

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

Epidemiological evidence for the role of physical activity in reducing risk of type 2 diabetes and cardiovascular disease

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Bassuk, Shari S., and JoAnn E. Manson. Epidemiological evidence for the role of physical activity in reducing risk of type 2 diabetes and cardiovascular disease. *J Appl Physiol* 99: 1193–1204, 2005; doi:10.1152/jappphysiol.00160.2005.—Epidemiological studies suggest that physically active individuals have a 30–50% lower risk of developing type 2 diabetes than do sedentary persons and that physical activity confers a similar risk reduction for coronary heart disease. Risk reductions are observed with as little as 30 min of moderate-intensity activity per day. Protective mechanisms of physical activity include the regulation of body weight; the reduction of insulin resistance, hypertension, atherogenic dyslipidemia, and inflammation; and the enhancement of insulin sensitivity, glycemic control, and fibrinolytic and endothelial function. Public health initiatives promoting moderate increases in physical activity may offer the best balance between efficacy and feasibility to improve metabolic and cardiovascular health in largely sedentary populations.

epidemiology; clinical trials; cohort studies; coronary heart disease; type 2 diabetes mellitus

THE INCIDENCE OF DIABETES in the United States is increasing sharply, with ~1.3 million new cases occurring annually in recent years (17). Type 2 diabetes affects more than 16 million Americans, or almost 8% of US adults. In addition, an estimated 34% of the population have impaired fasting glucose levels, 15% have impaired glucose tolerance (IGT), and 40% have one or both of these conditions (9). A major cause of cardiovascular morbidity and mortality, diabetes increases the risk of developing coronary heart disease (CHD) by three- to sevenfold in women and by two- to threefold in men (67). The economic costs of diabetes and cardiovascular disease (CVD) in this country have been estimated at \$132.0 billion (34) and \$351.8 billion (73) per year, respectively. These amounts include both direct health care costs and indirect costs from lost productivity due to illness or death.

A sedentary lifestyle should be considered an important modifiable risk factor for type 2 diabetes and CVD in the general population. Researchers agree that physical activity provides metabolic and cardiovascular benefits, although the amount or “dose,” a function of intensity, frequency, and duration, of activity required for optimal health continues to be debated. A 2002 review of prospective studies published between 1990 and 2000 concluded that the reduction in the risk of type 2 diabetes associated with a physically active, compared with a sedentary, lifestyle is 30–50%, and that physical activity confers a similar risk reduction for CHD (91). Physical activity may slow the initiation and progression of type 2

diabetes and its cardiovascular sequelae via favorable effects on body weight, insulin sensitivity, glycemic control, blood pressure, lipid profile, fibrinolysis, endothelial function, and inflammatory defense systems. This article reviews recent observational and clinical trial data on the role of physical activity in the prevention of type 2 diabetes and CVD. Dose-response issues and implications for public health practice are discussed.

Exercise intensity is typically measured in kilocalories burned per minute of activity or in a unit called the metabolic equivalent (MET), defined as the ratio of the metabolic rate during exercise to the metabolic rate at rest. Moderate-intensity activities, such as brisk walking, are those that burn 3.5–7 kcal/min, or equivalently, those that expend 3–6 METs. Vigorous activities, such as running, are those that burn >7 kcal/min or expend >6 METs. The traditional belief that physical activity must be vigorous to be salutary has been challenged in the last decade by epidemiological studies showing otherwise. Earlier guidelines advocating vigorous exercise for at least 20 min three times per week have been supplemented by a 1995 recommendation by the Centers for Disease Control and the American College of Sports Medicine that adults engage in 30 min of moderate-intensity physical activity on most, and preferably all, days of the week (78), a standard also endorsed by the US Surgeon General since 1996 (100). In 2002, the Institute of Medicine (IOM) doubled the daily moderate-intensity activity goal to 60 min, stating that 0.5 h is not sufficient to maintain a healthy weight or to achieve maximal health benefits (44). The IOM guideline was issued in a report focused on nutrition goals for the US public.

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Although the IOM has received praise for highlighting physical activity as an essential part of a healthy lifestyle, its recommendation has also been criticized for not balancing the issue of efficacy with that of feasibility, both of which are needed to achieve a public health goal. National data indicate that 73% of US women and 66% of men fail to meet the 30-min guideline; and 41% of women and 35% of men engage in no leisure-time physical activity at all (Fig. 1) (88). Raising the bar even higher may erode any motivation that the American public, which already largely views the less stringent standard as too onerous, might muster to increase its activity level. On the basis of this fact and on our review of available epidemiological data, we, along with many researchers and policymakers, believe that the primary public health message should continue to be that moderately intense exercise for 0.5 h/day confers significant metabolic and cardiovascular benefits. Indeed, physical activity guidelines issued in 2004 by the American Diabetes Association in a joint statement with the American Heart Association and the American Cancer Society reaffirm the 30-min goal for the prevention of type 2 diabetes, CVD, and some types of cancer (17). The World Health Organization included the 30-min guideline in its 2004 blueprint for fighting these and other chronic diseases (111). In January 2005, the US Department of Health and Human Services and the US Department of Agriculture, while concurring with the IOM's recommendation of 60 min of daily activity for weight control, also espoused the 30-min goal for disease risk reduction (101). The 30-min recommendation does not imply the absence of a dose-response relationship between physical activity and metabolic or cardiovascular outcomes; another 0.5 h of activity per day would, on average, be expected to confer additional protection against the development of diabetes and CVD and would assist with weight control and prevention of obesity in populations with low baseline activity.

PHYSICAL ACTIVITY AND RISK OF TYPE 2 DIABETES

Prospective Observational Studies

Cohort studies consistently show a marked reduction in the incidence of type 2 diabetes among physically active individuals compared with their sedentary peers, and recent investi-

gations provide empirical support for the prescription of 30 min/day of moderate-intensity activity. In these studies, exposure data are derived from self-reported physical activity questionnaires. Among more than 70,000 initially healthy US women aged 40–65 yr participating in the Nurses' Health Study, walking briskly for at least 2.5 h/wk (i.e., 30 min/day for 5 days/wk) was associated with a 25% reduction in diabetes over 8 yr of follow-up among those reporting no vigorous exercise, after adjustment for age, body mass index (BMI), and other risk factors for diabetes (38). This is a conservative estimate that excludes the risk reduction attributable to lower body mass from physical activity. Given equivalent total exercise energy expenditures, brisk walking and more vigorous exercise were associated with similar magnitudes of risk reduction. In the Women's Health Study, a 6.9-yr follow-up of nearly 38,000 US female health professionals aged 45 yr and older, participants who reported walking 2–3 h/wk were 34% less likely to develop diabetes than women who reported not walking (107). In the Iowa Women's Health Study, which tracked more than 34,000 participants aged 55–69 yr for 12 yr, women engaging in moderate-intensity exercise at least once per week, two to four times per week, and more than four times per week were 10, 14, and 27% less likely, respectively, to develop diabetes than women engaging in such exercise less than once per week (21). In a cohort of 4,369 middle-aged Finnish women and men followed by Hu and colleagues (43) for 9.4 yr, individuals who walked or cycled to work for at least 30 min/day experienced a 36% reduction in diabetes incidence compared with their counterparts who did not engage in these activities. All of these estimates reflect adjustment for the effects of BMI and potential confounders.

