# Interleukin-18 and physical function in old age: A replication study and meta-analysis

Kate Thomas

# 🔥Talk outline

- Background

- The cohorts

- Measures of physical function

- Replication analysis

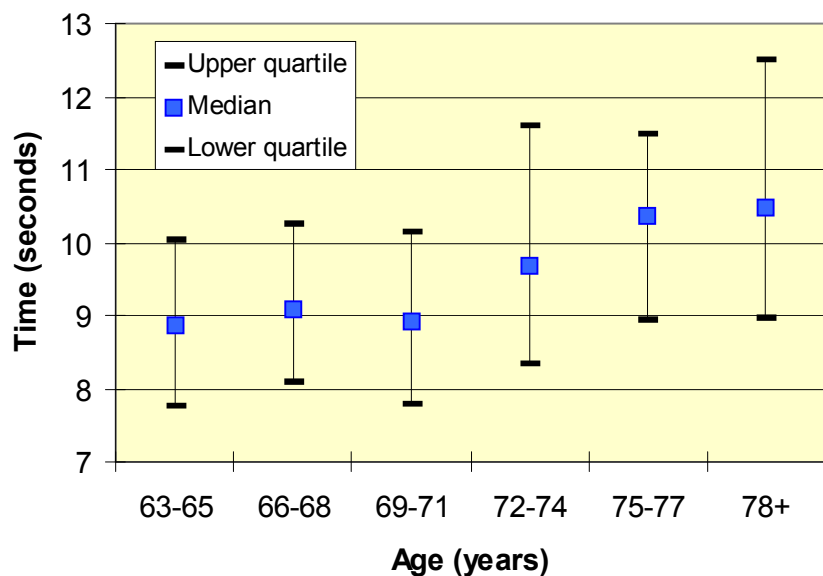- Meta-analysis

- Discussion



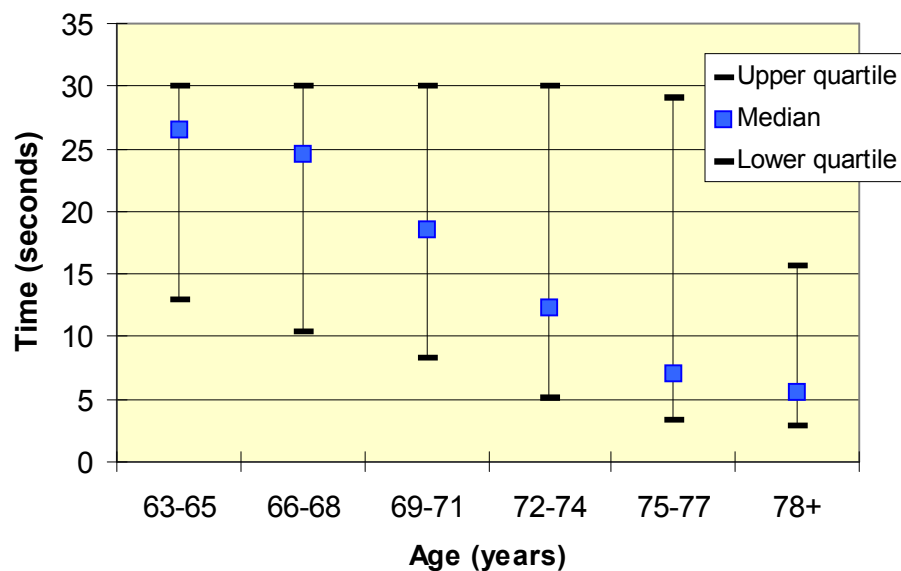University of BRISTOL

# Background

- Physical function in old age is a meaningful health outcome for the quality of life of the individual

- Older people being able to function independently in the community has public health relevance

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# Physical function and age

**Get up and go test by age group**

**Flamingo test by age group**

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# Interleukin-18

- Interleukin-18 (IL-18) is pro-inflammatory cytokine and is an important regulator of innate and acquired immune responses

- Increased IL-18 serum concentrations are associated with higher risk of conditions that play a role in disability

- Inflammation is an important factor in ageing therefore IL-18 could contribute to physical disability in old age

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# Previous study

- Higher IL-18 serum concentrations were associated with poorer physical functioning in old age

- Minor, C, allele of the rs5744256 SNP in IL-18 was associated with a 0.25 standard deviation reduction in serum IL-18 per allele

