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RESPIRATORY INFECTION

ABSTRACT & COMMENTARY

South African Geranium for Bronchitis in Children and Adolescents: Just What the Doctor Ordered?

By *Craig Schneider, MD*

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Dr. Schneider reports no financial relationships relevant to this field of study.

SOURCE: Kamin W, et al. Treatment of acute bronchitis with EPs 7630: Randomized, controlled trial in children and adolescents. *Pediatr Int* 2012;54:219-226.

Acute bronchitis — inflammation of the large airways presenting with cough — is one of the most common diagnoses seen in primary care. Usually caused by viral infections, it is self-limited and antibiotics generally are not recommended. Safe and effective alternative treatments for this common condition would be a welcome addition for busy clinicians and their suffering patients.

The authors randomized 220 patients between the ages of 1 and 18 with acute bronchitis symptoms beginning less than 48 hours prior to assessment to receive either a standardized ethanolic root extract (1:8-10, 11% ethanol) of *Pelargonium sidoides*

(South African geranium) designated EPs 7630 or a matched placebo. There were no significant demographic or anthropometric data differences between the groups. Over the next 7 days, patients ages 1-6 years received 10 drops three times daily (TID), ages 7-12 received 20 drops TID, and ages 13-18 received 30 drops TID. Investigators and patients were blinded to treatment. Examinations were performed at the first visit, between days 3-5, and again on day 7.

Investigator-rated change in bronchitis severity score (BSS) (total score for severity of cough, pulmonary rales, and dyspnea using a 5-point rating scale from absent to very severe) from day 0 to day 7 constituted

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the primary efficacy variable. Secondary variables included change in individual symptoms within the BSS, and change in general symptoms including lack of appetite, headache, vomiting, diarrhea, onset of treatment effect, health status, and quality of life using the FGK questionnaire (used in Germany to assess health status of children). Treatment outcomes were assessed by both patient (or caregiver) and investigator using the Integrative Medicine Outcomes Scale (IMOS), a 5-point rating scale (complete recovery, major improvement, slight-to-moderate improvement, no change, deterioration). Satisfaction with treatment was assessed using the Integrative Medicine Patient Satisfaction Scale, a 5-point rating scale (very satisfied, satisfied, undecided, dissatisfied, very dissatisfied) completed by patient or caregiver. Additional secondary endpoints included duration of bed rest and ability to attend kindergarten, school, or work. Investigators monitored adverse events, vital signs, and laboratory safety parameters.

All patients were included in safety, tolerability, and efficacy analysis using intention-to-treat principles. Only two patients dropped out of each group. Antibiotics eventually were prescribed in five patients treated with EPs 7630 and three in the placebo group.

BSS scores dropped by 4.4 ± 1.6 in the EPs 7630 group between day 0 and day 7, vs a drop of 2.9 ± 1.4 points in the placebo group ($P < 0.0001$, analysis of covariance). The results were significant in each age group. For cough and pulmonary rates, the mean reduction in BSS from day 0 to day 7 was greater in the EPs 7630 group ($P < 0.0001$, two-sided t-test, each, confidence interval 95%). Of the other general symptoms, only lack of appetite improved significantly in the EPs 7630 group ($P = 0.0003$, two-sided t-test). Patients and caregivers reported onset of treatment effect significantly earlier in the EPs 7630 group compared to placebo ($P < 0.0001$, two-sided Mantel-Haenszel X^2 -test). At day 7, the EPs 7630 group reported significantly better IMOS scores than placebo group ($P < 0.0001$, two-sided Mantel-Haenszel X^2 -test) with

similar assessments by both patients and investigators. Satisfaction of patients receiving EPs 7630 also was significantly higher than placebo ($P < 0.0001$, two-sided Mantel-Haenszel X^2 -test).

Improvement of health status and quality of life as assessed by FKG improved for both groups, with improvement only statistically significant for the EPs 7630 group for the item "I am feeling ill" ($P = 0.0485$, two-sided t-test). At the beginning of the study, the authors report that no patients in the EPs 7630 group and only one in the placebo group was able to attend kindergarten, school, or work. By day 7, 64 patients (57.7%) in the EPs 7630 group, but only 19 patients (17.4%) of the placebo group were back to kindergarten, school, or work.

Three non-serious, adverse effects in two of the 111 patients in the EPs 7630 group were reported, and a causal relationship was excluded for each. "Only marginal group differences" were noted in clinical laboratory parameters, but no specifics were reported.

