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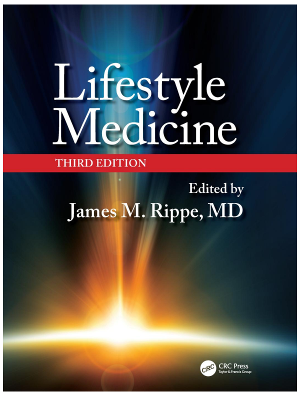

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James M. Rippe

Physical Activity and Fitness in the Prevention of Cardiovascular Disease

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CHAPTER

3

Physical Activity and Fitness in the Prevention of Cardiovascular Disease

Robert F. Zoeller Jr., PhD

Cardiovascular disease (CVD), as defined by the Centers for Disease Control and Prevention (CDC), encompasses coronary heart disease (CHD), stroke, hypertension, and heart failure.[1] CVD accounts for nearly one in three deaths in the United States. Approximately 2,150 Americans die from some manifestation of CVD every day—roughly one every 40 seconds.[1] CVD has been the leading cause of death since 1900 and remains so despite a decades-long decline in CVD mortality.[1]

It's predicted that some 635,000 Americans will experience a first myocardial infarction this year, and approximately 300,000 will be victims of a reinfarction.[1] It's estimated that another 155,000 infarctions will be "silent," with no symptoms or with symptoms other than angina which are missed or ignored.[1] Collectively, this means that an American experiences a coronary event every 34 seconds. Compared to those who are very physically active, the risk of CHD in sedentary individuals is 150 to 240% higher.[1] Unfortunately, only about a quarter of all Americans engage in enough exercise to meet the minimum standards of the Centers for Disease Control and Prevention (CDC): at least 150 minutes per week of moderate-intensity aerobic exercise or at least 75 minutes of vigorous exercise and muscle-strengthening activities at least two days per week.[2] Given that the greatest reduction in risk for CHD appears to be for those engaging in even modest amounts of physical activity compared with the most physically inactive,[3] even relatively small increases in physical activity could result in a significant decrease in CHD for a large portion of the American population. For example, epidemiological data suggest that the estimated 2.3% decline in physical inactivity between 1980 and 2000 prevented or at least postponed 17,445 deaths due to CHD in the United States.[4]

In spite of the overwhelming evidence implicating physical inactivity as an important and significant risk factor for CHD, fewer than half of adults meet even the minimum recommendation for aerobic exercise.[5] Statistics for young people are even more alarming, with fewer than 20% of adolescents performing the recommended 60 minutes or more of daily physical activity.[6]

Despite the documented lack of physical activity in the United States, and the well-established benefits of regular exercise, many physicians are not encouraging their patients to exercise and lose weight.[7–9] Of equal importance, they do not appear to be adequately prepared to provide recommendations for exercise and physical activity. For example, a survey of 175 primary care physicians revealed that only 12% were aware of the recommendations of the American College of Sports Medicine (ACSM) for physical activity.[9] An evaluation of 51 internal medicine residents reported that while 88% were confident in

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their knowledge of the benefits of exercise, only about 25% demonstrated adequate knowledge useful for patient counseling.[10]

Healthcare professionals need to promote physical activity with all of their patients. In that regard, an understanding of the health benefits associated with physical fitness and regular physical activity is fundamental. This chapter reviews the evidence linking greater physical activity and fitness with primary prevention of cardiovascular and metabolic disease through effective risk factor management. Recommendations for exercise are also provided both in general terms and for specific conditions.

3.1 PHYSICAL FITNESS VS. PHYSICAL ACTIVITY

Physical fitness, specifically cardiorespiratory fitness, is defined here as the ability to deliver and utilize oxygen during sustained activity and typically quantified as maximal oxygen uptake (VO_{2max}). When respiratory gases are measured with a metabolic cart during a maximal graded exercise test, VO_{2max} is valid and reliable. However, submaximal tests or those relying on indirect measures such as time to exhaustion are subject to considerable error. Measures of physical activity, on the other hand, usually rely on retrospective self-reported data (i.e., physical activity questionnaires). Non-vocational or leisure-time physical activity (LTPA) is most commonly assessed. Vocational physical activity, household chores, and biking or walking to work are also sometimes quantified but less often. The definitions of physical activity vary greatly from study to study, and the components of physical activity or exercise such as intensity, duration, and frequency are often not reported or inadequately assessed.

The categorization of physical activity (i.e., low, moderate, or high) also varies from study to study. Many studies use different criteria for moderate and vigorous-intensity exercise or activity. ACSM defines moderate physical activity as any activity requiring 50–70% of VO_{2max} or maximal heart rate.[11] Vigorous physical activity is anything greater than 70% VO_{2max} or maximal heart rate.[11] Walking or brisk walking is generally recommended as the type of exercise that meets the criteria for moderate physical activity. However, it is important to understand that the intensity of walking, or any exercise for that matter, is relative to an individual's age, physical condition, and fitness level. For example, based on the ACSM Guidelines for Exercise Testing and Prescription,[11] even brisk walking may not be of sufficient intensity to meet the minimum criteria for moderate physical activity in a normal, healthy individual of college age. Conversely, brisk walking might be considered vigorous activity for someone over the age of 65. As such, any exercise recommendations should be applied relative to the individual's capabilities and limitations.

Surprisingly, physical fitness has been shown to be only modestly correlated with physical activity, with correlations ranging from 0.09[12] to 0.60.[13] In a meta-analysis of seven physical fitness and 16 physical activity cohorts cited in the 1996 Surgeon General's Report,[14] Williams[5]

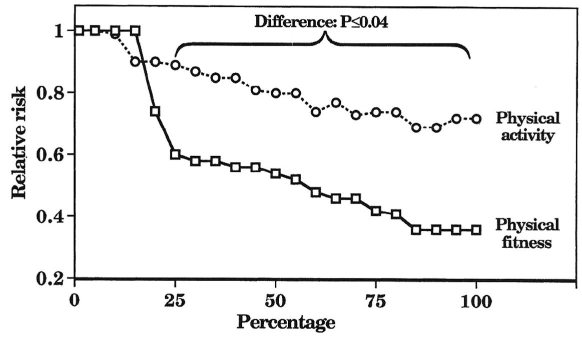

Figure 3.1 Estimated Dose–Response Curve for the Relative Risk of either CHD or CVD by Sample Percentages of Fitness and Physical Activity. Studies weighted by Person-Years of Experience.

found that the risk of CHD or CVD decreased linearly with increasing percentiles of physical activity. He also found that the reduction in risk for CHD or CVD associated with increasing percentiles of physical fitness demonstrated a precipitous decrease occurring just before the 25th percentile of the physical fitness distribution. Further, at all percentiles ≥ 25th, the reduction in risk for CHD and CVD was significantly greater for physical fitness compared to physical activity (Figure 3.1).

