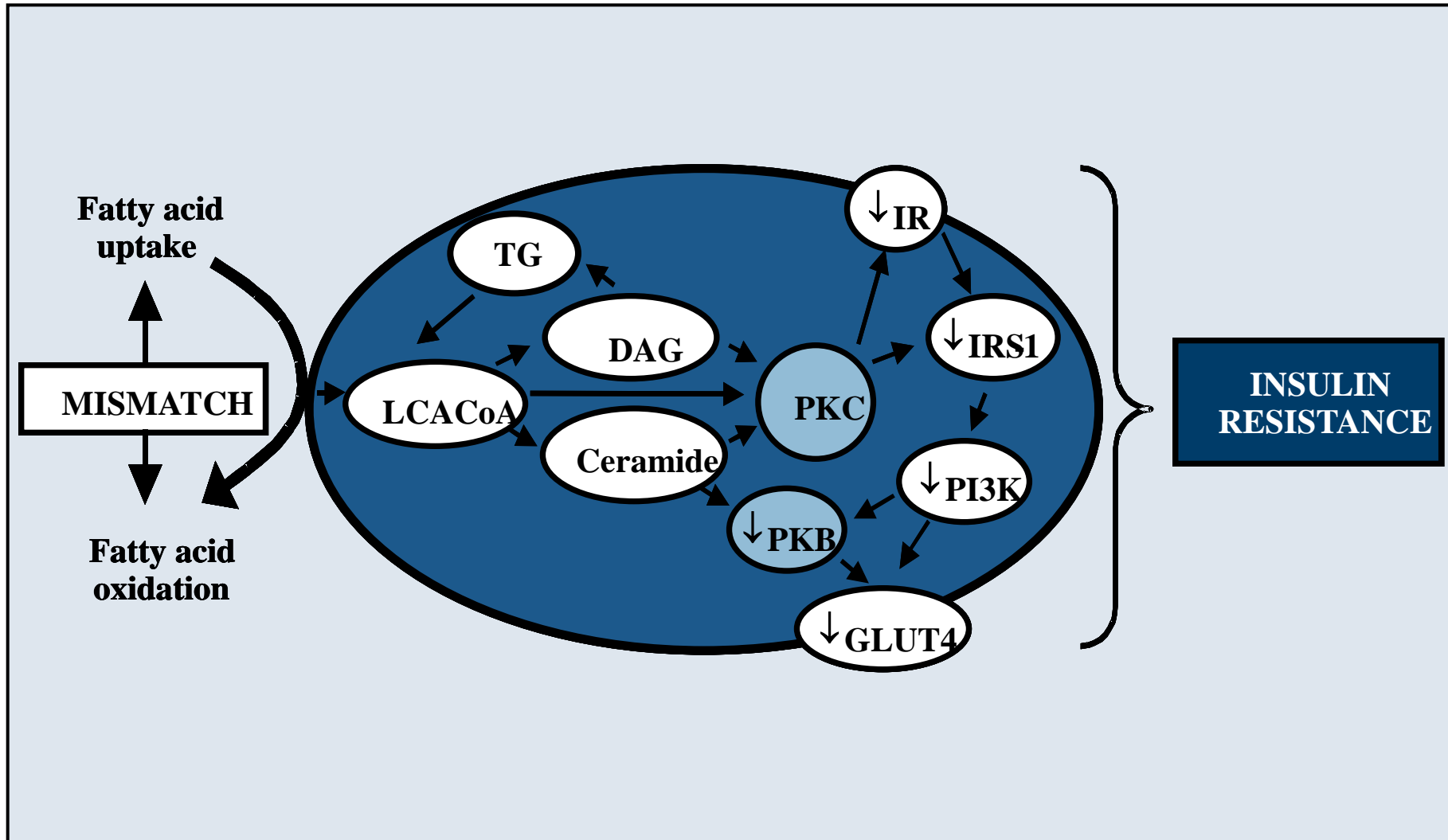




Relationship between fitness and physical activity in European and South Asian men



Impaired skeletal muscle oxidative capacity as a mechanism for greater insulin resistance in South Asians?





University
of Glasgow

Fat oxidation during submaximal exercise in South Asian and European men

South Asian man

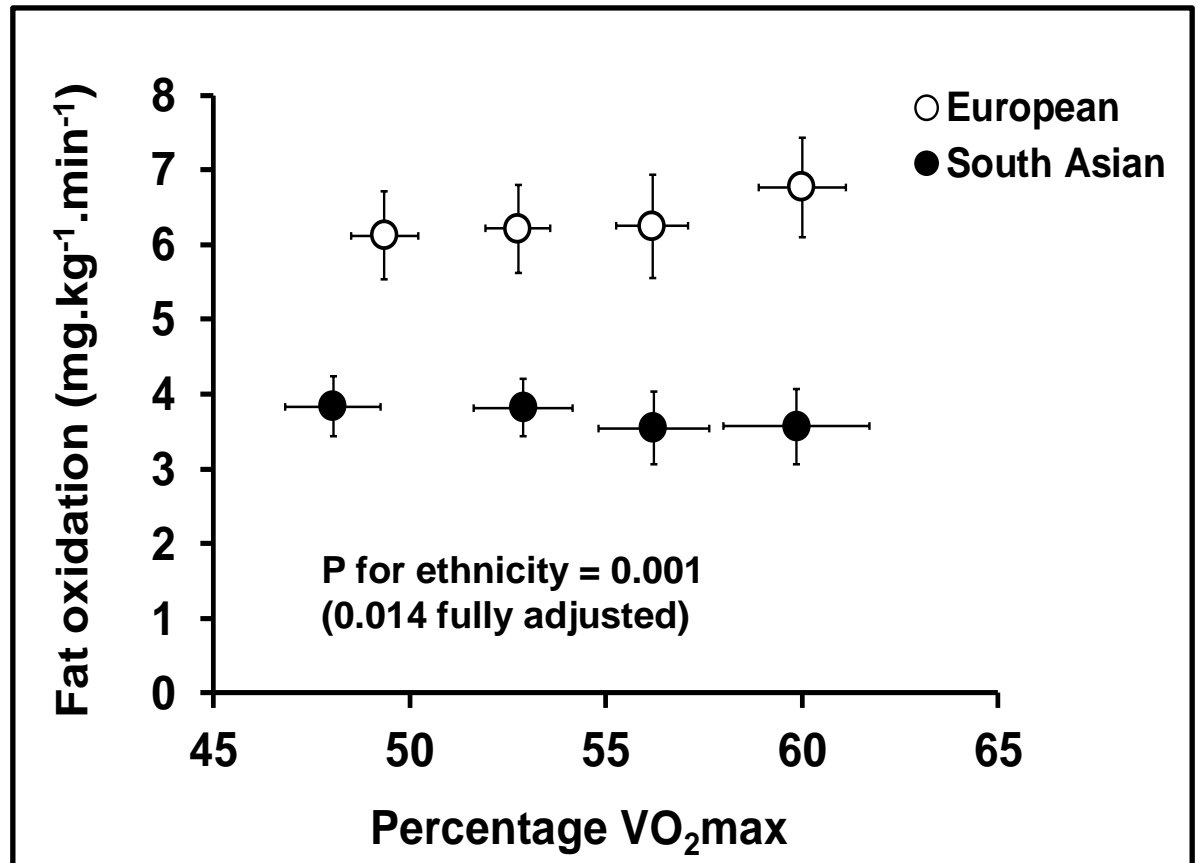
European man



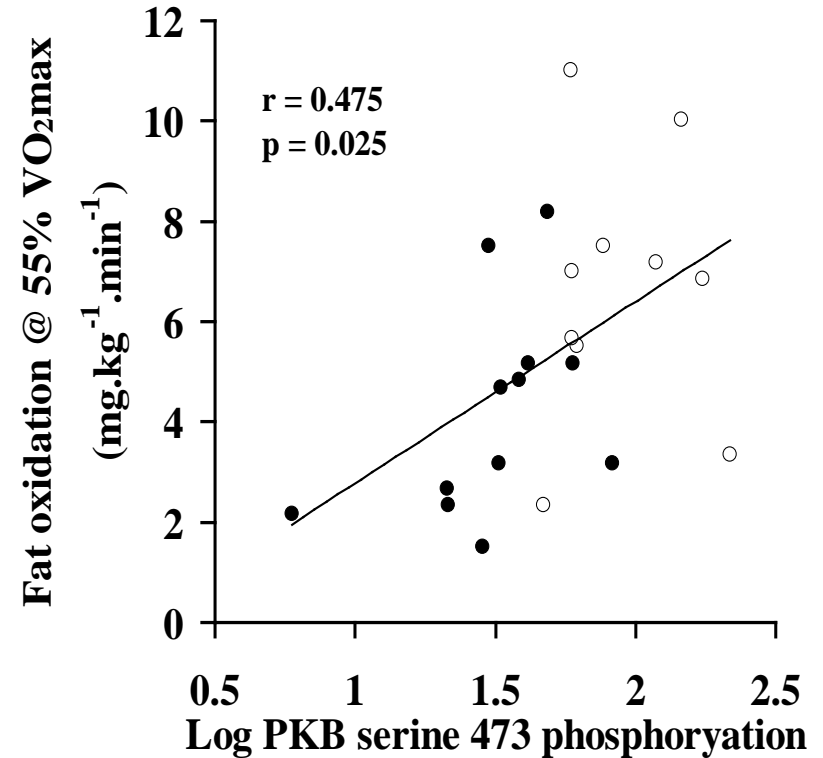
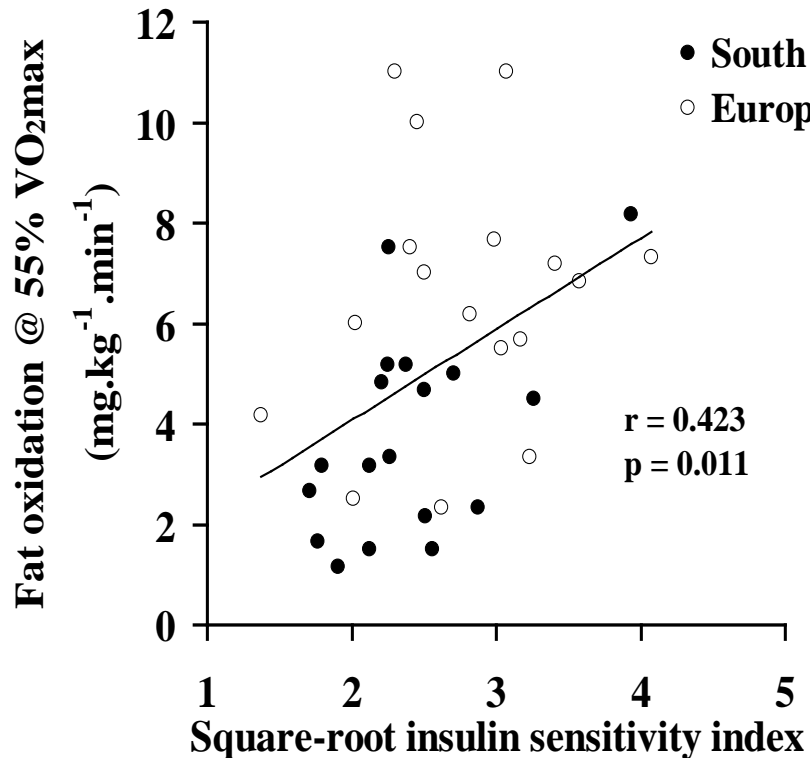
Fat oxidation during submaximal exercise in South Asian and European men

South Asian man

European man



Substrate utilisation during exercise and insulin sensitivity in South Asian and European men



Do we need ethnicity-specific public health guidelines to reflect innate ethnic differences in disease risk?

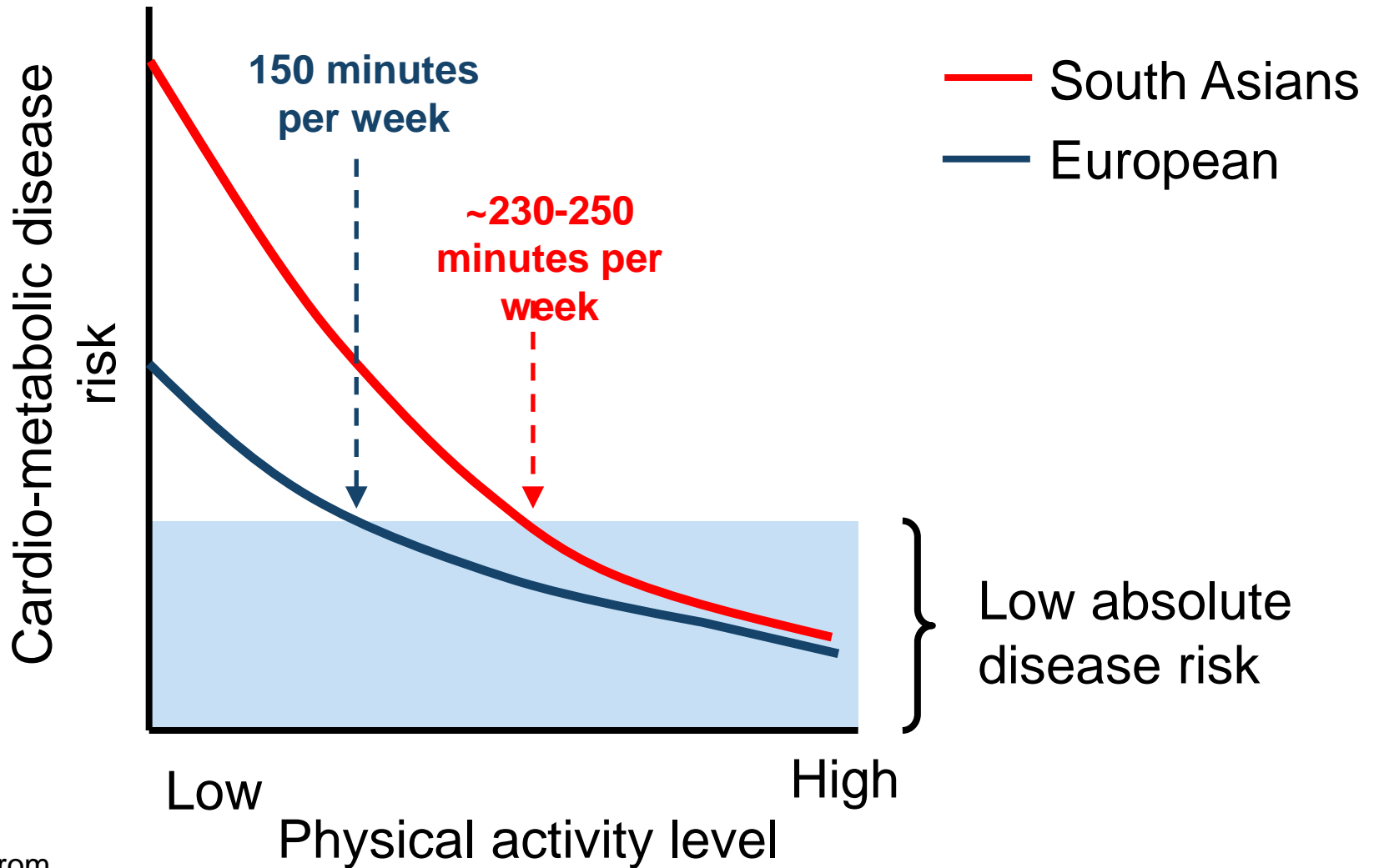
A brief history of physical activity guidelines (for adults)



2011

- **150 minutes of moderate or 75 minutes of vigorous physical activity per week in bouts of at least 10 minutes**
- **Muscle strengthening activities 2 x per week**
- **Minimise the amount of time spent sedentary (sitting)**

Ethnicity and physical activity



Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3)

JBS3 Board

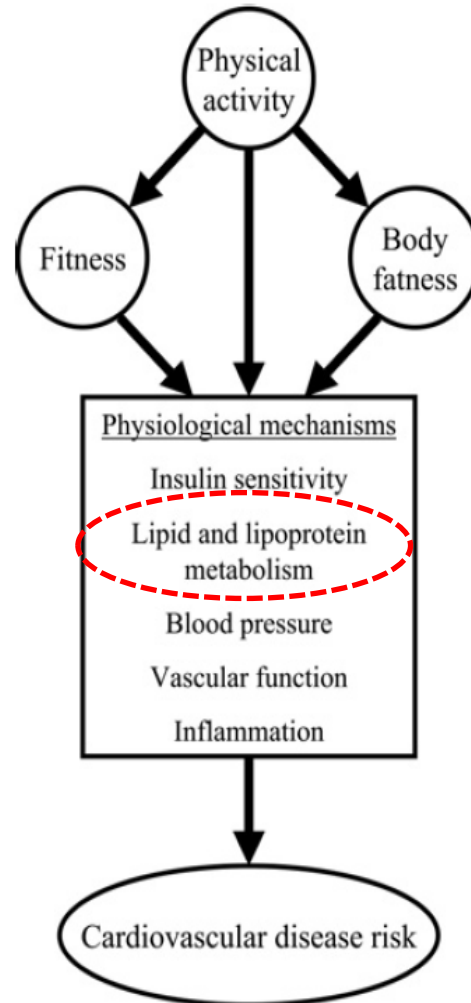
There is recent evidence that certain ethnic groups (eg, South Asian men) may benefit from higher levels of physical activity to improve CVD risk profiles.¹⁶⁶

- 166 Celis-Morales CA, Ghouri N, Bailey ME, *et al.* Should physical activity recommendations be ethnicity-specific? Evidence from a cross-sectional study of South Asian and European men. *PLoS ONE* 2013;8:e82568.