COMMENTARY

Acute bronchitis is a clinical diagnosis that, although usually not serious, is an uncomfortable experience for patients and a frequent cause of lost days at school and work (for patients and their caregivers). If, as suggested by the authors, taking EPs 7630 speeds return to school and work as significantly as reported in this study, this could make an enormous positive socioeconomic impact if it were widely used.

This study appears well-designed and carefully conducted. Acknowledged weaknesses include use of outcomes that are subjective and measurement instruments that are not validated. EPs 7630 does possess documented plausible mechanisms of action for its use in treating bronchitis. These include stimulation of tumor necrosis factor and interleukin release, as well as enhanced interferon and natural killer cell activity, increased phagocytosis, and reduced bacterial adhesion.¹ EPs 7630 is also reportedly mucolytic and improves cilia function in vitro.

Summary Points

- EPs 7630 appears to be safe and effective in children ages 1-18 years with acute bronchitis when used as directed for 7 days.
- Children in the treatment group were able to return to kindergarten, school, or work significantly earlier than those in the placebo group.
- In the United States, EPs 7630 is sold by Nature's Way as Umcka ColdCare (numerous products available, varying dosages) and by Integrative Therapeutics as ViraClear EPs 7630 (a 1X homeopathic preparation).

The results of this study are consistent with most of the other published work looking at EPs 7630.^{2,3} However, as with most studies on this product, conflict of interest is apparent, with financial support for it coming directly from Dr. Willmar Schwabe GmbH & Co KG, Karlsruhe, Germany, the manufacturer of EPs 7630. The population studied was located in Russia and it is possible that patterns of infection, and illness behaviors including time before return to work and home care measures, may vary compared to those in other parts of the globe.

Although we do not know about long-term safety, the recommended 7-day course appears to be safe and well-tolerated. It is not yet known if EPs 7630 is safe to use in pregnancy or lactation, and thus it should not be recommended in this population.

There is widespread agreement in the health care community that routine antibiotic treatment is not recommended for uncomplicated acute bronchitis unless *Bordetella pertussis* is suspected. However,

providers often feel pressured by patients and their caregivers to provide antibiotics, and this often becomes a time-consuming process of education if not a struggle that can lead to challenges in the provider-patient relationship. Safe and effective nonantibiotic treatments for common viral conditions would be a welcome addition for busy clinicians and their suffering patients.

In adults, symptomatic care with over-the-counter cough and cold preparations are often recommended, but we also know that such preparations (antitussives, antihistamines, decongestants, and their combinations) are not more effective than placebo in children. The FDA recommends these not be used at all in children younger than 2 years and supports not using them in children younger than 4 years of age as well.⁴

As we look for collaborative, nonantibiotic approaches to treating acute bronchitis that are acceptable to both provider and patient, that can reduce the risk of adverse effects of inappropriate treatment while limiting growth of antibiotic resistance, and that potentially can benefit the economy overall as patients and their caregivers are able to return to their productive lives sooner, South African geranium as EPs 7630 might be just what the doctor ordered. ■

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CARDIOVASCULAR DISEASE

ABSTRACT & COMMENTARY

Dietary Anthocyanins for Coronary Artery Disease: Berry Good Results

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Dr. Marcolina reports no financial relationships relevant to this field of study.

SYNOPSIS: A multivariate analysis of a population-based study of 1898 women aged 18-75 years found that dietary intake of plant-derived anthocyanin pigments, primarily from grapes and berries, was associated with lower blood pressure readings as well as lower arterial stiffness determinations as measured by pulse wave velocities. This suggests that specific dietary phytonutrients may mitigate two important risk factors for coronary artery disease.

SOURCE: Jennings A, et al. Higher anthocyanin intake is associated with lower arterial stiffness and central blood pressure in women. *Am J Clin Nutr* 2012; 96:781-788.

The authors performed a cross-sectional study to examine the association between the intake of dietary flavonoid subclasses, measured by the use of validated food frequency questionnaires, and in vivo measurements of blood pressure and arterial stiffness in a cohort of healthy female twins with a mean age of 46. The arterial stiffness was measured by means of the carotid to femoral pulse wave velocity (PWV) via a standardized system for which a normative database has recently been established, dependent on both age and blood pressure.¹ The PWV has a large body of evidence that demonstrates its association with incident cardiovascular disease independent of traditional risk factors (hypertension, dyslipidemia, family history, smoking, and diabetes) in patient populations.^{2,3}

