Published in final edited form as:
Med Sci Sports Exerc. 2013 April ; 45(4): 691–697. doi:10.1249/MSS.0b013e3182784e9f.

Physical Activity, Genes for Physical Fitness, and Risk of Coronary Heart Disease

Andrea K. Chomistek[1], **Daniel I. Chasman**[2], **Nancy R. Cook**[2,3], **Eric B. Rimm**[1,3,4], and **I-Min Lee**[2,3]

[1]Department of Nutrition, Harvard School of Public Health, Boston, MA

[2]Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

[3]Department of Epidemiology, Harvard School of Public Health, Boston, MA

[4]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Abstract

Purpose—Both physical activity and physical fitness are associated with decreased coronary heart disease (CHD) risk. Our objective was to determine whether genes associated with physical fitness modify the association between physical activity and CHD.

Methods—We conducted a prospective cohort study among 23,016 initially healthy women in the Women's Genome Health Study. Leisure-time physical activity was reported at entry and during follow-up. 58 single nucleotide polymorphisms associated with physical fitness were identified from published literature and summed to create four separate genetic scores related to phenotypes of endurance, muscle strength, VO_2max, and overall fitness.

Results—During a median of 14.4 years, 320 incident CHD events occurred. Increased physical activity was associated with lower CHD risk in multivariable-adjusted models (P = 0.0008). Independent of physical activity, only muscle strength genetic score was inversely associated with CHD risk (P = 0.05). There was no evidence that the inverse relation between physical activity and CHD was modified by any of the genetic scores for physical fitness. For overall fitness genetic score, the hazard ratio (HR) per 500 kcal/week of physical activity was 0.85 (95% CI: 0.72, 1.00) in the highest quartile of genetic score; 0.79 (95% CI: 0.67, 0.92) in the lowest quartile (*P,* interaction = 0.50). For VO_2max genetic score, the HR was 0.86 (95% CI 0.72, 1.02) and 0.84 (95% CI 0.72, 0.98), respectively (*P,* interaction = 0.59).

Conclusions—In this large prospective cohort of women, genes associated with physical fitness did not modify the inverse association between physical activity and CHD risk.

Keywords

exercise; epidemiology; genetics; cardiovascular disease

Corresponding Author: Andrea K. Chomistek, ScD, Department of Nutrition, Harvard School of Public Health, 655 Huntington Avenue, Building 2, Boston, MA 02115, Telephone: 617-909-6034/Fax: 617-432-2435, akaye@hsph.harvard.edu.

CONFLICT OF INTEREST

None. The results of the present study do not constitute endorsement by ACSM.

INTRODUCTION

There is substantial evidence of an inverse relation between physical activity and cardiovascular disease (CVD) (22). Active individuals have approximately 30% lower risk of coronary heart disease (CHD) than inactive individuals(12, 19, 27).

Physical fitness is also associated with lower CVD risk (14, 31). In a recent meta-analysis, the pooled rate ratio of CHD/CVD comparing individuals with high cardiorespiratory fitness (CRF) to those with low CRF was 0.71 (95% CI 0.68–0.76), similar to the risk reduction for physical activity (14).

While sometimes used interchangeably, physical activity and fitness represent separate, but related, constructs. Physical activity is a behavior, defined as voluntary movement produced by skeletal muscles that results in energy expenditure, whereas physical fitness is a set of attributes people have or achieve related to health or athletic ability. Components of physical fitness include CRF, which relates to the ability of circulation and respiration to supply oxygen during sustained exercise, and muscular strength, which relates to the amount of external force that a muscle can exert (7). Several factors influence fitness, including age, sex, and physical activity(16).

One mechanism proposed for the benefit of physical activity is the direct effect on increased physical fitness. However, while exercise increases fitness, it is not the only determinant. There are considerable individual differences in fitness responses to habitual physical activity, even when all persons perform the same amount of exercise(2). The most extensive data on individual differences in response to exercise training were provided by the HERITAGE Family Study in which 742 healthy but sedentary subjects followed a highly standardized endurance-training program for 20 weeks. With its family-based design, the HERITAGE study was designed to investigate the role of genotype in responses to aerobic exercise training. The training program induced several beneficial changes in CRF and other risk factors, but with marked interindividual differences. For example, training responses varied from no change in maximal oxygen consumption (VO_2max) up to 100% increase in some individuals (2, 3, 28).

The differences between subjects in their response to physical activity may be explained, in part, by genetic variation. Many genetic loci have been studied in relation to performance and health-related fitness phenotypes. Polymorphisms in several genes have been found to be associated with baseline CRF, including *ADRB1* (β2-adrenergic receptor) and *ADRB2* (β2-adrenergic receptor), and baseline muscle strength, including *VDR* (vitamin D receptor) (6). Additionally, a few genetic variants have also been found to be associated with changes in CRF and muscle strength in response to exercise training including *AMPD1* (adenosine monophosphate deaminase) and *ACTN3* (α-actinin-3 protein), respectively (6).