These findings are supported in a more recent comparison of fitness versus physical activity in predicting all-cause mortality in a cohort of 842 men referred for exercise testing.[12] While both physical activity and fitness were strong predictors of all-cause mortality, physical fitness was a stronger predictor of mortality than activity level. A 1000 kcal per week increase in physical activity was found to be similar to a one MET (metabolic equivalent; oxygen uptake of 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$) improvement in fitness, with both conferring a 15–20% reduction in mortality. Of equal, if not greater, interest is the fact that these data also demonstrated that 40% of the reduction in mortality occurred between the least active or fit and the next least fit or active groups, suggesting that even modest increases in physical activity or fitness, especially in those who are inactive, may result in a significant reduction in mortality.

3.2 GENERAL RECOMMENDATIONS FOR PHYSICAL ACTIVITY

In 1996, the Surgeon General's Report on Physical Activity and Health recommended "people of all ages [should] include a minimum of 30 minutes of physical activity of moderate intensity (such as brisk walking) on most, if not all, days of the week. It is also acknowledged that for most people, greater health benefits can be obtained by engaging in physical activity of more vigorous intensity or of longer duration."[14] More recently, the 2008 Physical Activity Guidelines for Americans[15] provide updated and more specific recommendations for different age groups and some clinical populations. Below is a very brief summary of their recommendations.

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3.2.1 Adults

- All adults should avoid inactivity. Some physical activity is better than none, and adults who participate in any amount of physical activity gain some health benefits.
- For substantial health benefits, adults should do at least 150 minutes a week of moderate-intensity or 75 minutes a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity.
- Adults should also do muscle-strengthening activities that are moderate or high intensity and involve all major muscle groups on two or more days a week, as these activities provide additional health benefits.

3.2.2 Children and Adolescents

- Children and adolescents should do 60 minutes (one hour) or more of physical activity daily.
- Aerobic: Most of the 60 or more minutes a day should be either moderate- or vigorous-intensity aerobic physical activity, and should include vigorous-intensity physical activity at least three days a week.
- It is important to encourage young people to participate in physical activities that are appropriate for their age, that are enjoyable, and that offer variety.

3.2.3 Older Adults

- When older adults cannot do 150 minutes of moderate-intensity aerobic activity a week because of chronic conditions, they should be as physically active as their abilities and conditions allow.
- Older adults should do exercises that maintain or improve balance if they are at risk of falling.
- Older adults should determine their level of effort for physical activity relative to their level of fitness.
- Older adults with chronic conditions should understand whether and how their conditions affect their ability to do regular physical activity safely.

3.3 WOMEN AND CHD

One in three women have some form of CVD; 6.6 million have been diagnosed with CHD.[1] In 2013 alone, 398,086 women died from CVD—about one death every 80 seconds.[1] Just over 40% of these deaths was attributable to CHD, including 50,742 from MI.[1] On average, new and recurrent MI as well as fatal CHD impact 405,000 women each year.[1] Because women typically have heart attacks at older ages than men do, they're more likely to die from them within a few weeks.[1]

Despite these overwhelming statistics, surveys indicate that some 44% of women still do not know that CHD is by far the number one killer of women in the United States.[1] And while regular physical activity has been demonstrated to significantly reduce the risk of CVD in women, they are on average less physically active than men, with only 46.1% of women compared with 54.2% of men engaging in moderate-to-vigorous activity three or more days per week.[5]

Although a greater exercise volume and/or intensity appears to produce greater health benefits for most people, the literature examining the relationship between exercise intensity and risk for CHD is not unequivocal.[3] A meta-analysis of 16 gender-specific physical activity cohorts found that the risk for CHD decreased linearly with increasing percentiles of physical activity, but examination of the individual cohorts revealed considerable variation in the outcomes.[3] Specifically, there is evidence to suggest that the dose-response relationship between exercise intensity and risk for CHD or mortality may differ between men and women.[16–20] For example, based on data from the Nurses' Health Study, a cohort of 72,488 female nurses 40 to 65 years old, Manson et al.[17] concluded that "the reduction in risk for CHD for women who walked at a brisk pace three or more hours per week was similar to those women who engaged in regular vigorous (≥6 MET) exercise." In 2001, data from the Women's Health Study[16] showed that walking one to 1.5 hours per week was associated with a 51% reduction in risk for CHD, but walking ≥ 2 hours per week conferred no greater reduction in risk. More vigorous activity was not associated with a lower risk for CHD, (comparing highest with lowest). Similarly, the relationship between walking pace and risk for CHD did not demonstrate a linear trend.

Other studies have not demonstrated an association between physical activity/inactivity and CHD and/or mortality in women, with one review reporting no relationship between physical inactivity and CHD in 10 of 14 studies.[18] More recently, Blair et al.[19] found that all-cause mortality rates in women did not differ across the range of physical activity levels. The Framingham Study also found no association between physical activity level and mortality in women.[20] In contrast, a 2004 meta-analysis of 30 longitudinal studies examining the impact of physical activity on the risk for CVD in women showed a dose-response relationship with a 20–40% reduction in risk for CVD in the most active women, compared to those who were sedentary.[21]

This inconsistency in findings has been observed elsewhere[17] and may be the result of real gender differences or may reflect differences in study participants and/or design. For example, in the 16 studies he examined, Williams[3] found that the intervals (tertiles, quartiles, etc.) reported differed greatly, with nine studies using three levels, six using four levels and one study using six levels. In particular, the apparent gender differences in the response to physical activity may also be mediated by the physical activity levels of the study participants. As an example, in 2001, the most active 20% of women in the Women's Health Study expended ≥ 1500 kcal per week in LTPA, whereas men in the highest quintile of physical activity in the Harvard Alumni Health Study reported expending ≥ 3129 kcal per week in LTPA.[3] Interestingly, very recent physical activity data acquired by accelerometer from over 17,000 older women in the Women's Health Study showed a clear dose-response relationship between time engaged in "moderate to vigorous" physical activity.[22] Those women who exercised just over an hour per

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day at this intensity had mortality rates almost 65% lower than women who were sedentary.