Metabolic benefits of moderate-intensity exercise have also been observed in male populations. In the Kuipio Ischemic Heart Disease Risk Factor Study, which followed 897 Finnish men aged 42–60 yr for 4.2 yr, respondents who performed at least 40 min/wk of leisure-time physical activity with an intensity of ≥ 5.5 METs were 56% less likely to develop diabetes than men who did not achieve this level of physical activity, after factoring out the effects of BMI and other covariates (62). Among men at elevated risk of diabetes by virtue of being overweight, hypertensive, or having a parental history of diabetes, a protective effect of physical activity was observed at a lower intensity threshold of 4.5 METs. In the Health Professionals Follow-up Study, which followed nearly 38,000 US male health professionals aged 40–75 yr for 10 yr, each 10 MET-h increment in weekly walking energy expenditure was associated with a statistically significant 11% reduction in diabetes risk; an equivalent increase in weekly vigorous activity conferred a 12% reduction in diabetes risk (36). In a 14-yr follow-up of 5,990 male University of Pennsylvania alumni aged 39–68 yr, each 500-kcal increase in weekly leisure-time energy expenditure (for a 75-kg person, this represents 1 h of jogging at 5 miles/h, biking at 10 miles/h, or swimming with light to moderate effort) was associated with a statistically significant 6% reduction in the risk of developing diabetes, after controlling for BMI and other factors (32). The inverse gradient persisted even after exclusion of vigorous sports activities from the exposure variable. Other studies have shown similar benefits of moderate activity in preventing risk of type 2 diabetes in men (75, 105).

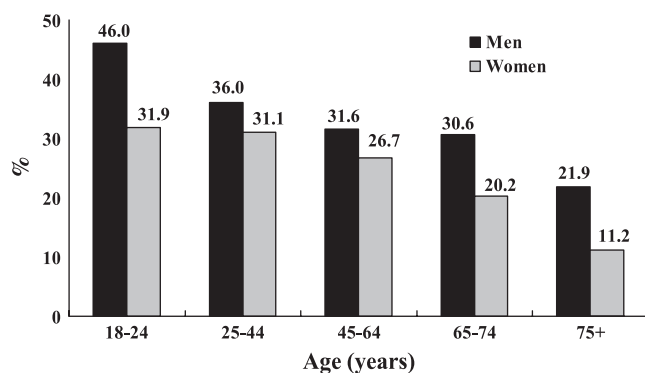


Fig. 1. Percentage of US adults engaging in regular leisure-time activity by gender and age. Regular activity is defined as light-to-moderate activity 5 times or more per week for 30 min each time, or vigorous activity 3 or more times per week for 20 min or more each time. Data are from Schoenborn and Barnes (88).

Gender-stratified analyses from some prospective studies that included both male and female participants suggest that the inverse association between physical activity and risk of diabetes may be somewhat stronger for women than for men, perhaps due to generally lower baseline activity levels for former compared with the latter. In the National Health and Nutrition Examination Survey (NHANES) I Epidemiologic Follow-up Study, which tracked more than 11,000 US adults for 16 yr, physical activity level was predictive of incident diabetes in women but not men (61). In a 10-yr follow-up of 1,864 middle-aged residents of Northeastern Finland by Haapanen and colleagues (27), a comparison of participants whose level of physical activity placed them in the bottom and top tertiles of the sex-specific sample distributions of leisure-time energy expenditure revealed an adjusted relative risk (RR) of 2.64 among women (≤ 900 kcal/wk vs. $> 1,500$ kcal/wk) and 1.54 among men ($\leq 1,100$ kcal/wk vs. $> 1,900$ kcal/wk). In the MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, which followed 6,166 participants for 6 yr, physical inactivity, defined as nonparticipation in sports activities, was predictive of an 81% increase and a 20% increase in diabetes risk among women and men, respectively (70). A 6-yr follow-up of 1,728 Pima Indians in Arizona, a community with one of the world's highest incidences of type 2 diabetes and a high prevalence of obesity, indicated that ≥ 16 MET-h per week of recreational physical activity (vs. less activity) was associated with a 26% reduction in diabetes incidence in women and a 12% reduction in men, after controlling for age and BMI (54). On the other hand, results from the 10-yr Whitehall II Study of more than 10,000 middle-aged British government employees suggest that gender does not importantly influence the relationship between physical activity and diabetes risk (55). Compared with their counterparts reporting high activity (≥ 1.5 h/wk of vigorous activity), women who reported low activity (< 1.5 h/wk of vigorous or moderate-intensity activity) or intermediate activity (≥ 1.5 h/wk of moderate-intensity activity but < 1.5 h/wk of vigorous activity) had a 71 and 38% increase in risk of developing diabetes, respectively, after adjustment for BMI and other covariates; the corresponding figures for men were 52 and 66%. A parallel analysis of data from two large single-sex cohorts in the United States, the 8-yr Nurses' Health Study (66) and the 5-yr Physicians' Health Study (65), also does not support the idea that physical activity is more protective against diabetes in women than men. For women in the Nurses' Health Study, the age-adjusted RRs associated with vigorous exercise zero, one, two, three, and four or more times per week were 1.0 (referent), 0.74, 0.55, 0.73, and 0.63 (66). For men in the Physicians' Health Study, the age-adjusted RRs associated with vigorous exercise zero, one, two to four, and five or more times per week were 1.0 (referent), 0.77, 0.62, and 0.58 (65). Indeed, additional adjustment for BMI attenuated the exercise-diabetes relationship to a far greater degree in women than in men, such that physical activity appeared more strongly related to diabetes risk in the latter group.

