Physical Activity and Inflammatory Markers Over 10 Years Follow-Up in Men and Women From the Whitehall II Cohort Study

Mark Hamer, PhD; Severine Sabia, PhD; G. David Batty, PhD; Martin J. Shipley, MSc; Adam G. Tabák, MD, PhD; Archana Singh-Manoux, PhD; Mika Kivimaki, PhD

Background—Inflammatory processes are putative mechanisms underlying the cardioprotective effects of physical activity. An inverse association between physical activity and inflammation has been demonstrated, but no long-term prospective data are available. We therefore examined the association between physical activity and inflammatory markers over a 10-year follow-up period.

Methods and Results—Participants were 4289 men and women (mean age, 49.2 years) from the Whitehall II cohort study. Self-reported physical activity and inflammatory markers (serum high-sensitivity C-reactive protein and interleukin-6) were measured at baseline (1991) and follow-up (2002). Forty-nine percent of the participants adhered to standard physical activity recommendations for cardiovascular health (2.5 h/wk moderate to vigorous physical activity) across all assessments. Physically active participants at baseline had lower C-reactive protein and interleukin-6 levels, and this difference remained stable over time. Compared with participants who rarely adhered to physical activity guidelines over the 10-year follow-up, the high-adherence group displayed lower loge C-reactive protein ($\beta = -0.07; 95\%$ confidence interval, $-0.12$ to $-0.02$) and loge interleukin-6 ($\beta = -0.07; 95\%$ confidence interval, $-0.10$ to $-0.03$) at follow-up after adjustment for a range of covariates. Compared with participants who remained stable, those who reported an increase in physical activity of at least 2.5 h/wk displayed lower log C-reactive protein ($\beta$ coefficient $= -0.05; 95\%$ confidence interval, $-0.10$ to $-0.001$) and loge interleukin-6 ($\beta$ coefficient $= -0.06; 95\%$ confidence interval, $-0.09$ to $-0.03$) at follow-up.

Conclusions—Regular physical activity is associated with lower markers of inflammation over 10 years of follow-up and thus may be important in preventing the proinflammatory state seen with aging. (Circulation. 2012;126:928-933.)

Key Words: C-reactive protein ■ epidemiology ■ exercise ■ inflammation

The anti-inflammatory effects of exercise are thought to be mechanisms that explain the well-documented cardioprotective effects of physical activity.\(^1\)\(^-\)\(^4\) Evidence from epidemiological studies has demonstrated an inverse association between physical activity and markers of low-grade systemic inflammation.\(^5\) However, the majority of existing evidence is drawn from cross-sectional analyses, and few studies have examined the association between long-term physical activity behavior and low-grade inflammation prospectively. Cross-sectional data make it difficult to discount reverse causation effects. For example, some evidence suggests that low-grade inflammation is a marker of sarcopenia;\(^6\) thus, functional limitations might explain associations between systemic inflammation and low activity in aging populations.\(^7\) Tracking low-grade inflammation is particularly relevant in an aging population because inflammatory markers gradually rise with increasing age, and this proinflammatory status underlies biological mechanisms responsible for cardiovascular disease and other age-related diseases.\(^8\)\(^-\)\(^10\)

Clinical Perspective on p 933

Because the majority of health benefits from exercise are established through long-term training adaptations, it is difficult to draw firm conclusions from short-term exercise trials often lasting <6 months. Indeed, this might partly explain the equivocal nature of clinical trial data on exercise and inflammatory markers.\(^11\) Thus, in the present study, we examined the association between physical activity and inflammatory markers over a 10-year follow-up period using a well-characterized population-based cohort study.

Methods

Participants

Participants were drawn from the Whitehall II population–based cohort.\(^12\) The Whitehall II study is an ongoing prospective cohort study.
study that consists of 10,308 participants (6,895 men and 3,413 women 35–55 years of age) recruited from the British civil service in 1985 to investigate social and occupational influences on cardiovascular disease risk. The baseline medical examination (phase 1) took place during 1985 to 1988; subsequent phases have alternated between questionnaire alone (phases 2, 4, 6, and 8) and phases including both a medical examination and a questionnaire (phases 1, 3, 5, 7, and 9). For the purposes of the present study, phase 3 (1991–1993) was regarded as the baseline when inflammatory markers were first assessed, and phase 7 (2002–2004) was regarded as the follow-up. The mean follow-up time between phases 3 and 7 was 11.3 years (range, 9.5–12.9 years). Participants gave full written informed consent to participate in the study, and ethics approval was obtained from the University College London Hospital Committee on the Ethics of Human Research.

