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Part G. Section 2: Cardiorespiratory Health

Introduction

Cardiovascular diseases (CVD) account for the majority of premature morbidity and mortality in the developed world. The influence of physical activity and the prevention and treatment of cardiovascular disease is therefore of great importance. In considering the effects of physical activity on cardiovascular health, one must address not only its influence on the development of symptomatic disease (e.g., heart attack and stroke) but also the influence on risk factors that are known to contribute to the development of symptomatic disease and are often indicative of sub-clinical asymptomatic vascular pathology. Most of the modifiable risk factors for cardiovascular diseases are metabolic in nature and are, in turn, modifiable by changes in physical activity. These metabolic risk factors include hypertension, atherogenic dyslipidemia, the axis of insulin resistance to metabolic syndrome to frank type 2 diabetes, and obesity. In turn, both physical inactivity and poor cardiorespiratory fitness are major risk factors for cardiovascular diseases.

Review of the Science

Overview of Questions Addressed

In this critical review of the knowledge base about the relations between cardiovascular disease and physical activity, cardiovascular disease should be construed to include coronary heart disease, cerebrovascular disease, and peripheral arterial disease. This section of the report reviews the data regarding this relation in two parts, sequentially addressing a series of questions about the presence and the nature of the relationship between physical activity and cardiorespiratory health. First, the section addresses the primarily observational data about physical activity and cardiovascular disease in separate sections dealing with coronary heart disease, cerebrovascular disease and stroke, and peripheral arterial disease. Then, using data from experimental studies, it explores the evidence of the relation between physical activity and several cardiovascular disease risk markers: hypertension, atherogenic dyslipidemia, vascular health and cardiorespiratory fitness. Influences of physical activity on insulin resistance, glucose control, metabolic syndrome and diabetes are addressed in *Part G. Section 3: Metabolic Health* and relations between physical activity and obesity are addressed in *Part G. Section 4: Energy Balance*. Within each disease or risk factor

category, this section reviews the supporting evidence and provides conclusions about the following 3 questions.

1. What is the nature of the relationship with physical activity?

2. What is known about the dose-response relationship with different characteristics of physical activity?

3. What is known about whether the effects of physical activity exposure can be obtained in smaller multiple bouts per day (accumulation) versus single daily bouts?

Data Sources and Process Used To Answer Questions

The Cardiorespiratory Subcommittee focused its review on studies performed since the publication of the *Surgeon General's Report on Physical Activity and Health* in 1996 (1), emphasizing disease prevention as opposed to disease treatment. The subcommittee drew heavily from the *Physical Activity Guidelines for Americans* Scientific Database (see *Part F: Scientific Literature Search Methodology,* for a detailed description of the Scientific Database). In addition, the subcommittee relied on expert knowledge of the authors to identify specific published studies that are critical for the knowledge base that may predate 1996, post-date the collation of the Scientific Database, or for outcomes that were not identified as part of the Scientific Database process (e.g., vascular health markers). Also, reviews in some subject areas (hypertension and atherogenic dyslipidemia) relied in part upon meta-analyses. Finally, for some topics (e.g., cardiorespiratory fitness), separate literature searches were performed in the PubMed database.

All of the prospective cohort and case-control studies included in this review provide self-report information on the habitual physical activity of the subjects, a standardized assessment of CVD clinical events and a comparison of event rates in subjects assigned to 2 or more categories of physical activity. For interventional experimental studies, the analysis was restricted to randomized controlled trials (RCTs) that had a sedentary (non physical activity intervention control arm or period) and studied at least 25 subjects per arm, unless the findings were highly significant with a lower number.

In general, the reviews and discussions address physical activity performed in the context of dedicated sessions of exercise. The assumption is that the specified exercise activity is performed in addition to and on top of normal physical activity performed as a part of activities of daily living. The data are primarily confined to dynamic aerobic (endurance) exercise, as the long-term cardiovascular prevention benefits of resistance and flexibility exercises are relatively little studied to date (2). An exception to this approach occurs when measures of total activity or occupational activity are use as exposure variables in prospective cohort or case-control studies.

Special Considerations and Limitations

The relation between dynamic aerobic exercise and cardiovascular health outcomes, including cardiorespiratory fitness is complex and can be thought of as a series of point estimates within a 3-dimensional matrix of continuous variables: exercise exposure, disease activity, and the magnitude of the response. The major limitation to exercise exposure recommendations for cardiovascular health outcomes is that any recommendation poorly conveys the concept that the location of any point estimate along each of these 3 axes is along a continuum of exposure and response, and should not be viewed as an absolute threshold below which no benefits accrue and above which benefits always accrue.

Continuum of Exercise Exposure

It is well accepted that aerobic exercise exposures can be characterized by an interaction between bout intensity, frequency, duration, and longevity of the program (3;4). The product of these characteristics can be thought of as volume and can be represented by the total energy expenditure (EE) of the exercise exposure. Exercise volume is referred to as the major focus of the exercise recommendation in some recent statements (5), thus allowing for the mixing of exercise bouts of varying intensity, frequency and duration. As recommendations are intended to be adopted for an individual's life-time, longevity is not considered here. However, it is clear that most benefits resulting from changes in physical activity and exercise patterns accrue over days, weeks, months and even years of exposure, and that the study and understanding of such time lines are of scientific and clinical interest and should be investigated further. Most of the data from experimental studies presented here regarding dose-response associations address the issue of varying intensities of exercise and do not control for bout duration, frequency, or total volume of the exercise exposure. In most observational studies, the major variable used as an exposure is activity amount (e.g., minutes, metabolic equivalent [MET]-minutes per day, miles per week) with the other exposure frequently being activity intensity. However, because total weekly EE usually is not controlled, it is possible that the effects of higher intensities observed in these studies might reflect the higher volumes performed, and that the volume of the activity exposure is the important operative. As will be apparent from the relation of exercise volume to the other variables, one cannot fix volume and also simultaneously study either intensity, frequency, or duration effects while controlling the other two. Relatively few interventional experimental studies examine exercise intensity while controlling for EE and even fewer study frequency or duration effects while controlling for EE. This makes the construction of a precise exercise dose for any given response problematic.

Continuum of Disease Progression

Cardiovascular disease is a continuum from asymptomatic fatty vascular streaks, to severe symptomatic coronary heart disease, to fatal myocardial necrosis and death. The same is true for cerebrovascular disease and stroke. The goal of this section is to focus primarily on primary cardiovascular disease prevention. As part of that process, we have explored some

treatment effects on cardiovascular risk factors (e.g., atherogenic dyslipidemia and hypertension), the favorable modulation of which, by pharmacologic or lifestyle therapy, have been shown to be related to reductions in cardiovascular risk as well. The modulation of these risk markers may be the mechanism through which physical activity acts to reduce cardiovascular clinical events, as well. One should be aware that the activity exposure beneficial for primary cardiovascular health (the factors studied in this chapter) and prevention may or not apply to patients with clinically active and apparent cardiovascular disease, such as those in rehabilitation programs.

Role of Physical Inactivity in Disease Progression

A note about the importance of acknowledging the health risks of inactivity in studies of the effects of physical activity on cardiovascular risk factors is indicated here. In studies that include a sedentary inactive non-intervention control group for comparison to the exercise intervention groups, the inactive group consistently tends to demonstrate a worsening in health parameters over time. This is the health cost of physical inactivity, to be contrasted with the health benefits of regular physical activity. That is, the lack of physical activity in normal life leads to worsening in some parameters absent other life style changes, such as in diet. In some instances, the lack of worsening in some parameters over time demonstrated in intervention groups would appear to be an indication that the exercise or physical activity intervention has no effect, whereas, in fact, when compared to inactive control groups, a significant difference in response over time is observed.

Continuum of the Response

The response of biological parameters to dynamic aerobic exercise, and likely to resistance training as well, is a continuum from undetectable changes to highly significant, robust and clinical important ones that are highly dependent on the exercise exposure variables previously discussed. Consequently, it is likely that no given minimal intensity, frequency, duration or volume of exercise will result in a favorable response for any given outcome. Similarly, it is unlikely that any of these exercise variables has a level for **optimal** outcome. Furthermore, increases in exercise exposure do have tangible adverse outcomes that are primarily musculoskeletal and cardiovascular (see *Part G. Section 10: Adverse Events*). Thus, potential increases in favorable outcomes of increasing exercise exposure must be balanced by the potential for increases in unfavorable outcomes.

Question 1: What Is the Relationship Between Physical Activity and Cardiovascular Morbidity and Mortality?

Conclusion

The results of recently published studies continue to support a strong inverse relation between the amount of habitual physical activity performed and CHD and CVD morbidity or mortality. For both men and women at middle age or older, remaining sedentary is a

major independent risk factor, with persons reporting moderate amounts of activity having a 20% lower risk and those reporting activity of higher amounts or intensity having approximately a 30% lower risk than least active persons. These may be underestimates of the risk reductions (with the underestimate being on the order of 10%) because multivariate models in many studies include adjustments for hypertension, dyslipidemia, and glucose tolerance, conditions that may represent biological intermediates in the causal pathway. Although still limited, data also indicate habitual physical activity benefits the cardiovascular health of people of various races and ethnicities.

Introduction

Physical Activity and Health: A Report of the Surgeon General concluded by saying, "The epidemiologic literature supports an inverse association and a dose-response gradient between physical activity level or cardiorespiratory fitness and both CVD in general and CHD in particular. A smaller body of research supports similar findings for hypertension. The biological mechanisms for these effects are plausible and supported by a wealth of clinical and observational studies. It is unclear whether physical activity provides a protective role against stroke" (1, p.112). Since 1996, a large volume of research has been directed at better defining the relation between physical activity and various CVD clinical outcomes, the mechanisms by which the cardiovascular benefits of physical activity are likely mediated, and the characteristics of the dose of activity (type, intensity, frequency, session duration, and total volume) associated with lower CVD clinical event rates.

The following material provides an overview of the scientific literature since 1996 directed at establishing the effects of physical activity on various clinical cardiovascular outcomes and the issue of dose-response. The main focus is on the primary prevention of clinical events; therefore, most of the evidence comes from prospective cohort studies of at-risk populations. All of the studies included in this review provide self-report information on the habitual physical activity of the subjects, a standardized assessment of cardiovascular clinical events, and a comparison of event rates in subjects assigned to 2 or more categories of physical activity. These comparisons consisted of a measure of the relative risk (RR) for the groups and 95% confidence intervals for the measure of risk, including risk ratios, hazard ratios or odds ratios. In all the cited studies, the multivariate adjusted relative risks were recorded and used in any analysis. These adjustments varied from study to study but usually included at a minimum age, body mass index (BMI), cigarette smoking, blood pressure, and blood lipid concentrations. It is understood that using multivariate adjustments, which in some cases include measures of BMI, blood pressure, and blood lipids, could inappropriately decrease the magnitude of the relation between the physical activity exposure and the clinical outcome because some of the benefit of the activity might be mediated through these variables ("intermediate" or "mediator" variables). However, we considered this a more conservative approach than adjusting just for age and other selected demographic variables. In studies where RRs for more active versus the least active persons are presented using both limited adjustments and multivariate adjustments that accounted for potential "intermediate" variables, the RRs for limited adjustments show greater effects in

the range of 10% (6-8). To determine whether a dose-response pattern existed between physical activity characteristics and the clinical outcome, data for at least 3 activity categories needed to be provided. The *Physical Activity Guidelines for Americans* Scientific Database was used to identify eligible studies published between January 1996 and June 2007. Also, selected studies that did not meet criteria for inclusion in the Database but provided ancillary data related to specific issues have been considered in this review, including meta-analyses and systematic reviews.

Rationale

Between January 1995 and June 2007, more than 60 studies were published that met the subcommittee's search criteria investigating the effects of habitual physical activity on cardiovascular morbidity and/or mortality in men and women throughout a wide age span and of various race and ethnicities. Much of the self-reported physical activity was performed during leisure time, but also included are data from occupational, household, and commuting activities. A majority of these data come from prospective cohort studies with the results from a limited number of case-control studies included. Studies tended to report outcomes for various clinical manifestations of *coronary heart disease* (e.g., fatal or nonfatal myocardial infarction, ischemic heart disease, cardiac death), a more general category of *cardiovascular disease* that could include a variety of manifestations of atherothrombotic vascular disease (e.g., coronary heart disease, stroke, other vascular disorders), and *stroke or cerebrovascular disease*. Data were organized from these studies by CHD, CVD, and stroke and then by sex with an emphasis on the magnitude of any relation and whether evidence of a dose response existed. The relation between a measure of physical activity and a CVD clinical outcome was considered significant if the 95% confidence interval did not include 1.0. A significant dose-response relation usually was based on *P* for trend being <0.05.

Coronary Heart Disease

The results of studies investigating the relation between habitual physical activity and CHD morbidity and/or mortality published since 1996 quite consistently show lower event rates in more physically active men and women than for their least active counterparts. Most notable has been the large increase in the number of studies that have included data on women, with 19 studies reporting data on women and 9 with data on men and women combined (see Table G2-1 for a summary of the studies and Table G2-A1 for selected data from individual studies) (Table G2-A1 can be accessed at http://www.health.gov/paguidelines/report/).

