Newcastle University

NIHR - Dementia Prevention and Enhanced Care

DePEC

Workstream 2.1

DEVELOPMENT OF ACCURATE AND SIMPLE TOOLS TO IDENTIFY INDIVIDUALS AT HIGH RISK OF DEMENTIA

WS2.1 Deliverables

1) Update systematic review of dementia risk prediction models

   Completed, and published.

Dementia risk prediction in the are screening models accurate?

Blossom C. M. Stephan, Tobias Kurth, Fiona E. Matthews, Carol Brayne

Abstract | Early identification of individuals at risk of dementia will become c strategies for this condition are developed. Various dementia prediction mo including clinic-based criteria for mild cognitive impairment, and more-broad synthesize information from known dementia risk factors, such as poor cog of the predictive accuracy of such models will be important if they are to be or to screen the entire older population (individuals aged ≥65 years). This a recent progress in the development of dementia prediction models for use i 25 articles relating to dementia risk screening met our inclusion criteria for predictive accuracy of each model shows that most are poor at discriminati risk cases. The best models incorporate diverse sources of information acr poor accuracy is associated with single-factor models, long follow-up interva of all-cause dementia. A parsimonious and cost-effective consensus model accurately identifies individuals with a high risk of future dementia.

Stephan, B. C. M. *et al. Nat. Rev. Neurol.* advance online publication 25 May 2010; doi:10.1038/n

Introduction

The rise in the incidence of dementia with the change in the global age demographic is a source of major public health concern, as the disability associated with this condition, part leads to high persor the promise of futu expected increase ir early and accurate i at a high risk of de research priority. incorporate know proposed to achiev tive utility of such n included in daily cl older population (i

In this Review, models that have samples. The meth articles for review mates of sensitivity receiver operating ability of each mod duals (that is, peop follow-up) and not who have not dev perfect prediction values of 100%; how observed unless the ultrasound for abc population-based (>90%) of both ser to ensure that misc such threshold valu in disease prevalen specificity estimat

Competing interests
The authors and the Journal Editor H. Wood declare no competing interests.The CME questions author D. Lie has served as a nonproduct speaker for "Topics in Health" for Merck Speaker Services.

PLOS | ONE

RESEARCH ARTICLE

Current Developments in Dem Prediction Modelling: An Upd Review

Eugene Y. H. Tang[1]*, Stephanie L. Harrison[1], Linda Erringt Jelle Visser[4,5], Gerald Novak[6], Carole Dufouil[7], Carol Brayr J. Launer[8], Blossom C. M. Stephan[1]

1 Institute of Health and Society, Newcastle University Institute of Agei upon Tyne, NE2 4AX, United Kingdom, **2** Medical School, Newcastle U 4HH, United Kingdom, **3** Boehringer Ingelheim Pharmaceuticals, Inc., Connecticut, 06877, United States of America, **4** Maastricht University Neuropsychology, School for Mental Health and Neuroscience, Maastr University Medical Centre, Department of Neurology, Alzheimer Centre The Netherlands, **6** Janssen Pharmaceutical Research and Developm Titusville, New Jersey, 08560, United States of America, **7** Inserm Res Neuroepidemiology, F-33000, Bordeaux, France, **8** Department of Put Cambridge University, Cambridge, CB2 0SR, United Kingdom, **9** Labo and Biometry, National Institute on Aging, National Institutes of Health States of America

* e.y.h.tang@newcastle.ac.uk

Abstract

Background

Accurate identification of individuals at high risk of dementia sion criteria for clinical trials and development of preventativ have been developed for predicting dementia. To evaluate t systematic review in 2010 and updated this in 2014 due to th lished in this area. Here we include a critique of the variable assessment of model prognostic performance.

Methods

Our previous systematic review was updated with a search 2014 in electronic databases (MEDLINE, Embase, Scopus, examining risk of dementia in non-demented individuals and ity, specificity or the area under the curve (AUC) or c-statisti

Findings

In total, 1,234 articles were identified from the search; 21 art developments in dementia risk prediction include the testing non-traditional dementia risk factors, incorporation of diet, p and model development in specific subgroups of the popula

Citation: Tang EYH, Harrison SL, Errington L, Gordon MF, Visser PJ, Novak G, et al. (2015) Current Developments in Dementia Risk Prediction Modelling: An Updated Systematic Review. PLoS ONE 10(9): e0136181. doi:10.1371/journal.pone.0136181

Editor: Gianluigi Forloni, "Mario Negri" Institute for Pharmacological Research, ITALY

Received: April 3, 2015

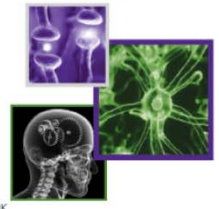
Accepted: July 30, 2015

Published: September 3, 2015

Data Availability Statement: All relevant data are within the paper and its Supporting Information file.