Physical Activity Assessment

Physical activity was assessed at phases 3, 5 (1997–1999), and 7 with a self-reported questionnaire. At phase 3, the physical activity assessment consisted of 3 questions about duration and frequency per week spent at light-, moderate-, and vigorous-intensity physical activity. At phases 5 and 7, the physical activity questions consisted of 20 items on frequency and duration of participation in walking, cycling, sports, gardening, housework, and home maintenance.13 Frequency and duration of each activity were combined to compute hours per week of moderate to vigorous physical activity. The 20-item self-reported physical activity questionnaire is a modified version of the previously validated Minnesota Leisure-Time Physical Activity Questionnaire.14 In addition, the self-reported physical activity measure has demonstrated predictive validity for mortality in the Whitehall II study.15 Although assessed slightly differently, physical activity (hours per week of moderate to vigorous exercise) measured at phase 3 was correlated with physical activity measured at phases 5 (Spearman r = 0.41, P < 0.001) and 7 (r = 0.36, P < 0.001). Similar correlations were observed between physical activity at phases 5 and 7 (r = 0.51, P < 0.001) when assessed with an identical questionnaire.

Clinical Assessment and Inflammatory Markers

The procedures for the clinical examination have been described elsewhere.16 Briefly, measurements included height, weight, and hip circumference, blood pressure, and a fasting blood sample taken from the antecubital fossa. Fasting serum was collected between 8 AM and 1 PM and was stored at −70°C. Samples from phases 3 and 7 were analyzed at the same time. The inflammatory marker C-reactive protein (CRP) was measured with a high-sensitivity immunonephelometric assay in a BN ProSpec nephelometer (Dade Behring, Milton Keynes, UK). Interleukin-6 (IL-6) was measured with a high-sensitivity ELISA (R&D Systems, Oxford, UK). Values lower than the detection limit (0.15 mg/L for CRP, 0.08 pg/mL for IL-6) were assigned a value equal to half the detection limit. To measure short-term biological variation and laboratory error, a repeated sample was taken from a subset of 150 participants for CRP and 241 participants for IL-6 at phase 3 (average elapsed time between samples, 32 days [SD = 10.5 days]) and from 533 for CRP and 329 for IL-6 at phase 7 (average elapsed time, 24 days [SD = 11.0 days]). Intra-assay and interassay coefficients of variation were 4.7% and 8.3% for CRP and 7.5% and 8.9% for IL-6 at phases 3 and 7, respectively. A questionnaire was completed on age, civil service employment grade (a measure of socioeconomic status), smoking habits, health status, and hormone replacement therapy (HRT; women only).

Statistical Analysis

The inflammatory markers displayed a skewed distribution, and normality was obtained after natural logarithmic (loge) transformation. Participants were categorized according to whether they adhered to the physical activity guidelines (at least 2.5 h/wk of moderate to vigorous physical activity) that are widely used and have been quantitatively validated for cardiovascular outcomes.16,17 To examine associations between baseline physical activity and change in inflammatory markers between phases 3 and 7, we adopted a linear-mixed-models approach and fit the intercept as a random effect.18 The model included terms for baseline physical activity, time (phase 3 corresponds to time 0 and phase 7 to time 1, so that coefficients associated with time correspond to a 10-year change), and an interaction term between physical activity and time to estimate the association between baseline physical activity and change in inflammatory markers over the follow-up. This model also included covariates that were associated with both physical activity and inflammatory markers. To examine the effects of long-term physical activity exposure over the 3 assessments, participants were categorized as rarely (once or less through follow-up), sometimes (on 2 phases), or always (on all 3 follow-up phases) meeting guidelines. We fit general linear models to examine the association between long-term physical activity exposure (number of times meeting the guideline over follow-up) and inflammatory markers at follow-up, adjusting for age, sex, smoking, employment grade, body mass index (BMI), and chronic illness. In separate sensitivity analyses, we adjusted for waist-to-hip ratio instead of BMI and modeled BMI change. We also investigated associations between changes in physical activity (calculated as the difference in hours per week of moderate to vigorous activity between phases 5 and 7) and inflammatory markers using general linear models. Finally, we used linear mixed models to examine associations between baseline inflammation (categorized as CRP < 1.1, 1.1 to < 3.0, and ≥ 3.0 mg/L) and change in moderate to vigorous physical activity (hours per week) between phases 3 and 7, fitting the intercept as a random-effect term and an interaction term between CRP category and time. All analyses were conducted with SPSS version 20 (SPSS, Chicago, IL) using 2-sided tests with a significance level of P < 0.05.

