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Invited Commentary

Invited Commentary: Physical Activity, Mortality, and Genetics

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The importance of regular physical activity to human health has been recognized for a long time, and a physically active lifestyle is now defined as a major component of public health policies. The independent contribution of regular physical activity to lower morbidity and mortality rates is generally accepted, and the biologic mechanisms mediating these health effects are actively investigated. A few years ago, data from the Finnish Twin Registry suggested that genetic selection may account for some of the physical-activity-related benefits on mortality rates. However, results from the Swedish Twin Registry study reported by Carlsson et al. in the current issue of the *Journal* (Am J Epidemiol 2007;166:255–259) do not support the genetic selection hypothesis. In this commentary, the authors review the nature of the associations among physical activity level, fitness, and longevity, with special reference to the role of human genetic variation, and discuss potential reasons for different outcomes of these large twin studies.

mortality; motor activity; questionnaires; selection (genetics); Sweden; twins

The importance of regular physical activity to human health has been recognized for a long time, as evidenced by ancient Chinese and Indian texts from the third millennium BC and writings of Hippocrates from 500 BC. Modern scientific research on physical activity and health dates back to the early 20th century, when the first exercise physiology and medicine laboratories were established. In the 1950s, the first epidemiologic studies targeting physical activity were published, but physical activity epidemiology started to gain momentum in the late 1970s and 1980s, culminating in the 1990s in a series of reviews and consensus statements that were instrumental in shaping current recommendations. Although a physically active lifestyle is now defined as a major component of public health policies, the concept of the health benefits of regular exercise was met initially by considerable skepticism from the scientific and medical establishment. For many years, the improved risk factor profile commonly observed with regular exercise was usually credited to body weight or adiposity losses, with little or no independent effect of physical activity per se. The latter view has evolved. It is now generally recognized that a sedentary lifestyle or poor fitness is an independent risk factor for a variety of health outcomes.

A few years ago, data from the Finnish Twin Registry suggested that genetic selection may account for some of the physical-activity-related benefits on mortality rates (1). Although the authors of the study were very cautious in interpreting their results, others occasionally used the results as evidence that physically active persons simply happen to have ''better genes'' and are therefore healthier than sedentary subjects and thus live longer. In the current issue of the *Journal*, Carlsson et al. (2) report the results of similar analyses in a larger, but otherwise fairly comparable cohort from the Swedish Twin Registry. However, because the Swedish study found no support for the genetic selection hypothesis, which of these two studies is correct? Before addressing the latter question, we first need to examine the nature of the associations among physical activity level, fitness, and longevity, with special reference to the role of human genetic variation. We will do so using a simple conceptual model.

Figure 1 posits that physical activity increases fitness, which in turn diminishes the risk of premature death. A large body of data supports the proposition that this path is operational. For instance, regular exercise increases cardiorespiratory endurance, tolerance to physical exertion,

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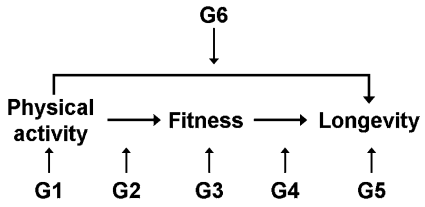

FIGURE 1. Simple conceptual model defining the associations among physical activity level, fitness, and longevity. The model allows for the contributions of genetic differences. Refer to the text for the definition of paths G1 to G6.

high density lipoprotein cholesterol, and insulin sensitivity while decreasing adiposity, blood pressure, blood triglycerides, and inflammatory markers. Thus, those who are physically active on a regular basis are more fit and generally have a better risk factor profile for a variety of common chronic disorders. They also enjoy, on average, a lower risk of premature death, as evidenced by numerous prospective studies. The model also posits a second path linking physical activity to mortality rates, and it is direct. This path implies that there is an influence of physical activity per se on longevity, an influence not mediated by an increase in fitness or by an improvement in the risk factor profile. Indeed, studies suggest that the acute effects of an exercise bout, including its impact on the flow of substrates, the secretion of many hormones, the transient decrease in postexercise blood pressure below resting, the muscle-contraction-induced increase in glucose uptake, and many other biologic events, can be defined as ''healthy.'' This view is supported by a large body of data indicating that regular physical activity is associated with lower mortality rates. Needless to say, the associations among physical activity, fitness, and longevity are more complex than this simple model suggests, and more can be found on this topic in a previous publication (3).

We are concerned here primarily about the role that genetic variation may play in the associations defined in figure 1. Here, paths from genetic variation to other components of the model are abbreviated G1 to G6. In brief, G1 represents the influence of sequence variation in genes on physical activity behavior. Family and twin studies have provided evidence for significant genetic effects on physical activity level as well as on indicators of sedentarism (4), which have been supported by molecular genetic studies in humans (5, 6) and in animals (7–10). G3 refers to the genetic path to fitness. A substantial body of data from genetic epidemiology studies shows moderate-to-high heritability estimates for many components of fitness, including cardiorespiratory endurance, muscular strength, and endurance, as well as others (11). As for G5, it represents all the genetic influences on life span and various morbidities, such as coronary heart disease, diabetes, hypertension, and cancer.

