Physical activity, fitness and cardiovascular disease risk in adults: interactions with insulin resistance and obesity

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ABSTRACT

There is a considerable body of evidence gathered from studies over the past half a century indicating that a high level of physical activity and a moderately high or high degree of cardiorespiratory fitness reduces the risk of CVD (cardiovascular disease). Recent data suggest that high levels of physical activity or fitness may be particularly beneficial to individuals with insulin-resistant conditions, such as the metabolic syndrome, Type II diabetes or obesity. These individuals, if unfit and sedentary, exhibit increased CVD risk, but their dose–response relationship for physical activity/fitness appears to be particularly steep such that, when they undertake high levels of activity (or have high fitness), their level of risk becomes closer to that of their normal weight or non-diabetic peers. This may be due to effects of physical activity in normalizing the metabolic dysfunction particularly associated with insulin-resistant conditions.

EPIDEMIOLOGY OF PHYSICAL ACTIVITY, FITNESS AND CVD (CARDIOVASCULAR DISEASE)

Over 50 years ago, Professor Jerry Morris published his seminal studies [1] in the Lancet showing that London bus conductors, who spent their working lives walking up and down the steps of double-decker buses, had lower CHD (coronary heart disease) mortality rates than the drivers of the same buses, and that London postmen, who spent their days walking to deliver letters, had a lower incidence of CHD mortality than the more sedentary clerks and telephonists working in the postal offices. During the half-century since Professor Morris’s initial insights, there has been considerable study into the role of physical activity and fitness in CVDs. Broadly, two epidemiological approaches have been adopted, with studies either using questionnaires to evaluate physical activity levels or objective fitness tests to measure cardiorespiratory fitness (hereafter termed ‘fitness’): the latter being a physiological ‘characteristic’ largely conferred by the former ‘behaviour’ (although it should be noted that heritable factors are estimated to contribute between 10–50% of the variance in fitness [2,3]). Meta-analyses of epidemiological studies evaluating the effects of physical activity or fitness on CVDs, incorporating over

Key words: cardiovascular disease, fitness, insulin resistance, obesity, physical activity, Type II diabetes.

Abbreviations: ACLS, Aerobics Center Longitudinal Study; AMPK, AMP-activated protein kinase; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CI, confidence interval; CPT I, carnitine palmityltransferase I; CRP, C-reactive protein; CVD, cardiovascular disease; DAG, diacylglycerol; GS, glycogen synthase; HDL, high-density lipoprotein; HL, hepatic lipase; HOMA, homeostasis model assessment; IGT, impaired glucose tolerance; IL, interleukin; IRS, insulin receptor substrate; IVGTT, intravenous glucose tolerance test; LCACoA, long-chain acyl-CoA; LDL, low-density lipoprotein; MAPK, mitogen-activated protein kinase; NO, nitric oxide; PI3K, phosphoinositide-3-kinase; TG, triacylglycerol; TNF-α, tumour necrosis factor-α; V̇O₂max, maximal oxygen uptake.

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2.5 million person-years of observation, reveal a clear inverse dose–response relationship between physical activity/fitness and CVD risk in both men and women, with active or fit groups reducing their CVD risk by approx. one-third to a half compared with their sedentary/unfit counterparts [4–6]. The relative risk of CVD mortality associated with low fitness (bottom 20 % of the population) is at least as great as that associated with smoking, hypertension and hypercholesterolaemia [7] and, although the majority of data have been collected on middle-aged men, there is evidence that high fitness and/or physical activity levels reduce the risk of cardiovascular mortality in women [4] and older adults [8]. In addition, high physical activity/fitness levels are also strongly associated with reduced cardiovascular mortality in men with pre-existing CVD [9–11], although in such studies it is possible that reverse causality may contribute to this effect (i.e. severe disease may have limited the activity/fitness levels of some men).

**PHYSICAL ACTIVITY/FITNESS AND CVD RISK IN INSULIN-RESISTANT POPULATIONS**

Insulin-resistant conditions such as the metabolic syndrome – a multifaceted metabolic disorder encompassing insulin resistance, central obesity, dyslipidaemia and hypertension – and Type II diabetes are increasing in prevalence in both developed and developing countries. It is estimated that the worldwide incidence of diabetes was approx. 171 million adults (approx. 2.8 % of the population) in 2000; this is expected to at least double over the next 25 years [12]. Recent estimates suggest that prevalence of the metabolic syndrome is approx. 15–30 % in middle-aged European/American adults [13,14]. Type II diabetes increases risk of cardiovascular mortality 2–4-fold [15–17], and recent data suggest that the metabolic syndrome increases cardiovascular risk to a similar degree [13,14]. There are suggestions that the increased cardiovascular risk associated with Type II diabetes is mediated by the effects of insulin resistance/metabolic syndrome. Data from the Third National Health and Nutrition Examination Survey (NHANES III) indicated that, while prevalence of coronary heart disease was increased in middle-aged/older adults possessing the metabolic syndrome whether they were diabetic or not, CHD prevalence in diabetic adults without the metabolic syndrome was no higher than the background population [18].

One emerging aspect of the epidemiological literature is that physical activity/fitness can offer some (but not complete) protection against the excess risk of CVD associated with insulin-resistant conditions. A report from the Whitehall study (n = 6408; [19]) examined the effects of leisure time physical activity and usual walking pace on CHD mortality in men with normoglycaemia and men with IGT (impaired glucose tolerance) or diabetes. In this study [19], there was a steeper dose–response relationship between level of physical activity (or usual walking pace) and CHD mortality risk in men with IGT/diabetes compared with normoglycaemic men. Thus men with IGT/diabetes with a high level of physical activity (or a fast usual walking pace) experienced a greater reduction in CHD mortality risk compared with their inactive counterparts than was observed when comparing CHD mortality risk in active compared with inactive normoglycaemic men (Figure 1). This is in broad agreement with an early report from the ACLS (Aerobics Center Longitudinal Study; n = 8715; [20]), which found that, after adjusting for other risk factors, the relative risk of all-cause mortality associated with low fitness (bottom 20 % of the population) was 1.38 for men with fasting glucose < 6.4 mmol/l, 1.61 for men with fasting glucose 6.4–7.8 mmol/l and 1.92 for men with fasting glucose ≥ 7.8 mmol/l or with physician-diagnosed diabetes, compared with fitter men with the same glycaemic status, although the 95 % CI (confidence interval) included one in the latter two groups. A more recent paper from the ACLS (n = 19 223; [21]) reported that, although unifit (bottom 20 % of the population) men with the metabolic syndrome [according to NCEP-ATPIII (National Cholesterol Education Program Adult Treatment Panel III) criteria] experienced a cardiovascular mortality rate of 31.0 deaths/10 000 man-years of observation, this dropped to 11.9 deaths/10 000 man-years in men with the metabolic syndrome who were fit. In men without the metabolic syndrome, cardiovascular mortality rates were 19.0 and 5.0 deaths/10 000 man-years for unfit and fit men respectively [21]. Although it is important to note that a greater proportion of men with the metabolic syndrome were classified as unfit than men without the metabolic syndrome (35 compared with 9 % respectively), it is clear that cardiovascular fitness sharply attenuated the excess CVD risk associated with the condition.