Results

At baseline, 7,366 participants had available data on all variables; after exclusion of participants with missing data through follow-up, however, the final analytic sample comprised 4,289 participants (3,092 men, 1,197 women). Participants excluded were slightly older (age, 50.1 versus 49.2 years; P < 0.001), were less physically active (3.3 versus 3.6 h/wk moderate to vigorous physical activity; P = 0.003), and had higher baseline loge CRP values (0.87 versus 0.75; P < 0.001) compared with those included. However, these absolute differences in characteristics between the groups were trivial, attaining statistical significance only because of the large sample size. Approximately half the sample (49%) adhered to the physical activity recommendation (2.5 h/wk of moderate to vigorous physical activity) across all assessments (50% at phase 3 [baseline], 83.7% at phase 5, 83.3% at phase 7). Participants who always met the physical activity guidelines were more likely to be men, to be from higher employment grades, and to have lower BMI (Table 1).

Baseline Physical Activity and Change in Inflammatory Markers

Meeting the physical activity guideline at baseline was inversely associated with baseline loge CRP (β coefficient = −0.04; 95% CI, −0.07 to −0.01; P = 0.007) and loge IL-6 (β coefficient = −0.04; 95% CI, −0.06 to −0.02; P < 0.001) after adjustments for age, sex, smoking, employment grade, BMI, and chronic illness (Table 2). On average, there was an increase in both inflammatory markers from baseline to follow-up: loge CRP increased from 0.75 to 0.94 (P < 0.001) and loge IL-6 from 0.93 to 1.08 (P < 0.001), corresponding to a change of 0.44 mg/L (21%) in CRP and 0.41 pg/mL (16%) in IL-6 over 10...
years. There was no statistically significant association between baseline physical activity and change in \( \log_e \) CRP (\( P=0.10 \)) or \( \log_e \) IL-6 (\( P=0.39 \)) over follow-up (Table 2), suggesting that the difference in inflammation levels persisted but did not increase across time (Figure).

**Habitual Physical Activity Over 10 Years and Inflammatory Markers at Follow-Up**

Compared with participants who rarely adhered to physical activity guidelines through follow-up, the high-adherence group displayed lower \( \log_e \) CRP (\( \beta \) coefficient=−0.07; 95% CI, −0.12 to −0.02) and \( \log_e \) IL-6 (\( \beta \) coefficient=−0.07; 95% CI, −0.10 to −0.03) at follow-up after adjustment for age, sex, smoking, employment grade, BMI, and chronic illness (Table 3). These coefficients corresponded to a fully adjusted difference of 0.18 mg/L in CRP and 0.20 pg/mL in IL-6 between individuals who adhered consistently compared with those who did not adhere to physical activity guidelines over 10 years. When we adjusted for waist circumference as a marker of central adiposity (instead of BMI), the effect estimate was slightly attenuated for \( \log_e \) CRP (\( \beta \) coefficient=−0.04; 95% CI, −0.10 to 0.01) but changed little for \( \log_e \) IL-6 (\( \beta \) coefficient=−0.06; 95% CI, −0.09 to −0.02). Participants who were consistently physically active over follow-up gained less weight compared with those who were rarely active (average BMI increase, 1.4±1.8 versus 1.6±2.2 kg/m\(^2\); \( P=0.04 \)). However, adjusting for change in BMI during follow-up (instead of BMI at baseline) did not alter the association between physical activity and inflammatory markers.

We examined the associations for change in physical activity (Table 4). To retain consistency, we calculated changes in activity between phases 5 and 7 when the same questionnaire

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**Table 1. Descriptive Characteristics of the Sample at Baseline in Relation to Habitual Physical Activity Through Follow-Up (n=4289)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rarely (n=681)</th>
<th>Sometimes (n=1503)</th>
<th>Always (n=2105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>48.7±5.7</td>
<td>49.4±5.9</td>
<td>49.1±6.0</td>
</tr>
<tr>
<td>Men, %</td>
<td>56.8</td>
<td>63.9</td>
<td>82.9</td>
</tr>
<tr>
<td>Low-grade employees, %</td>
<td>21.6</td>
<td>12.2</td>
<td>6.5</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>13.2</td>
<td>10.6</td>
<td>10.1</td>
</tr>
<tr>
<td>Chronic illness, %</td>
<td>35.8</td>
<td>35.2</td>
<td>29.9</td>
</tr>
<tr>
<td>Average MVPA, h/wk</td>
<td>1.1±1.9</td>
<td>1.3±1.5</td>
<td>6.0±3.9</td>
</tr>
<tr>
<td>Body mass index, kg/m(^2)</td>
<td>25.3±3.9</td>
<td>25.1±3.6</td>
<td>24.9±3.2</td>
</tr>
<tr>
<td>CRP,† mg/L</td>
<td>2.29±1.90</td>
<td>2.16±1.81</td>
<td>2.05±1.74</td>
</tr>
<tr>
<td>IL-6,† pg/mL</td>
<td>2.70±1.55</td>
<td>2.61±1.47</td>
<td>2.45±1.42</td>
</tr>
</tbody>
</table>

MVPA indicates moderate to vigorous physical activity; CRP, C-reactive protein; and IL-6, interleukin-6.

