The Relationship Between Cardiorespiratory Fitness, Cardiovascular Protection, and Metabolic Control

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First reports linking physical activity to cardiovascular protection

In 1953 it was discovered that London bus conductors who walked between levels of double-decker buses had a lower cardiovascular mortality rate than sedentary bus drivers. A similar difference in cardiovascular disease was seen among postmen who delivered letters door-to-door compared to post office telephonists[1] (Figure 1). Data below recorded by the Central Record of Staff Statistics at the London Transport and Postal Office in 1949-1950 demonstrate lower coronary heart disease (CHD) mortality rates and total CHD death among more active workers. This study was the first to report a relationship between physical activity in the workplace and subsequent mortality. Following this report, a wealth of epidemiologic data has confirmed that physical activity is associated with a reduction in total mortality and in cardiovascular related death[2-11].

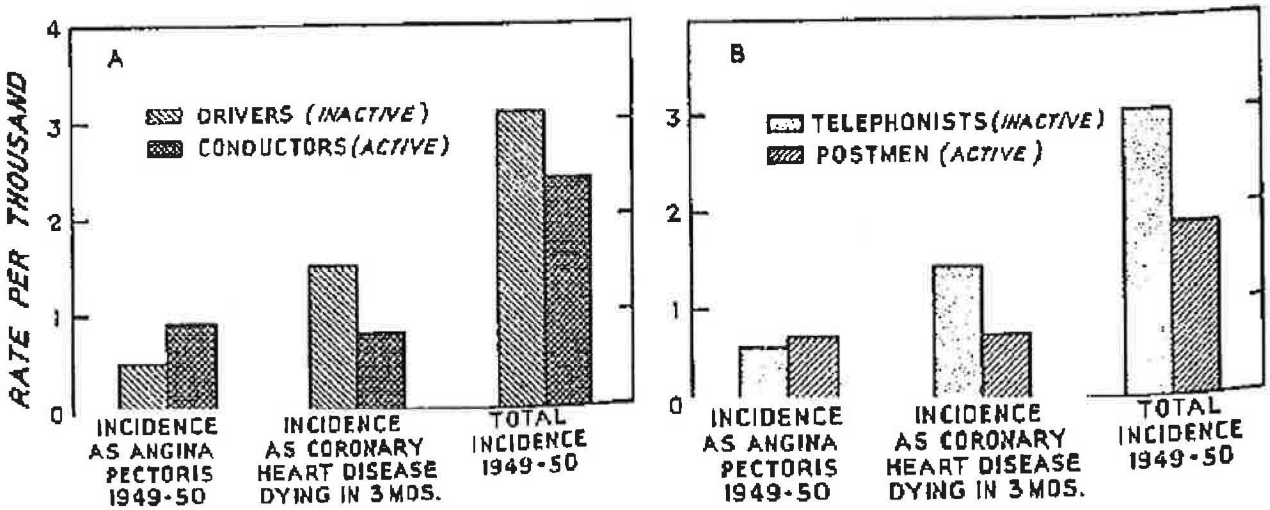

Figure 1: Coronary heart disease events and early and late mortality in sedentary and active workers, men aged 35-64, in London 1949-1952. Morris JN et al. *Lancet.* 1953;265(6796):1111-1120.

Cardiorespiratory fitness and CV risk: extending beyond physical activity

Cardiorespiratory fitness is defined as the functional capacity of the heart and lungs and reflects the efficiency of oxygen uptake and transport to muscle and the utilization of oxygen by muscle during exercise[12]. Measurement of cardiorespiratory fitness is assessed during maximal exercise testing, using bike ergometer[13] or treadmill exercise tests[14], and is estimated by final speed and grade and reported as maximal oxygen consumption (V02 max) or maximal metabolic equivalents (METs)[15]. Cardiorespiratory fitness is a risk factor that encompasses physical activity and exercise training but is also determined by other factors (see below). Cardiorespiratory fitness is postulated to better reflect the adverse consequences of a sedentary lifestyle compared to self-reported physical activity[16] and reduce the measurement error from self-reported physical activity questionnaires.

What factors determine fitness?

Non-modifiable risk factors

1. Age and sex

Several non-modifiable factors including age[7] and gender[17] impact cardiovascular fitness. Age-related changes in fitness include reductions in maximal heart rate, ejection fraction, and maximal cardiac output[18]. Women have lower cardiorespiratory fitness even after indexing for differences in body surface area; this may be due in part to lower cardiac output and peripheral oxygen extraction than men during maximal exercise[17]. The Baltimore Longitudinal Study of Aging assessed cardiorespiratory fitness in a community-dwelling cohort free of cardiovascular disease in men and women 21-87 years of age[19]. Figure 2 shows the 10-year longitudinal change in peak cardiorespiratory fitness (V02 max) by gender across six decades. Fitness estimates were systematically lower for women compared to men across all age ranges. In addition, age-related decline was not linear but accelerated at higher age decades. Similar results have been shown when assessing age-related decline in the Cooper Center Longitudinal Study, a cohort of Caucasian men and women 18-90 years of age referred for preventive health screening[20].

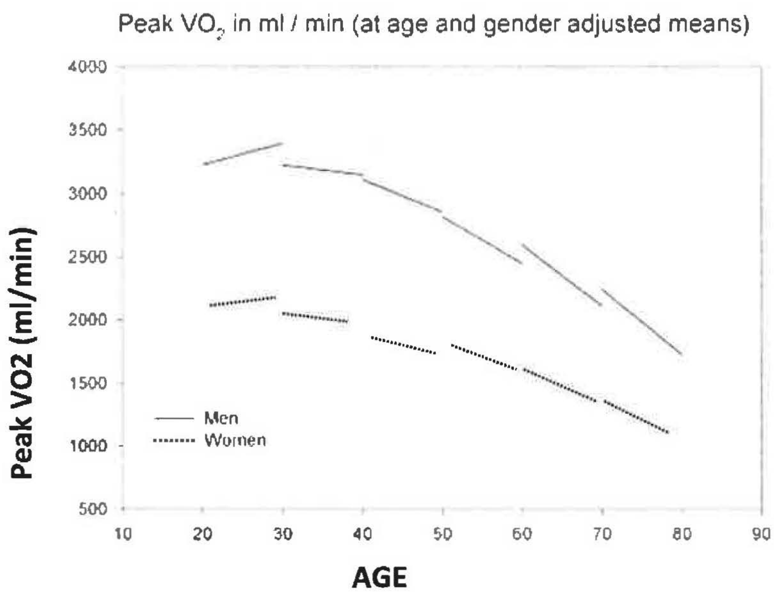

Figure 2: Longitudinal change in cardiorespiratory fitness by gender and age decade from the Baltimore Longitudinal Study of Aging. Fleg et al. *Circulation.* 2005;112: 674-682.

2. Ethnicity

Both the Cardiovascular Risk Factors in Young Adults (CARDIA) and US National Health and Nutrition Examination Survey (NHANES) have measured cardiorespiratory fitness among different ethnic groups. In a study by Sidney et al. from the CARDIA cohort, fitness estimates in young adults were higher in Caucasian men (14.2 METs) compared to African-American men (13.4 METs)[21]. Ethnic differences were even greater when comparing Caucasian to African-African women (11.7 versus 9.7 METs). The US National Health and Nutrition Examination Survey (1999-2002) collected submaximal cardiorespiratory fitness estimates in 2205 individuals 20-49 years old[22]. In a study by Sanders et al, prevalence of low cardiorespiratory fitness was highest among African-American women and men, 28% and 35%, respectively (Figure 3). While these data give some insight into ethnic differences and low fitness, there is a paucity of data regarding the range of fitness estimates across different ethnic groups and the factors that contribute to these differences.