Taken together, these data suggest that physical activity may be particularly effective in reducing the excess CVD risk experienced by insulin-resistant individuals, but this suggestion requires confirmation in further studies.

**INTERACTIONS BETWEEN OBESITY, PHYSICAL ACTIVITY, FITNESS AND CVD RISK**

As insulin resistance increases with increasing adiposity, particularly abdominal adiposity [22], the overweight and obese form a large sector of the population with increased insulin resistance who may benefit particularly from high levels of fitness or physical activity.

The concept that a high level of physical activity and/or fitness might offer protection from the adverse cardiovascular consequences of obesity has gained considerable momentum over recent years. As early as 1970, Ralph Paffenbarger and co-workers [23] reported data from their seminal study of San Francisco Longshoremen
Figure 1  Leisure-time physical activity and age-adjusted CHD mortality rates in normoglycaemic men (n = 6056) and men with IGT/diabetes (n = 352) in the Whitehall study

CHD mortality decreased with increasing leisure-time activity in both normoglycaemic men (P = 0.006 for trend) and men with IGT/diabetes (P = 0.003 for trend), but the magnitude of the association between activity and CHD mortality was stronger in the men with IGT/diabetes (P = 0.03 for interaction). Figure was drawn from data in [19].

(dockworkers), suggesting a possible interaction between physical activity, fatness and cardiovascular risk. Longshoremen who were above the average weight-for-height and employed in inactive jobs experienced approx. 1.7 times the CHD death incidence as men below average weight-for-height who were also employed in inactive jobs, whereas men above average weight-for-height employed in active jobs only experienced approx. 1.1 times the CHD death incidence as their colleagues who were below average weight-for-height also employed in active jobs [23]. Since then a number of reports (summarized in Tables 1 and 2) have examined the relationship between physical activity or fitness, body habitus and CVD or CHD incidence [24–39]. Taken together, the weight of evidence from epidemiological studies of physical activity or fitness and body fatness indicates that a physically active lifestyle and/or a moderately high level of fitness (i.e. not in the bottom 20% of the population) reduces the risk of CVD/CHD in the overweight and obese to the extent that an active or fit overweight or obese individual is likely to exhibit lower CVD risk than an inactive or unfit individual of ‘normal’ weight. However, a fit/active person who is overweight or obese probably still exhibits increased CVD risk compared with a fit/active normal weight person. Furthermore, the magnitude of CVD risk reduction associated with high activity may be greater in the overweight/obese than in their leaner counterparts (i.e. the dose–response relationship between increased activity/fitness and CVD risk reduction may be steeper in overweight/obese groups compared with lean groups).

Thus, in terms of CVD risk management, it is important for the overweight and obese to adopt and maintain a physically active lifestyle, irrespective of whether they lose weight, and for both overweight/obese individuals and healthcare workers to appreciate that the benefits of physical activity go beyond its role in facilitating weight loss. This latter point is important as the weight of available evidence suggests that, using currently available intervention strategies, the chance of an obese individual sustaining substantial long-term weight loss is very low [40,41]. Thus, while being fit/active and lean/normal weight maximizes CVD risk reduction, this ideal is likely to be unachievable for many obese individuals, and becoming fit/active while remaining fat may be a more sustainable goal. Although the authors fully appreciate the beneficial effects of weight loss for the obese, on a purely pragmatic level, it is perhaps time to consider promoting ‘active living’ (which may or may not induce weight loss) rather than weight loss itself as a primary goal of lifestyle-based obesity management programmes. The long-term (i.e. over years rather than months) efficacy of ‘active living’ compared with weight-loss interventions in attenuating cardiovascular risk in obese populations requires testing in a randomized controlled trial. However, given the difficulties of obesity management, it is also clear that prevention of obesity in the first place must remain our ultimate goal, and this is likely to require
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<td>Paffenbarger (1970) [23]</td>
<td>3263 US male dockworkers aged 35–64 years on entry.</td>
<td>16</td>
<td>Physical activity level based on occupational activity (estimated difference between more and less active jobs ( \sim ) 925 kcal/day).</td>
<td>Above or below mean body-weight-for-height</td>
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<td>Relative risk of CHD death for less active vs more active occupations: 1.08 for below average weight-for-height, and 1.56 for above average weight-for-height.</td>
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<td>Paffenbarger (1978) [24]</td>
<td>16 936 US male Harvard Alumni aged 35–74 years on entry.</td>
<td>6–10</td>
<td>Self-reported physical activity by questionnaire, converted into estimated kcal/week.</td>
<td></td>
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<td>Relative risk of non-fatal or fatal heart attack for physical activity level (&lt;) 2000 kcal/week vs (\geq) 2000 kcal/week: 1.68 ((P &lt; 0.001)) for BMI &lt; 26.7 kg/m(^2), and 1.33 ((P = 0.206)) for BMI (\geq) 26.7 kg/m(^2).</td>
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<td>Morris (1980) [25]</td>
<td>17 944 English male civil servants aged 40–65 years on entry.</td>
<td>8.5</td>
<td>5 min by 5 min self-reported physical activity on previous Friday and Saturday.</td>
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<td>Age</td>
<td>Rate percentage for first CHD attack for men reporting no vigorous exercise vs reporting vigorous exercise: 5.2 vs 2.4 for BMI &lt; 23.0 kg/m(^2), 6.9 vs 3.3 for BMI 23.1–25.0 kg/m(^2), 6.9 vs 4.4 for BMI 25.1–28.0 kg/m(^2), and 8.8 vs 0.7 for BMI &gt; 28.1 kg/m(^2).</td>
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<td>Salonen (1988) [27]</td>
<td>15 088 Finnish men and women aged 30–59 years on entry.</td>
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<td>Crude rate of ischaemic heart disease death (per 1000 persons) for sedentary occupation/low-leisure-time activity vs sedentary occupation/high-leisure-time activity vs active occupation/low-leisure-time activity vs active occupation/high-leisure-time activity; men, 25.86 vs 19.90 vs 14.08 vs 8.10 for BMI &lt; 27 kg/m(^2), and 41.67 vs 8.64 vs 17.14 vs 7.37 for BMI (\geq) 27 kg/m(^2); and women, 0.00 vs 1.15 vs 3.18 vs 0.45 for BMI &lt; 27 kg/m(^2), and 0.00 vs 6.15 vs 2.05 for BMI (\geq) 27 kg/m(^2).</td>
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<tr>
<td>Morris (1990) [28]</td>
<td>9376 English male civil servants aged 45–64 years on entry.</td>
<td>9.33</td>
<td></td>
<td>Self-reported height and body mass</td>
<td>Age, family history, height, energy output, health beliefs, smoking, health-conscious diet, weight change in past year and cardiovascular history</td>
<td>Rate per 1000 man-years of non-fatal and fatal CHD for group 4 vs group 3 vs group 2 vs group 1: 5.5 vs 4.3 vs 3.4 vs 1.9 for BMI &lt; 24 kg/m(^2), 6.2 vs 5.7 vs 6.0 vs 2.4 for BMI 24–26.9 kg/m(^2), and 7.3 vs 7.1 vs 4.8 vs 1.3 for BMI (\geq) 27 kg/m(^2).</td>
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Self-reported leisure-time physical activity. Height and body mass measured by investigators —