*Meeting physical activity guidelines (at least 2.5 h/wk of MVPA); “rarely” includes those meeting the guidelines once or less through follow-up; “sometimes,” on 2 phases; and “always,” on all 3 follow-up phases.

†Geometric mean.

**Table 2. Linear Mixed Models to Examine the Association Between Meeting Physical Activity Guidelines at Baseline on Inflammatory Markers Over Phases 3 through 7**

<table>
<thead>
<tr>
<th>Meeting Physical Activity Guidelines at Baseline</th>
<th>Loge C-Reactive Protein</th>
<th>Loge Interleukin-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Model 1</td>
<td>Model 2</td>
</tr>
<tr>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Yes</td>
<td>−0.06 (−0.09 to −0.04)</td>
<td>−0.04 (−0.07 to −0.01)</td>
</tr>
<tr>
<td>Interaction term, physical activity by time</td>
<td>0.03 (−0.01 to 0.06)</td>
<td>0.03 (−0.01 to 0.06)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval. Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, smoking, employment grade, body mass index, and chronic illness. Physical activity–by–time interaction term calculated from meeting the physical activity recommendation (no=0, yes=1) and time (phase 3 corresponds to time 0, phase 7 to time 1).
Sensitivity Analyses

To account for nonspecific inflammatory responses, we reran the analyses after removing 823 participants who had reported acute infections such as cold or influenza 2 weeks before the phase 7 clinical assessment. This did not, however, change the results; eg, compared with participants rarely meeting physical activity guidelines, those who always met the guidelines had significantly lower logₐ CRP (β coefficient = −0.06; 95% CI, −0.11 to −0.005). We ran additional analyses to account for potential effects of HRT in women. Of the cohort, 586 women never used HRT, 211 constantly used HRT, 26 stopped HRT, and 336 started HRT through follow-up (n = 38 missing data). Compared with the women who never used HRT, only those who started using HRT through follow-up displayed elevated logₐ CRP at follow-up (age adjusted coefficient = 0.11; 95% CI, 0.03–0.19). We reran the analyses for physical activity and inflammatory markers in women, making additional adjustments for HRT use (as categorized above: never, constant, stopped, or started). The results still showed that compared with women who rarely adhered to physical activity guidelines, the high-adherence group displayed lower logₐ CRP (fully adjusted β coefficient = −0.10; 95% CI, −0.20 to −0.01; P = 0.04) and logₐ IL-6 (β coefficient = −0.07; 95% CI, −0.13 to −0.01; P = 0.02) at follow-up.

Association of Basal Inflammatory Markers With Physical Activity Change

We also examined the association between baseline inflammatory markers and change in h/wk moderate to vigorous physical activity from phase 3 to 7 using linear mixed models. Participants with CRP ≥3 mg/L at baseline demonstrated decreased moderate to vigorous physical activity at phase 7 (estimate for CRP-by-time interaction = −1.14; 95% CI, −0.35 to −1.92; P = 0.004) compared with those with CRP <1 mg/L after adjustments for age, sex, smoking, employment grade, BMI, and chronic illness.