Epidemiological investigations that have examined whether physical activity confers greater protection against type 2 diabetes in participants with a higher baseline risk of the disorder than in their lower-risk counterparts have yielded inconsistent results. For example, exercise-associated risk reductions have been more pronounced among overweight indi-

viduals than among their lean counterparts in some (32, 65) but not all (7, 21, 36, 54, 66, 107) cohorts. In the Finnish sample of Hu and colleagues (42), the protective effect of physical activity was most apparent for men who were obese and/or hyperglycemic at baseline, and in the University of Pennsylvania alumni (32) and the Kuipio (62) cohorts, the effect was strongest for those who were overweight, were hypertensive, and/or had a family history of diabetes. On the other hand, in the Nurses' Health Study (37, 66), the magnitude of the exercise-diabetes association did not significantly vary according to these three factors (Fig. 2). The Health Professionals Follow-up Study also found that BMI and family history of diabetes were not important effect modifiers (Fig. 3) (36). Baseline data from the ongoing European Prospective Investigation into Cancer (EPIC)-Norfolk Study of 6,473 men and women aged 45–74 yr do suggest a stronger association between physical inactivity and diabetes prevalence among individuals with a family history of diabetes than among those without such a history, but prospective analyses are not yet available (85).

Even in studies showing a stronger protective effect of physical activity in high-risk participants than in low-risk participants, a high physical activity level does not completely offset the elevated diabetes risk conferred by excess body weight or family history. In the University of Pennsylvania study, for example, the diabetes incidence rates among overweight men with high ($\geq 2,000$ kcal/wk) and low (< 500 kcal/wk) recreational energy expenditures were 33.2 cases and 49.5 cases per 10,000 person-yr, respectively, whereas the corresponding incidence rates in lean men were 12.0 cases and 12.1 cases per 10,000 person-yr (32). In other studies, physical activity appeared to reduce the diabetes incidence in the high-risk group to that of physically inactive persons in the low-risk group. For example, in the Kuipio cohort, the 4-yr cumulative incidence of diabetes among high-risk men (i.e., men who were overweight, hypertensive, and had a positive family history of diabetes) with high [moderate-intensity (≥ 5.5 METs) exercise for ≥ 40 min/wk] and lower levels of physical activity was 16 and 44%, respectively, whereas the cumulative incidence among low-risk men with high and lower levels of activity was 8 and 16%, respectively (62). In the EPIC-Norfolk study, diabetes prevalence among participants with a family history of the disorder who had high and low occupational activity was 3.7 and 8.6%, respectively, whereas the corresponding prevalence in participants without a family history was 2.2 and 3.4% (85).

Cardiorespiratory Fitness Studies

The above studies, which used self-reported physical activity patterns as the exposure variable, provide direct support for current public health guidelines for exercise in diabetes prevention. These guidelines target physical activity, a behavior, rather than physical fitness, an attained physiological state. However, cardiorespiratory fitness as assessed by bicycle ergometer or treadmill test has also been shown to correlate inversely with type 2 diabetes incidence (62, 86, 106). In the Kuipio Ischemic Heart Disease Risk Factor Study, men in the lowest quartile of cardiorespiratory fitness [maximal oxygen uptake ($\dot{V}O_{2\max}$) < 25.8 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$] were more than four times as likely to develop diabetes as men in the highest

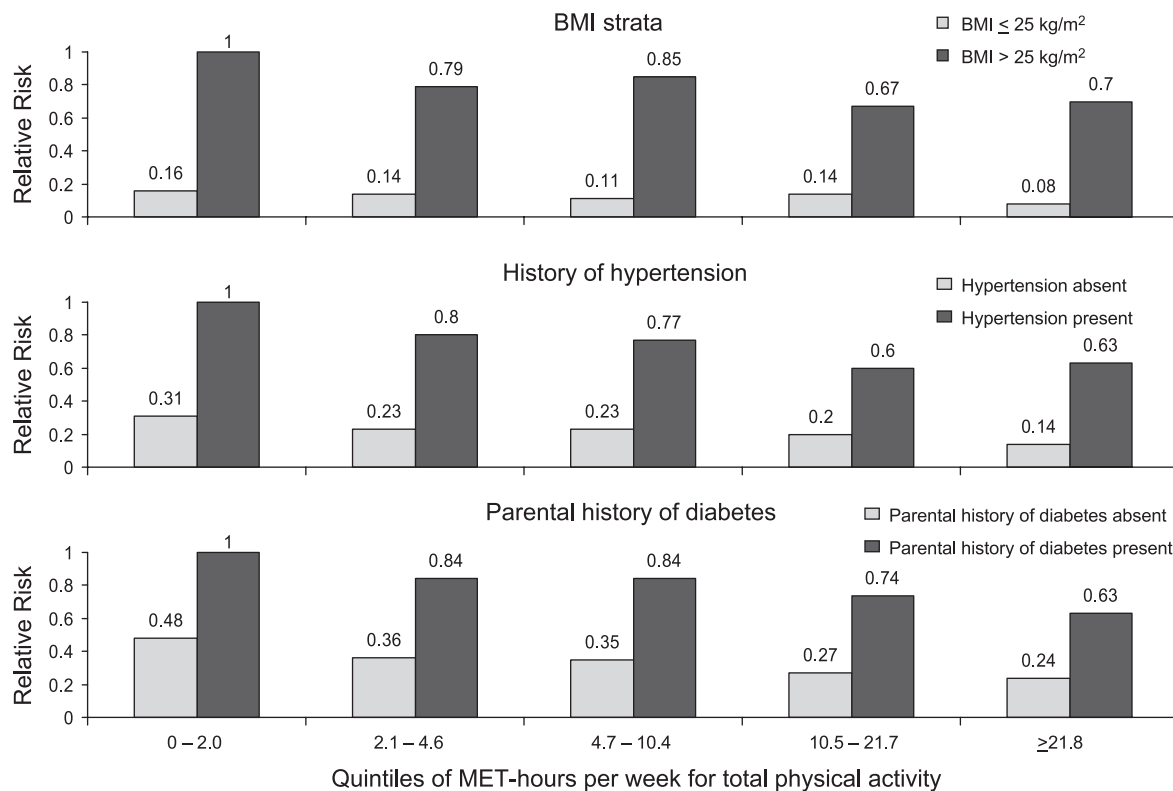


Fig. 2. Multivariate relative risks of type 2 diabetes according to physical activity, after 8 yr of follow-up, Nurses' Health Study. Relative risks are adjusted for age, cigarette smoking, alcohol consumption, menopausal status/hormone replacement, history of hypertension, history of hypercholesterolemia, and parental history of diabetes. BMI, body mass index; MET, metabolic equivalent. From Hu et al. (38) *JAMA* 282: 1433–1439, 1999. Copyright © 1999 American Medical Association. All rights reserved.