Funding: Tang EYH is supported by an NIHR Academic Clinical Fellowship. The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under EMIF grant agreement no. 115372, resources of which are composed of financial contributions from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies in kind contribution. This research (LJL) was also supported in part by the Intramural research Program of the NIH, National institute on Aging. The funders

Neurodegenerative Disease Management



Editorial

Dementia risk assessment tools: an update

Eugene Yee Hing Tang*[,1,2], Louise Robinson[1,2] & Blossom Christa Maree Stephan[1,2]
[1]Institute of Health & Society, Newcastle University, Baddiley-Clark, Richardson Road, Newcastle upon Tyne, NE2 4AX, UK
[2]Newcastle University Institute of Ageing, Newcastle University, Campus for Ageing & Vitality, Newcastle upon Tyne, NE4 5PL, UK
* Author for correspondence: Tel.: +44 (0)191 208 8758; e.y.h.tang@newcastle.ac.uk

"Given the fear and stigma surrounding dementia [16], it is important to seek the views of patients and their families before implementing risk assessment in clinical practice to assist with preventive treatment and future planning."

First draft submitted: 1 September 2017; Accepted for publication: 20 September 2017; Published online: 21 November 2017

Keywords: Alzheimer's disease • dementia • risk factors

In the absence of effective treatments for dementia there has been an international focus towards risk reduction similar to other branches of medicine for example, cardiovascular disease [1]. It has been suggested that around a third of Alzheimer's disease (AD) cases [2] and about a quarter to a third of dementia cases [3] could be prevented through the modification of key risk factors linked to health and lifestyle with examples including low educational attainment and physical inactivity. Some of these factors have been incorporated into models to predict an individual's risk of future dementia. However, previous systematic reviews have found that although some risk tools predict dementia with reasonable accuracy, none are currently recommended for use in clinical settings [4,5]. Since the last systematic review in 2015 there have been further models published. Therefore, the aim of this editorial is to provide an update on new developments in the dementia risk prediction modeling literature.

Current developments in dementia risk prediction modeling

Recent updates include: development of new genetic risk scores incorporating non-apolipoprotein (*APOE*) risk genes that are associated with incident AD [6]; development of a United Kingdom (UK)-based model, incorporating variables that are easily accessible in primary care [7] and testing of model size reduction and incorporating simple variables to reduce the cost/expertise needed for dementia risk score calculation [8]; extension of usage of risk scores into the clinical trial setting; and qualitative assessment of dementia risk reduction. A summary of each of these developments is included below.

Genetic risk scores

Previous genetic risk scores have assessed the benefits of using *APOE ε4* and non-*APOE ε4* genes (*PICALM* and *CLU*) to improve predictive models for incident AD [9]. There have been further models based on genetic risk scores produced since then. One example is a genetic risk score developed in 2016 that used common genetic variants associated with AD [6]. The authors observed that the aggregate measure of single nucleotide polymorphisms was more significantly associated with incident AD even without the inclusion of *APOE ε4* [6]. The authors assessed a risk model that incorporated age, sex, education and *APOE* in risk prediction after 7-year follow-up and found that when the genetic risk score was added to the risk model there was a small improvement in discrimination [6]. These scores could be used in trials to include those found to be at risk but asymptomatic from the disease.

Reducing model complexity

Although no economic analysis has been previously undertaken, a key criticism of past models was that they often contain resource intensive (in terms of data collection) and costly (in terms of equipment and expertise needed) variables reducing feasibility of implementation. Four studies have focused on reducing model calculation cost and complexity. They first developed a score estimating of 5-, 10- and 20-year dementia risk and focused specifically on risk factors (including age, marital status, body mass index (BMI), stroke, diabetes, ischemic attack

Future Medicine

WS2.1 Deliverables

1) Update systematic review of dementia risk prediction models
   Completed, and published.

