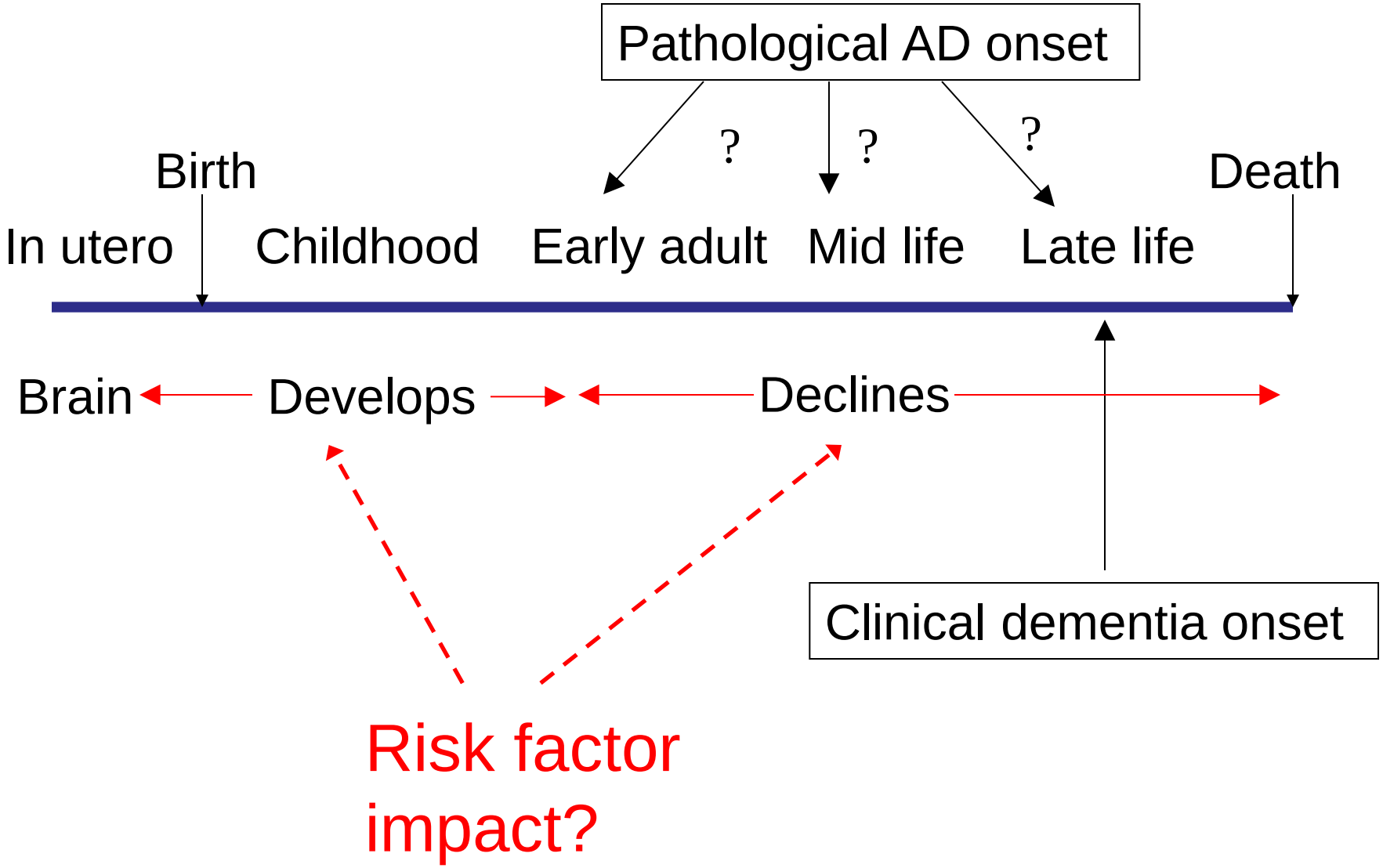
Markers of early life development and risk for dementia in late life