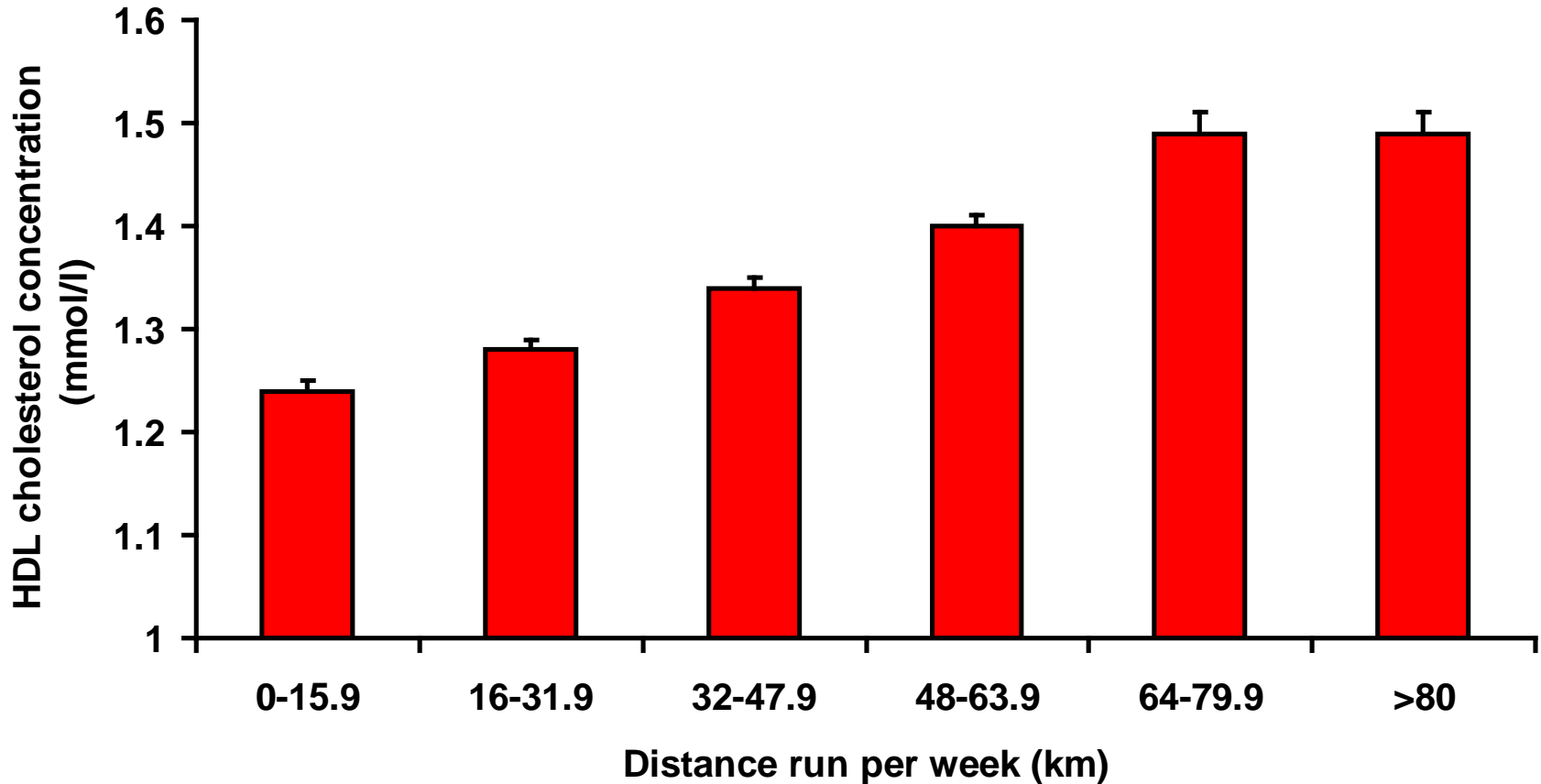
Physical activity and postprandial lipoprotein metabolism



Mechanisms behind protective effect of physical activity



HDL cholesterol in runners



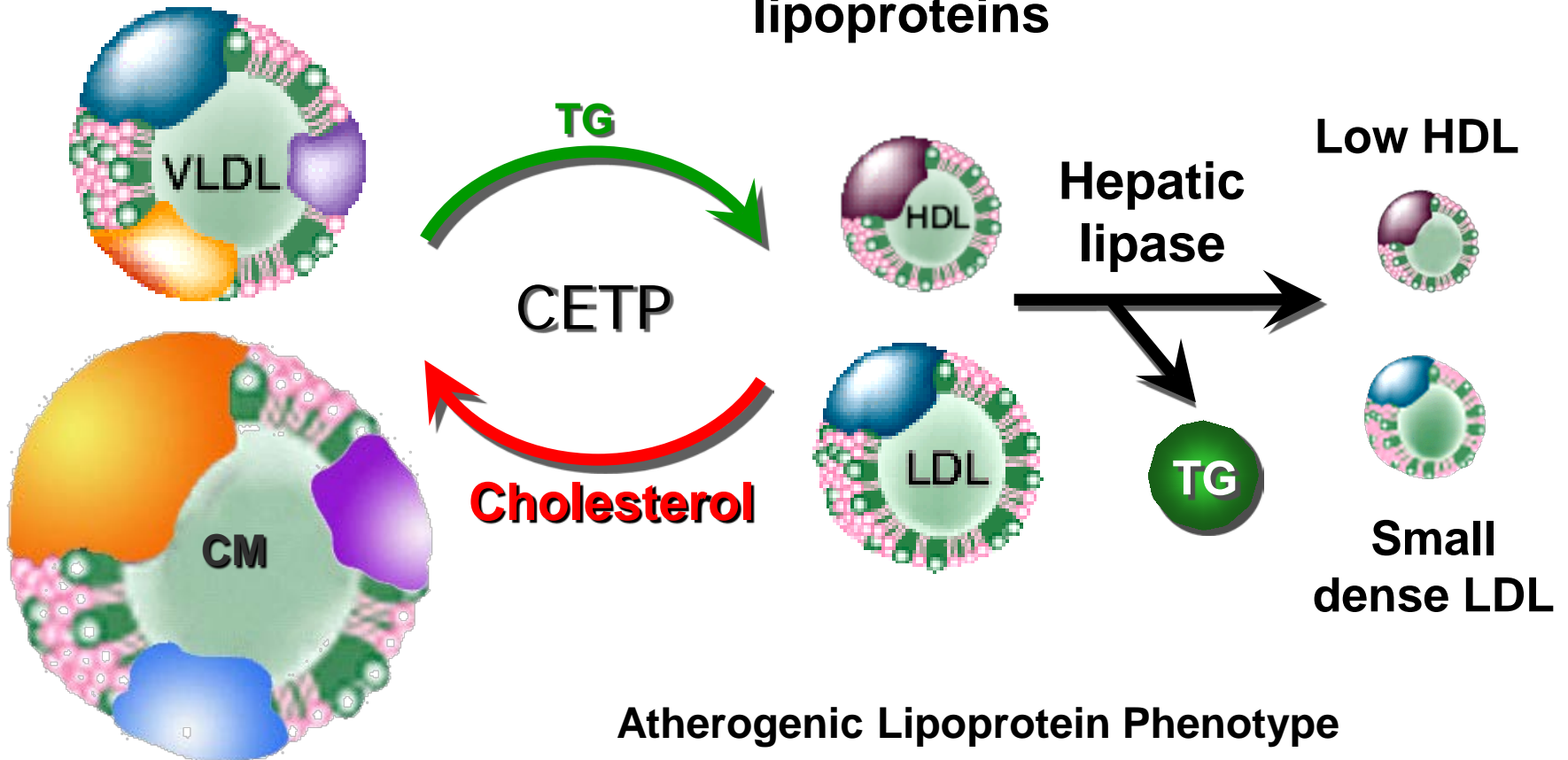
N = 8283 men

Williams (1997), Arch Intern Med, 157:191-198

Neutral Lipid Exchange

Triglyceride-rich
lipoproteins

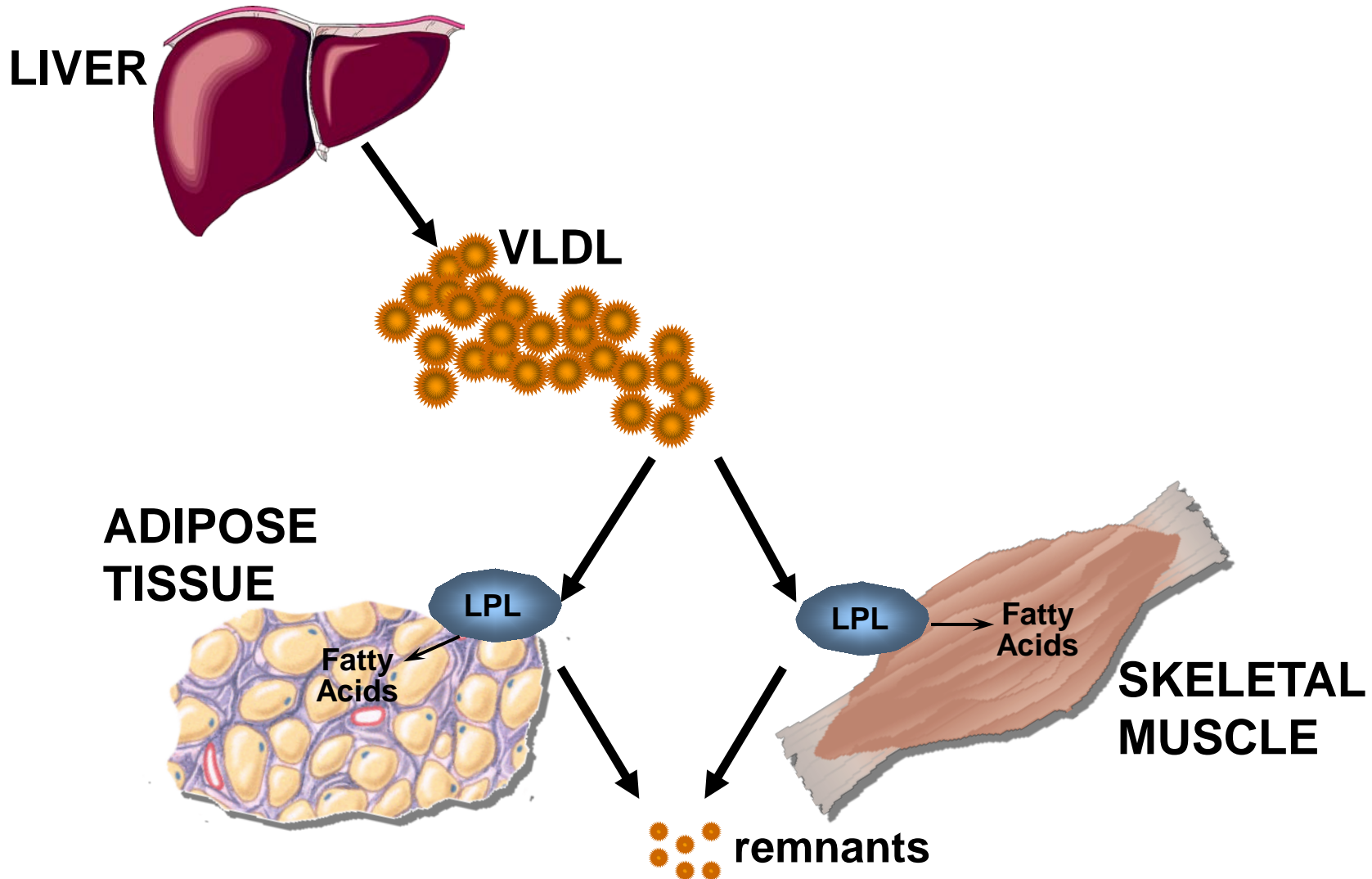
Cholesterol-rich
lipoproteins



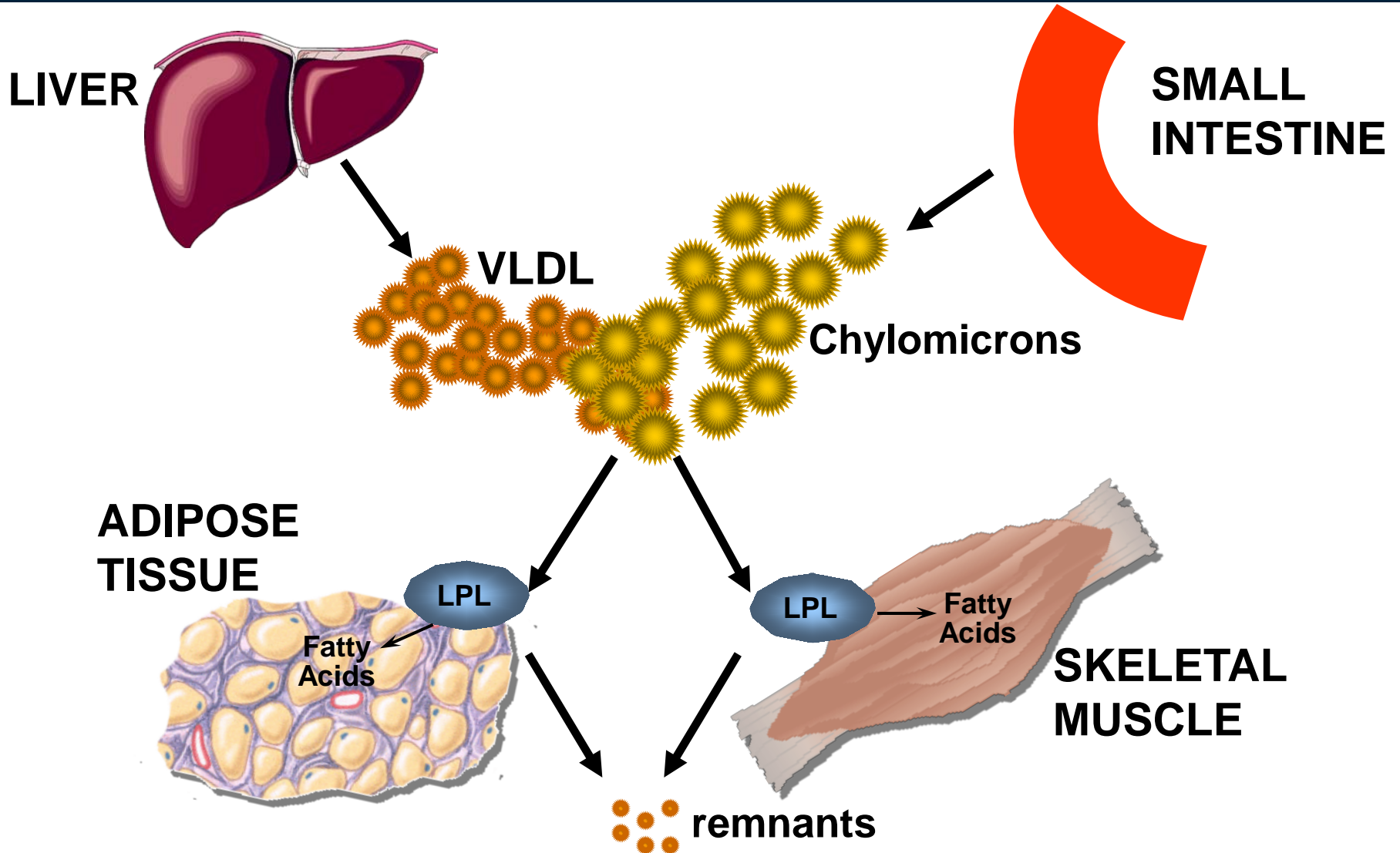


- Postprandial lipoproteins and their remnants may directly deposit into the arterial wall
- High postprandial triglyceride concentrations contribute to the ‘atherogenic lipoprotein phenotype’
- Endothelial function is impaired following ingestion of a high fat meal
- Pro-thrombotic and pro-inflammatory changes are evident postprandially

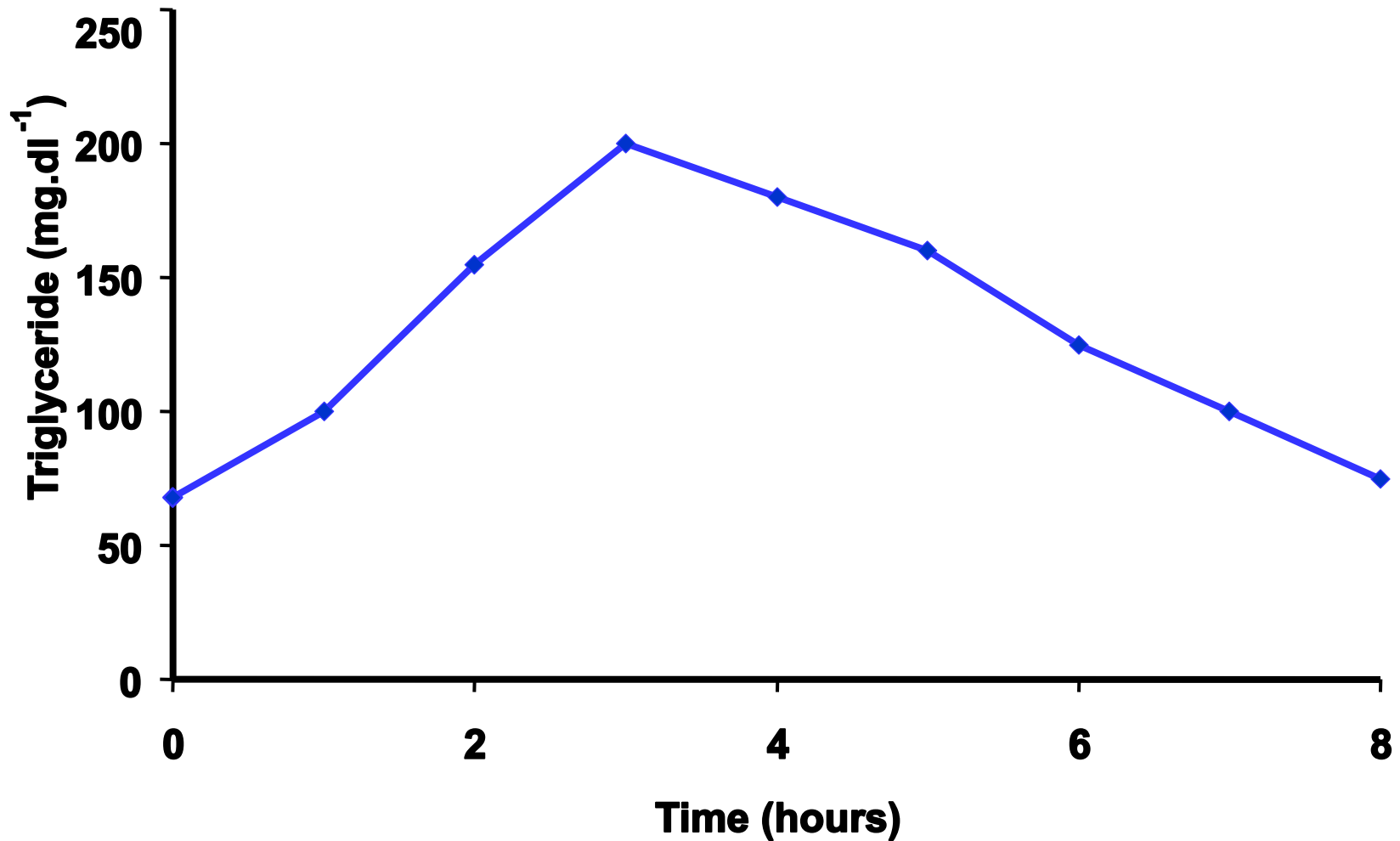
Triglyceride metabolism in the fasted state