Dietary flavonoids, classified as the plant pigments, are a diverse group of bioactive phytochemicals consumed in fruit, vegetables, and beverages such as tea, wine, and fruit juices. The anthocyanins are a class of these flavonoid compounds, which impart the dark blue, red, and purple colors to the berry fruits. Although a common basic chemical structure is shared by all classes of flavonoids, the differences in linkages, oxidation states, and functional side groups alter absorption, volume of distribution, metabolism, and bioactivity, which underscores the importance of investigating composite dietary flavonoid subclass intakes, as was done in this study.⁴

After adjustment for age, smoking, physical activity, body mass index, hormone replacement therapy use, statin and antihypertensive medication use, menopausal status, family history of hypertension or heart disease, use of vitamins, oral contraceptives, and intakes of energy (kcal/day) alcohol, saturated fatty acids, monounsaturated fatty acids,

Summary Points

- Consumption of the dietary anthocyanins contained in berries is associated with lower levels of blood pressure and vascular stiffness.
- Incorporation of different berry fruits into the daily diet may be part of a public health strategy to reduce cardiovascular disease.

polyunsaturated fatty acids, fiber, and sodium, comparison of extreme quintiles of intake revealed that only a higher intake of the anthocyanin subclass of flavonoids was associated with significantly lower blood pressure (peripheral, central systolic, and mean arterial) and pulse wave velocities. The key results are listed in Table 1.

The primary food sources of the anthocyanins consumed in this study were wine, grapes, and berries. There was an approximately 44 mg/day difference in intake between extreme quintiles of anthocyanin intake, which equates to approximately one to two portions of strawberries, grapes, blueberries, or raspberries (*See Table 2*).⁵

COMMENTARY

The national health objectives outlined in Healthy People 2010 recommend at least two servings of fruit daily for people age 2 and older. Currently, however, only 32% of adults and 13% of adolescents comply with these recommendations.^{6,7}

Table 1. Measures of Blood Pressure and Arterial Stiffness by Quintile of Anthocyanin Subclass Intake

Measure	Quintile 1	Quintile 5	P trend
pSBP (mmHg)	121 ± 1.0	117 ± 0.9	0.009
cSBP (mmHg)	112 ± 0.9	109 ± 0.9	0.017
MAP (mmHg)	93.5 ± 0.8	91.2 ± 0.7	0.037
PWV (m/s)	9.37 ± 0.1	9.00 ± 0.2	0.044

Key: pSBP: peripheral systolic blood pressure; cSBP: central systolic blood pressure; MAP: mean arterial pressure; PWV: pulse wave velocity.

From a nutritional standpoint, there are several reasons to choose berries as part of a healthy diet. In addition to the anthocyanin content, berries also contain natural antioxidants such as vitamins C and E and the micronutrients folic acid, calcium, selenium, alpha- and beta-carotene, and lutein. They are also low in calories and high in moisture and fiber.⁸ Several dietary intervention studies^{9,10,11} with various types of berries have shown that berry consumption during meals significantly decreases postprandial oxidative stress, especially lipid peroxidation, which is associated with coronary artery disease.¹²

The most popular berries consumed in the United States are strawberries and blueberries. Cranberries, both as juice and juice blends, also are popular sources of dietary phytochemicals.¹³ The anthocyanin content of these and other varieties of berries can be quite variable and is dependent on the different cultivated varieties and growing conditions, although it is generally proportional to the intensity of the fruit color and increases with the ripening process. Since post-harvest processes such as freezing, pressing, and vacuum drying markedly decrease the anthocyanin content of the fruit, consumption of fresh fruit is desirable when possible.^{14,15}

Conventionally grown strawberries, blueberries, and grapes, however, can be highly contaminated with organophosphate insecticides and have been included in the “Dirty Dozen” list of the Environmental Working Group’s 2012 Shopper’s Guide™.¹⁶ Organic cultivation of these fruits can mitigate this exposure. The higher price of organically cultivated fruits can be offset by prioritizing organic purchases to these specific fruits.

Two markers of arterial disease — blood pressure and arterial stiffness measured via the PWV method — were evaluated in this study. Arterial stiffness provides an assessment of both structure and function of the artery and is determined by dynamic factors such as sympathetic tone, blood pressure, and endothelium-derived vasodilators as well as intrinsic properties of the arterial wall such as wall thickness, relative collagen and elastin content, and degree of calcification.¹⁷

A recent database was established from a normotensive European population free from overt cardiovascular disease and diabetes and untreated with either antihypertensives or lipid-lowering drugs. They found that although PWV values increase with age from 6 m/s in normotensive (blood pressure > 120/80 mm Hg and < 135/85 mm Hg) subjects under 30 years to greater than 10 m/s