two quartiles of fitness ($\dot{V}O_{2\max} \geq 31.1 \text{ ml O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) after adjustment for BMI, baseline blood glucose, and other covariates (62). In the 6-yr Aerobics Center Longitudinal Study of 8,633 US men aged 30–79 yr, participants in the lowest quintile of fitness at baseline were 1.7 times as likely to develop impaired fasting glucose and 2.6 times as likely to develop diabetes than were participants in the top two fitness quintiles (106). The inverse gradient occurred in men with high or normal BMI, those with or without a family history of diabetes, and those with normal or impaired fasting blood glucose at baseline. In a 14-yr follow-up of 4,747 20- to 40-yr-old male employees of the Tokyo Gas Company, the adjusted RRs of developing diabetes across increasing quintiles of fitness (mean $\dot{V}O_{2\max}$ of 32.4, 38.0, 42.4, and 51.1 $\text{ml O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) were 1.0 (referent), 0.78, 0.63, and 0.56 (86). Comparable studies in women are lacking.

Methodological Considerations

When interpreting the inverse associations between physical activity and diabetes reported in observational studies, one must consider the possibility that unmeasured or unknown factors may influence the selection and participation of study respondents (selection bias), the possibility that unmeasured or unknown third factors may account for the association (confounding), and the possibility that imperfectly measured exposure or disease status could influence the results (misclassification). Surveillance bias should also be considered; for example, respondents with putative risk factors such as physical inactivity may be more likely to be screened by their physi-

cians for diabetes and diagnosed with the condition earlier than other respondents, leading to an overestimate of the strength of the exercise–diabetes relationship. In addition, physical activity questionnaires may more accurately capture actual activity levels in some groups than in others (e.g., normal-weight vs. obese persons), causing spurious interaction effects. However, the consistency of the main-effects results across studies, including studies that relied on exercise testing rather than physical activity questionnaires to assess exposure or on glucose tolerance or fasting glucose tests rather than self-reported diagnoses to assess outcome, supports a causal association, as does the biological plausibility due to the known salutary effects of increased physical activity on the metabolic risk factor profile.

Intervention Studies

Intervention studies in high-risk populations provide strong evidence that regular physical activity can prevent or postpone the onset of type 2 diabetes. A nonrandomized study in Swedish men aged 46–49 yr at baseline assessed the effects of a structured diet and exercise intervention in persons with either IGT or diabetes compared with a routine-treatment control group of persons with either IGT or normal glucose tolerance (16). The physical activity goal consisted of two 45- to 60-min sessions per week of activities such as walking, jogging, calisthenics, soccer, and badminton. (The more intense activities were not a major part of the intervention until late in the training period.) Among participants with IGT, the 5-yr incidence of diabetes was 10.6% in the intervention group com-

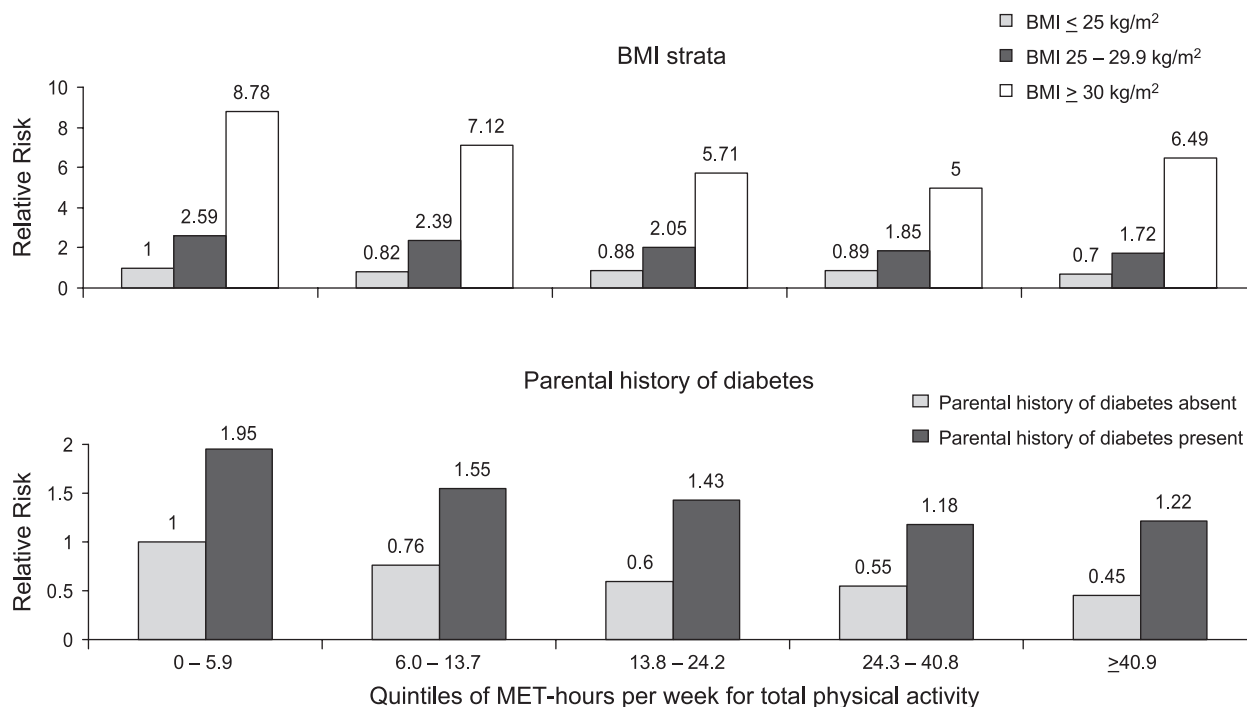


Fig. 3. Multivariate relative risks of type 2 diabetes according to physical activity, after 10 yr of follow-up, Health Professionals Follow-up Study. Relative risks are adjusted for age, cigarette smoking, alcohol consumption, history of hypertension, history of hypercholesterolemia, and parental history of diabetes. Data are from Hu et al. (36).

pared with 28.6% in the control group. In addition, more than half (54%) of the men with diabetes at baseline no longer had glucose levels diagnostic for the disorder at 5 yr. After 12 yr, mortality in the IGT intervention group was lower than mortality in the IGT control group (6.5 vs. 14.0 per 1,000 person-yr) and similar to that in the normal glucose tolerance control group (6.5 vs. 6.2 per 1,000 person-yr) (15).