Triglyceride metabolism in the postprandial state

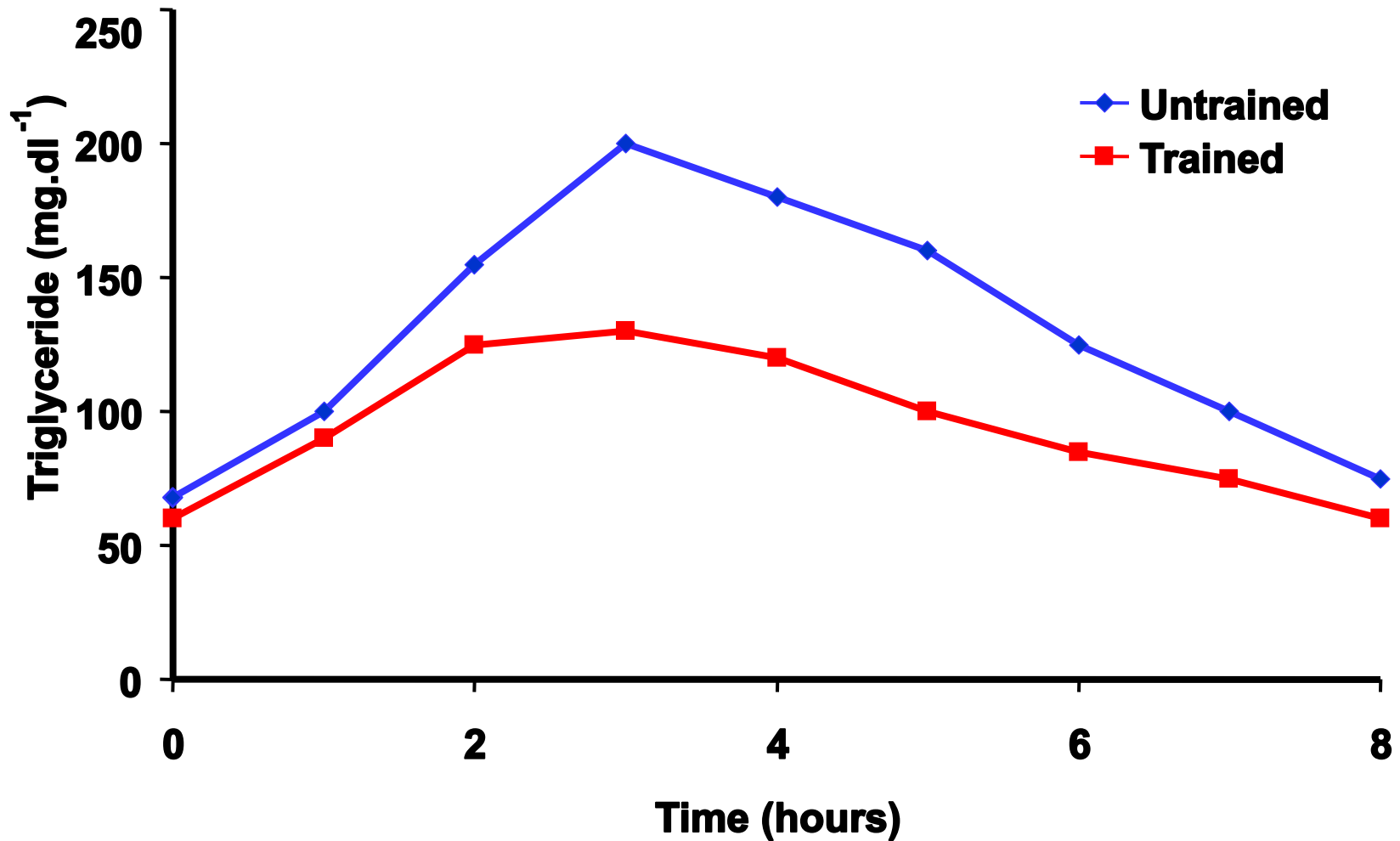


Postprandial lipaemia in trained and untrained men



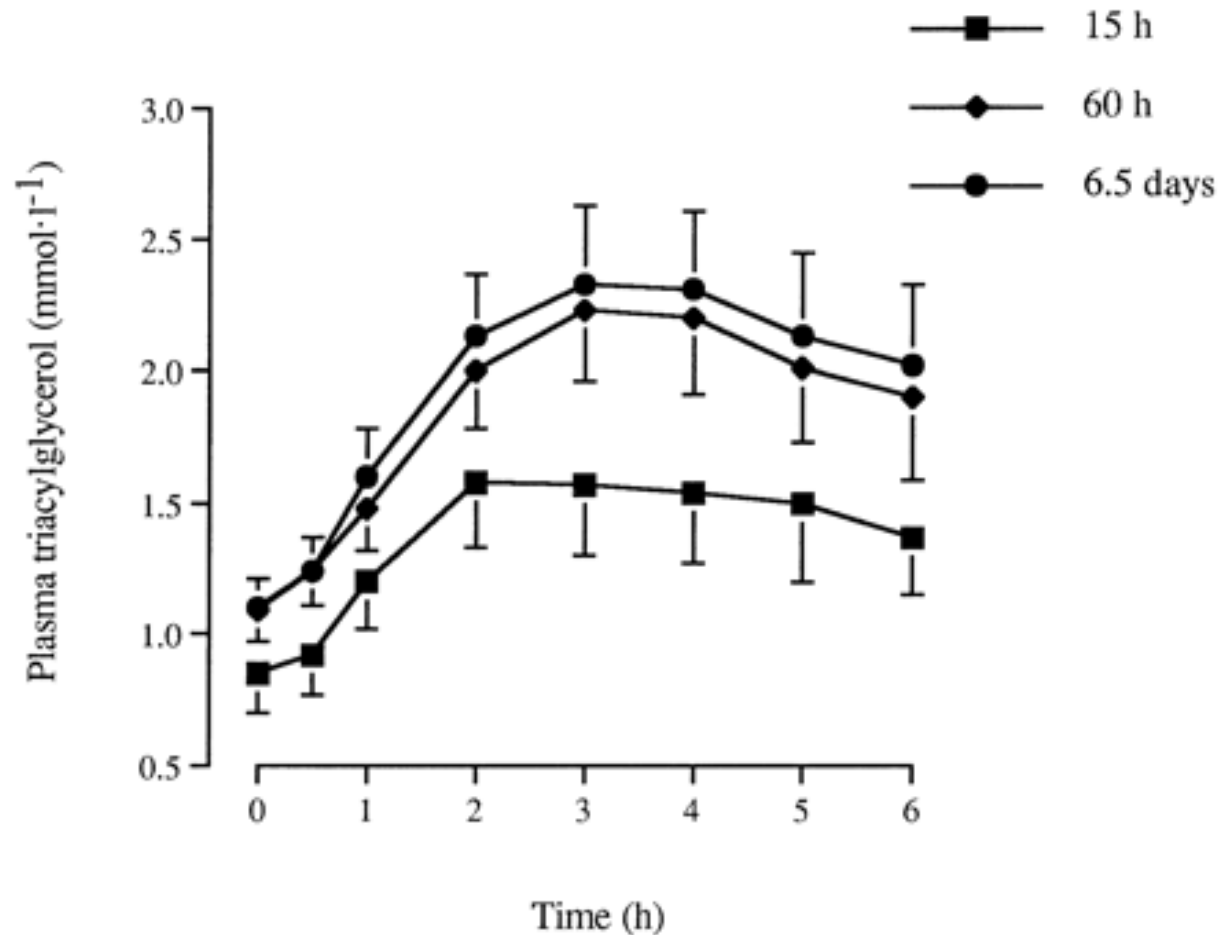
Merrill et al (1989), Arteriosclerosis, 9:217-223

Postprandial lipaemia in trained and untrained men



**Long-term training
adaptation
or
acute effect of recent
exercise?**





Experimental protocol

Day 1

Exercise or
Rest



Day 2

Oral fat tolerance test



0



2



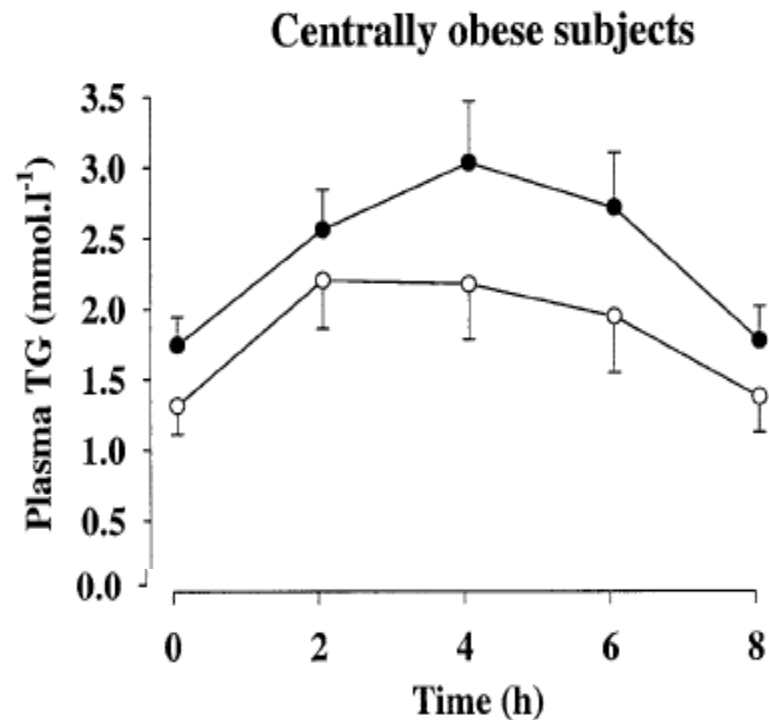
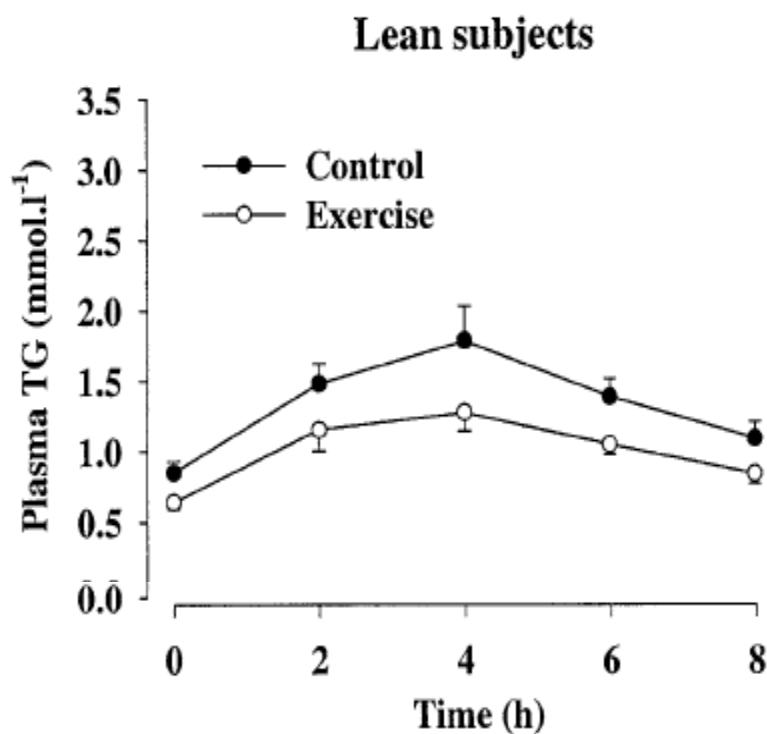
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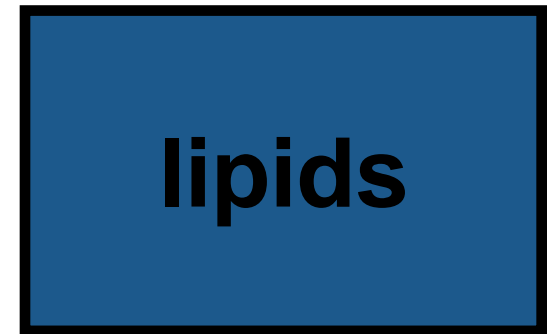
6

Time (hours)

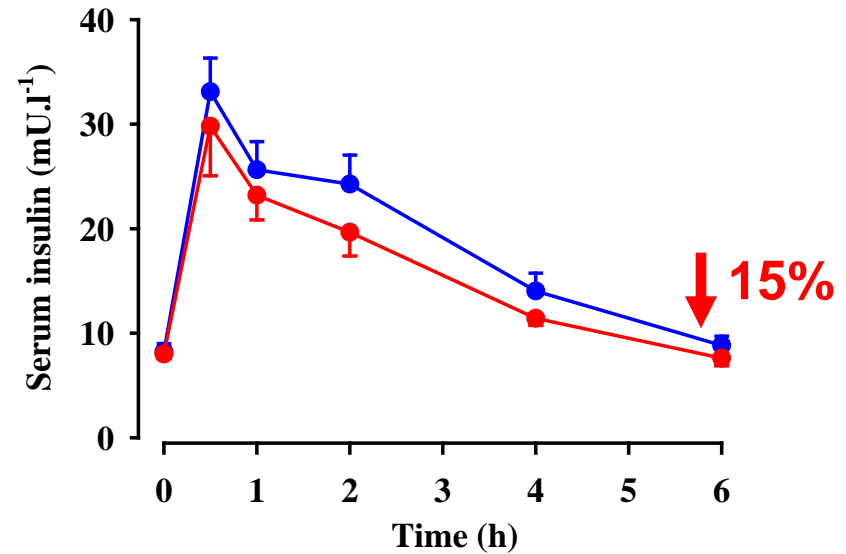
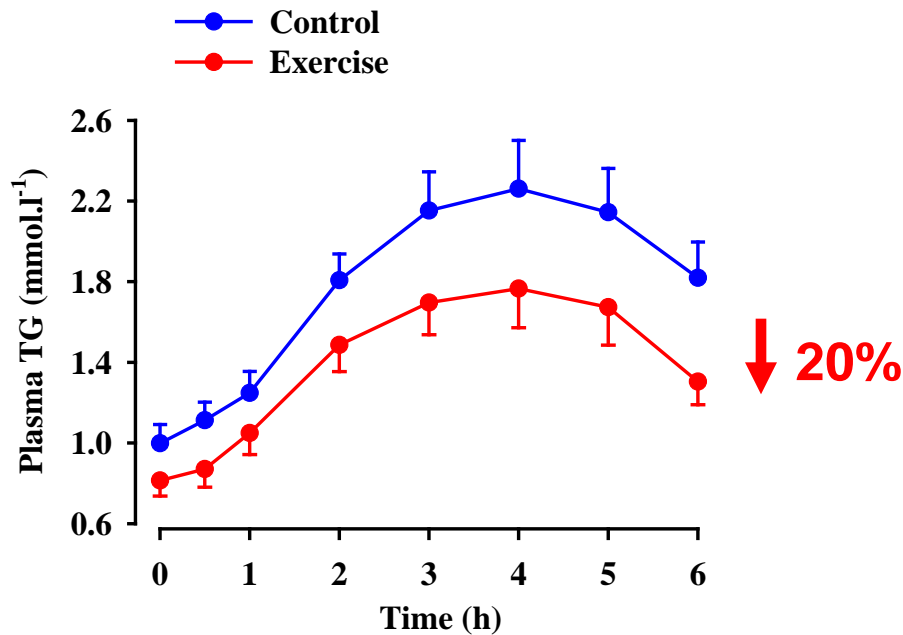
Moderate exercise and postprandial TG concentrations in lean and obese men



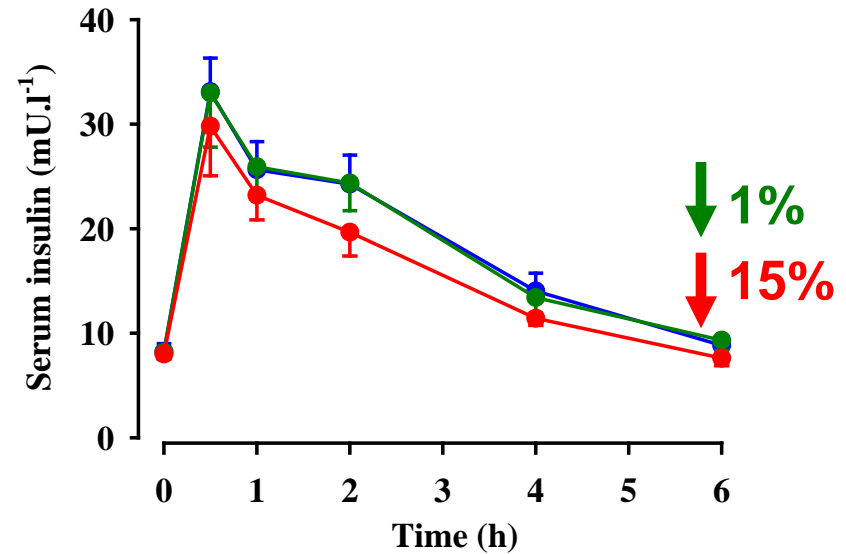
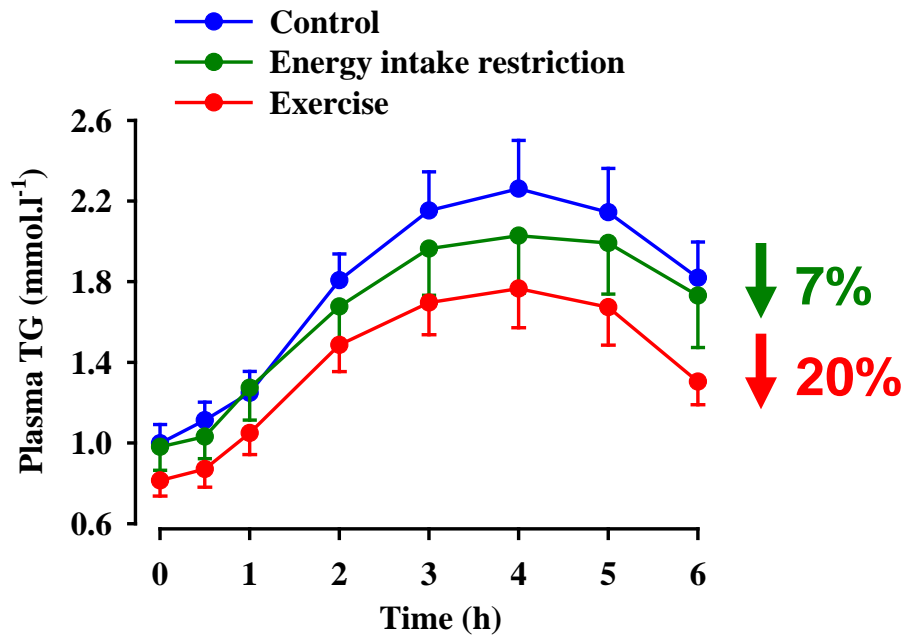
Energy deficit?