Table 2. Anthocyanin Content of Common Fruits⁵

Fruit	Anthocyanin Content (mg/100 g of edible fresh fruit)
Strawberries	34
Raspberries (red)	39
Grapes (red)	45
Cherries (sweet)	80
Blackberries	90
Cranberries	92
Blueberries	163
Chokeberries (Aronia berries)	437

after 70 years of age, this increase with age is more pronounced when the blood pressure increases. There was also considerable overlap of PWV values between younger and older subjects, possibly due to cardiovascular risk factors not quantifiable in the database such as family history. Although PWV is increasingly included in the assessment of patients involved in large-scale clinical studies, it is not yet available for routine clinical office because it is not clear how to use the reference data values to stratify patients’ cardiovascular risk.¹

Current guidelines in the United States for the prevention and treatment of hypertension from the JNC-7 (Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure)¹⁸ promote the additional benefits of lifestyle modifications to antihypertensive drug therapy with a focus on the importance of the Dietary Approaches to Stop Hypertension (DASH) diet, which emphasizes increased daily consumption of fruit, vegetables, and low-fat dairy products.¹⁹

Although the cross-sectional design of this study precludes the ability to confer causality between dietary anthocyanin intake and lowering of blood pressure and arterial stiffness, additional prospective, controlled, randomized dietary intervention trials to investigate this association could result in more specific dietary recommendations as part of an overall public health strategy to reduce cardiovascular disease. ■

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LONGEVITY

ABSTRACT & COMMENTARY

Spending More Leisure Time Physically Active Can Add Years to Your Life

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Dr. O'Mathúna reports no financial relationships relevant to this field of study.

SYNOPSIS: A pooled analysis of data from six prospective cohort studies found that more leisure time physical activity was associated with a reduced risk of mortality and increased life expectancy beyond age 40. Associations were found at all levels of body mass index. Subgroup analyses identified greater increases in life expectancy for blacks than whites, for former smokers than current smokers or those who never smoked, and for those with a history of cancer or heart disease.

SOURCE: Moore SC, et al. Leisure time physical activity of moderate to vigorous intensity and mortality: A large pooled cohort analysis. *PLoS Med* 2012;9:e1001335; Epub 2012 Nov 6.

The association between physical activity and risk of mortality is well established. Numerous epidemiological studies show that physical activity reduces the risk of mortality by about 30%. One specific study found strong evidence that physical activity in adults reduces the risk of

coronary heart disease, high blood pressure, stroke, type 2 diabetes, breast and colon cancers, depression, and falling.¹ More specifically, between 6-10% of the worldwide disease burden for each of these diseases is due to physical inactivity. However, few studies have quantified the number of years gained with

different levels of physical activity or examined how this is impacted by body mass index (BMI). Also, little is known about the impact of variables like race, smoking history, and cancer or heart disease on the association between activity and longevity. This study focused on the impact of physical activity on longevity for people older than age 40 years.

To explore these factors, the authors examined data from six prospective cohort studies that are part of the National Cancer Institute Cohort Consortium. Five were conducted in the United States and one in Sweden. Each study included members of the general population with a focus on risk factors for different diseases. To be eligible, studies had to have a prospective design, at least 5 years' follow-up, at least 1000 deaths among non-Hispanic white participants, and assessment of height, weight, smoking status, and time spent in leisure time physical activity. The combined study population was 56% female and 96.4% white, and the median age at baseline was 61 years (range, 21-98).

The primary exposure was leisure time physical activity of either moderate or vigorous intensity. Leisure time physical activities are activities that people voluntarily engage in and that are not required for a job, housework, transportation, or other essentials of daily living. They include sports, exercising, gardening, and recreational walking. Moderate-intensity activities require moderate effort and noticeably increase the heart rate. They include brisk walking and gardening. Vigorous activity requires a large effort, and leads to rapid breathing and a substantial increase in heart rate. This includes running, cycling, and fast swimming. Participants self-reported the time spent weekly engaged in moderate and vigorous leisure time exercise.

Complete data on physical activity, BMI, and mortality risk existed for 632,091 people aged 40 years or older and who were not underweight. Among those 40 and older, 80,767 deaths occurred during a median 10-year period. Physical activity was calculated in units of metabolic equivalent hours per week (MET-h/wk). Five MET-h/wk is equivalent to about 100 minutes of brisk walking per week.