The studies of women reporting CHD clinical events included more than 200,000 subjects aged 20 to 85 years. For the prospective cohort studies, the median RR of having a CHD clinical event for women reporting participation in moderate intensity or amount of physical activity compared to women reporting no or only light intensity activity was 0.78, while the RR for women performing vigorous or high amounts of activity as compared to women eporting no or light activity was 0.62. These RRs are quite similar to those resulting from a

Table G2.1. Summary of Prospective Cohort Studies and Case-Control Studies Published in the English Language Since 1996 Reporting on the Relation Between Habitual Physical Activity and the Prevention of Coronary Heart Disease, Cardiovascular Disease, or Stroke

Data summaries for each study in this review are included in the Appendix.

Men

Condition Prevented	Prospective Cohort Studies Number of Studies Reporting RR	Prospective Cohort Studies Median RR M/L	Prospective Cohort Studies Median RR H/L	Prospective Cohort Studies Number of Studies Reporting D-R	Prospective Cohort Studies Number of Studies D-R Sig.	Case-Control Studies Number of Studies Reporting RR	Case-Control Studies Median RR M/L	Case-Control Studies Median RR H/L	Case-Control Studies Number of Studies Reporting D-R	Case-Control Studies Number of Studies D-R Sig.
Coronary Heart Disease	17	0.81	0.68	11	7	6	0.65	0.53	2	2
Cardiovascular Disease	10	0.78	0.70	3	2	1	0.65	0.67	0	0
Total Stroke	11	0.65	0.72	6	5	0	–	–	–	–

Women

Condition Prevented	Prospective Cohort Studies Number of Studies Reporting RR	Prospective Cohort Studies Median RR M/L	Prospective Cohort Studies Median RR H/L	Prospective Cohort Studies Number of Studies Reporting D-R	Prospective Cohort Studies Number of Studies D-R Sig.	Case-Control Studies Number of Studies Reporting RR	Case-Control Studies Median RR M/L	Case-Control Studies Median RR H/L	Case-Control Studies Number of Studies Reporting D-R	Case-Control Studies Number of Studies D-R Sig.
Coronary Heart Disease	13	0.78	0.62	8	5	6	0.62	0.44	3	1
Cardiovascular Disease	12	0.80	0.72	6	5	1	0.89	0.71	0	0
Total Stroke	8	0.82	0.72	5	4	0	–	–	–	–

Table G2.1. **Summary of Prospective Cohort Studies and Case-Control Studies Published in the English Language Since 1996 Reporting on the Relation Between Habitual Physical Activity and the Prevention of Coronary Heart Disease, Cardiovascular Disease, or Stroke (continued)**

Men and Women (Data Combined)

Condition Prevented	Prospective Cohort Studies Number of Studies Reporting RR	Prospective Cohort Studies Median RR M/L	Prospective Cohort Studies Median RR H/L	Prospective Cohort Studies Number of Studies Reporting D-R	Prospective Cohort Studies Number of Studies D-R Sig.	Case-Control Studies Number of Studies Reporting RR	Case-Control Studies Median RR M/L	Case-Control Studies Median RR H/L	Case-Control Studies Number of Studies Reporting D-R	Case-Control Studies Number of Studies D-R Sig.
Coronary Heart Disease	5	0.74	0.63	1	1	4	0.61	0.48	3	1
Cardiovascular Disease	5	0.87	0.72	2	1	0	–	–	–	–
Total Stroke	4	0.67	0.75	2	1	2	0.68	0.48	0	0

D-R, dose-response; H/L, high intensity or high amount vs. light intensity/amount; M/L, moderate intensity/amount vs. light intensity/amount; RR, relative risk (includes risk ratio, odds ratio or hazard ratio); Sig., significant.

meta-analysis of many of the same studies that were published between 1996 and 2003 (9). The conclusion from this meta-analysis for CHD was that physical activity was associated with a lower risk of CHD (as well as CVD and stroke) in a dose-response fashion with pooled RRs for both moderate amounts and high amounts being significant when compared to no or light activity. In the 6 case-control studies reported for women, the median RR was 0.62 for moderate versus no or light activity and 0.44 for vigorous intensity or high amounts of activity versus no or light activity.

Of the studies reporting on CHD in men, 16 were prospective cohort studies and 4 were case-control studies. Approximately 124,000 men aged 15 to 96 years at baseline were included as subjects. Most studies reported on leisure-time physical activity (LTPA) with a few studies including occupational activity, commuting, and sports participation. Among the prospective cohort studies, the median RR was 0.81 for moderate intensity or amount of activity versus no or light activity and 0.68 for vigorous intensity or high amounts versus light or no activity. For the 6 case-control studies, the median RR was 0.65 for moderate versus no or light activity and 0.53 for vigorous intensity or high amounts versus no or light activity. These values are of a similar magnitude to those reported in a systematic review of studies published between 1953 and 2000 (10) and in a meta-analysis published in 2001 that included data from studies published before and after the *Surgeon General's Report on Physical Activity and Health* (11). The lower CHD event rate for more active men was reported for both nonfatal and fatal CHD with no systematic difference in CHD incidence versus CHD mortality.

Five prospective cohort studies and 4 case-control studies were published in which the results for CHD events for men and women were combined. In the prospective cohort studies, the median RR was 0.74 for moderate intensity or amount versus no or light activity and 0.63 for high intensity or amount versus no or light activity. In the case-control studies, the RR was 0.61 for moderate activity versus no or light activity and 0.48 for high amounts or intensity versus no or light activity.

Cardiovascular Disease

In prospective cohort studies published since 1996 that included data on the relation between habitual physical activity and CVD in women (n=12), the median RR was 0.80 for those reporting moderate intensity or amount versus no or light activity and 0.72 for vigorous versus no or light activity. In the one case-control study reporting on CVD in women, the RR was 0.89 for moderate intensity versus no or light activity and 0.71 for high versus no or light activity. (See Table G2-A2 for selected data from these prospective cohort and case-control studies. This table can be accessed at http://www.health.gov/paguidelines/report/.) Here again, the amount and quality of data evaluating the relation between physical activity and CVD clinical events in women has substantially increased since 1996, with at least 350,000 women included in the reported studies. Overall, the CVD data reported on men are very similar to those for women: In 10 prospective cohort studies the median RR for CVD events was 0.78 for moderate versus no or light activity and 0.70 for high intensity or amount versus no or light activity. In the one case-control study, the RR was 0.65 for

moderate versus light activity and 0.67 for high versus no or light activity. Although data are not provided in the reports, it is very likely that a majority of the CVD events included in these studies were the result of coronary heart disease.

Effects of Sex, Age, or Race and Ethnicity

Although the magnitude of median RRs for CHD for both moderate versus light activity and high versus light activity are somewhat lower in women than in men (Table G2-1), physically active men and women both typically have a lower risk for CHD than do their least active counterparts. Comparisons between the sexes are difficult across studies because of some evidence that the activity levels in the least active women are less than for the least active men, age distributions within age categories (e.g., 40 to 65 years, 65 to 79 years) are different from study to study, and CHD event rates within age categories differ between men and women. In the studies that included data for both men and women (12-20), even fewer presented results for men and women separately and in some studies that do, the number of CHD events in women is relatively small, thus substantially limiting the reliability of any analysis (19). In a case-control study published by Fransson and colleagues (20) evaluating the association between various types of physical activity and acute myocardial infarction, women appeared to be somewhat more protected than men. The RR for fatal and nonfatal MI in women comparing most active versus least active for total activity was 0.16 (95% CI 0.07-0.37), and the RR for the same comparison in men was 0.46 (95% CI 0.31-0.69). For women, the RR for LTPA more than 3 times per week versus seldom was 0.31 (95% CI 0.15-0.66); for men the RR was 0.53 (95% CI 0.38-0.73). It should be noted that rarely is a distinction made in these studies between associations in pre- and post-menopausal women, and whether they are different in these two populations when studied separately. Consequently, no evidence exists that effects of physical activity on CHD are different whether the study population is men, pre-menopausal, or post-menopausal women.

The inverse association between physical activity and CHD events has been reported for adults across a wide range of ages, with the magnitude of the association for older men and women (aged 65 years and older) at least as strong as for younger adults. Because CVD morbidity and mortality rates are low in men younger than age 45 years and women younger than age 55 years, very few data are available on the relation between physical activity levels and CVD clinical events in younger adults or youth. None of the meta-analyses on physical activity and CVD events published since 1995 has evaluated the effect of age on the magnitude of the relation, and only a limited number of studies have compared different age categories within their population. Manson and colleagues (21) had a sufficiently large sample of women (n=73,743) and cardiovascular events (n=1,551) in the Women's Health Initiative Observational Study to analyze the relation between LTPA and CVD incidence for 3 age groups, 50 to 59 years, 60 to 69 years, and 70 to 79 years. When activity was classified by MET-hours per week in quintiles, all 3 age groups showed a significant difference (*P* for trend <0.001) when the highest versus the lowest quintiles were compared (RR = 0.45, 0.50 and 0.64, respectively) with the lowest quintile being the reference (1.0) the adjusted RRs for quintiles 2 through 5 for women aged 50 to 59 years were 0.68, 0.63, 0.54, 0.45, respectively. For women aged 60 to 69, the RRs were 0.79, 0.63, 0.56, 0.50, respectively,

and for women aged 70 to 79, they were 0.93, 0.86, 0.75, 0.64, respectively. Other studies have not showed any meaningful difference in the relation between physical activity level and CVD events in different age categories. For example, women in the College Alumni Health Study contrasting those younger than age 45 years versus those 45 years and older at baseline (22), combined data on men and women contrasting aged 65 years and younger versus those older than 65 years (23), or those aged 65 to 74 years versus aged 75 years and older (24). In a small prospective cohort study in men evaluating various risk factors for CHD, high-intensity activity was related to CHD events in those older than age 65 years (0.36, 95% CI 0.13-1.05) but not in those aged 65 years and younger (25). In the Buffalo Blood Pressure Study, older women (aged 60 years and older) were not protected from CVD mortality by high levels of total activity, though physical activity provided some protection for women younger than aged 60 years. However the number of CVD events was small in both groups (26).

Few studies conducted in the United States have had an adequate sample size and clinical outcomes to evaluate the association between physical activity and CVD clinical events in race or ethnic groups other than non-Hispanic whites. The Women's Health Initiative Observational Study (21) included 61,574 white women and 5,661 black women with a mean follow-up of 3.2 years. The relation between total physical activity level (quintiles of MET-hours per week) and CVD clinical events was significant for both groups of women with RR for the highest versus lowest quintile of activity for white women being 0.56 (*P* for trend <0.001) and for black women 0.48 (*P* for trend = 0.02). In contrast to these results, a report on the Atherosclerosis Risk in Communities (ARIC) study population indicated that although activity level and CVD clinical events had a significant inverse relation in white men and women, no such relation was found for either back men or women (19). The authors suggested that this lack of association in blacks may be due to the limited number of blacks reporting vigorous physical activity (5% in black men versus 15% in white men). However, outside the United States, where the relation between physical activity level and CVD clinical events has been evaluated in other race and ethnic populations, there is no indication that the favorable association frequently reported for non-Hispanic white men and women does not occur in other race and ethnic populations. For example, physically active Japanese men and women living in Japan (27) and older Japanese men living in Hawaii (28) had lower CVD mortality rates than the least active. Similar results have been reported for Chinese women living in Shanghai (29) and Chinese men and women living in Hong Kong (30). In a case-control study including men and women conducted in New Delhi and Bangalore India, at least 145 MET-minutes per day of LTPA versus no activity had a RR for myocardial infarction of 0.44 (95% CI 0.27-0.41). Time spent in non-work sedentary activity also was directly associated with risk of myocardial infarction (the RR for at least 215 minutes per day of sedentary activity versus fewer than 70 minutes per day was 1.58 [95% CI 1.05-2.36]).

Change in Physical Activity and Cardiovascular Disease Clinical Events

Most reports from prospective observational studies have presented the relation between physical activity measured on one occasion and the rate of CVD clinical events over various

periods of follow-up. However, a few studies have obtained self-reported activity 2 or more times, typically 3 to 15 years apart, and related change in activity during this interval with CVD clinical events during a follow-up period. The goal of this approach is to determine whether an increase in activity is associated with lower event rates than observed for subjects who remain inactive. Also, do subjects who move from an active to an inactive category have higher CVD event rates than subjects who remain physically active? Men in the Harvard Alumni Study who increased their physical activity index to 2,000 kilocalories per week or more (measured in 1962 or 1964 and again in 1977) compared to men who remained inactive had a 17% lower CHD death rate (P= 0.51), while men who took up moderately vigorous sports had a 41% lower risk (P= 0.04) (31). Similar results have been reported for British men. Those who reported an increase in activity over 12 to 14 years had a RR for CVD mortality of 0.66 (95% CI 0.35-1.23) compared to men who remained sedentary, while men who remained active had a RR of 0.54 (95% CI 0.31-0.94) compared to continuously sedentary men (32).