Dementia risk
- a lifecourse perspective



Sociodemographic and socioeconomic/ cognitive reserve risk factors for incident 10/66 dementia

Risk factor	RR*	95% CI	Heterogeneity Higgins I^2
Base model (mutually adjusted)			
Age	1.67	1.56-1.79	49 (0-76)
Sex (m vs f)	0.72	0.61-0.84	25 (0-64)
Education (per level)	0.89	0.81-0.97	50 (0-77)
Lower occupation attainment (per level)	1.04	0.95-1.13	0 (0-65)
More assets (per asset)	0.93	0.88-1.00	63 (24-82)
Extensions to base model (adjusted for base model but not each other)			
Literacy	0.68	0.55-0.84	53 (1-78)
Animal naming (per word)	0.93	0.91-0.94	61 (19-81)
Luria (Fist-Edge-Palm) – higher score worse performance	1.28	1.18-1.38	76 (54-88)

Prince et al Lancet 2012

Proxy indicators of early life development

- Skull circumference
  - Related to intercranial volume
  - Stable over the adult life course
  - Reflects early life neurodevelopment

- Leg length
  - Related to trunk height (and overall height)
  - Unlike overall height, it is more stable over the adult life course
  - Particularly sensitive to breastfeeding and diet in infancy

Developmental risk factors for dementia

- Skull circumference is inversely associated with
  - cognitive deficit in AD (Graves et al, 1996, Schofield et al,1997)
  - cognitive impairment in community samples (Reynolds et al 1999)
  - dementia, but few community-based studies (Schofield et al, 1997; Mortimer et al, 2003)
- Leg length is inversely associated with
  - dementia (Kim et al 2003)
  - cognitive decline (Mak et al 2006)
- Most studies are cross-sectional
  - selective mortality?
  - reverse causality?

Associations between leg length and age, gender and education

	Age	Gender	Education
	Younger> older	M>F	Higher> lower
Leg length	+	++	+
Skull circ	+	++	+/-

- Age effect absent in less developed settings
- Gender effect more prominent in China and India
- Education effect more prominent on leg length than skull circumference

Prince et al – International Psychogeriatrics 2010

Mean population height by year and world region, from historical records (Baten et al, 2012)