2) Undertake systematic review of MCI operationalization and prevalence in LMIC
   Draft manuscript

3) Submit data request to the 10/66 Study Data Management Committee
   Completed

4) Undertake dementia risk prediction model analysis – 10/66 Study data
   Draft manuscript

5) Undertake external model validation using data from Malaysia and Tanzania
   To be completed

Dementia risk prediction model analysis

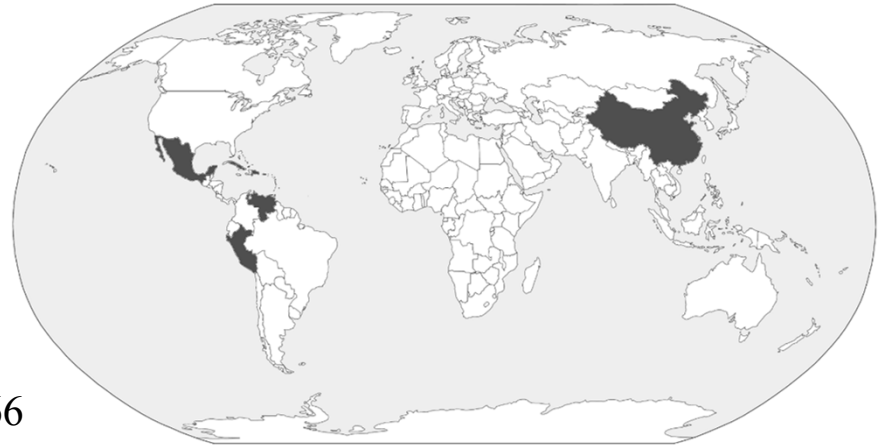
- The aim is to find a model that is able to identify individuals with a high risk of developing dementia over a relative short time.
  - This model could be used to select individuals for dementia prevention trials.

- First part of this work is:
  - Investigate whether current dementia risk prediction models, developed in high income countries (HICs), are able to predict risk of developing dementia in elderly from low and middle income countries (LMICs).

10/66 Study cohort

- Individuals ≥ 65 years
- From: Cuba, Dominican Republic, Peru, Venezuela, Mexico, Puerto Rico and China.

- Baseline interviewing was undertaken in 2004 to 2006, in all countries except Puerto Rico (baseline: 2007 to 2010).
- Participants were re-seen at approximately three to five years follow-up.



- The sample size was approximately 2,000 participants per country, and the response rate was 86%.

- All cause dementia was diagnosed according to the 10/66 diagnosis algorithm.

Summary results previous workshop

- Thirteen dementia risk prediction models selected and tested in the 10/66 cohort.

- Some dementia risk prediction models developed in HIC appear to translate well to LMICs.
  - However, the performance of the models varied across the 10 / 66 countries.

- The best performing models incorporated information on age, gender and cognitive test performance.

Update analysis

- Testing models with two different approaches.

- Approach 1 (as presented last workshop):
  - Testing the models using the exact same variables / risk factors as were used in the original model development study.
  - However, the dementia models are updated to the 10/66 setting.
  - This means that magnitude at which each factor of the model increases an individual risk was recalculated in the 10/66 study.
    - i.e. recalculation of risk scores of each variable incorporated in the model.
- Approach 2 (added to the previous shown analysis):
  - Testing the models using the exact same variables as were used in the original model development study,

  and the exact same risk scores for each variable as found in the original cohort.

- In addition, a second look was given to the dementia model selection.
- And, the effect of age on the performance of the models was tested.

Overview methods

- Five dementia risk prediction models selected
  - All developed in high income country cohorts.
  - Models incorporate demographics, disease status (e.g. diabetes), lifestyle (e.g. smoking), physical functioning (e.g. need help with money), and neurocognitive test performance variables.
- Discriminative model performance was tested in 10 / 66 cohort
  (i.e. complete cohort, and country specific study samples)
  - 1) Models tested using development specific statistics
    - Complete risk score calculated according to original publication
    - Age only risk score calculated according to original publication
    - Cox regression or logistic regression modelling
  - 2) Models tested using updated risk scores
    - The risk score was re-calculated for each variable included in the models.
    - Age was in each tested model incorporated as continuous variable.
    - Competing risk regression modelling
- Model performance tested with Harrell's c-statistic / AUC
  - Ability to discriminate between low and high risk cases
  - C-statistics values of 0.8–1 (excellent models), 0.7–0.8 (good models) and <0.7 (models of questionable utility)

Selected dementia models

1) ANU-ADRI risk score (age, education, diabetes, depression, TBI, smoking, alcohol intake, social engagement, PA, cognitive activity, fish intake, and pesticide exposure)

2) CAIDE risk score (age, education, gender, systolic blood pressure, obesity, cholesterol status, and PA)

3) BDSI risk score (age, education, underweight, diabetes, stroke, need help with money / medication, and depression)

4) AGECODE risk score (age, subjective memory impairment, verbal fluency, delayed recall, MMSE and IADL)

5) Framingham risk score (age, marital status, BMI, stroke, diabetes, TIA, and cancer)

