MAYO CLINIC

Quantitating the Dose of Physical Activity in Secondary Prevention: Relation of Exercise Intensity to Survival

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With the enormous current and projected economic burden of cardiovascular disease (CVD), which is expected to triple in the next 20 years,[1] therapeutic strategies to improve cardiovascular outcomes and reduce cardiovascular mortality are urgently needed. Accordingly, interventions that may reduce the risk of recurrent cardiovascular events and/or the need for repeated coronary revascularization procedures, including aggressive lifestyle modification and complementary cardioprotective medications, collectively referred to as secondary prevention (Figure 1), are critically important.[3,4] Structured exercise training, increased lifestyle physical activity (PA), or both have been reported in numerous randomized controlled trials and meta-analyses to reduce the overall mortality associated with atherosclerotic coronary artery disease (CAD). One systematic review and meta-analysis of 33 PA studies, including 883,372 participants, reported risk reductions of 30% to 50% for cardiovascular mortality and 20% to 50% for all-cause mortality, with pooled risk reductions of 35% and 33%, respectively.[5] These epidemiologic analyses, when combined with adjunctive experimental and clinical investigations providing biologic plausibility,[6,7] and other relevant reports,[8-12] support a cause-and-effect relation between increased levels of PA and cardiorespiratory fitness (CRF) and reduced cardiovascular mortality, rather than merely associations between these variables.[13,14] Progressive exercise after an acute cardiovascular event and/or coronary revascularization procedure is often prescribed as an integral component of a secondary prevention program in outpatient cardiac rehabilitation. Nevertheless, delineating the optimal cardioprotective dosage, including the modulating impact of variations in the associated frequency, intensity, and duration on subsequent mortality in patients with known CAD, has remained controversial and elusive.

Recently, researchers developed a new fitness metric, using the frequency, duration, and intensity of PA, the latter estimated from continuous heart rate (HR) monitoring in the Nord-Trøndelag Health Study (HUNT) Fitness Study cohort, to clarify the relation between exercise dose and health outcomes.[15] Termed the personalized activity intelligence (PAI) score, it is derived from the cumulative 7-day modulations in activity HR over time, and gives more credit (ie, a higher PAI score) for vigorous exercise than for mild-to-moderate PA. For example, when compared with an hour-long 3-mile walk, a 30-minute strenuous bike ride earns 8 times the PAI score, 7 vs 56, respectively.[16]

According to a recently published investigation regarding the prevention of CVD in the general population, using the HUNT study database over an average follow-up of 26.2 years, men and women achieving a weekly PAI score of greater than or equal to 100 had a 20% ± 3% reduced risk of CVD mortality, compared with an inactive control group.[15] The findings indicated that this exercise dosage could potentially increase the lifespan by up to 10 years for persons younger than 50 years. In aggregate, these data, and other relevant investigations,[17,18] suggest that large daily fluctuations in HR and associated energy expenditure, which can be assessed using the PAI score, appear to confer not only increased survival but decreased health care costs as well. The study by Kieffer et al[19] published in the current issue of *Mayo Clinic Proceedings* extends these analyses to a large cohort of patients with self-reported CVD, defined as angina pectoris, previous myocardial infarction, stroke, or combinations thereof, in the HUNT database, with specific reference to selected subgroups of coronary patients, regardless of whether contemporary PA recommendations were simultaneously being met.

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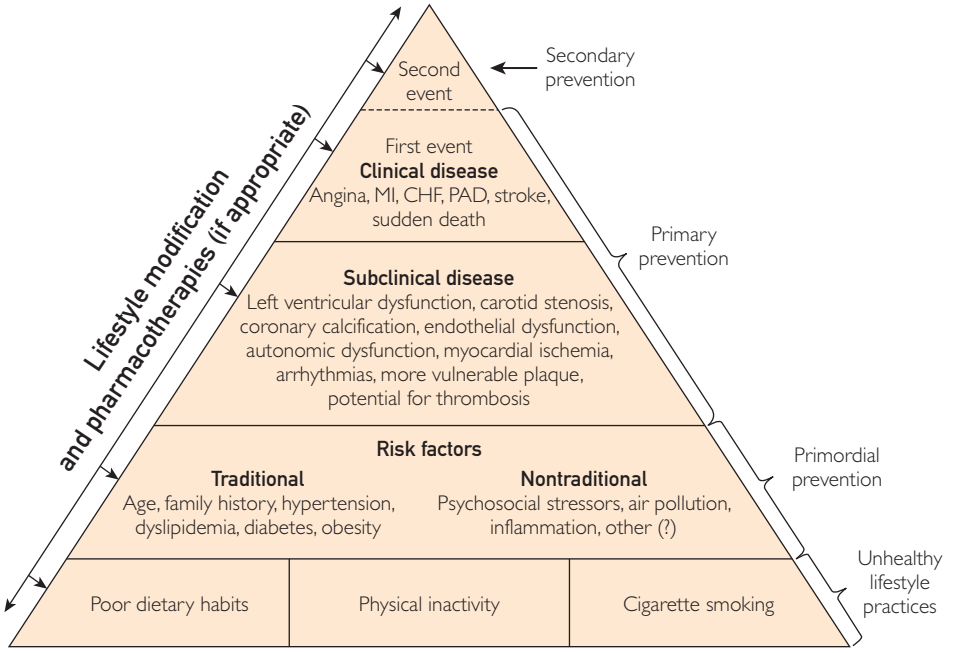

FIGURE 1. Unhealthy lifestyle habits lead to traditional risk factors, the progression of cardiovascular disease, and ultimately, adverse outcomes or clinical end points, with specific reference to the types of prevention interventions: primordial (prevention of risk factors), primary (treatment of risk factors), and secondary (prevention of recurrent cardiovascular events). Bona fide interventions include lifestyle modification, pharmacotherapies (eg, aspirin, β-adrenergic blockers, statins, angiotensin-converting enzyme inhibitors), and emergent or elective coronary revascularization, when clinically indicated. CHF = congestive heart failure; MI = myocardial infarction; PAD = peripheral arterial disease. From *Circulation*, with permission.[2]

Using a study population of 3133 patients with CVD (mean age, 67.6±10.3 years; 64% men) with complete baseline data on PAI, based on directly monitored HR fluctuations, habitual PA, and pertinent demographic and clinical characteristics, the investigators divided participants into 4 groups to further clarify the association between PAI and subsequent risk of mortality.[19] These groups included the following: those with a PAI score of 0 (inactive, reference group); those with a PAI score of 50 or less; those with a PAI score of 51 to 99; and those with a PAI score of 100 or more. Over an average follow-up of 12.5 years, after adjusting for potential confounders in a multiadjusted model, participants attaining a weekly PAI score of 100 or more had a 36% and 24% lower risk of cardiovascular and all-cause mortality, respectively, as compared with the inactive group, irrespective of whether they were following contemporary PA guidelines.[20] After adjusting for sex, those attaining a PAI score of less than 100 demonstrated an average of 4.7 years of life lost as compared with their counterparts achieving a PAI score of 100 or more. Relative to younger (≤70 years) vs older (>70 years) participants, the corresponding years of life lost were 4.3 and 3.3, respectively. In contrast to the reverse J-shaped hypothesis regarding exercise,[21] there were no further reductions or loss of survival benefit beyond obtaining a weekly PAI score of 100 or more. Moreover, achieving a PAI score of 100 or more was associated with similar mortality risk reductions for both sexes and different age groups. Subgroup analyses were, for the most part, unremarkable.

Despite several acknowledged observational study limitations (eg, cannot imply cause and effect, self-reported data, PA and PAI assessed at baseline only, no information