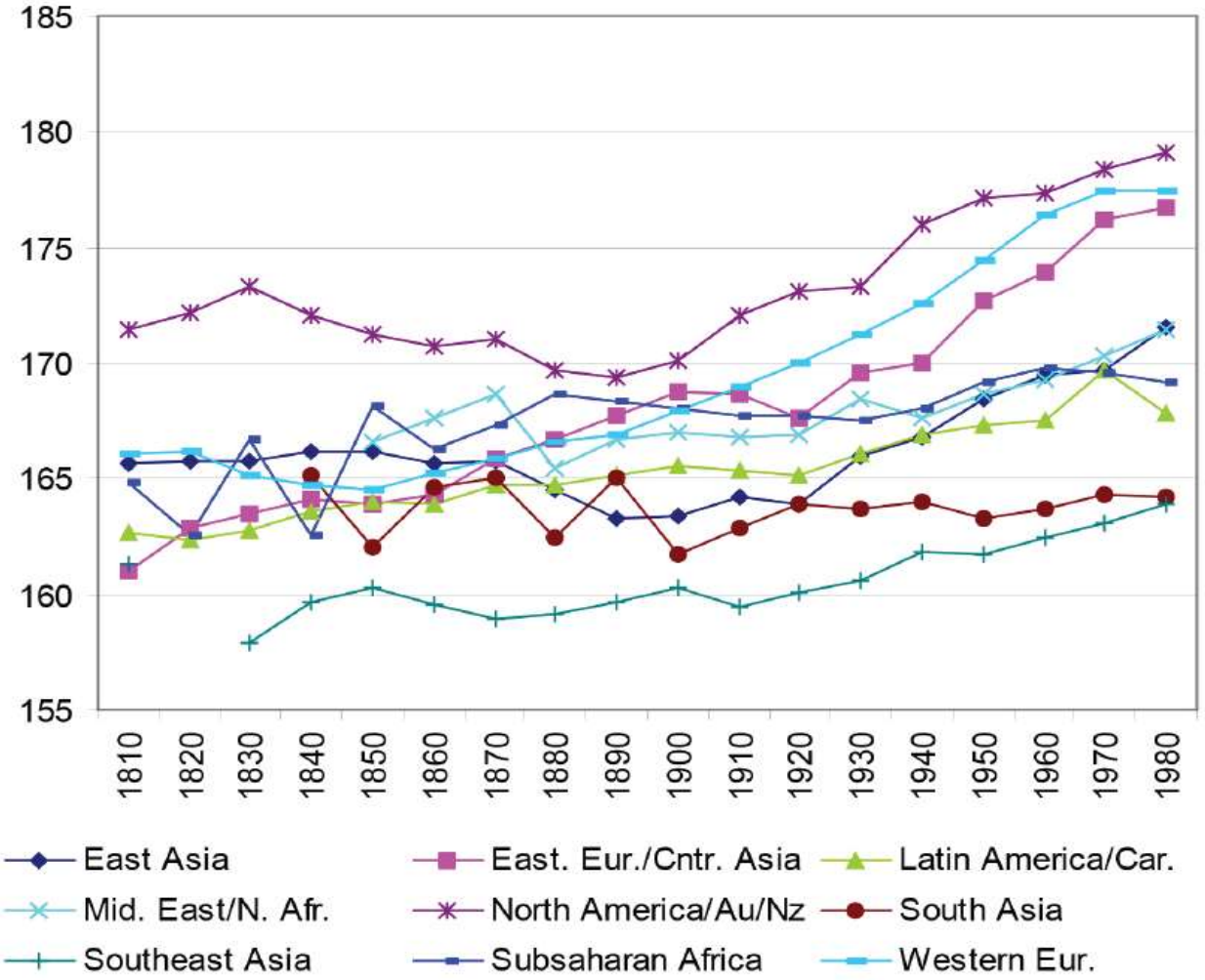
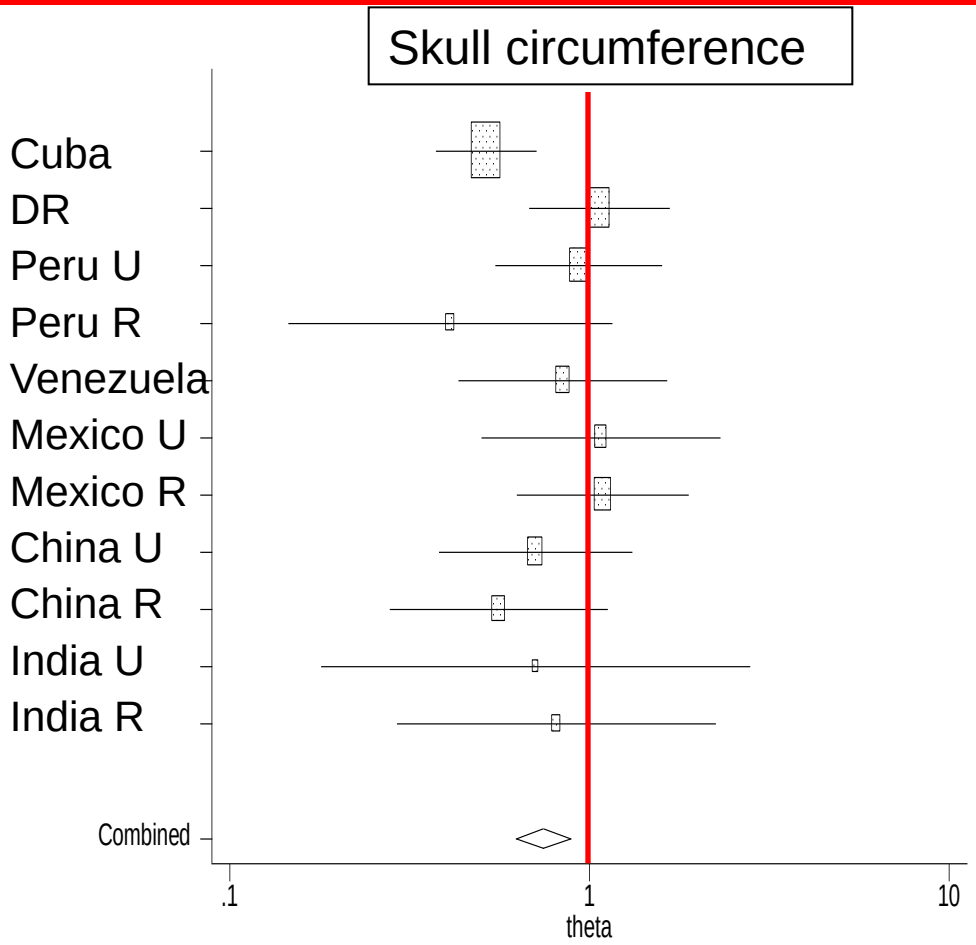