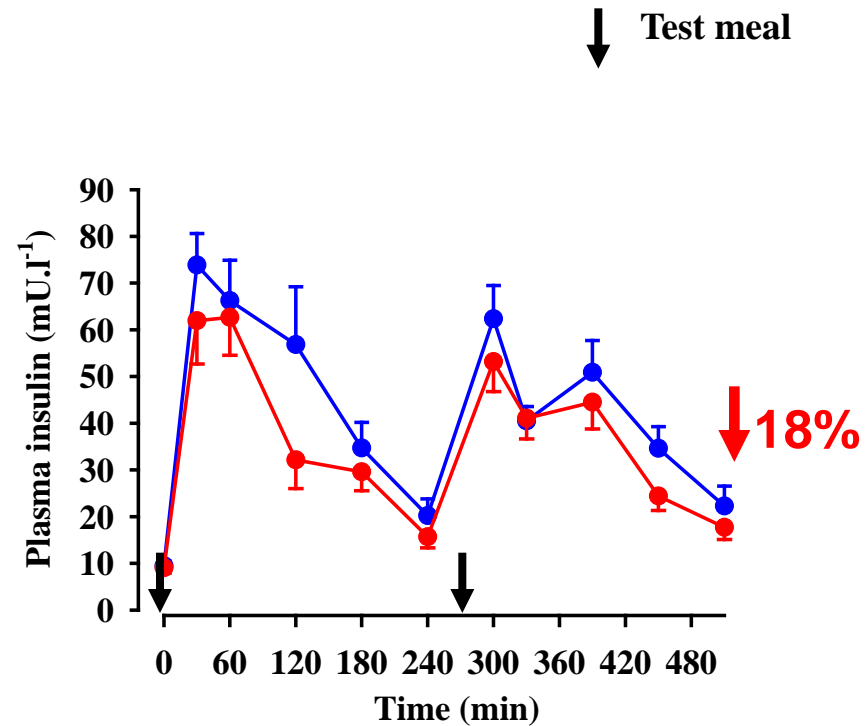
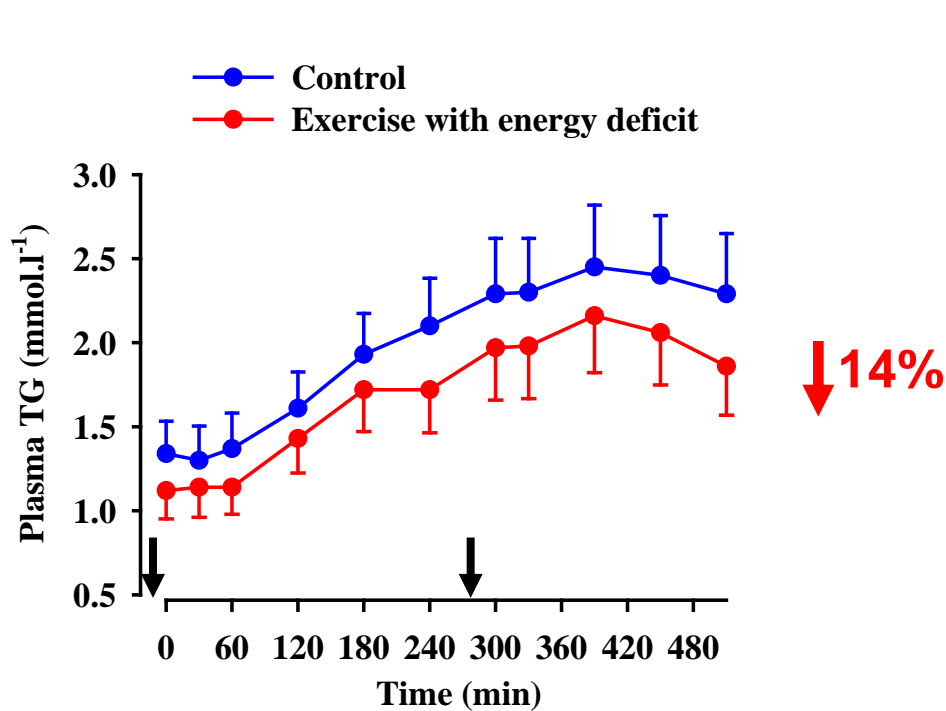
Exercise, energy intake restriction and postprandial metabolism



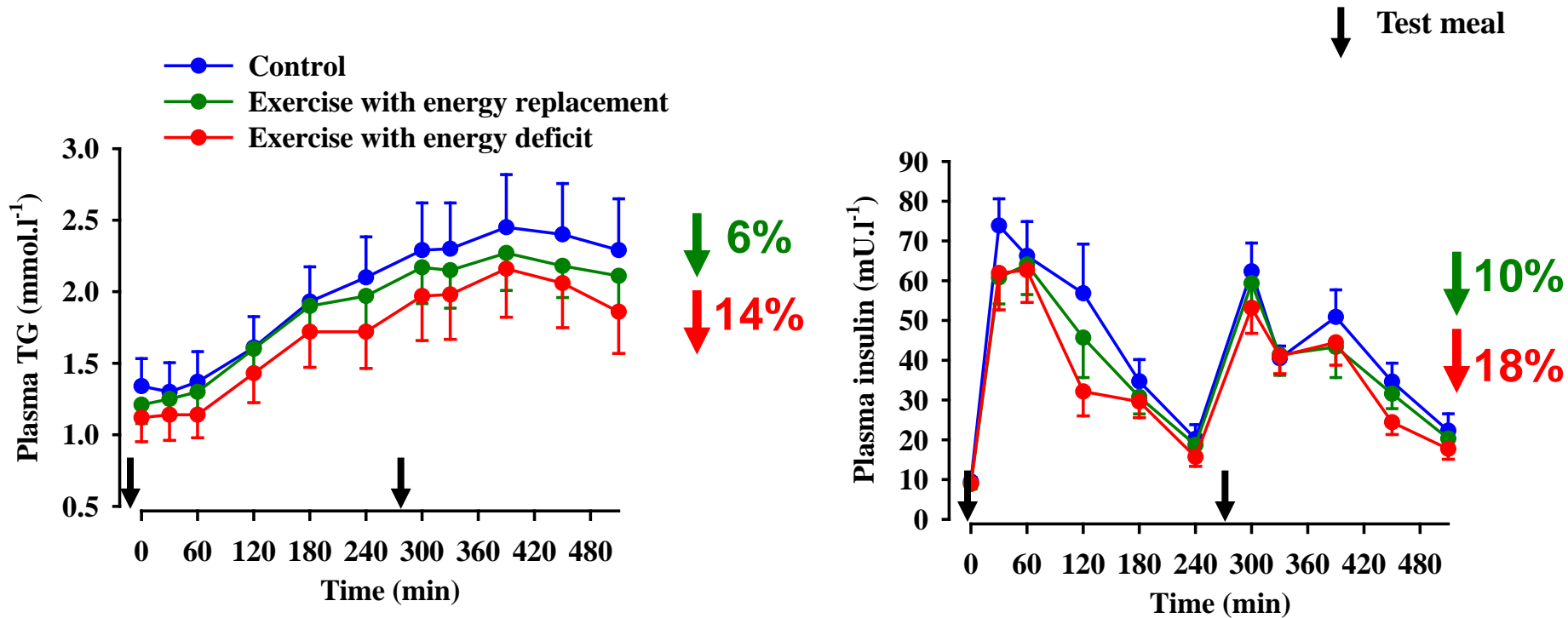
Exercise, energy intake restriction and postprandial metabolism



Exercise with and without energy deficit and postprandial metabolism

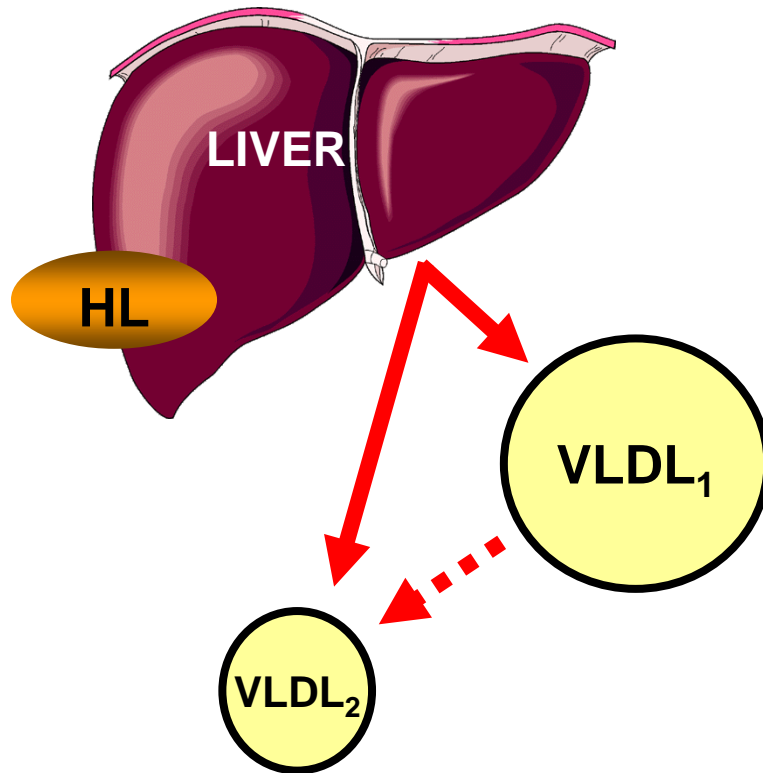


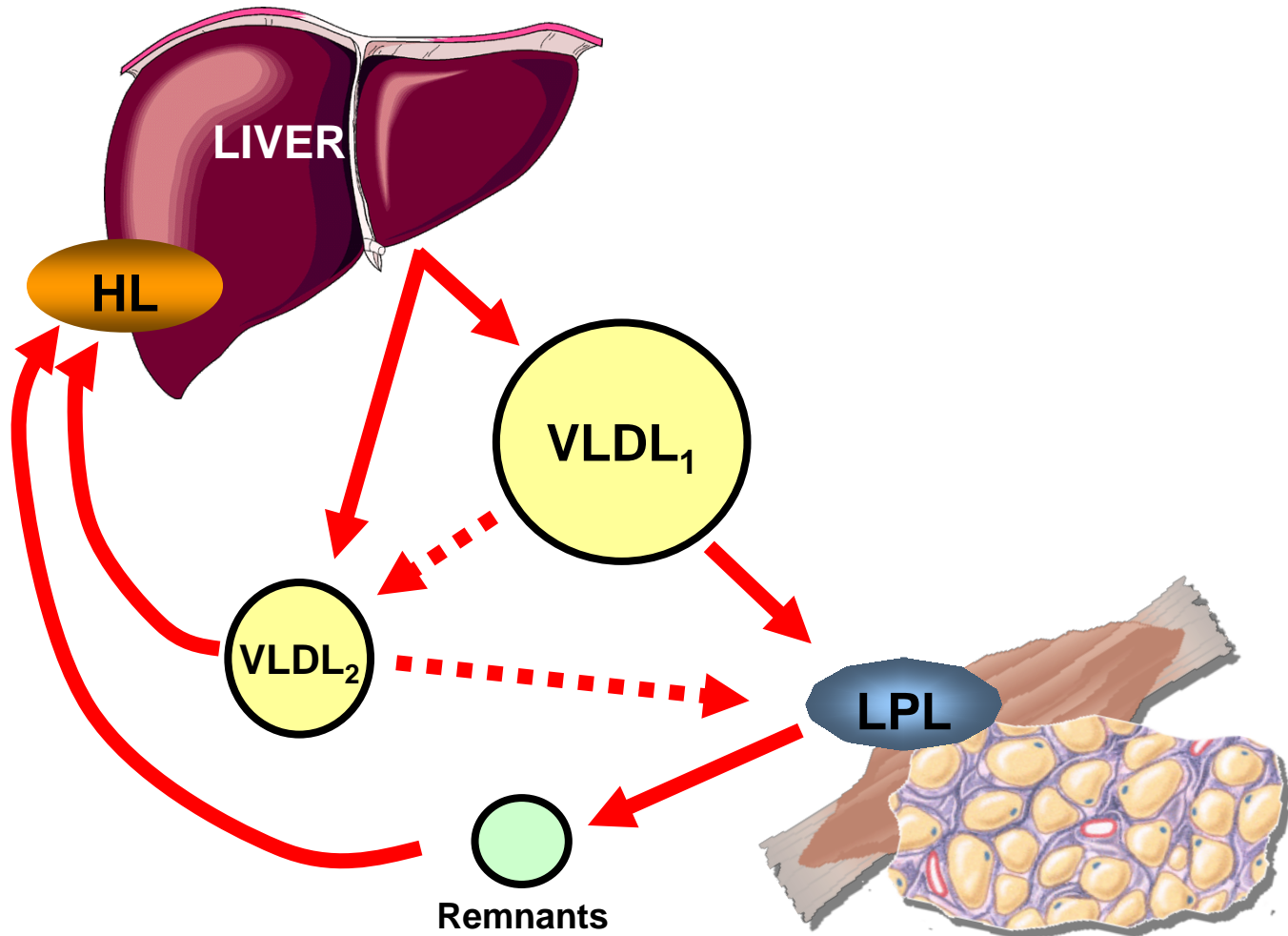
Exercise with and without energy deficit and postprandial metabolism

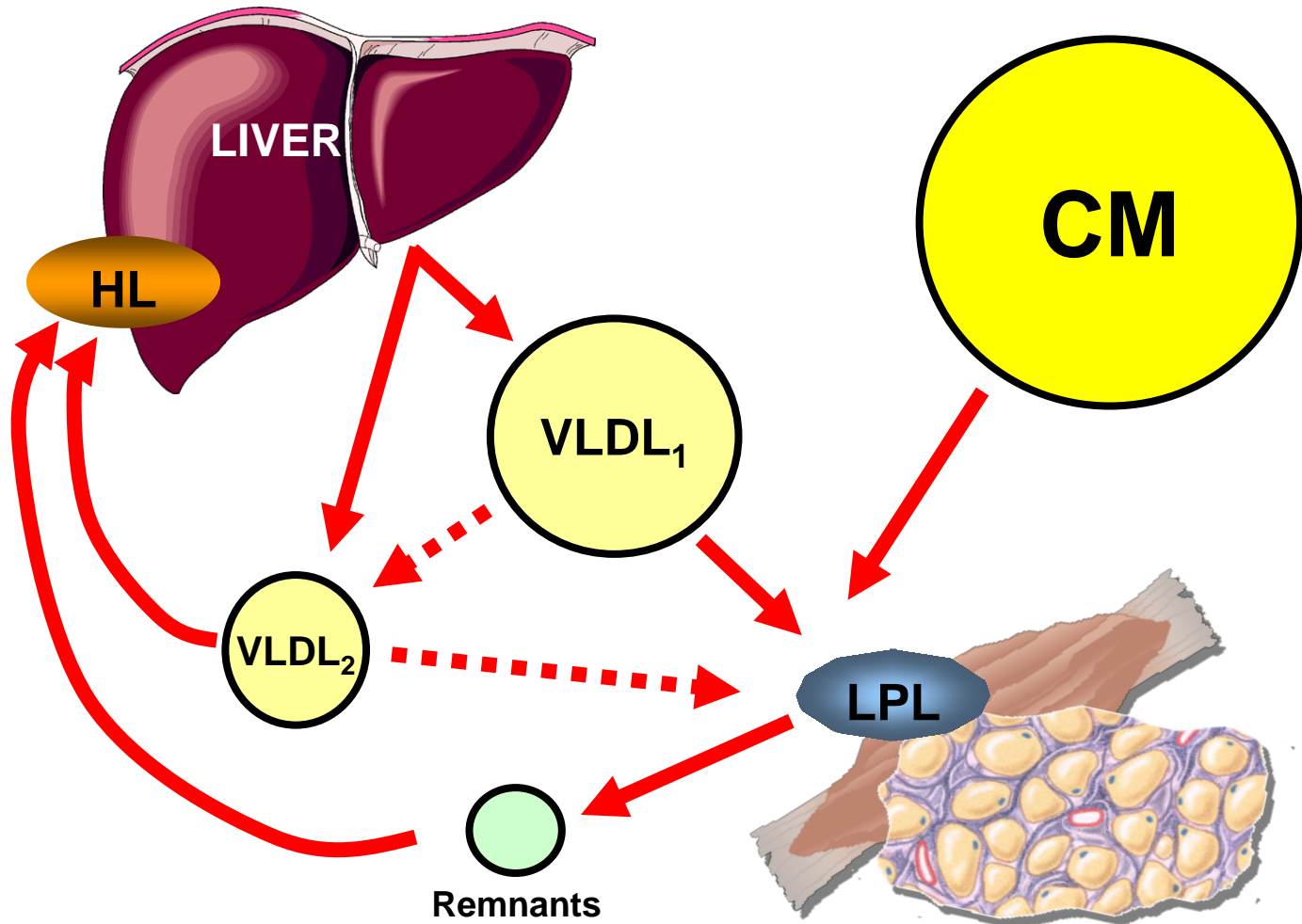


Mechanisms?