Deaths from CHD per 1000 person-years of observation for sedentary vs moderately active vs regular exercise/athletic sport participation: 4.6 vs 5.0 vs 3.0 for BMI < 24.1 kg/m², 6.2 vs 3.8 vs 3.1 for BMI 24.1–26.6 kg/m², and 7.4 vs 5.3 vs 4.3 for BMI ≥ 26.6 kg/m².


Self-reported leisure-time physical activity from 23-item questionnaire. Activity level categorized as low (0–1100 kcal/week), moderate (1101–1900 kcal/week) or high (≥ 1900 kcal/week). Self-reported height and body mass Age

Incidence of CHD (cases per 1000 person-years) for low vs moderate vs high activity: 14.3 vs 9.6 vs 7.3 for BMI < 27 kg/m², and 20.5 vs 11.9 vs 11.1 for BMI ≥ 27 kg/m².

Wessel (2004) [31] 936 US women with chest discomfort and/or suspected myocardial ischaemia aged 58 ± 12 years on entry (mean ± S.D.).

Self-reported physical activity by questionnaire used to estimate cardiorespiratory fitness. According to activity level women categorized as 'not fit' or 'fit'. Height and body mass measured by investigators —

Percentages of women experiencing any adverse event (all-cause death or hospitalization for non-fatal myocardial infarction, stroke, congestive heart failure, unstable angina or other vascular events) or a major adverse event (death, non-fatal myocardial infarction or non-fatal stroke) during follow-up for women categorized as not fit vs fit. All adverse events: 42.9 vs 23.9 for BMI < 30 kg/m², and 41.6 vs 28.4 for BMI ≥ 30 kg/m². Major adverse events: 16.8 vs 5.6 for BMI < 30 kg/m², and 14.3 vs 9.5 for BMI ≥ 30 kg/m².


Self-reported physical activity from eight-item physical activity questionnaire and estimate of h/week of physical activity over past year. Self-reported height and body mass Age, smoking, parental history of CHD, menopausal status, hormone use

Relative risk of death from CVD (with 95% CI) for < 1.0 vs 1.0–3.4 vs > 3.5 h/week of physical activity: 1.89 (1.51–2.37) vs 1.51 (1.22–1.87) vs 1.00 (reference) for BMI < 25 kg/m², 2.52 (1.96–3.25) vs 2.06 (1.62–2.60) vs 1.58 (1.15–2.16) for BMI 25.0–29.9 kg/m², and 4.73 (3.68–6.09) vs 4.26 (3.33–5.44) vs 2.87 (1.94–4.25) for BMI ≥ 30 kg/m².


Self-reported occupational and leisure-time physical activity by questionnaire merged into overall low-, moderate- and high-activity categories. Low-activity classed as inactive; moderate/high-activity classed as active. Height, body mass and waist and hip circumferences measured by investigators. WC and WHR were divided into quartiles 1–3 (Q1–3) and quartile 4 (Q4) —

Age, study year, SBP, total and HDL-cholesterol, education, smoking, diabetes at baseline.

Hazard ratio for CVD incidence for inactive vs active groups. Men, 1.42 vs 1.00 for BMI < 30 kg/m², and 2.02 vs 1.35 for BMI ≥ 30 kg/m². Women, 1.70 vs 1.00 for BMI < 30 kg/m², and 2.02 vs 1.56 for BMI ≥ 30 kg/m².

Men, 1.19 vs 1.00 for WC Q1–3; 2.16 vs 1.27 for WC Q4. Women, 1.92 vs 1.00 for WC Q1–3; 1.77 vs 1.43 for WC Q4. Men, 1.21 vs 1.00 for WHR Q1–3, and 2.42 vs 1.43 for WHR Q4. Women, 2.00 vs 1.00 for WHR Q1–3, and 1.36 vs 1.24 for WHR Q4.
Table 2  Epidemiological studies of fitness, body fatness and CHD or CVD risk
MET, metabolic unit (calculated as the exercising metabolic rate divided by the resting metabolic rate; 1 MET is equivalent to an oxygen uptake of 3.5 ml · min⁻¹ · kg⁻¹ of body weight).