- C allele of rs5744256 was associated with improved walking times

Frayling TM et al (2007) J Gerontol A Biol Sci Med Sci; 62(1):73-8

# IL-18 and physical function



IL-18 genotype → IL-18 serum concentration

IL-18 genotype → Physical function

IL-18 serum concentration ↔ Physical function
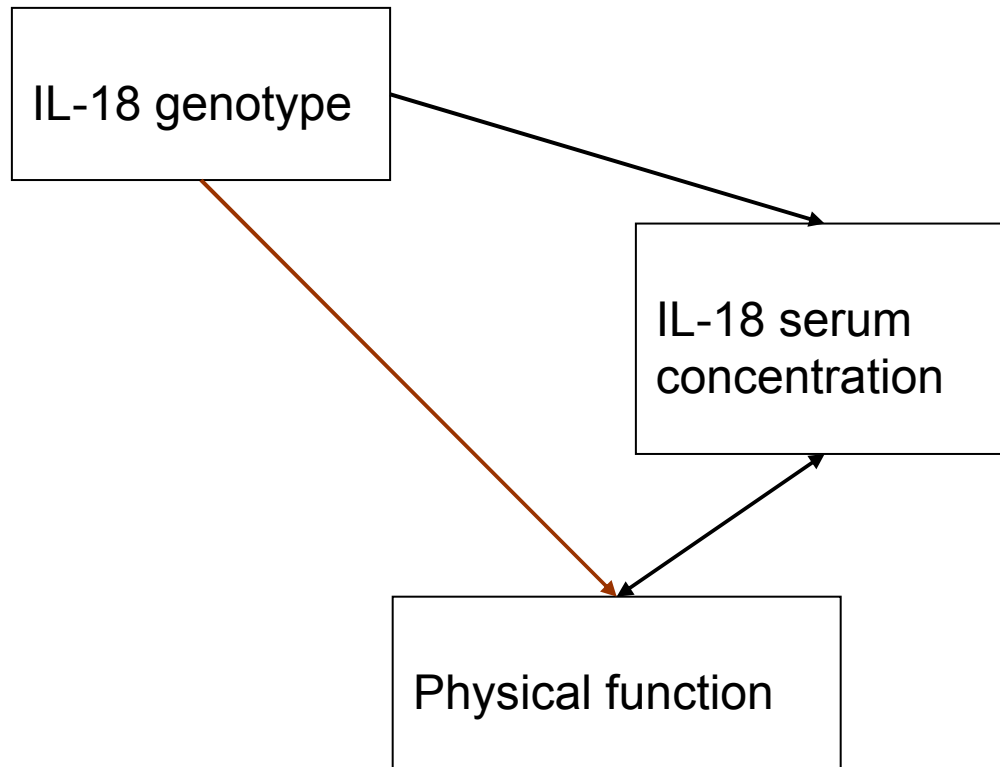
# Summary of datasets

| Study | Test | N | Age (years) Mean (SD) | Age (years) Range | % Male |
|-------|------|---|-----------------------|-------------------|--------|
| **ELSA** | **8-ft (2.4-m) walk** | **2955** | **68.3 (5.6)** | **60-79** | **46%** |
| **Caerphilly** | **Get up and go test** | **765** | **72.6 (4.1)** | **60-83** | **100%** |
| **Boyd Orr** | **Get up and go test** | **387** | **70.7 (4.3)** | **64-82** | **45%** |
| InCHIANTI | 4-m walk | 796 | 72.4 (5.9) | 60-85 | 44% |
| Iowa-EPESE | 8-ft (2.4-m) walk | 1238 | 77.1 (4.0) | 71-85 | 36% |

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# Physical function tests

| Study | Test | Test time (seconds) | | |
| | | Mean (SD) | Median | Range |
|---|---|---|---|---|
| ELSA | 8-ft walk | 2.8 (1.4) | 2.5 | 1-26 |
| Caerphilly | Get up and go test | 11.0 (3.2) | 10.3 | 6-32 |
| Boyd Orr | Get up and go test | 10.1 (4.3) | 9.3 | 6-61 |
| InCHIANTI | 4-m walk | 4.3 (2.1) | 3.9 | 1-44 |
| Iowa-EPESE | 8-ft walk | 4.2 (2.6) | 3.6 | 1-45 |