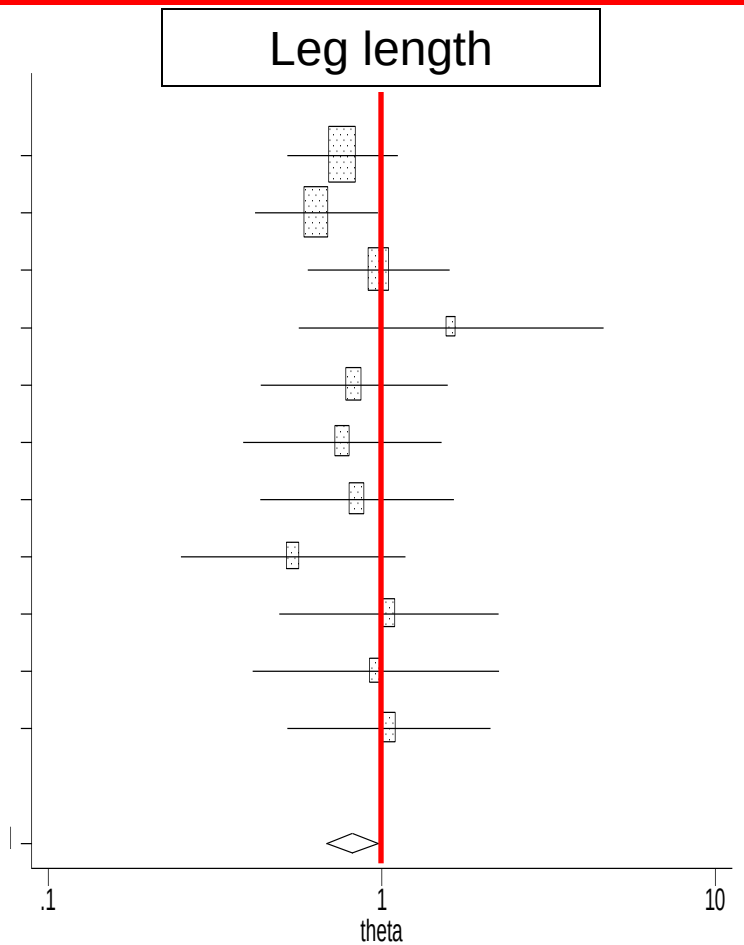


