

## HIGHLIGHTED TOPIC | *Role of Exercise in Reducing the Risk of Diabetes and Obesity*

### Physical activity and diabetes prevention

Michael J. LaMonte, Steven N. Blair, and Timothy S. Church

*Centers for Integrated Health Research, The Cooper Institute, Dallas, Texas*

**LaMonte, Michael J., Steven N. Blair, and Timothy S. Church.** Physical activity and diabetes prevention. *J Appl Physiol* 99: 1205–1213, 2005; doi:10.1152/japplphysiol.00193.2005.—Diabetes has reached epidemic proportions worldwide and is associated with a large economic burden, increased risk of cardiovascular disease, and premature mortality. Hyperglycemia is the hallmark clinical manifestation of diabetes and evolves through a multifactorial etiology of genetic, environmental, and behavioral enablers. Approximately 90% of diabetes cases are the non-insulin-dependent phenotype, which is characterized by a progressive deterioration in insulin-mediated glucose disposal, particularly by peripheral tissues. Our hypothesis is that the most proximal behavioral cause of insulin resistance is physical inactivity. Indeed, several streams of scientific research have demonstrated a role for physical activity in the etiology and prevention of diabetes and its related morbidity. In this review we will discuss some of the key observational and experimental studies that have examined associations among physical activity, cardiorespiratory fitness, and non-insulin-dependent diabetes.

non-insulin-dependent; prevention; mortality; cardiorespiratory fitness

INASMUCH AS THE HUMAN GENETIC CONSTITUTION has remained unchanged over the past 50,000 years or so, it is likely that an evolutionary mismatch between the patterns of nutrient intake and physical activity of our hunter-gatherer ancestors and that of modern industrialized societies underlies the global epidemic of chronic diseases such as diabetes (18). The focus of this mini-review will be on the role of physical activity in the prevention of Type 2 diabetes. We also will address the effect of physical activity on the risk of cardiovascular and all-cause mortality in individuals with Type 2 diabetes.

An important distinction to make is that physical activity refers to a behavior, specifically a body movement that occurs from skeletal muscle contraction and results in increased energy expenditure above resting metabolic rate (77). Exercise, or “exercise training,” is a specific type of physical activity that is performed with the intention of enhancing components of physical fitness (77). The major component of physical fitness that has been related to the primary prevention of diabetes is aerobic power or “cardiorespiratory fitness.” Although determinants of cardiorespiratory fitness include age, sex, health status, and genetics, the principal determinant is habitual physical activity levels. Thus cardiorespiratory fitness can be used as an objective surrogate measure of recent physical activity patterns. It is possible that other components of physical fitness such as muscular strength or endurance may relate to some aspects of diabetes occurrence; however, few data from large prospective studies exist in support of these relationships. Therefore, only data relating physical activity or cardiorespi-

ratory fitness levels with diabetes risk will be presented herein. Although data from small laboratory and community studies have contributed to the current understanding of the role that physical activity has in diabetes prevention, this review will be restricted to large prospective observational and experimental studies. The role of physical activity in relation to Type 1 diabetes is an important topic, but it is beyond the scope of this review. The word “diabetes” will henceforth refer exclusively to Type 2 diabetes throughout this report.

#### BACKGROUND

The global economic and disease burden associated with diabetes is large and continues to grow (49, 83, 84). In 1995, ~135 million adults had diabetes worldwide, and this number is projected to be 300 million in 2025 (49). Nearly 1 million deaths were associated with diabetes worldwide in 2002 (83). Diabetes is particularly burdensome in developed countries where an overabundance of energy-dense foods and sedentary lifestyles are key underpinnings of the current diabetes epidemic (49). In the US during the period 1999–2000, ~16.7 million individuals (8.6% of the population)  $\geq 20$  years of age were afflicted by diabetes (13). It is estimated that  $\approx 90$ –95% of diabetes cases in the US are Type 2 diabetes (31). Diabetes is the sixth leading cause of death among US adults (51) and is associated with a substantially increased risk of cardiovascular morbidity and mortality (25, 37). The American Heart Association has designated diabetes a major modifiable independent risk factor for coronary heart disease (CHD) (25), and diabetes is now considered a CHD-risk equivalent in conventional clinical risk assessment guidelines (20). The American Diabetes Association estimates that in 2002 the direct medical costs attributed to diabetes were \$92 billion and the indirect costs (disability, work loss, premature mortality) were \$40 billion

Address for reprint requests and other correspondence: M. J. LaMonte, The Cooper Institute, 12330 Preston Rd., Dallas, TX 75230 (e-mail: mlamonte@cooperinst.org).

(www.diabetes.org). Clearly cost-effective strategies for preventing and managing diabetes could provide important economic benefits in addition to reducing human suffering and improving quality of life.

