Interleukin-18 Polymorphism and Physical Functioning in Older People: A Replication Study and Meta-Analysis

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Background. Levels of the proinflammatory cytokine interleukin-18 (IL-18) are raised in old age and are associated with reduced physical functioning. Previous studies have indicated that the C allele of the rs5744256 polymorphism in the IL-18 gene is strongly associated with reduced circulating IL-18 levels. This variant has previously been associated with improved locomotor performance in old age, but the finding requires independent replication.

Methods. We examined the association between the IL-18 polymorphism rs5744256 and physical functioning in three cohorts with a total of 4,107 participants aged 60–85 years: the English Longitudinal Study of Ageing, Caerphilly, and Boyd Orr. We meta-analyzed (N = 6,141) the results with data from the original paper reporting this association: Iowa-Established Populations for Epidemiological Study of the Elderly and InCHIANTI Study cohorts. Physical functioning was assessed by timed walks or the get up and go test. As locomotor performance tests differed between the cohorts and the distributions of times to complete the test (in seconds) were positively skewed, we used the reciprocal transformation and computed study-specific z scores.

Results. Based on the three new studies, the estimated linear regression coefficient per C allele was 0.011 (95% confidence interval [95% CI]: −0.04 to 0.06). A meta-analysis that pooled the data from all studies showed weak evidence of an effect, with a regression coefficient of 0.047 (95% CI: 0.010 to 0.083).

Conclusions. We did not replicate an association between the IL-18 rs5744256 polymorphism and the physical function in people aged 60–85 years. However, pooling data from all studies suggested a weak association of the C allele of the rs5744256 single nucleotide polymorphism on improving walking times in old age.

Key Words: Interleukin-18 polymorphism—IL-18—Ageing—Physical function—Gait speed—Walk time.

LOCOMOTOR function is a meaningful health outcome as the ability to perform day-to-day activities in a normal manner is of importance to an individual’s quality of life. Understanding the causes of reduced locomotor function in old age and the identification of potential prevention strategies are also critically important public health issues. It has been hypothesized that the proinflammatory cytokine interleukin-18 (IL-18), which is an important regulator of innate and acquired immune responses (1), could contribute to early-onset physical disability in older people (2); increased IL-18 serum concentrations increase with age (3) and are associated with a higher risk of conditions that play a role in disability (4, 5), and inflammation is important factor in ageing (6, 7). For a more detailed discussion of biological mechanisms, see a recent review by Dinarello (7).

Frayling and colleagues (2) provided evidence that higher IL-18 serum concentrations were associated with poorer physical functioning in old age, measured by standard physical performance tests, using data from two studies involving 1,671 participants aged 60–85 years: the InCHIANTI study and Iowa-Established Populations for Epidemiological Study of the Elderly (Iowa-EPESE). The authors also found that the minor, C, allele of the rs5744256 single nucleotide polymorphism (SNP) in IL-18 was associated with a 0.25 SD reduction in serum IL-18 per allele. It was hypothesized that IL-18 gene alleles that reduce circulating IL-18 levels would be associated with improved physical functioning. In support of this hypothesis, it was found that the C allele of rs5744256 was associated with improved walking times in both cohorts (p values = 0.016 and 0.026, respectively). As the association between the genotype and the physical functioning is unlikely...
to be explained by reverse causality or confounding (8), this finding suggests that circulating IL-18 levels may be causally related to poor physical function in old age. However, the genotype–physical functioning association could have arisen by chance because the p values for the association did not reach genome wide thresholds for statistical significance (2). To test the robustness of the association of the IL-18 rs5744256 SNP with physical function, we investigate whether there is an association in a further three cohorts: the English Longitudinal Study of Ageing (ELSA), Caerphilly, and Boyd Orr, in total involving 4,107 participants aged 60–85 years. To summarize the total evidence (based on 6,141 participants), we then meta-analyzed the new results together with data from InCHIANTI and Iowa-EPESE, the cohorts which first demonstrated an association (2).