Women in the Nurses' Health Study who reported increases in their LTPA between 1980 and 1986 with follow-up to 1994 had lower CVD event rates than women who remained sedentary (6). When the increase in activity for women who were sedentary in 1980 was expressed in quartiles of METs, the RRs for quartile 1 through quartile 4 were 0.85, 0.79, 0.67 and 0.71, respectively (P for trend=0.03). Women aged 65 years of age and older who had physical activity assessed twice (5.7 years apart) and changed from being inactive to active had a RR for CVD mortality of 0.64 (95% CI 0.42-0.97) compared to women who remained inactive, and women who remained active had a RR of 0.68 (95% CI 0.58-0.82). Although data on the association between change in activity and CVD clinical events in prospective observational studies does not provide the same level of evidence as data from RCTs, these results do add to the strength of the evidence linking higher levels of physical activity with lower CVD risk. In the studies cited, the change in activity preceded the clinical events and the direction of the association is consistent with an increase in activity causing a reduction in risk.

Question 2: What Are the Dose-Response Relations Between Physical Activity and Cardiovascular Morbidity and Mortality?

Conclusion

The inverse association between CVD clinical events and habitual physical activity exists across a wide range of types, amounts, and intensities of activity. People at highest risk are those who are least active and spend much of their day in activities that consume low amounts of energy. When compared to very sedentary persons, men and women who perform small amounts of moderate-intensity activity, such as 60 minutes per week of walking at a brisk pace, exhibit fewer CVD clinical events. People who perform more activity and/or at a faster pace are at an even lower risk, with much of the benefit derived when men and women are performing 150 or more minutes per week of moderate-intensity (3 to less than 6 METs) physical activity. Greater amounts of activity appear to provide

greater benefit but the shapes of any dose-response relations have not been well defined. Vigorous-intensity activity (equal to or more than 6 METs) when performed for a similar duration as moderate-intensity activity results in greater energy expenditure and is associated with lower CVD event-rates. Much of the recent data are based on LTPA, but performing physical activity during an occupation, around the home, or while commuting all appear to provide benefit as well.

Rationale

In the studies reporting on CHD or CVD, the median RR difference for high levels of activity versus inactive or light activity categories was somewhat greater than the difference in the median RR for moderate levels of activity versus inactive or light activity, thus indicating a somewhat greater benefit from higher amounts or intensities of activity versus moderate intensity and amounts of activity. In the cohort studies that had 3 or more physical activity levels, authors frequently evaluated dose-response by calculating the linear trend and testing this trend for significance. If the *P* for trend was ≤0.05, then the dose response was considered significant. For CHD in women, 7 studies reported *P* values for dose response, and 3 of them were significant. Six studies reported dose response for CVD in women, with 5 reaching significance. For men, 7 of 11 studies reporting dose response for CHD were significant as were 2 of the 3 studies reporting on CVD. For studies that combined data on men and women, the one study that reported dose-response for CHD found it to be significant, and 1 of the 2 studies reporting on CVD was significant.

From a public health perspective, it is important to recognize that when the reference group in the population being studied is very sedentary, modest amounts of moderate intensity activity are associated with significantly reduced rates of CHD and CVD. For example, in 3 large prospective cohort studies of women in the United States (6;7;21), those who walked in the range of 1 to 2 hours per week versus non-walkers produced RRs for CVD or CHD events of 0.75 (95% CI 0.63-0.89; (21), 0.70 (95% CI 0.51-0.95; (6)), and 0.49 (95% CI 0.28-0.86; (7)) (Figure G2-1). The *P* for trend with multivariate adjustment for categories of walking amount (MET-minutes per week or duration (minutes per week) was significant (*P* <0.001) in all 3 studies. Also, walking at a faster pace was associated with a lower risk of CHD or CVD in these 3 studies, with those who walked at a pace 3.0 miles per hour and greater having a significantly lower RR than non-walkers (0.76, 0.70 and 0.52). The *P* for trend across walking pace was significant for all 3 studies. Other studies have reported on walking and CVD with either significantly lower RRs for men and women who walk regularly versus non-walkers (24) or favorable but non-significant trends for increased walking (22;28;33;34). There was no difference in a large study of Chinese women living in Shanghai where the least active reference group included walking from 0 to 3.4 MET-hours per week (29). In this study, the amount of walking in the reference group of Chinese women was sufficiently high that additional walking may not provided additional protection against CVD. Overall, these data on walking and CVD indicate that when brisk walking is performed 3 hours per week by otherwise sedentary persons, especially women, the CVD clinical event rate is significantly lower than for persons who do little walking or other physical activities.

Figure G2.1   Relative Risk of CVD in Women — Walking Amount/Week
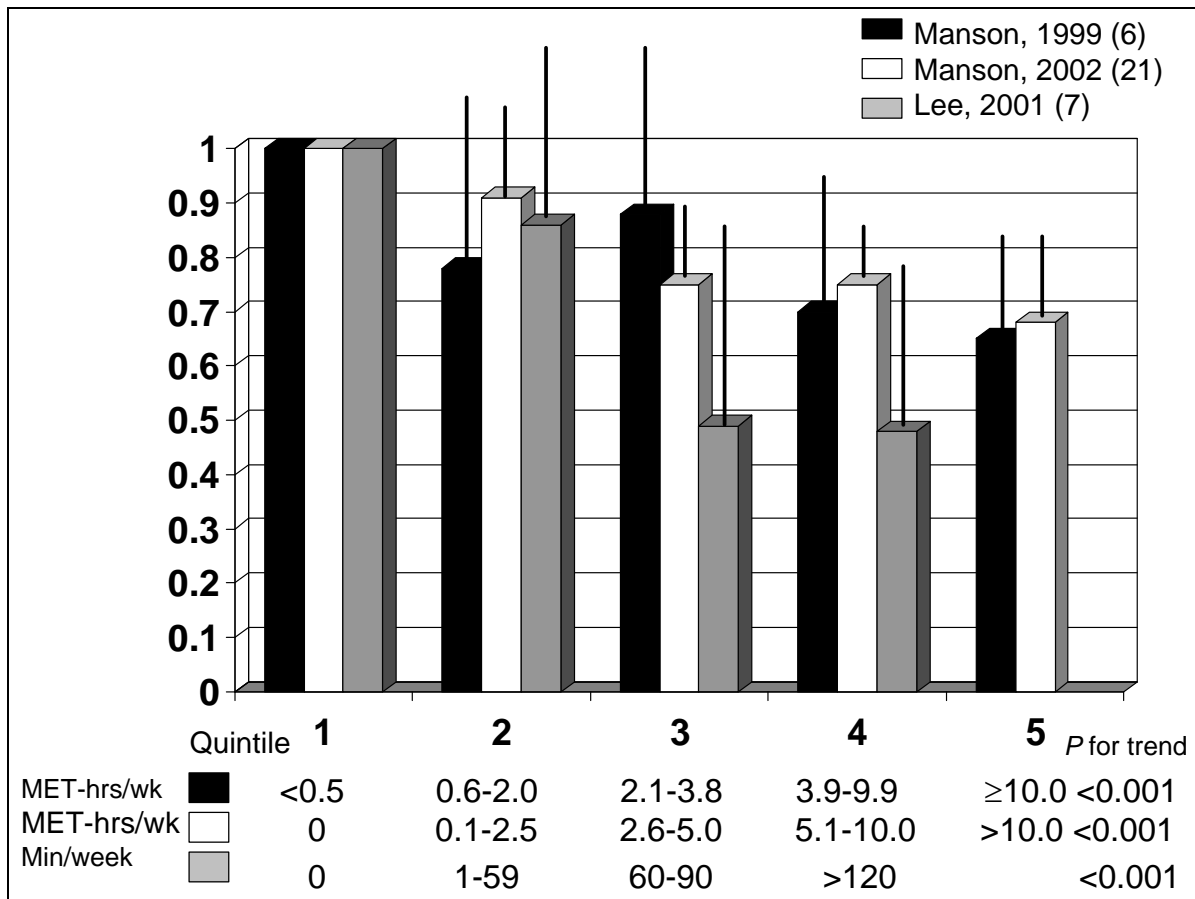
Figure G2.1.   Data Points

Studies	1	2	3	4	5
Manson, 1999	1	0.78	0.88	0.7	0.65
Manson, 2002	1	0.91	0.75	0.75	0.68
Lee, 2001	1	0.86	0.49	0.48	

Question 3: What Is the Relationship Between Physical Activity and Cerebrovascular Disease and Stroke?

Conclusion

More physically active men and women generally have a lower risk of stroke incidence or mortality than the least active, with more active persons demonstrating a 25% to 30% lower risk for all strokes. A favorable relation exists between physical activity level and stroke (both for ischemic and for hemorrhagic stroke), but the data on these stroke subtypes are still quite limited. The benefits appear to be derived from a variety of activity types, including activity during leisure time, occupational activity, and walking. Overall, the relationship between activity and stroke is not influenced by sex or age, and very little data exist for race and ethnicity other than for non-Hispanic whites.

Rationale

The Surgeon General's Report on Physical Activity and Health concluded that "the existing data do not unequivocally support an association between physical activity and stroke risk" (1, p.103). This conclusion was based on a review of 14 observational studies (4 included women), of which 8 showed an inverse relationship between physical activity and stroke. The other studies showed no significant association, with 2 studies suggesting a U-shaped relationship with higher stroke risk in the least and most active categories. Since 1996, studies meeting the criteria for this review include data from studies on women (n=8), men (n=11), and men and women combined (n=6). (See Table G2-A3 for selected data from these prospective cohort and case-control studies. This table can be accessed at http://www.health.gov/paguidelines/report/.) In addition, 2 meta-analyses of physical activity and stroke have been published (35;36). In most studies, data are reported on all strokes, and in some studies data also are provided separately for ischemic and hemorrhagic stroke. In women, the median RR was 0.82 for all strokes combined for moderate-intensity activity versus no or light activity and 0.72 for high-intensity or amount versus no or light activity. For all strokes in men, the median RR was 0.65 for moderate-intensity versus no or light activity and 0.72 for high-intensity or amount versus no or light activity. In the studies reporting combined data on men and women, the median RR for the prospective cohort studies (n=4) was 0.67 for moderate-intensity versus no or light activity and 0.75 for high-intensity or amount versus no or light activity. For the 2 case-control studies, the median RR was 0.68 for moderate versus low activity and 0.48 for high versus low activity.

The meta-analysis by Wendel-Vos and colleagues (36) included data from 31 studies published in English before 2001, including 24 prospective cohort studies and 7 case-control studies. Based on these analyses, the authors concluded that moderately active men and women had lower rates of ischemic, hemorrhagic, and all strokes than did the least active subjects. When persons who reported moderate-intensity occupational activity were compared with persons who reported light-intensity occupational activity, the RR was 0.64 (95% CI 0.48-0.87). They also observed an RR of 0.85 (95% CI 0.78-0.93) for moderate

versus light LTPA. High-level occupational activity appears to protect against ischemic stroke compared with both moderate (0.77, 95% CI 0.60-0.98) and inactive occupational levels (0.57, 95% CI 0.60-0.98). Persons reporting high-level compared to low-level LTPA were at significantly lower risk for all strokes (0.78, 95% CI 0.71-0.85), ischemic stroke (0.79, 95% CI 0.69-0.91), and hemorrhagic stroke (0.74, 95% CI 0.57-0.96). Both moderately active men and women had a lower RR for hemorrhagic stroke than their inactive counterparts (men = 0.54, 95% CI 0.36-0.81; women = 0.76, 95% CI 0.67-0.86; P=0.07 for difference between men and women). Studies conducted in Europe showed a stronger inverse association between active and inactive persons (0.47, 95% CI 0.33-0.66) compared to studies conducted in the United States (0.82, 95% CI 0.75-0.90). The overall results of the meta-analysis on physical activity and stroke published a year earlier (35) were similar to the results of this meta-analysis. When Lee and colleagues included data from both cohort and case-control studies, the RR for stroke incidence or mortality for the most active versus the least active was 0.73 (95% CI 0.67-0.79) and for moderately active versus the least active the RR was 0.80 (95% CI 0.74-0.86).

The inverse association between physical activity level and stroke risk appears very similar for men and women in the few studies that report sex-specific data. Vatten and colleagues (37) followed 34,868 Norwegian women and 32,872 men for 16 years and documented cause-specific mortality. The P for trend for total activity and stroke mortality was 0.009 for men and <0.001 for women, and the RR for high activity versus never active was significant for both sexes. In Japan, 31,023 men and 42,242 women were followed for an average of 9.7 years, and walking and sports participation were inversely related to CVD mortality (27). The relationship of walking time to all stroke or ischemic stroke mortality was very similar for men and women as was the time spent in sports participation. Because the occurrence of stroke is very low for those younger than age 55 years, very few reports are available on the relation of physical activity to stroke morbidity or mortality in younger and middle-aged populations. Data from the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study (38) indicate no systematic difference in the relationship of LTPA amount to either total or non-hemorrhagic stroke in men or women aged 45 to 64 years versus 65 to 74 years at baseline (the age x low activity interaction term was not significant). Overall, the strongest and most consistent association between activity level and stroke in this study was seen in white women.

Although stroke rates tend to be higher in African American men and women than in other race/ethnicities in the United States, no studies have adequately addressed the relation of physical activity level and stroke risk in any race/ethnicity other than non-Hispanic whites.

Question 4: What Is the Relationship Between Physical Activity and Peripheral Arterial Disease?

Conclusion

No large RCTs have been conducted to investigate exercise training in peripheral arterial disease (PAD). Little is known regarding exercise dose response (intensity, duration or frequency) or different modalities (walking, cycling, resistance training) of exercise to prevent PAD because most of the studies have followed the same exercise prescription, which has used supervised treadmill walking at a similar dose. Furthermore, even less is known about how subpopulations differ in responses to exercise training, such as whether sexes respond differently or whether an interaction exists between type 2 diabetes and exercise responsiveness in persons with PAD.