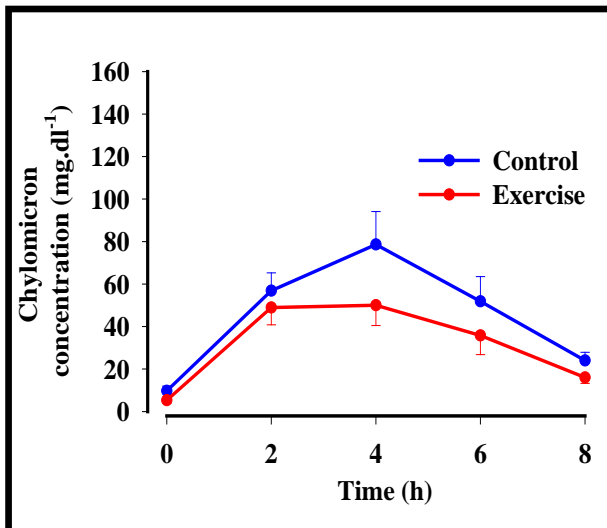




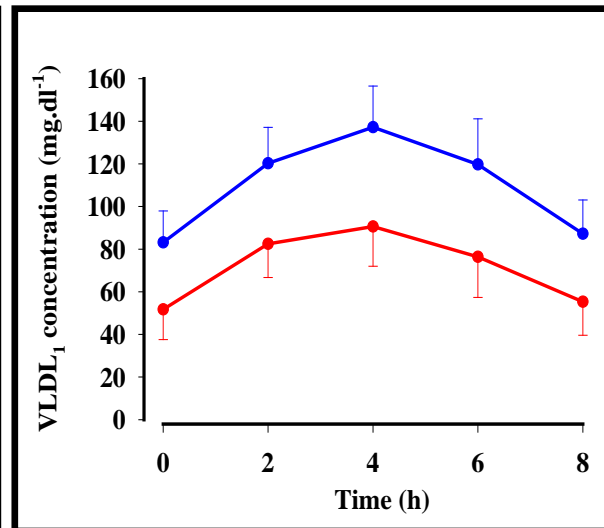




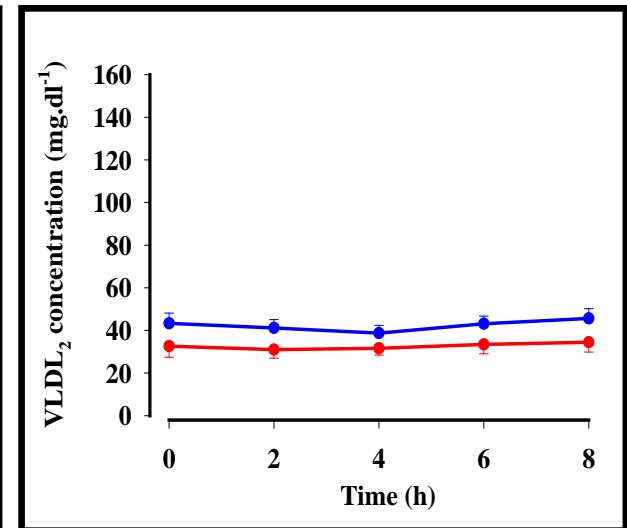
Chylomicrons

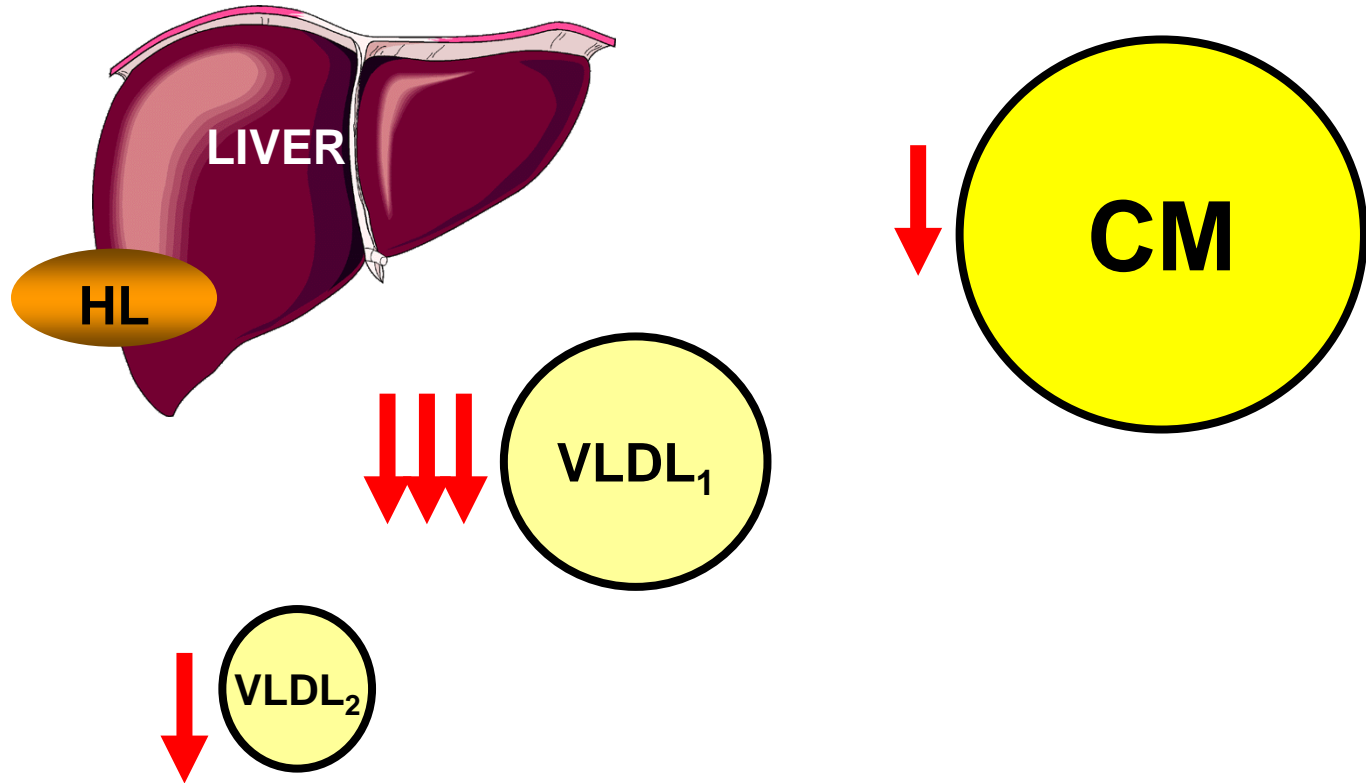


Large VLDL (VLDL₁)



Small VLDL (VLDL₂)





↓
**Concentration of
VLDL₁**



↓
**Production of
VLDL₁**



↓
**Concentration of
VLDL₁**



↓
**Production of
VLDL₁**



↓
**Concentration of
VLDL₁**




↑
**Clearance of
VLDL₁**

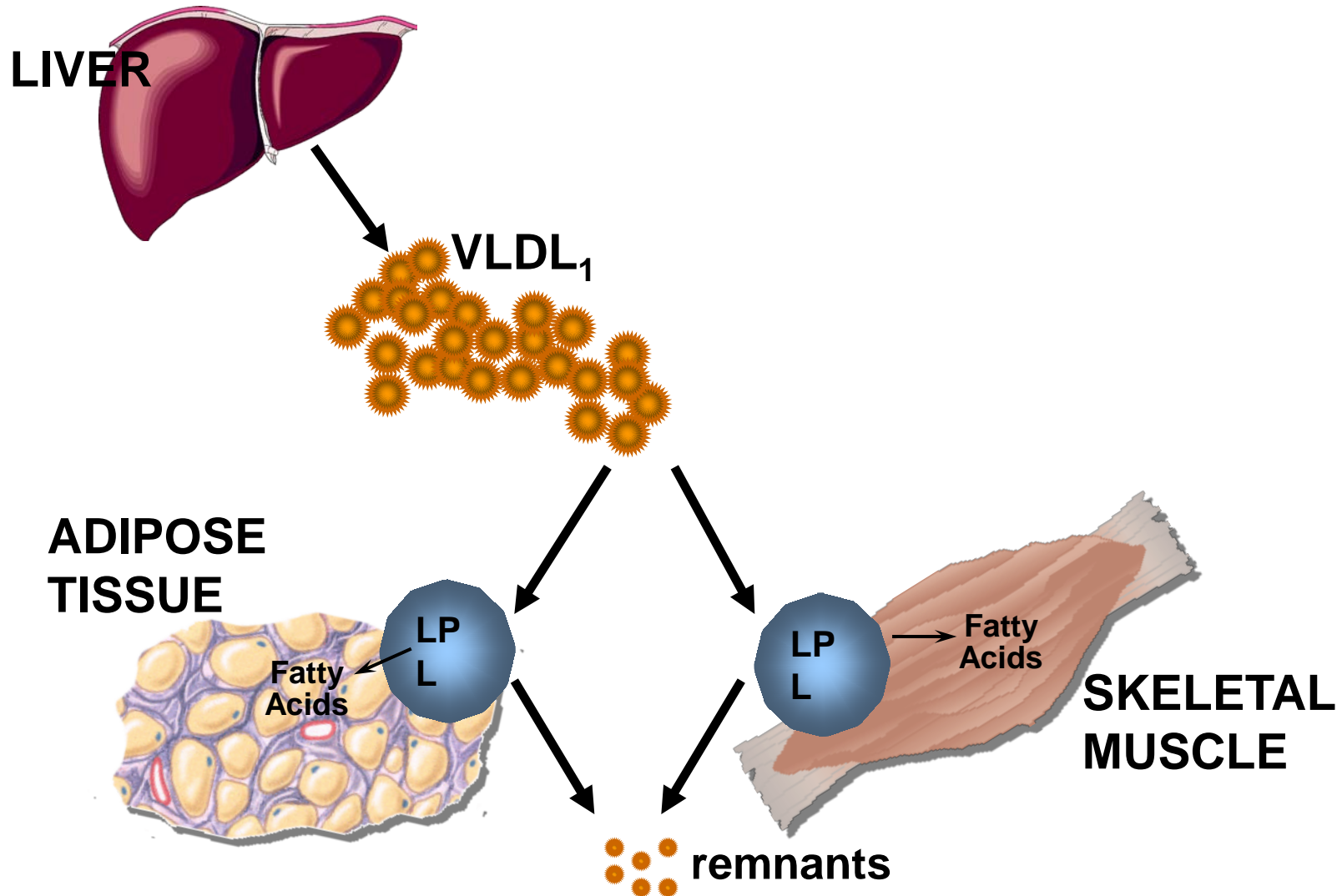


Development of a novel method to determine very low density lipoprotein kinetics

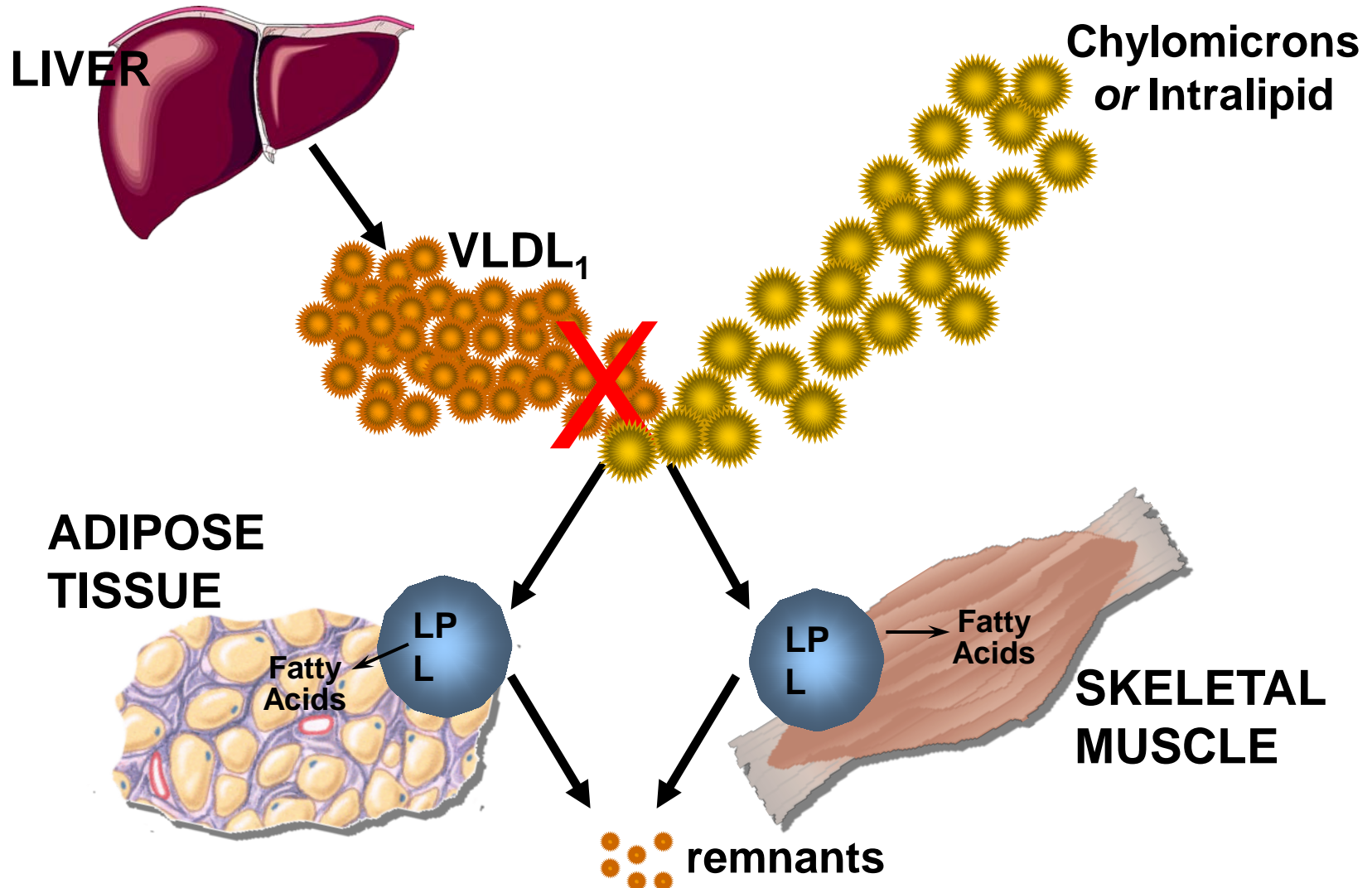
Iqbal A. R. Al-Shayji,^{*,†} Jason M. R. Gill,^{1,†} Josephine Cooney,^{*} Samira Siddiqui,^{*,§}
and Muriel J. Caslake^{*}

Department of Vascular Biochemistry,^{*} and Institute of Diet, Exercise, and Lifestyle, Institute of Biomedical and Life Sciences,[†] University of Glasgow, Glasgow, United Kingdom; and Renal Unit,[§] Glasgow Royal Infirmary, Glasgow, United Kingdom

In conclusion, we have developed a novel method to determine TRL kinetics. The Intralipid method provides a relatively straightforward and cost-effective way of determining VLDL₁-TG and VLDL₁-apoB production rates and the clearance rate of chylomicron-like particles that does not require specialized equipment, such as a mass spectrometer. We believe that this method will increase the scope for the study of TRL kinetics, particularly in circumstances in which issues related to funding or equipment availability preclude the use of more traditional isotopic tracer methods. 



Effect of Chylomicrons (CM) & CM-like Particles on VLDL₁ Clearance

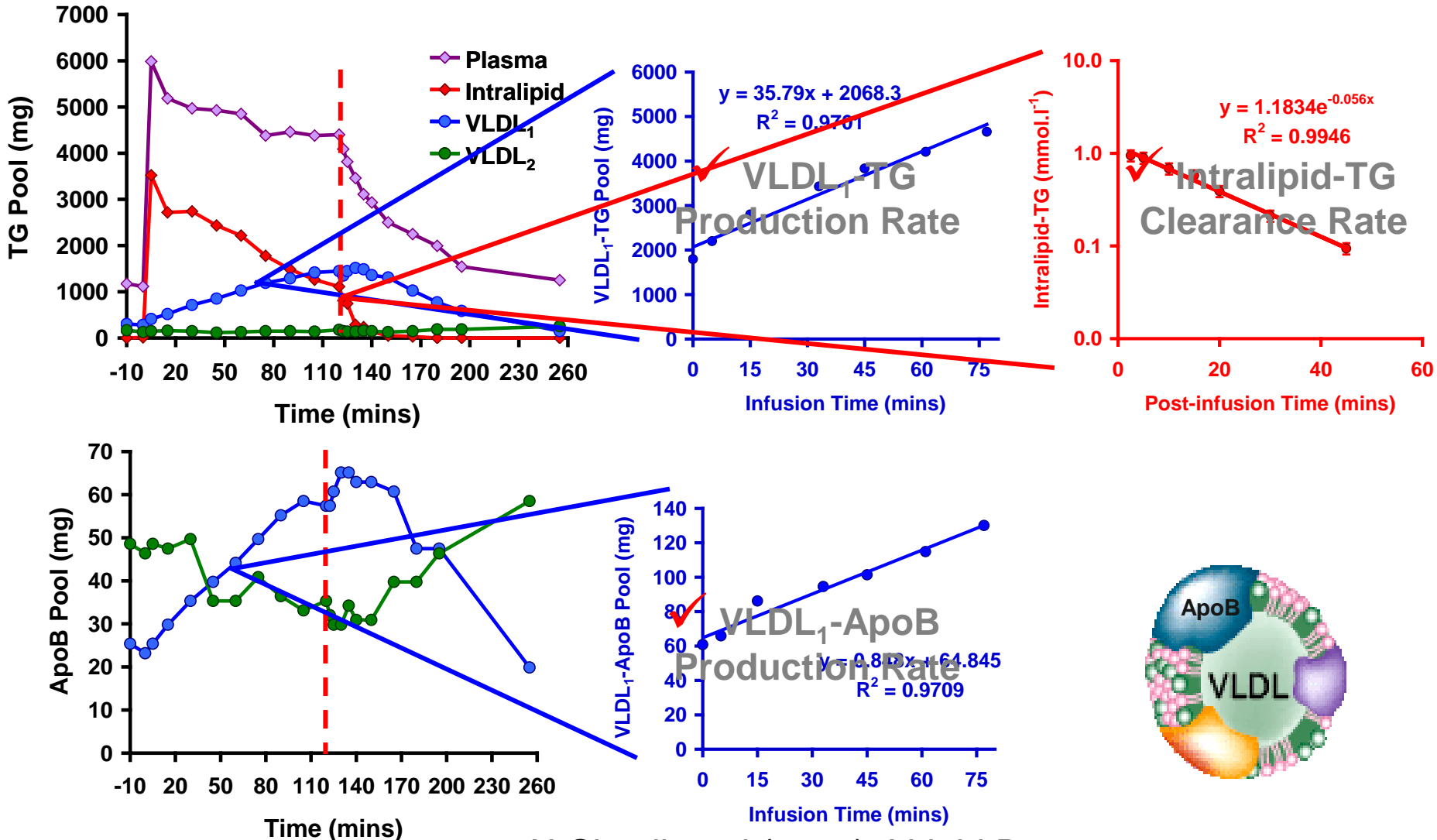


The 'Intralipid Method'



- Bolus Intralipid dose:
 0.1 g.kg^{-1} body mass
- $0.1 \text{ g.kg}^{-1}.\text{h}^{-1}$ Intralipid
infusion for 75 mins
- Two fasting baseline
and multiple EDTA
blood samples are
drawn before, during
and post-infusion
- Intralipid, VLDL_1 and
 VLDL_2 fractions are
separated by density
gradient
ultracentrifugation.