Three randomized studies of exercise and diet in the prevention of type 2 diabetes have been conducted (Table 1). In the Da Qing IGT and Diabetes Study, 577 middle-aged Chi-

nese women and men with IGT were randomized to one of three treatment groups (diet only, exercise only, or diet plus exercise) or to a control group (77). Participants assigned to exercise were encouraged to increase their daily physical activity by 1 or more units, with a unit defined as 30 min of mild-intensity activity (e.g., walking), 20 min of moderate-intensity activity (e.g., brisk walking or cycling), 10 min of strenuous activity (e.g., slow running or climbing stairs), or 5 min of very strenuous activity (e.g., jumping rope or swimming). Over 6 yr, the three interventions were associated with

Table 1. Randomized clinical trials of exercise/diet and incidence of type 2 diabetes

Study	Study Population	Intervention(s)	Length, yr	Reduction in Risk of type 2 Diabetes in Intervention Group(s) Compared With Control Group
Da Qing Impaired Glucose Tolerance and Diabetes Study [Pan et al. (77)]	577 men and women with impaired glucose tolerance; mean age, 45 yr; mean BMI, 25.8 kg/m ²	Diet only; exercise only; diet plus exercise; control	6	Diet only: 31% ($P < 0.03$) Exercise only: 46% ($P < 0.0005$) Diet plus exercise: 42% ($P < 0.005$)
Finnish Diabetes Prevention Trial [Tuomilehto et al. (99)]	522 men and women with impaired glucose tolerance; mean age, 55 yr; mean BMI, 31 kg/m ²	Lifestyle modification program (goal of weight loss $\geq 5\%$; diet composed of $<30\%$ kcal from fat, $<10\%$ kcal from saturated fat, and ≥ 15 g fiber/1,000 kcal; moderate-intensity exercise ≥ 30 min/day) or control	3.2	58% ($P < 0.001$)
US Diabetes Prevention Program [Knowler et al. (52)]	3,234 men and women with elevated fasting and postload glucose; mean age, 51 yr; mean BMI, 34 kg/m ²	Lifestyle modification program (goal of weight loss $\geq 7\%$ and exercise ≥ 150 min/wk); or metformin (850 mg twice daily); or placebo	2.8	Lifestyle modification: 58% (95% CI, 48–66%) Metformin: 31% (95% CI, 17–43%)

BMI, body mass index; CI, confidence interval.

statistically significant reductions of 31, 46, and 42% in diabetes risk, respectively. Similar reductions in diabetes incidence were observed in both lean and overweight individuals. Among participants with initial BMI of <25 kg/m², diabetes incidence rates in the diet-only, exercise-only, diet plus exercise, and control groups were 8.3, 5.1, 6.8, and 13.3 per 100 person-yr, respectively ($P < 0.05$ for the 2 exercise-group vs. control comparisons); among participants with initial BMI of ≥ 25 kg/m², the corresponding rates were 11.5, 10.8, 11.4, and 17.2 per 100 person-yr, respectively ($P < 0.05$ for the 3 treatment vs. control comparisons).

In the Finnish Diabetes Prevention Study, 522 middle-aged, overweight women and men with IGT were randomly assigned to an intensive lifestyle intervention designed to promote healthy eating and exercise patterns or to a control group (99). Members of the diet and exercise intervention group lost significantly more weight than did the control group (3.5 vs. 0.8 kg) and reduced their risk of developing diabetes by 58% over 3 yr. There was a strong correlation between the number of lifestyle goals achieved during the first year of the trial (loss of more than 5% of body weight, reduction in fat intake to less than 30% of calories, reduction in saturated fat intake to less than 10% of calories, increase in fiber intake to at least 15 grams per 1,000 kcal, and performing the equivalent of at least 150 min of moderate-intensity exercise per week) and diabetes incidence. Of note, improvements in exercise reduced the risk of diabetes even when participants did not attain the weight-loss goal. Among intervention group members who did not lose at least 5% of their initial body weight, those who achieved the exercise goal were only one-fifth as likely to develop diabetes compared with their counterparts who maintained a sedentary lifestyle, and the association remained strong after adjustment for baseline BMI. The corresponding exercise-associated risk reduction in the control group was $\sim 40\%$. Data from a subsample of participants who consented to a frequently sampled intravenous glucose tolerance test at baseline and at the end of the trial suggest that improved insulin sensitivity, rather than preserved insulin secretion, largely explained the reduction in diabetes incidence in this cohort (102).

The US Diabetes Prevention Program, which randomly assigned 3,234 women and men aged 25–85 yr with IGT and BMI of ≥ 24 kg/m² to either a diet and exercise program, the biguanide drug metformin, or placebo, also reported a 58% reduction in diabetes risk associated with the lifestyle intervention (vs. placebo) (52). (Metformin was also effective; the drug vs. placebo comparison yielded a 31% risk reduction.) On average, participants assigned to lifestyle modification performed moderate-intensity exercise for 150 min/wk and lost 5–7% of their body weight during 3 yr of follow-up. This study oversampled older people and members of ethnic groups that suffer disproportionately from diabetes (African-, Hispanic-, and Asian-Americans; Pacific Islanders; and American Indians) and found that the lifestyle intervention was associated with a reduced diabetes risk in all age and ethnic groups, as well as in both genders. The effect of the lifestyle intervention on diabetes risk also did not significantly vary by baseline BMI (for BMI <30 , 30 to <35 , and ≥ 35 kg/m², risk reductions were 65, 61, and 51%, respectively).

PHYSICAL ACTIVITY AND RISK OF CHD

Observational epidemiological studies in populations unselected for diabetes status suggest that 30 min/day of moderate-intensity activity is effective in preventing CHD. Among nearly 74,000 postmenopausal women in the Women's Health Initiative, walking briskly for at least 2.5 h/wk was associated with a 30% reduction in cardiovascular events over 3.2 yr of follow-up (63). After adjustment for total exercise energy expenditure, brisk walking and more vigorous exercise were associated with similar risk reductions in cardiovascular events. In the Nurses' Health Study, 3 h of brisk walking per week had the same protective effect as 1.5 h of vigorous exercise per week (64); women engaging in either type of exercise had a 30–40% lower rate of myocardial infarction than sedentary women. In the Women's Health Study, walking at least 1 h/wk was associated with a 50% reduction in CHD risk over 7 years in individuals reporting no vigorous physical activities such as running or bicycling (58). Among 1,564 middle-aged University of Pennsylvania alumnae followed for 3 decades, walking ≥ 10 blocks per day compared with walking <4 blocks per day was associated with a 33% reduction in CVD incidence (89). In the Health Professionals Follow-up Study, men who walked briskly for at least 30 min/day were 18% less likely to develop CHD during 12 yr of follow-up than were men who did not meet this activity criterion (98). In the Honolulu Heart Program, men aged 71–93 yr who walked 1.5 miles/day experienced half the risk of CHD of those who walked <0.25 mile/day (28). In the 10-yr Zutphen Elderly Study, men aged 64–84 yr who walked or cycled at least three times per week for 20 min experienced a 31% reduction in CHD mortality compared with their less active counterparts (4). Studies in men suggest that vigorous exercise is associated with even greater reductions in the risk of CVD than is moderate-intensity exercise (4, 57, 98, 112). For example, in the Health Professionals Follow-up Study, each 1-MET increase in exercise intensity was associated with a 4% reduction in CHD risk independent of total exercise energy expenditure (98).

