Interactions of exercise and diet in health prevention

Dr Jason Gill
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• Physical activity and health outcomes – does one size fit all?

• Physical activity and postprandial lipoprotein metabolism

• Physical activity, dietary intake and energy balance
Referendum on the United Kingdom's membership of the European Union

Vote only once by putting a cross \( \times \) in the box next to your choice.

Should the United Kingdom remain a member of the European Union or leave the European Union?

- Remain a member of the European Union \( \times \)
- Leave the European Union
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.\textsuperscript{7} Hazard ratio for all-cause mortality of smoking was obtained from meta-analysis studies.\textsuperscript{8,9} All inactivity data were obtained from Lee and colleagues.\textsuperscript{5}

A brief history of physical activity guidelines (for adults)

Start Active, Stay Active
A report on physical activity for health from the four home countries’ Chief Medical Officers

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?


Risk of vascular or metabolic disease

High-risk populations
Low-risk populations

Low absolute disease risk
Lean subjects

Time (h) 0 2 4 6 8
Plasma insulin (µU.ml⁻¹)

Centrally obese subjects

Time (h) 0 2 4 6 8
Plasma insulin (µU.ml⁻¹)

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


(n = 495,786)
Fitness, physical activity and risk of mortality in UK Biobank


(n = 76,702)
Five-sixths of the World’s population is not of White European origin.
Ethnicity, BMI and diabetes prevalence in UK Biobank

Diabetes risk progression

Sattar and Gill (2015) Lancet Diabetes Endocrinol
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
Lifestyle reduces absolute diabetes incidence by ~5-7 cases per 100 in patients with IGT

Sattar and Gill (2015) Lancet Diabetes Endocrinol
Diabetes risk progression

Sattar and Gill (2015) Lancet Diabetes Endocrinol
Diabetes risk progression

Sattar and Gill (2015) Lancet Diabetes Endocrinol
Diabetes risk progression

Sattar and Gill (2015) Lancet Diabetes Endocrinol
Diabetes risk progression

Sattar and Gill (2015) Lancet Diabetes Endocrinol
The Indian Diabetes Prevention Programme

Diabetes risk progression

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

Sattar and Gill (2015) Lancet Diabetes Endocrinol
Diabetes risk progression

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

Sattar and Gill (2015) Lancet Diabetes Endocrinol
Hypothesised mechanisms for South Asians’ increased diabetes risk

- Genetic factors?
- Fetal programming?
- Epigenetic factors
- Lifestyle factors (urbanisation, diet, physical activity)

- Lower brown adipose tissue activity / volume?
- Higher percentage fat mass
- Lower capacity for subcutaneous fat storage
- Lower percentage lean mass
- Lower cardiorespiratory fitness
- Lower capacity for muscle fat oxidation
- Lower beta cell capacity?

- Greater proportion of deep subcutaneous / visceral fat
- Greater ectopic fat (e.g. liver)
- Increased insulin resistance
- Lifelong compensatory hyperinsulinaemia
- Earlier beta cell insufficiency/failure

- Increased type 2 diabetes

Sattar and Gill (2015) Lancet Diabetes Endocrinol
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Sattar and Gill (2015) Lancet Diabetes Endocrinol
## Adiposity, fitness and insulin resistance in South Asian and European men

<table>
<thead>
<tr>
<th></th>
<th>South Asians (n = 20)</th>
<th>Europeans (n = 19)</th>
<th>P (unadjusted)</th>
<th>P (adjusted for age, BMI and fat mass)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>26.9 ± 3.9</td>
<td>24.5 ± 5.5</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>BMI (kg.m(^{-2}))</td>
<td>23.6 ± 2.9</td>
<td>22.6 ± 2.7</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>Total fat mass (kg)</td>
<td>18.4 ± 5.3</td>
<td>13.6 ± 5.2</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>(\text{VO}_2\text{max (ml.kg}^{-1}.\text{min}^{-1}))</td>
<td>40.6 ± 6.6</td>
<td>52.4 ± 5.7</td>
<td>&lt; 0.0005</td>
<td>0.001</td>
</tr>
<tr>
<td>(\text{VO}_2\text{max (ml.kg}^{-1} \text{fat-free mass.min}^{-1}))</td>
<td>54.1 ± 6.6</td>
<td>64.3 ± 5.8</td>
<td>&lt; 0.0005</td>
<td>0.001</td>
</tr>
<tr>
<td>Fasting glucose (mmol.l(^{-1}))</td>
<td>5.14 ± 0.47</td>
<td>5.24 ± 0.52</td>
<td>0.53</td>
<td>0.94</td>
</tr>
<tr>
<td>Fasting insulin (mU.l(^{-1}))</td>
<td>6.56 ± 3.53</td>
<td>5.39 ± 4.20</td>
<td>0.11</td>
<td>0.023</td>
</tr>
<tr>
<td>2 hour insulin (mU.l(^{-1}))</td>
<td>46.6 ± 29.6</td>
<td>27.5 ± 5.3</td>
<td>0.017</td>
<td>0.043</td>
</tr>
<tr>
<td>Insulin sensitivity index</td>
<td>5.89 ± 2.93</td>
<td>7.96 ± 3.49</td>
<td>0.048</td>
<td>0.012</td>
</tr>
</tbody>
</table>

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

Breeding rats for low fitness makes them insulin resistant.