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# Distribution walk times (ELSA)
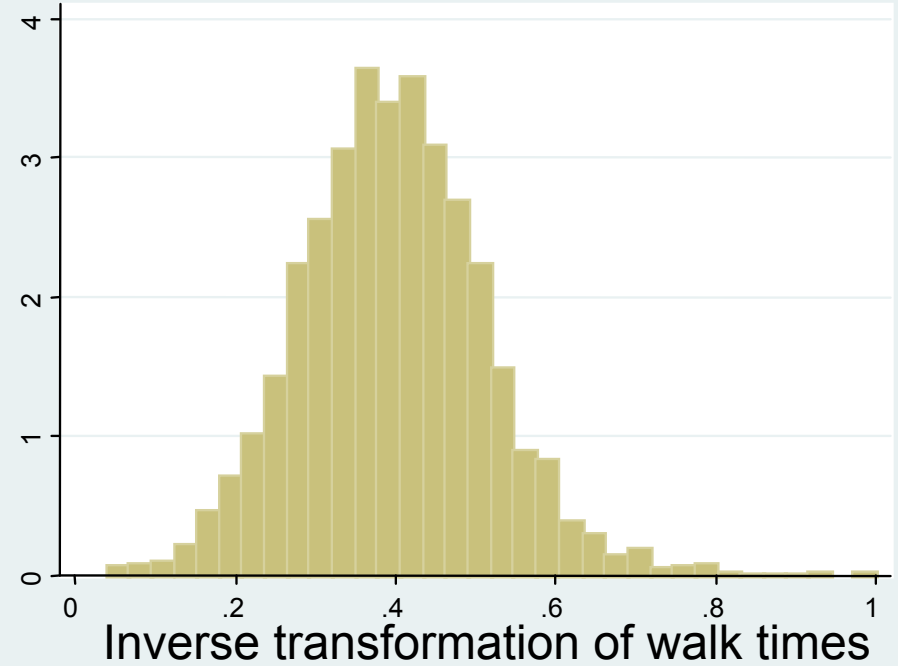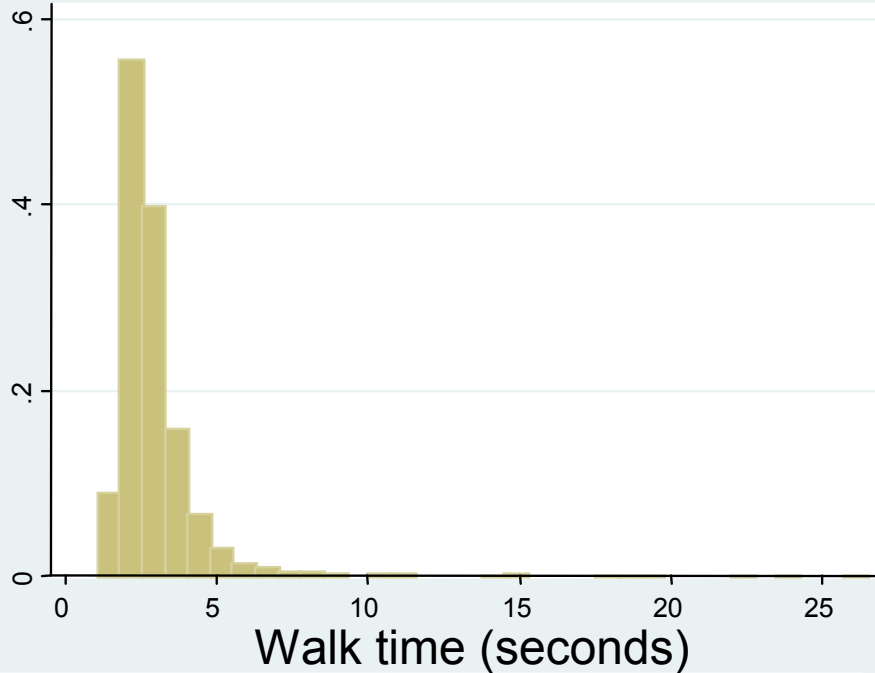
# Replication analysis

Association of the IL-18 rs5744256 single nucleotide polymorphism with walking times

| Study | Median time (seconds) | | | | | | Regression coefficient (95% CI) | p |
|---|---|---|---|---|---|---|---|---|
| | TT | | Genotype TC | | CC | | | |
| | N (%) | Median | N (%) | Median | N (%) | Median | | |
| ELSA | 1636 (55.4%) | 2.53 | 1118 (37.8%) | 2.50 | 201 (6.8%) | 2.56 | 0.021 (-0.03 to 0.08) | 0.45 |
| Caerphilly | 429 (56.1%) | 10.30 | 292 (38.2%) | 10.32 | 44 (5.8%) | 10.14 | -0.038 (-0.15 to 0.07) | 0.49 |
| Boyd Orr | 219 (56.6%) | 9.17 | 132 (34.1%) | 9.71 | 36 (9.3%) | 8.87 | 0.021 (-0.13 to 0.17) | 0.78 |

The linear regression model adjusts for age, age squared and sex; the dependent variable is the inverse transformed, standardised times

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# Meta-analysis

- Calculates a summary effect estimate which is a weighted average of the estimated effects from individual studies

- Analysis performed using Stata 10 using the *metan* command

- Forest plots draw attention to the studies with the greatest weight

- The diamond represents the overall summary estimate, with confidence intervals given by its width

# Fixed and random effects meta-analysis

- Fixed-effects model using the Mantel–Haenszel method, assumption that the true effect does not differ between studies

- Random-effects model using the DerSimonian and Laird method, assumption the effect varies between studies

- $I^2$ value to evaluate the percentage of variation across studies due to heterogeneity