The limited data on the relation between physical fitness and risk for CVD and/or mortality in women suggests a greater similarity with studies of men, when compared with studies of physical activity. A relatively recent review of the literature revealed that low exercise capacity and slow recovery heart rate predicted CVD and mortality in both men and women.[23] Data from the St. James Women Take Heart Project demonstrated a 17% reduction in mortality in women for every one MET increase in exercise capacity.[24] As such, it would appear that women who engage in exercise vigorous enough to improve aerobic fitness gain health benefits comparable to their male counterparts.

3.4 STROKE

While the incidence of stroke and its associated mortality rate has been declining since at least 2001, it is estimated that 795,000 people in the United States experience a new (~ 610,000) or recurrent (~ 185,000) stroke each year.[1] Of these, the large majority are ischemic (~ 87%), with the remainder being hemorrhagic in nature.[1] The risk of a stroke for African-Americans is nearly double that for Caucasians and tends to occur at a younger age.[1] Hispanics, particularly Mexican-Americans, have significantly higher rates of ischemic stroke and at a younger age.[1] Annually, 55,000 more women than men have a stroke, with the incidence in women aged 45–54 years especially high.[1]

Some 200,000 to 500,000 transient ischemic attacks (TIAs) are estimated to occur in the United States each year, and the incidence is higher in men, African-Americans, and Mexican-Americans.[1] The occurrence of a TIA increases the risk of a stroke both in the short term and the long term.[1] Approximately 15% of all strokes are preceded by a TIA, and about 12–13% of individuals will die within a year of a TIA.[1]

The most important risk factors for stroke include a history of TIA, preexisting CHD, age, hypertension, diabetes mellitus, cigarette smoking, and atrial fibrillation.[1] Physical inactivity has also been shown to increase the risk of a stroke and stroke mortality, but its relationship to cerebral events is less well understood than that for CHD.[1] Meta-analyses have shown that the reduction in risk for stroke associated with aerobic exercise/activity ranges between 20 and 40% depending on the type of stroke and study design.[25,26] The benefit for women is less clear and may not be as great as that for men.[25] It remains unresolved as to whether or not a dose-response relationship exists between level of physical activity and stroke risk. While those studies that looked at different levels of physical activity generally found a greater benefit for higher levels of physical activity, there was a real lack of consistency their findings.[25] In addition, the criteria for different levels of physical activity are not uniform, varying from study to study and often poorly quantified. As such, an exercise prescription to optimize the reduction in risk for stroke remains undetermined. Currently, the American Heart Association recommends moderately intense aerobic physical activity for *at least* 30 minutes per day to reduce the risk of ischemic stroke.[27] While there is evidence that greater muscular strength in youth is associated with a modestly reduced risk (~ 5–10%) for stroke later in life,[28] the relationship between muscular strength, strength training, and stroke risk remains virtually unexplored.

3.5 HYPERTENSION

Based on data from the National Health and Nutrition Examination Survey (NHANES), it's estimated that some 80 million adults or almost one in three American adults suffer from hypertension (systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg).[1] The prevalence in African-American adults is among the highest in the world. Looking at all Americans with hypertension, 82.7% were aware of it, 76.5% were being treated, and only 54.1% had it under control. A meta-analysis of 61 studies involving more than one million individuals demonstrated that mortality associated with both ischemic heart disease (IHD) and stroke increases linearly from levels as low as 115 mmHg systolic and 75 mmHg diastolic blood pressure.[29] For every 20 mmHg systolic or 10 mmHg diastolic increase in blood pressure, there is a doubling of mortality from both IHD and stroke.[29] Those with hypertension have a shorter life expectancy, shorter life expectancy free of CVD, and can expect to live more years with CVD compared with those who are normotensive.[1]

Regular physical activity has been shown to be an effective way to lower blood pressure in 75% of persons with hypertension.[30,31] Compared with sedentary adults, those who are physically active have a lower incidence of hypertension,[32–34] with blood pressures that average five mmHg lower.[35] Higher levels of occupational and/or LTPA are associated with lower BP.[30,34,35] These data have led to recommendations for regular physical activity as lifestyle therapy for the prevention and management of hypertension.

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII)[36] recommends regular aerobic physical activity such as brisk walking at least 30 min per day most days of the week for the prevention and management of hypertension. In a meta-analysis of 44 trials of at least four weeks duration and after controlling for other factors, increased physical activity was associated with a small but significant decrease of 3/2 mmHg in normotensive subjects and 7/6 mmHg in hypertensive subjects.[37] The training intensity in these studies averaged 65% of heart rate or VO_2 reserve. However, the characteristics of the training programs (intensity, duration, and frequency) explained less than 5% of variance in blood pressure response. Weekly energy expenditure was not significantly related to the changes in systolic or diastolic blood pressure. Vigorous exercise was not found to be different from moderate-intensity exercise in its ability to reduce blood pressure, with some studies showing that exercise at 40% of VO_2 reserve to produce a greater reduction in systolic blood pressure than exercise at 65 to 75%

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of VO_2 reserve.[38,39] As such, and per JNC VII, regular moderate-intensity exercise is recommended for the prevention and management of hypertension.