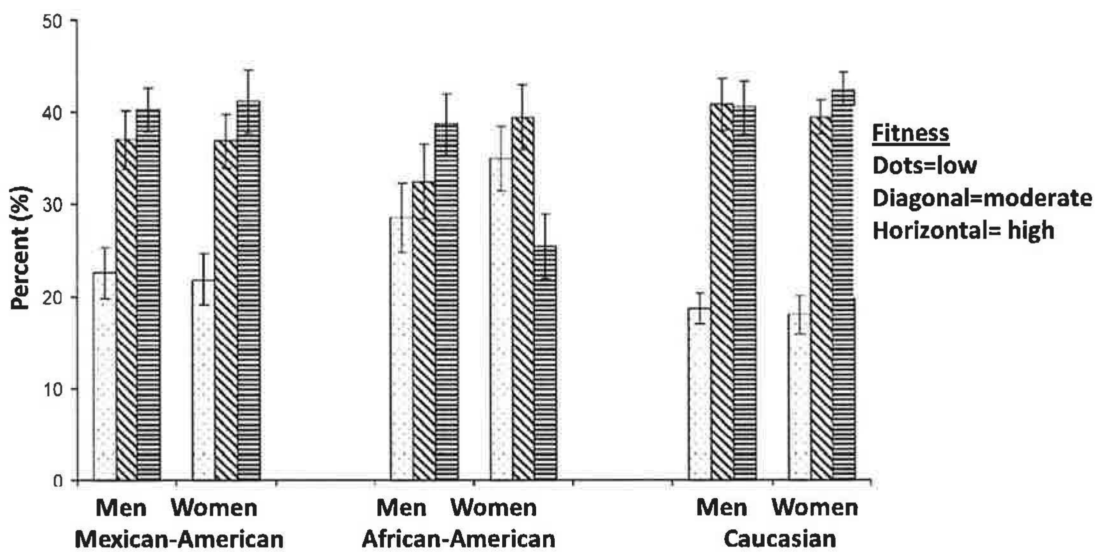

Figure 3: Estimates of the prevalence of low fitness in the US Population by sex and race/ethnicity in adults (20-49), NHANES 1999-2002. Sanders et al. *Med Sci Sports Exerc.* 2006;38(4):701-706.

3. Genetics

Family studies provide evidence that genetic factors contribute to innate or untrained cardiopulmonary fitness. The heritability of maximum oxygen consumption (V02 max)[23-25], which is highly correlated with exercise stress time on treadmill (R=0.92 in men and R=0.94 in women)[26, 27], has been estimated to be ~30-50%. To date, common variation in the genome contributing to the fitness phenotype has not been elucidated or reproduced[28]. Limitations include the absence of a well-characterized phenotype in a large populations and ability to account for environmental confounders and other health problems in population-based studies.

Modifiable determinants of fitness

1. Body weight

Body composition and body weight are reversible causes of poor fitness performance. Body weight contributes to the variability in fitness between trained and sedentary subjects. Cross-sectional population studies have shown an important relationship between fitness achieved and body composition as assessed by body mass index (BMI) and waist circumference[29]. In both adolescents and adults from NHANES, body composition is inversely associated with fitness achieved (in METs) for men and women (Figure 4).

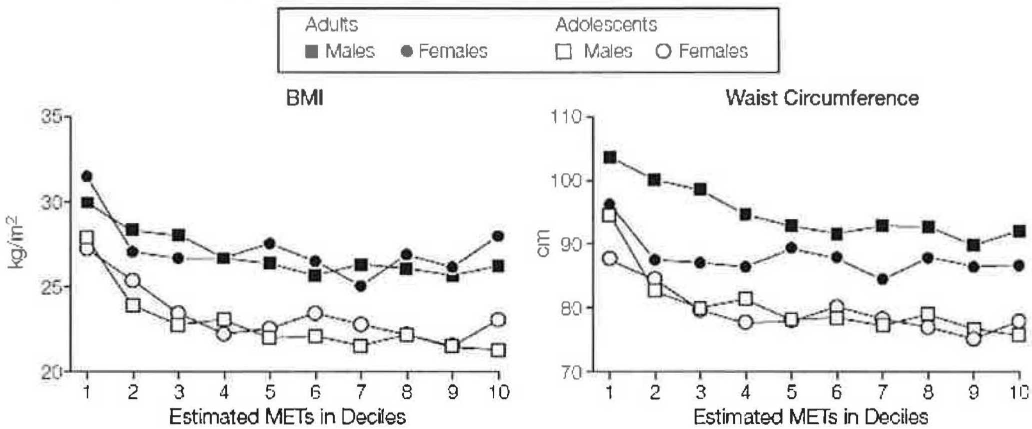

Figure 4: Age and race-adjusted means of BMI (left panel) and waist circumference (right panel), by deciles of estimated fitness in female and male US adolescents (12-19 years) and adults (20-49 Years), NHANES 1999-2002. Carnethon et al. *JAMA* 2005; 294(23): 2981-2988.

Similar results have been demonstrated between fitness and body weight (BMI) in the Cooper Center Longitudinal Study (CCLS). Among both men and women, there is a strong inverse relationship between time achieved on treadmill (strestim) and BMI (Figure 5). For both men and women, obesity alone is associated with low fitness (defined in CCLS as 10 METs in men and 9 METs in women) (Figure 6). Specifically, normal weight (BMI <25 kg/m^2) men have a fitness level of 13.0 METs compared to 9.8 METs for the obese men (BMI $\geq$30 kg/m^2) ($p<0.001$). Similarly, normal weight women achieve a fitness level of 10.3 METs versus 7.6 METs for obese women ($p<0.001$).

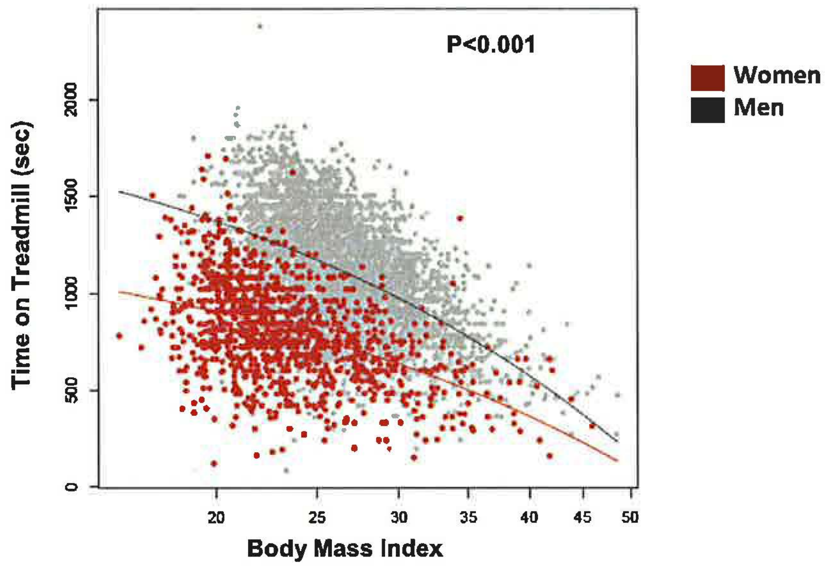

Figure 5: Correlation between fitness (stresstim) versus body mass index among Caucasian men and women in the Cooper Center Longitudinal Study. Data for 50 year old subjects shown.

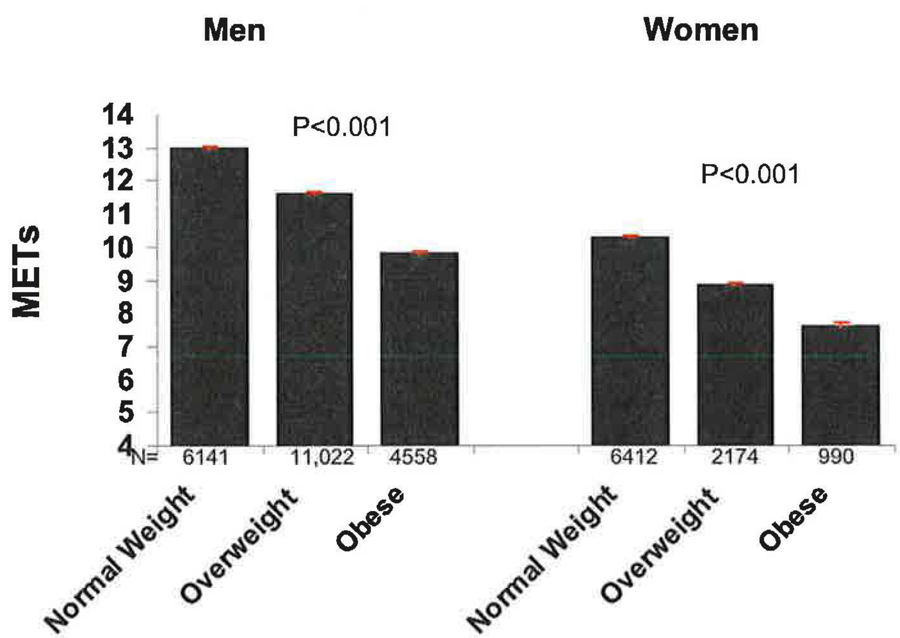

Figure 6: Cardiorespiratory fitness estimates (METs) by BMI category among men and women in the CCLS 1990-present. Normal weight (BMI <25 kg/m²); overweight (BMI 25-30 kg/m²); obese (BMI ≥30 kg/m²).