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<td>Farrell (1998)</td>
<td>25 341 US men</td>
<td>8.4</td>
<td>Balke protocol treadmill test. Subjects classified as low (bottom 20 % of population), moderate (21–40 %) or high (61–100 %) fitness.</td>
<td>Height and body mass measured by investigators</td>
<td>Age, year of baseline examination, health status and smoking status</td>
<td>Rate of CVD mortality (per 10 000 person-years) for low- vs moderate- vs high-fit groups: 14.5 vs 9.6 vs 6.7 for BMI &lt; 27 kg/m², and 17.9 vs 10.6 vs 9.5 for BMI ≥ 27 kg/m².</td>
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<td>Lee (1998)</td>
<td>21 856 US men aged 30–83 years on entry.</td>
<td>8.1</td>
<td>Balke protocol treadmill test. Subjects classified as unfit (bottom 20 % of population) or fit (all others).</td>
<td>Height and body mass measured by investigators</td>
<td>Age, examination year, smoking habit and alcohol intake.</td>
<td>Relative risk of CVD mortality (with 95 % CI) for unfit vs fit groups: 2.8 (1.43–5.49) vs 1.0 for BMI 19.0–&lt; 25.0 kg/m², 3.7 (2.05–6.50) vs 1.8 (1.07–3.01) for BMI 25.0–&lt; 27.8 kg/m², and 4.8 (2.85–8.05) vs 1.8 (results not reported in text, but estimated from Figure) for BMI ≥ 27.8 kg/m².</td>
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<tr>
<td>Lee (1999)</td>
<td>21 925 US men aged 30–83 years on entry.</td>
<td>8</td>
<td>Balke protocol treadmill test. Subjects classified as unfit (bottom 20 % of population) or fit (all others).</td>
<td>Percentage body fat measured by skinfolds or hydrostatic weighing</td>
<td>Age, examination year, smoking habit and alcohol intake and parental history of ischaemic heart disease.</td>
<td>Relative risk of CVD mortality (with 95 % CI) for unfit vs fit groups: 3.16 (1.12–8.92) vs 1.00 for &lt; 16.7 % body fat, 2.94 (1.48–5.83) vs 11.43 (0.77–2.67) for 16.7 to &lt; 25 % body fat, and 4.11 (2.85–7.68) vs 1.35 (0.66–2.76) for ≥ 25 % body fat.</td>
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<td>Wei (1999)</td>
<td>25 714 US men aged 43.8 ± 10.1 years on entry (mean ± S.D.)</td>
<td>10</td>
<td>Balke protocol treadmill test. Subjects classified as low fitness according to maximal MET score: age 20–39 years, &lt; 10.5 METs; 40–49 years, &lt; 9.9 METs; 50–59 years, &lt; 8.8 METs; and ≥ 60 years, ≤ 7.5 METs.</td>
<td>Height and body mass measured by investigators</td>
<td>Age and examination year.</td>
<td>Relative risk of CVD mortality (with 95 % CI) for low fitness vs moderate/high fitness groups: 3.1 (2.2–4.5) vs 1.0 for BMI 18.5–24.9 kg/m², 4.5 (3.4–6.0) vs 1.5 (1.1–2.0) for BMI 25.0–29.9 kg/m², and 5.0 (3.6–7.0) vs 1.6 (1.0–2.8) for BMI ≥ 30.0 kg/m².</td>
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<td>Stevens (2002)</td>
<td>2860 US men and 2506 US women aged 30–75 years on entry.</td>
<td>22–26</td>
<td>Bruce protocol treadmill test. Subjects classified as unfit (bottom 20 % of population) or fit (all others).</td>
<td>Height and body mass measured by investigators.</td>
<td>Age, education, smoking, alcohol and Keys score.</td>
<td>Hazard ratio for CVD mortality for unfit vs fit groups. Men, 1.55 vs 1.00 for not-fat group (BMI ≤ 28.6 kg/m²), and 1.67 vs 1.39 for fat group (BMI ≥ 28.7 kg/m²). Women, 1.53 vs 1.00 for not-fat group (BMI ≤ 27.6 kg/m²), and 1.95 vs 1.39 for fat group (BMI ≥ 27.7 kg/m²).</td>
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<td>Stevens (2004)</td>
<td>1716 US men and 1359 Russian men aged 40–59 years on entry.</td>
<td>18–23</td>
<td>Bruce protocol treadmill test. Subjects classified as unfit (bottom 20 % of population) or fit (all others).</td>
<td>Height and body mass measured by investigators. Subjects classified as fat (highest 20 % of population for BMI) or not fat (all others).</td>
<td>Age, education, smoking, alcohol and Keys Score.</td>
<td>Hazard ratio for CVD mortality for unfit vs fit groups. US men, 1.62 vs 1.00 for not-fat group (BMI ≤ 28.5 kg/m²), and 1.56 vs 1.32 for fat group (BMI ≥ 28.6 kg/m²). Russian men, 1.85 vs 1.00 for not-fat group (BMI ≤ 28.5 kg/m²), and 3.05 vs 0.94 for fat group (BMI ≥ 28.6 kg/m²).</td>
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changes to both the intake and output sides of the energy balance equation [42].

One point to note when considering the epidemiological evidence relating to physical activity or fitness, fatness and CVD/CHD risk is that the threshold for defining the fatter groups was often quite low. In all reports the BMI (body mass index) threshold for the fatter group was \(\leq 30 \text{ kg/m}^2\). Someone with a BMI of 40 kg/m\(^2\) is metabolically very different from someone with a BMI of 30 kg/m\(^2\), and there are very few data available to assess the effects of physical activity/fitness in CVD/CHD risk reduction in very obese populations. Caution is therefore advised in extrapolating currently available data to very obese population groups. In the context of the global obesity pandemic, there will be an increasing number of people falling into this category and more research is required to assess the potential benefits of physical activity in these individuals.

**MECHANISMS RESPONSIBLE FOR THE PROTECTIVE EFFECTS OF PHYSICAL ACTIVITY AND FITNESS**

Physical activity and fitness are known to influence a number of the traditional risk factors for CVD, including reducing BP (blood pressure) [43], increasing HDL (high-density lipoprotein)-cholesterol [although, interestingly, not consistently lowering total cholesterol or LDL (low-density lipoprotein)-cholesterol] [44] and reducing body fatness [45]. However, even after controlling for these factors, physical activity/fitness has still been shown to be an independent risk factor for CVD [46], indicating that, as well as influencing these traditional risk factors, physical activity influences CVD risk through other non-classical mechanisms. Potential mechanisms by which physical activity and fitness can influence CVD risk are shown in Figure 2, and some of the non-classical mechanisms are described briefly below.