Since physical activity decreases CHD risk partly through improvement in physical fitness, and because of heterogeneity in fitness improvement in response to exercise, the question has been raised: if individuals cannot improve their fitness through physical activity because of an unfavorable genetic profile, will they still experience decreased CHD risk from habitual exercise? To address this, we examined the association between leisure-time physical activity and coronary heart disease incidence among groups of individuals over a range of genetic predispositions to baseline physical fitness and fitness improvements with exercise. As much of the prior evidence relating physical activity with lower CHD risk has focused on aerobic activity, we hypothesized that genetic variants associated with endurance phenotypes would be more likely to modify the association between physical activity and CHD risk than variants associated with muscle strength phenotypes.

METHODS

Study Population

The Women's Genome Health Study (WGHS)(25) is a prospective cohort study derived from the Women's Health Study (WHS) (8, 17, 26). The WHS is a completed randomized trial testing low-dose aspirin and vitamin E for prevention of CVD and cancer among 39,876 initially healthy female health professionals ages 45 years and older at study entry (1992 to 1995). Following trial completion in 2004 (average follow-up, 10 years), participants were followed in an observational study. At baseline, women reported medical history and lifestyle characteristics on questionnaires, with information updated yearly during the trial and continuing in observational follow-up. The WGHS comprises a subgroup of over 25,000 women who provided a baseline blood sample and consented to ongoing analyses using genetic data. For this study, analyses were restricted to 23,016 participants of European ancestry for whom complete data were available for the genetic risk scores and physical activity. The study was approved by the institutional review board of Brigham and Women's Hospital (Boston, Massachusetts).

Assessment of Leisure-Time Physical Activity

Each participant reported average time per week during the previous year spent on 8 recreational activities: walking/hiking, jogging, running, bicycling, aerobic exercise/dance, lap swimming, tennis/squash/racquetball, and lower-intensity exercise/yoga/stretching/toning(18). Number of flights of stairs climbed daily was also reported. A metabolic equivalent task (MET) score was assigned to each activity based on its energy cost. One MET corresponds to an energy expenditure of approximately 1 kcal/kg of body weight per hour; thus, energy expenditure in kilocalories per week was estimated by multiplying the MET score by body weight and hours per week. This assessment of physical activity has been shown to be valid and reliable(33); for example, the correlation between four 1-week activity diaries kept over one year and questionnaire estimates of physical activity was 0.62.

Physical activity was assessed at baseline and updated at months 36, 72, and 96 during the trial, at trial conclusion (120 months), and year 2 (144 months) of observational follow-up.

Genetic Marker Selection

The single nucleotide polymorphisms (SNPs) that comprise the genetic risk scores in this analysis were selected from "The Human Gene Map for Performance and Health-Related Fitness Phenotypes: The 2006–2007 Update"(6). The goal of the gene map was to review all genes shown to be related to physical performance or health-related fitness phenotypes in at least one study. Studies regarding effects of genes on fitness phenotypes were only included if the focus was on exercise, exercise training, or athletes compared with controls. The most recent version covered the peer-reviewed literature published through December 2007. From this list, we focused on performance phenotypes, including endurance and muscle strength. Additionally, we consulted two annual reviews on exercise and fitness genomics which summarized findings from 2008 to 2010 (10, 24).

The original reports for all identified SNPs were reviewed to confirm the published allele for the fitness phenotype (i.e., that associated with better performance). This allele was then designated the "fitness allele". To ensure that our results reflected independent effects of the fitness alleles, SNPs in each chromosome were pruned to ensure lack of linkage disequilibrium ($r^2 < 0.5$) using the pairwise pruning function in PLINK (v. 1.07, http://pngu.mgh.harvard.edu/purcell/plink/)(23).

In addition to selecting SNPs from the human gene map for fitness, we also investigated specific SNPs related to maximal aerobic capacity that were identified through RNA expression profiling(30) and a recent genome-wide association study (4). In the first study, RNA expression profiling was used to produce a molecular classifier that predicted VO_2max training response. This RNA-based classifier was then used to identify candidate genes for genotyping in the HERITAGE Family Study. Eleven SNPs were found that explained 23% of the total variance (and ~50% of the estimated genetic variance) in gains in VO_2max following aerobic training (30). As this is a substantial proportion of variance explained, we included these 11 SNPs in this analysis. Additionally, a genome-wide association study (GWAS) also conducted in the HERITAGE Family Study recently identified another set of genetic variants associated with the response of VO_2max to exercise training (4). We included the 15 most strongly associated SNPs from among the 21 SNPs they identified in this GWAS. Thus, 26 SNPs associated with VO_2max training response were investigated in the current analysis.