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

Ghouri et al. (2013) Diabetologia, 56:2238-49
Impaired skeletal muscle oxidative capacity as a mechanism for greater insulin resistance in South Asians?

Fatty acid uptake

Fatty acid oxidation

MISMATCH

TG → LCACoA → Ceramide → PKC → ↓IR → ↓IRS1 → ↓PI3K → ↓GLUT4

DAG → ↓PKB

INSULIN RESISTANCE
Fat oxidation during submaximal exercise in South Asian and European men
Fat oxidation during submaximal exercise in South Asian and European men

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?
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


Physical activity level

- Low: 150 minutes per week
- High: ~230-250 minutes per week

Cardio-metabolic disease risk

Low absolute disease risk

South Asians

European
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.\textsuperscript{166}

Mechanisms behind protective effect of physical activity

HDL cholesterol in runners

N = 8283 men

Neutral Lipid Exchange

Triglyceride-rich lipoproteins

Cholesterol-rich lipoproteins

Hepatic lipase

Low HDL

Small dense LDL

Atherogenic Lipoprotein Phenotype
Role of postprandial lipid metabolism in the progression of atherosclerosis

- 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

- LIVER
- VLDL
- ADIPOSE TISSUE
- Fatty Acids
- REMNANTS
- SKELETAL MUSCLE
- LPL
- Fatty Acids
Triglyceride metabolism in the postprandial state

LIVER

ADIPOSE TISSUE

VLDL

SKELETAL MUSCLE

SMALL INTESTINE

Chylomicrons

LPL

Fatty Acids

remnants
Postprandial lipaemia in trained and untrained men

Postprandial lipaemia in trained and untrained men

Long-term training adaptation or acute effect of recent exercise?
Detraining and postprandial lipaemia

Hardman et al (1998), JAP, 84:1895-1901
Experimental protocol

Day 1
- Exercise or
  Rest

Day 2
- Oral fat tolerance test

Time (hours):
0  2  4  6
Moderate exercise and postprandial TG concentrations in lean and obese men

Energy deficit?

exercise → lipids
Exercise, energy intake restriction and postprandial metabolism

Exercise, energy intake restriction and postprandial metabolism

Exercise with and without energy deficit and postprandial metabolism

Control  
Exercise with energy deficit

Plasma TG (mmol.L⁻¹)

Time (min)

0  60  120  180  240  300  360  420  480

0.5  1.0  1.5  2.0  2.5  3.0


Test meal

14%

18%
Exercise with and without energy deficit and postprandial metabolism

- Control
- Exercise with energy replacement
- Exercise with energy deficit

Mechanisms?

exercise

lipids
Triglyceride-rich lipoprotein metabolism

- LIVER
- VLDL₁
- VLDL₂
- HL
Triglyceride-rich lipoprotein metabolism
Triglyceride-rich lipoprotein metabolism

- **LIVER**
- **LPL**
- **CM**
- **VLDL$_1$**
- **VLDL$_2$**
- **HL**
- **Remnants**
Moderate exercise and postprandial TG-rich lipoprotein concentrations

Effects of exercise on triglyceride-rich lipoprotein metabolism

- Liver (LIVER)
- Very Low-Density Lipoprotein 1 (VLDL₁)
- Very Low-Density Lipoprotein 2 (VLDL₂)
- Chylomicrons (CM)
- Hepatic Lipase (HL)
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,† 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.
VLDL₁ Metabolism in the Fasted State

LIVER

VLDL₁

ADIPOSE TISSUE

Fatty Acids

LPL

remnants

SKELETAL MUSCLE

Fatty Acids
Effect of Chylomicrons (CM) & CM-like Particles on VLDL$_1$ Clearance

- LIVER
- ADIPOSE TISSUE
- SKELETAL MUSCLE
- VLDL$_1$
- Chylomicrons or Intralipid
- Fatty Acids
- LP L
- Fatty Acids
- LP L
- remnants
Bolus Intralipid dose: 0.1 g.kg⁻¹ body mass

0.1 g.kg⁻¹.h⁻¹ Intralipid infusion for 75 mins

Two fasting baseline and multiple EDTA blood samples are drawn before, during and post-infusion

Intralipid, VLDL₁ and VLDL₂ fractions are separated by density gradient ultracentrifugation.