Prospective studies have also found that walking is predictive of reduced CVD incidence or CVD mortality among persons with type 2 diabetes (3, 26, 39, 41, 97). Among Nurses' Health Study participants with diabetes who reported no vigorous exercise, for example, the 14-yr RRs for incident cardiovascular events across increasing quartiles of walking energy expenditure were 1.0 (referent), 0.85, 0.63, and 0.56, after adjustment for BMI and other covariates (39). In an 8-yr follow-up of 2,449 adults with diabetes in the National Health Interview Survey, walking ≥ 2 h/wk was associated with a 41% reduction in CVD mortality compared with not walking (26). In an 18.4-yr follow-up of 3,316 Finnish men and women aged 25–74 yr with diabetes, the adjusted RRs associated with low, moderate, and high leisure-time physical activity were 1.00 (referent), 0.83, and 0.67 for CVD mortality (41). Among men with diabetes in the Health Professionals Follow-up Study, the RR for incident CVD comparing those in the highest quintile of walking energy expenditure with those in the lowest quintile was 0.66; the corresponding statistic for total exercise energy expenditure was 0.67 (97).

A recent randomized trial from Denmark included 0.5 h of brisk walking three to five times per week as part of a

multifaceted approach to managing diabetes (24). In this study, 160 patients with type 2 diabetes were assigned to receive conventional treatment from their general practitioners or intensive treatment, including a stepwise implementation of behavior modification and pharmacological therapy, overseen by a physician, nurse, and dietician at the academic center conducting the trial. During the 8-yr follow-up, the intensive-treatment group experienced a 53% reduction in cardiovascular events compared with the conventional-treatment group. An ongoing large-scale trial, the Look AHEAD (Action for Health in Diabetes) study funded by the National Institute of Diabetes and Digestive and Kidney Diseases, should provide additional information about the long-term (≥ 10 yr) effects of sustained weight loss through exercise and decreased caloric intake on the risk of CVD in obese persons with diabetes (84). A positive finding may encourage individuals with diabetes to boost their activity levels. In the nationally representative NHANES III survey, 31% of respondents with diabetes reported no regular leisure-time physical activity, and another 38% reported less than recommended levels of physical activity (74).

Although most studies of physical activity have focused on aerobic exercise, resistance exercise may also be important in reducing the incidence of diabetes and CVD. Men in the Health Professionals Follow-up Study who trained with weights for at least 30 min/wk were 23% less likely to develop CHD over 8 yr of follow-up than their counterparts who did not train with weights (98). Aerobic and resistance exercise also confer other benefits, most notably improved bone density and the preservation of musculoskeletal function (100). Nevertheless, fewer than 20% of US adults aged 45 yr and older report ever engaging in strengthening activities (Fig. 4) (88).

PROTECTIVE MECHANISMS

Observational and experimental data indicate that regular physical activity has beneficial effects on many risk factors for diabetes and CVD, including regulating body weight, enhancing insulin sensitivity and glycemic control, and reducing blood pressure, atherogenic dyslipidemia [i.e., elevated triglycerides, low high-density lipoprotein (HDL) cholesterol, and other lipoprotein abnormalities], inflammation, fibrinolysis, and endothelial dysfunction. Indeed, bouts of activity lasting as little as 10 min have been shown to improve the metabolic and

cardiovascular risk profile of otherwise sedentary individuals (47, 72, 96).

Body Weight

The primary rationale for the aforementioned guideline of at least 60 min of moderate-intensity physical activity per day is that lesser amounts of activity have not been consistently shown to ensure weight maintenance within the healthy BMI range of 18.5–25.0 kg/m² or to promote weight loss in the absence of caloric restriction. Exercising for weight control may be particularly salient for women, because data from the NHANES surveys indicate that caloric intakes of US women increased by a higher percentage than those of US men during the last 30 yr. From 1971 to 2000, the daily caloric intake of the average woman rose by 22%, from 1,542 to 1,877 kcal, while the average man increased his intake by 7%, from 2,450 to 2,618 kcal (10). During this time, the prevalence of obesity soared. The World Health Organization and the United States' National Institutes of Health define overweight as a BMI of 25–29.9 kg/m² and obesity as a BMI of 30 kg/m² or greater. Using this definition, in the NHANES survey of 1960–1962, an estimated 31.6% of adults were overweight and 13.4% were obese. By the NHANES survey of 1999–2000, the proportion of overweight adults had increased only slightly, to 34.0%, while the proportion of obese adults more than doubled, to 30.5% (19, 20). An estimated 33.4% of US women and 27.5% of men are obese. Although comparable data on national trends in physical activity during this period are not available, activity levels among US adults were stable during the 1990s (8), suggesting that poor dietary habits are at least as responsible as sedentary lifestyle for the ballooning waistlines of the American public.

Some data do suggest that 1 h of activity per day may be necessary to control weight without practicing dietary restraint. In an IOM-compiled database of some 400 healthy stable-weight adults whose energy expenditures had been estimated with the doubly labeled water method, considered the gold standard of energy expenditure measurement, persons with a BMI between 18.5 and 25.0 kg/m² expended a daily energy equivalent of substantially more than 1 h of moderate activity (44). Moreover, descriptive studies of formerly obese individuals suggest that 80 min/day of moderate-intensity activity or 35 min/day of vigorous activity is necessary for long-term weight-loss maintenance (51, 87, 110). In the National Weight Control Registry, a sample of 629 women and 155 men who lost an average of 30 kg and maintained a minimum weight loss of 13.6 kg for 5 yr, the self-reported median weekly leisure-time exercise energy expenditure was 2,800 kcal, or 1.5 h/day of brisk walking for a 65-kg woman (51). On the other hand, findings from randomized trials of exercise in overweight, sedentary individuals who were asked to adhere to their usual diet indicate that lesser amounts of physical activity can also have a beneficial effect on weight control (13, 46, 92). In addition, a recent study using nationally representative data has estimated that a mere 100 kcal/day change in energy balance could prevent weight gain in the majority of US adults aged 20–40 yr, and that modest increases in physical activity, such as an additional 15 min of walking per day, or reductions in caloric intake, such as small decreases in portion sizes, would produce the desired change (33).