Kinetic Data Obtained from the 'Intralipid Method'



Effects of moderate exercise on VLDL₁ and Intralipid kinetics in overweight/obese middle-aged men

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Submitted 22 September 2011; accepted in final form 14 November 2011

Al-Shayji IA, Caslake MJ, Gill JM. Effects of moderate exercise on VLDL₁ and Intralipid kinetics in overweight/obese middle-aged men. *Am J Physiol Endocrinol Metab* 302: E349–E355, 2012. First published November 15, 2011; doi:10.1152/ajpendo.00498.2011.—Prior moderate exercise reduces plasma triglyceride (TG)-rich lipoprotein concentrations, mainly in the large very low-density lipoprotein (VLDL₁) fraction, but the mechanism responsible is unclear. We investigated the effects of brisk walking on TG-rich lipoprotein kinetics using a novel method. Twelve overweight/obese middle-aged men underwent two kinetic studies, involving infusion of Intralipid to block VLDL₁ catabolism, in random order. On the afternoon prior to infusion, subjects either walked on a treadmill for 2 h at ~50% maximal oxygen uptake or performed no exercise. Multiple blood samples were taken during and after infusion for separation of Intralipid (S_f 400) and VLDL₁ (S_f 60–400). VLDL₁-TG and -apoB production rates were calculated from their linear rises during infusion; fractional catabolic rates (FCR) were calculated by dividing linear rises by fasting concentrations. Intralipid-TG FCR was determined from the postinfusion exponential decay. Exercise reduced fasting VLDL₁-TG concentration by 30% ($P = 0.007$) and increased TG enrichment of VLDL₁ particles [30% decrease in cholesterol/ester

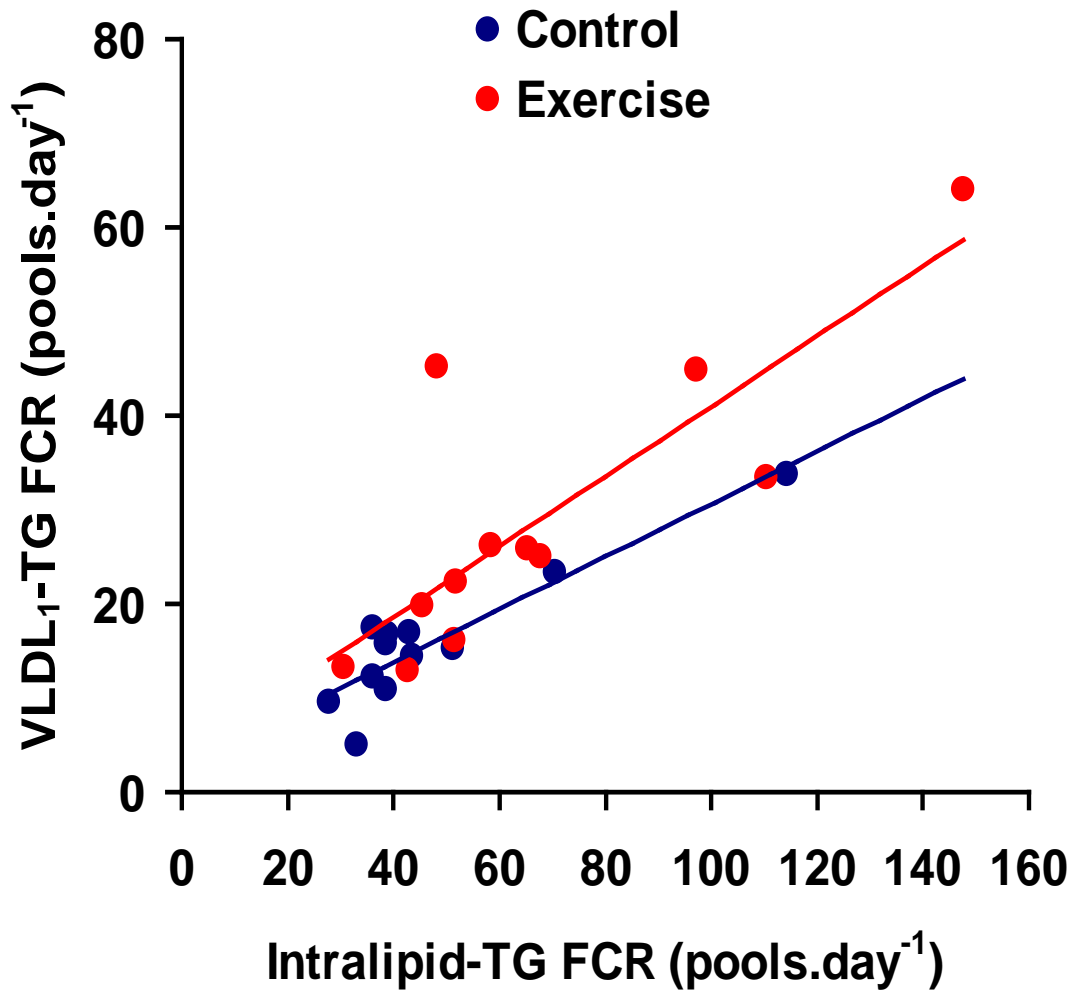
VLDL₁ (S_f 60–400) fraction (16), than in intestinally derived chylomicrons. As high concentrations of VLDL₁ are the major determinant of elevated plasma TG levels (27, 39), and VLDL₁ are the primary precursor particles for atherogenic small-dense LDL (34), reducing VLDL₁ concentration is likely to induce clinically important changes to the atherosclerotic risk profile. Exercise-induced reduction in circulating VLDL₁ could reflect reduced hepatic VLDL₁ production, increased lipoprotein lipase (LPL)-mediated VLDL₁ clearance, or a combination of the two. Stable-isotope kinetic studies have demonstrated that, in nonobese, recreationally active young men, moderate-intensity exercise sessions of 90–120 min duration can increase clearance of total VLDL-TG (29, 40) and decrease total hepatic VLDL-apolipoprotein B (apoB) production (29). However, these studies considered all VLDL as a single lipoprotein class, and lipoprotein kinetic studies have shown that VLDL is metabolically heterogeneous, with accumulating evidence demonstrating that both the production and catabolism of large TG-rich VLDL₁ (S_f 60–400) and smaller cholesterol-rich

Effects of moderate exercise on TRL kinetics

	Control	Exercise	Change (%)
Fasting plasma TG (mmol/l)	1.54 ± 0.16	1.21 ± 0.15*	-21%
Fasting VLDL ₁ concentration (mg/dl)	94.9 ± 14.1	62.9 ± 11.4*	-34%
VLDL ₁ -TG production rate (mg/h)	1272 ± 156	1432 ± 148	+13%
VLDL ₁ -apoB production rate (mg/h)	37.2 ± 7.4	41.5 ± 5.4	+12%
Intralipid-TG FCR (pools/d)	47.6 ± 6.8	68.1 ± 9.7*	+43%
VLDL ₁ -TG FCR (pools/d)	16.0 ± 2.1	29.1 ± 4.4*	+82%
VLDL ₁ -apoB FCR (pools/d)	10.4 ± 2.0	25.6 ± 5.1*	+146%

***p < 0.05 for Control vs Exercise**

Effects of moderate exercise on TRL kinetics



Exercise

$$y = 0.37x + 3.69$$

$$r = 0.82, p = 0.001$$

Control

$$y = 0.28x + 2.68$$

$$r = 0.91, p < 0.0005$$

Exercise increases relative affinity for VLDL₁ clearance compared to chylomicron-like particle clearance

Moderate exercise increases affinity of large very low density lipoproteins for hydrolysis by lipoprotein lipase

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Context: Postprandial triglyceride (TG) concentration is independently associated with cardiovascular disease risk. Exercise reduces postprandial TG concentrations but the mechanisms responsible are unclear.

Objective: To determine the effects of exercise on affinity of chylomicrons, large very low density lipoproteins (VLDL₁) and smaller VLDL (VLDL₂) for lipoprotein lipase (LPL) mediated TG hydrolysis.

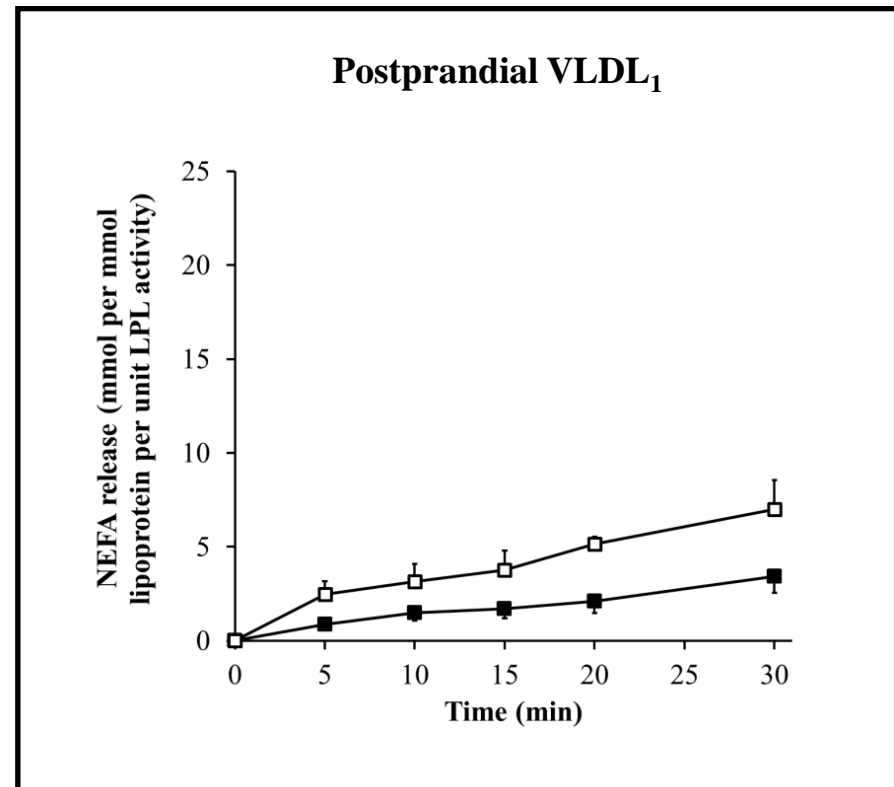
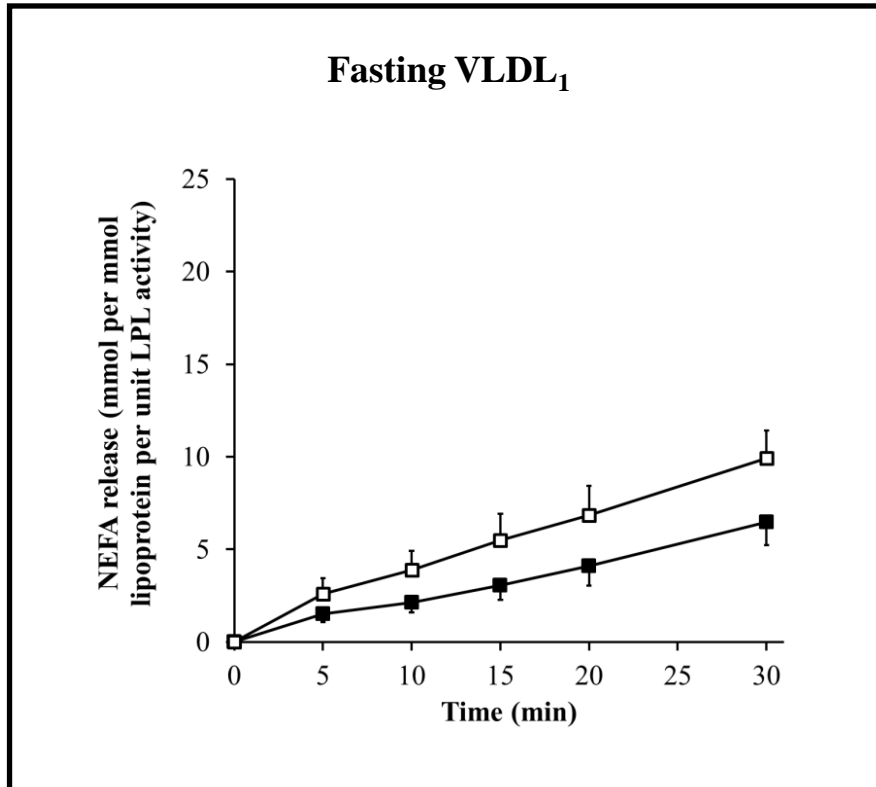


Table 3. Lipoprotein Affinity for LPL

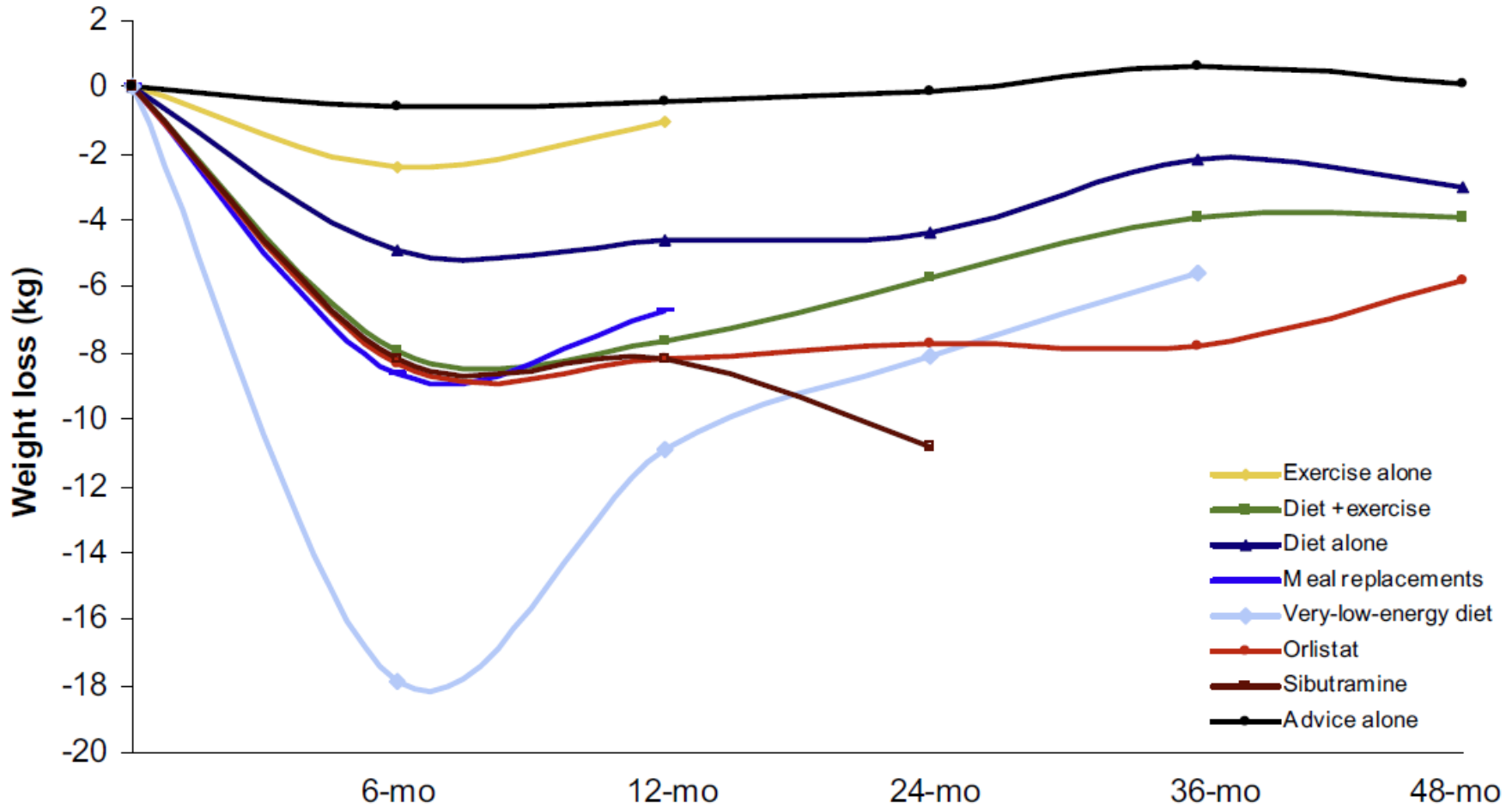
NEFA release (mmol·min ⁻¹ per mmol lipoprotein per unit LPL activity)						
Fasting (0 min)			Postprandial (240 min)			
Control	Exercise	p-value	Control	Exercise	p-value	
Chylomicrons			1.25 (0.94 to 1.66)	1.52 (0.98 to 2.34)	0.53*	
VLDL ₁	0.16 (0.09 to 0.29)	0.35 (0.24 to 0.52)	0.018*	0.08 (0.03 to 0.19)	0.25 (0.15 to 0.42)	0.002*
VLDL ₂	0.013 (0.004 to 0.044)	0.018 (0.007 to 0.049)	0.60	0.021 (0.006 to 0.070)	0.013 (0.004 to 0.048)	0.34

Values are mean \pm SEM, $n = 10$. *Statistical analysis performed on log-transformed data, and values are geometric mean (95% confidence interval)

Physical activity, dietary intake and energy balance



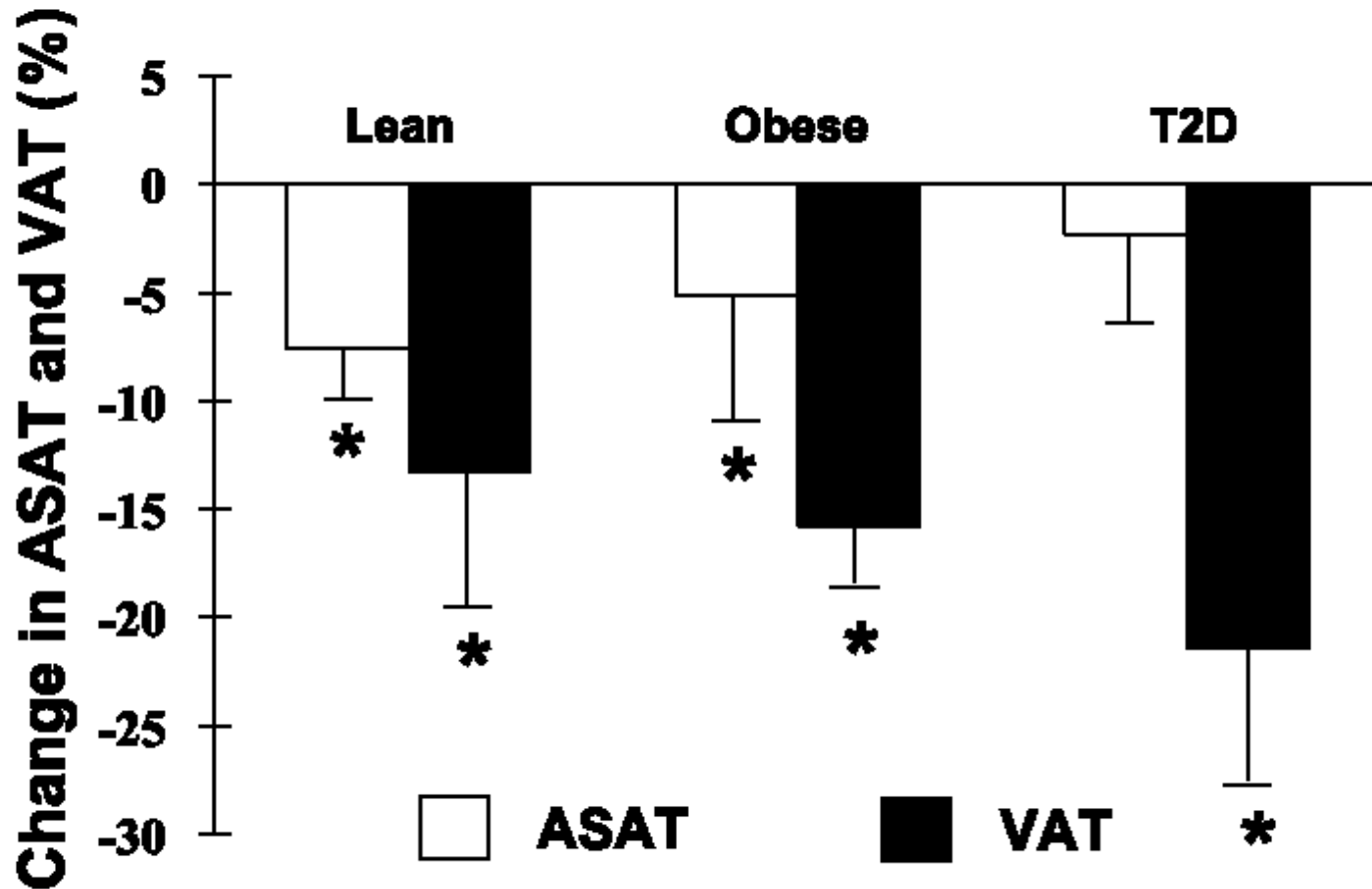
Weight loss outcomes in clinical trials: Systematic review and meta-analysis