Rationale

Exercise for Primary Prevention of Peripheral Arterial Disease

Only a handful of cross-sectional primary prevention studies have been performed to relate ankle brachial index (ABI), an indicator of severity of peripheral lower extremity arterial occlusion, with physical activity (Table G2-A4, which summarizes these studies, can be accessed at http://www.health.gov/paguidelines/report/.) Activity questionnaires have been used to examine retrospectively the relationship between physical activity and abnormal ABIs. In the Edinburgh Artery Study (39), for example, the amount of physical activity performed between the ages of 35 to 45 years was inversely related to prevalence of PAD at ages 55 to 74 years, but only in men. Further, this relation held only for men who had smoked at some time in the past. Gardner and colleagues (40) observed that the amount of physical activity was related to ABI measures in those without PAD, suggesting that regular habitual exercise may be related to the presence of sub-clinical asymptomatic PAD.

Exercise for Secondary Prevention of Peripheral Arterial Disease

Exercise training is a powerful secondary preventive measure for those with established PAD (Tables G2-A5 and G2-A6, which summarize these studies, can be accessed at http://www.health.gov/paguidelines/report/). Several meta-analyses and review articles summarize this body of literature (Table G2-A7, which summarizes these studies, can be accessed at http://www.health.gov/paguidelines/report/) (41-49). Although these studies unequivocally demonstrate exercise training to be beneficial for improving maximal walking ability, many lack necessary criteria such as large sample sizes, randomized and controlled designs, assessments of sex and dose-response effects, and differential responses in symptomatic (intermittent claudication) versus asymptomatic individuals needed to make strong specific clinical exercise recommendations. Despite these shortcomings, the data demonstrate that adherence to a structured supervised exercise program is currently regarded as the most effective treatment for symptomatic PAD. In all of the clinical studies noted above, the 2 most commonly measured variables used to determine the effectiveness of a

PAD therapy are peak walking time (PWT) and claudication onset time (COT). It is clear that exercise improves both PWT and COT in patients with PAD (50-64).

Based on the evaluation of meta-analyses and clinical studies, the average improvement following exercise training in PWT is near 100%, with COT improving consistently to an even greater degree (to the magnitude of 130% or more). Other responsive variables, primarily measured in small studies, are peak oxygen consumption, walking economy, daily physical activity, 6-minute walk time, leg blood flow, and quality of life. Interestingly, although some studies have demonstrated improved leg blood flow and ABI, these indices have not convincingly been related to functional markers. It appears that improved oxidative metabolism in the skeletal muscle may explain some of the improvements in exercise tolerance (50;52). Whether increased growth of small blood vessels (angiogenesis) and oxidative machinery (enzymes, mitochondria) are responsible for the improved muscle metabolism following exercise training is being explored. Findings also suggest that improvements can be augmented beyond those resulting from a traditional 12-week exercise program. As much as an additional 50% improvement in PWT may be achieved with continued therapy to up to 24 weeks (51). Twelve to 24 weeks of exercise training produced improvements in free-living accelerometer-derived daily physical activity, walking economy measured by constant workload oxygen consumption (slow component of VO_2). Although a traditional exercise prescription for PAD recommends that patients endure a moderate rather than severe level of claudication pain during training bouts, limited evidence indicates that a lower exercise intensity than the pain threshold elicits similar results as exercise above the pain threshold as long as the same dose in minutes is maintained (63).

The Relationship Between Daily Physical Activity and Peripheral Arterial Disease

Studies have confirmed that the severity of PAD is related to daily free-living physical activity. (Table G2-A8, which summarizes these studies, can be accessed at http://www.health.gov/paguidelines/report/.) Studies show that, among individuals with PAD, daily physical activity is reduced approximately 40% compared to matched healthy controls and that the degree of claudication (as measured by ABI and PWT) is related to daily physical activity within a PAD population (65;66). These findings have been confirmed using accelerometers and performance score questionnaires that have related the decrease in daily physical activity to impairments in the lower extremity. A progressive decline in leisure-time activities of both moderate and high intensities has been identified in individuals with PAD (67). The loss of daily physical activity corresponds with decreasing ABI values and COT. Furthermore, a relation appears to exist between free-living physical activity and microcirculation in the calf muscle (66). The natural progression of PAD has been assessed and determined to be inversely related to self-reported physical activity as assessed by COT, 6-minute walk test, and calf blood flow (68). All of these studies demonstrate that, despite a lack of randomized controlled exercise studies to evaluate the effect of exercise training on preventing PAD, a lack of exercise contributes to disease progression, symptom status, and additional inactivity in those who have PAD.

Although most studies comparing supervised versus home-based programs conclude that supervised exercise is better, this remains inconclusive. No study has investigated the effects of an exercise program on asymptomatic patients with known PAD to determine whether exercise can prevent the onset of claudication or disease worsening. In addition, little is known about the role of resistance training, as no definitive trial has directly compared traditional walking exercise to resistance training in the PAD population.

Question 5: What Is the Relationship Between Physical Activity and Hypertension?

Conclusion

Both aerobic and progressive resistance exercise yield important reductions in systolic and diastolic blood pressure (BP) in adult humans, although the evidence for aerobic exercise is more convincing. Traditional aerobic training programs of 40 minutes of moderate- to high-intensity exercise training 3 to 5 times per week and that involve more than 800 MET-minutes of aerobic exercise per week appear to have reproducible effects on BP reduction.

Rationale

In this section we update the evidence of the effects of chronic exercise on resting BP in adults generated since the release of the *Surgeon General's Report on Physical Activity and Health* (1). This update is limited to a review of previous meta-analyses that met the following criteria: (1) RCTs only, (2) meta-analyses published in the English language between January 1, 1995 and September 30, 2007, (3) adults aged 18 years and older, (4) aerobic or progressive resistance training as the only intervention, (5) non-intervention control group, (6) resting or ambulatory systolic and diastolic BP as a primary outcome in each meta-analysis.

Relationship Between Aerobic Exercise and Blood Pressure

Ten meta-analyses dealing with the effects of aerobic exercise on resting BP in adults have been published since 1996 (69-78). Six of these meta-analyses were comprehensive (69;72;74-77) and the remaining 4 focused on either women (71), older adults (73), overweight and obese subjects (70), or walking as the only intervention (78). The most recent and inclusive meta-analysis that included data partitioned according to hypertensive, prehypertensive, and normotensive adults included a total of 72 studies, 105 exercise groups, and 3,936 men and women with a between-study age range of 21 to 83 years (median age = 47 years) (76). Across all categories, mean reductions in resting BP ranged from 2 to 5 mmHg (2% to 4%) for resting systolic BP and 2 to 3 mmHg (2% to 3%) for resting diastolic BP. Reductions were greater in hypertensive subjects (systolic BP, −6.9 mmHg; diastolic BP, −4.9 mmHg) than in prehypertensive (systolic BP, −3.1 mmHg; diastolic BP, −1.7 mmHg) and normotensive (systolic BP, −2.4 mmHg; diastolic BP, −1.6 mmHg) subjects. Changes were equivalent to relative reductions of approximately 5% for both resting systolic and diastolic BP in hypertensive subjects, 1% (systolic BP) and 2% (diastolic BP) in

prehypertensive subjects, and 2% for both resting systolic and diastolic BP in normotensive subjects. Significant reductions of 3.3 mmHg (2%) and 3.5 mmHg (4%) also were observed for daytime ambulatory systolic and diastolic BP with no significant change in nighttime BP. Changes in ambulatory BP are especially noteworthy because the assessment of the measure may better predict target end-organ damage (79). Changes in both resting and ambulatory BP were independent of changes in body weight (76). Similar changes in resting BP also were found for the other inclusive meta-analyses (69;72;74-77) as well as meta-analyses that focused on women (71), older adults (73), overweight and obese subjects (70), and walking (78).

Dose-Response Relations Between Aerobic Exercise and Blood Pressure

The vast majority of studies included in the meta-analyses conducted since the release of the *Surgeon General's Report on Physical Activity and Health* (1) have tended to follow traditional guidelines for the prescription of aerobic exercise in adults as recommended by the American College of Sports Medicine (5;80;81). For example, for the most recently published meta-analysis dealing with the effects of aerobic exercise on resting BP (77), the pooled median length of training was 16 weeks, with a frequency of 3 days per week. However, the analysis included studies in which subjects exercised up to 7 days per week, with a duration of 40 minutes per session and intensity of 65% of maximal heart rate reserve. No consistent relations were observed between changes in resting systolic and diastolic BP and the length, frequency, duration, and intensity of training (77). The most common forms of exercise used in these RCTs were walking, jogging, and stationary cycling, although other types of exercise, such as aerobic dance, also were included. Other meta-analyses also have failed to find a relation between training program characteristics and changes in resting BP (69-72;74-76;78). In contrast, one meta-analysis did report larger decreases in resting systolic and diastolic BP with a greater duration (minutes) of training per session as well as greater decreases in resting systolic BP with lower training intensities (73).

Relation Between Progressive Resistance Exercise and Blood Pressure

Since the release of the *Surgeon General's Report on Physical Activity and Health* (1), 3 meta-analyses (45;77;82) have been conducted on the effects of progressive resistance exercise on resting systolic and diastolic BP. However, as 2 of these included the same data (77;82), this discussion is limited to the one that contained more complete data on progressive resistance training (82). This meta-analysis included 9 RCTs and 12 exercise groups comprising 341 men and women aged 20 to 72 years (median age = 69 years). The vast majority of subjects were not hypertensive (baseline resting systolic/diastolic BP values, 131.6/80.9 mmHg) (82). With the one static (isometric) training study deleted from the analysis, a statistically significant reduction of 3.1 mmHg was found for resting diastolic BP with a trend for a reduction in systolic BP of 3.1 mmHg. Similar and statistically significant reductions of 2% and 4% also were found for resting systolic and diastolic BP in an earlier meta-analysis that excluded static training studies (45).

Progressive Resistance Exercise and Blood Pressure

For the most recent meta-analysis (82) progressive resistance training took place over a mean duration of 16.4 weeks, 2 to 3 days per week at 61% of one-repetition maximum. The mean number of exercises was 10 while the number of sets was 2. Omitting the static study, the number of repetitions ranged from 8 to 25. Ten of the 12 groups (83%) used exercises that involved both the upper and lower body. Three of the 9 studies in the meta-analysis used a circuit training protocol, one used a static protocol, and the remainder used more conventional types of training protocols. No differences in resting systolic and diastolic BP were found between traditional and circuit training protocols.

Significance of Exercise-Induced Reductions in Blood Pressure

Although the reductions in BP as a result of aerobic and progressive resistance training may appear to be small, especially for normotensive and prehypertensive groups, they are clinically significant. It has been estimated that as little as a 2 mmHg reduction in population average resting systolic BP can reduce mortality from coronary heart disease, stroke, and all causes by 4%, 6% and 3%, respectively, while a reduction of 5 mmHg can reduce mortality risk by 9%, 14%, and 7% (83). The potential numbers of annual lives saved in the United States as a result of these reductions has been estimated at 11,800 for a 2 mmHg reduction in resting systolic BP and 27,600 for a 5 mmHg reduction (83).

Question 6. What Is the Relationship Between Physical Activity and Atherogenic Dyslipidemia?

Conclusion

For the purposes of this review, atherogenic dyslipidemia is defined as the presence of abnormally low serum concentrations of high-density lipoprotein (HDL) cholesterol and elevated concentrations of high triglycerides (TG) and small, dense low-density lipoprotein (LDL) cholesterol. The response of serum lipoproteins to changes in habitual physical activity have been well studied. In general, both HDL cholesterol and serum TG reproducibly and favorably respond to changes in habitual physical activity, with increases in HDL cholesterol and decreases in serum TG, mostly related to the volume of exercise training and responding with threshold volumes in the range of 7 to 15 miles per week of regular exercise (equating to an approximate 600 to 800 MET-minutes). Some evidence indicates that women are less responsive than men to change in habitual exercise, perhaps due to the observation that those with the largest baseline abnormalities (lower HDL and higher TG) gain the greatest benefit and men on average have lower HDL and higher TG than do women. However, when weekly volume or energy expenditure is controlled for men and women, the sex-related differences seem to be mitigated. Some inconsistent evidence suggests that LDL cholesterol may respond favorably to exercise training under some conditions; when it does, it is at the same volume thresholds as observed for HDL and TG. Finally, more recent studies have observed that fractionated serum lipoproteins respond

favorably to aerobic exercise training in a dose-response fashion that is related to the weekly volume of exercise.

Rationale

A large volume of information is available on the exercise responsiveness of serum lipoproteins and dose-response effects, much of it accumulated before the 1996 *Surgeon General's Report*. For this review of the literature regarding the relation between habitual exercise and serum lipoproteins, we have relied mostly upon meta-analyses and reviews assembled since 1996. The relevant information is well summarized in 2 relatively recent reviews from Durstine and colleagues (84) and Leon and Sanchez (85). Most of the information before 1996 is based upon responses in total cholesterol and fractionated lipids (i.e., HDL, LDL, and TG). Recently some new information has emerged on the response of lipoprotein sub-fractions to exercise training (86;87).