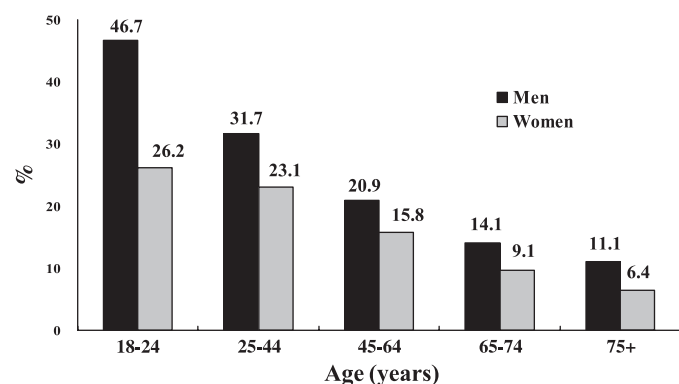


Fig. 4. Percentage of US adults engaging in regular strengthening activities by gender and age. Strengthening activities are defined as leisure-time physical activities specifically designed to strengthen muscles. Data are from Schoenborn and Barnes (88).

Although the exact shape of the dose-response curve between physical activity and body weight is uncertain, focusing on weight control as the *raison d'être* for engaging in physical activity gives an incomplete assessment of exercise's impact on metabolic and cardiovascular health. With few exceptions, prospective observational studies and clinical trials find that inverse relationships between physical activity and risk of diabetes or CVD persist even after factoring out the effects of BMI, suggesting that the metabolic and cardiovascular benefits derived from physical activity are not solely a function of weight regulation. Of course, this observation does not negate the strong deleterious impact of overweight and obesity; epidemiological studies indicate that an estimated 70% of type 2 diabetes cases and 25% of CHD cases are attributable to excess weight and that each kilogram of weight gained during midlife increases diabetes risk by 4.5% and CHD risk by 3.1% (12, 23, 109).

Insulin Sensitivity and Glycemic Control

Observational and clinical trial data suggest that regular physical activity, either alone or combined with dietary therapy, improves insulin sensitivity, glycemic control, and the metabolic profile among both nondiabetic and diabetic populations (91). Moderate- and high-intensity exercise may confer comparable benefits. The Insulin Resistance Atherosclerosis Study reported significant cross-sectional relationships of similar magnitude between both moderate- and vigorous-intensity physical activity and insulin sensitivity among middle-aged men and women with and without type 2 diabetes (68). Increases in moderate-intensity and vigorous physical activity of 200 kcal/day were associated with increases in insulin sensitivity of 2.9 and 2.6%, respectively. (By comparison, a 1-unit decrement in BMI was associated with a 3.2% increase in insulin sensitivity.) After adjustment for BMI and waist-to-hip ratio, the increases were somewhat attenuated (1.7 and 1.9%, respectively) but still statistically significant. The Cross-Cultural Activity Participation Study found that 30-min increases in "moderate/vigorous" and "moderate" physical activity per day were cross-sectionally associated with 6.7 and 6.6% lower fasting insulin levels, respectively, among women aged 40–83 yr unselected for diabetes status; after adjustment for BMI and central obesity, these percentages were 3.4 and 5.2% (both $P < 0.05$) (45). In the British Regional Heart Study, both moderate and vigorous activities were inversely associated with insulin level at baseline, and adjustment for insulin and other components of the metabolic syndrome, including hypertension and atherogenic dyslipidemia, appeared to explain a large proportion of the reduction in diabetes risk associated with physical activity observed in this cohort of 5,159 initially healthy middle-aged men followed for 16.8 yr (105).

Intervention studies in nondiabetic populations find a similar pattern of results. For example, a 6-mo trial that randomly assigned middle-aged, overweight women and men with dyslipidemia to various exercise regimens or to a nonexercising control group found that equivalent durations of moderate-intensity and vigorous exercise were associated with nearly identical improvements in insulin sensitivity (35). Compared with sedentary controls, participants who performed 170 min/wk of moderate-intensity exercise and those who spent the same amount of time engaged in vigorous exercise experienced

an 88 and 83% increase in insulin sensitivity, respectively; these improvements were not accounted for by weight loss. A meta-analysis of 14 trials (11 of which were randomized; 504 participants) of physical activity interventions lasting 8 wk or more found that exercise training reduced glycosylated hemoglobin (HbA_{1c}) levels among middle-aged diabetic individuals (6). Aerobic exercise interventions, which, on average, consisted of three 53-min sessions per week of walking or cycling over an 18-wk period, were associated with a mean 0.67% reduction in HbA_{1c} level; resistance training (2–3 sets ranging from 10 to 20 repetitions at 50% of respondents' repetition maximum) yielded a comparable reduction of 0.64%. These benefits appeared to be independent of change in weight or body composition. To appreciate the clinical significance of these findings, consider that, in a 10-yr observational follow-up of participants with diabetes in the large United Kingdom Prospective Diabetes Study, each 1% reduction in HbA_{1c} level was associated with a 14% reduction in myocardial infarction, a 37% reduction in microvascular complications, and a 21% reduction in diabetes-related mortality (95).

Blood Pressure

Data from prospective observational studies (5, 27, 31, 40, 76, 79) and randomized clinical trials also indicate that regular moderate-intensity exercise lowers blood pressure as or more effectively than does high-intensity exercise; such effects occur in both normotensive and hypertensive individuals and are independent of weight loss. In a meta-analysis of 54 randomized trials (2,419 participants), aerobic exercise was associated with a mean reduction in blood pressure of 3.9/2.6 mmHg across all initial blood pressure levels, with a mean reduction of 4.9/3.7 mmHg in hypertensive patients; the degree of blood pressure reduction did not differ by frequency or intensity of exercise (108). Another meta-analysis of 47 aerobic exercise trials (2,543 participants) reported mean blood pressure decreases of 2/1 mmHg (2%/1%) in normotensive persons and decreases of 6/5 mmHg (4%/5%) in hypertensive persons (48). In a meta-analysis of 16 trials (650 participants) that employed walking as the sole intervention, decreases of 3/2 mmHg occurred in both normotensive and hypertensive persons after a mean of 25 wk of treatment (50). Resistance exercise may also reduce blood pressure. In a meta-analysis of 11 trials (320 participants) of strength training (on average, three 38-min sessions per week over a 14-wk period, with 1–4 sets ranging from 4 to 50 repetitions at 35% of participants' repetition maximum), blood pressure decreases of 3/3 mmHg (2%/4%) were observed (49).