The etiology of diabetes is a complex multifactorial process with both lifestyle and genetic origins (14, 30). The defining phenotype of diabetes is hyperglycemia, which results from disturbances in insulin sensitivity and insulin secretion (28, 59, 67). Figure 1 illustrates a conceptual model of the pathogenic processes that lead to the expression of diabetes. At a given level of genetic susceptibility, perturbations in the homeostatic regulation of carbohydrate and lipid metabolism are fundamental antecedents to the progression of diabetes (14, 30, 45, 69). Impaired substrate clearance by skeletal muscle and adipose tissue, and to a lesser degree oversecretion of substrate by hepatocytes and portal adipocytes, have been identified as key aspects of metabolic dysfunction that are associated with insulin resistance and impaired insulin secretion and ultimately hyperglycemia (6, 14, 28, 30, 45, 59). Although several clinical and lifestyle factors are thought to play a role in the progression to diabetes (69), our hypothesis is that the most proximal behavioral cause of insulin resistance is physical inactivity (33, 45). The remainder of this review will present evidence for physical inactivity and low cardiorespiratory fitness as antecedents to diabetes and as modifiers of the associations between diabetes and chronic disease outcomes such as cardiovascular disease and premature mortality. Potential mechanisms through which regular physical activity affects glucose homeostasis will be identified but not discussed in detail. Readers are referred elsewhere for expanded reviews on the development, consequences, and management of diabetes (3–5, 14, 23, 27, 30, 31, 45).

#### PHYSICAL ACTIVITY, FITNESS, AND DIABETES

Current evidence supports the hypothesis that sedentary habits and low cardiorespiratory fitness are involved at several points in the progression from normal glucose metabolism to Type 2 diabetes and that they are independent predictors of cardiovascular events and premature mortality in individuals with diagnosed diabetes (3, 5, 26, 68). Figure 2 shows a

simplified schematic of this progression. Physical inactivity can initiate and accelerate the pathogenesis of diabetes and subsequent morbidity and mortality. Conversely, regular physical activity can retard the progression from one stage to another, and it may even reverse the process. The remainder of this section presents a selective review of large observational and experimental studies supporting the role of physical activity and fitness in the steps outlined in Fig. 2.

#### Physical Activity and Fitness in the Primary Prevention of Diabetes

It is only since about 1990 that compelling evidence from large prospective studies began to emerge on the role of regular physical activity and adequate levels of cardiorespiratory fitness in the prevention of diabetes.

**Observational studies.** One of the first large scale observational studies was by Helmrach and colleagues (34). They reported on 5,990 male University of Pennsylvania alumni aged 39–68 years at baseline who were followed an average of 14 years through which 202 cases of physician-diagnosed diabetes occurred during 98,524 man-years of observation. After adjustment for age, body mass index (BMI), hypertension, and parental history of diabetes, the investigators observed on average a 6% lower risk of diabetes for each 500 kcal/wk of self-reported leisure-time physical activity ( $P < 0.01$ ).

Manson et al. (62) reported on physical activity and diabetes risk in 87,253 US female nurses aged 34–59 years at baseline who were followed an average of 8 years, during which 1,303 cases of diabetes occurred during 670,397 woman-years of exposure. Women who reported vigorous exercise at least once per week had a 33% lower age-adjusted risk of developing diabetes compared with women reporting no exercise ( $P < 0.0001$ ). Further adjustment for BMI and other potential confounders did not eliminate the significant inverse association between physical activity and diabetes incidence. Manson et al. (61) reported near identical findings in 21,271 US male physicians aged 40–84 years at baseline who were followed through 105,141 man-years, during which 285 cases of diabetes occurred. An inverse gradient of age-adjusted diabetes rates