3.5.1 Resistance Exercise Training and Blood Pressure

Resistance training is generally recommended as an adjunct to aerobic activity. On average, studies have reported three mmHg reductions in resting systolic and DBP following progressive weight lifting programs.[33,40–42] Although this decrease may seem small, a three mmHg reduction lowers the risk of CHD, stroke, and all-cause mortality.[33] Two to three days per week of total body resistance training is generally recommended.[16,43–45] However, as with aerobic exercise, the "optimal" exercise prescription for strength training is not known. More specifically, low-to-moderate intensity strength training (30–40% of a one repetition maximum (1RM) for upper body exercises, and 50–60% 1RM for lower body exercises) is currently recommended by some for the prevention and management of high blood pressure[30,45] Rezk et al.[46] showed that both single bouts of high- or low-intensity resistance exercise lower SBP, but only low-intensity training lowered DBP. Other studies reported that high-intensity resistance training reduced neither SBP nor DBP, and actually raised SBP in some individuals.[47]

The currently recommended strength training program to optimize BP reduction is one to three sets of 10–15 repetitions for each of the major muscle groups (thighs [hamstrings and quadriceps], hips, back, chest, arms, and abdominals), two to three days per week.[33,45]

3.6 HEART FAILURE

It's estimated that some 5.7 million Americans suffer from heart failure (HF, also known as congestive heart failure).[1] The risk of developing HF increases with age; by the age of 40, both men and women have a one in five risk of developing HF at some time in their lives.[1] Both the incidence and prevalence of HF are particularly high in minorities, especially African-Americans.[1] Heart failure occurs earlier and mortality is higher in African-Americans than in Caucasians.[1]

Surprisingly few studies have examined the relationship between physical activity and primary prevention of heart failure. Two large longitudinal studies exploring this association found that compared to sedentary individuals, those who engaged in regular vigorous exercise had a 15–35% lower risk for developing heart failure.[48,49] Vigorous activity was defined as activities "vigorous enough to work up a sweat,"[48] such as running, jogging, swimming, heavy gardening or competitive sports."[49] The reduction in risk was correlated with the frequency of vigorous exercise in a dose-response manner.[48] Activity of a moderate intensity, defined as > 4 hr/week of walking, cycling, or light gardening was associated with ~15% reduction in risk. Pooled data from three large cohort studies showed a strong and negative dose-response relationship between LTPA and risk for heart failure. Those individuals whose LTPA exceeded 1,000 MET · min/week had a risk for heart failure that was 19% less than that of their sedentary counterparts.[50]

3.7 DIABETES

The latest available data from NHANES estimates that 12.8% of Americans over the age of 19 have diabetes mellitus (DM), of which > 90% are classified as Type II (T2DM).[1] Insulin resistance often precedes the onset of T2DM and is prevalent in the prediabetic states of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). Over 35% of Americans are classified as pre-diabetic, with IFG and/or IGT.[1] This means that more than 47% of all adults have some degree of abnormal glycoregulation![1] The prevalence of CHD has been estimated to be as high as 55% in adult diabetics, and T2DM is an independent risk factor for myocardial infarction and CVD in both men and women.[51,52] T2DM is a predictor of ischemic stroke and heart failure, and DM increases the overall CV risk in patients with preexisting heart failure.[53,54] Compared to non-diabetics, mortality from CHD has been reported to be twice as great in diabetic men and four to five times greater in diabetic women.[55] Cardiovascular disease is responsible for at least two-thirds of deaths in adults with DM.[55]

3.7.1 The Metabolic Syndrome, CVD, and T2DM

The clustering of risk factors known as the metabolic syndrome (see section below for definition and more information) is predictive of both T2DM and CVD. It is associated with a twofold increase in the risk for cardiovascular events.[56] Abdominal obesity, in particular, is an independent risk factor for insulin resistance[57,58] and T2DM.[59] Much of the increased risk of CHD and CVD associated with T2DM can be attributed to the presence of the metabolic syndrome.[60] One study reported ten-year cardiovascular mortality to be 3.55 times greater in men with metabolic syndrome compared to those without the condition.[61]

Numerous studies have demonstrated an inverse relationship between physical activity and/or fitness and the risk for developing T2DM.[62–70] Men of low fitness have a two to three times greater risk of developing T2DM compared to those in the higher fitness categories.[62,63] Similarly, physical activity shares an inverse relationship with the risk for T2DM in a dose-response manner. Even just daily walking for more than 30 minutes has been shown to reduce the risk of developing T2DM by 20–45%.[66,69–72] Brisk/faster walking was associated with a lower risk independent of time spent walking.[66,69,70] In an interventional trial involving 18 previously sedentary middle-aged men and women, six months of walking (minimum of three days per week for 30 minutes) resulted in improved insulin sensitivity.[73] Sedentary behaviors such as excessive television watching have been demonstrated to increase the risk for T2DM even after controlling for diet and physical activity levels. It has been estimated

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that 43% of new cases of diabetes could be prevented by watching TV less than 10 hours per week and engaging in brisk walking for 30 minutes or more per day.[71] Modest improvements in diet and exercise habits have been shown to reduce the incidence of T2DM even in those at highest risk for developing it—those with IFG and/or IGT.[74–76]

3.7.2 Glycemic Control

Studies of aerobic exercise training have shown significant but modest reductions in glycosylated hemoglobin (HbA_{1c}, long-term index of glycemic control) of about 8% from baseline.[77,78] The exercise intensity in these studies accounted for almost 83% of the differences in post-intervention HbA_{1c} compared to 21% determined by exercise volume. Those interventions with an intensity > 65% of VO_{2max} demonstrated the greatest improvement in HbA_{1c}. As such, exercise interventions for glycemic control should include some vigorous exercise.[79]

3.7.3 Strength Training

Resistance training, especially in combination with aerobic exercise training, can significantly improve HbA_{1c} levels, fasting blood glucose, and insulin sensitivity.[80] Additionally, other risk factors such as blood pressure have been shown to be significantly reduced in diabetics with a program combining strength and aerobic training compared with either aerobic or resistance training alone.[80] As such, the American Diabetes Association now recommends strength training, in addition to aerobic exercise training, as part of a program to prevent or manage T2DM.[81] Weight training has been found to be safe in persons with CVD, ST depression, myocardial ischemia, ventricular dysrhythmias, and other cardiovascular complications.[81] The myocardial demands of high-intensity weight training are comparable to activities such as stair-climbing, walking uphill, or carrying 20–30 lbs of groceries.[81]

Below are some of the specific recommendations from the American Diabetes Association Consensus Statement on Physical Activity/Exercise and Type II Diabetes:[81]