ANU-ADRI score

- The Australian National University Alzheimer's Disease Risk Index (ANU-ADRI) score.
  - Variables for the model selected from the literature.
  - And, risk scores for each individual variable of the model calculated following meta-analysis.
- The final model consisted of eleven risk factors and four protective factors, namely:
  - Age, sex, education, BMI (only for people < 60 years), diabetes, depression, serum cholesterol (only for people < 60 years), TBI, smoking, alcohol intake, social engagement, physical activity (PA), cognitive activity, fish intake and pesticide exposure.
- The discriminative performance of the risk score was tested in three independent cohorts:
  - The Rush Memory and Aging Project (MAP)
    - USA; n = 903; age ≥53 years; mean follow-up = 6 years);
  - The Kungsholmen Project (KP)
    - Sweden; n = 905; age ≥75 years; mean follow-up = 6 years)
  - The Cardiovascular Health Study (CHS)
    - USA; n = 2,496; age ≥65 years; mean follow-up = 3.5 years).

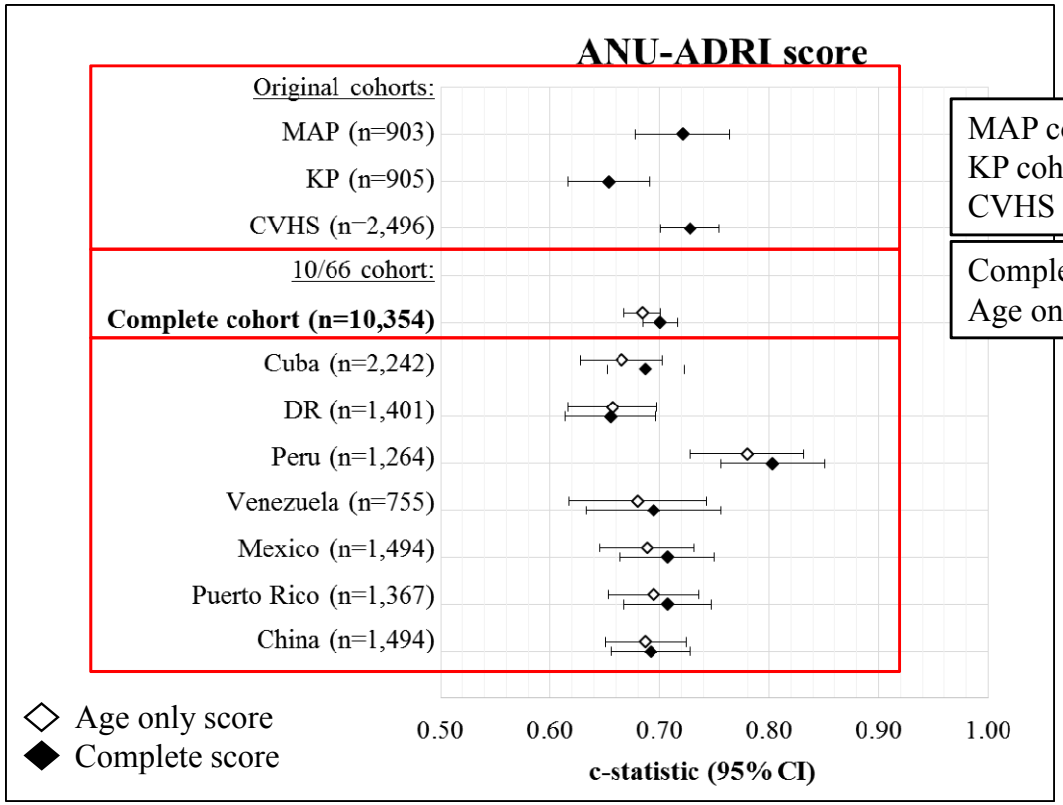
ANU-ADRI score

Variable	Risk score
Age	
< 65 years	0
65 - 70 years	1 men | 5 women
70 - 75 years	12 men | 14 women
75 - 80 years	18 men | 21 women
80 - 85 years	33 men | 35 women
≥ 90 years	38 men | 41 women
Education	
Completed secondary school	0
Completed primary school	3
No education / primary school not completed	6
Diabetes	3
Symptoms of depression	2
Traumatic brain injury	4
Smoking	
Never	0
Ever	1
Current	4

Variable	Risk score
Light / moderate alcohol intake	-3
Social engagement	
Lowest	6
Low to medium	4
Medium to high	1
Highest	0
Physical activity	
Not (very) physical active	0
Fairly physical active	-2
Very physical active	-3
Fish intake	
Never	0
Some days	-3
Most days	-4
Every day	-5

The total individual risk score can range between the -11 and 66 points.

