Individual participant data meta-analysis in observational research

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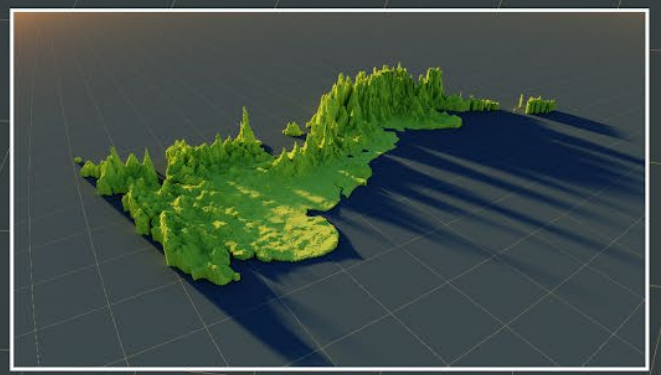
Where does all the rain fall?

Exactly where you'd expect

This is a 3D representation of rainfall in Great Britain in 2017. The higher the peaks, the more rain fell in that area. The data are based on 1 km gridded estimates of monthly rainfall and are published by the UK Centre for Ecology and Hydrology under an Open Government Licence. The big grid squares are 100km x 100km.



The vertical dimension is exaggerated, to emphasise the variation

Alasdair Rae

Data source: CEH, 2020

The problem

Clinical and policy decisions need to be made using the best available evidence

BUT

Individual studies can be of low statistical power and subject to chance findings

Systematic review & meta-analysis

Systematic review and meta-analysis can increase statistical power and reduce uncertainty in findings

Well-established methods spanning observational and interventional research

The traditional approach: study-level (aggregate) meta-analysis

Involves extracting published effect estimates from study reports

Relatively cheap and time efficient

BUT

Reliant on what is reported in the main study

Considerable variation in analysis methods and reporting

Inconsistency in adjustment for potentially important variables

Problematic to investigate effects in important subgroups, including ethnicity and sociodemographic factors

Is the association between blood pressure and mortality in older adults different with frailty? A systematic review and meta-analysis

Oliver M Todd ✉, Chris Wilkinson, Matthew Hale, Nee Ling Wong, Marlous Hall, James P Sheppard, Richard J McManus, Kenneth Rockwood, John Young, Chris P Gale, Andrew Clegg

Age and Ageing, Volume 48, Issue 5, September 2019, Pages 627–635,
https://doi.org/10.1093/ageing/afz072
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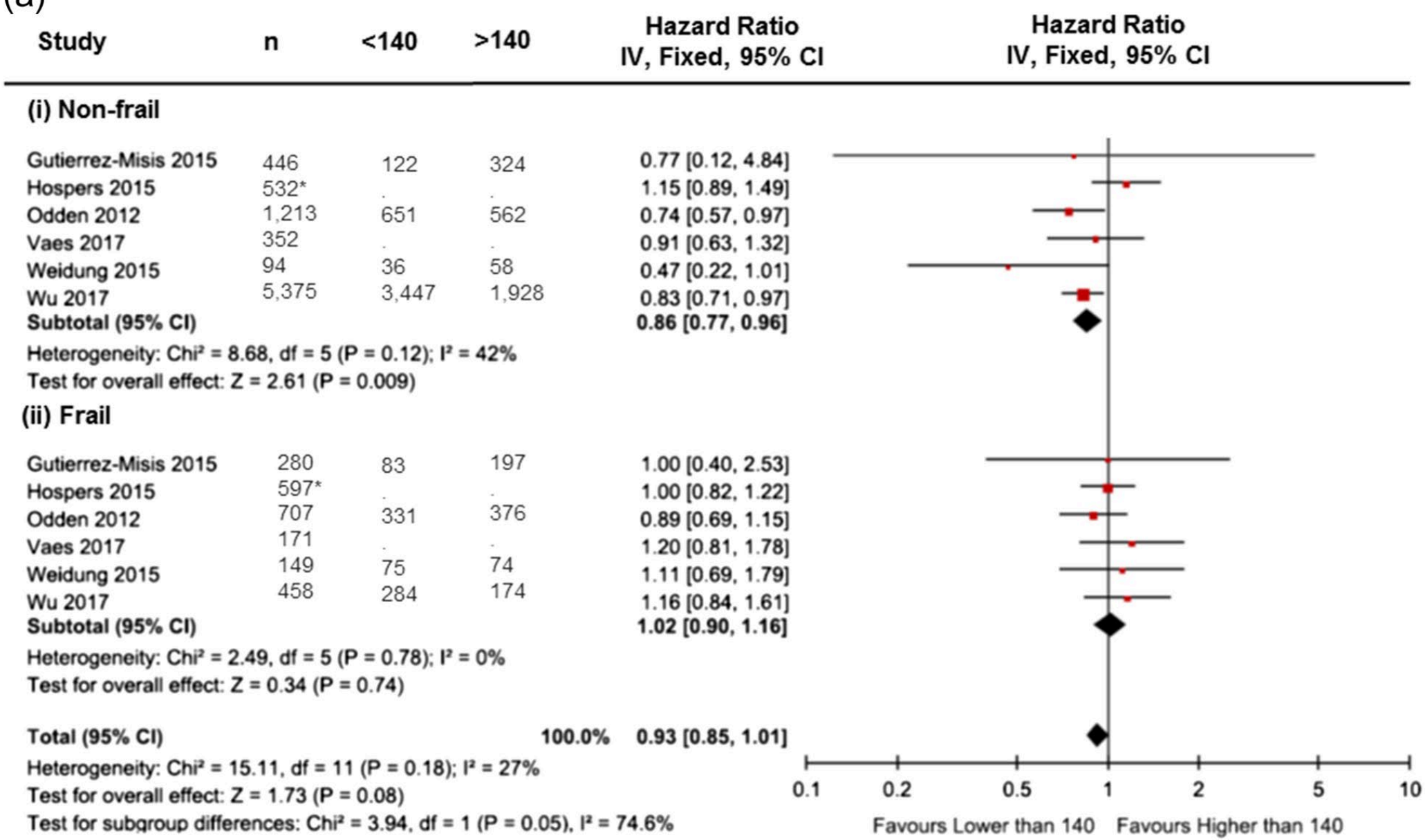
(a)