- People with IGT should begin and continue a program of weight control, including at least 150 minutes per week of moderate-to-vigorous physical activity and a healthful diet with modest energy restriction.
- To improve glycemic control, assist with weight maintenance, and reduce risk for cardiovascular disease (CVD), the panel recommends 150 minutes per week or more of moderate-intensity aerobic physical activity and/or 90 minutes per week or more of vigorous aerobic exercise. The physical activity should be distributed over at least three days per week, with no more than two consecutive days without physical activity.
- Compared with lower volumes of activity, performing at least four hours per week of moderate-to-vigorous aerobic and/or resistance exercise is associated with greater CVD risk reduction.
- For long-term maintenance of major weight loss (≥13.6 kg or 30 lb), larger volumes of exercise (seven hours per week of moderate or vigorous aerobic physical activity) may be helpful.
- Unless contraindicated, people with type 2 diabetes should be encouraged to perform resistance exercise three times per week, targeting all major muscle groups. This should progress to three sets of eight to ten repetitions at a weight that cannot be lifted more than eight to ten times. Initial supervision and periodic reassessments by a qualified exercise specialist are recommended to ensure that resistance exercises are performed correctly in order to maximize health benefits and minimize the risk of injury.

3.8 OBESITY

Based on the most recent data from the National Health and Nutrition Examination Survey (NHANES), and using body mass index (BMI, body weight in kg/(height in meters)^2) as the criterion measure, the prevalence of overweight and obesity in the United States decreased among those of higher socioeconomic status but increased among those of lower socioeconomic status.[1] The overall prevalence of extreme obesity in U.S. youth continues to increase, especially among adolescent boys. In adults, overweight is defined as a BMI of 25–29.9 kg/m^2. Obesity is defined as a BMI ≥ 30; extreme (formerly morbid) obesity is defined as a BMI ≥ 40. Overall, 69% of U.S. adults were overweight or obese (73% of men compared to 65% of women).[1] Among men, non-Hispanic blacks were less likely to be overweight or obese (69%) compared with Hispanics (80%) and non-Hispanic whites (73%).[1] In women, non-Hispanic blacks (82%) and Hispanics (76%) were much more likely to be overweight or obese compared with non-Hispanic whites (61%).[1] Among all U.S. adults, 35% were obese (34% of men vs. 36% of women).[1] Hispanic and non-Hispanic black males (38%) were more likely to be obese than non-Hispanic white men (34%).[1] Among women, non-Hispanic blacks (58%) and Hispanics (43%) were more likely to be obese than non-Hispanic whites (33%).[1]

Over the last two decades, it has become increasingly apparent that abdominal adipose tissue has unique metabolic properties and may be more predictive of CVD, the metabolic syndrome, and diabetes than BMI or measures of overall adiposity.[82–86] Abdominal or central obesity is most commonly assessed measuring by waist circumference or waist-to-hip ratio (WHR). From 1988–1994 to 1999–2000 (most recent data available), mean waist circumference of adult Americans increased from 95.3 cm to 98.6 cm in males and from 88.7 cm to 92.2 cm in females.[87]

Despite these rather alarming trends, only 40.3% of obese patients were advised to lose weight by their family physician in 2004, down from 42.3% in 1994.[88] An evaluation of an academic pediatric hospital found that little more than half (53%) of the children who met the NHANES criteria for overweight (>95th percentile for BMI) were identified as such by their primary care physician.[89] Interestingly, while a majority (69%) of the

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children's charts contained an "adequate" dietary history, only 15% included information regarding physical activity and/or television watching.

3.9 CENTRAL ADIPOSITY, INFLAMMATION, AND CVD

Atherosclerosis has now come to be understood as an inflammatory disease.[90–93] A growing body of evidence further demonstrates that greater adipose tissue mass, especially visceral adipose tissue, directly contributes to systemic inflammation.[94–96] The pro-inflammatory state associated with abdominal obesity has been proposed as a common underlying condition linking CVD, insulin resistance/type 2 diabetes, and the metabolic syndrome.[97–99] A complete discussion of the complex physiology and mechanisms of adipose-related inflammation is beyond the scope of this chapter. However, it can be stated that it is increasingly evident that visceral adipose tissue secretes a veritable host of pro-inflammatory cytokines. Greater levels of central adiposity have been shown to be associated with higher circulating levels of these pro-inflammatory proteins, such as interleukin-6 (IL-6), tumor necrosis factor–alpha (TNF-alpha), and C-reactive protein (CRP).[100–102]

A published review of lifestyle interventions and systemic inflammation observed that 9 of 12 studies reviewed demonstrated an inverse relationship between physical activity or fitness and markers of inflammation, after controlling for BMI or other measures of adiposity.[103] For example, in a 20-year follow-up of 4,252 elderly men (aged 40–59 at baseline), Wannamethee et al.[104] found that physical activity level was inversely associated with levels of CRP and other inflammatory markers, even after adjusting for BMI and other covariates. In those men who went from "at least lightly active" to inactive, the levels of these markers were similar to those men who had been inactive throughout the follow-up period. Those who were inactive at baseline but increased their level of activity had levels similar to those men who had remained continuously active.

The HERITAGE Family Study examined the effects of 20 weeks of exercise training on C-reactive protein (CRP) levels in 652 sedentary, but healthy, adults.[105] The training program was performed on cycle ergometers three days per week progressing to 50 minutes at 75% of baseline VO_{2max}. This protocol resulted in a substantial (17.8%) increase in VO_{2max}. However, reduction in CRP levels occurred only in the individuals with high baseline levels of CRP. The positive relationship between baseline CRP levels and exercise-induced changes has been observed elsewhere[106] and may explain, at least in part, why some studies have not found that an exercise intervention reduces levels of inflammatory markers.[107–112]

3.9.1 The "Fitness vs. Fatness" debate

It is well established that both increased body fat and low levels of physical activity and/or fitness are associated with increased mortality and with T2DM and CVD. However, it is not precisely clear as to the relative importance of these factors or how they interact. An extensive review of the literature addressing the fitness vs. fatness debate as it pertains to CHD and/or CVD concluded that a "physically active lifestyle and/or a moderately high fitness level (i.e., not in the bottom 20% of the population) reduces the risk of CVD/CHD in overweight or obese persons."[113] While they suggest that overweight or obese individuals who are physically fit or active have levels of risk that approach those associated with those of lean, unfit persons, they also concede that their risk is still greater than those who are fit/active and of normal weight. The authors further observed that the risk reduction associated with increased fitness or activity is greater in those who are overweight or obese compared with those of normal weight. Finally, they recommend that physical activity should be encouraged, regardless of whether or not that activity induces weight loss. This recommendation is supported by the majority of the studies reviewed that found physical activity/fitness to be independent risk factors for CHD/CVD.