Four genetic scores for fitness were constructed on an a priori basis. The first score was the sum of fitness alleles from SNPs influencing all three phenotypes—endurance, muscle strength, and VO_2max — with SNPs affecting multiple phenotypes included only once. We also created three other genetic scores based on each phenotype separately. Simple counts of the number of alleles were used and additive and independent effects for each allele were assumed.

DNA samples were genotyped with the Infinium II technology from Illumina (Human HAP300 panel), as previously described(25). For SNPs that were not directly genotyped, the MACH 1.0.16 program (http://www.sph.umich.edu/csg/abecasis/mach/index.html), which has been shown to have high accuracy(21), and data from HapMap (13) were used to impute additional genotypes.

We identified 56 SNPs associated with endurance or muscle strength phenotypes from the human gene map for fitness. [In addition to these 56 SNPs, other polymorphisms (e.g., insertion/deletion polymorphisms, short tandem repeats, etc.) were on the gene map; they were not included in this analysis]. After including 26 SNPs for VO_2max, 82 SNPs were searched for within the genotyped or imputed data in the WGHS; 14 SNPs were not available. After removing SNPs included as haplotypes and pruning to eliminate correlated SNPs in high linkage disequilibrium ($r^2 > 0.5$), 58 SNPs were used to construct the overall fitness genetic score (Table, Supplemental Digital Content 1; References, Supplemental Digital Content 4). Of these 58 SNPs, 18 were previously found to be associated with endurance phenotypes, 12 with muscle strength phenotypes, 2 with both endurance and muscle strength, and 26 with VO_2max (Table, Supplemental Digital Content 1). We also had the SNP for the ACE I/D polymorphism (rs4343); however, this SNP was not included due to lack of consensus across studies regarding the fitness allele. Of the 58 SNPs selected, genotypes for 37 were measureddirectly and genotypes for 21 were imputed(minimum MACH R^2 of 0.6 between the imputed allele dose and estimated true genotype). Fractional values of the likelihood-weighted mean estimate of the number of alleleswere used in the genetic score.

Ascertainment of Coronary Heart Disease

The endpoint of interest was incident CHD which included nonfatal myocardial infarction and coronary death. Women reported events on follow-up questionnaires every 6 or 12 months, and medical records were obtained to confirm self-reports. Only CHD events confirmed using medical records as previously described (26)were included. This analysis included endpoints ascertained as of February 2009, when the median follow-up was 14.4 years (interquartile range 13.4 – 14.8 years).

Statistical Analysis

All analyses were conducted using SAS version 9.2 (SAS Institute Inc, Cary, North Carolina) software. We first examined the association between leisure-time physical activity, assessed at baseline and updated during follow-up, and CHD risk. Simple updated levels of physical activity, in which outcomes were predicted from the most recent questionnaire, were used. For example, events that occurred between baseline and 36 months were examined in relation to physical activity level reported on the baseline questionnaire; events from 36 months to 72 months were examined in relation to the physical activity reported on the 36 month questionnaire; and so forth. We categorized women into approximate quartiles of energy expended: less than 200, 200 to 599, 600 to 1499, and 1500+ kcal/wk. Cox proportional hazards models were used to estimate hazard ratios (HR), as measures of relative risk, for CHD as a function of physical activity, adjusted for age (in years) and randomized treatment assignment (aspirin, vitamin E). The HR for each quartile was calculated using the lowest quartile (< 200 kcal/week) as the reference group. Tests for linear trend for increasing quartiles of physical activity were performed by designating the median level of physical activity in each category as the score for that category and then modeling the scores as a continuous variable. In multivariable models, we additionally adjusted for smoking status (never, past, or current smoker); alcohol consumption (4 categories); saturated fat, fiber, and fruit and vegetable intake (quintiles); menopausal status (pre- or postmenopausal); postmenopausal hormone use (never, past, or current); and parental history of MI before age 60 years (yes/no).

Participants were then categorized into quartiles for each of the four genetic scores based on number of fitness alleles: overall fitness, endurance, muscle strength, and VO_2max training response. We examined the association between each fitness genetic risk score and risk of CHD. To test for linear trend across quartiles of genetic score, the median number of fitness alleles for each category of genetic risk score was modeled as a continuous variable. Thus, the HR for the medians represents the risk per fitness allele.