**METHODS**

**English Longitudinal Study of Ageing**

Detailed information on the study design has been reported elsewhere (9). The ELSA sample was drawn from households with one or more residents aged 50 years or older who were originally participants in the Health Survey for England, in years 1998, 1999, and 2001. The second wave of the ELSA survey took place in 2004, with blood samples collected from approximately 3,600 participants aged between 65 and 79 years.

**Caerphilly Prospective Study**

The Caerphilly Prospective Study (CaPS) recruited 2,512 men aged 45–59 years between 1979 and 1983 from the town of Caerphilly, South Wales, and the adjacent villages (10). Since baseline phase I, the men have been seen at phases II (1984–1988), III (1989–1993), IV (1993–1996), and V (2002–2004). In each phase, participants attended a clinic, completed a questionnaire, had anthropometric measurements, and blood samples were taken. Ethical approval was given by the Ethics Committee of the Division of Medicine of the former South Glamorgan Area Health Authority.

**Boyd Orr**

The Boyd Orr study is an historical cohort based on the Carnegie (Boyd Orr) Survey of Diet and Health in Pre-War Britain, 1937–1939 (11,12). Of the original 4,999 participants (who were a mean age of 7 y at the time of survey), 4,379 (88%) have been traced and flagged using the National Health Service Central Register and its equivalent in Edinburgh. In 2002, all 732 study members who lived near clinics in Bristol, London, Wisbech, Aberdeen, and Dundee were contacted, which resulted in 405 participants who took part in a detailed clinical examination to obtain physiological measurements and blood assays when aged 63–83 years. Ethical approval was obtained from the Multicenter Research Ethics Committee for Scotland. All participants gave informed consent.

**InCHIANTI**

The InCHIANTI study is a population-based study in two small towns in the Tuscany region of Italy (13). The study is representative of the population aged 65 years and older. In 1998, 1,260 participants aged 65 years and older were randomly selected from the population registry of the two towns, with 1,154 (89%) people enrolling in the project. Study participants responded to a structured home interview, a full medical, neurological, and functional examination and blood samples were taken. Participants received an extensive description of the study and participated after written informed consent. The study protocol complied with the Declaration of Helsinki and was approved by the Italian National Institute of Research and Care on Aging Ethical Committee.

**Iowa-EPESE**

Between 1981 and 1983, the entire population aged 65 years and older, living in two Iowa counties, was surveyed (14). Follow-up data were collected annually for 7 years. Blood specimens were obtained from those participants re-interviewed for the sixth annual follow-up in 1988. Genotype data were available for 1,645 individuals across the whole cohort. The original study was approved by the University of Iowa Institutional Review Board.

**Assessment of Physical Function**

The get up and go test (15) is a standardized objective measure of functional leg strength, power, mobility, and balance that is strongly correlated with activities of daily living and integrates a number of basic mobility manoeuvres considered necessary for successful ageing and protection from later disability. The participant is observed and timed while he or she rises from a chair, walks 3 m, turns, walks back, and sits down. The test was performed using the same standardized protocol in both the Boyd Orr and the Caerphilly cohorts, and the researchers were trained by the same investigator.

The timed walk was the time taken by the respondent to walk at their usual pace a distance of 8 feet (2.4 m) in ELSA and Iowa-EPESE and 4 and 7 m in InCHIANTI. The 4-m walk has been used as the main measure in InCHIANTI. The 4-m walk has been used as the main measure in InCHIANTI. In all the studies, the tests were performed on the participants twice and the mean time was used for each individual. In all these tests, reduced walking time refers to faster (not slower) walking speed.

**Genotyping**

We used modified TaqMan assays at KBiosciences (Hoddesdon, UK) to generate genotypes from the rs5744256 SNP in the Boyd Orr, Caerphilly, and InCHIANTI DNA samples. SNP genotypes in the Iowa-EPESE DNA samples were generated using custom TaqMan allele discrimination assays developed by Applied Biosystems, Foster City, CA. SNP genotypes in ELSA were generated as part of a 1536
Goldengate custom SNP panel by Illumina (San Diego, CA) using high-throughput BeadArrayTM technology. Call rates across the five studies ranged from 87% to 99% (Iowa-EPESE 87%, InCHIANTI 98%, ELSA 99%, Caerphilly 98%, and Boyd Orr 95%). SNP genotypes satisfied Hardy–Weinberg equilibrium across all studies ($p > 0.1$). Duplicate error rates were below 5% for ELSA, Boyd Orr, InCHIANTI, and Iowa-EPESE, but duplicates were not included in CaPS.