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# Meta-analysis, all studies
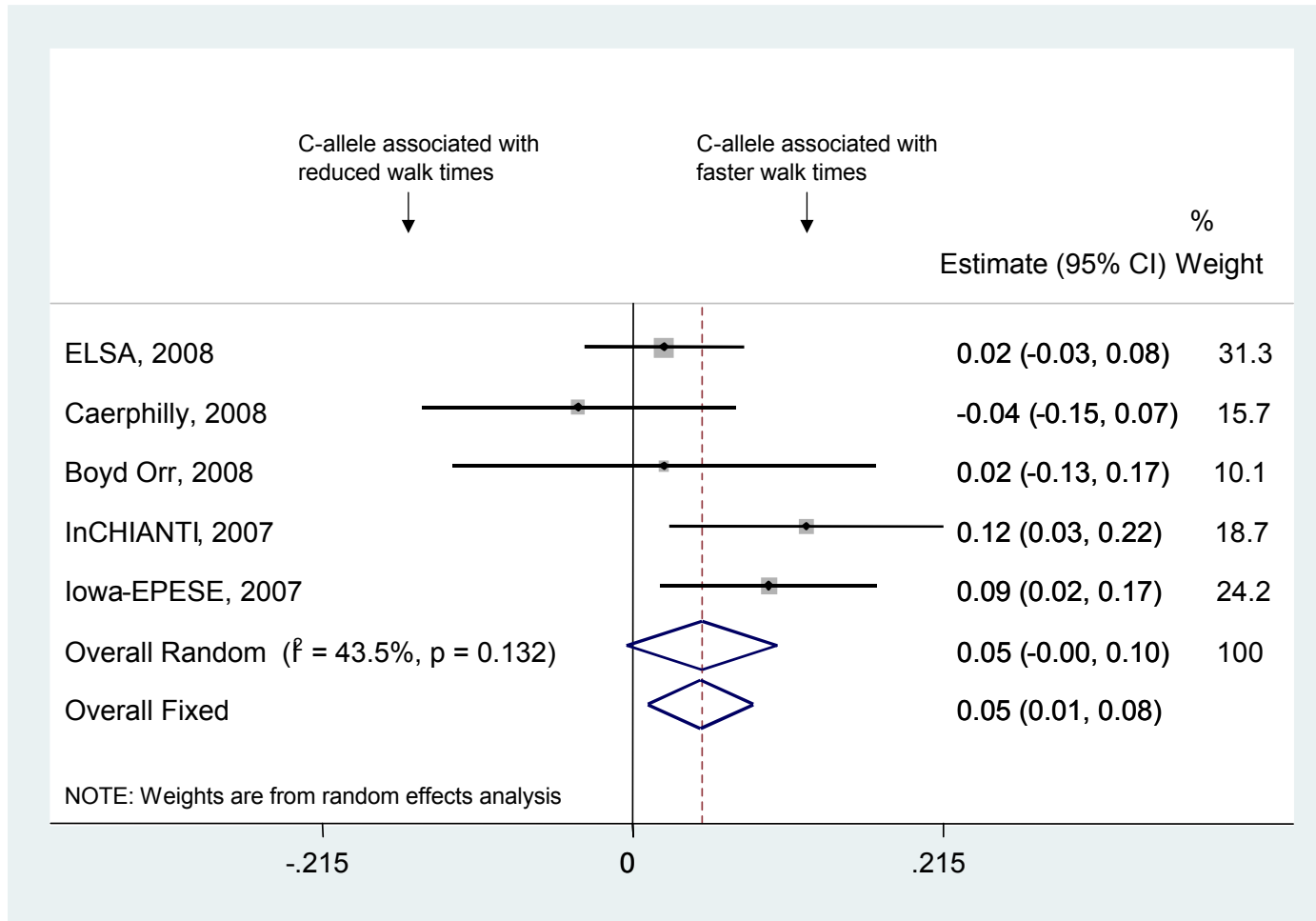
# Sensitivity analysis

Linear regression on the inverse transformed times for rescaled age by 5 year age band

| Study | Test | Age coeff | 95% CI | p |
|---|---|---|---|---|
| ELSA | 2.4m walk | -0.25 | -0.28 to -0.22 | <0.001 |
| Iowa-EPESE | 2.4m walk | -0.32 | -0.37 to -0.26 | <0.001 |
| InCHIANTI | 4m walk | -0.32 | -0.37 to -0.27 | <0.001 |
| InCHIANTI | 7m walk | -0.41 | -0.46 to -0.36 | <0.001 |
| Caerphilly | Get up & go | -0.31 | -0.39 to -0.23 | <0.001 |
| Boyd Orr | Get up & go | -0.32 | -0.43 to -0.21 | <0.001 |

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# Discussion

- Statistical power

- Winner's curse?

- Differences in tests that were used to measure physical function

- Further studies needed

# Acknowledgements

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