To assess whether the genes for physical fitness modified the association between regular physical activity and CHD risk, we utilized the score for each quartile of physical activity representing the median level of physical activity in each category, as described above. We then modeled CHD risk as a function of physical activity score within quartiles of each genetic score. If SNPs associated with higher baseline fitness or better fitness response to exercise modified the association between physical activity and CHD, then the HR for the physical activity-CHD association would be expected to be higher (i.e., smaller magnitude of risk reduction) in the lowest quartile of genetic score (i.e., fewest alleles associated with higher baseline fitness or better fitness response, or a low fitness genetic score) and lowest (i.e., larger magnitude of risk reduction) in the highest quartile of fitness genetic score (i.e., most alleles associated with better fitness, or a high fitness genetic score). To test for interaction, we used the median number of fitness alleles for each category of genetic risk score to construct a continuous variable for genetic score and then included an interaction term between physical activity score and genetic score in the model.

RESULTS

The 58 SNPs included in the genetic risk scores are listed in the Table, Supplemental Digital Content 1. Each SNP was first tested for a main effect association with CHD risk. Additionally, we examined the interactions between each SNP and physical activity with risk of CHD. If it were true that SNPs associated with higher baseline fitness or a better fitness response to exercise modified the association between physical activity and CHD, then the β coefficient for the interaction term between the SNP and physical activity should be less than zero (i.e. negative) as possessing the fitness allele would enhance the benefit of

physical activity on CHD risk. Out of 58 SNPs, 33 went in the expected direction based on our hypothesis. However, the interaction with only 1 SNP (rs10500872) was statistically significant (p = 0.03), but this would not be the case if adjusted for multiple comparisons.

The mean score (number of alleles associated with higher baseline fitness or better fitness response) for the overall genetic score (58 SNPs) was 60.3 (SD, 4.6) with a range from 41.6 to 77.2. For the endurance genetic score (20 SNPs), this was 24.6 (SD 2.9; range, 11.2–35.0); muscle strength genetic score (14 SNPs), 16.4 (2.2; 6.1–24.8); and VO_2max genetic score (26 SNPs), 22.6 (2.8; 12.0–34.9).

Table, Supplemental Digital Content 2 shows baseline characteristics of WGHS participants according to quartiles of the four genetic scores (lower quartiles represent women possessing the fewest alleles associated with higher baseline fitness or better fitness response; higher quartiles, most alleles associated with better fitness). There was no association between any of the genetic scores and physical activity.

There was a significant inverse association between leisure-time physical activity and risk of CHD (P_{trend} = 0.0008) (Table 1). In multivariable-adjusted models, the HR was 0.56 (95% CI: 0.41, 0.77) for women who reported 1500 kcal/wk of physical activity compared to women reporting < 200 kcal/wk. When treated as a continuous variable, the HR of CHD for a 500 kcal/wk increase in physical activity (i.e., meeting physical activity recommendations for an inactive individual) was 0.88 (95% CI: 0.82, 0.95).

We then examined the association between genetic scores for fitness and risk of CHD (Table 2). There was a borderline statistically significant association between the muscle strength genetic score and CHD risk (P_{trend} = 0.05). The multivariable-adjusted HR of CHD for women in the highest quartile of muscle strength genetic score compared to the lowest quartile was 0.73 (95% CI: 0.54, 0.99). There was no association between the other genetic scores for fitness and CHD risk.

We found little evidence that the association between physical activity and CHD was different among women in the various fitness genetic score categories (Table 3). Leisure-time physical activity was associated with lower CHD risk across categories of each of four genetic scores for physical fitness. Although the association between physical activity and CHD appeared stronger in some strata compared to others, none of the interactions between genetic score and physical activity were statistically significant (Table 3). In a secondary analysis, we restricted the overall genetic score to eight SNPs (*ADRB1,* rs1801253; *ADRB2*, rs1042713 and rs1042714; *AMPD1,* rs17602729; *PPARGC1A,* rs8192678; *ACTN3,* rs1815739; *CNTF,* rs1800169l; *VDR,* rs1544410) whose associations with performance phenotypes have been validated (i.e., observed in more than one study). This analysis also did not indicate stronger inverse associations between physical activity and CHD risk among women with high genetic scores for physical fitness (Table, Supplemental Digital Content 3).

DISCUSSION

To our knowledge, this is the first study to investigate the question: if a person possesses genetic variants associated with low baseline fitness or poor fitness response to exercise training, do they experience less of the benefit on CHD risk accorded by physical activity? In a large group of women from the Women's Genome Health Study, we found this not to be so. We did not find evidence of a significant interaction between any of four genetic scores, constructed using different fitness alleles, and physical activity in the association with incident CHD. That is, habitual leisure-time physical activity was inversely associated

with risk of CHD, with risk reductions of similar magnitude, across groups of women according to fitness genetic score.