**Lipoprotein subclass distribution and postprandial lipoprotein metabolism**

In addition to raising HDL-cholesterol concentration, it has been demonstrated that increasing physical activity induces a shift in lipoprotein subclass distribution, increasing the mean size of HDL and LDL particles [47], an atheroprotective effect as small-dense LDL and small HDL are features of the atherogenic lipoprotein phenotype [48], which is strongly implicated in the atherosclerotic disease process [49]. Exercise also reduces plasma TG (triglycerides) concentrations, particularly in the postprandial state [50]: this is likely to underpin much of the effect of exercise on HDL concentrations and HDL and LDL size, by reducing the potential for CETP (cholesteryl ester transfer protein)-mediated neutral lipid exchange between TG-rich lipo-

![Figure 2: Mechanisms by which physical activity is likely to influence CVD risk](image)

Inflammation

Evidence from a large number of mechanistic and epidemiological studies indicates that inflammation plays a central role in the progression of atherosclerotic diseases [56]. A number of epidemiological studies have demonstrated that increasing levels of physical activity are associated with lower circulating concentrations of inflammatory markers (such as CRP (C-reactive protein), SAA (serum amyloid A) and TNF-\(\alpha\) (tumour necrosis proteins and HDL and LDL [51,52]. The TG-lowering effects of exercise are largely a consequence of acute changes following recent exercise, rather than an exercise-training (i.e. fitness) effect [53,54], and the magnitude of the TG change following an exercise session is related to the energy expenditure of exercise, independent of exercise intensity [50]. It seems likely that a combination of increased lipoprotein-lipase-mediated TG clearance into exercised skeletal muscle and reduced hepatic production of VLDLs (very-LDLs) are responsible for this TG-lowering effect [50]. Thus the favourable lipoprotein profile evident in regular exercisers is likely to be mainly as a consequence of repeated acute effects of single exercise sessions on TG metabolism. A detailed evaluation of this topic is beyond the scope of the present review and for a detailed overview the reader is directed to recent reviews by Gill [55] and Gill and Hardman [50].
Physical activity, although further research in this area designed to reflect chronic low-grade inflammation [78]. Escherichia coli endotoxin in an experimental model in plasma TNF-α receptors [81]. Both acute exercise and infusion of recombinant IL-6 have been shown to inhibit the rise in plasma TNF-α in response to injection of low-dose Escherichia coli endotoxin in an experimental model designed to reflect chronic low-grade inflammation [78]. Thus it is possible that skeletal muscle production of IL-6 in response to acute exercise could be an important mediator of the long-term anti-inflammatory effects of physical activity, although further research in this area is needed. For a more detailed overview of the effects of exercise on inflammation, the interested reader is directed to recent reviews by Bruunsgaard [82] and Petersen and Pedersen [83].

Endothelial function

The production of NO (nitric oxide) by the vascular endothelium provides an important first-line defence against many atherogenic processes by maintaining vascular tone, inhibiting platelet aggregation, decreasing endothelial permeability, decreasing the expression of adhesion molecules and inhibiting vascular smooth muscle proliferation. Endothelial dysfunction, characterized by an impairment of endothelial NO production, is implicated in all stages of the atherosclerotic disease process, is associated with the presence of traditional CHD risk factors and is an independent predictor of future cardiovascular events [84]. Studies on the effects of exercise training on endothelial function in healthy volunteers with a high level of endothelial function at baseline are mixed, with some studies demonstrating an improvement (e.g., [85,86]), but others showing no effect (e.g., [87,88]). However, in groups with lower endothelial function, such as healthy older sedentary adults [89], adults with hypertension [86], Type II diabetes [90] or the metabolic syndrome [91], or patients with coronary artery disease [92,93] or heart failure [94,95], a number of weeks of exercise training has often been shown to substantially improve endothelial function, although in one study of patients with elevated LDL-cholesterol a 3-month diet and exercise intervention did not improve endothelial function, despite increasing cardiorespiratory fitness and reducing LDL-cholesterol concentrations [96]. We have recently demonstrated [97] that endothelial function in the cutaneous microcirculation is improved following a single moderate intensity exercise session in middle-aged adults. The mechanisms responsible for this improvement are not straightforward. Physical activity may influence endothelial function through its effects on other CHD risk factors, such as insulin resistance and HDL-cholesterol [98,99]. Certainly, Higashi et al. [86] found the exercise-training-induced change in forearm endothelial function was strongly correlated with the training-induced changes in total cholesterol/HDL-cholesterol ratio and LDL-cholesterol concentration. However, a relatively large report pooling data from exercise intervention studies (three exercise sessions/week for 8 weeks) in a diverse range of patient populations (untreated and treated hypercholesterolaemia, coronary artery disease patients, Type II diabetics, heart failure patients and normal controls) found that the exercise-induced changes in endothelial function in both conduit vessel (78% improvement, \( P < 0.0001; \ n = 47 \); assessed by flow-mediated dilatation) and resistance (57% improvement, \( P < 0.001; \ n = 71 \); assessed by venous occlusion plethysmography) vessels did not correlate with exercise-induced changes in cardiorespiratory fitness, lipids, glucose, glycated haemoglobin, BP or indices of body fatness [100], suggesting that exercise-induced changes in endothelial function may, at least in part, occur independently from the effects of exercise on ‘traditional’ CHD risk factors. It seems likely that exercise-induced increases in blood flow to skeletal muscles and the myocardium leading to increased sheer stress on the endothelial monolayer plays an important role in mediating exercise-induced changes in endothelial function. It
has been hypothesized that increased endothelial shear stress from repeated exercise sessions initially induces a up-regulation of eNOS (endothelial NO synthase) gene expression, which facilitates vasodilation, and then leads to longer-term structural adaptations to increase the lumen diameter [101,102]. It has also been suggested that exercise-training-induced increases to vascular antioxidant defences might play a role [102], but further research in this field is needed to more clearly elucidate the mechanisms involved. The interested reader is directed to recent reviews by Maiorana et al. [101] and Rush et al. [102] for a more detailed overview.