The response of HDL cholesterol to exercise training traditionally has been well studied. As illustrated in a recent meta-analysis of exercise-induced effects on HDL cholesterol (88), the volume of exercise exposure is the primary determinant of exercise-induced modulations of HDL at a EE threshold of 10 to 12 MET-hours per week. Thus, although some evidence exists that exercise intensity may be related to HDL increasing as a result of exercise, this effect becomes insignificant when total exercise volume is controlled.

Women seem to be more resistant to modulation of TG through exercise interventions than are men, although this is not a consistent finding. In some studies, TG appear to be more responsive to lower volumes of exercise training than the volumes to which HDL is responsive, mimicking the responses in insulin action to which TG levels are closely tied (87). However, the sum of the literature seems to indicate that triglycerides are consistently, reproducibly and robustly responsive to exercise training of volumes that are comparable to those that induce changes in HDL (10 to 20 MET-hours per week) and that moderate-intensity exercise results in more sustained changes in TG than does high-intensity exercise once the training stimulus is removed (87).

LDL cholesterol is generally found not to be responsive to exercise training interventions. However, in the few circumstances when LDL has been observed to be modulated by exercise, it requires approximately 12 MET-hours per week of exercise to favorably influence LDL. Recently, studies of the modulation of fractionated lipoproteins with exercise training have shown that HDL, TG, and LDL size and number are favorably modulated in a dose-response fashion to exercise training related to training volume and that 800 MET-minutes of exercise per week was required for an effect different from that of a sedentary control group, whose LDL parameters tended to worsen over time in the absence of other lifestyle changes (87). More work is needed to understand the magnitude, consistency, and mechanism of these effects.

Question 7: What Is the Relationship Between Physical Activity and Vascular Health?

Conclusion

Habitual aerobic exercise appears to induce favorable responses in measures of vascular health. Exercise training initially increases brachial artery flow-mediated dilation (BAFMD—a measure of endothelial vascular health) with later normalization of BAFMD as vessels become structurally larger. Habitual aerobic exercise appears to slow the progression of age-related central arterial stiffening in healthy subjects. Increased levels of habitual physical activity are associated with slowed progression of carotid intimal medial thickening (CIMT) in cross-sectional and prospective cohort studies. No significant dose-response data are available for any of these measures.

Rationale

This section summarizes the effects of chronic aerobic exercise training on measures of vascular health, including BAFMD, arterial stiffness, and CIMT.

Brachial Artery Flow-Mediated Dilation

Dysfunction of endothelial cells is an early event in the process of atherosclerosis (89), and is associated with risk factors for cardiovascular disease (90-92). These relations have led to the use of endothelium-mediated vascular responsiveness as a surrogate biomarker of vascular health. Brachial artery flow-mediated dilation, a non-invasive measure of endothelial function, has been shown to correlate with measures of coronary artery function (93;94) and independently predicts cardiovascular events in patients with established disease (95-100). Due to its non-invasive nature and relative ease of use, BAFMD has become increasingly used as a research tool to monitor the efficacy of interventions on vascular health.

This section provides a review of the current published data on the effects of exercise training as the primary intervention on BAFMD. A total of 300 abstracts were initially retrieved and reduced to 22 separate intervention groups (57;99;101-119). All data included were from RCTs with a minimum exercise training intervention of at least 1 week and BAFMD data reported at both pre- and post-exercise training. Studies include data from both apparently healthy subjects as well as those with chronic heart failure, obesity, dyslipidemia, coronary heart disease, metabolic syndrome, uncomplicated myocardial infarction, heart transplant, and diabetes.

The results from this literature review provide convincing evidence that exercise training produces significant changes in the vascular health biomarker BAFMD. Figure G2-2 graphically illustrates the effect sizes seen in all intervention groups. Fifteen of the

Figure G2.2. Effect Sizes Seen in Interventions in Which BAFMD Is Used as a Vascular Health Biomarker
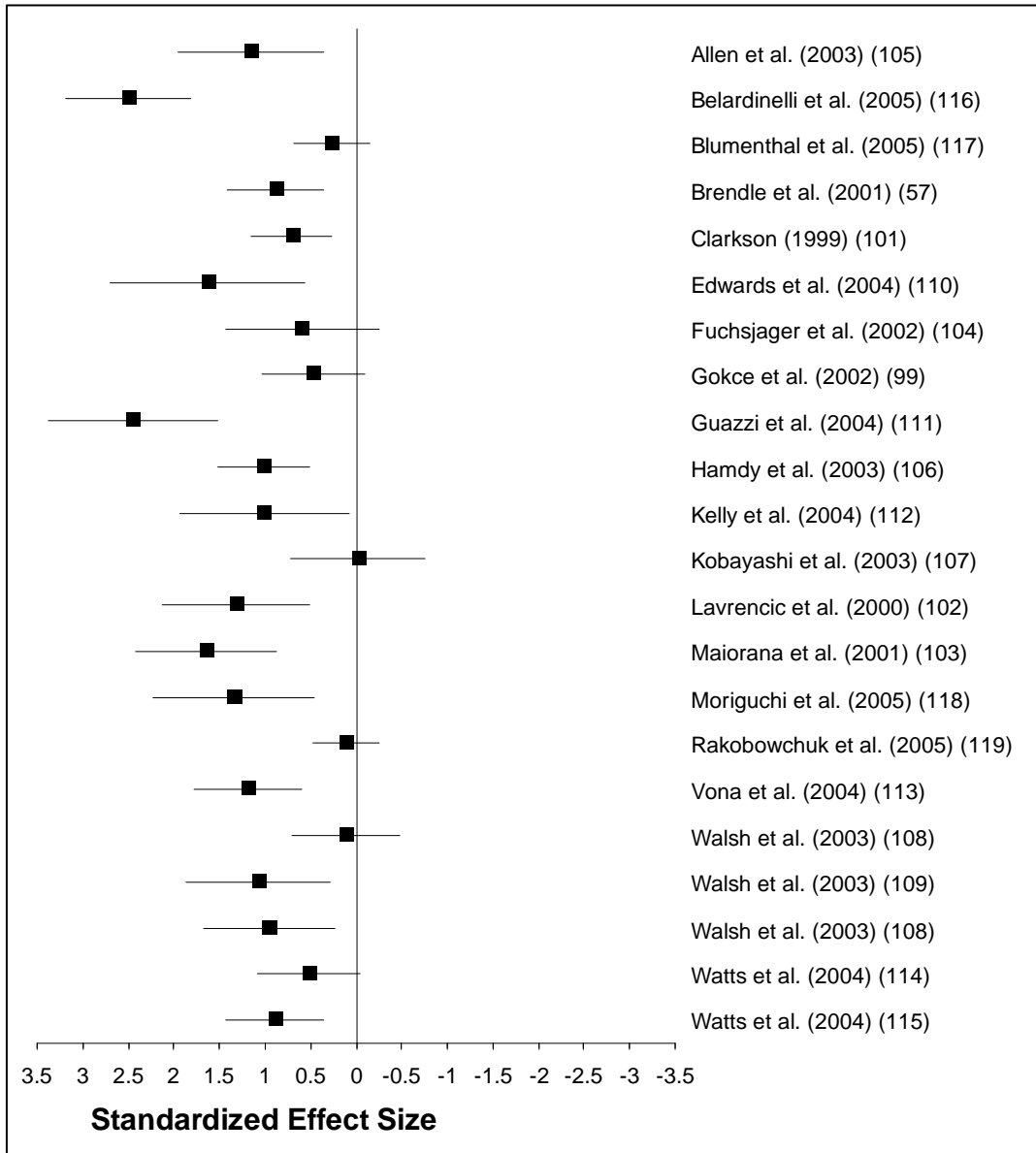
Figure developed from Clark O; Djulbegovic B. Forest plots in Excel software (data sheet). 2001. Available at www.evidencias.com.

Figure G2.2.   Data Points

Upper Limit of the Confidance Interval	Lower Limit of the Confidance Interval	Point Estimate	Studies
1.96	0.36	1.16	Allen et al. (2003) (105)
3.18	1.82	2.5	Belardinelli et al. (2005) (116)
0.69	-0.14	0.27	Blumenthal et al. (2005) (117)
1.42	0.35	0.88	Brendle et al. (2001) (57)
1.15	0.27	0.71	Clarkson (1999) (101)
2.7	0.56	1.63	Edwards et al. (2004) (110)
1.44	-0.25	0.6	Fuchsjager et al. (2002) (104)
1.04	-0.09	0.47	Gokce et al. (2002) (99)
3.38	1.52	2.45	Guazzi et al. (2004) (111)
1.52	0.52	1.02	Hamdy et al. (2003) (106)
1.94	0.08	1.01	Kelly et al. (2004) (112)
0.72	-0.76	-0.02	Kobayashi et al. (2003) (107)
2.12	0.51	1.31	Lavrencic et al. (2000) (102)
2.42	0.88	1.65	Maiorana et al. (2001) (103)
2.23	0.46	1.35	Moriguchi et al. (2005) (118)
0.48	-0.26	0.11	Rakobowchuk et al. (2005) (119)
1.78	0.6	1.19	Vona et al. (2004) (113)
0.71	-0.47	0.12	Walsh et al. (2003) (108)
1.86	0.28	1.07	Walsh et al. (2003) (109)
1.68	0.23	0.96	Walsh et al. (2003) (108)
1.08	-0.04	0.52	Watts et al. (2004) (114)
1.43	0.36	0.89	Watts et al. (2004) (115)

22 intervention groups included in the analysis showed a statistically significant improvement in BAFMD (confidence intervals did not contain zero) in response to exercise training. Of the remaining 7 studies, only one produced a negative effect size (107).

Several factors modulate the magnitude of exercise-induced responses in BAFMD. The most influential of these appears to be health status before the exercise training intervention. That is, the magnitude of BAFMD improvement following training is, in part, a function of the initial or pre-training level. Subjects with cardiovascular disease exhibit greater improvements in BAFMD following exercise training but start with a lower pre-training BAFMD. Apparently healthy subjects also show improvement in BAFMD but not to the same degree as those with cardiovascular disease. The data on apparently healthy subjects come from only 3 studies and so should be interpreted with some caution (101;105;119). Interestingly, age does not appear to influence the magnitude of BAFMD response, suggesting it is modifiable in both young and old.

A second important moderator of response is the type of exercise performed. Changes in BAFMD were noted in most studies regardless of modality. However, the greatest affect was seen in those studies using aerobic exercise alone (14 studies) or in combination with resistance training (6 studies). The evidence for resistance training alone (2 studies) are less convincing, suggesting resistance training by itself may not be as effective in improving BAFMD.

A third moderator of response is length of the training period. Shorter periods of exercise training (8 weeks or less) result in larger changes in BAFMD compared to longer periods of training (more than 8 weeks). This implies that changes in BAFMD occur rapidly after initiating training but may diminish with time. This is consistent with the theory that vascular responses to aerobic exercise training consist of a series of stress-response-adaptation responses, where exercise is the stressor, increased BAFMD is the initial response, and structural vessel enlargement is the eventual adaptation (with subsequent normalization of the BAFMD response) (120).

As noted, the modality-specific (aerobic versus resistance) exercise training responses requires further study. Similarly, the dose-response effects of aerobic exercise training are notably understudied.

Carotid Intimal-Medial Thickening

Most studies on this outcome are prospective or case-control observational studies. Relatively few studies have examined the effects of exercise training on CIMT or progression. From 7 available cross-sectional studies, 4 report lower CIMT in subjects with higher physical activity levels (121;122) or higher VO_{2peak} (123;124). The remaining 3 studies found no difference between active and sedentary groups (125-127). The discrepancies between these study results could be related to differences in age and health of participants, methods of activity measurement and reporting, concomitant lifestyle changes, length of measurement, and differences in the techniques used to quantify CIMT.

The results from interventional studies make it even more difficult to draw definitive conclusions. From 8 available studies (127-134), only 3 appear to have reported the effects of exercise training isolated from other concurrent treatments (127;130;132) and none of these showed significant effects (135). Unfortunately, 2 of these studies were underpowered to detect CIMT progression, and the third was a pharmaceutical trial where exercise served as a control and no changes were observed after 4 years (132).

A lack of adequately powered exercise interventional studies is understandable if one considers the small size of the pooled annual rates of changes in CIMT progression that occur among control groups from randomized placebo-controlled trials. For studies using multiple IMT measures from several interrogation angles and carotid segments, the mean maximum progression rate was 0.0176 millimeters per year with a median SD of 0.05 (136). Given that sample size calculations rely heavily on rates of change, precision of the measurement, and projected effectiveness of the intervention, the subject numbers required and length of exercise training assessment period would have to be much longer than is traditional in such studies. For example, for a 30% treatment effect, average change in mean-max CIMT of 0.0352 ± 0.05 millimeters over 2 years, and using as two-tailed alpha, one would need 468 subjects in each arm of the trial to have 90% power.

Arterial Stiffness

Central arterial stiffening occurs with aging (137) but is often both a consequence and mechanism of atherosclerotic vasculopathy. The investigation of arterial stiffness has increased in recent years due to the development of noninvasive assessment techniques (138-140). However, there appears to be a lack of consensus regarding the most accurate and reliable method to measure arterial stiffness, complicating the determination of the efficacy of exercise training responses. The most frequently reported assessment methodologies are pulse wave velocity, pulse wave analysis, and distensibility/compliance (change in diameter/change in pressure).