Based on the results of this analysis, a genetic predisposition that reduces an individual's baseline physical fitness or ability to become physically fit from exercise training--based on SNPs currently identified--does not preclude achieving cardiovascular disease benefit from physical activity. However, it is important to note that many genes summarized in the human fitness gene map are based on only one study with positive findings, so it is possible that some of the SNPs included in this analysis may be false positives. For example, only 33 of the 58 SNPs included in the genetic scores were in the expected direction when we examined interactions between individual SNPs and physical activity with risk of CHD. In an attempt to improve the validity of the genetic score, in a secondary analysis we included only eight SNPs whose associations have been replicated and obtained similar results.

Ideally, we would have liked to only include SNPs that have been found to be associated with a fitness (either endurance or muscle strength) response to exercise training as these SNPs would be most relevant for the purpose of this study. Unfortunately, few of the SNPs in the human fitness gene map that are associated with the endurance and muscle strength phenotypes were studied in the context of response to exercise training. Given the small number, we decided to include all SNPs related to the phenotypes of endurance and muscle strength. As a result, the genetic scores for endurance and muscle strength were not specific for exercise response, but rather both baseline endurance and muscle strength as well as response to training. Nonetheless, all the SNPs included in the VO_2max genetic score had been selected based on associations with training response and there was no evidence of effect modification of the association between physical activity and CHD by this set of SNPs.

The results obtained are supported by other lines of evidence. One mechanism proposed for the beneficial effect of regular physical activity on CHD is that activity increases physical fitness which in turn lowers CHD risk. Nonetheless, this may only be one pathway through which physical activity lowers CHD risk; there likely are other pathways that operate independently of improvements in fitness. For example, physical activity also improves blood pressure, lipoprotein levels, and glucose tolerance (15, 20), enhances cardiac mechanical and metabolic function (11), and improves hemostatic factors (20). Such improvements likely occur, in part, through mechanisms unrelated to improvements in physical fitness (32).

We did observe a main effect association between the muscle strength genetic score and risk of CHD, where women in the highest quartile had decreased CHD risk compared to women in the lowest quartile. Although most studies showing physical activity to be associated with lower CHD risk have focused on aerobic activity, there is evidence that resistance training has beneficial effects on cardiovascular risk factors(5) and is inversely associated with CHD risk(29). Our unexpected observation warrants further examination.

Strengths of our study include the large sample size, detailed information on physical activity, and long duration of follow-up. However, limitations include the fact that physical activity was self-reported, so measurement is less precise. We used simple updated levels of physical activity in our analysis as opposed to change in physical activity between time points. Although previous studies have shown that changes in physical activity over time are also predictive of outcomes, most have examined change over two time points (1, 9). As we had data collected over several time points, it was easier operationally to use simple updated levels of physical activity. Our study only included women of European ancestry and may not be generalizable to other groups. Also, we were unable to include all of the genetic loci

from the human gene map as some were not single nucleotide polymorphisms or genotyped in our study; thus, the potential contributions of these markers were not examined. Additionally, other SNPs associated with the physical fitness phenotype may yet be identified. Therefore, our genetic score may have accounted for a small proportion of the genetic variation for physical fitness. The fact that many of the SNPs included in this analysis did not go in the expected direction when we examined interactions between individual SNPs and physical activity with CHD risk, and the SNPs that did go in the correct direction often had small effect sizes, could result in less power to detect a significant interaction between the fitness genetic scores and physical activity as more noise was added to the genetic score instead of true allelic effects. Importantly, we did not have a direct measure of fitness in this cohort, so we could not determine the extent to which the genetic scores were associated with fitness in our study population.

In conclusion, in this large prospective cohort of women, genetic variants associated with physical fitness did not modify the inverse association between leisure-time physical activity and risk of coronary heart disease. Thus, the present findings suggest that women will reduce their risk of developing CHD by being physically active, regardless of their genetic predisposition for physical fitness. However, as this is the first study to examine this hypothesis, additional studies are needed to confirm these results.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The Women's Health Study and Women's Genome Health Study are supported by grants CA-047988, HL-043851, HL-080467, HL-099355, and HL-69757 from the National Institutes of Health, Bethesda, MD. The Women's Genome Health study is also supported by grants from the Donald W. Reynolds Foundation and the Fondation Leducq, with collaborative scientific support and funding for genotyping provided by Amgen. Dr. Chomistek was supported by an institutional training grant (HL07575) from the National Heart, Lung, and Blood Institute.

Funding/support: The Women's Health Study and Women's Genome Health Study are supported by grants CA-047988, HL-043851, HL-080467, HL-099355, and HL-69757 from the National Institutes of Health, Bethesda, MD. The Women's Genome Health study is also supported by grants from the Donald W. Reynolds Foundation and the Fondation Leducq, with collaborative scientific support and funding for genotyping provided by Amgen. Dr. Chomistek was supported by an institutional training grant (HL07575) from the National Heart, Lung, and Blood Institute.