Groups were defined as those with no leisure activity, low levels of leisure activity (up to 3.74 MET-h/wk or 75 minutes brisk walking per week), and the minimum recommended physical activity level (7.5 MET-h/wk or 150 minutes brisk walking per week). With each group comparison, higher levels of moderate to vigorous leisure activity were associated with lower risk of mortality and longer life expectancy after 40. Compared with no leisure activity, low levels and minimum recommended

Summary Points

- Leisure time physical activity at moderate and vigorous intensity increases people's life expectancy after 40 years.
- Even a little exercise helps, with greatest gains at the equivalent of 300 min brisk walking per week.
- Greater benefits were achieved for blacks compared to whites, former smokers compared to non-smokers, and those with a history of heart disease or cancer compared to those without such histories.

levels increased life expectancy by 1.8 and 2.5 years, respectively (95% confidence interval [CI] 1.6-2.0 and 2.2-2.7, respectively). Those at or slightly above the minimum recommended levels increased life expectancy by 3.4 years (95% CI 3.2-3.6). Those at two or three times the minimum level had longer life expectancy of 4.2 and 4.5 years, respectively (95% CI 4.0-4.5 and 4.3-4.7, respectively). The greatest gains occurred at 15 MET-h/wk or about 300 min brisk walking per week.

When BMI was added to the analyses, low physical activity was associated with lower life expectancy and higher risk of death in all BMI groups. For example, for those with normal weight (BMI 18.5-24.9 kg/m²), those with no leisure activity had 4.7 fewer years of life than those meeting the minimum recommended levels. For those in the overweight category (BMI 25.0-29.9 kg/m²), it was 3.9 fewer years; those in obese class I (BMI 30.0-34.9 kg/m²), 3.4 fewer years; and those in obese class II+ (BMI ≥ 35.0 kg/m²), 2.7 fewer years. In each physical activity group, being obese (but not being overweight) was associated with shorter life expectancy.

The large number of pooled participants allowed a number of subgroup analyses to be performed. These found little difference according to gender, but stronger associations for black individuals, former smokers, and those with a history of cancer or heart disease. For example, for those meeting the minimum recommended leisure activity levels compared to those with no leisure activity, the years of life gained after 40 were 3.4 for whites, and 5.3 for blacks; years gained were 4.1 for former smokers, 3.0 for those who never smoked, and 2.6 for current smokers; years gained were 5.3 for cancer survivors, 4.3 for those with heart disease,

and 2.8 for those with neither. Association with education was complex, possibly confounded by socioeconomic factors that were not a focus of this study. At all activity levels, those with some college or post-high school training had greater gains in life expectancy than college graduates or those with no more than high school education (the latter two groups being about equivalent).

In every category, adding even low amounts of leisure time physical activity was associated with increased longevity. The authors concluded, “This finding may help convince currently inactive persons that a modest physical activity program is ‘worth it’ for health benefits, even if it may not result in weight control.”

COMMENTARY

This study provides additional and more robust evidence to support public health efforts to increase people’s activity levels. By pooling data from a number of large studies, this analysis supports the findings of earlier, smaller studies. One of the intriguing comparisons was that being inactive and in obese class II+ (BMI ≥ 35.0 kg/m²) is associated with 7.2 years of life lost, while long-term cigarette smoking reduces life expectancy by about 10 years.

This study lends support to 2008 Physical Activity Guidelines Advisory Committee recommendations of 150 minutes per week of moderate intensity activity, or 75 min/wk of vigorous activity for adults aged 18-64 years.² The guidelines noted additional benefits would be achieved by 300 min/wk of moderate or 150 min/wk of vigorous activity. These were based on an estimated 20% reduced risk of mortality with the minimum recommended activity and 39% risk reduction with the higher levels. The guidelines cautioned that larger studies were needed to confirm these findings, which the current study provides. This study found equivalent risk reductions of 19% and 41% with much larger numbers of participants. Similar results have been found in other North American and European studies, and also recently with a Taiwanese study, suggesting these

benefits may be transcultural.³ The World Health Organization has adopted the same guidelines and makes these available in a number of languages.⁴

The main limitation with the current study is the reliance on self-reported data. Errors in recalling activity amounts and intensities, as well as body weight, may have impacted the findings. In addition, the focus on moderate-to-vigorous intensity activities may have missed the contribution of less-intense activities. Although statistical methods were used to account for heterogeneity in pooling the six studies, it is possible that unaccounted differences may have influenced the findings. A limitation in generalizing the results is the preponderance of white adults, with only 3% black and 1% other. This reflects the recruitment strategies in the original six studies.