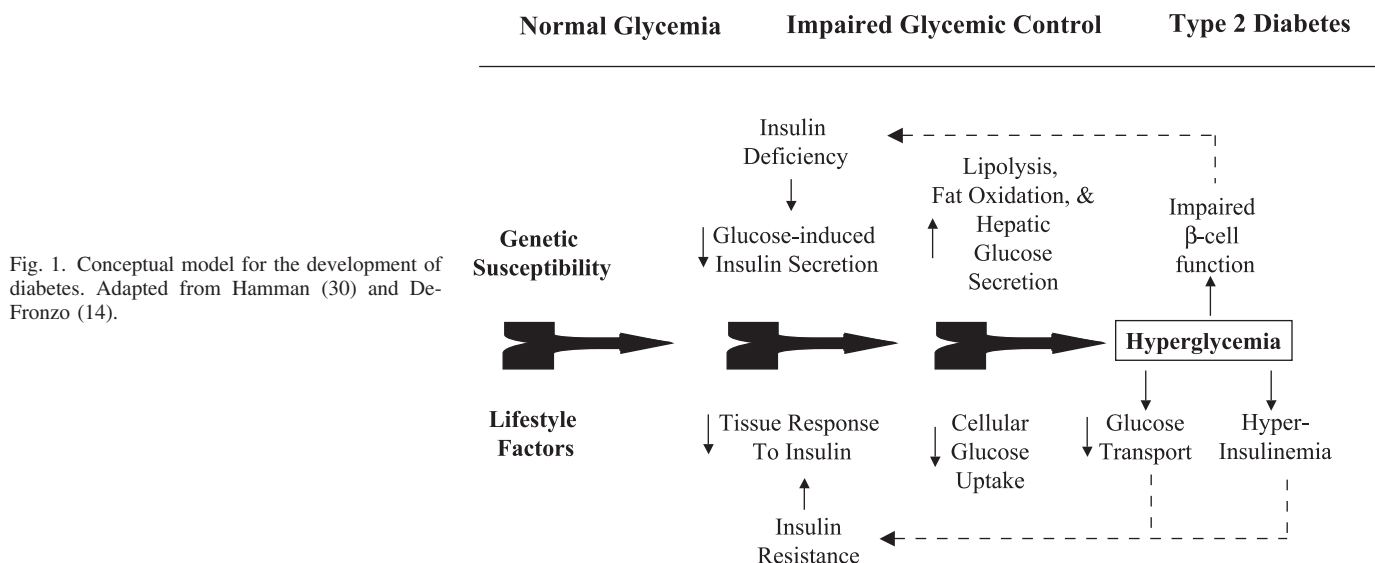


Fig. 1. Conceptual model for the development of diabetes. Adapted from Hamman (30) and DeFronzo (14).

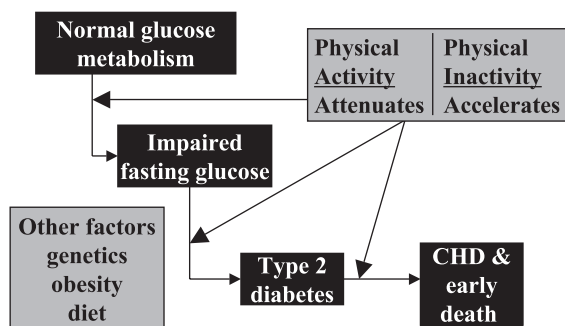


Fig. 2. Schematic of the relation of physical activity with the progression from normal glucose metabolism to clinical diabetes and increased risk of cardiovascular diseases and other complications. Genetic susceptibility and other factors such as diet and obesity also play a role in the progression. CHD, coronary heart disease.

was observed across levels of self-reported vigorous exercise (Fig. 3). The inverse association between physical activity and diabetes risk remained significant after further adjustment for BMI. Several other investigators reported in the early 1990s that physical activity was inversely and independently associated with the risk of developing diabetes. The consistency in the pattern and strength of the data allowed for a conclusion of causality in the US Surgeon General's Report on Physical Activity and Health that was published in 1996 (77).

Since the publication of the Surgeon General's Report, additional prospective observational data have been reported on the association between physical activity and incident diabetes in established cohorts of men in the British Regional Heart Study (78), men and women in the Study of Eastern Finns (43), and women in the Iowa Women's Health Study (22), Nurses' Health Study (39, 40), Women's Health Study (81), and Women's Health Initiative Observational Study (38). In each investigation, significant graded inverse associations were consistently observed between levels of self-reported physical activity and incident diabetes over long follow-up periods. The associations remained significant after extensive adjustment for confounding, including BMI. One of the most recent studies was on 86,708 racially diverse women who were  $\approx 63$  years old at baseline and followed an average of 5 years for the development of diabetes (38). In analyses among all women combined and after extensive adjustment for confounders including BMI, significant inverse gradients of diabetes risk were seen across quartiles of total energy expenditure and energy expended during walking activity. Compared with women in the lowest quartile, the risk of developing diabetes was 22% ( $P < 0.01$ ) and 18% ( $P < 0.01$ ) lower for women in the highest quartile of total and walking energy expenditure, respectively. Race-specific analyses were significant only in Caucasian women, which may have been due to insufficient statistical power for subgroup analysis according to race-ethnicity. This also may reflect the imprecision of self-reported physical activity exposures particularly in women (1, 54).