80 studies, n = 26,455
(18,199 completers)

Franz et al (2007) *J Am Diet Assoc.* 107:1755-1767

Effects of exercise training, without weight loss, on body fat



Lee et al (2005) J Appl Physiol 99:1220-1225

60 min moderate exercise, 5 x per week for 13 weeks

The substrate balance equation

Fat intake
CHO intake
Protein intake

Fat expenditure
CHO expenditure
Protein expenditure



Fat balance
CHO balance
Protein balance

Fat oxidation and weight gain in Pima Indians

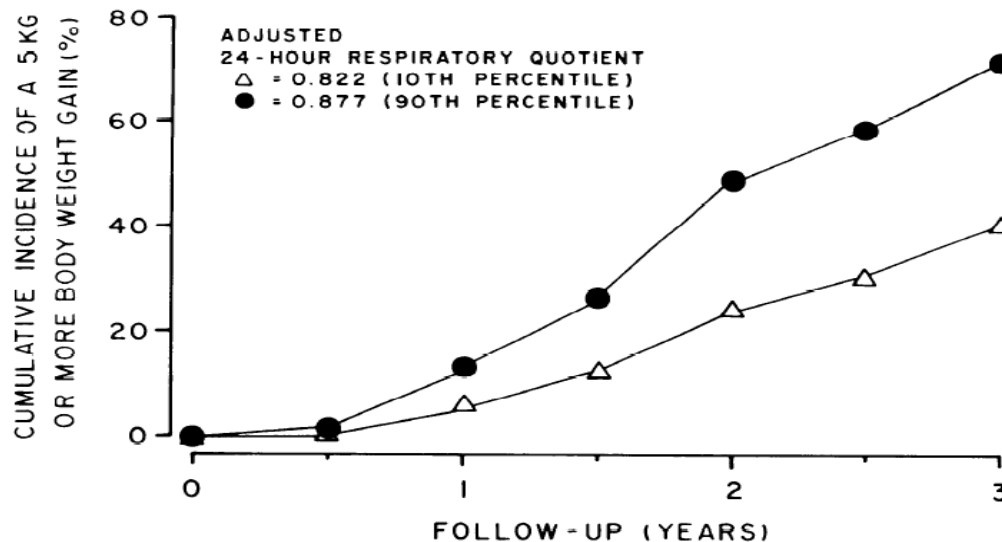
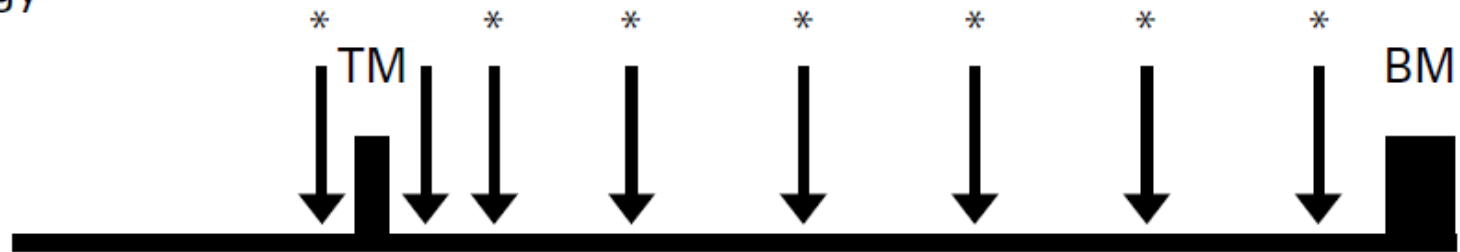


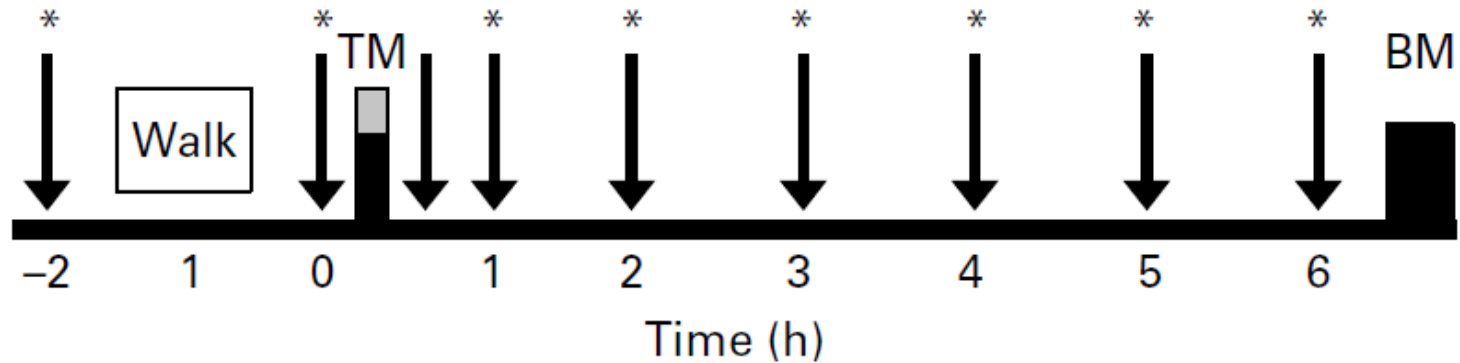
FIG. 4. Cumulative incidence of 5 kg body wt gain or more at 10th and 90th percentile of adjusted 24-h respiratory quotient (RQ; 0.822 and 0.877, respectively) measured in 111 subjects on whom follow-up measurements were available. No. of subjects studied at each time interval was 109 after 6 mo, 95 after 1 yr, 79 after 1.5 yr, 57 after 2 yr, 43 after 2.5 yr, and 18 after 3 yr. Cumulative incidence was calculated by proportional-hazards model adjusting 24-h RQ for differences in rate of body wt change on metabolic ward, acute energy balance, percent body fat, and sex and controlling for energy expenditure adjusted for fat-free mass and fat mass. With outcome defined as a weight gain of 5 kg, ratio of hazard rates for a person at 90th percentile of adjusted RQ compared with one at 10th percentile was 2.5 (95% confidence interval 1.3–4.9).

Substrate metabolism and feeding behaviour under high and low energy turnover conditions

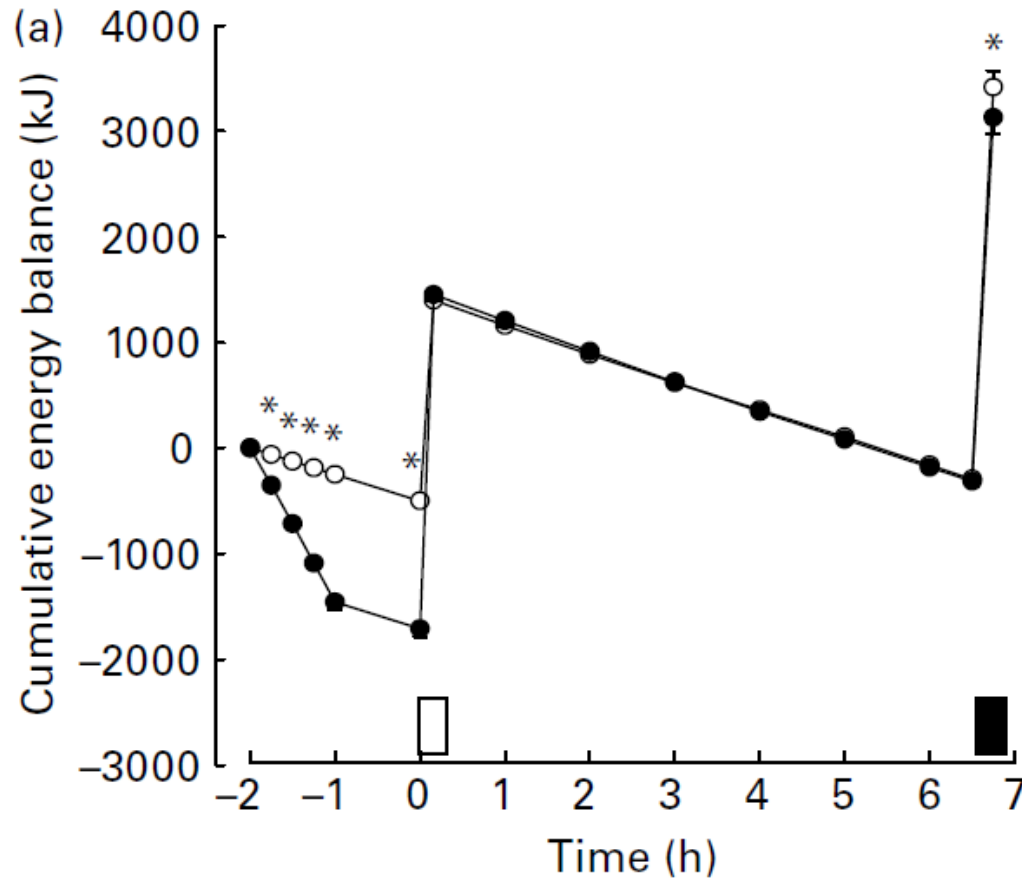
Low energy
turnover



High energy
turnover

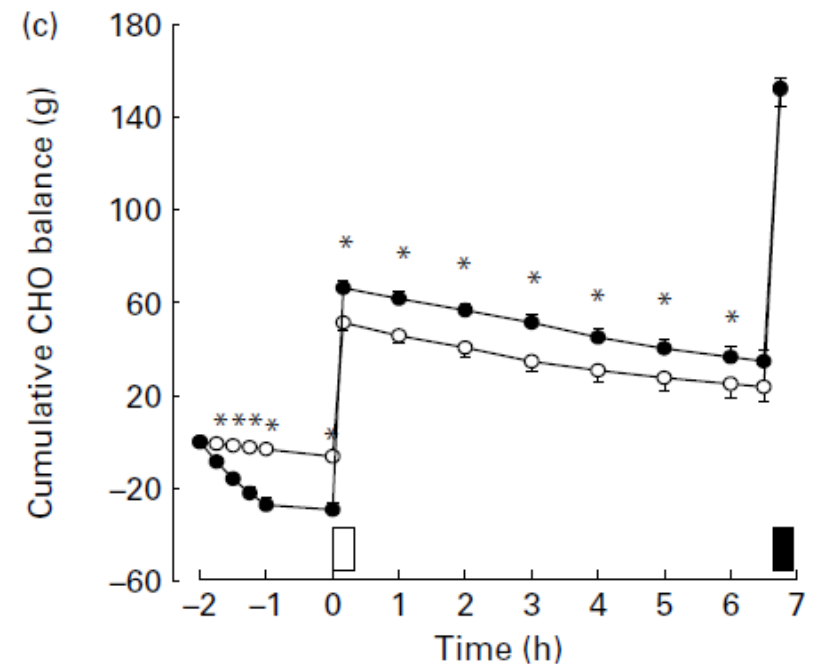
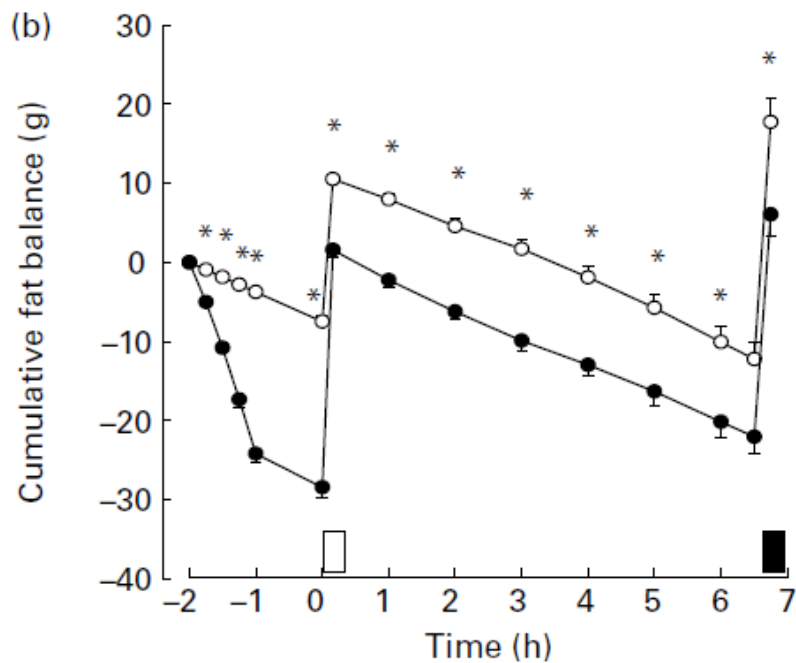


Substrate metabolism and feeding behaviour under high and low energy turnover conditions

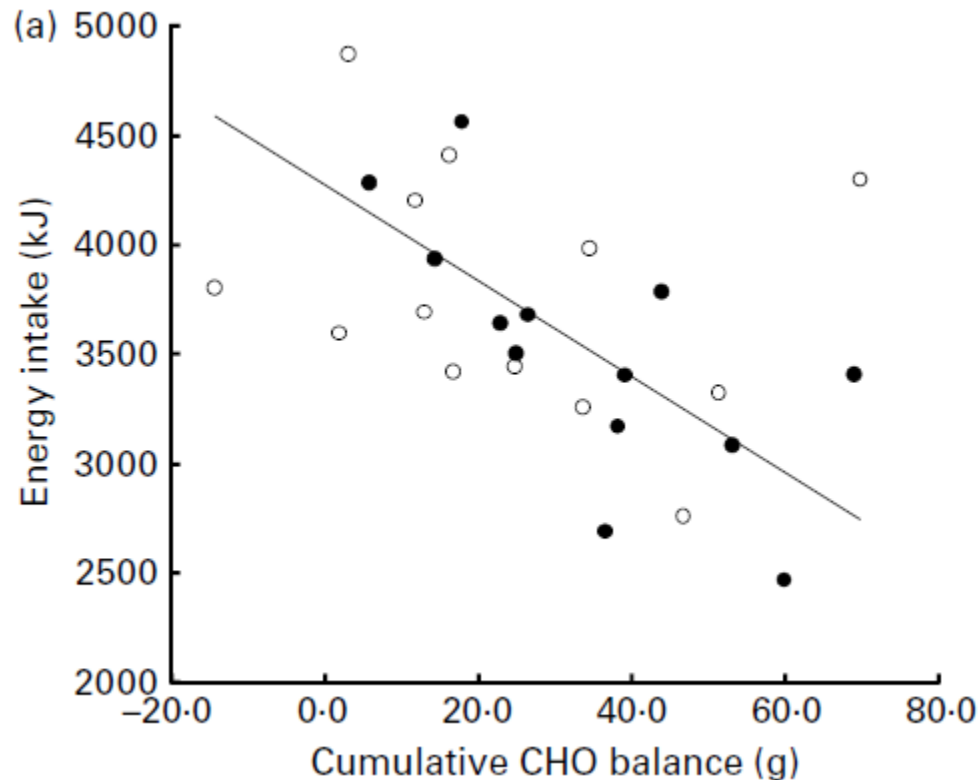


Burton et al (2010) Br J Nutr 104:1249-1259

Substrate metabolism and feeding behaviour under high and low energy turnover conditions

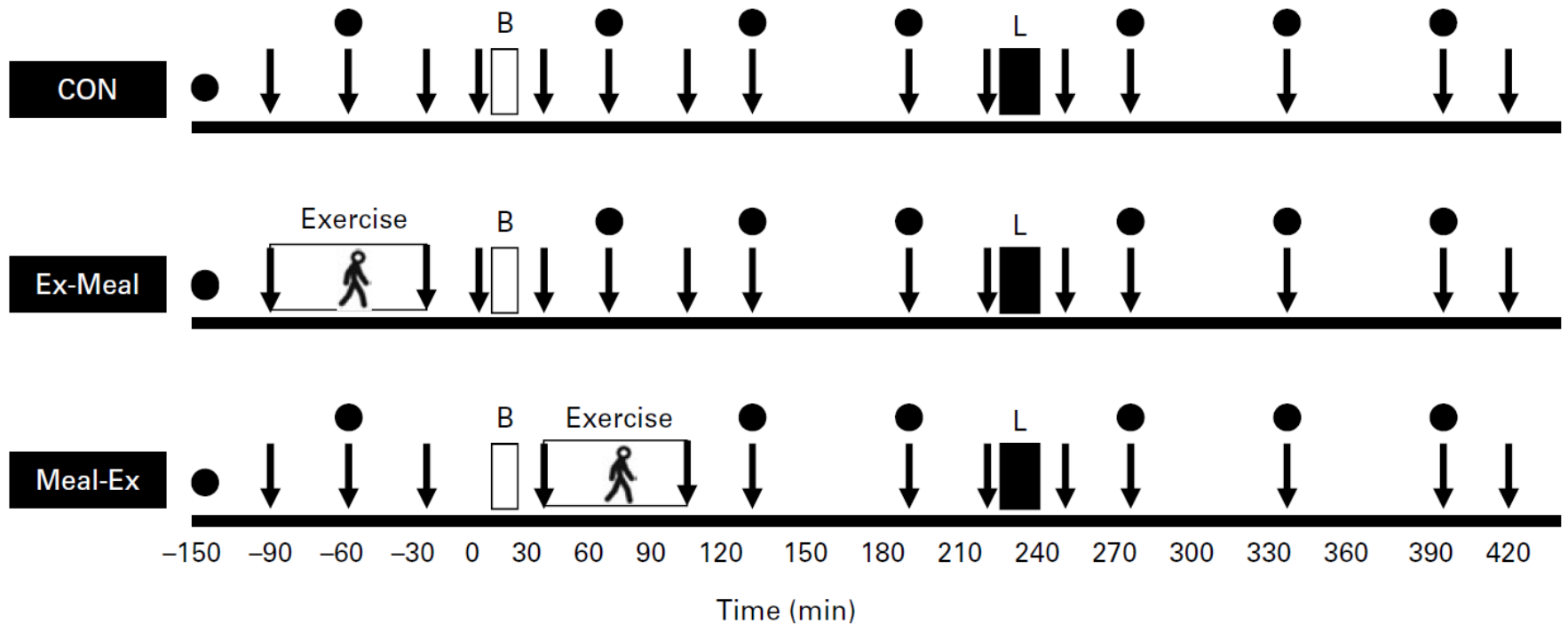


Substrate metabolism and feeding behaviour under high and low energy turnover conditions