In addition to the impact of baseline body weight on cardiorespiratory fitness, change in body weight is an important determinant of changing fitness. Increases in adiposity with aging is associated with a decline in fitness[30], as reflected in reduced performance during exercise testing at follow-up[21]. Figure 7 demonstrates the strong negative impact of significant weight gain on achieved fitness levels among 1,962 young adults in CARDIA[21]. In this study, a seven year weight gain of greater than 20 lbs was associated with a 20% reduction in cardiorespiratory fitness levels, with African-American men having the greatest loss in fitness for each weight category.

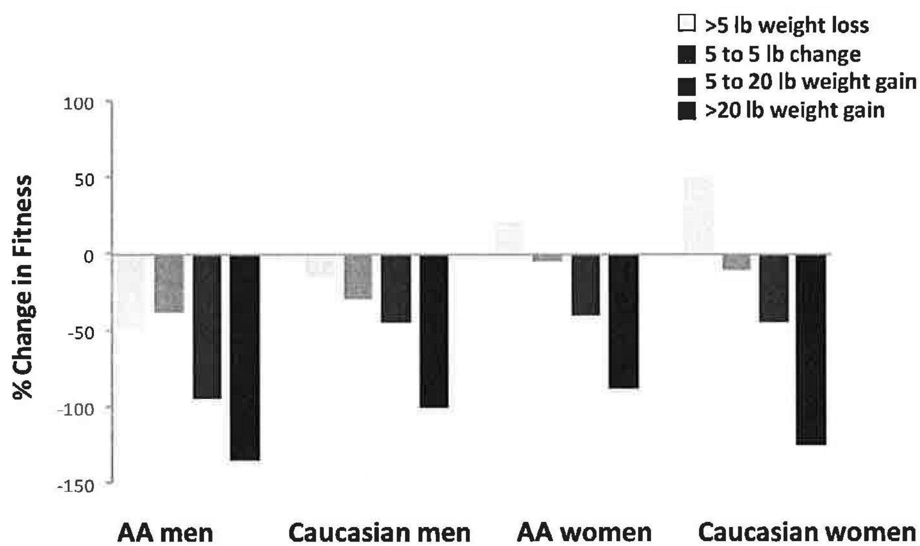

Figure 7: Mean 7-year change in exercise test duration by change in body weight across sex and ethnic group in CARDIA (N=1,962). AA= African-American. Adapted from Sidney et al. *Med. Science Sports Exer.* 1998; 30(3): 427-433.

2. Physical activity

In contrast to body weight, physical activity and exercise training are associated with improvements in cardiorespiratory fitness and can offset fitness decline by improving maximal workload, resting end-diastolic volume, stroke index, and cardiac index[18]. Below are the cross-sectional data from the Cooper Center Longitudinal Study (CCLS) showing a graded association between cardiorespiratory fitness and physical activity index (PAI 0 = sedentary; 1 = non-running activities; 2 = 0-10 miles/week running; 3 = 11-20 miles/week running; 4 = >20 miles/week running) for both men and women (Figure 8).

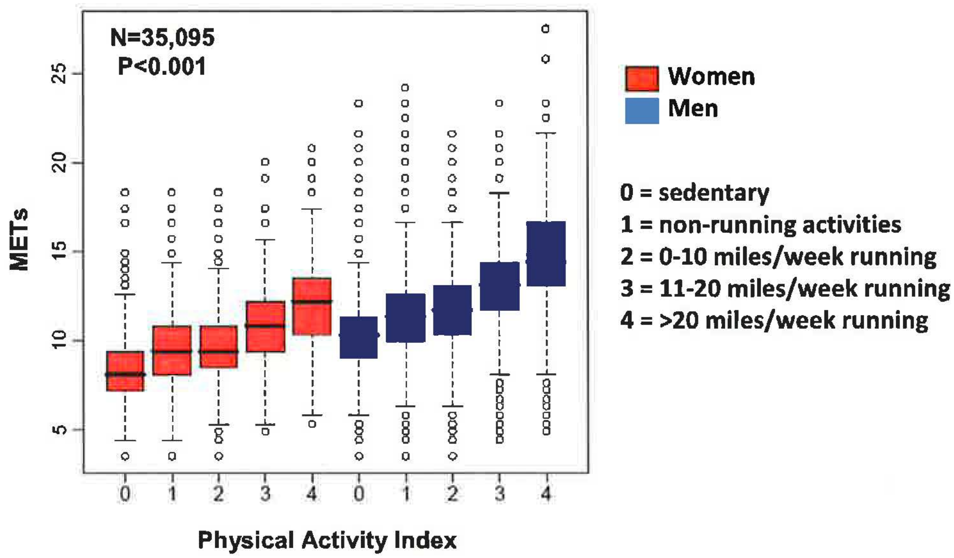

Figure 8: The relationship between cardiorespiratory fitness (METs) and Physical Activity Index (PAI=0-4) for women and men in the CCLS

Sedentary Behavior and Obesity

Body weight and physical activity remain the most important modifiable risk factors associated with cardiorespiratory fitness (Lakoski, in analysis). When assessing both body mass index (BMI) category and physical activity simultaneously (Figure 9), an obese/sedentary phenotype was associated with the lowest MET level achieved compared to either risk factor alone. This was even more pronounced for sedentary/overweight and sedentary/obese women. Interestingly, on average obese men who were physically active were able to avoid a low fitness designation (below red line designates low fitness for men and women in CCLS). This was not true for women, as both sedentary and non-sedentary obese women were classified as low fit. Thus, obesity plays an important role in determining fitness levels on Caucasian men and women, with sedentary behavior contributing importantly to fitness level achieved, though not offsetting the impact of obesity on adverse fitness levels, especially among women.

In summary, both non-modifiable and modifiable factors play an important role in determining fitness, though other factors not described may also contribute. The following section will describe how avoiding a low fitness phenotype impacts future cardiovascular risk.

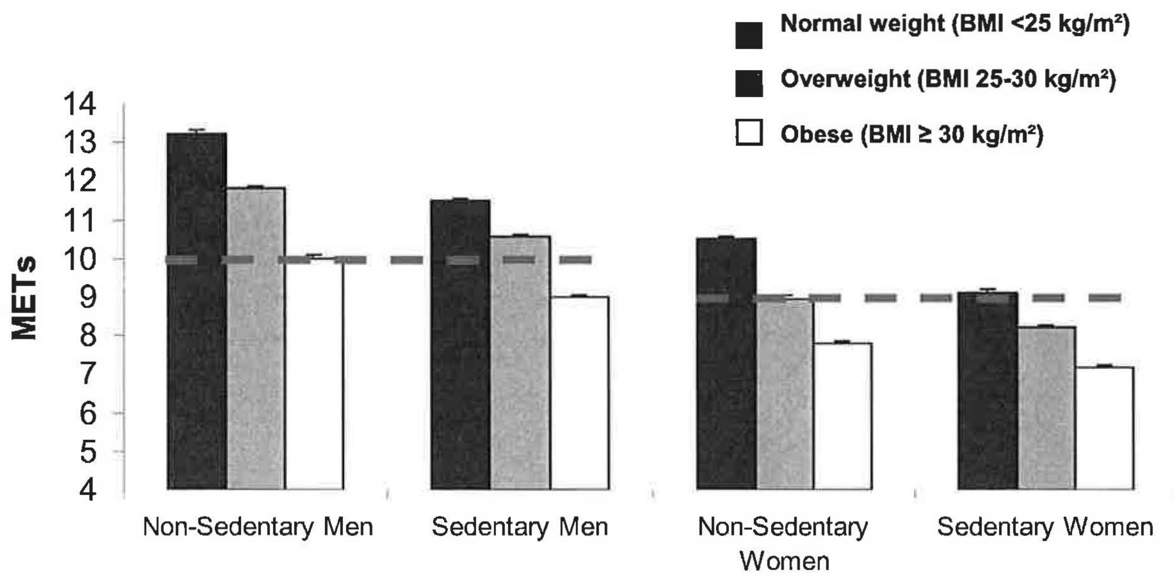

Figure 9: The Interrelationship between BMI category, sedentary behavior and fitness (METs) for men and women in the CCLS.