**Literature Search**

We performed a Web of Science literature search using the search terms “interleukin-18” or “IL-18” combined with “locomotor disability,” “physical function,” “physical performance,” “gait speed,” or “get up and go test” and undertook a cited reference search on the original paper (2). We found that to date, no other studies have investigated the association.

**Statistical Methods**

All analyses were carried out using Stata version 10. Analyses were restricted to participants aged 60–85 years because only a small percentage of cohort members older than 85 years completed the physical test. To avoid confounding by ethnicity, we limited analyses of the Iowa-EPESE and ELSA studies to white participants. All members of the InCHIANTI cohort are of white ethnic origin. Unfortunately, ethnicity data were never obtained in the Caerphilly and Boyd Orr cohorts. We know from investigators that there could be no more than two black men in the Caerphilly sample and no men of Asian origin. To the best of our knowledge, there are no non-white participants in the Boyd Orr sample who attended the clinical examination.

The walk or get up and go times were positively skewed, so we used the reciprocal transformation. There were large differences in the walking times between studies because of the differences in the protocols of the performance tests, so the transformed times were standardized into study-specific $z$ scores. The associations of the IL-18 rs5744256 SNP with the transformed standardized times in each of the Boyd Orr, Caerphilly, and ELSA cohorts were analyzed using linear regression, adjusting for age, age squared, and sex (we term this analysis on the new cohorts the “replication” analysis, as distinct from the meta-analysis of all data). The study-specific effect estimates were then meta-analyzed in a random effects model to give an overall estimate of effect. In line with the original publication (2), we assumed an additive model, testing for trend with the increasing number of C alleles (TT, TC, and CC genotypes). The interpretation of regression coefficients on the transformed standardized times is that a positive coefficient indicates a reduction in walk time per additional C allele, suggesting a beneficial effect of this allele on physical function; in contrast, a negative coefficient indicates an increased walk time per additional C allele.

A meta-analysis was carried out to examine the overall association of the IL-18 rs5744256 SNP and physical function, on all studies and for the studies with the timed walk test only (ELSA, Iowa-EPESE, and InCHIANTI). To evaluate the percentage of variation between studies that cannot be attributed to within-study variation, we used the $I^2$ value (16) and 95% confidence intervals (95% CIs) based on the statistical significance of $Q$ (17). A fixed effects model using the Mantel–Haenszel method and a random effects model using the DerSimonian and Laird method were used to pool the results of all five studies.

A sensitivity analysis was performed to assess the possibility of selection bias as a result of excluding participants with missing walk times. The walk time for each study was divided into quintiles and then the calculation of quintiles was repeated, this time assuming that participants with missing walk times had the slowest walking times for that study. The distribution of the rs5744256 SNP by the calculated quintiles was compared to look for any differences that might suggest a different genotype distribution among those with missing data.

A further sensitivity analysis was carried out to investigate which of the physical performance measures is the most discriminative for measuring frailty in old age. For each study, we regressed the inverse transformed standardized performance times on age, which was rescaled by 5-year age bands. For InCHIANTI, we did this for both the 4- and 7-m walks. The more sensitive measures will have larger regression coefficients, whereas less sensitive measures will not detect similar years-of-age equivalent sized changes.

**Results**

A summary of key variables in the data sets for the five studies is shown in Table 1, for participants aged 60–85 years with genotype and timed walk information. The mean and median walk times vary considerably between studies, due to the differences in the type of tests that were carried out, indicating the need to standardize the walk times by computing study-specific $z$ scores.