Kinetic Data Obtained from the ‘Intralipid Method’

Effects of moderate exercise on VLDL\(_1\) and Intralipid kinetics in overweight/obese middle-aged men

Iqbal A. R. Al-Shayji, Muriel J. Caslake, and Jason M. R. Gill

Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, Scotland, United Kingdom

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

Al-Shayji IA, Caslake MJ, Gill JM. Effects of moderate exercise on VLDL\(_1\) 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 (VLDL\(_1\)) 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 VLDL\(_1\) catabolism, in random order. On the afternoon prior to infusion, subjects either walked on a treadmill for 2 h at \(\sim\)50% maximal oxygen uptake or performed no exercise. Multiple blood samples were taken during and after infusion for separation of Intralipid (S\(_{400}\)) and VLDL\(_1\) (S\(_{60–400}\)). VLDL\(_1\)-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 VLDL\(_1\)-TG concentration by 30\% (P = 0.007) and increased TG enrichment of VLDL\(_1\) particles by 30\%, decrease in cholesterol ester VLDL\(_1\) (S\(_{60–400}\)) fraction (16), than in intestinally derived chylomicrons. As high concentrations of VLDL\(_1\) are the major determinant of elevated plasma TG levels (27, 39), and VLDL\(_1\) are the primary precursor particles for atherogenic small-dense LDL (34), reducing VLDL\(_1\) concentration is likely to induce clinically important changes to the atherosclerotic risk profile. Exercise-induced reduction in circulating VLDL\(_1\) could reflect reduced hepatic VLDL\(_1\) production, increased lipoprotein lipase (LPL)-mediated VLDL\(_1\) 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 VLDL\(_1\) (S\(_{60–400}\)) and smaller cholesterol-rich
### Effects of moderate exercise on TRL kinetics

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Exercise</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fasting plasma TG (mmol/l)</strong></td>
<td>1.54 ± 0.16</td>
<td>1.21 ± 0.15*</td>
<td>-21%</td>
</tr>
<tr>
<td><strong>Fasting VLDL$_1$ concentration (mg/dl)</strong></td>
<td>94.9 ± 14.1</td>
<td>62.9 ± 11.4*</td>
<td>-34%</td>
</tr>
<tr>
<td><strong>VLDL$_1$-TG production rate (mg/h)</strong></td>
<td>1272 ± 156</td>
<td>1432 ± 148</td>
<td>+13%</td>
</tr>
<tr>
<td><strong>VLDL$_1$-apoB production rate (mg/h)</strong></td>
<td>37.2 ± 7.4</td>
<td>41.5 ± 5.4</td>
<td>+12%</td>
</tr>
<tr>
<td><strong>Intralipid-TG FCR (pools/d)</strong></td>
<td>47.6 ± 6.8</td>
<td>68.1 ± 9.7*</td>
<td>+43%</td>
</tr>
<tr>
<td><strong>VLDL$_1$-TG FCR (pools/d)</strong></td>
<td>16.0 ± 2.1</td>
<td>29.1 ± 4.4*</td>
<td>+82%</td>
</tr>
<tr>
<td><strong>VLDL$_1$-apoB FCR (pools/d)</strong></td>
<td>10.4 ± 2.0</td>
<td>25.6 ± 5.1*</td>
<td>+146%</td>
</tr>
</tbody>
</table>

* $p < 0.05$ for Control vs Exercise

Effects of moderate exercise on TRL kinetics

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

Khloud Ghafouri, Josephine Cooney, Dorothy K. Bedford, John Wilson, Muriel J. Caslake*, Jason M.R. Gill*

Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, U.K.

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.
Effects of moderate exercise on affinity of TRL for LPL

Ghafouri et al. (2015) J Clin Endocrinol Metab 100:2205-13
Table 3. Lipoprotein Affinity for LPL

<table>
<thead>
<tr>
<th></th>
<th>NEFA release (mmol·min⁻¹ per mmol lipoprotein per unit LPL activity)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fasting (0 min)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>Chylomicrons</td>
<td></td>
</tr>
<tr>
<td>VLDL₁</td>
<td>0.16 (0.09 to 0.29)</td>
</tr>
<tr>
<td>VLDL₂</td>
<td>0.013 (0.004 to 0.044)</td>
</tr>
</tbody>
</table>

Values are mean ± 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)
Effects of exercise training, without weight loss, on body fat


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

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

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

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

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

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

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 weight loss response to exercise

Differences in dietary compensation


Differences in physical activity compensation

Individual variability in weight loss response to exercise

Individual variability in weight loss response to exercise

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