Using these outcome measures, habitual aerobic exercise appears to slow the progression of age-related central arterial stiffening in healthy subjects as reported in several cross-sectional studies (137;141-143). Furthermore, 4 training intervention studies report significant improvements in measures of central stiffness across sex and age ranges (141-144). Interestingly, the benefits in central elastic arteries were not replicated in peripheral muscular arteries (142;145), suggesting that training-specific responses, or different mechanisms are active in different arterial beds.

The benefits of short-term aerobic exercise training on central stiffness in patient populations are less clear. One study reported a decrease in aortic pulse wave reflection in chronic hemodialysis patients following 3 months of aerobic training. This measure returned to pre-training levels 1 month after training ceased (detraining) (146). Another showed favorable changes in coronary artery disease subjects within 12 weeks (110), although other studies reported no effects of training in hypertensive (147;148) or diabetic (149) subjects.

Finally, the effects of resistance training on central arterial stiffness are conflicting. Two cross-sectional studies report a decrease in central but not peripheral arterial compliance in comparison to sedentary controls (143;150). In contrast, of 4 available case controlled interventional studies, 2 report increases in measures of central arterial stiffness (151;152) and 2 report no significant effect (153;154). These differences appear to be related to intensity, with higher training intensities eliciting higher central stiffness values. Clearly, large-scale prospective studies are warranted to clarify these discrepancies and to further elucidate the possible mechanisms involved in the observed changes.

Question 8: What Is the Relationship Between Physical Activity and Cardiorespiratory Fitness?

Conclusion

Cardiorespiratory fitness is a sensitive and useful measure of changes in response to physical activity. It demonstrates dose-response relations with overall exercise volume and also with each of the various components of exercise volume (intensity, frequency, duration, and longevity). It appears that one can acquire improvements in cardiorespiratory fitness in bouts as small as 10 minutes each, while holding volume constant. It is unclear whether there is a relation between the duration of exercise bouts and fitness responses, when total volume is held constant, especially for vigorous intensity exercise. Changes in fitness during exercise interventions correspond with changes in cardiovascular risk, but do not always correspond with changes in cardiovascular risk factors.

Rationale

Cardiorespiratory fitness, as measured by a number of relatively simple and inexpensive clinical maneuvers, provides strong and independent prognostic information about overall morbidity and mortality. This relationship extends to men, women, and adolescents. It is valid in apparently healthy individuals; in patients with a broad range of maladies, including several types of cancer and cardiovascular disease; and in at-risk individuals with type 2 diabetes, metabolic syndrome, and hypertension (1;155;156). Fitness is also a marker for functional capacity and ability to perform activities of daily living, especially in older individuals. Finally, it is used as an outcome measure of adherence and physical activity exposure in intervention studies. For example, men who improve their fitness (as assessed by exercise duration) improve their cardiovascular risk. In one report, long-term cardiovascular risk decreased by 8% for every minute increase in exercise capacity (157). Due to the correlation between fitness and health status, the responsiveness to changes in physical activity, and its usefulness as a marker of physical activity levels, cardiorespiratory fitness is an important health outcome measure in and of itself and is often quoted as an outcome in health-related physical activity studies. That said, favorable changes in fitness do not always correspond to change in health outcomes in response to exercise recommendations (158). The data for this section was acquired from an independent literature search of the PubMed database using "cardiorespiratory fitness" as a search term

and identifying meta-analyses and review articles from both the 1996 date to the present and before 1996.

Cardiovascular fitness, as measured by any one of a number of parameters associated with exercise testing (peak VO_2, resting heart rate, lactate level or heart rate at submaximal exercise level, VO_2 at ventilatory threshold, time to exhaustion, and others) is extremely sensitive to changes in physical activity levels and habitual exercise. This is often referred to as a training effect. The training effect shows a strong dose-response relation to changes in exercise pattern of various types. Changes in fitness are dependent upon the frequency, duration, and intensity of exercise bouts and are also dependent upon the longevity of the exercise training program or intervention (reviewed in 3). The product of exercise frequency, bout duration, and intensity over time is often referred to as exercise volume and is proportional to exercise-related energy expenditure. A rich literature exists about the specific relation between the characteristics of exercise exposure and changes in cardiorespiratory fitness in the short and long term (3;4;159;160) in individuals of all ages, including older men and women (161-163). An example of the changes in cardiorespiratory fitness with training programs of various intensities and amounts (volumes) is demonstrated in Figure G2-3 (164). As shown, effects on cardiorespiratory fitness of exercise occur both with increasing intensity at the same volume, and increasing volume at the same intensity. The groups are clearly distinguishable by differences in group mean differences over time. However, it is also clear that baseline fitness and the ability to respond to an exercise intervention have numerous inputs other than physical activity pattern, one of which is genetic (165). Using the same study population as in the previous figure, when individual responses to training stimuli are displayed as individual data points ordered by magnitude of response, it is apparent that the identical stimulus can result in a broad range of responses, from negative to positive (Figure G2-4). That is, even a strong stimulus (high-volume, high-intensity exercise) can result in no significant improvement or even deterioration in cardiorespiratory fitness in some individuals, while resulting in a large magnitude of change, much larger than the group mean, in others. This observation has implications for the construction of physical activity recommendations, depending on whether the goal is to significantly move the population mean (e.g., 50%) or to affect a significant response in the vast majority of individuals, in which case a more robust exposure may be required.

As previously noted, changes in cardiorespiratory fitness in response to an exercise intervention depend upon a number of parameters, including the characteristics of the exercise stimulus, baseline fitness, sex, age, body mass index, and others. In addition, health benefits that accrue with an exercise program are often, but not always, correlated with changes in fitness (160). Two recent studies illustrate the dose-response relations between exercise exposure and fitness, as well as to several seminal cardiovascular risk markers. The results from the DREW (166) and STRRIDE (158;164) studies are summarized in Table G2-2. Cardiorespiratory fitness (peak VO_2) can be expressed in absolute terms (liters of oxygen consumption per minute) or relative to body mass (ml/kg/min). Exercise exposure in volume can be expressed as energy expenditure or as multiples of resting oxygen consumption (METs), times duration (e.g., MET-hour), where 1 MET approximately equals 3.5 ml/kg/min).

Figure G2.3. Changes in Peak VO$_2$ by Exercise Group
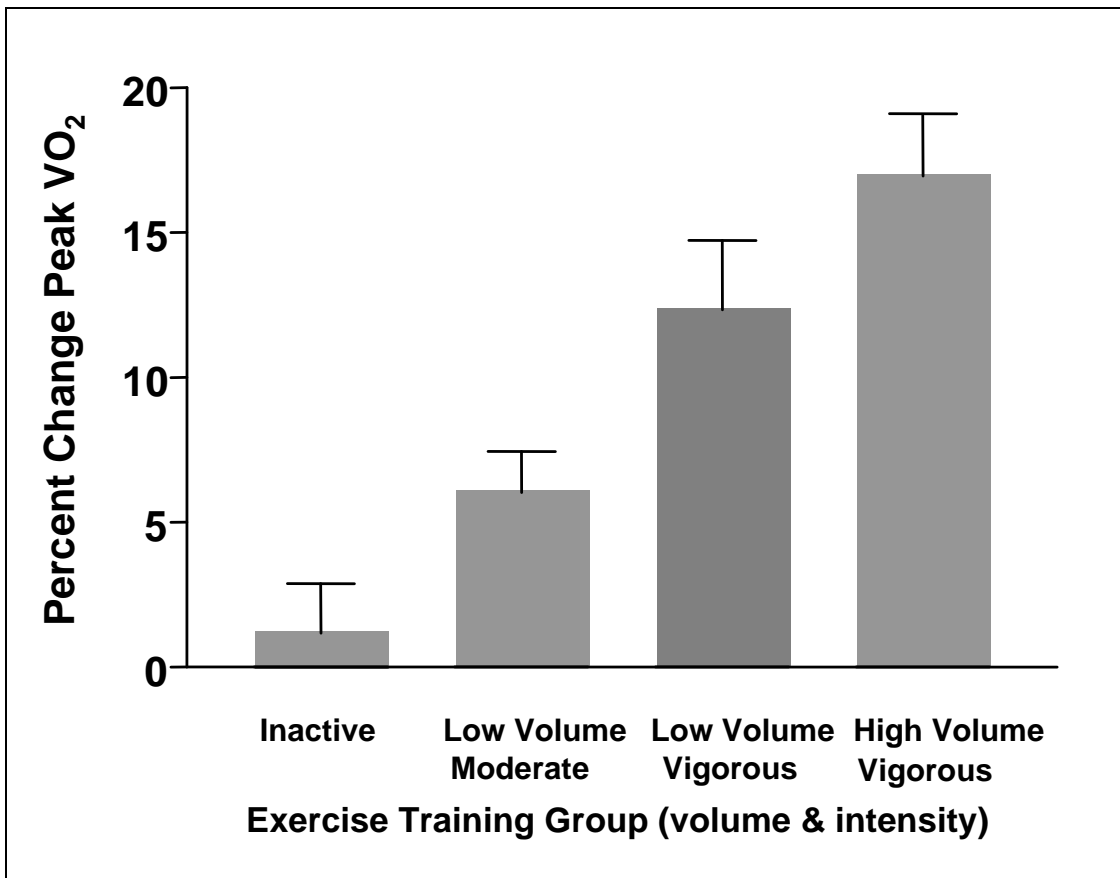
Figure G2.4. Changes in Peak VO$_2$ by Exercise Group and Ordered by Change
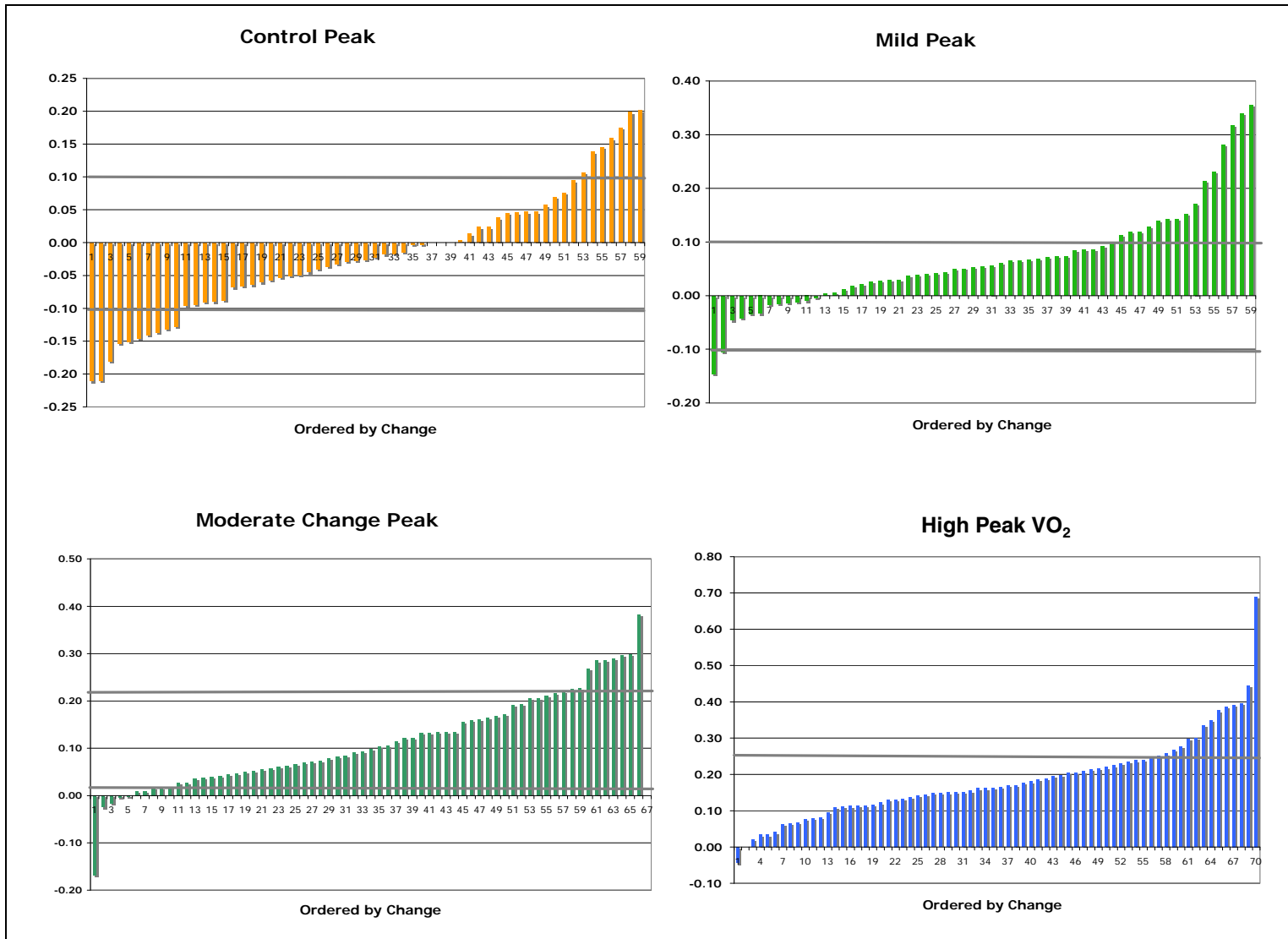
Figure G2.4.   Data Points