**Replication Analysis**

The associations of the IL-18 SNP with the standardized walk times in the ELSA, Caerphilly, and Boyd Orr cohorts are shown in Table 2. The raw data (median time in seconds for the get up and go and walking test) indicate little variation and no consistent pattern of an increase or decrease in walking time across alleles for each study. In all three studies, the confidence interval for the regression coefficient contains 0, indicating no evidence of an association between the rs5744256 SNP and physical function. When data from the three studies were combined in a meta-analysis, the overall estimate of effect was 0.010 (95% CI: −0.04 to 0.06; $p = 0.66$) per C allele, after adjusting for age, age squared, and sex (Figure 1). This compares to the pooled effect estimate of 0.012 (95% CI: −0.02 to 0.04; $p = 0.49$) per C allele, after adjusting for age, age squared, and sex (Figure 2). This represents a significant increase in the magnitude of the effect estimate.
from the studies in the original paper (2) based here on the transformed standardized walk times, of 0.104 (95% CI: 0.045 to 0.163; \( p = 0.001 \)).

The sensitivity analysis comparing the distribution of the rs5744256 SNP with the walk time quintiles for each study showed no difference in the distributions of rs5744256 alleles whether those with missing walk time are excluded or if it is assumed that missing walk time implies a person who is likely to have the slowest walk times (results not presented).

Meta-Analysis of New and Previously Published Data

In total, we have data on 6,141 participants from five studies. The forest plot from the random effects meta-analysis is shown in Figure 1. The \( I^2 \) value was 44% (95% CI: 0%–79%). This indicates moderate heterogeneity across studies but, with a wide confidence interval, we cannot rule out a high level of heterogeneity; given this and the fact that there were differences in the physical function tests performed in each study, we present both the random effects and the fixed effects meta-analyses. The random effects pooled estimate is 0.048 (95% CI: −0.004 to 0.101), which is similar in magnitude to the pooled estimate from a fixed effects meta-analysis (0.047; 95% CI: 0.010 to 0.083). When performing the meta-analysis for only studies with the timed walk test (ELSA, InCHIANTI, and Iowa-EPESE), the pooled fixed effects estimate is 0.06 (95% CI: 0.02 to 0.10; results not presented in figures).

When using the 7-m walk for the InCHIANTI cohort, rather than the 4-m walk (results not presented), the random effects pooled estimate is slightly stronger at 0.054 (95% CI: −0.007 to 0.116) and the pooled estimate from a fixed effects meta-analysis is 0.053 (95% CI: 0.017 to 0.089). The results from the sensitivity analysis showing the associations of age (rescaled by 5-y age bands) on the inverse transformed and standardized physical performance measures are shown in Table 3. These results show that in InCHIANTI, the 7-m walk is more discriminative for measuring frailty in old age (regression coefficient = −0.41, 95% CI: −0.46 to −0.36) compared with the 4-m walk in the same study (regression coefficient = −0.32, 95% CI: −0.37 to −0.27). The get up and go test is consistent with the timed walks, with a regression coefficient for the rescaled age of −0.31 (95% CI: −0.39 to −0.23) in Caerphilly and −0.32 (95% CI: −0.43 to −0.21) in Boyd Orr. The 2.4-m walk in ELSA has a smaller regression coefficient of −0.25 (95% CI: −0.28 to −0.22). A chi-square test for heterogeneity between studies is 28.31 (\( p < 0.001 \)).

### Table 1. Summary of Data Sets, Ages 60–85 Years

<table>
<thead>
<tr>
<th>Analysis Type</th>
<th>Study</th>
<th>Tested Physical Performance</th>
<th>Age (y)</th>
<th>Test Time (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N (%) Median Time (s)</td>
<td>N (%) Median Time (s)</td>
<td>N (%) Median Time (s)</td>
</tr>
<tr>
<td>Replication analysis</td>
<td>ELSA</td>
<td>8-ft (2.4-m) walk</td>
<td>2,955</td>
<td>68.3 (5.6) 60–79</td>
</tr>
<tr>
<td></td>
<td>Caerphilly</td>
<td>Get up and go test</td>
<td>765</td>
<td>72.6 (4.1) 60–83</td>
</tr>
<tr>
<td></td>
<td>Boyd Orr</td>
<td>Get up and go test</td>
<td>387</td>
<td>70.7 (4.3) 64–82</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>InCHIANTI</td>
<td>4-m walk</td>
<td>796</td>
<td>72.4 (5.9) 60–85</td>
</tr>
<tr>
<td></td>
<td>Iowa-EPESE</td>
<td>8-ft (2.4-m) walk</td>
<td>1,238</td>
<td>77.1 (4.0) 71–85</td>
</tr>
</tbody>
</table>

**Note:** For participants with complete data on age, sex, rs5744256, and physical function. ELSA = English Longitudinal Study of Ageing; Iowa-EPESE = Iowa Established Populations for Epidemiological Study of the Elderly.