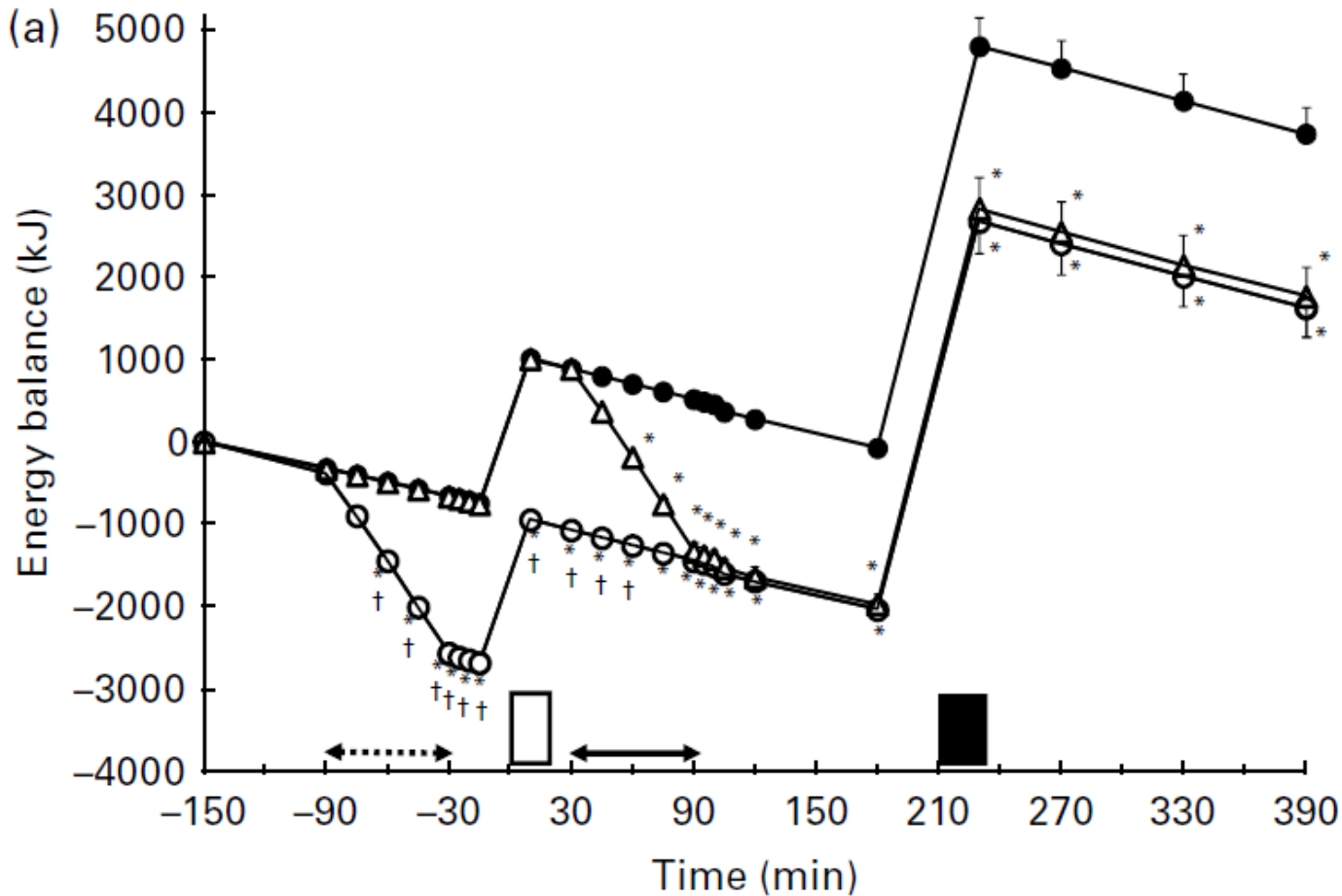


Burton et al (2010) Br J Nutr 104:1249-1259

Effects of exercise before or after breakfast on energy and fat balance

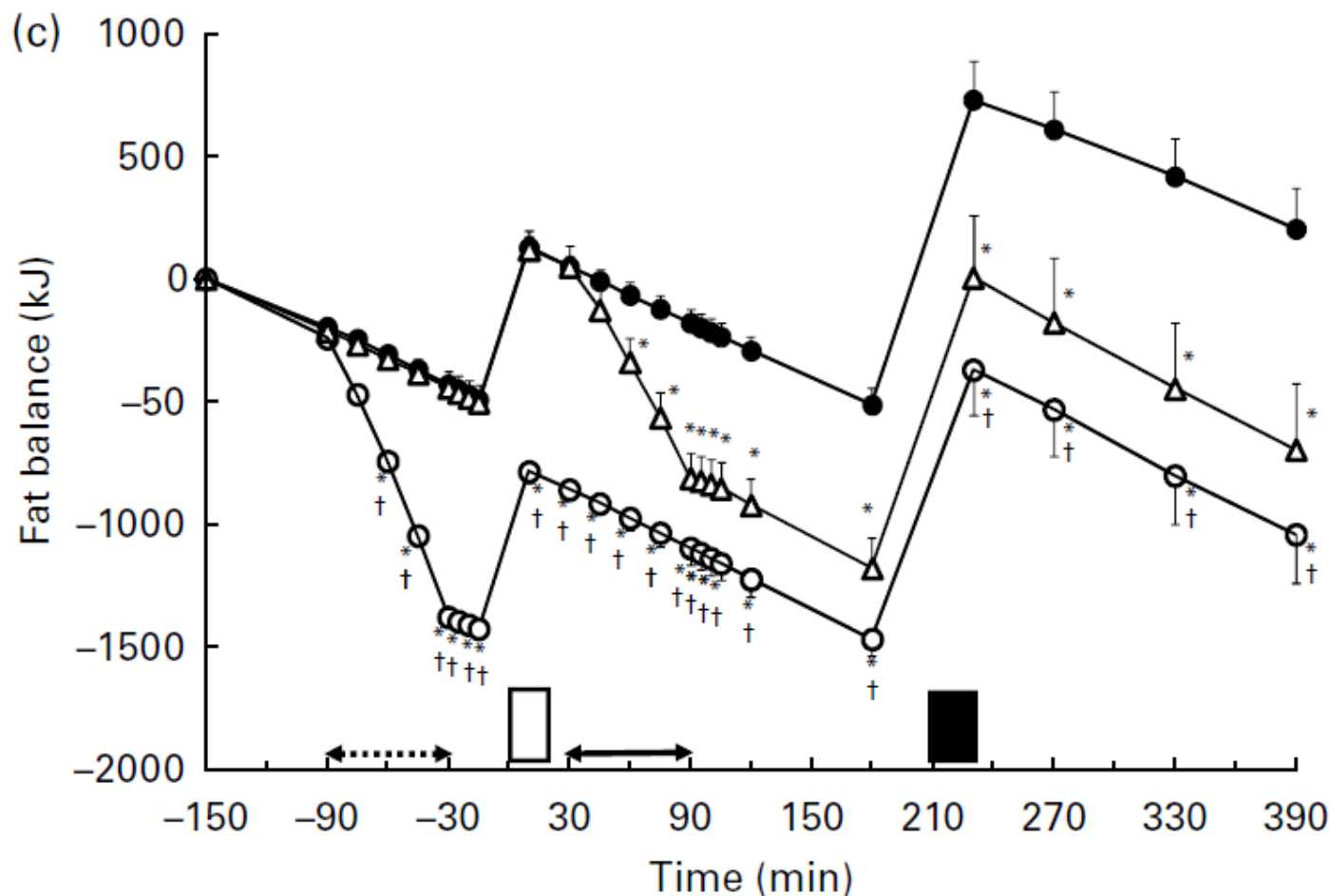


Effects of exercise before or after breakfast on energy and fat balance



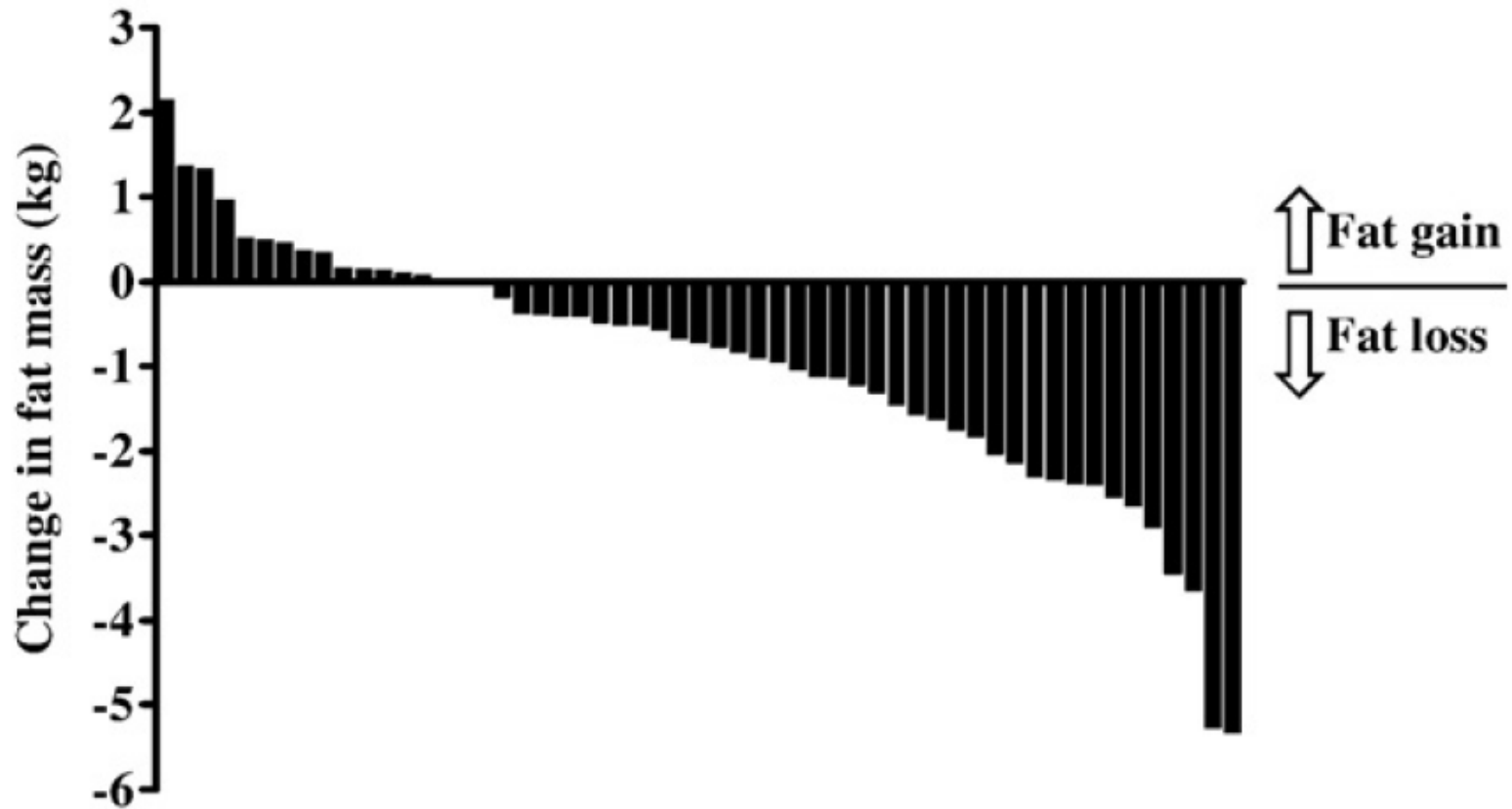
Farah et al (2013) Br J Nutr 109: 2297-2307

Effects of exercise before or after breakfast on energy and fat balance



Longer-term effects of exercise on body fat

Individual variability in weight loss response to exercise





Factors influencing individual variability of in weight loss response to exercise



Differences in dietary compensation

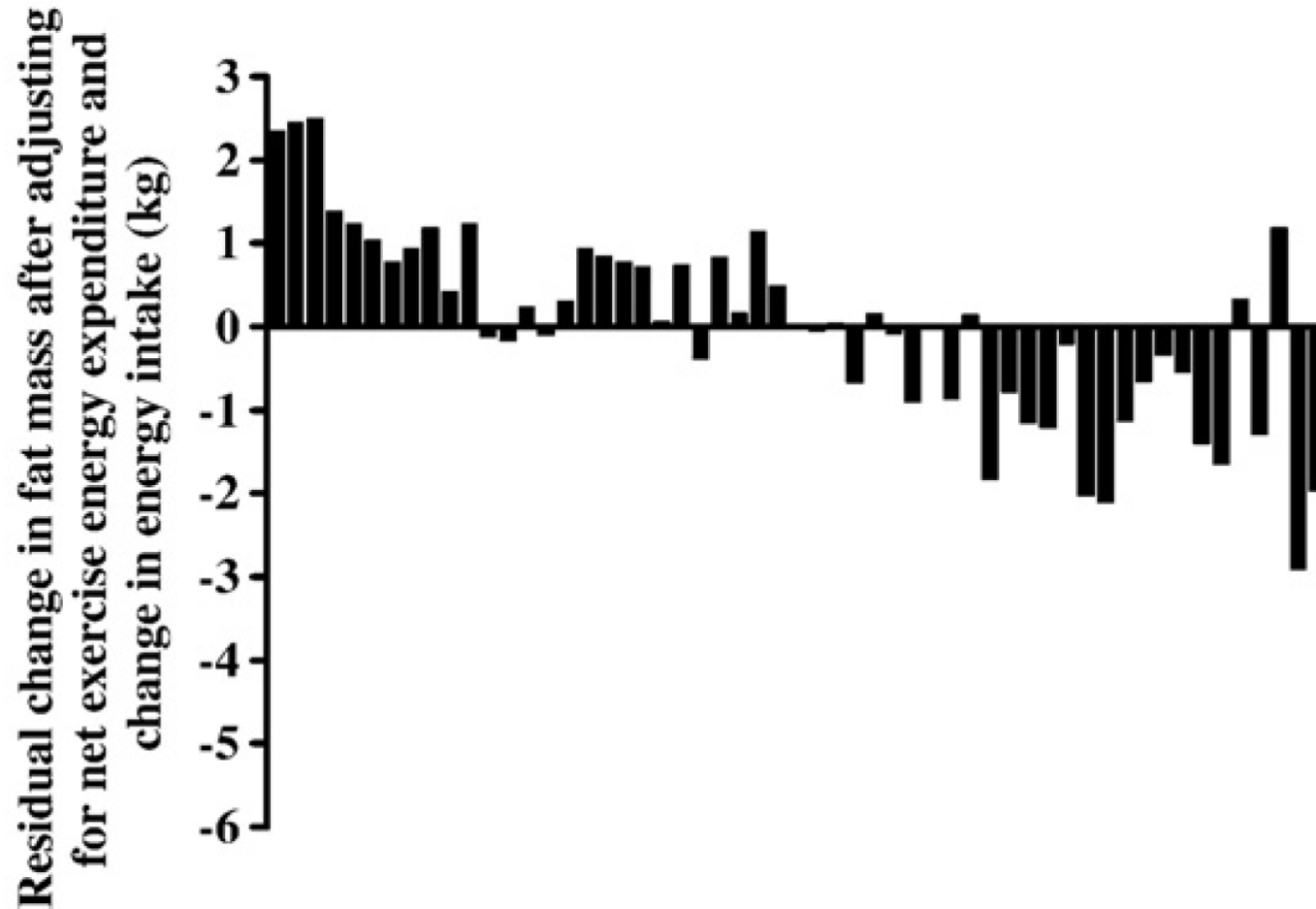
King et al (2008) *Int J Obes* 32:177-84



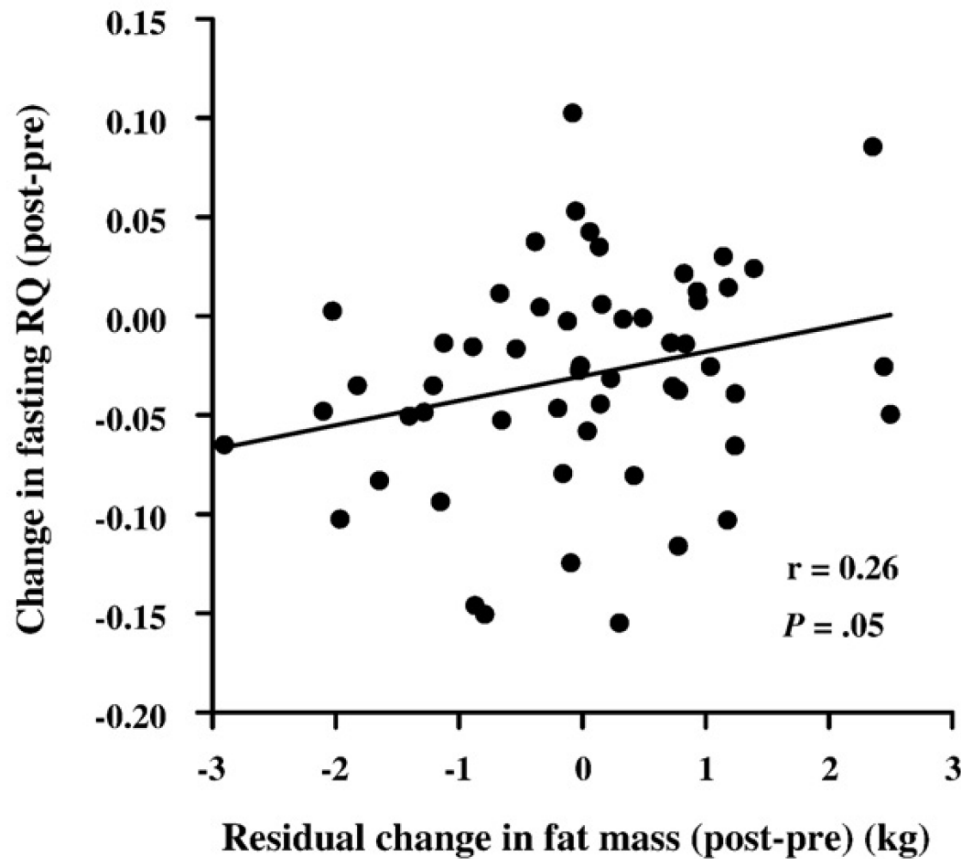
Differences in physical activity compensation

Manthou et al (2010) *Med Sci Sports Exerc*
42:1221-1228

Individual variability in weight loss response to exercise



Individual variability in weight loss response to exercise



Funders

- Diabetes UK
- Translational Medicine Research Initiative
- Chest Heart and Stroke Scotland
- European Commission
- MRC



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