Evidence linking cardiorespiratory fitness to CV protection

Cardiorespiratory fitness has been measured in large scale studies and shown to predict cardiovascular-related death and all-cause mortality [13, 14, 31-36]. One of the first studies published in 1983 by Peters et al. measured fitness by bicycle ergometry in 2,779 asymptomatic, healthy workers less than 55 years of age and followed subjects for 5 years for subsequent myocardial infarction[13]. Individuals achieving a fitness level lower than the median for the group had a 2.2 times greater risk for CHD after adjusting for standard risk factors. This risk was even greater among individuals who had at least two risk factors such as hypercholesterolemia or smoking for CHD (RR 6.6, CI: 2.3-27.8). Following this study, the independent relationship between cardiorespiratory fitness and all-cause mortality was shown for both asymptomatic men and women[14]. Studying 10,224 men and 3120 women in the preventive health setting in Dallas, Texas (CCLS), low fit men and women had a greater relative risk for mortality (men RR 1.82, CI: 1.38-2.40; women RR 3.92, CI: 1.39-11.04) compared to high fit subjects. This study was extended to assessing the impact of fitness on CVD mortality across BMI subcategories among men[37]. Low fitness was associated with higher adjusted relative risk for CVD death among normal weight (RR 1.7, CI: 1.1-2.5), overweight (RR 1.9, CI: 1.4-2.5), and obese (RR 2.0, CI: 1.2-3.6).

Myers et al. went on to show a similar relationship between fitness and CHD risk in a study of 6213 consecutive men referred for treadmill exercise testing, confirming fitness as a predictor of risk in both asymptomatic and symptomatic individuals[38].

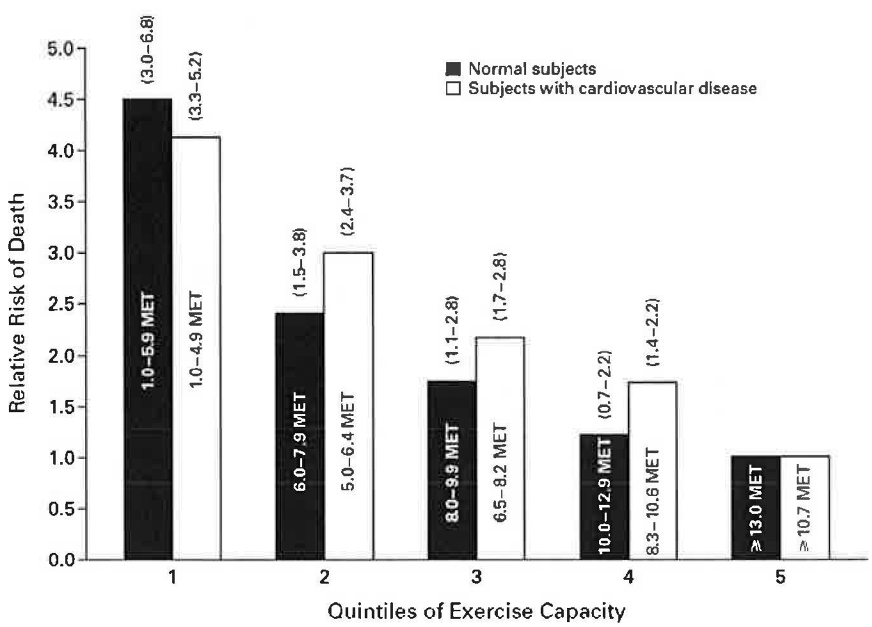

Figure 10: Age-adjusted relative risks of death according to quintile of cardiorespiratory fitness and normal subjects and those with cardiovascular disease (quintile 5 is the referent). Myers, J. *NEJM* 2002;346:798-801.

Figure 10 demonstrates the relative risk of death among normal subjects and those with a cardiovascular history by quintile of exercise capacity achieved on treadmill. For both groups (asymptomatic subjects and those with a history of CHD), individuals with the lowest fitness level (quintile 1) had a greater than 4 times higher risk of death compared to those who achieved a high fitness level (the top 20th percentile of fitness).

In 2005, Mora et al. demonstrated the importance of cardiorespiratory fitness beyond traditional risk factor assessment in predicting cardiovascular death in asymptomatic men and women[39]. This study confirmed that fitness is a risk marker that provides incremental health information in addition to knowledge of standard risk factors (i.e.smoking, high cholesterol). Lastly, the accumulating evidence linking fitness to heart protection was recently published an analysis of 33 studies of 102,980 participants[40]. The meta-analysis concluded that high cardiorespiratory fitness was associated with a 2-fold reduction (RR 2.0: CI 1.66-2.42) in all-cause mortality and cardiovascular events in healthy men and women[40] (Figure 11). As a result of these and other similar studies, cardiorespiratory fitness is widely accepted as an important reversible cardiovascular risk factor, and has been integrated into the guidelines for cardiovascular prevention[41, 42], stroke prevention[43], and optimal health for women[44] and children[45].

Source	No. of Individuals: Low CRF	No. of Individuals: High CRF	No. of Deaths or Events: Low CRF	No. of Deaths or Events: High CRF	Crude RR (95% CI)
Slattery and Jacobs,[5] 1988	NA	NA	NA	NA	1.23 (1.17-1.30)
Hein et al,[42] 1992	976	994	78	47	1.43 (1.18-1.73)
Aijaz et al,[29] 2008	NA	NA	NA	NA	1.50 (1.28-1.76)
Villeneuve et al,[53] 1998	321	3935	8	80	1.52 (0.72-3.19)
Stevens et al,[21] 2002 [men]	NA	NA	260	64	1.59 (1.18-2.14)
Farrell et al,[38] 2002	1657	4521	75	57	1.75 (1.22-2.53)
Stevens et al,[21] 2002 [women]	NA	NA	208	33	1.84 (1.24-2.72)
Sandvik et al,[50] 1993	490	487	106	24	1.85 (0.90-3.80)
Kampert et al,[44] 1996	3436	7343	197	81	2.04 (1.55-2.68)
Stevens et al,[22] 2004	NA	NA	77	24	2.13 (1.34-3.38)
Laukkanen et al,[9] 2008	410	410	124	39	2.48 (1.66-3.71)
Sawada and Muto,[51] 1999	1793	1889	96	17	2.56 (1.47-4.47)
Erikksen et al,[36] 1998	357	357	97	37	2.62 (1.85-3.72)
Arraiz et al,[32] 1992	833	801	36	12	2.70 (1.36-5.35)
Gulati et al,[16] 2003	NA	NA	NA	NA	3.10 (2.05-4.69)
Myers et al,[47] 2002	NA	NA	NA	NA	4.52 (3.00-6.80)
Overall					2.00 (1.66-2.42)

$I^2 = 86.7\%$; $P < .001$

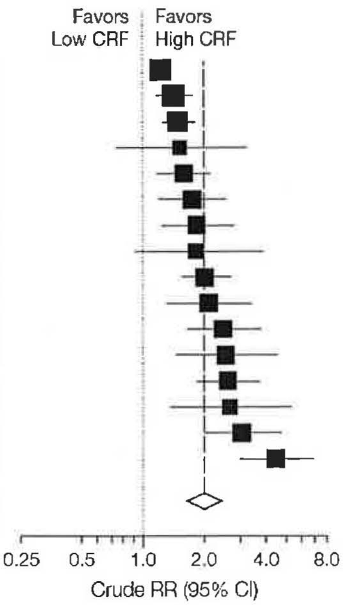

Figure 11: Meta-Analysis of all-cause mortality for individuals with low versus high cardiorespiratory fitness. Kodama et al. *JAMA* 2009; 301(19): 2024-2035.

Pathways to CV protection: Fitness and metabolic control?

Fitness is also associated with a variety of metabolic risk factors such as circulating levels of CRP[46, 47], LDL-cholesterol, low levels of HDL-cholesterol, and blood pressure[11, 29, 48]. The following section will focus on the epidemiologic data linking fitness with diabetes and several components of the metabolic syndrome.

1. Fitness and diabetes risk

Studies have confirmed that low levels of exercise and cardiorespiratory fitness are associated with risk for diabetes[49-58]. In addition, several studies have also assessed the joint impact of fitness and obesity on diabetes risk. Utilizing data on 4369 Finnish men and women between 45-64 years of age followed for a mean 9.4 years of follow-up, physical activity was found to be inversely associated with Type 2 diabetes[54]. Having a high level of physical activity and being non-obese was associated with the lowest rates of diabetes for both normal subjects and those with impaired insulin sensitivity (Figure 12). Similar results have been shown when measuring achieved fitness and diabetes risk among men in the CCLS[55]. In general, these studies confirm that fitness reduces risk for diabetes, but high fitness does not overcome the increase risk of diabetes among the obese.