### Table 2. Association of the IL-18 rs5744256 Single Nucleotide Polymorphism With Walking Times, Results from Replication Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Tested Physical Performance</th>
<th>Genotype</th>
<th>TT</th>
<th>TC</th>
<th>CC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>Median Time (s)</td>
<td>N (%) Median Time (s)</td>
<td>N (%) Median Time (s)</td>
<td>Total N</td>
</tr>
<tr>
<td>ELSA</td>
<td>8-ft (2.4-m) walk</td>
<td>1,636 (55.4)</td>
<td>2.53</td>
<td>1,118 (37.8) 2.50</td>
<td>201 (6.8) 2.56</td>
</tr>
<tr>
<td>Caerphilly</td>
<td>Get up and go test</td>
<td>429 (56.1) 10.30</td>
<td>292 (38.2) 10.32</td>
<td>44 (5.8) 10.14</td>
<td>765</td>
</tr>
<tr>
<td>Boyd Orr</td>
<td>Get up and go test</td>
<td>219 (56.6) 9.17</td>
<td>132 (34.1) 9.71</td>
<td>36 (9.3) 8.87</td>
<td>387</td>
</tr>
<tr>
<td>Pooled</td>
<td>8-ft (2.4-m) walk or get up and go test</td>
<td>2,281 (55.6)  N/A(^1)</td>
<td>1,542 (37.6)  N/A(^1)</td>
<td>281 (6.8)  N/A(^1)</td>
<td>4,107</td>
</tr>
</tbody>
</table>

**Notes:** ELSA = English Longitudinal Study of Ageing.

\(^1\)The linear regression model adjusts for age, age squared, and sex; the dependent variable is the inverse transformed standardized times. A positive coefficient indicates a reduction in walk time per C allele; a negative coefficient indicates an increase in walk time per additional C allele.

\(^2\)Not applicable to report the medium time for pooled physical performance tests.

**Discussion**

In this study, we examined the association between the IL-18 SNP and physical function in 60- to 85-year olds, using data from three studies: ELSA, Caerphilly, and Boyd Orr. In addition, we carried out a meta-analysis that included data from the InCHIANTI and Iowa-EPESE cohorts, which were used in the publication that first reported on this association (2). We were unable to replicate the findings from the original publication as confidence intervals for the regression coefficients contained 0 for all three new studies, separately and when combined. Pooling the results from all five studies in the meta-analysis provided some evidence that the minor
C, allele of the rs5744256 SNP in IL-18 was associated with better locomotor performance in 60- to 85-year olds.

It is not unusual to find weaker associations or no evidence of an association when replicating genetic association studies (18). Ioannidis described the winner’s curse as being present when the first “positive” study, even on a true association, provides inflated estimates compared with the truth (19). Our replication analysis and meta-analysis of all five studies suggests that either there is no causal association between the C allele of the rs5744256 IL-18 SNP and physical function or that if there is a causal link, the magnitude of the genetic effect is much smaller than originally estimated. The raw data of time in seconds varied very little across alleles in ELSA, Caerphilly, and Boyd Orr, with no consistent pattern of an increase or decrease of walking time. The public health significance of such a small effect is likely to be minimal.

A possible explanation of our inability to replicate the previous findings could include type II error because the Caerphilly and Boyd Orr cohorts were relatively small with sample sizes of 765 and 387 participants, respectively. Small sample sizes could be a problem if the effect size is smaller than the original reported association. However, ELSA is the largest of all five studies, with a sample size of 2,955. A false-negative result based on the individual ELSA study seems unlikely. For the replication analysis with the combined sample size of 4,107, we have over 80% power to pick up an effect size of 0.045 (the lower 95% confidence limit for the pooled effect estimate from the studies originally reporting an association based on the transformed standardized walk times).