Control Peak

RVO_2_1	RVO_2_2	Diff 2-1	1-DX
26.88	21.22	0.79	-0.21
28.7	22.67	0.79	-0.21
24.55	20.13	0.82	-0.18
27.9	23.62	0.85	-0.15
23.8	20.2	0.85	-0.15
31.5	26.9	0.85	-0.15
29.55	25.4	0.86	-0.14
25.71	22.2	0.86	-0.14
35	30.4	0.87	-0.13
39.7	34.6	0.87	-0.13
29.4	26.6	0.90	-0.10
29.27	26.52	0.91	-0.09
25.3	23	0.91	-0.09
30.85	28.08	0.91	-0.09
20.4	18.6	0.91	-0.09
20.5	19.1	0.93	-0.07
42.4	39.6	0.93	-0.07
21.9	20.5	0.94	-0.06
32.39	30.44	0.94	-0.06
35.3	33.3	0.94	-0.06
28.1	26.6	0.95	-0.05
29.3	27.8	0.95	-0.05
37.77	35.9	0.95	-0.05
25.1	23.97	0.95	-0.05

RVO_2_1	RVO_2_2	Diff 2-1	1-DX
27.6	26.5	0.96	-0.04
27.2	26.2	0.96	-0.04
21.4	20.7	0.97	-0.03
15.17	14.73	0.97	-0.03
36	35	0.97	-0.03
22.8	22.2	0.97	-0.03
30.69	30	0.98	-0.02
33.7	33.1	0.98	-0.02
28.5	28	0.98	-0.02
26.8	26.4	0.99	-0.01
33.5	33.4	1.00	0.00
34.9	34.8	1.00	0.00
21.6	21.6	1.00	0.00
26.5	26.5	1.00	0.00
27	27	1.00	0.00
26	26.1	1.00	0.00
37.3	37.8	1.01	0.01
21	21.5	1.02	0.02
29.4	30.1	1.02	0.02
18.7	19.4	1.04	0.04
17.9	18.7	1.04	0.04
34.98	36.57	1.05	0.05
21.3	22.3	1.05	0.05
21.3	22.3	1.05	0.05

RVO_2_1	RVO_2_2	Diff 2-1	1-DX
24.4	25.8	1.06	0.06
23.1	24.7	1.07	0.07
30.4	32.7	1.08	0.08
17.57	19.23	1.09	0.09
25.3	28	1.11	0.11
21	23.9	1.14	0.14
24.1	27.6	1.15	0.15
25.8	29.9	1.16	0.16
19.81	23.27	1.17	0.17
18.1	21.7	1.20	0.20
22.4	26.9	1.20	0.20
27.9			
21.4			
33.8			
22.5			
22.7			
23.5			
28.6			
19.1			
33.6			
	32.75		
28.7			
33.43			
19.2			

Figure G2.4. Data Points (continued)

Mild Peak

RVO_2_1	RVO_2_2	Diff 2-1	1-DX
23.9667	20.4667	0.85	-0.15
24.3333	21.7667	0.89	-0.11
30.6	29.2	0.95	-0.05
43	41.2	0.96	-0.04
20.5667	19.8667	0.97	-0.03
33.2966	32.1774	0.97	-0.03
29.6	29.1	0.98	-0.02
26.3	25.9	0.98	-0.02
22.1	21.8	0.99	-0.01
32.5	32.1	0.99	-0.01
21.3067	21.1	0.99	-0.01
26.4	26.3	1.00	0.00
23.8	23.9	1.00	0.00
18.1	18.2	1.01	0.01
24.8	25.1	1.01	0.01
27.6	28.1	1.02	0.02
24	24.5	1.02	0.02
42.5	43.6	1.03	0.03
22.2	22.8	1.03	0.03
31.3	32.2	1.03	0.03
24.815	25.5333	1.03	0.03
21.7	22.5	1.04	0.04
33.5	34.8	1.04	0.04
27.6	28.7	1.04	0.04
23.8833	24.8667	1.04	0.04
21.3	22.2	1.04	0.04
30.6	32.1	1.05	0.05
35.7	37.5	1.05	0.05
24.6	25.9	1.05	0.05

RVO_2_1	RVO_2_2	Diff 2-1	1-DX
29.3	30.9	1.05	0.05
21.2	22.4	1.06	0.06
26.5	28.1	1.06	0.06
26.1	27.8	1.07	0.07
35	37.3	1.07	0.07
28.5	30.4	1.07	0.07
21.5907	23.0738	1.07	0.07
22.5	24.1	1.07	0.07
30.3	32.5	1.07	0.07
24.6	26.4	1.07	0.07
33.4	36.2	1.08	0.08
38.4	41.7	1.09	0.09
26.4373	28.7136	1.09	0.09
21.9033	23.9333	1.09	0.09
18	19.8	1.10	0.10
29.4755	32.803	1.11	0.11
31.4	35.1	1.12	0.12
19.5	21.8	1.12	0.12
24.1	27.2	1.13	0.13
17.84	20.3333	1.14	0.14
33.2833	38	1.14	0.14
26.5213	30.2995	1.14	0.14
20.1333	23.2	1.15	0.15
39.1	45.8	1.17	0.17
21.5	26.1	1.21	0.21
30	36.9	1.23	0.23
19.3667	24.8	1.28	0.28
24.6	32.4	1.32	0.32
22.023	29.503	1.34	0.34

RVO_2_1	RVO_2_2	Diff 2-1	1-DX
22.8	30.9	1.36	0.36
17.7			
19.7			
24			
29.8			
21.3			
26.9			
22.3			
20.2			
24.3			
27.9			
26			
28			
20.8			
32.1			
27.3			
26.6			
26.3			
20.5			
22			
27.2			
22.4			
23.52			
17.94			
27.24			
27.89			
20.22			
33.6			
27.33			
22.35			

Figure G2.4. Data Points (continued)

Moderate Change Peak

RVO$_2$_1	RVO$_2$_2	Diff 2-1	1-DX
28.3712	23.6123	0.83	-0.17
29.3333	28.6	0.98	-0.02
23.8	23.4	0.98	-0.02
26.8	26.7	1.00	0.00
35.7	35.6	1.00	0.00
21.5	21.7	1.01	0.01
26.7667	27.0333	1.01	0.01
37.2	37.8	1.02	0.02
36.3	36.9	1.02	0.02
39.3	40	1.02	0.02
39.7	40.8	1.03	0.03
32.4	33.3	1.03	0.03
35.1	36.4	1.04	0.04
20.7	21.5	1.04	0.04
25	26	1.04	0.04
33.188	34.5905	1.04	0.04
27	28.2	1.04	0.04
27.7	29	1.05	0.05
33.3	35	1.05	0.05
36.4	38.3	1.05	0.05
32.5	34.3	1.06	0.06
31.4333	33.2333	1.06	0.06
39.6	42	1.06	0.06
35.1	37.3	1.06	0.06
34.4	36.7	1.07	0.07
34.4	36.8	1.07	0.07
31.7	34	1.07	0.07
24.4	26.2	1.07	0.07
38.3	41.3	1.08	0.08
20.7	22.4	1.08	0.08

RVO$_2$_1	RVO$_2$_2	Diff 2-1	1-DX
35.5	38.5	1.08	0.08
24	26.2	1.09	0.09
23.7	25.9	1.09	0.09
25.0233	27.5	1.10	0.10
26.1	28.8	1.10	0.10
25.4	28.1	1.11	0.11
33.1	36.9	1.11	0.11
31.2	35	1.12	0.12
28.6	32.1	1.12	0.12
30.2	34.2	1.13	0.13
34.0955	38.633	1.13	0.13
23.1	26.2	1.13	0.13
19.3	21.9	1.13	0.13
37.1	42.1	1.13	0.13
24.4	28.2	1.16	0.16
32.8	38	1.16	0.16
22.1533	25.7333	1.16	0.16
36.5	42.5	1.16	0.16
34	39.7	1.17	0.17
26.2	30.7	1.17	0.17
24	28.6	1.19	0.19
20.2	24.1	1.19	0.19
23.8	28.7	1.21	0.21
25.378	30.603	1.21	0.21
34.9	42.3	1.21	0.21
17.5	21.3	1.22	0.22
26.4	32.2	1.22	0.22
21.3	26.1	1.23	0.23
34.8	42.7	1.23	0.23
28	35.5	1.27	0.27

RVO$_2$_1	RVO$_2$_2	Diff 2-1	1-DX
31.9	41	1.29	0.29
30.4	39.1	1.29	0.29
27.2	35.1	1.29	0.29
35.9016	46.5667	1.30	0.30
25.8	33.5	1.30	0.30
19.64	27.1667	1.38	0.38
17.8155	31.978	1.79	
21			
23.1			
22.8			
20.5			
19.3			
22.9			
31.3			
28.4			
23.9			
22.7			
17.3			
38.4			
37.5			
41.8			
37			
23			
26.1			
39.9			
33.1			
24.3			
22.3			
26			
21.9			

RVO$_2$_1	RVO$_2$_2	Diff 2-1	1-DX
24.7			
35.4			
24.3			
32.9			
24.1			
25			
37.8			
37.4			
36.2			
27.2			
26.1			
26.6			
22.3			
20.7			
21			
27.4			
23.9			
21.8			
37.16			
26.8			
23.73			
22.9			
34.9			
15.8			
31.8			
26.04			
12.2			
17.81			
21.56			
18.01			

Figure G2.4. Data Points (continued)

High Peak VO$_2$

RVO$_2$_1	RVO$_2$_2	Diff 2-1	1-DX	RVO$_2$_1	RVO$_2$_2	Diff 2-1	1-DX	RVO$_2$_1	RVO$_2$_2	Diff 2-1	1-DX	RVO$_2$_1	RVO$_2$_2	Diff 2-1	1-DX
31.2714	29.8931	0.96	-0.04	25.5	29.3	1.15	0.15	21.3	26.4	1.24	0.24	35			
24.2333	24.24	1.00	0.00	22.4267	25.8	1.15	0.15	31.4	39.2	1.25	0.25	19.1			
24.7	25.2	1.02	0.02	23.9	27.5	1.15	0.15	20.2355	25.323	1.25	0.25	26.5			
38.5	39.8	1.03	0.03	21.8	25.1	1.15	0.15	30.3	38.1	1.26	0.26	16.8			
30.69	31.7367	1.03	0.03	19.933	23.013	1.15	0.15	34.2	43.4	1.27	0.27	30.6			
29.6	30.8	1.04	0.04	29.7	34.5	1.16	0.16	23.5	30	1.28	0.28	37.3			
36.9	39.2	1.06	0.06	31.5	36.6	1.16	0.16	25.158	32.6655	1.30	0.30	18.8			
35.3	37.6	1.07	0.07	26.5	30.8	1.16	0.16	33.3	43.3	1.30	0.30	30.9			
31.6	33.7	1.07	0.07	36.4	42.4	1.16	0.16	26.3	35.1	1.33	0.33	30.5			
34.1965	36.8	1.08	0.08	30.1	35.2	1.17	0.17	29.5	39.8	1.35	0.35	27.9			
32.75	35.3333	1.08	0.08	21.8	25.5	1.17	0.17	29.9333	41.2	1.38	0.38	27.3			
26.1	28.2	1.08	0.08	21.5	25.3	1.18	0.18	30.4357	42.2	1.39	0.39	21.6			
31.7	34.7	1.09	0.09	29.9	35.3	1.18	0.18	33.2	46.2	1.39	0.39	20.9			
20.2	22.4	1.11	0.11	19.4	23	1.19	0.19	22	30.7	1.40	0.40	23.9			
25.0167	27.8	1.11	0.11	34.6	41.1	1.19	0.19	28.1	40.6	1.44	0.44	23.7			
21.8615	24.3222	1.11	0.11	19.5	23.3	1.19	0.19	17.1	28.9	1.69	0.69	38.63			
34.3	38.2	1.11	0.11	24.8	29.7	1.20	0.20	14.5				25.33			
29.7643	33.1667	1.11	0.11	32.2	38.8	1.20	0.20	17.8				21.34			
27.3	30.5	1.12	0.12	30.8533	37.2	1.21	0.21	27.2				27.12			
24.5333	27.5333	1.12	0.12	20.2	24.4	1.21	0.21	21.3				13.95			
31.5	35.6	1.13	0.13	25.3	30.7	1.21	0.21	18.3				23.39			
23.7	26.8	1.13	0.13	24.13	29.35	1.22	0.22	26.9				26			
30.5	34.55	1.13	0.13	32.3	39.4	1.22	0.22	25.6				27.16			
32.4667	36.9	1.14	0.14	32.3667	39.6333	1.22	0.22	23.9				26.89			
27.3	31.2	1.14	0.14	35.9	44.2	1.23	0.23	26.3				18.79			
28.3	32.4	1.14	0.14	33.3	41.1	1.23	0.23	32.7				22.6667			
36.1633	41.5333	1.15	0.15	30.6	37.9	1.24	0.24	27.8							

Table G2.2. Table of Baseline Characteristics, Exercise Prescriptions, Training Programs, and Outcome Measures in Two Randomized Controlled Aerobic Exercise Training Studies