Even with these limitations, this study provides further evidence of the importance and beneficial contribution of physical activities to health. It provides evidence of benefit in outcomes to which people can easily relate — years of life lost or gained. In addition, it provides evidence that particular groups of people, such as blacks, former smokers, and those with a history of cancer or heart disease, may experience additional benefit from engaging in moderate to vigorous leisure time physical activities. These findings can provide confidence in making recommendations to almost everyone to find leisure time activities they enjoy. ■

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METABOLIC SYNDROME

ABSTRACT & COMMENTARY

Do All Levels of Physical Activity Reduce the Risk of Developing Metabolic Syndrome? Sometimes More Is Better

By German H. Rodriguez, MD, and Zehra Siddiqui, DO

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SYNOPSIS: A cross-sectional and longitudinal analysis of the impact of different activity levels on the risk of developing metabolic syndrome on a large random sample of the Danish population found that higher activity levels were associated with a decreased risk of developing metabolic syndrome over the 10-year follow-up period.

SOURCE: Laursen AH, et al. Intensity versus duration of physical activity: Implications for the metabolic syndrome. A prospective cohort study. *BMJ Open* 2012;2:e001711 doi:10.1136/bmjopen-2012-001711.

Laursen et al analyzed data from the Copenhagen City Heart Study (CCHS) to explore the relationship between leisure time physical activity (LTPA), walking, and jogging on the risk of developing metabolic syndrome. Initially, this study looked at a random sample of men and women living within a specified area of Copenhagen in 1976 with follow ups being conducted in 1981-1983, 1991-1994, and 2001-2003.

The data, constructed from a sample of 10,135 people age 21-98 years, were explored using cross-sectional analysis for the period from 1991-1994. Of these, 6088 participants were included in the longitudinal analysis conducted in the period from 2001-2003. A self-administered questionnaire was used to assess the physical activity habits of those interviewed. Physical activity was divided into LTPA, jogging, and walking habits. LTPA was classified into four group types: 1) sedentary, 2) light PA, 3) moderate PA, and 4) high PA. Walking was divided into three categories depending on the hours per day (0-0.5, 0.5-1, and > 1). Walking and jogging speeds were categorized as slow, average, fast, and very fast. Each person self-reported the amount of activity and the intensity of this activity. Variables such as tobacco use, alcohol consumption, education, and cohabitation also were studied.

Metabolic syndrome was defined according to modified American Heart Association (AHA) criteria¹: central obesity, elevated triglycerides, low HDL, and blood pressure above 135/85 mm HG. A higher non-fasting glucose value was used instead of that described in the AHA criteria because no fasting samples were available. If three or more of these factors were present, the person was considered to have metabolic syndrome. Persons with metabolic syndrome at baseline were excluded from the study. Data were compared across groups using one-way analysis of variance. Associations between exercise volume and intensity and metabolic syndrome risk were studied using logistic regression analysis.

The cross-sectional analysis of each of the different baseline demographic characteristics was compared depending on the level of LPTA. In women, the prevalence of metabolic syndrome in the sedentary group was 31% (odds ratio [OR] 0.66; 95%

Summary Points

- Higher activity level is associated to lower risk of developing metabolic syndrome.
- Low-intensity physical activity such as walking is not associated with a lower risk of developing metabolic syndrome.
- Although this was a large cross-sectional and longitudinal analysis, there are issues that complicate clinical applicability of the findings: stark difference in the genetic makeup of the U.S. and Danish populations, study data were obtained from self-administered questionnaires, and there were no data on dietary habits.

confidence interval [CI] 0.55-0.80; $P < 0.001$) as compared to 10.9% (OR 0.37; CI 0.19-0.73; $P < 0.001$) in the group with a high level of LTPA. In men, the corresponding values were 36.8% (OR 0.72; CI 0.59-0.88; $P < 0.001$) and 13.9% (OR 0.38; CI 0.25-0.59; $P < 0.001$). This potentially demonstrates a clear association between a higher intensity of LTPA and decreased metabolic syndrome prevalence. There was no clear association between time spent doing a light physical activity such as walking and the risk of developing metabolic syndrome.

At the 10-year follow-up, 3968 subjects were evaluated. Of these, 585 subjects (15.4%) had developed metabolic syndrome. The incidence of metabolic syndrome varied from 19.4% (OR 0.86; CI 0.062-1.19; $P < 0.0001$) in the sedentary group to 11.8% (OR 0.57; CI 0.41-0.80) in the moderate or highly active groups. There was also a significant difference in the risk of developing metabolic syndrome between the low and high activity level group, but the difference was found to be less significant when compared to the cross-sectional analysis. Walking volume and light physical activity did not decrease the risk of developing metabolic syndrome.

COMMENTARY

Metabolic syndrome is a steadily growing problem in society. Some early reports found the prevalence to be between 21-23%.² More recent publications have found the prevalence to be near 34%.³ There has been higher prevalence found in certain groups, including Mexican American men.