References

1. Blair SN, Kohl HW III, Barlow CE, Paffenbarger RS Jr, Gibbons LW, Macera CA. Changes in physical fitness and all-cause mortality: a prospective study of healthy and unhealthy men. JAMA. 1995; 273 (14):1093–1098. [PubMed: 7707596]
2. Bouchard C, Rankinen T. Individual differences in response to regular physical activity. Med Sci Sports Exerc. 2001; 33:S446–S451. [PubMed: 11427769]
3. Bouchard C, An P, Rice T, et al. Familial aggregation of VO2max response to exercise training: results from the HERITAGE Family Study. J Appl Physiol. 1999; 87:1003–1008. [PubMed: 10484570]
4. Bouchard C, Sarzynski MA, Rice TK, Kraus WE, Church TS, Sung YJ, Rao DC, Rankinen T. Genomic predictors of the maximal O_2 uptake response to standardized exercise training programs. J Appl Physiol. 2011; 110:1160–1170. [PubMed: 21183627]
5. Braith RW, Stewart KJ. Resistance exercise training. Its role in the prevention of cardiovascular disease. Circulation. 2006; 113:2642–2650. [PubMed: 16754812]

6. Bray MS, Hagberg JM, Perusse L, et al. The human gene map for performance and health-related fitness phenotypes: the 2006–2007 update. Med Sci Sports Exerc. 2009; 41:35–73. [PubMed: 19123262]
7. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise and physical fitness: definitions and distinctions for health-related research. Public Health Rep. 1985; 100:126–130. [PubMed: 3920711]
8. Cook NR, Lee IM, Gaziano JM, et al. Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. JAMA. 2005; 294:47–55. [PubMed: 15998890]
9. Gregg EW, Cauley JA, Stone K, et al. Relationship of changes in physical activity and mortality among older women. JAMA. 2003; 289(18):2379–86. [PubMed: 12746361]
10. Hagberg JM, Rankinen T, Loos RJF, et al. Advances in exercise, fitness, and performance genomics in 2010. Med Sci Sports Exerc. 2011; 43:743–52. [PubMed: 21499051]
11. Hambrecht R, Wolf A, Gielen S, et al. Effect of exercise on coronary endothelial function in patients with coronary artery disease. The New England Journal of Medicine. 2000; 342:454–60. [PubMed: 10675425]
12. Haskell WL, Lee IM, Pate RR, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Circulation. 2007; 116 (9):1081–93. [PubMed: 17671237]
13. The International HapMap Consortium. A second generation human haplotype map of over 3.1 million SNPs. Nature. 2007; 449(7164):851–861. [PubMed: 17943122]
14. Kodama S, Saito K, Tanaka S, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. JAMA. 2009; 301(19):2024–2035. [PubMed: 19454641]
15. Kraus WE, Houmard JA, Duscha BD, et al. Effects of the amount and intensity of exercise on plasma lipoproteins. The New England Journal of Medicine. 2002; 347:1483–92. [PubMed: 12421890]
16. Lee, IM. Epidemiologic Methods in Physical Activity Studies. Oxford: Oxford University Press; 2009. p. 328
17. Lee IM, Cook NR, Gaziano JM, et al. Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: a randomized controlled trial. JAMA. 2005; 294:56–65. [PubMed: 15998891]
18. Lee IM, Rexrode KM, Cook NR, Manson JE, Buring JE. Physical activity and coronary heart disease in women: is "no pain, no gain" passe? JAMA. 2001; 285(11):1447–1454. [PubMed: 11255420]
19. Manson JE, Hu FB, Rich-Edwards JW, et al. A prospective study of walking as compared with vigorous exercise in the prevention of coronary heart disease in women. N Engl J Med. 1999; 341(9):650–8. [PubMed: 10460816]
20. Mora S, Lee IM, Buring JE, Ridker PM. Association of physical activity and body mass index with novel and traditional cardiovascular biomarkers in women. The Journal of the American Medical Association. 2006; 295:1412–9.
21. Pei Y-F, Li J, Zhang L, Papasian CJ, et al. Analyses and comparison of accuracy of different genotype imputation methods. PLoS One. 2008; 3(10):e3551. [PubMed: 18958166]
22. Physical Activity Guidelines Advisory Committee. Physical Activity Guidelines Advisory Committee Report, 2008. Washington, DC: U.S. Department of Health and Human Services; 2008. p. 683
23. Purcell S, Neale B, Todd-Brown K, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet. 2007; 81(3):559–575. [PubMed: 17701901]
24. Rankinen T, Roth SM, Bray MS, et al. Advances in exercise, fitness, and performance genomics. Med Sci Sports Exerc. 2010; 42:835–46. [PubMed: 20400881]
25. Ridker PM, Chasman DI, Zee RYL, et al. for the Women's Genome Health Study Working Group. Rationale, design, and methodology of the Women's Genome Health Study: a genome-wide association study of more than 25 000 initially healthy American women. Clin Chem. 2008; 54 (2):249–255. [PubMed: 18070814]

26. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med. 2005; 352:1293–1304. [PubMed: 15753114]
27. Sattelmair J, Pertman J, Ding EL, Kohl HW 3rd, Haskell W, Lee IM. Dose-response between physical activity and risk of coronary heart disease: a meta-analysis. Circulation. 2011; 124(7): 789–95. [PubMed: 21810663]
28. Skinner JS, Wilmore KM, Krasnoff JB, et al. Adaptation to a standardized training program and changes in fitness in a large, heterogeneous population: the HERITAGE Family Study. Med Sci Sports Exerc. 2000; 32:157–161. [PubMed: 10647543]
29. Tanasescu M, Leitzmann MF, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Exercise type and intensity in relation to coronary heart disease in men. JAMA. 2002; 288(16):1994–2000. [PubMed: 12387651]
30. Timmons JA, Knudsen S, Rankinen T, et al. Using molecular classification to predict gains in maximal aerobic capacity following endurance exercise training in humans. Journal of Applied Physiology. 2010; 108:1487–1496. [PubMed: 20133430]
31. Williams PT. Physical fitness and activity as separate heart disease risk factors: a meta-analysis. Med Sci Sports Exerc. 2001; 33(5):754–761. [PubMed: 11323544]
32. Wilmore JH, Green JS, Stanforth PR, et al. Relationship of changes in maximal and submaximal aerobic fitness to changes in cardiovascular disease and non-insulin-dependent diabetes mellitus risk factors with endurance training: the HERITAGE Family Study. Metabolism. 2001; 50(11): 1255–63. [PubMed: 11699041]
33. Wolf AM, Hunter DJ, Colditz GA, et al. Reproducibility and validity of a self-administered physical activity questionnaire. Int J Epidemiol. 1994; 23:991–999. [PubMed: 7860180]

Table 1

Hazard ratios (95% CI) of coronary heart disease according to categories of physical activity

	Physical activity (kcal/week)					
	< 200	**200 – 599**	**600 – 1499**	**≥ 1500**	**HR for 500 kcal/week increase**	***P* for trend**
Median, kcal/week	66.5	370.2	968.3	2250.6		
Person-years	70,357	56,354	87,219	100,615		
Events	131	64	62	63		
Age- and treatment- adjusted HR (95% CI)	1.00	0.59 (0.44, 0.80)	0.43 (0.32, 0.58)	0.49 (0.36, 0.66)	0.85 (0.79, 0.92)	<.0001
Multivariable HR (95% CI) *	1.00	0.66 (0.49, 0.89)	0.50 (0.36, 0.67)	0.56 (0.41, 0.77)	0.88 (0.82, 0.95)	0.0008

* Adjusted for age, randomized treatment assignment; smoking status; consumption of alcohol, saturated fat, fiber, fruits, and vegetables; menopausal status; postmenopausal hormone use; parental history of MI.

Table 2

Hazard ratios (95% CI) of coronary heart disease according to categories of genetic scores for physical fitness

Overall Fitness Genetic Score						
	1 (≤ 57.20)	**2 (57.21 – 60.20)**	**3 (60.21 – 63.40)**	**4 (>63.40)**	**HR using medians**	**P for trend**
Median score	55.0	58.8	61.8	65.6		
Person-years	79,287	76,792	79,781	78,685		
Events	83	86	81	70		
Age- and treatment-adjusted HR (95% CI)	1.00	1.04 (0.77, 1.41)	0.95 (0.70, 1.29)	0.82 (0.60, 1.13)	0.98 (0.95, 1.01)	0.20
Multivariable HR (95% CI) *	1.00	1.04 (0.77, 1.40)	0.93 (0.69, 1.27)	0.81 (0.59, 1.12)	0.98 (0.95, 1.01)	0.16
Endurance Genetic Score						
	1 (≤ 22.70)	2 (22.71 – 24.70)	3 (24.71 – 26.60)	4 (> 26.60)	HR using medians	P for trend
Median score	21.1	23.8	25.6	28.0		
Person-years	80,018	77,793	77,181	79,553		
Events	78	82	89	71		
Age- and treatment-adjusted HR (95% CI)	1.00	1.09 (0.80, 1.48)	1.15 (0.85, 1.56)	0.90 (0.65, 1.24)	0.99 (0.95, 1.03)	0.65
Multivariable HR (95% CI) *	1.00	1.07 (0.78, 1.46)	1.13 (0.83, 1.53)	0.90 (0.65, 1.24)	0.99 (0.95, 1.03)	0.62
Muscle Strength Genetic Score						
	1 (≤ 15.00)	2 (15.01 – 16.40)	3 (16.41 – 17.95)	4 (> 17.95)	HR using medians	P for trend
Median score	14.0	15.9	17.0	19.0		
Person-years	82,019	78,514	75,199	78,813		
Events	99	75	75	71		
Age- and treatment-adjusted HR (95% CI)	1.00	0.80 (0.59, 1.07)	0.82 (0.61, 1.11)	0.75 (0.55, 1.01)	0.95 (0.89, 1.00)	0.07
Multivariable HR (95% CI) *	1.00	0.78 (0.58, 1.05)	0.83 (0.61, 1.12)	0.73 (0.54, 0.99)	0.94 (0.89, 1.00)	0.05
VO_2max Genetic Score						
	1 (≤ 20.90)	2 (20.91 – 22.80)	3 (22.81 – 24.60)	4 (> 24.60)	HR using medians	P for trend
Median score	19.2	21.9	23.6	26.0		