Fig. 1 - Height development by world region (no interpolations, weighted by population size).

Prevalence Ratios* - association between skull circumference/ leg length (largest vs. smallest quarters) and 10/66 dementia



PR = 0.75 (0.63-0.89)



PR= 0.82 (0.68-0.98)

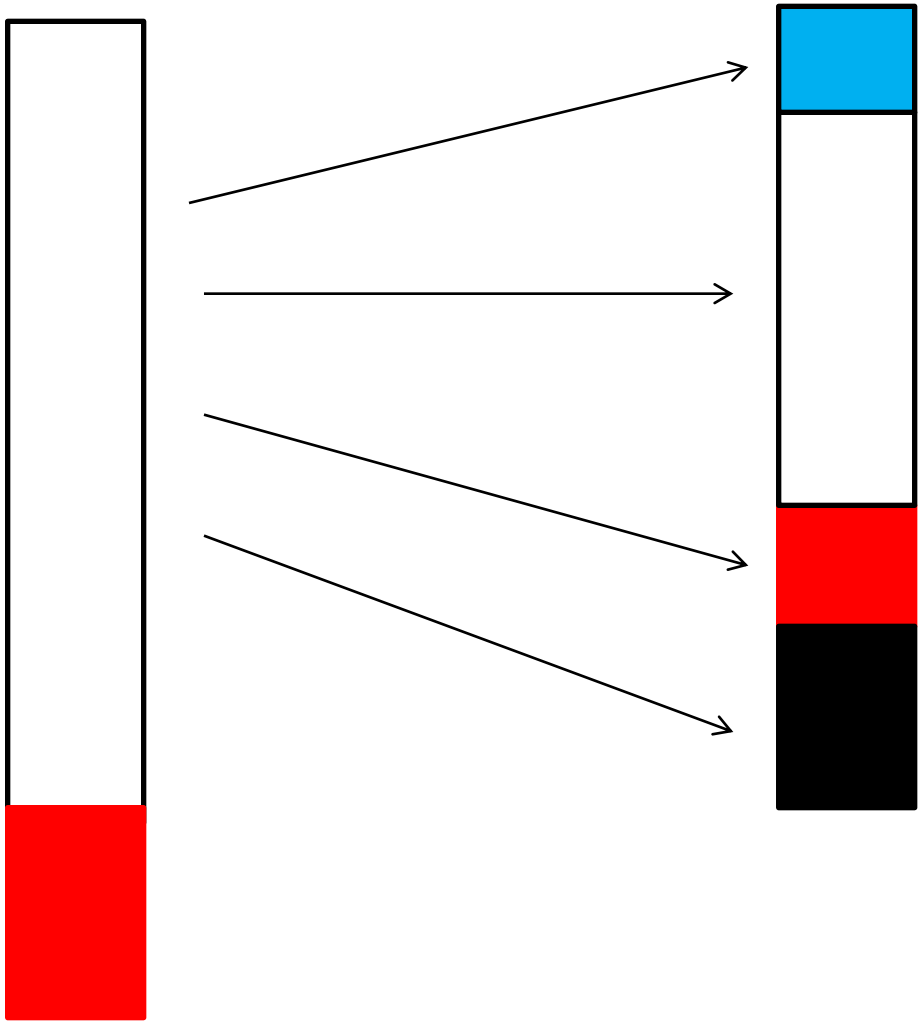
** Controlling for age, gender, education and family history of dementia*

Prince et al – International Psychogeriatrics 2010

Incidence study aims and objectives

- Test the hypotheses that smaller skull circumference and shorter leg length are associated with risk for incident dementia
  - In large, representative population-based cohort studies
  - Checking for consistency of findings across cultural settings
  - Adjusting for the ‘competing risk’ of dementia-free death
- Effect modification
  - Is the effect of leg length modified by gender (only apparent in women – Mak et al 1993)
  - Is the effect of skull circumference modified by education (cognitive reserve – Mortimer et al)
- Reverse causality?
  - Is there a trend towards skull shrinkage and leg shortening over time?
  - If so, is this more pronounced among those
    - a) who have dementia at baseline?
    - b) who go on to develop dementia?