Addressing obesity begins with the understanding that weight gain is caused by a cumulative positive energy balance where energy intake exceeds energy expenditure. As such, weight loss can *only* occur in the presence of a negative energy balance. Maintenance of body weight, therefore, requires that energy intake matches energy expenditure. While the concept of energy balance or imbalance is conceptually simple, the respective roles of diet and exercise in weight loss and management is less clear. Below is a brief summary of recent and relevant investigations of the role of physical activity in (1) preventing weight gain, (2) causing weight loss, and (3) maintaining weight loss.

3.9.2 Preventing Weight Gain

In 2003, the International Association for the Study of Obesity (IASO) released the following statement regarding physical activity and prevention of unhealthy weight gain: "The current physical activity guideline for adults of 30 minutes of moderate intensity activity daily, preferably all days of the week, is of importance for limiting health risks for a number of chronic diseases including coronary heart disease and diabetes. However for preventing weight gain or regain this guideline is likely to be insufficient for many individuals in the current environment. There is compelling evidence that prevention of weight regain in formerly obese individuals requires 60–90 minutes of moderate intensity activity or lesser amounts of vigorous intensity activity … For children, even more activity time is recommended. A good approach for many individuals to obtain the recommended level of physical activity is to reduce sedentary behavior by incorporating more incidental and leisure-time activity into the daily routine."[114]

3.9.3 Physical Activity and Sustained Weight Loss

Unfortunately, most studies do not support increasing physical activity, either alone or in combination with a

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calorie restrictive diet, as an effective means to produce short-term weight loss.[115–117] However, physical activity appears to play a major role in long-term maintenance of weight loss.[115–118] An extensive review of the role of exercise in promoting weight loss combined data sets and used weighted mean differences (WMD) to explore the efficacy of exercise interventions.[118] The randomized clinical trials (RCTs) in this review only included studies that incorporated a follow-up of at least 12 months' duration to assess long-term maintenance of weight loss. A summary of their findings follows:

- Compared to diet alone, diet plus exercise produced significantly greater weight loss at 12 months (WMD = –1.95 kg),18 months (WMD = –7.83 kg), and 36 months (WMD = –8.22 kg). In addition, there were small but significantly greater differences/improvements in HDL and triglycerides at 12 months. At 18 months, diet plus exercise demonstrated large and significantly greater reductions in systolic blood pressure (WMD = –8.90 mm Hg) and diastolic blood pressure (WMD = –12.10 mm Hg).
- A separate analysis in this review compared diet plus behavior therapy with diet plus behavior therapy and exercise. The addition of exercise produced significantly greater weight loss at 12 months (WMD = –3.02 kg) and at 24 months (WMD = –2.16 kg). There were no significant differences between groups for cholesterol, blood pressure, or glucose.

These data suggest that regular physical activity is advantageous for sustained weight loss.

3.9.4 How Much Physical Activity Is Required for Sustained Weight Loss?

There is a general consensus that 2,500–2,800 kcal per week (60–90 minutes per day of moderate-intensity physical activity) is required for long-term weight loss, as reflected in the recommendations and consensus statements of the U.S. Department of Health and Human Services,[119] the ACSM,[120] and the IASO.[114] These recommendations are supported by data from the National Weight Control Registry (NWCR), a database of approximately 5,000 individuals who have minimally lost 30 lbs for at least one year (average weight loss is about 30 kg for an average of 5.5 years).[121] Data collected on these "successful losers" indicates that more than 90% of participants expend ~ 2,800 kcals per week in physical activity.

3.9.5 Resistance Training and Weight Loss

Despite claims in the popular literature, strength training is not recommended as the primary mode of exercise for weight loss.[120] While strength/resistance training has been shown to preserve fat-free mass when coupled with a calorie- restrictive diet, it has not been shown to enhance weight loss either alone or in combination with a dietary intervention.[115,117,118,120] Despite the apparent ability of resistance training to maintain muscle mass in the presence of calorie deficit, it does not appear to be able to prevent the decrease in resting energy expenditure associated with weight loss.[120,122] In the absence of a dietary intervention, some studies have shown that high-intensity resistance training can significantly increase resting energy expenditure for 16 hours or more.[123–127] However, these findings are based on a very small number of subjects and are not supported by the results of other investigations.[128–130] As such, in the absence of stronger evidence, resistance training is not recommended as the primary form of exercise to promote or enhance weight loss.[120] However, weight training may provide an advantage in maintaining fat-free mass and enhancing body composition with a weight loss intervention.[120]

3.10 LIPIDS

The role of blood lipids in the pathology of atherosclerosis is well established, and dyslipidemia is understood to be an important contributing factor for CHD.[131] Dyslipidemia includes elevations in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG), and low levels of high-density lipoprotein cholesterol (HDLC).[131] In addition, newer lipid and lipoprotein measures such as lipoprotein particle size and number, apolipoproteins, and triglyceride-rich lipoproteins (TRL) are emerging as risk factors that may also increase CVD risk.[132] The National Cholesterol Education Program Adult Treatment Panel III has published guidelines establishing lipid and lipoprotein modification goals for both primary and secondary prevention.[131] However, data from NHANES indicate that many Americans have not achieved recommended levels for all lipids and lipoproteins.[133]