Another explanation for failure to reproduce the results of the original paper could be due to the differences in tests that were used to measure physical function. In the Caerphilly and Boyd Orr cohorts, the participants were asked to rise from a chair as well as to walk 6 m. In ELSA, InCHIANTI, and Iowa-EPESE, there was only the timed walk aspect of physical function or that if there is a causal link, the magnitude of the genetic effect is much smaller than originally estimated. The raw data of time in seconds varied very little across alleles in ELSA, Caerphilly, and Boyd Orr, with no consistent pattern of an increase or decrease of walking time. The public health significance of such a small effect is likely to be minimal.

### Table 3. Associations of Age (rescaled by 5-y age bands) on the Inverse Transformed and Standardized Physical Performance Measures

<table>
<thead>
<tr>
<th>Study</th>
<th>Tested Physical Performance</th>
<th>Regression Coefficient* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELSA</td>
<td>8-ft (2.4-m) walk</td>
<td>-0.25 (-0.28 to -0.22)</td>
</tr>
<tr>
<td>Iowa-EPESE</td>
<td>8-ft (2.4-m) walk</td>
<td>-0.32 (-0.37 to -0.26)</td>
</tr>
<tr>
<td>InCHIANTI</td>
<td>4-m walk</td>
<td>-0.32 (-0.37 to -0.27)</td>
</tr>
<tr>
<td>InCHIANTI</td>
<td>7-m walk</td>
<td>-0.41 (-0.46 to -0.36)</td>
</tr>
<tr>
<td>Caerphilly</td>
<td>Get up and go</td>
<td>-0.31 (-0.39 to -0.23)</td>
</tr>
<tr>
<td>Boyd Orr</td>
<td>Get up and go</td>
<td>-0.32 (-0.43 to -0.21)</td>
</tr>
</tbody>
</table>

*Change in transformed standardized walk times per 5-year increase in age.

**Notes:** 95% CI = 95% confidence interval; ELSA = English Longitudinal Study of Ageing; Iowa-EPESE = Iowa-Established Populations for Epidemiological Study of the Elderly.

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**Figure 1. Forest plot for the association of the IL-18 rs5744256 single nucleotide polymorphism and physical function, meta-analysis of new and previously published data.** Notes: Effect estimates are based on the inverse transformed standardized times and provide the regression coefficient per C allele. ELSA = English Longitudinal Study of Ageing; Iowa-EPESE = Iowa-Established Populations for Epidemiological Study of the Elderly.
the test, with a varying distance to walk. Both timed walking and the get up and go test are measuring aspects of muscular strength and neurological processing. Gait speed and the get up and go test are highly correlated with a correlation coefficient of $-0.61$ (15). The sensitivity analysis revealed that a walk of a longer distance could be a better discriminatory of the underlying latent trait of frailty, but the get up and go test was not different to the timed walks. A longer timed walk may also be beneficial as it probably has less measurement error. Although it is unlikely that the differences in performance tests accounts for all heterogeneity, it could explain some of the inconsistency of findings.

There were some potential weaknesses that may have influenced our findings. The set of participants used for analysis in this study was selected on the basis of the availability of the outcome variable. As with other longitudinal cohort studies, there has been attrition of the original samples, which may account for some differences between the study populations. Loss to follow-up is unlikely to be associated with genotype: in the sensitivity analysis, the distribution of the rs5744256 SNP by walk time quintiles remained unchanged when assuming people with a missing walk time had the slowest score. Although we cannot test this directly, we would not expect loss to follow-up to affect the analyses between genotype and outcome.

**Conclusion**

We were unable to replicate the findings of an association between the IL-18 rs5744256 SNP and physical function in people aged 60–85 years of white ethnic origin. However, pooling the data from all studies shows a weak association of the C allele of rs5744256 SNP on improving walking times in old age. The public health significance of such a small effect is likely to be minimal.

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**References**