It is estimated that common cardiovascular metabolic risk factor clusters (similar to those described for metabolic syndrome) cost the U.S. economy \$17.3 billion in lost productivity.⁴ After accounting for the natural evolution of the components of metabolic syndrome and their long-term complications, it becomes apparent that it is very difficult to accurately determine the real costs to our society.

A myriad of preventive and therapeutic approaches are available in the management of metabolic syndrome.⁵ Many cross-sectional analyses have studied the impact of physical activity on metabolic syndrome. The lack of longitudinal data has failed to clearly demarcate whether low activity level was a risk for metabolic syndrome or the result of it. Laursen et al aimed to analyze the impact of LTPA, walking, and jogging on the risk of developing metabolic syndrome through both a longitudinal and cross-sectional analysis.

The cross-sectional analysis in this study shows a strong association between higher LTPA and decreased risk of developing metabolic syndrome with a clear dose-response relationship. The data showed that the persons who self-reported a higher activity level were younger and had lower heart rate and blood pressure values. This potentially indicated there was a high level of cardiorespiratory fitness at baseline. This is significant as some authors have reported lower incidence of metabolic syndrome in younger populations.⁶ The longitudinal analysis also showed similar results but with a weaker correlation when compared to the cross-sectional analysis.

The study had some shortcomings. The assessment of activity level was based on self-administered questionnaires instead of more objective measures. There was no evaluation of the dietary habits of any of the studied population groups. A modified glucose value was used in the metabolic syndrome diagnostic criteria. There was a large difference in the number of persons in the initial analysis (10,135) compared to those included in the fourth survey (3992); 2140 of these patients died in the period between the third and fourth survey. If the investigators had analyzed the cardiovascular causes of death and correlated with activity level, it could potentially test their hypothesis beyond the risk of developing metabolic

syndrome to see the impact of different activity levels on mortality in the population studied.

It still remains to be studied what effects the findings of this study have on each of the individual components of metabolic syndrome even though previous analysis of the CCHS data has shown that jogging and walking speed are protective of all-cause and CVD mortality.⁷

The study authors implied that their analysis of a large Dutch population signified that their results are applicable to larger populations. Even though as primary care providers we would like to agree wholeheartedly, it is important to point out the differences of the mostly homogenous population of Denmark in comparison to the genetically varied population of the United States. In 2010, an estimated 35.7% of the U.S. population older than 20 years of age was obese.⁸ In 2006, the prevalence of obesity in Denmark was estimated to be 11.4%.⁹

The bottom line of this study is: 1) higher activity level was associated with a lower risk of developing metabolic syndrome, and 2) low-intensity physical activity such as walking was not associated to a decreased risk of developing metabolic syndrome. Most physicians recommend an exercise regimen to their patients with or at risk for developing metabolic syndrome because it is a low-cost intervention with minimal side effects and numerous health benefits. Health care providers should be supportive of any activity level, given that some patients are limited by concomitant comorbidities and it is important to avoid musculoskeletal injuries that could discourage a previously sedentary patient. Regardless, this study shows us that health care providers should consider endorsing safe increases in activity level to achieve the greatest benefit in every patient because sometimes more actually is better. ■

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CARDIOVASCULAR DISEASE

ABSTRACT & COMMENTARY

Long-Term Exercise Training in Heart Failure

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Dr. Crawford reports no financial relationships relevant to this field of study.

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SOURCES: Belardinelli R, et al. 10-year exercise training in chronic heart failure: A randomized controlled trial. *J Am Coll Cardiol* 2012;60:1521-1528. Whellan D. Long-term exercise training and adherence: It is not just exercise. *J Am Coll Cardiol* 2012;60:1529-1530.

Exercise training is associated with short-term improvements in functional capacity in heart failure patients, but its effect on mortality and heart failure readmissions have been mixed. Thus, these investigators from Italy and New York studied 135 stable heart failure patients who were divided into a supervised exercise training group (70% peak oxygen consumption, two times a week for 10 years) and a non-trained group. Inclusion criteria included left ventricular ejection fraction < 40% and the ability to exercise. The etiology of heart failure was ischemic in 80% and their average age was about 60 years at intake. Each patient underwent a formal re-evaluation with cardiopulmonary exercise testing every 12 months by observers blinded to the study groups. The primary outcomes were peak oxygen consumption, quality of life, mortality, heart failure exacerbation, and cardiac ischemic events. Any of the cardiovascular events ended the patients' participation in the study. Of the 135 enrolled, 123 completed the 10-year study (63 trained and 60 non-trained). Peak oxygen consumption was not different between the two groups at intake, but increased in the training group by 15% and decreased 2.5% in the non-trained group at 1 year. This difference persisted during the study and was mirrored by a slower resting heart rate in the training group. Ejection fraction was not different at intake between the two groups, but after 4 years was significantly higher in the training group (41% vs 34%, $P < 0.01$ at 5 years). Quality of life also improved significantly in the training group and was sustained for the duration. The safety of training was excellent. Clinical events were less common in the training group (12 vs 35; hazard ratio [HR] = 0.55, 95% confidence interval [CI], 0.26-0.72; $P < 0.0001$). Specifically, cardiac death was less common in the training group (4 vs 10; HR = 0.68,