**Insulin resistance**

It is likely that the effects of physical activity on insulin sensitivity are central to its effects in reducing cardiovascular risk, particularly in insulin-resistant individuals. Few epidemiological studies of physical activity/fitness and CVD risk have assessed insulin resistance, but inclusion of surrogates for insulin sensitivity (fasting insulin, pro-insulin and split pro-insulin concentrations) in cardiovascular risk models attenuated the increased risk of CVD mortality associated with an inactive lifestyle in the ULSAM (Uppsala Longitudinal Study of Adult Men) [103], and even a relatively crude adjustment for non-fasting insulin concentrations reduced the trend for protection from diabetes with increasing physical activity in the British Regional Heart Study [104], implying that at least part of the protective effect of physical activity operates through insulin-sensitizing mechanisms. Furthermore, a number of recent large-scale clinical trials have shown that the lifestyle intervention incorporating increased physical activity is effective at preventing diabetes [105–108] and preventing or reversing the metabolic syndrome [109,110] in insulin-resistant population groups.

Insulin sensitivity and responsiveness (assessed by euglycaemic–hyperinsulinaemic clamp) has been shown to be improved for at least 2 days following a single session of exercise [111,112] and the magnitude of this effect is augmented by a period of exercise training [112,113], suggesting that exercise influences insulin action by both acute and chronic mechanisms. The molecular mechanisms by which physical activity can improve insulin action have been extensively reviewed on a number of occasions (e.g., [114–117]), but have not been fully elucidated and it is beyond the scope of this review to consider this in detail. Briefly, immediately following exercise there is an acute increase in glucose uptake in skeletal muscle, which is thought to be mediated through insulin-independent CaMK (Ca²⁺/calmodulin-independent protein kinase), MAPK (mitogen-activated protein kinase) and AMPK (AMP-activated protein kinase) pathways leading to increased GLUT-4 translocation to the cell surface [115–118]. An increase in insulin signalling through the IRS (insulin receptor sub-strate)-1-associated PI3K (phosphoinositide 3-kinase) pathway is sometimes also observed, but an increase in insulin signalling does not appear to be necessary to induce this initial enhancement of glucose uptake [117]. These effects last in the order of hours and appear to be related, at least in part, to carbohydrate availability and muscle glycogen depletion [114,116]. Superimposed on these immediate changes, more persistent effects of a single exercise session or exercise training may include increased insulin signalling [115,117], but others have reported exercise-training-induced increases in insulin-stimulated glucose uptake without up-regulation of the IRS-1-associated PI3K pathway [117].

One mechanism by which regular exercise may improve insulin sensitivity is by increasing skeletal muscle oxidative capacity. A relative oversupply of lipid in skeletal muscle due to a mismatch between fatty acid uptake and fatty acid oxidation can precipitate insulin resistance in muscle by increasing an accumulation of TG and the lipid intermediates, such as LCACoA (long-chain acyl-CoA), DAG (diacylglycerol) and ceramide [119]. Specifically, LCACoA, DAG and ceramide can inhibit insulin action through the activation of PKC (protein kinase C), which then inhibits IR (insulin receptor) tyrosine kinase activity and tyrosine phosphorylation of IRS-1, and also by inhibiting PKB (protein kinase B) [120,121]. Increasing evidence suggests that deficiencies in the oxidative capacity of skeletal muscle, especially with respect to oxidation of fatty acids, are likely to contribute to insulin resistance: activities of the muscle mitochondrial oxidative enzymes [citrate synthase and β-HAD (β-hydroxyacyl CoA dehydrogenase)] are reported to be strong predictors of whole-body glucose uptake during a euglycaemic–hyperinsulinaemic clamp [122], and activity of the mitochondrial enzyme CPT I (carnitine palmitoyltransferase I), the rate-limiting enzyme for entry of LCACoA into mitochondria, is reduced in insulin-resistant muscle [123,124]. Thus regular exercise could conceivably improve insulin sensitivity through it effects on skeletal muscle oxidative capacity. There are some data in the literature to support this suggestion. It has been reported that \( \text{VO}_{2\max} \) (maximal oxygen uptake; which, although not limited by skeletal muscle oxygen extraction [125], correlates strongly with skeletal muscle oxidative enzyme activities in heterogeneous populations [126,127]) is a strong predictor of insulin sensitivity and this is independent of visceral adiposity and family history of Type II diabetes [122,128,129]. A recent study reported that, in rats selectively bred for high- or low-aerobic capacity from the same founder population, the animals bred for low-aerobic capacity had significantly reduced expression of a number of skeletal muscle mitochondrial proteins (and 58 % lower \( \text{VO}_{2\max} \)), and also exhibited 131 % higher fasting insulin and 20 % higher fasting glucose than their counterparts bred for high-aerobic capacity [130], consistent with substantially
greater insulin resistance. Furthermore, in two previous reports, exercise-training-induced increases in \( V_{0} \text{max} \) [131] and fasting fat oxidation [132] were strong predictors of training-induced increases in insulin sensitivity, suggesting that training-induced increases in muscle oxidative capacity and fatty acid oxidation might contribute to the exercise-training-induced enhancement of insulin sensitivity, although further studies are needed to directly assess the effects of exercise-training-induced changes in skeletal muscle oxidative capacity on insulin action.