One of the proposed mechanisms by which regular physical activity reduces the risk for CHD is its effect on blood lipids, especially the increases in HDL-C and reduction in TG levels.[134–136] Cross-sectional studies have consistently shown a positive association between the volume and intensity of aerobic activities and HDL-C levels, and a negative association with TG levels.[137] However, reviews of the literature reveal a surprisingly inconsistent response of other blood lipids to regular aerobic exercise.[137,138] These findings may be further confounded by concurrent changes in body weight or composition. In studies without a dietary intervention, the most commonly reported change in lipids was an increase in HDL averaging 4.6%, ranging from a decrease of 5.8% to an increase of 25%. Simultaneous reductions in TG (3.7%), LDL-C (5.0%), but not TC, were also observed.[137] Changes in TC and LDL-C are much less frequently reported, are modest when they do occur, and may be more attributable to weight loss than the exercise intervention per se. As such, regular exercise alone cannot be recommended as an effective strategy to lower TC or LDL-C.[136]

Relatively few studies have attempted to evaluate the effect of the exercise prescription (intensity, volume, etc.) on blood lipids and, as such, there is no consensus on the optimal exercise regime for improving cholesterol profile. In most of the studies reviewed, the exercise intervention was performed at moderate-to-high intensity three to five

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times per week for at least 30 minutes per session. Total caloric expenditure, as opposed to exercise intensity, has been proposed to be of greatest importance for blood lipids, and a threshold of between 1,200 and 2,500 kcals per week has been proposed.[139]

A meta-analysis of studies that explored the effect of strength training on blood lipids, dating back to 1955, found that strength training resulted in modest but significant improvements in blood lipid profiles (but not HDL-C).[140] However, while earlier studies generally demonstrated an improvement in blood lipid profile with resistance training, at least some suffered from design flaws, including no or poor dietary control,[140–143] no control group,[140–142] or no control for fat loss.[141,142,144] Better designed and/or more recent studies have not found an improvement in lipoprotein profiles with resistance/strength training.[145–150]

3.11 METABOLIC SYNDROME

The clustering of established risk factors for CVD and T2DM has been recognized for decades.[151–166] In 1988, Gerald Reaven drew immense attention to risk factor clustering and CVD in his now famous "Banting Lecture" at the annual meeting of the American Diabetes Association.[155] He described a constellation of risk factors leading to development of T2DM and CVD which he termed *Syndrome X*. Reaven postulated the etiology and clinical course of three major related diseases—T2DM, CVD, and hypertension, all having a common foundation of insulin resistance and hyperinsulinemia. However, at that time, adiposity was not considered a major etiological factor.

The metabolic syndrome has been recognized as a global public health problem that is strongly linked as a seminal cause of CVD and T2DM, both of which are responsible for premature mortality and morbidity worldwide.[167–169] The metabolic syndrome is characterized by the clustering of specific cardiovascular risk factors, including insulin resistance (IR), central obesity, hypertension, and atherogenic dyslipidemia (specifically, elevated triglycerides and low levels of high-density lipoprotein cholesterol (HDL-C).[169–174] Also, depending on the medical society definition applied, microalbuminuria may also be considered another risk factor.[174]

3.11.1 Different Medical Society Definitions of the Metabolic Syndrome

In establishing an *official diagnosis* for the metabolic syndrome, the American Association of Clinical Endocrinologists (AACE) championed the creation of the International Classification of Disease 9th revision (ICD-9) Code 277.7 for the metabolic syndrome.[173] Currently, there are five working medical society definitions proposed for the diagnosis of the metabolic syndrome. Table 3.1 summarizes the various definitions published by the following medical societies: (1) the World Health Organization (WHO),[174] (2) the European Group for the Study of Insulin Resistance (EGIR),[172] (3) the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI) definition,[174] which refers to the updated National Cholesterol Education Program (NCEP) (2001) definition,[175] (4) the American College of Endocrinology (ACE) and the American Association of Clinical Endocrinologists (AACE) consensus definition for epidemiological research,[173] and (5) the International Diabetes Federation (IDF).[174]

The majority of the recent research focusing on the metabolic syndrome involved the use of the NCEP definition because of its clinical utility (see Table 3.1). The NCEP definition requires that three of the following five criteria be present for a diagnosis of the metabolic syndrome: (1) impaired fasting glucose (IFG) represented by a fasting blood sugar ≥ 110 milligrams per deciliter (mg/dL), including T2DM; (2) HDL-C < 40 mg/dL in men and < 50 mg/dL in women; (3) triglycerides ≥ 150 mg/dL; (4) an augmented waist circumference (WC) of ≥ 102 centimeters (cm) in men and ≥ 88 cm in women; (5) or a blood pressure value of ≥ 130/85 millimeters of mercury (mmHg).

3.11.2 Current Prevalence Estimates

It is estimated that close to one billion people worldwide have the metabolic syndrome.[176] Global prevalence estimates of the metabolic syndrome vary considerably, depending on the population under study, the definition applied, and the study design utilized. Using the NCEP definition, the age-adjusted prevalence for the metabolic syndrome in the United States is estimated to be 34.6%. These data also showed a 10% increase in the prevalence of the metabolic syndrome in U.S. adults, from 1988 to 2002. With the metabolic syndrome becoming more common in westernized societies,[176] the prevalence and incidence are anticipated to increase in line with the prevalence and incidence of obesity[176] and T2DM.[177]

3.11.3 Physical Activity and Prevalence of the Metabolic Syndrome

The association between physical activity or inactivity and prevalence of the metabolic syndrome is not clear, at least based on cross-sectional studies.[178–186] In most studies, the initial analysis often shows a negative relationship between physical activity level and the prevalence or risk of metabolic syndrome, but this association typically disappears after controlling for other factors such as gender, age, education, socioeconomic status, or other risk factors (e.g., smoking).

Several longitudinal studies showed that increased levels of physical activity, especially of vigorous intensity, were associated with significantly and dramatically reduced risk for developing the metabolic syndrome and in a dose-response manner. Interventional studies are fewer in number, but at least one study showed that 20 weeks of vigorous exercise performed for 30 minutes three times per week resulted in a decreased prevalence of the metabolic syndrome (16.9% to 11.8%) in 621 men and women aged 17 to 65 years.[177] That is, of the 105 participants with the metabolic syndrome at baseline, 32 no longer had the syndrome at the end of the study.