Cardiorespiratory fitness, an objective measure of recent physical activity patterns (64, 73), is stronger than self-reported physical activity as a predictor of several health outcomes (7). This is because fitness exposures are less prone to misclassification and because factors other than activity may influence both fitness levels and health status through related biological pathways. Few large prospective studies have related baseline

measures of cardiorespiratory fitness with diabetes risk (10, 60, 70, 80). The majority of the cohort studies described earlier relied on self-reported data to define baseline health status and to identify diabetes cases during follow-up. These studies were not able to control for baseline glucose levels in analyses of physical activity exposures and incident diabetes. It is now known that increased diabetes risk exists in individuals whose fasting glucose is in the moderate to high normal range (4, 58). Thus, although study participants were free of diagnosed diabetes at baseline, nondiabetic fasting hyperglycemia may have confounded associations between physical activity and diabetes in these previous investigations. Reliance on self-reported diabetes outcomes is an important study limitation because nearly 30% of diabetes cases are undiagnosed (13). Thus a study relying on self-reported diabetes cases will have substantial misclassification on the outcome. Four recent studies have addressed both of these limitations.

Each of the existing prospective studies of baseline fitness exposures and incident diabetes has shown that higher levels of fitness protect against the development of diabetes in women and men (10, 60, 70, 80). The first published report was by Lynch et al. (60) on a study of 897 Finnish men aged 42–60 years at baseline who were followed for 4 years, at which time 46 cases of diabetes were identified from 2-h postload glucose concentrations. Cardiorespiratory fitness was measured at baseline with ventilatory gas analysis during a maximal bicycle ergometry test. After adjusting for several confounders including age, BMI, and baseline glucose levels, odds ratios [95% confidence interval (CI)] for incident diabetes were 1.0 (referent), 0.77 (0.32–1.85), 0.26 (0.08–0.82), and 0.15 (0.03–0.79) in men in the first, second, third, and fourth quartile of fitness, respectively. The number of cases was small in each fitness category (17, 14, 6, and 2, respectively), which may have contributed to the wide CIs and the inclusion of unity in the second quartile.

We investigated the relation of cardiorespiratory fitness to the risk of developing impaired fasting glucose (IFG; 110–125.9 mg/dl) and diabetes (glucose  $\geq 126$  mg/dl) in men in the Aerobics Center Longitudinal Study (ACLS) (80). Strengths of this study include objective measures of both the exposure, cardiorespiratory fitness determined by a maximal treadmill exercise test, and the outcome, glycemic status (IFG and diabetes) determined by fasting plasma glucose measurements rather than self-reported diagnosis. We followed 8,633 men

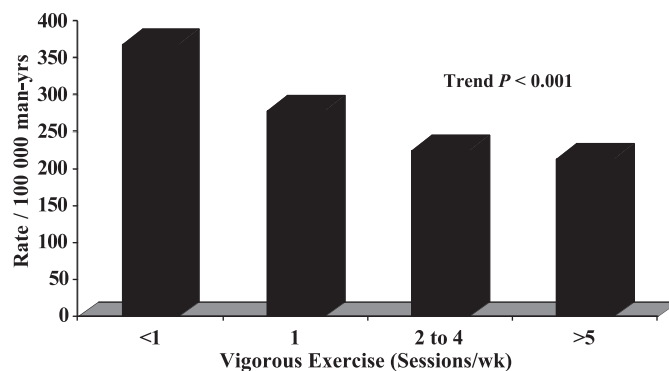


Fig. 3. Age-adjusted rates of diabetes by physical activity levels in US male physicians. Used with permission from Manson et al. (61). *JAMA* 268: 63–67, 1992. Copyright © 1992, American Medical Association. All rights reserved.



aged 30–79 years and free of diabetes at baseline who had two clinical examinations an average of 6 years apart. First we examined the association between fitness and the incidence of IFG, one of the initial pathogenic derangements in the progression of diabetes (see Figs. 1 and 2). There were 7,442 men who had normal fasting glucose values at baseline, of whom 593 were diagnosed with IFG at the second examination. A change in the relative odds of impaired fasting glucose was observed across categories of cardiorespiratory fitness, even after extensive adjustment for confounders including BMI (Fig. 4).

Next we examined the association between fitness and incident diabetes. In this study, the case diagnosis was based on a fasting plasma glucose level of  $\geq 126$  mg/dl rather than relying on a self-reported history of diabetes. Thus the objective measures of both exposure and outcome in the ACLS report are likely to provide a more reliable estimate of the true effect of inactivity/low fitness on diabetes risk than are studies with self-reported physical activity exposures and diabetes outcomes. Figure 4 shows a significant inverse gradient of risk for objectively diagnosed diabetes across cardiorespiratory fitness groups, even after extensive adjustment for confounding including BMI ( $P < 0.001$ ).

