

# Association of Physical Activity and Inflammation With All-Cause, Cardiovascular-Related, and Cancer-Related Mortality

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#### Abstract

**Objective**: To investigate the association between physical activity (PA) and risk of mortality in a large middle-aged cohort stratified by inflammatory status.

**Patients and Methods:** A total of 336,560 individuals (mean age, 39.7 years; 58% male) who underwent comprehensive health screenings were enrolled in this prospective cohort study. They were grouped according to self-reported PA level using a questionnaire: no regular PA with a sedentary lifestyle, regular but insufficient PA (below the guidelines), sufficient PA (concordant with the guidelines), and health-enhancing PA. Inflammation was assessed via high-sensitivity C-reactive protein (hsCRP) level. Study end points were all-cause, cardiovascular-related, and cancer-related mortality.

**Results:** During the 1,976,882 person-years of follow-up (median follow-up duration, 6.17 years), 2062 deaths occurred. Compared with a sedentary lifestyle, the hazard ratios (95% CIs) on the multivariable Cox proportional hazards regression analyses for all-cause mortality by PA level were 0.95 (0.84-1.07), 0.85 (0.72-0.99), and 0.75 (0.60-0.93) (*P* for trend=.003), and those for cardiovascular- and cancerrelated mortality were 0.95, 0.80, and 0.55 (*P* for trend=.05) and 0.82, 0.83, and 0.78 (*P* for trend=.01), respectively. Compared with participants with low hsCRP levels and no regular PA had a significantly higher risk of mortality (1.59 [1.38-1.84]). **Conclusion:** Higher PA levels were associated with a dose-dependent reduced risk of cardiovascular-related, cancer-related, and all-cause mortality. Individuals with high hsCRP levels and no regular PA had the highest risk of mortality.

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onsiderable research has evaluated the association between physical activity (PA) and cardiovascularrelated and overall mortality in the general population, and the contribution of PA to health outcomes is independent even with the consideration of traditional cardiovascular risk markers and genetic factors.<sup>1-7</sup> Therefore, guidelines recommend at least 150 minutes of moderate-intensity PA, 75 minutes of vigorous-intensity PA, or an equivalent combination of moderate- and vigorous-intensity PA weekly.<sup>8,9</sup> Also, PA acts in a variety of ways to affect cancer risk and may reduce the risk of several types of cancer.<sup>10-13</sup> The American Cancer Society's most recent guidelines recommend that patients with cancer exercise regularly during and after treatment.<sup>14</sup>

Many studies have found that high degrees of inflammation represented by elevated highsensitivity *C*-reactive protein (hsCRP) levels are associated with traditional risk factors and independently increase the risk of cardiovascular disease (CVD) and mortality.<sup>15-18</sup>

The biological mechanisms through which increased PA or structured exercise training decreases the risk of mortality or cardiac events are incompletely understood. Several studies support the hypothesis that the lower mortality risk and health benefits associated with increased PA might be partly explained by the inverse correlation between increased PA and inflammatory risk markers.<sup>19-22</sup> Another study found that inflammatory risk factors and blood pressure made the largest contribution to the inverse association



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between PA and cardiovascular events in a healthy sample.  $^{\rm 23}$ 

However, there are few data about the effect of PA level on mortality according to inflammatory status. Therefore, we tested the associations between PA and hsCRP levels and cardiovascular, cancer-related, and all-cause mortality stratified by inflammatory markers using hsCRP in a very large, well-characterized, and predominantly ethnically homogeneous middle-aged Korean cohort. Moreover, to minimize the effect of occult antecedent disease, we conducted a sensitivity analysis and excluded individuals who died within 1 year after baseline to minimize the potential problem of reverse causality underpinning any associations.

#### METHODS

#### **Study Population**

The Kangbuk Samsung Health Study is a cohort study of South Korean men and women 18 years and older who underwent a comprehensive annual or biennial health examination at the Kangbuk Samsung Hospital Health Screening Centers in Seoul and Suwon, South Korea. This study population consisted of 396,951 individuals who participated from January 1, 2002, through December 31, 2012. The purpose of the screening program was to promote health through the early detection of chronic diseases and their risk factors. In addition, the Korean Industrial Safety and Health Law demands that working individuals participate in an annual or biennial health examination. Participants were employees or spouses of employees working for companies or local governmental organizations who registered individually for the program.

For this analysis, we excluded individuals who met 1 or more of the following criteria: missing data for smoking, alcohol intake, exercise, or hsCRP level at baseline (n=54,957); history of malignancy or inflammatory status (n=5432); and unknown mortality status (n=2). Ultimately, the total number of eligible participants was 336,560 (median follow-up duration, 6.17 years; mean  $\pm$  SD, 5.87 $\pm$ 3.23 years) (Figure 1). Supplemental Table 1 (available online at http://www.mayoclinicproceedings. org) shows the baseline characteristics of the

cohort according to the inclusion and exclusion criteria. This study was approved by the institutional review board of Kangbuk Samsung Hospital, Seoul, South Korea. The requirement for informed consent was waived because the data were deidentified.

#### Measurements

As part of the health screening program, individuals completed self-administered questiontheir naires regarding medical and socioeconomic history and medication use. We assessed baseline PA level using a selfadministered, validated, Korean version of the International Physical Activity Questionnaire Short Form (IPAQ-SF) after January 2011.<sup>24,25</sup> Before that time, a similar form of questionnaire was used because the IPAQ-SF had not been officially adopted. The specific question was: "During the past 7 days, on how many days did you do vigorousintensity PA, such as heavy lifting, digging, aerobics, or fast bicycling, or moderateintensity PA, such as carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking." If the answer was "1 or more," additional questions were asked, such as "How much time did you usually spend performing moderate- or vigorous-intensity PA on 1 of those days?" The questionnaire enables the calculation of metabolic equivalents (METs) (MET-minutes per week) derived by assigning standardized MET values of 4 and 8 for moderate- and vigorous-intensity activities, respectively.



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