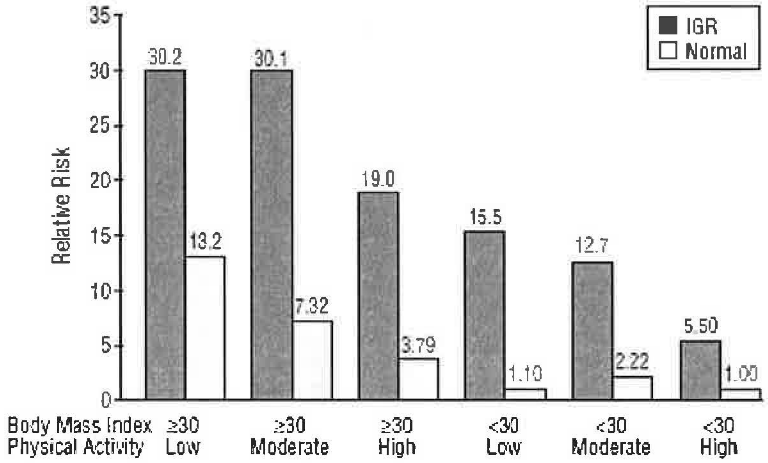

Figure 12: Relative risk of type 2 diabetes according to joint levels of physical activity and BMI, and glucose tolerance status. Adjusted for age, sex, study year, SBP, smoking, and education. Hu et al. *Archives*. 2004; 164: 892-896.

The data concerning fitness and future risk for diabetes among young adults has been well-studied in CARDIA. The CARDIA study assessed whether cardiorespiratory fitness in 4478 men and women between the ages of 18-30 years old predicted future metabolic risk at 15-year follow-up[29]. In the study, hypertension, diabetes, the metabolic syndrome, and hypercholesterolemia developed in 648, 156, 556, and 477 individuals respectively. Low fitness was associated with the development of each studied risk factor. After adjusting for baseline BMI, fitness remained associated with future risk of hypertension, metabolic syndrome, and diabetes risk, but not hypercholesterolemia (Figure 13).

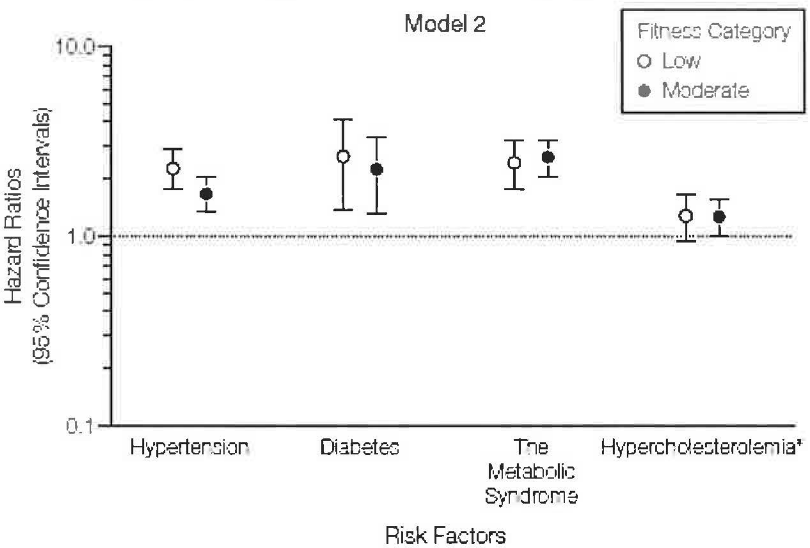

Figure 13: Association between fitness category and incident risk factors (high fitness as referent) in CARDIA. Model 2 adjusted for traditional risk factors + BMI. Carnethon et al. *JAMA* 2005; 294(23): 2981-2988.

When assessing only obese subjects (BMI≥30), the relationship was not statistically significant for hypertension (RR 1.27, CI: 0.56-2.88), the metabolic syndrome (1.26, CI: 0.63-2.49), or diabetes (1.06, CI: 0.33-3.42), though significant and robust for nonobese subjects in regards to fitness and risk for hypertension (2.59, CI: 2.02-3.32), metabolic syndrome (4.05, CI: 3.01-5.46), and diabetes (3.66, CI: 2.02-6.63). These results demonstrate the importance of fitness for future metabolic risk among young adults, most predominately among non-obese subjects.

In a follow-up study, investigators in CARDIA also assessed incident diabetes by sex and race group based on baseline fitness and loss of fitness in young adulthood[58]. Figure 14 demonstrates the risk of diabetes over a 20 year period based on treadmill duration at baseline. For each race-sex group, fitness in young adulthood predicted future risk of diabetes. However, when accounting for baseline BMI, this risk was attenuated and not statistically significant for African-American men or Caucasian and African-American women (Figure). In addition, BMI modified the relationship between fitness and incident diabetes among African-American men and women (P<0.001 for men). Restated, the relationship between fitness and future risk of diabetes was mediated in large part by obesity status at baseline, most robustly among African-Americans. In addition, loss of fitness over a 7-year period was associated with future risk of diabetes but attenuated after BMI adjustment for women (1.46, CI: 1.15-1.85) and men (2.03, CI; 1.43-2.87).

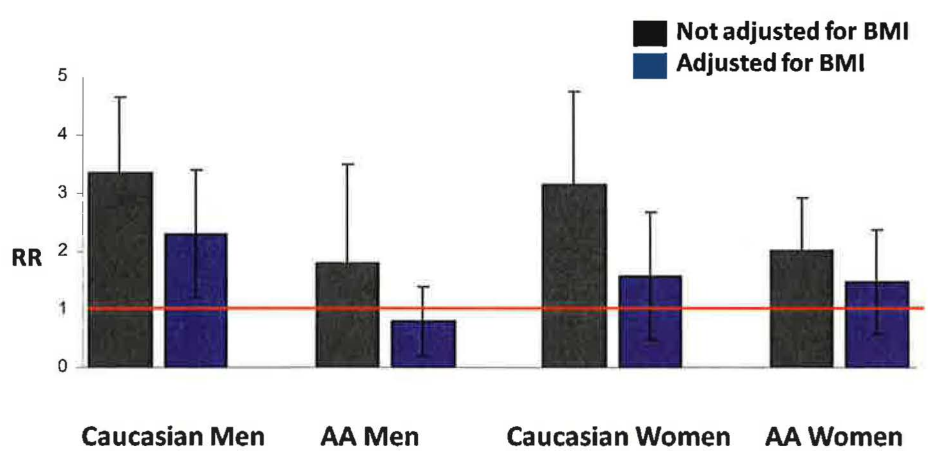

Figure 14: Association between baseline fitness (treadmill time, per -2.7 min) and releative risk of type 2 diabetes over 20 years. Adapted from Carnethon et al. *Diabetes Care* 32: 1284-1288, 2009.

Fitness, obesity, and visceral adiposity

Interestingly, physical activity or fitness without weight reduction or alteration in visceral adipose tissue accumulation appears to have a much lesser impact on diabetes. In a study by Arsenault et al., 169 asymptomatic middle-aged men without diabetes underwent bicycle ergometry to assess fitness and also had measurements of abdominal adiposity by computed tomography[59]. Figure 15 shows no significant difference in levels of glucose or insulin during oral glucose tolerance test between high and low fitness status after matching by BMI and visceral adiposity. In addition, Figure 16 further demonstrates that an adverse metabolic triad (defined as hyperinsulinemia, hyperapolipoprotein B, and small LDL particles) was most striking among those with a higher burden of visceral adipose tissue irrespective of fitness status. These data suggest that accumulation of visceral adiposity is associated metabolic deterioration regardless of fitness level.