We further examined the association between fitness and incident diabetes in men grouped according to their baseline fasting glucose levels. Strong inverse gradients of age-adjusted diabetes rates were observed across fitness levels in men with IFG as well as normal glycemia at baseline (Fig. 5). Similar patterns of inverse associations between fitness and diabetes were seen in men grouped by age ( $<45$  vs.  $\geq 45$  years), BMI ( $<27$  vs.  $\geq 27$  kg/m<sup>2</sup>), and family history of diabetes (present vs. absent). We believe the ACLS analyses described here provide some of the most objective and compelling evidence of the importance of moderate and higher cardiorespiratory fitness levels in the prevention of both impaired glycemic control and overt clinical diabetes. Genetic factors influence both fitness and glucose homeostasis (9a). We have shown that average age-adjusted maximal fitness levels did not vary by the presence or absence of parental diabetes, and the association between fitness and diabetes risk is robust against adjustment for familial diabetes (80). Although we do not discount the important role that genetics play in diabetes expression, these observations provide evidence that genetic transmission does not account fully for the associations observed in our study. We have also shown that for most women and men, moderate

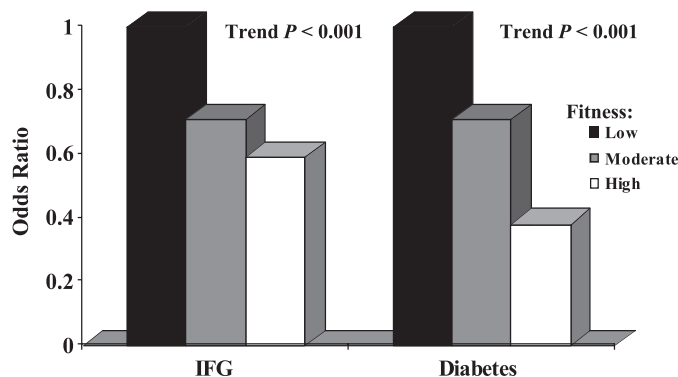


Fig. 4. Adjusted odds ratios for incident impaired fasting glucose (IFG) and diabetes by cardiorespiratory fitness level in men in the Aerobics Center Longitudinal Study. Adapted from Wei et al. (80).

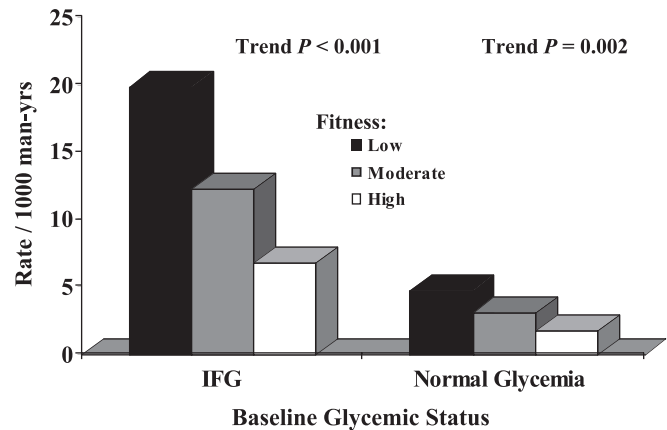


Fig. 5. Age-adjusted rates of diabetes by cardiorespiratory fitness in men with normal glycemia and impaired fasting glucose (IFG) at baseline. Adapted from Wei et al. (80).

and higher levels of fitness (e.g.,  $>6$ – $10$  METs depending on age and sex, where  $1$  MET =  $3.5$  ml O<sub>2</sub> uptake  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup>) can be achieved by regular participation in moderate and vigorous intensity physical activities (9, 16, 73) of similar volume as prescribed in current public health (66, 77) and clinical (3, 5) recommendations. We believe that existing observational data provide strong unequivocal evidence underscoring the importance of an active and fit lifestyle in the primary prevention of diabetes (10, 22, 38–40, 43, 60, 70, 77, 78, 80, 81).

**Experimental studies.** Although observational data suggest a causal association between physical activity and diabetes, experimental evidence is required for a definitive test of the hypothesis that higher levels of activity delay the progression to diabetes. Several recently conducted randomized trials have shown that an intensive lifestyle intervention, including physical activity, delays the incidence of diabetes in high-risk individuals with impaired glycemic control (19, 50, 65, 76, 82).

Pan et al. (65) studied the 6-year progression to diabetes in a group of Chinese participants with impaired glucose tolerance who were assigned to four intervention groups: control, diet, exercise, or diet plus exercise. Those in the exercise group were 46% less likely to develop diabetes than those in the control group ( $P < 0.001$ ), and this was comparable to the risk reduction in the combined diet and exercise group (42% reduction) and better than that observed in the diet-only group (31% reduction).