**INDIVIDUAL DIFFERENCES IN THE INSULIN SENSITIVITY RESPONSE TO EXERCISE TRAINING**

One clear finding is that there are marked differences in individual responsiveness to an exercise intervention programme in terms of changes in insulin sensitivity and glucose metabolism. In the HERITAGE Family Study, in which IVGTT (intravenous glucose tolerance test) data are available for 596 adults who all undertook the same 20-week exercise intervention, the mean training-induced improvements in insulin sensitivity and glucose effectiveness were 10 and 11%, respectively (both \( P < 0.001 \)) [133]. However, 42% of participants experienced no improvement in insulin sensitivity and 45% experienced no improvement in glucose effectiveness. This may, in part, be due to inherent variability in the study protocol (there was no control group to determine the test-retest repeatability of the IVGTT protocol employed), but a large part of this variability in individual responsiveness is likely to be real. The molecular and genetic determinants of differences in training responsiveness are likely to be complex and the HERITAGE investigators have subsequently published a series of further studies attempting to elucidate these [134–136]. In one report [134], skeletal muscle gene expression responses to training, were examined using microarray technology in eight subjects who showed large improvements in insulin sensitivity with training and eight subjects who showed no improvement. Interestingly, the authors [134] reported no obvious differences in the expression of genes encoding proteins involved in insulin signalling pathways (IRS-1, IRS-2, PI3K, MAPK and AMPK), glucose transport (GLUT-1 and GLUT-4), glycogen metabolism (GS (glycogen synthase) and GSK-3 (GS kinase-3)), glycolysis (HKII (hexokinase II) and PFK (phosphofructokinase)), mitochondrial function (COX4 (cytochrome c oxidase subunit 4) and ND4 (NADH-dehydrogenase subunit 4)), mitochondrial biogenesis (PGC-1 (peroxisome-proliferator-activated receptor \( \gamma \) co-activator-1), NRF (nuclear respiratory factor -1 and -2 and TFAM (mitochondrial transcription factor A)) or fatty acid oxidation (CPT I, UCP3 (uncoupling protein 3) and NADH6) between the high and low responders. However, a number of other genes showed differential post-training expression between the groups. In particular, SKI (V-Ski oncogen), which can induce oncogenic transformation and terminal muscle differentiation, FHL1 (four-and-a-half LIM domain 1), which plays a key role in muscle development and is particularly expressed in oxidative fibres, and TTN (titin), which plays a role in the maintenance of sarcomere organisation and myofibrillar elasticity and may also participate in myofibrillar cell signalling, were overexpressed 50–470% post-training in the high responders compared with the low responders [134]. In a further report from the HERITAGE cohort, genome-wide multipoint variance component linkage scans for 654 markers to identify quantitative trait loci influencing training-induced changes in insulin sensitivity, glucose effectiveness, acute insulin response to glucose and disposition index (insulin sensitivity \( \times \) acute insulin response to glucose, after adjustments for differences in pre-training values) found ten markers in whites and 14 markers in blacks with a LOD score \( \geq 1 \) [135]. The strongest linkage was found on chromosome 19q13 in the region from the skeletal muscle glycogen synthase (GYS1) gene locus to D19S245 (54–62 Mb) for the training response in glucose effectiveness in blacks with a maximum LOD score of 3.1. However, as this linkage was only seen in blacks, and not whites, a degree of caution is advised when interpreting this finding. Recently, Teran-Garcia et al. [136] have demonstrated that the \(-514C > T\) polymorphism of the HL (hepatic lipase) gene, which influenced both post-heparin HL (CC > CT > TT) and lipoprotein lipase (CC < CT < TT) activities, was a strong predictor of the exercise-training-induced change in insulin sensitivity in the HERITAGE cohort, possession of the T allele reducing responsiveness to training in a dose-dependent manner in both blacks (\( P < 0.008 \)) and whites (\( P < 0.002 \)) (i.e. CC > CT > TT for training-induced improvement in insulin sensitivity). These recent reports have made an important initial contribution to our understanding of factors which may influence individual differences in training responsiveness, but clearly much further study in this field is required to elucidate the genetic and molecular determinants underpinning why people differ in their responsiveness to exercise training in terms of effects on insulin action and glucose metabolism.

**PHYSICAL ACTIVITY AND INSULIN SENSITIVITY IN INSULIN-RESISTANT GROUPS**

Notwithstanding any known effects of genetic variations or differential gene expression on exercise-induced changes to insulin sensitivity, there is some evidence to
suggest that the potential for physical activity to improve insulin sensitivity may be greater in groups who are more insulin resistant or susceptible to insulin resistance when sedentary. In the HERITAGE Family Study, baseline values for insulin sensitivity and glucose effectiveness accounted for 20–50% of the variance in the magnitude of the exercise training response [135], with low baseline values predicting a larger training response (P. An, personal communication). Data from our laboratory [97] suggest that a 90-min session of prior moderate exercise reduces postprandial hyperinsulinaemia to a greater extent in centrally obese insulin-resistant men than age-matched lean insulin-sensitive men (11% compared with 3% reduction respectively), suggestive of a greater effect of exercise on insulin sensitivity in the obese men (Figure 3). Similarly, it has been reported that a 50-min session of brisk walking performed on the day prior to a 75 g OGTT (oral glucose tolerance test) significantly reduced postprandial insulin concentrations in a group of Mexican American women [137], who are more insulin resistant than non-Hispanic white women [138], but not in age- and body-fat-matched non-Hispanic American women [137], again suggesting a larger insulin-sensitizing effect of exercise in insulin-resistant populations. Furthermore, we have reported that in the daughters of patients with Type II diabetes, who have approximate 3 times the risk of developing diabetes compared with those with no diabetes family history [139,140] and are often more insulin resistant than matched control subjects [141–143], habitual daily activity level influences insulin sensitivity to a greater extent than it does in matched controls with non-diabetic parents (Figure 4) [144]. Thus, although daughters with low levels of habitual activity were relatively insulin resistant [by HOMA (homeostasis model assessment)] [145], daughters with high habitual activity were no more insulin resistant than women with no diabetes family history. Similarly, in a small study, Ahn et al. [146] reported that, while unfit sons of patients with Type II diabetes exhibited greater glycaemic and insulinaemic responses to a 75 g oral glucose load than unfit or fit age-, sex- and BMI-matched controls with no family of diabetes, fit sons exhibited similar glycaemic and insulinaemic responses to fit control subjects. The authors [146] extended their observations using the euglycaemic–hyperinsulinaemic clamp technique, reporting that glucose disposal rates were lower in unfit sons of patients with Type II than unfit or fit controls, but in fit sons glucose disposal rates were similar to unfit, but lower than fit, controls [146]. In addition, data from the Newcastle Heart Project suggests that the correlation between habitual physical activity level and 2-h post-glucose-load insulin concentrations is stronger among both men and women of South Asian ethnic origin [147], who are more insulin resistant than Europeans [148], than in a European comparison group, although South Asians were less active than the Europeans overall.