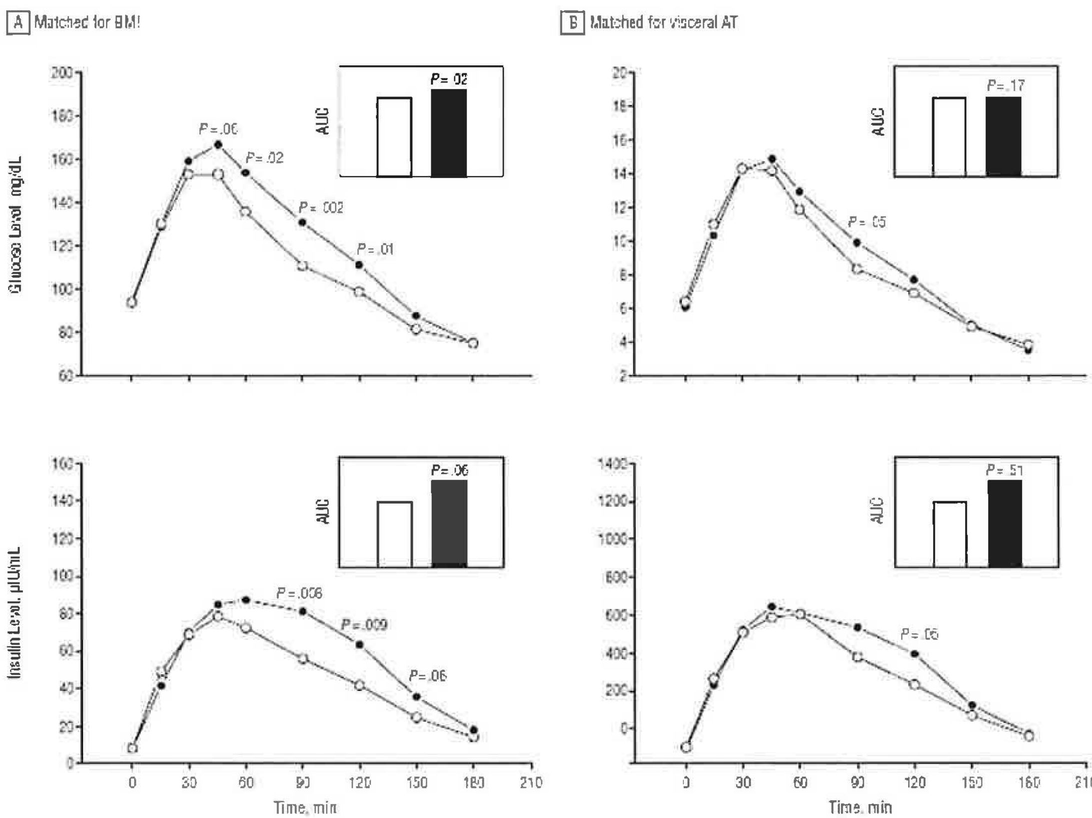

Figure 15: Area under the curve of plasma glucose and insulin levels among men match for BMI or visceral adipose tissue with high (open circle) and low (solid) levels of cardiorespiratory fitness. Arsenault et al. *Archives* 2007; 167 (14): 1518-1525.

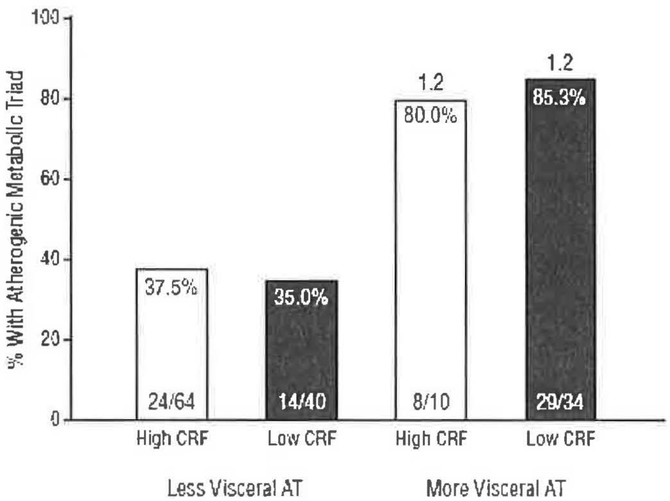

Figure 16: Proportion of metabolic triad among men classified according to more or less visceral adipose tissue with high or low cardiorespiratory fitness. Arsenault et al. Archives 2007; 167 (14): 1518-1525.

An important follow-up question to these cross-sectional data is whether a fitness intervention reduces visceral fat accumulation. In one such study by Lynch et al., 40 obese and sedentary postmenopausal women participated in a weight loss and walking intervention for 6 months[60]. Visceral adipose tissue and other measures of body weight were measured by computed tomography before and after intervention. Women with an average 10% increase in V02 max reduced visceral adipose tissue by an average 20%, while those without fitness improvement had similar reductions in body fat but substantially less reduction in visceral fat (p<0.02, Figure 17).

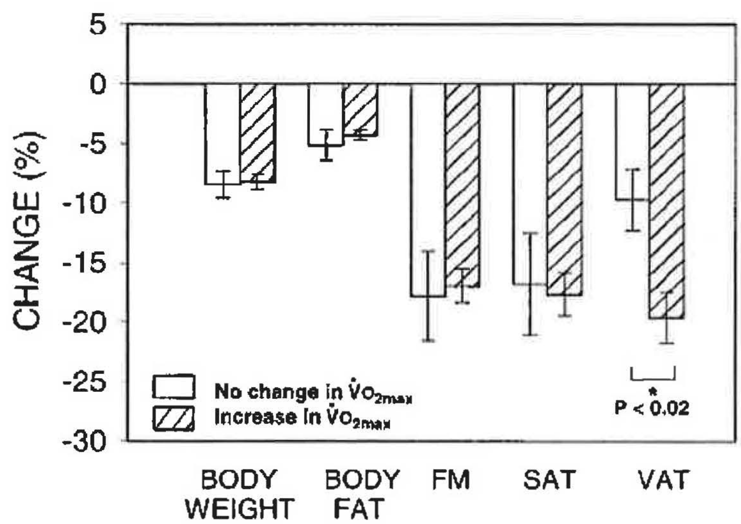

Figure 17: Change in indices of body weight, body fat, fat mass (FM), subcutaneous tissue (SAT) and visceral adipose tissue area (VAT) in those who had no change (white box) or increase in V02 max (diagonal box). Lynch et al. *J Appl Physiol* 90: 990104, 2001.

These data suggest that a successful physical activity intervention most prominently impacts visceral adiposity[61]. In addition, the above studies suggest that metabolic protection through fitness may only be achieved with reduction in detrimental fat depots. Understanding whether fitness also impacts specific areas of fat accumulation within liver[62] or muscle[63] to reduce metabolic risk requires further elucidation and a goal of this research program.

Fitness with weight loss leads to reduction in diabetes risk

One important public health message is that weight reduction through physical activity interventions have beneficial health consequences for overall metabolic health. In a landmark clinical trial from the Diabetes Prevention Program Research Group, the impact of both physical activity and weight loss on diabetes prevention was demonstrated in 3234 subjects over a mean 2.8 years[64]. Figure 18 shows both weight loss and improvement in physical activity over the time period. Intensive weight loss/physical activity intervention reduced the incidence of diabetes by 58% compared to placebo, and this was greater than the 31% reduction with medication (metformin) (Figure 19). These data showed convincingly that exercise and weight loss are important for prevention of diabetes in a high-risk subset. Ten year follow-up data from the Diabetes Prevention Program Research Group demonstrated continued impact of lifestyle group on diabetes prevention[65].

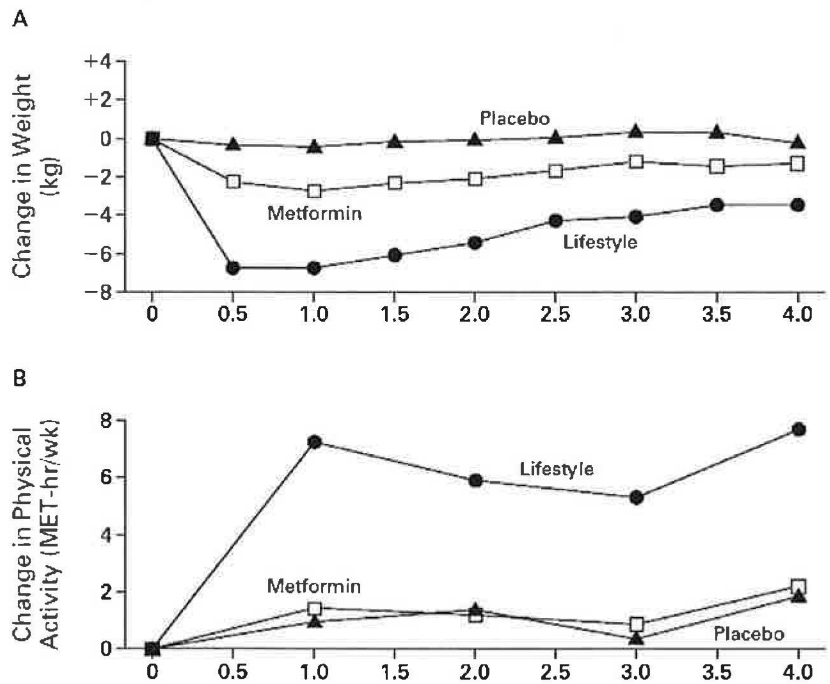

Figure 18: Change in weight and physical activity over 4 years by intervention. Diabetes Prevention Research Group. ***NEJM*** **2002; 346: 393-403.**