Modelling dementia incidence (competing risk)



Dementia free 'at risk' cohort

Prevalent dementia

Lost to follow-up

Interviewed – no dementia

Interviewed – incident dementia

Dementia free death

COMPETING RISK

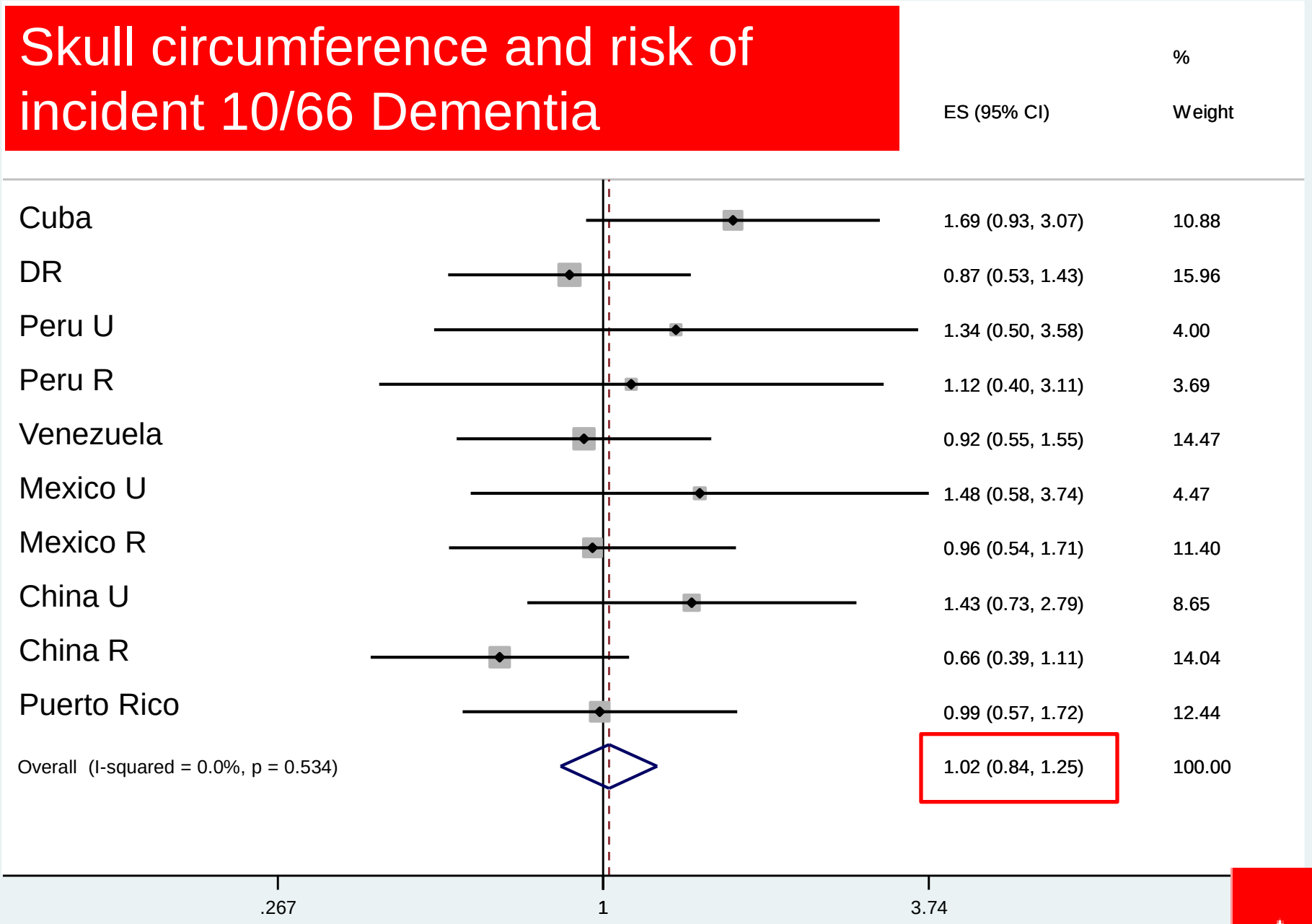
Results

Incidence wave, by country

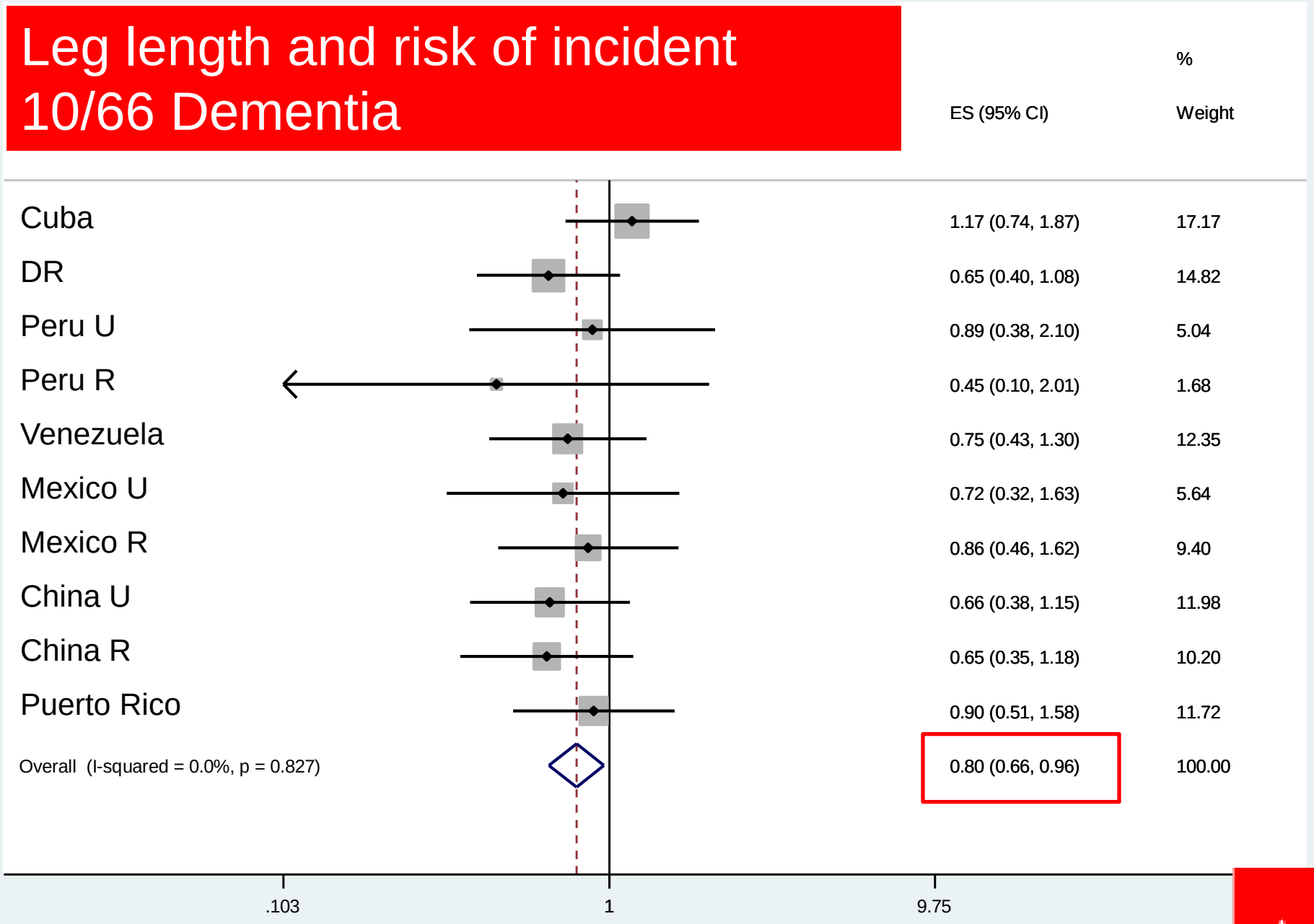
Country	Cohort	Inter-viewed	Dead	Lost to follow-up	Median follow-up (years)	Person years (dementia)
Cuba	2813	2007	608	198	4.5	8701
DR	2011	1197	467	347	5.1	5561
Puerto Rico	2009	1268	299	442	4.4	5509
Peru	1933	1311	152	470	3.3	3914
Venezuela	1965	1257	200	508	4.3	5269
Mexico	2003	1462	209	332	3.0	4164
China	2162	1452	515	195	5.1	7109
Total	14896	9954	2450	2492		40227
Total (%)		67%	16%	17%		