Study
n
<140
>140
Hazard Ratio
IV, Fixed, 95% CI
Hazard Ratio
IV, Fixed, 95% CI
(i) Non-frail
Gutierrez-Misis 2015 446 122 324 0.77 [0.12, 4.84]
Hospers 2015 532* . . 1.15 [0.89, 1.49]
Odden 2012 1,213 651 562 0.74 [0.57, 0.97]
Vaes 2017 352 . . 0.91 [0.63, 1.32]
Weidung 2015 94 36 58 0.47 [0.22, 1.01]
Wu 2017 5,375 3,447 1,928 0.83 [0.71, 0.97]
Subtotal (95% CI) 0.86 [0.77, 0.96]
Heterogeneity: Chi² = 8.68, df = 5 (P = 0.12); I² = 42%
Test for overall effect: Z = 2.61 (P = 0.009)
(ii) Frail
Gutierrez-Misis 2015 280 83 197 1.00 [0.40, 2.53]
Hospers 2015 597* . . 1.00 [0.82, 1.22]
Odden 2012 707 331 376 0.89 [0.69, 1.15]
Vaes 2017 171 . . 1.20 [0.81, 1.78]
Weidung 2015 149 75 74 1.11 [0.69, 1.79]
Wu 2017 458 284 174 1.16 [0.84, 1.61]
Subtotal (95% CI) 1.02 [0.90, 1.16]
Heterogeneity: Chi² = 2.49, df = 5 (P = 0.78); I² = 0%
Test for overall effect: Z = 0.34 (P = 0.74)
Total (95% CI) 100.0% 0.93 [0.85, 1.01]
Heterogeneity: Chi² = 15.11, df = 11 (P = 0.18); I² = 27%
Test for overall effect: Z = 1.73 (P = 0.08)
Test for subgroup differences: Chi² = 3.94, df = 1 (P = 0.05), I² = 74.6%
0.1
0.2
0.5
1
2
5
10
Favours Lower than 140
Favours Higher than 140

What is individual participant data meta-analysis

- Individual participant data meta-analysis (IPD MA) involves the collection and synthesis of original raw study data
- Advantages include:
  - Application of consistent eligibility criteria
  - Opportunity to address missing data across studies
  - Consistent adjustment for key variables
  - Use of standardised statistical analysis
  - Development and validation of prognostic models & examination of multiple individual-level factors
  - Correlation between multiple endpoints can be accounted for when participants provide data at multiple timepoints

Riley, Lambert, Abo-Zaid BMJ 2010

Research

Physical inactivity, cardiometabolic disease, and risk of dementia: an individual-participant meta-analysis

BMJ 2019 ; 365 doi: https://doi.org/10.1136/bmj.l1495 (Published 17 April 2019)
Cite this as: *BMJ* 2019;365:l1495

Conclusions In analyses that addressed bias due to reverse causation, physical inactivity was not associated with all-cause dementia or Alzheimer's disease, although an indication of excess dementia risk was observed in a subgroup of physically inactive individuals who developed cardiometabolic disease.

Key challenges of IPD MA

- Time
- Cost
- Data sharing & ethics
- Complexity of data preparation and analytical approaches

- Efforts to establish research collaboratives and harmonization of data across longitudinal studies of ageing can help address some of these challenges

Some potential applications of IPD MA using pooled data from longitudinal ageing research studies

- Development and validation of prognostic models, especially those that include biomarkers/genetic data, or use machine learning methods
- Investigation of prognostic factors where there is inconsistent adjustment for potentially important variables
- Investigation of the epidemiology of ageing in important groups, including ethnic minority groups