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TABLE 3.1 Metabolic syndrome definitions issued by various medical societies

	WHO 1999	EGIR 1999	ACE/AACE 2003	IDF 2005	AHA/NHLBI 2005
Requisite Criteria	IGT, IFG, type 2 diabetes, insulin in top quartile of population	Insulin in top quartile of population	High risk [a];BM1 > 25 kg/m² or WC > 102 cm (men) or > 88 cm (women)	WC ≥ 94 cm (men) and ≥ 80 cm (women), and population-specific for ethnic groups [b]	N/A
Other Criteria	Plus ≥ 2 of:	Plus ≥ 2 of:	Plus ≥ 2 of:	Plus ≥ 2 of:	Plus ≥ 2 of:
Glucose	N/A	≥100 mg/dL, 2-hour post OGTT ≥ 140 mg/dL but not diabetes	≥100 mg/dL, 2-hour post OGTT ≥ 140 mg/dL but not diabetes	≥100 mg/dL, diabetes	≥100 mg/dL, diabetes or Rx
Obesity	W:H ratio > 0.9 (men) or >.85 (women); BMI > 30 kg/m²	WC ≥ 94 cm (men) or ≥ 80 cm (women)	N/A	N/A	WC ≥ 102 cm (men) or ≥ 88 cm (women)
Lipids	TG ≥ 150 mg/dL and/or HDL-C < 35 mg/dL (men) or < 39 mg/dL (women)	TG > 180 mg/dL and/or HDL-C < 39 mg/dL in men or women or Rx	TG > 150 mg/dL or HDL-C < 40 mg/dL (men) or < 50 mg/dL (women)	TG ≥ 150 mg/dL or Rx or HDL-C < 40 mg/dL (men) or < 50 mg/dL (women) or Rx	TG ≥ 150 mg/dL or HDL-C < 40 mg/dL (men) or < 50 mg/dL (women) or Rx
Hypertension	≥140/90 mmHg or Rx	≥140/90 mmHg or Rx	>130/85 mmHg or Rx	≥130/85 mmHg or Rx	≥130/85 mmHg or Rx
Other	Microalbuminaria ACR ≥ 30 mg/g				

WC, waist circumference; W:H, waist hip; TG, triglycerides; OGTT, oral glucose tolerance test; Rx, medication; ACR, albumin: creatinine ratio; others designated in text. WHO = World Health Organization EGIR = European Group for the study of Insulin Resistance AHA/NHLBI = American Heart Association/National Heart, Lung, and Blood Institute ACE/AACE = American College of Endocrinology/American Association of Clinical Endocrinologists IDF = International Diabetes Federation.

[a] Family history of type 2 or gestational diabetes, known CVD, polycystic ovary syndrome, physically inactive lifestyle, >40 years of age, and ethnic populations at high risk for type 2 diabetes.

[b] In this analysis Mexican-American men were classified using a WC cut-off value of ≥ 90 cm and Mexican-American women ≥ 80 cm.[9]

3.11.4 Cardiorespiratory Fitness and the Metabolic Syndrome

The relationship between cardiorespiratory fitness, as measured by VO_{2max}, and the metabolic syndrome has not been studied as extensively as that with physical activity. However, cardiorespiratory fitness can be more objectively measured and may be more predictive of the metabolic syndrome than physical activity, per se. Cardiorespiratory fitness has been shown to be predictive of the metabolic syndrome, with men of low fitness ($VO_{2max} < 29.1$ ml · kg^{-1} · min^{-1}) being almost seven times more likely to have metabolic syndrome compared with those men with a $VO_{2max} \geq 35.5$ ml · kg^{-1} · min^{-1}.[181] Over a four-year period, and after controlling for age, BMI, socioeconomic status, presence of CVD, smoking, and alcohol consumption, the incidence of metabolic syndrome was found to be 47% and 75% lower in middle-aged men with a VO_{2max} of 29.0 -35.6 and ≥ 37.0 ml · kg^{-1} · min^{-1}, respectively, compared with those men whose VO_{2max} was less than 28.9 ml · kg^{-1} · min^{-1}.

The relationship between aerobic fitness and the prevalence of the metabolic syndrome appears to hold for women as well. Women with a VO_{2max} of 11 METs or greater had a prevalence of the metabolic syndrome that was one-third to one-fourth that of women of lower fitness.[186]

The precise amount and intensity of physical activity required to prevent or reverse the clustering of risk factors known as the metabolic syndrome has yet to be definitely determined. While there is evidence to suggest that regular, moderate-intensity physical activity (such as walking 30 minutes on most, if not every, day of the week) may be preventive of the metabolic syndrome, other evidence suggests that activity of greater intensity may be required to optimally minimize risk. Greater cardiorespiratory fitness has demonstrated an even stronger negative association with the metabolic syndrome. Attainment of higher levels of fitness requires more vigorous physical activity.[11]

3.11.5 Muscular Strength and the Metabolic Syndrome

Evidence from the Aerobics Center Longitudinal Study (ACLS) suggests that even after controlling for age, examination date, smoking status, alcohol intake, number of metabolic syndrome risk factors at baseline, family history of diabetes, hypertension, and early onset coronary artery disease, men above the 75th percentile for muscular strength have a 24% lower risk for developing the metabolic syndrome compared to men in the lowest strength category.[187] Others have also illustrated the benefits of resistance training and increases in muscular strength on metabolic risk.[188–192] Muscular fitness appears to add another level of protection against the metabolic syndrome in men and may help with daily and long-term glycemic control. However, strength training is recommended as an adjunct to regular aerobic exercise but not the sole or primary form of activity to prevent or manage the metabolic syndrome.[193]

3.12 CONCLUSION

Cardiovascular disease, in all its forms, represents the greatest threat, by far, to health and longevity in the United States and the world. The major risk factors for CVD are well known, and their prevention and/or management are crucial in reducing the prevalence of CHD, stroke, hypertension, and heart failure. Greater physical activity and especially greater cardiovascular fitness have been shown to significantly reduce the risk of CVD. The reduction in risk is largely mediated via the risk factors as described in this chapter. As such, an appropriate and individually prescribed program of regular physical activity or exercise should be a standard lifestyle intervention for individuals of all ages and abilities.

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