Prina et al – IJE 2016, in press

Skull circumference and risk of incident 10/66 Dementia



Leg length and risk of incident 10/66 Dementia



Changes in leg length and skull circumference, from baseline to follow-up, by baseline cognitive status (data pooled across sites)

	Change in leg length from baseline to follow-up		Change in skull circumference from baseline to follow-up	
	N	Change score (95% CI)	n	Change score (95% CI)
1. Cognitively normal	6555	-0.85 (-0.99 to -0.71)	6760	-0.20 (-0.23 to -0.16)
2. CIND[1]	366	-1.31 (-1.87 to -0.75)	375	-0.08 (-0.23 to +0.07)
3. Dementia	442	-2.67 (-3.18 to -2.17)	480	-0.33 (-0.45 to -0.20)
All	7383	-0.99 (-1.12 to -0.85)	7615	-0.20 (-0.23 to -0.17)
Overall effect of baseline cognitive status	F=21.1, 2 df, p<0.001		F=6.6, 2 df, p=0.03	
Scheffe test	p-value for group comparison		p-value for group comparison	
3 versus 1	p<0.001		p=0.13	
3 versus 2	p=0.004		p=0.04	
2 versus 1	p=0.34		p=0.30	

1. ‘Cognitive Impairment No Dementia’

Sensitivity analyses

Original association	**0.80 (0.66-0.96)**
Sensitivity analysis	Hazard ratio
Controlling also for frailty	0.82 (0.67-0.99)
Excluding outliers for change in leg length	0.76 (0.60-0.97)
Per centimetre increment in leg length	0.986 (0.977-0.995)
Per centimetre change in leg length from baseline to follow-up	1.006 (0.992-1.020)
Interaction with sex	1.03 (0.90-1.18)

Conclusions

- Leg length, but not skull circumference is inversely associated with the incidence of dementia
- Leg length measurements decrease over time, particularly among those with cognitive impairment and dementia
- Reverse causality is unlikely to explain the association since change in leg length does not predict dementia onset
- Salience of leg length suggests an important mechanism linked to early life nutrition
- This may be an important explanation for declining incidence rates in high income countries

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The 10/66 Dementia Research Group

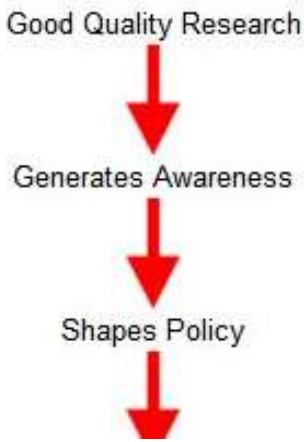
The 10/66 Dementia Research Group is a collective of researchers carrying out population-based research into dementia, non-communicable diseases and ageing in low and middle income countries.

10/66 refers to the two-thirds (66%) of people with dementia living in low and middle income countries, and the 10% or less of population-based research that has been carried out in those regions.

10/66 is a part of Alzheimer's Disease International, and is co-ordinated from the Institute of Psychiatry, King's College London.

Latest 10/66 News

- Newsletter Released *(01/06/08)* More...
- Latest Paper Published *(13/05/08)* More...
- New Findings from Chicago Conference *(20/03/08)* More...



www.alz.co.uk/1066