Of considerable interest are the G2 and G4 pathways because they imply that there are individual differences in the influence of one component of the model on another and that genetic variation modulates these influences. We are beginning to have data to support the contention that G2 and G4 are operational. For instance, there are marked interindividual differences in the response of fitness phenotypes to regular exercise (12), and these differences are not randomly distributed but clearly aggregate in families. In the HERITAGE Family Study, the heritability estimates for endurance-training-induced changes in cardiovascular disease and diabetes risk factors have ranged from 20 percent to 60 percent (12). Data on the genotype-by-physical-activity interactions on mortality rates are still missing (the G6 path), but there is already evidence for genotype-by-physical-activity interactions on coronary heart disease and breast cancer (13, 14). For example, regular physical activity may postpone the onset of breast cancer among women who have a genetic predisposition to breast cancer (i.e., carriers of mutations in *BRCA1* and *BRCA2* genes) (14). Thus, the associations among physical activity, fitness, and mortality rate are quite complex, and human genetic variation is potentially contributing at all levels.

The study by Carlsson et al. (2) first tests the hypothesis that there is a direct path from physical activity level to all-cause or cardiovascular disease mortality. They report lower mortality rates (a 36 percent reduction for men and 25 percent for women) with high physical activity level for all-cause mortality and for cardiovascular mortality as well (45 percent for men and 66 percent for women). In other words, their data support the contention that there is a direct path from physical activity level to mortality rates. Next, they ask whether genetic variation played a role in the association by comparing members of dizygotic and monozygotic twin pairs discordant for physical activity level. This comparison constitutes a partial test of G6 as defined in our conceptual model. Even though the risk reduction for all-cause mortality was about 20 percent and 32 percent for cardiovascular disease mortality, these estimates were deemed comparable to those obtained when a potential genetic effect was not incorporated in their analyses. No statistical test for the differences among the various estimates was offered.

It is important to try to understand why the results of the earlier Finnish twin study (1) and the present Swedish twin study (2) are so different. Carlsson et al. discussed several factors that may account for the differences in findings. The small number of discordant monozygotic twins in the Finnish study was clearly a limiting factor, which may be to some extent related to the lower monozygotic-to-dizygotic twin ratio among the Finnish twins sample compared with the Swedish cohort (0.46 vs. 0.67). It must be noted that the number of deaths among those defined as highly active in both twin studies was still fairly small. The Swedish twin study relied on a single estimate of physical activity level derived from a fairly simple questionnaire, whereas the physical activity estimates were based on more detailed questionnaires collected twice, in 1975 and 1981, in the Finnish study. Another difference in study design was that persons with chronic diseases at baseline (~11.5 percent of the eligible subjects) were excluded from the Finnish study but were included in the data analyses in the Swedish study (14–15 percent of the subjects). In addition, the prevalence of smoking was considerably higher in the Swedish cohort (~43 percent) than among the Finnish twins (~30 percent).

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Despite the results of Carlsson et al. (2), it remains possible that there are genetic differences among people that modulate the effects of a physically active lifestyle on the risk of premature death. A more definitive test of the G6 path will require complex designs and very large sample sizes. Useful data could come from large studies of twins followed until the death of both members has been registered, with pairs of twins stratified on physical activity level at baseline and at intermediate time points during the follow-up period. This process would enable comparison of mortality rates in pairs defined as consistently sedentary, moderately active, or very active and establishment of whether there is twin resemblance in lifespan or cause of death within level of activity. The design would provide for an indirect test of an interaction between genotype and physical activity level. A more direct test should eventually be possible with large samples of unrelated persons stratified by physical activity level and genotype at key candidate genes and followed until death.

A potential confounding factor especially in twin studies has to do with epigenetics. An epigenetic effect refers to chemical modification (e.g., methylation) of DNA and histone proteins that may change gene expression without affecting the DNA sequence of the gene. Epigenetic effects may translate into nongenetic phenotypic differences that resemble those associated with DNA sequence variants. Even though they begin to occur soon after fertilization, these epigenetic modifications continue to take place during the whole fetal life and potentially throughout the lifespan. Moreover, the epigenetic changes are thought to be fairly stable. Data from animal models suggest that epigenetics may affect spontaneous physical activity levels. In rats, maternal undernutrition during pregnancy resulted in differences in postnatal locomotor behavior. In one experiment, the ad libitum–fed offspring of dietary-restricted mothers were consistently less active than the offspring of normally fed mothers well into adulthood (15).

Similar data in humans are still missing. However, some historical events may have relevance for the comparison of Finnish and Swedish twin data. They relate to what happened in Finland and Sweden when the majority of the twins in both registries were born. During the first half of the 20th century, Finland experienced firsthand two major wars, while Sweden was only minimally affected. During both wars, Finland experienced several periods of restricted food availability, which affected the nutritional status of women and children. An interesting question is what kinds of epigenetic consequences, if any, these periods of restricted food supply had and whether they could explain some of the differences in outcomes between two seemingly comparable twin studies.

Although research on genetics, physical activity, and health is still in its infancy, there is already substantial evidence to conclude that physical activity affects health status and to recognize that our genome modulates the associations between physical activity and health at multiple levels. Thus, it is very timely to investigate how genes and behaviors interact in the prevention of common chronic diseases and in the protection against premature death.

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