Med Sci Sports Exerc. Author manuscript; available in PMC 2014 April 01.

	Overall Fitness Genetic Score					
	1 (≤ 57.20)	**2 (57.21 – 60.20)**	**3 (60.21 – 63.40)**	**4 (>63.40)**	**HR using medians**	**P for trend**
Person-years	78,208	79,587	78,104	78,645		
Events	77	94	84	65		
Age- and treatment-adjusted HR (95% CI)	1.00	1.19 (0.88, 1.60)	1.08 (0.80, 1.48)	0.83 (0.59, 1.16)	0.97 (0.93, 1.02)	0.25
Multivariable HR (95% CI)*	1.00	1.18 (0.87, 1.60)	1.09 (0.80, 1.49)	0.82 (0.59, 1.14)	0.97 (0.93, 1.02)	0.23

*Adjusted for age; randomized treatment assignment; physical activity; smoking status; consumption of alcohol, saturated fat, fiber, fruits, and vegetables; menopausal status; postmenopausal hormone use; parental history of MI.

Table 3

Hazard ratios (95% CI) of coronary heart disease according to physical activity and genetic score categories

	HR for 500 kcal/week increase in physical activity		
Subgroup defined by:	**Events**	**Age- and treatment-adjusted HR (95% CI)**	**Multivariable HR (95% CI)***
All women	320	0.85 (0.79, 0.92)	0.88 (0.82, 0.95)
Overall fitness genetic score			
1st quartile: ≤ 57.20	83	0.77 (0.66, 0.90)	0.79 (0.67, 0.92)
2nd quartile: 57.21 – 60.20	86	0.88 (0.77, 1.01)	0.93 (0.81, 1.06)
3rd quartile: 60.21 – 63.40	81	0.93 (0.81, 1.06)	0.95 (0.82, 1.09)
4th quartile: > 63.40	70	0.81 (0.69, 0.96)	0.85 (0.72, 1.00)
P for interaction		0.60	0.50
Endurance genetic score			
1st quartile: ≤ 22.70	78	0.87 (0.75, 1.01)	0.88 (0.76, 1.02)
2nd quartile: 22.71 – 24.70	82	0.79 (0.68, 0.92)	0.81 (0.69, 0.95)
3rd quartile: 24.71 – 26.60	89	0.82 (0.71, 0.94)	0.85 (0.74, 0.98)
4th quartile: > 26.60	71	0.94 (0.82, 1.09)	0.98 (0.85, 1.14)
P for interaction		0.52	0.50
Muscle strength genetic score			
1st quartile: ≤ 15.00	99	0.85 (0.74, 0.97)	0.87 (0.76, 1.00)
2nd quartile: 15.01 – 16.40	75	0.85 (0.73, 0.99)	0.89 (0.76, 1.03)
3rd quartile: 16.41 – 17.95	75	0.88 (0.76, 1.02)	0.90 (0.78, 1.05)
4th quartile: > 17.95	71	0.82 (0.70, 0.97)	0.86 (0.73, 1.01)
P for interaction		0.79	0.86
VO_2max genetic score			
1st quartile: ≤ 20.90	77	0.82 (0.71, 0.96)	0.84 (0.72, 0.98)
2nd quartile: 20.91 – 22.80	94	0.83 (0.72, 0.95)	0.85 (0.74, 0.97)
3rd quartile: 22.81 – 24.60	84	0.91 (0.79, 1.04)	0.97 (0.84, 1.11)
4th quartile: > 24.60	65	0.84 (0.71, 1.00)	0.86 (0.72, 1.02)
P for interaction		0.71	0.59

*Adjusted for age; randomized treatment assignment; smoking status; consumption of alcohol, saturated fat, fiber, fruits, and vegetables; menopausal status; postmenopausal hormone use; parental history of MI.