Two large randomized controlled studies conducted in Finland and the US examined the effect of a comprehensive lifestyle intervention on the progression to diabetes in high-risk women and men with impaired glycemic control (50, 76). In both studies, the lifestyle intervention included regular physical activity ( $\approx 150$  min/wk of moderate to vigorous intensity activities), modest weight loss ( $\approx 7\%$  of baseline weight was targeted), reduction in fat intake, and increase in whole grains, fruits, and vegetables. Results of the studies were remarkably similar. During a mean follow-up of 3–4 years, the risk of developing diabetes was  $\approx 60\%$  lower for those in the lifestyle intervention compared with those in the control group. In the US study, the 60% reduction in diabetes incidence in the lifestyle group also was significantly greater than the 31% reduction seen in individuals assigned to the group that re-

ceived an insulin-sensitizing drug as the intervention (50). Although the lifestyle intervention was multifaceted and the evaluation of individual intervention components should be interpreted with caution, in the Finnish trial there is evidence that regular physical activity had substantial benefit even without weight loss. Study participants who met the intervention target of ~4 h of moderate intensity activity/week, but who did not meet the weight loss goal, had a 70% lower risk of developing diabetes than those in the control arm ( $P < 0.05$ ), even after adjusting for differences in baseline BMI (53, 76).

In summary, there is an extensive body of observational and experimental evidence supporting the hypothesis that an active and fit way of life prevents initial dysregulation in glucose homeostasis and substantially delays the progression from a state of impaired glycemic control to frank diabetes. The beneficial effects of physical activity in preventing diabetes appear to be independent of other risk indicators such as IFG; parental history of diabetes, overweight, or obesity; and other clinical predictors of diabetes. Despite the evidence reviewed here, algorithms that have been proposed to identify individuals at high risk for developing diabetes do not include measures of physical activity or fitness, and this oversight should be corrected (63, 71, 72).

#### *Physical Activity, Fitness, and Risk of Clinical Events in Individuals With Diabetes*

As indicated in Fig. 2, we hypothesize that regular physical activity provides health benefits in individuals who have already expressed clinical diabetes. Indeed, several prospective observational studies have shown that among individuals with impaired fasting glucose or diabetes, higher levels of activity and fitness are associated with a lower incidence of cardiovascular events and mortality from all causes and cardiovascular disease (8, 12, 24, 41, 42, 52, 74, 79).

We have undertaken several studies on the association between fitness and mortality outcomes in participants in the ACLS with impaired fasting glucose or clinically diagnosed diabetes (8, 12, 52, 79). Our first report was on 10,224 men and 3,120 women in the ACLS who were followed for 85,049 man-years and 25,433 woman-years, during which 240 and 43 deaths occurred, respectively (8). In women and men, age-adjusted death rates were inversely associated with cardiorespiratory fitness levels in fasting glucose strata of  $<100$  mg/dl, 100–120 mg/dl, and  $>120$  mg/dl. Wei et al. (79) reported associations for fitness and physical activity levels with all-cause mortality in 1,263 men in the ACLS diagnosed with diabetes (baseline fasting glucose  $\geq 126$  mg/dl) who were followed for an average of 12 years during which 180 deaths occurred during 14,777 man-years of exposure (79). After adjusting for age, BMI, baseline glucose levels, and other confounders, the relative risk (95% CI) of mortality was 1.7 (1.2–2.3) and 2.8 (2.0–3.8) in men with low levels of physical activity and fitness, respectively. The stronger association with mortality for fitness than self-reported activity partly reflects the higher precision of classification for objectively measured fitness exposures. Our overall findings of an inverse association for physical activity and fitness with mortality in individuals with diagnosed diabetes are quite consistent with recently reported data from other established prospective cohort studies that have shown inverse associations for self-reported physical

activity exposures with cardiovascular events and mortality in women as well as men (24, 41, 42, 74).

Obesity often coexists with diabetes and is presumed to multiplicatively increase the risk of mortal events in diabetic individuals who are obese. We hypothesized that higher levels of fitness would protect against premature mortality even in overweight and obese individuals with diagnosed diabetes. Church et al. (12) prospectively related fitness with all-cause mortality in 2,196 men who were 23–79 years old and had clinically diagnosed diabetes at baseline. During 32,161 man-years there were 275 deaths. After extensive adjustment for confounding, including baseline glucose and BMI, the relative risk (95% CI) for mortality was 1.0 (referent), 0.63 (0.36–1.07), 0.36 (0.21–0.61), and 0.22 (0.13–0.38), trend  $P < 0.001$ , across incremental quartiles of maximal MET levels of cardiorespiratory fitness. After grouping the men into BMI-defined categories of normal weight ( $<25$  kg/m<sup>2</sup>), overweight (25–29.9 kg/m<sup>2</sup>), and obese ( $\geq 30$  kg/m<sup>2</sup>), steep inverse gradients of age-adjusted mortality risk were seen across quartiles of fitness in each BMI category (Fig. 6). Similar findings have been reported in 5,125 US female nurses who reported a history of diabetes at baseline and were followed through 31,432 woman-years during which 323 cardiovascular events occurred (41). After extensive adjustment for confounders, the investigators observed inverse gradients of cardiovascular events across quartiles of self-reported moderate to vigorous physical activity in women who were obese (BMI  $>30$  kg/m<sup>2</sup>; trend  $P = 0.02$ ) and nonobese (BMI  $\leq 30$  kg/m<sup>2</sup>; trend  $P = 0.08$ ).