Women: DREW (N~120) *

Group Prescriptions Training Volume (kcal/kg/wk)	Group Prescriptions Training Intensity (Percent Peak VO₂)	Baseline Peak VO₂ (mL/kg/min)	Training Program Training Prescription (MET-hr/wk)	Training Program Training Prescription (MET-min/wk)	Training Program Training METs	Training Program Training Minutes per Week	Change in Peak VO₂	Outcomes Change in Relative Peak VO₂ (mL/kg/min)	Outcomes Change in Peak VO₂ (METs)	Outcomes Change in Body Mass Index	Outcomes Change in Waist Circumference	Outcomes Change in Blood Pressure	Outcomes Change in Blood Blood Lipids	Outcomes Change in FBG/ISI
4.0	50%	15.5	3.8	229	2.2	72	4.5%	0.70	0.20	NS	Decrease	NS	NS	NS
8.0	50%	14.9	7.6	457	2.2	136	7.0%	1.04	0.30	NS	Decrease	NS	NS	NS
12.0	50%	16.0	11.4	685	2.3	192	8.5%	1.36	0.39	NS	Decrease	Decr. SBP	NS	NS

Women: STRRIDE (N~30) †

Group Prescriptions Training Volume (kcal/kg/wk)	Group Prescriptions Training Intensity (Percent Peak VO₂)	Baseline Peak VO₂ (mL/kg/min)	Training Program Training Prescription (MET-hr/wk)	Training Program Training Prescription (MET-min/wk)	Training Program Training METs	Training Program Training Minutes per Week	Change in Peak VO₂	Outcomes Change in Relative Peak VO₂ (mL/kg/min)	Outcomes Change in Peak VO₂ (METs)	Outcomes Change in Body Mass Index	Outcomes Change in Waist Circumference	Outcomes Change in Blood Pressure	Outcomes Change in Blood Blood Lipids	Outcomes Change in FBG/ISI
14.0	50%	23.4	13.3	800	3.3	193	6.5%	1.52	0.43	NS	NS	NS	Decr. TG	Lg. Incr. ISI
14.0	75%	23.9	13.3	800	5.1	134	14.3%	3.42	0.98	NS	NS	NS	NS	Incr. ISI
23.0	75%	24.1	21.9	1,314	5.2	195	16.4%	3.95	1.13	Decrease	Decrease	NS	NS	Incr. ISI

Men: STRRIDE (N~30) †

Group Prescriptions Training Volume (kcal/kg/wk)	Group Prescriptions Training Intensity (Percent Peak VO₂)	Baseline Peak VO₂ (mL/kg/min)	Training Program Training Prescription (MET-hr/wk)	Training Program Training Prescription (MET-min/wk)	Training Program Training METs	Training Program Training Minutes per Week	Change in Peak VO₂	Outcomes Change in Relative Peak VO₂ (mL/kg/min)	Outcomes Change in Peak VO₂ (METs)	Outcomes Change in Body Mass Index	Outcomes Change in Waist Circumference	Outcomes Change in Blood Pressure	Outcomes Change in Blood Blood Lipids	Outcomes Change in FBG/ISI
14.0	50%	30.0	13.3	800	4.3	161	7.4%	2.22	0.63	Decrease	Decrease	NS	Decr. TG	Lg. Incr. ISI
14.0	75%	33.6	13.3	800	7.2	99	11.2%	3.76	1.08	NS	Decrease	NS	NS	Incr. ISI
23.0	75%	31.0	21.9	1,314	6.6	152	20.0%	6.20	1.77	Decrease	Decrease	Decr. SBP	Incr. HDL/ Decr. TG	Lg. Incr. ISI

Table G2.2.   Table of Baseline Characteristics, Exercise Prescriptions, Training Programs, and Outcome Measures in Two Randomized Controlled Aerobic Exercise Training Studies (continued)

Men and Women: STRRIDE (N~60) [†]

Group Prescriptions Training Volume (kcal/kg/wk)	Group Prescriptions Training Intensity (Percent Peak VO$_2$)	Baseline Peak VO$_2$ (mL/kg/min)	Training Program Training Prescription (MET-hr/wk)	Training Program Training Prescription (MET-min/wk)	Training Program Training METs	Training Program Training Minutes per Week	Change in Peak VO$_2$	Outcomes Change in Relative Peak VO$_2$ (mL/kg/min)	Outcomes Change in Peak VO$_2$ (METs)	Outcomes Change in Body Mass Index	Outcomes Change in Waist Circumference	Outcomes Change in Blood Pressure	Outcomes Change in Blood Blood Lipids	Outcomes Change in FBG/ISI
14.0	50%	26.8	13.3	800	3.8	176	7.0%	1.88	0.54	NS	Decrease	NS	Decr. TG	Lg. Incr. ISI
14.0	75%	29.1	13.3	800	6.2	116	12.6%	3.67	1.05	NS	Decrease	NS	NS	Incr. ISI
23.0	75%	28.2	21.9	1,314	6	170	18.5%	5.22	1.49	Decrease	Decrease	NS	Incr. HDL/ Decr. TG	Lg. Incr. ISI

* Church, JAMA, 2007 (166)
[†] Duscha, Chest, 2005 (164); Johnson, Am J Cardiol, 2007 (158)
Decr., decreased; FBG, fasting blood glucose; HDL, high-density lipoprotein cholesterol; Incr., increase; ISI, insulin sensitivity index, a parameter of insulin sensitivity derived from a frequently sampled glucose tolerance test; lg., large; MET, metabolic equivalent; NS, not significant; SBP, systolic blood pressure; TG, triglycerides.

Similarly, changes in fitness in response to an exercise intervention can be expressed in percent change or absolute change. Examples of each of these in the two study populations are illustrated in this table. Because relative VO_2 is normalized to body mass, it is relatively sensitive to changes in body mass during interventions. The observation that relative fitness measures (relative peak VO_2) at baseline are 50% lower in DREW women than in STRRIDE women, may be due in part to the higher BMIs of DREW women (30-40 kg•m^{-2}) than in STRRIDE women (25-30 kg•m^{-2}) and demonstrates the sensitivity of maximal fitness measures, and exercise prescriptions when expressed as a percentage of baseline fitness to BMI. However, the difference in body mass between the women in these two study groups does not completely account for the differences in cardiorespiratory fitness, as the mean absolute peak VO_2 for women in DREW was approximately 1.2 L/min and 1.8 L/min in STRRIDE women. Similarly, women generally have lower cardiorespiratory fitness than do men and, therefore, the same relative intensity of exercise (e.g., 50% peak VO_2) represents a lower energy expenditure in women than it does in men. Relative percent increases in fitness in response to a fixed intervention is highly dependent on baseline fitness level, although absolute fitness measures are not. Finally, it is apparent that fitness changes do not correlate with all outcome measures in a monotonic and linear fashion (e.g., insulin sensitivity). Examination of these two studies in combination seem to indicate that at least 800 MET-minutes per week of physical activity are required to produce improvements in health outcomes, irrespective of the relative percent increases in cardiorespiratory fitness.

Effects of Daily Fractionization (Accumulation) of Exercise Bouts on Cardiorespiratory Fitness and Cardiovascular Health

Many groups are highly interested in whether multiple short bouts of exercise (e.g., 3 bouts of 10 minutes) is equivalent to one long bout (e.g., 1 bout of 30 minutes) per day for improving fitness levels. It should be evident that the choice of interval over which one integrates and accumulates a physical activity exposure (e.g., day, week, month, or year) is somewhat artificial, but interest remains in the issue of whether the benefits of activity are the same when total daily activity is divided over the course of the day. Several investigators have compared short versus long exercise regimens in an attempt to address this question (167-179). Data for this section were obtained from a literature search. From the appendix table (Table G2-A9, which summarizes these studies, can be accessed at http://www.health.gov/paguidelines/report/), it is apparent that these studies do not provide a clear answer to effects on cardiorespiratory fitness. Among these 11 studies, a single long bout of exercise was superior to multiple daily bouts in 3 studies of improving cardiorespiratory fitness. Multiple, shorter bouts were more effective in 2 studies, no difference was observed in 5 studies, and 1 study reported no improvement in either single long or multiple short exercise bouts. A pattern does appear to form within the few well-designed studies, however. It appears that both single long bouts and multiple shorter bouts of aerobic exercise training do elicit significant improvements in fitness, and that the evidence is relatively strong that comparable fitness responses can be achieved with different fractionization of the volume, given that the daily volume of the exposure is the same.

Several factors likely play a role in the variability of the findings. Careful analysis of demographics and methods of each study indicate that the populations under study differ widely, from college students to middle aged and overweight individuals. It is possible that the more sedentary an individual is at baseline (e.g., the lower the peak VO_2), the less a difference is observed in fitness responses when the exposure is fractionated over the course of the day. This may be due to the fact that less fit individuals are exercising at lower absolute intensities (e.g., walking) and that fractionation has less influence on fitness responses when the intensity of the exercise is lower. If true, then as fitness levels increase, fitness responses should be more dependent on how the exposure is fractionated. This concept has not been tested but begs for further work.

Second, these studies differed quite a bit in exercise exposures (e.g., intensity, frequency). The intervention length ranges from 8 weeks to 18 weeks, while the intensity varies from 50% to 60% of predicted heart rate maximum to 70% to 80% of heart rate reserve. This variation is reflected in the large range of fitness changes reports, from no change to as much as 19% improvement. For example, in a study of young college students who trained at 50% to 60% of predicted heart rate maximum, no improvement in cardiorespiratory fitness was reported. It is very possible that the exercise exposure was not adequate for this population. That is, it is possible that one cannot distinguish the differences in responses between long and short bout activities when the total volume of the stimulus is insufficient to generate optimal responses—for example, where the total exercise time is fixed at 30 minutes of moderate-intensity activity, and a longer period of moderate-intensity activity or the same period of vigorous-intensity activity might better distinguish the responses to bout duration when total exercise volume is held constant. Moreover, although these studies report their results as fitness gains, not all studies use the same fitness measures. Many of the studies do not perform a maximal exercise test and only extrapolate a maximal value based upon a sub-maximal test.

Third, the other outcomes in these studies, cardiovascular risk markers, such as lipids, glucose control, and others show various responses to the interventions. When responses differ, the continuous exposure regimens seem to have more favorable outcomes than do fractionated regimens, although the data are too limited to provide a reliable estimate of the effects of fractionated exercise on such outcomes.

Overall Summary and Conclusions

The weight of evidence points toward a favorable relation between increases in habitual dynamic aerobic exercise and cardiovascular health outcomes, including coronary heart disease morbidity and mortality, stroke, control of blood pressure, atherogenic dyslipidemia, vascular function measures, and cardiorespiratory fitness. In addition, dynamic aerobic exercise is considered a standard of therapy for increasing functional performance in peripheral arterial disease. In many of these outcomes, including cardiovascular morbidity and mortality, there appears to be a more favorable response with increasing intensity of exercise bouts, although exercise volume is poorly controlled in some studies and may be

the important mediating exercise parameter. Also, the more powerful relation between exercise intensity and outcomes does not hold for all outcomes in experimental studies, especially when weekly volume or energy expenditure is held constant (160). In many, if not most, cardiovascular outcomes, favorable responses are notable and reproducible when the volume of physical activity exceeds 800 MET-minutes per week. A combination of endurance exercise bouts with different intensities, durations, and frequencies per day and week can achieve this level of exercise, which is approximately equivalent to 12 miles per week of walking or jogging at any intensity. As energy expenditure at a given perceived intensity is highly dependent upon baseline fitness level, sex, and type of activity, a volume target can be individualized with adjustment of bout intensity, duration, and frequency, both initially and as greater fitness levels are achieved. Given that more volume is likely to result in greater benefits but also higher injury and cardiovascular risk, the ultimate volume goal should be approached gradually upon the initiation of a program, especially in initially sedentary individuals.

Research Needs

In the course of reviewing the literature that contributed to the information presented in this chapter, several significant deficiencies in the published literature became apparent. More information addressing the following issues would have significantly improved the information base used to formulate physical activity recommendations. The Cardiorespiratory Health subcommittee encourages governmental agencies to highlight research in these areas before the next iteration of the *Physical Activity Guidelines for Americans.*

1. What is the time course of acquisition of the cardiovascular health benefits resulting from increases in habitual physical activity?

2. What are the cardiovascular health benefits of varying exercise bout duration, frequency, and intensity, while controlling for total volume?

3. What effect does daily exercise exposures accumulated in short bouts have on the acquired cardiovascular health benefits of habitual physical activity?

4. What are the effects of resistance training on cardiovascular health and what is the nature of dose-response effects (varying intensity, bout volume, and frequency of programs)?

5. Are there sex differences in cardiovascular health benefits of habitual exercise when controlling for volume?

6. What are the specific harmful effects of physical inactivity on cardiovascular health?

7. Are there responses that differ by ethnic and racial minority differences?

8. What are the specific effects of aerobic training, resistance training, and a combination on selected biomarkers of vascular health, such as brachial artery flow-mediated dilation? What are the dose-response effects?

9. What are the main characteristics of an exercise program for preventing and treating peripheral artery disease? What are the exercise dose-response patterns, sex differences, exercise modality options, and differential effects on diabetic patients with PAD, on asymptomatic patients, and are there biomarkers to predict exercise responders?

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