A further group prone to insulin resistance, who may particularly benefit from high levels of physical activity, are people who were small at birth. According to the ‘thrifty phenotype’ hypothesis, metabolic disturbances in utero, which often manifest in a small birth size, can lead to predisposition to CVD, diabetes and other metabolic disorders in later life [149–151]. Data from a large number of epidemiological studies in a wide range of populations suggests that low-birth weight, shortness or thinness at birth increases risk of insulin

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**Figure 3** Effect of prior exercise on postprandial insulin responses in lean and centrally obese men

Postprandial plasma insulin concentrations (main panels) and areas under the postprandial insulin versus time curve (insulin AUC; insets) following ingestion of a mixed meal containing 70 g of carbohydrate, 80 g of fat and 12 g of protein in lean (left-hand panel, mean BMI = 23.9 kg/m²; n = 10) and centrally obese (right-hand panel, mean BMI = 31.7 kg/m²; n = 10) middle-aged men after no exercise (Control; filled symbols) and 16–18 h following a 90-min treadmill walk (Exercise; open symbols). Exercise significantly reduced the insulin AUC in the centrally obese men (11% reduction; P < 0.05), but not the lean men (3% reduction; P value was not significant). Reprinted from J. Am. Coll. Cardiol., 44, J. M. R. Gill, A. Al-Mamari, W. R. Ferrell, S. J. Cleland, C. J. Packard, N. Sattar, J. R. Petrie and M. J. Caslake, Effects of prior moderate exercise on postprandial metabolism and vascular function in lean and centrally obese men, 2375–2382, Copyright (2004), with permission from American College of Cardiology Foundation.
resistance, the metabolic syndrome, diabetes and CVD [149–151]. The potential interactions between birth size, physical activity/fitness and insulin resistance have not been widely investigated, but has been considered in one epidemiological report, the Kuopio Ischemic Heart Disease Risk Factor Study [152]. In this study of 462 non-diabetic middle-aged Finnish men, low-birth weight or thinness at birth was associated with significantly reduced insulin sensitivity and a >2-fold increased risk of the metabolic syndrome. However, there was a significant interaction with physical activity and fitness levels, birth size and insulin sensitivity, such that, in men with habitual physical activity levels above the median for the group (>25 min of vigorous leisure-time physical activity/day) or with fitness above the 40th percentile, the adverse effect of low-birth weight or thinness at birth on insulin sensitivity was no longer evident. Similarly, smallness or thinness at birth was not associated with increased risk of the metabolic syndrome in active or fit men in contrast with inactive or unfit counterparts. This interaction is analogous with that observed in the offspring of patients with Type II diabetes [144,146].

Thus, taken together, the available data raise the possibility that interventions to increase physical activity/fitness levels may be particularly effective at improving insulin sensitivity in population groups who are more insulin resistant or have an increased predisposition to insulin resistance, although further large-scale intervention trials are needed to confirm these findings.

HOW MUCH ACTIVITY SHOULD WE RECOMMEND FOR INSULIN-RESISTANT GROUPS?

Current United Kingdom and United States physical activity for health guidelines are that all adults should ‘accumulate 30 min or more of moderate-intensity physical activity on most, preferably all, days of the week’ [153,154]. This is a general recommendation based on the weight of epidemiological and intervention study evidence regarding the nature of the dose–response relationship between physical activity and health and is the equivalent of expending approx. 200 kcal/day (where 1 kcal = 4.184 kJ) in meaningful activity; for example, walking briskly for 3.2 km would meet this target. It is important to note that these guidelines represent a pragmatic minimum activity target and it is clear that increasing physical activity beyond this minimum level will induce greater changes in both cardiovascular risk factors and incidence of CVD. However, as over two-thirds of adults in the United States and United Kingdom do not currently meet this activity target [46] and the dose–response relationship for physical activity and health benefits is likely to be curvilinear, with the maximal incremental benefit of increasing activity seen at low levels of baseline activity [153], this recommendation represents an achievable goal for most adults which, if implemented, is likely to induce a substantial reduction in population levels of CVD. It is, however, important to note that 30 min of moderate physical activity/day is likely to be insufficient for the maintenance of a healthy body weight in many individuals and the optimal physical activity ‘dose’ for obesity prevention is unclear. This may be as high as 60–90 min of moderate activity/day in groups susceptible to weight gain such as the formerly obese [45,154,155].

Although the current exercise recommendations represent general physical activity guidelines for the adult population, it is possible that insulin-resistant individuals, such as those with obesity, the metabolic syndrome and/or Type II diabetes, could benefit from a targeted exercise prescription. As these individuals, if sedentary,
are at increased cardiovascular risk, but their dose–response relationship for physical activity and CVD risk appears to be particularly steep such that when they undertake high levels of physical activity, their level of risk becomes much closer to (but probably does not reach) that of their normal weight or non-diabetic peers, adopting an active lifestyle is particularly important for these ‘high-risk’ populations. A suggested dose–response relationship is shown in Figure 5. Thus the general physical activity recommendation of 30 min/day may not be sufficient to maximize potential CVD risk reduction in insulin-resistant groups and perhaps we should be specifically recommending a higher physical activity target, for example, 60 min of moderate physical activity/day, in these populations. As the CVD risk of inactivity or low fitness is particularly high in these groups, specifically targeting resources for active living programmes on individuals such as these may be one strategy to help maximize potential CVD reductions at a population level.

CONCLUSIONS AND FUTURE DIRECTIONS

There is strong epidemiological, intervention trial and mechanistic evidence that physical activity/cardiorespiratory fitness offers protection against CVD. However, the magnitude of benefit is heterogeneous, with some individuals experiencing greater CVD risk reductions with increasing activity/fitness than others. Those who are insulin resistant or have an increased susceptibility to insulin resistance are at increased risk of CVD and are likely to benefit particularly from increased physical activity. These individuals should therefore be particularly encouraged to adopt and maintain an active lifestyle. Although achieving the current physical activity recommendation of 30 min of moderate physical activity/day is likely to substantially reduce CVD risk in these ‘at risk’ groups, adopting higher levels of physical activity may induce further clinically important risk reductions, although more data are required to elucidate the precise dose–response relationship for physical activity and CVD risk in insulin-resistant populations (see Figure 5). Further research is needed to establish how and why high levels of physical activity and fitness appear to be particularly beneficial in these groups and in other susceptible populations. Data emerging from studies evaluating specific genetic traits identifying risk of disease and potential responsiveness to an exercise intervention will hopefully enable further refinement of this strategy. This may lead to specific physical activity recommendations targeted towards population groups who could potentially benefit most from becoming more active.

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