There is compelling observational evidence that higher levels of physical activity and cardiorespiratory fitness confer substantial protection against mortality and premature cardiovascular disease in individuals with diabetes, irrespective of weight status. We believe physicians should be vigilant in counseling their patients with diabetes to increase their physical activity levels and improve their cardiorespiratory fitness to avert premature cardiovascular morbidity and mortality.

#### **BIOLOGICAL MECHANISMS**

A complete review of the known and hypothesized mechanisms through which physical activity and fitness influence

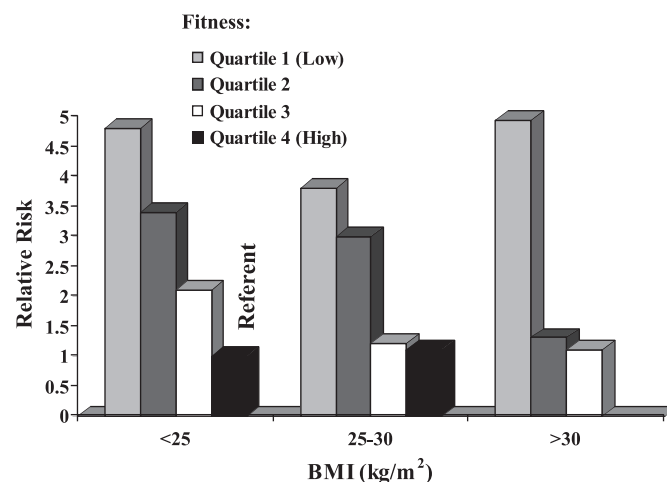


Fig. 6. Age-adjusted relative risk of all-cause mortality by fitness and BMI in men with diabetes. Adapted from Church et al. (12).

glucose homeostasis, confer protection against the development of diabetes, and delay mortality in patients with diabetes is beyond the scope of this review. Here, we will briefly summarize some key mechanisms and we refer readers to more extensive reviews that have been published elsewhere (23, 35, 36, 44, 45).

Table 1 lists several mechanisms that are thought to be involved with the favorable effect that regular physical activity has on glucose homeostasis and in the prevention of diabetes. Physical activity-induced improvements in glucose homeostasis occur both through acute responses and chronic adaptations. Several of the glucoregulatory effects appear to be acute or augmented-acute responses (32). Acute responses are changes in glucose uptake, transport, and/or disposal that occur during and some time after each bout of physical activity (3, 23, 44). With augmented acute responses, repeated bouts of activity result in a greater effect than a single bout. Chronic adaptations are changes in structure or function that occur from prolonged exposure to a specified dose of physical activity (3, 15, 23, 35, 36, 45). Thus it appears that the widest range of effects for improving or maintaining glucose homeostasis would occur through participation in an adequate dose of physical activity on a regular, perhaps daily basis (3, 66).

The mechanisms responsible for the reduced mortality risk in individuals with diabetes that are conferred through an active and fit way of life are likely to be complex and multifactorial. However, it is known that compared with sedentary individuals, those who are regularly physically active and fit have been shown to have lower blood pressure, better lipid profiles including LDL and HDL subfractions, lower amounts of visceral fat at a given level of body weight, lower markers of systemic inflammation, better cardiac function, healthier blood vessels, and higher heart rate variability, each of which may have an independent or contributory role in lowering the risk of mortality from cardiovascular diseases and perhaps certain cancers in individuals with diabetes (3, 9a, 11, 15, 17, 21, 26, 29, 37, 45–48, 55, 56, 75). Similar to observa-

tions made among individuals with clinically manifest CHD (57, 75), a physically active lifestyle may attenuate or reverse some of the pathophysiological abnormalities associated with the diabetic state, thus resulting in a relative protection against subsequent adverse health sequelae in individuals with diabetes.

## RESEARCH RECOMMENDATIONS

Some fundamental questions about physical activity and diabetes have been answered, as indicated in the previous sections of this report. It seems clear that a fit and active way of life delays initiation and progression of dysregulation of glucose metabolism ultimately leading to frank Type 2 diabetes. Furthermore, physical activity appears to reduce serious clinical complications and mortality risk in patients with diabetes. There are, however, numerous important questions that remain to be addressed regarding clinical and public health issues related to physical activity and diabetes.