Dyslipidemia

In contrast to the findings for insulin sensitivity and hypertension, strong dose-response associations between exercise intensity and blood lipids [specifically, triglyceride and HDL cholesterol levels (90)] have been reported in observational studies (60). A recent 8-mo randomized trial that assigned sedentary, dyslipidemic women and men aged 40–65 yr to various exercise programs or to a control group found that although exercise did not lower plasma levels of low-density lipoprotein (LDL) cholesterol, it did favorably alter various LDL subfraction parameters in addition to the expected im-

improvements in HDL cholesterol and triglycerides (53). These effects were far more pronounced among the “high-amount/high-intensity” exercise group, who expended the energy equivalent of jogging 17–18 miles/wk, than among the “low-amount/high-intensity” and “low-amount/moderate-intensity” groups, who expended the equivalent of jogging or walking 11 miles/wk, respectively. A comparison of the latter two exercise groups showed that they experienced similar improvements in lipoprotein profile to each other. On the basis of these results, the investigators suggest that lipoprotein profiles are more strongly related to amount, rather than intensity, of physical activity. Beneficial effects of aerobic exercise (walking at 70% heart rate reserve for three 50-min sessions/wk) and resistance training on plasma lipoprotein levels were also found in a 10-wk randomized trial of women aged 70–87 yr, further evidence that physical activity can ameliorate metabolic and cardiovascular risk even in the elderly (18). In both trials, the beneficial effects of exercise occurred without concurrent changes in diet.

Inflammation

Regular physical activity may favorably affect inflammatory responses and immune system function, critical processes in the pathogenesis of diabetes and CVD. In prospective studies, elevated levels of the inflammatory biomarker C-reactive protein (CRP) consistently predict incident diabetes and cardiovascular events (2).

Dose-response relationships between recreational or household-related physical activity and inflammatory markers, including CRP, interleukin-6, and white blood cell count, have been observed in several studies of populations unselected for diabetes (22, 25, 81, 104). In NHANES III, for example, the multivariate-adjusted RRs for elevated CRP (defined as ≥ 85 th percentile of the sex-specific distribution) were 0.98, 0.85, and 0.53 for respondents who engaged in light, moderate, and vigorous leisure-time activity, respectively, during the previous month compared with those engaging in no leisure-time activity during that time (22). In an analysis limited to respondents without diabetes, CHD, or other chronic conditions, frequency of physical activity was also associated in a dose-dependent manner with CRP level (1). Compared with those engaging in leisure-time physical activity 3 or fewer times per month, persons engaging in such activity 4–21 times per month and persons engaging in such activity 22 or more times per month were 23 and 37% less likely, respectively, to have an elevated CRP level. Cardiorespiratory fitness as assessed by exercise testing has also been shown to correlate inversely with CRP levels in persons with (69) and without diabetes (11, 56). Nearly all of these studies adjusted for BMI and other potential confounders.

Data from small intervention studies also suggest a beneficial effect of regular exercise on inflammation. For example, in a “before-after” trial of a 6-mo individualized exercise intervention in which 43 participants exercised for an average of 2.5 h/wk, mononuclear cell production of atherogenic cytokines fell by 58%, whereas the production of atheroprotective cytokines rose by 36% (94). A 35% decrease in CRP level was also noted.

Hemostasis

The protective effect of physical activity may result in part from its favorable influence on hemostatic factors. Among 1,507 adults aged 25–64 yr in the Northern Sweden MONICA Study, tissue plasminogen activator (tPA) activity increased linearly with greater leisure-time physical activity, whereas plasminogen activator inhibitor-1 activity decreased (14). In a 20-yr follow-up of men in the British Regional Heart Study, habitual leisure-time physical activity showed significant and inverse dose-response relationships with fibrinogen, plasma and blood viscosity, platelet count, coagulation factors VIII and IX, von Willebrand factor, fibrin D-dimer, and tPA antigen, even after adjustment for potential confounders (104). Randomized intervention studies have consistently found that regular moderate-intensity exercise produces significant improvements in fibrinolytic capacity in formerly sedentary individuals (59, 93). However, sparse and inconsistent data from trials testing the effect of regular physical activity performed at varying intensities on blood coagulation and platelet reactivity preclude definite conclusions regarding these pathways (59, 80).

Endothelial Function

Epidemiological data on the association between regular physical activity and endothelial function in healthy persons are lacking. However, in trials of patients with hypertension, hypercholesterolemia, diabetes, coronary artery disease, or heart failure, aerobic exercise has been shown to increase nitrous oxide and prostacyclin availability and to improve endothelial-dependent vasodilatation (29, 30, 71, 82, 103). Because the vascular endothelium is also involved in other aspects of metabolic and cardiovascular health, such as mediating the balance between fibrinolytic and prothrombotic processes, controlling inflammatory responses, and regulating blood pressure, it likely represents an important pathway by which exercise protects against diabetes and CVD.

CONCLUSION

Observational and clinical trial data suggest that as little as 30 min/day of moderate-intensity physical activity can reduce the incidence of type 2 diabetes and cardiovascular events. The mechanisms that underlie these protective effects likely include the regulation of body weight; the reduction of adiposity, insulin resistance, blood pressure, dyslipidemia, and inflammation; and the enhancement of insulin sensitivity, glucose tolerance, and fibrinolytic and endothelial function. Despite recent advances in basic and clinical research, however, our understanding of the physiological connection between physical activity and diabetes remains incomplete. Physical inactivity has been linked to so many potential risk factors for diabetes and its cardiovascular sequelae that researchers have not yet fully disentangled the more important and the less important pathways by which exercise lowers disease risk. Nevertheless, whether or not a complete picture of the relevant physiology is eventually achieved, the identification of strategies for facilitating sustained exercise at a level sufficient to result in measurable improvements to public health should be a top priority. In our largely sedentary society, the challenge to clinicians and policymakers is determining how best to promote appropriate levels of regular physical activity to their

patients and the general public, respectively. Based on our review of current scientific data, as well as a balancing of efficacy and feasibility concerns, we believe that the clinical and public health message regarding exercise for disease prevention should remain “30 min per day of moderate activity is good; and more is better, to a reasonable extent.” According to a well-known epidemiological axiom (83), the overall disease burden in a given population generally undergoes a more dramatic reduction when a large segment of the population adopts small improvements in health behaviors than when a small segment of the population adopts large improvements.

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