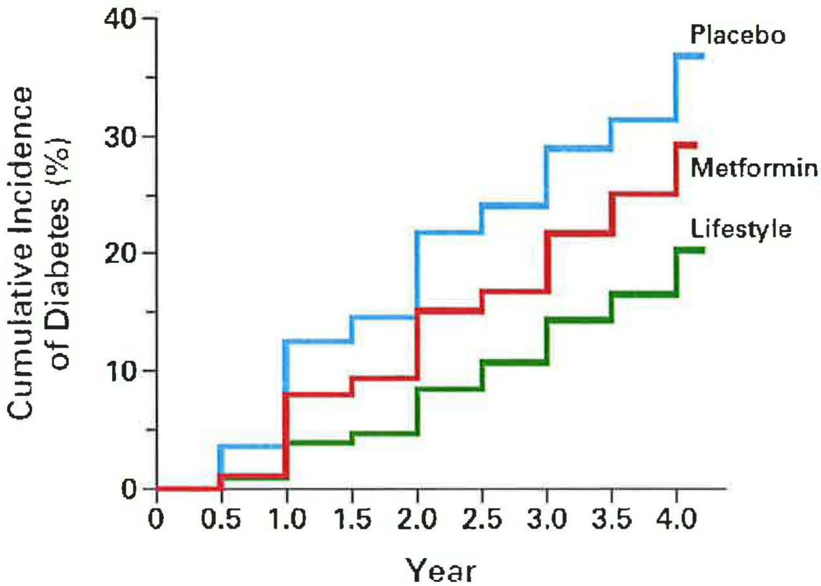

Figure 19: Cumulative incidence of diabetes by treatment arm. Diabetes Prevention Research Group. *NEJM* 2002; 346: 393-403.

These results have been supported by additional studies which have shown that physical activity will have a positive impact on health beyond mid-adulthood and into older age. In fact, derangements in glucose regulation are more common in older adults[66] due to age-related metabolic changes in both insulin secretion and action[67, 68]. Previous studies have shown relationships between impaired glucose tolerance[69] (IGT) and isolated post-challenge hyperglycemia on diabetes risk and subsequent complications from cardiovascular-related illnesses in older individuals[70]. Diabetic complications in older adults can also extend beyond CV risk to alterations in cognition[71]. In a recent study from the Cardiovascular Health Study, a study of older adults >65 years of age, associations between lifestyle factors and incident diabetes was determined at 10-year follow-up[72]. During 34, 5390 person-years, 337 new cases of drug-treated diabetes occurred. Overall, rate of incident diabetes was 35% lower for each additional lifestyle risk factor achieved. Physical activity level by self-report and diet were the most important predictors of incident diabetes in older adults, demonstrating the cumulative impact of positive lifestyle factors on diabetes. Since physical activity in older adulthood is clearly beneficial for metabolic health, additional research is needed to determine what level mid-life fitness and degree of fitness throughout the adult lifespan is needed to maintain an active lifestyle sufficient metabolic protection as older adults.

2. Fitness and blood pressure

Based on the data concerning the importance of assessing both fitness and obesity on metabolic outcomes, we sought to determine whether fitness or obesity is a more important determinant of systolic blood pressure, since hypertension is such an important risk factor for CVD. Epidemiological studies have shown that exercise and improved cardiorespiratory fitness are associated with lower hypertension risk independent of other risk factors[73-75]. Intervention studies have confirmed these observational data, demonstrating absolute reductions in systolic blood pressure of 3-4 mmHg achieved with exercise training[48]. In addition to cardiorespiratory fitness, other lifestyle factors are associated with hypertension, most notably obesity [76-79]. However, few studies have studied the relative impact of BMI and cardiorespiratory fitness on systolic blood pressure. When assessing both BMI and cardiorespiratory fitness concurrently, utilizing data from 35,000 men and women in the CCLS, we found a significant increase in systolic blood pressure by BMI quartile, independent of cardiorespiratory fitness category (Figure 20) ($p<0.001$ for all). For each cardiorespiratory fitness category, the absolute difference in SBP was modest (3-4 mmHg) compared to differences of 7-12 mmHg in SBP across quartile of BMI. Importantly, those in the lowest BMI quartile with a cardiorespiratory fitness level greater than the first quintile (>Q1) achieved the most incremental blood pressure benefit.

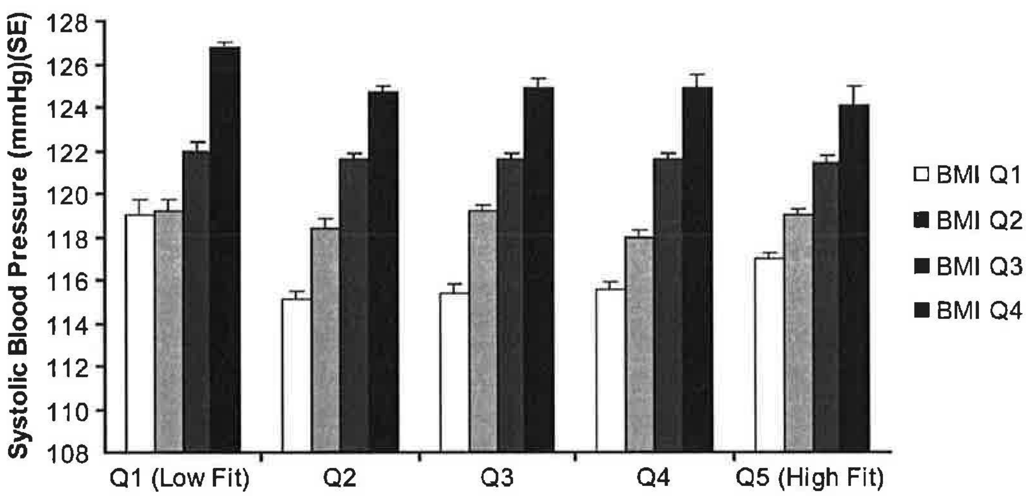

Figure 20: The Interrelationship between BMI, cardiorespiratory fitness, and systolic blood pressure. Cardiorespiratory fitness was defined as maximal exercise capacity by treadmill testing. BMI was categorized into sex-specific quartiles.

Categorizing BMI using clinical cut points from the CDC guidelines: normal weight (BMI<25), overweight ($25 \leq BMI < 30$), and obese ($BMI \geq 30$) provided similar results. Being normal weight, regardless of fitness status, was associated with lowest systolic blood pressure (116mmHg for both low and high fit subjects, $p=0.90$) (Figure 21). After excluding individuals with either a history of high blood pressure or a systolic blood pressure $\geq$ 140mmHg, results were similar.

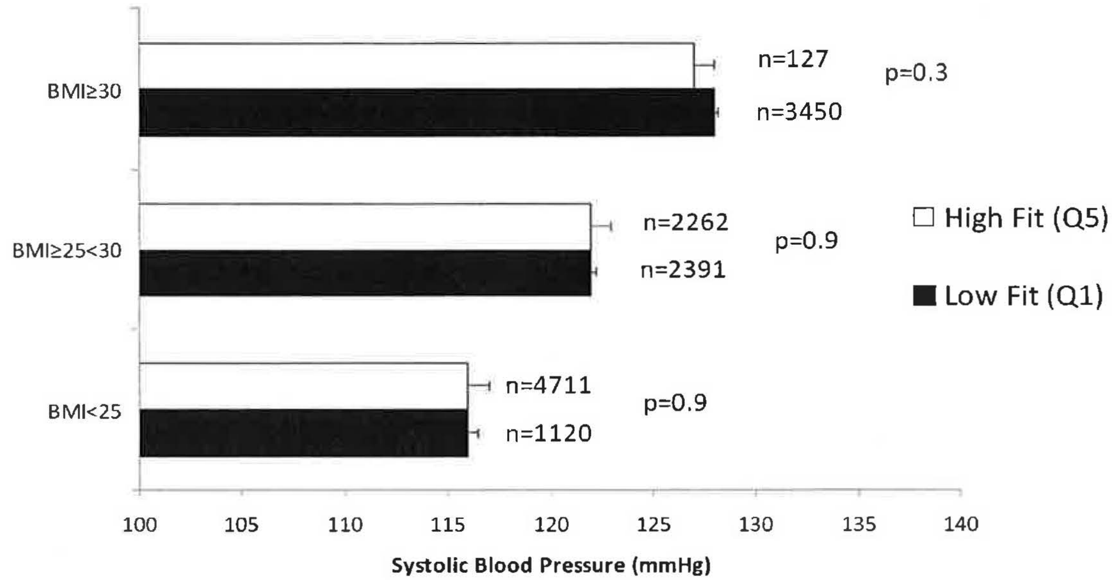

Figure 21: Relationship between BMI category and systolic blood pressure in high versus low fit individuals. BMI was categorized as normal weight (BMI<25), overweight (25≤BMI<30), and obese (BMI≥30). High fit individuals were defined as those in the top sex- and age-adjusted fitness quintile (Q5) compared to low fit individuals in the lowest sex- and age-adjusted fitness quintile (Q1).