*Efficacy versus effectiveness.* Lifestyle interventions, including physical activity, have been demonstrated to have beneficial effects in preventing diabetes in high-risk groups. For example, the Finnish Diabetes Study and the Diabetes Prevention Program were large, well-designed, well-conducted, state-of-the-art clinical trials, and the results are compelling. However, some key questions remain unanswered. Are the protective effects of increased physical activity mediated by or independent of dietary changes and weight loss? What is the extent to which lifestyle interventions can be extended into the general population at large? Can a family physician or internal medicine practitioner successfully implement dietary, physical activity, and weight loss programs so that a high percentage of patients can make lifestyle changes and reduce their risk?

*Population subgroups.* Prevention and treatment studies involving physical activity interventions need to be conducted in diverse subpopulations. Do the interventions have similar effects in younger and older participants, various racial or ethnic groups, those with various other health problems or diseases, and women and men? Considerably more data are needed from large representative populations with broad age ranges and with diverse race-ethnicity and socioeconomic status.

*Specific types, amounts, and intensities of physical activity.* There is a need for more research examining the different combinations of intensity, duration, and amount. For example, to what extent can activity be accumulated? Do six 5-min physical activity sessions per day provide the same benefit as one 30-min session? Does exercise intensity make any difference if the total volume of exercise is held constant? The consensus public health recommendation of 30 min of moderate intensity activity on at least 5 days/wk appears to help prevent or treat diabetes. Suppose a participant gets only one-half that amount, is there any benefit? Suppose a participant gets 60 min of activity/day, is there additional benefit beyond the 30-min recommendation, and if so, how much? Most of the research on physical activity and diabetes has used a general aerobic exercise prescription, although there is some evidence that resistance exercise also may provide benefits. More work on resistance exercise is needed, and investigations on the specific combinations of exercise type, amount, and intensity also are needed.

Table 1. *Biological mechanisms by which physical activity may enhance glucose homeostasis and confer protection against diabetes*

Structural changes in skeletal muscle
<ul style="list-style-type: none"> <li>• ↑ fiber size</li> <li>• ↑ percentage of Type IIa fibers (possibly Type I fibers)</li> <li>• ↑ capillary density and blood flow</li> </ul>
Biochemical changes in skeletal muscle
<ul style="list-style-type: none"> <li>• ↑ insulin signaling kinetics (↑ phosphatidylinositol 3-kinase and GLUT4 activity)</li> <li>• ↑ non-insulin signaling kinetics (↑ 5'-AMP-activated protein kinase activity)</li> <li>• ↑ enzymes related to glucose metabolism [hexokinase, glycogen synthase, and key oxidative enzymes (e.g., citrate synthase, aconitase, succinate dehydrogenase)]</li> <li>• ↑ myoglobin</li> </ul>
Systemic influences of physical activity
<ul style="list-style-type: none"> <li>• ↑ oxygen uptake and functional capacity at submaximal and maximal workloads</li> <li>• ↑ lipoprotein lipase and other key enzymes to improve lipemic control</li> <li>• ↓ excessive hepatic secretion of glucose and VLDL</li> <li>• Improvements in counter-regulatory hormone levels/activity (e.g., cortisol, IGF-I)</li> <li>• Improvements in comorbid conditions (e.g., hypertension, visceral obesity, systemic inflammation, dyslipidemia)</li> </ul>



**Studies on mechanisms.** Studies are needed that examine the role that physical activity has in modifying the expression of diabetes in individuals with genetic susceptibility. A better understanding of how acute and chronic activity exposures influence specific cellular mechanisms of glycemic control. Investigations also are needed to characterize the interaction of physical activity and insulin-sensitizing drugs as therapies in individuals with impaired glycemic control and frank diabetes.

## SUMMARY

Diabetes is a highly prevalent disease around the world, and it has a large economic, social, and personal suffering burden. Progressive deterioration in various components of glucose metabolism occurs over years, ultimately leading to a diagnosis of frank diabetes. It is clear that genetic susceptibility to diabetes is a prerequisite for developing the disease, but it is the gene-environment interaction that should attract attention in terms of developing effective public health strategies to reduce the burden of this disease. High-caloric-density diets, common in many populations, likely contribute to the development of obesity, which is clearly linked to higher risk of developing diabetes. However, we believe that the major behavioral causal factor in the increasing prevalence of diabetes is low levels of activity-related energy expenditure, brought about by technological advances that have largely engineered physical activity out of daily life. The evidence reviewed here provides compelling support for the hypothesis that sedentary habits are a major cause of diabetes. There also is strong evidence that an active and fit way of life reduces mortality risk in individuals with diabetes. Any strategy to deal with the global problem of increasing rates of diabetes and its complications must give major attention to physical inactivity and how to reverse it at the population level.

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