Discussion

Given that the majority of existing data on physical activity and markers of systemic inflammation are cross-sectional, the aim of this study was to explore the longitudinal association between physical activity and inflammatory markers over a 10-year follow-up period. The main findings show that physically active participants at baseline had lower logₐ CRP (fully adjusted β coefficient = −0.10; 95% CI, −0.20 to −0.01; P = 0.04) and logₐ IL-6 (β coefficient = −0.07; 95% CI, −0.13 to −0.01; P = 0.02) at follow-up. This did not, however, change the results; eg, compared with participants rarely meeting physical activity guidelines, those who always met the guidelines had significantly lower logₐ CRP at follow-up (fully adjusted β coefficient = −0.06; 95% CI, −0.11 to −0.005). We ran additional analyses to account for potential effects of HRT in women. Of the cohort, 586 women never used HRT, 211 constantly used HRT, 26 stopped HRT, and 336 started HRT through follow-up (n = 38 missing data). Compared with the women who never used HRT, only those who started using HRT through follow-up displayed elevated logₐ CRP at follow-up (age adjusted coefficient = 0.11; 95% CI, 0.03–0.19). We reran the analyses for physical activity and inflammatory markers in women, making additional adjustments for HRT use (as categorized above: never, constant, stopped, or started). The results still showed that compared with women who rarely adhered to physical activity guidelines, the high-adherence group displayed lower logₐ CRP (fully adjusted β coefficient = −0.10; 95% CI, −0.20 to −0.01; P = 0.04) and logₐ IL-6 (β coefficient = −0.07; 95% CI, −0.13 to −0.01; P = 0.02) at follow-up.
confounder of the association between physical activity and inflammatory markers in that physically active participants tend to have lower levels of adiposity, and adipose tissue is a key production site for several inflammatory markers. Previous data from the Whitehall II study have demonstrated that increases in BMI and waist circumference over time were associated with higher levels of inflammatory markers at follow-up, although the present findings were independent of changes in body composition. Another important finding showed that basal systemic inflammation was associated with a reduction in physical activity over follow-up after adjustment for confounders such as BMI and chronic illness. Inflammatory processes are thought to be involved in sarcopenia and functional decline, which explains why systemic inflammation may result in decreased activity in aging populations.

Physical activity, inflammation, and health are linked together in a complex fashion. Cytokines are secreted transiently in large doses by several metabolically active tissues during exercise, namely from the muscle during contraction and adipose tissue via exercise-related mechanisms. Paradoxically, regular (long-term) exercise training has consistently been associated with lower levels of systemic inflammatory markers and reduced adipose tissue inflammation. The expression of exercise-regulated muscle genes such as the transcriptional coactivator PGC1α is thought to promote anti-inflammatory effects through a transient release of cytokines and possibly explains some of the systemic and beneficial effects of exercise in nonmuscle tissue. In contrast, chronically elevated levels of low-grade systemic inflammation have been linked to the development of many diseases associated with inflammation, including cardiovascular disease, sarcopenia, neurodegeneration, and depression. Thus, the transient fluctuations of cytokines after exercise might contribute to the beneficial effects of exercise on organs other than muscle in a hormone-like fashion, whereas chronic, low-grade elevation of many of these same molecules is almost certainly proinflammatory and detrimental.

A notable strength of this study is the repeated serial measures taken over a 10-year follow-up period in a well-characterized cohort. This allowed us to track changes in physical activity, inflammatory markers, and other important clinical variables. Self-reported measures of physical activity are prone to reporting bias, although the questionnaire used in the present study is well validated and has demonstrated convergent validity in predicting mortality in the Whitehall II study. In addition, among a subcohort of 394 Whitehall II participants, we recently demonstrated that self-reported physical activity was associated with objectively (accelerometry) assessed activity at the 10-year follow-up across various activity categories. Although there was only modest correlation between physical activity measures at different phases of data collection, we observed an upward trend in physical activity. This might be explained by the fact that many participants from Whitehall II were in transition to retirement during this period. This is consistent with recent data from the French national gas and electricity company (GAZEL) cohort 4 years before and 4 years after retirement showing that leisure-time physical activity increased by 36% in men and 61% in women during the transition to retirement. Our findings on the association between baseline inflammatory markers and change in physical activity over follow-up should be interpreted with caution because we were unable to account for presence of sarcopenia. Nevertheless, the analyses were adjusted for chronic illness that incorporates factors such as functional limitations and history of cardiovascular disease.

Conclusions
The results show that physically active participants maintain lower levels of inflammatory markers over a 10-year period. Thus, physical activity may be important in preventing the proinflammatory state seen with aging.

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Disclosures
None.

References
CLINICAL PERSPECTIVE

The anti-inflammatory effects of exercise are thought to be mechanisms that explain the well-documented cardioprotective effects of physical activity. Although there are abundant cross-sectional data relating C-reactive protein and interleukin-6 levels to physical activity, longitudinal data are sparse, and this is a crucial issue for understanding the complex relationships between exercise, weight loss, and inflammation. The present study, which tracked physical activity and inflammatory markers over 10 years of follow-up in an aging cohort of 4289 men and women, showed that habitually active participants have persistently lower levels of inflammatory markers. In addition, an increase in 2.5 h/wk of moderate to vigorous physical activity through follow-up was associated with lower levels of interleukin-6. The associations observed between physical activity and inflammatory markers were independent of adiposity and changes in body composition. Given that inflammatory markers gradually rise with increasing age and that this proinflammatory status underlies biological mechanisms responsible for cardiovascular disease, physical activity may be regarded as an important factor for the prevention of age-related disease risk.
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