Our findings show that lower BMI is associated with markedly lower systolic blood pressure, even among non-hypertensives (10mmHg difference between normal and obese non-hypertensive subjects). We did not see a similar blood pressure benefit by high versus low cardiorespiratory fitness status. Recent evidence suggests obesity is such a strong determinant of hypertension that the benefits of other lifestyle factors are not obtained until individuals are normal weight[80]. Our findings are consistent with the observation that the impact of fitness on systolic blood pressure is most apparent in individuals who were normal weight. These data are supported by a recent meta-analysis among exercise intervention trials demonstrating a greater impact of fitness on hypertension among normal weight (-4 mmHg) compared to overweight (-2 mmHg) subjects[48]. The current cross-sectional data cannot assess temporal relationships directly. However, based on our current findings and the available literature, a reasonable hypothesis is that the primary goal for hypertension prevention appears to be best served by achieving or maintaining a normal body weight through any acceptable lifestyle, medical, or surgical intervention.

Goals for metabolic protection: extending interventions into childhood

Physical activity and subsequent cardiorespiratory fitness are important determinants of cardiovascular protection. Specifically, for metabolic risk, the interplay between fitness and obesity drives diabetes and components of the metabolic syndrome such as hypertension. Fitness can reduce diabetes risk and components of the metabolic syndrome, but being fit cannot overcome the detrimental impact of excess adiposity. This may be due to the fact that fitness appears to mediate metabolic protection by impacting visceral adiposity. The combination of a lean phenotype and physically active lifestyle is associated with the most favorable metabolic risk, whether focusing on diabetes, hypertension, or the metabolic syndrome in general.

Shown below are the challenges of achieving goals of lean-fit phenotype. In a prospective cohort study in Australia, 647 adolescents who had participated in anthropometry and fitness assessments as part of an Australian Health and Fitness Survey were re-studied 20 years later[81]. Persistently low levels of fitness and decreasing fitness over 20 years was associated with a high prevalence of obesity (25%) and insulin resistance (30-35%). In contrast, sustained high fitness and increasing fitness was related to a much lower prevalence of obesity (5%) and insulin resistance(~15%) at 20-year follow-up (Figure 22). In addition, low childhood fitness was highly correlated with persistently low fitness in adulthood. Therefore, childhood obesity propagates a low fit phenotype into adulthood, extending the deleterious effects of low fitness and weight gain on future metabolic outcomes.

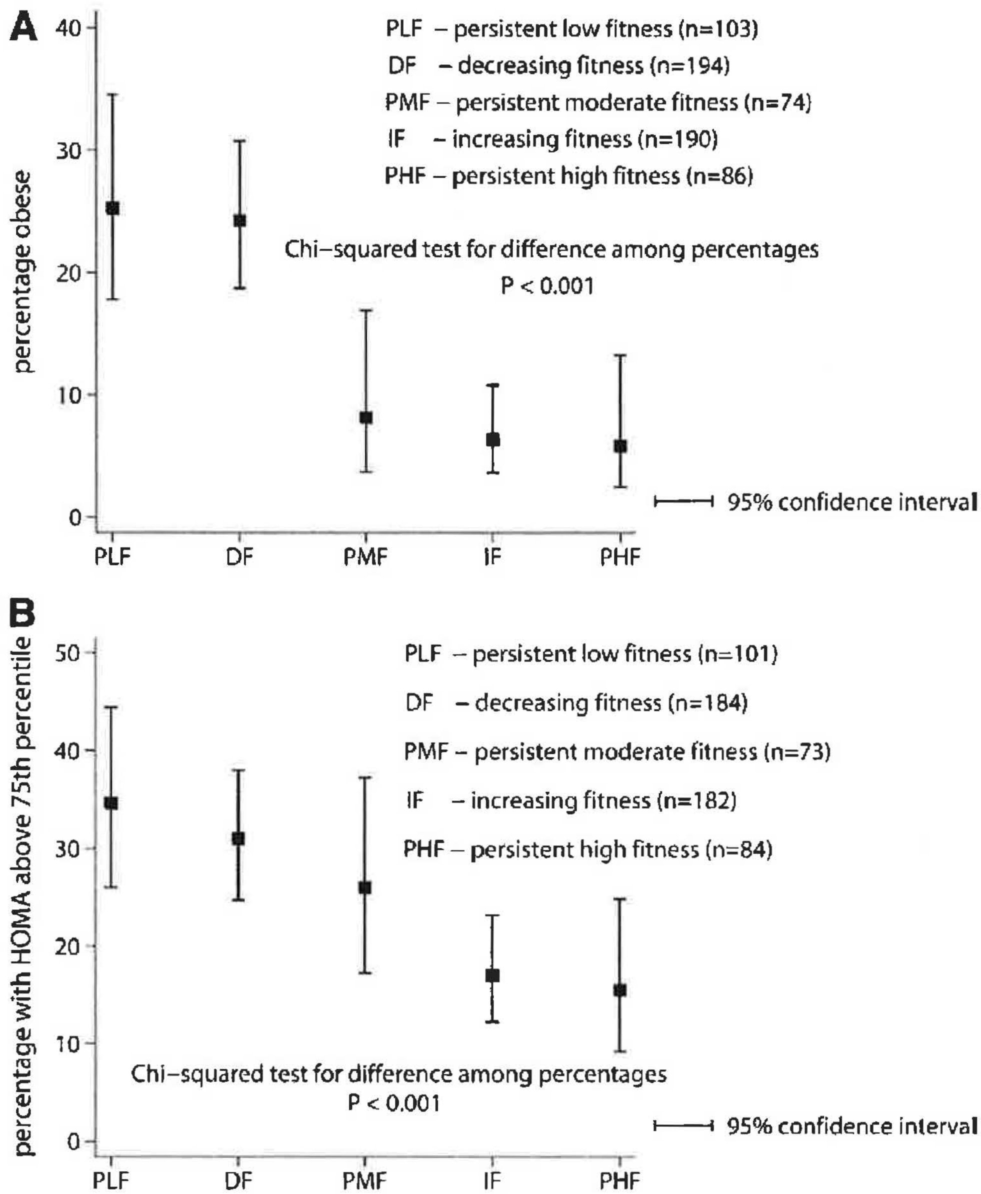

Figure 22: Fitness status and prevalence of obesity (A) and insulin resistance (B) at 20-year follow-up. Dwyer et al. *Diabetes Care* 2009 Apr; 32(4): 683-7.

Summary

In this protocol we have discussed the measurement of cardiorespiratory fitness and the factors determining fitness across populations. We have gone on to show the epidemiological evidence linking fitness to future cardiovascular risk, with low fitness having negative impact on CV outcomes. After understanding the global impact of fitness on health, we focused on potential pathways by which fitness provides protection, specifically metabolic control. We showed that fitness is associated with a reduction in diabetes risk, but does not offset the risk of diabetes among the obese. We took this one step further to show that diabetic protection from fitness most likely requires reduction in visceral adiposity or metabolically active fat depots to improve metabolic profiles. We then focused our attention on hypertension, an important CV risk factor. We found that the association between fitness and systolic blood pressure is modest compared to obesity and most evident among lean subjects, supporting the concept that weight control first plus fitness leads to hypertension protection. Lastly, we focused on the goals of the future, from a population perspective, concluding the importance of physical activity and a lean phenotype in childhood to promote future metabolic health and CV protection. We end with the knowledge that programs are needed to promote physical activity early in life to avoid the vicious circle of obesity-related loss of fitness and obesity-induced metabolic syndrome propagated by sedentary behavior. In addition, we passionately endeavor to discover new pathways and strategies to prevent obesity and subsequent adverse metabolic and CV outcomes.

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