Summary Points

- In 135 people with stable heart failure (ejection fraction < 40% and able to exercise), moderate supervised exercise training performed twice weekly for 10 years led to numerous cardiovascular benefits.
- The benefits of this study may be due to the supervised training and community education efforts, but the study was underpowered to detect a causal relationship.

95% CI 0.30-0.82; $P < 0.001$). Multivariate analysis showed that peak oxygen consumption and resting heart rate were the only independent predictors of events. The authors concluded that moderate, supervised exercise training performed twice a week for 10 years conferred sustained improvement in exercise tolerance, quality of life, and left ventricular systolic performance in patients with heart failure due to systolic dysfunction. These improvements were associated with lower cardiac morbidity and mortality rates.

COMMENTARY

The results of this study are remarkable and very different from the recently reported Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial, which showed no reduction in cardiac mortality with exercise training, despite a small but significant increase in peak oxygen consumption in the training group.¹ There

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are several differences between the two studies that may explain the results. First, this trial involved exercise training sessions supervised by a cardiologist, whereas HF-ACTION involved self-directed home-based exercise. Adherence to the program was 88% in this trial vs about 60% in HF-ACTION. Second, peak oxygen consumption increased 4% in HF-ACTION and 15% the first year in this study. Third, HF-Action was a 2.5 year study vs 10 years in this study. Some parameters, such as ejection fraction, took 5 years to improve in this study. Fourth, there may have been crossovers to supervised exercise training in HF-ACTION. Fifth, there were differences in medical and device therapy in the two studies. Beta-blocker use was 94% in HF-ACTION and 46% in this study. ICD use was 40% in HF-ACTION and 7% in this study. The authors focus on the supervision aspect as the key difference between the studies. The accompanying editorial suggests that the community aspects of the training sessions, which also included education, may have played a large role in the favorable outcomes.

Importantly, there is no way to be certain that the reduction in events was causally related to the exercise training. The study was underpowered for outcomes assessment; it was powered for changes

in peak oxygen consumption. However, the only independent predictors of the outcomes were related to exercise training: peak oxygen consumption and resting heart rate. It is noteworthy that HF-ACTION had 2331 subjects vs 123 in this study. So perhaps the reduction in outcomes in this study was an alpha or type I statistical error, which is more common in small studies. Clearly, a larger trial would have to be done to confirm the outcome results.

Despite these weaknesses, this is a compelling study. Exercise training was safe and seemed highly effective. So why not adopt it? The feasibility and cost of such a program in the United States for almost all heart-failure patients would not be favorable under our current health care system. However, we can certainly refer most patients to cardiac rehabilitation programs and encourage them to continue these programs on their own if possible. Also, it may be worth encouraging community groups to continue this effort if health care agencies can't fund it. At a minimum, it uniformly improves exercise performance and quality of life. ■

Reference

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CME QUESTIONS

1. **Although patients taking EPs 7630 returned to kindergarten, school, or work significantly earlier than those in the placebo group, they were not more satisfied with their treatment.**
 - a. 100 minutes brisk walking per week.
 - b. 150 minutes brisk walking per week.
 - c. 300 minutes brisk walking per week.
 - d. None of the above
2. **Post-harvest processing such as drying or freezing can affect anthocyanin content of berries.**
 - a. True
 - b. False
3. **The generally recommended minimum amount of physical activity is the equivalent of:**
 - a. 100 minutes brisk walking per week.
 - b. 150 minutes brisk walking per week.
 - c. 300 minutes brisk walking per week.
 - d. None of the above
4. **In the study by Laursen et al, a high level of leisure time physical activity was found to:**
 - a. have no impact on risk for developing metabolic syndrome.
 - b. lower risk of developing metabolic syndrome.
 - c. decrease all-cause CVD mortality.
 - d. Both B and C
 - e. None of the above

[IN FUTURE ISSUES]

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