Harrell's C statistic and 95%CI



MAP cohort: 0.72 (0.68 – 0.76)
KP cohort: 0.65 (0.62 – 0.69)
CVHS cohort: 0.73 (0.70 – 0.75)

Complete score: 0.70 (0.68 – 0.72)
Age only score: 0.68 (0.67 – 0.70)

AGECODE score

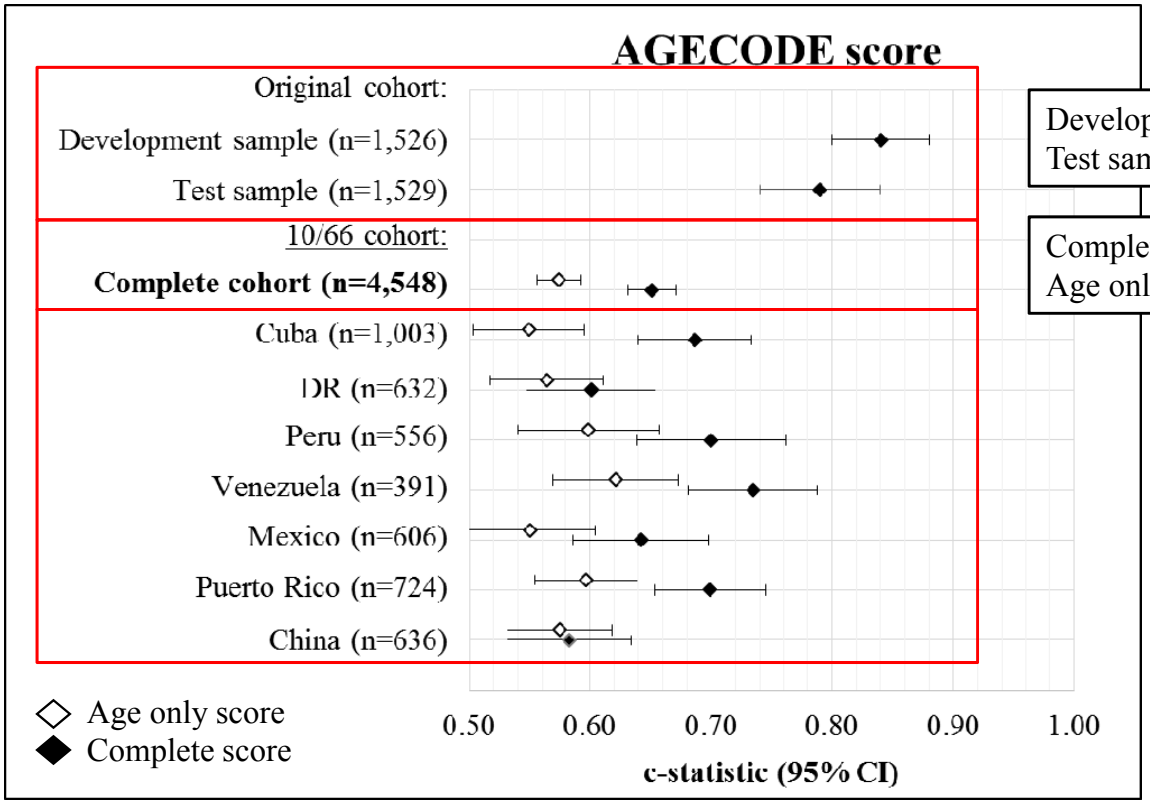
- The AGECODE score The Aging, Cognition and Dementia (AGECODE) score.
  - Dementia prediction score for individuals ≥ 75 years
- This score was developed following identification of predictors of dementia in the AGECODE study (Germany; n=3,055; age ≥75 years; mean follow-up = 3.8 years).
  - The final risk score consisted of 6 risk factors, namely: age, subjective memory impairment (SMI), verbal fluency, delayed recall, Mini Mental State Examination (MMSE), and IADL.
  - The beta-coefficients of the selected risk factors, following cox regression analysis, were converted into a risk score.
- No data was available in the 10/66 Study for the variable MMSE, instead is a comparable neuropsychological test score used (i.e. Clinical Dementia Rating; CDR).

AGECODE score

Variable	Risk score
Age	
75-79 years	0
≥ 80 years	3
Subjective memory impairment (SMI)	
0 points on the GMS SMI scale	0
1 - 3 points on the GMS SMI scale	2
>3 points on the GMS SMI scale	4
Verbal fluency < 18 animals named	4
Delayed recall	
7-10 words	0
5-6 words	2
0-4 words	4
CDR ≥ 0.5	4
≥1 reported difficulty with ADL/IADL	2

The total individual score can range between the 0 – 21 points.

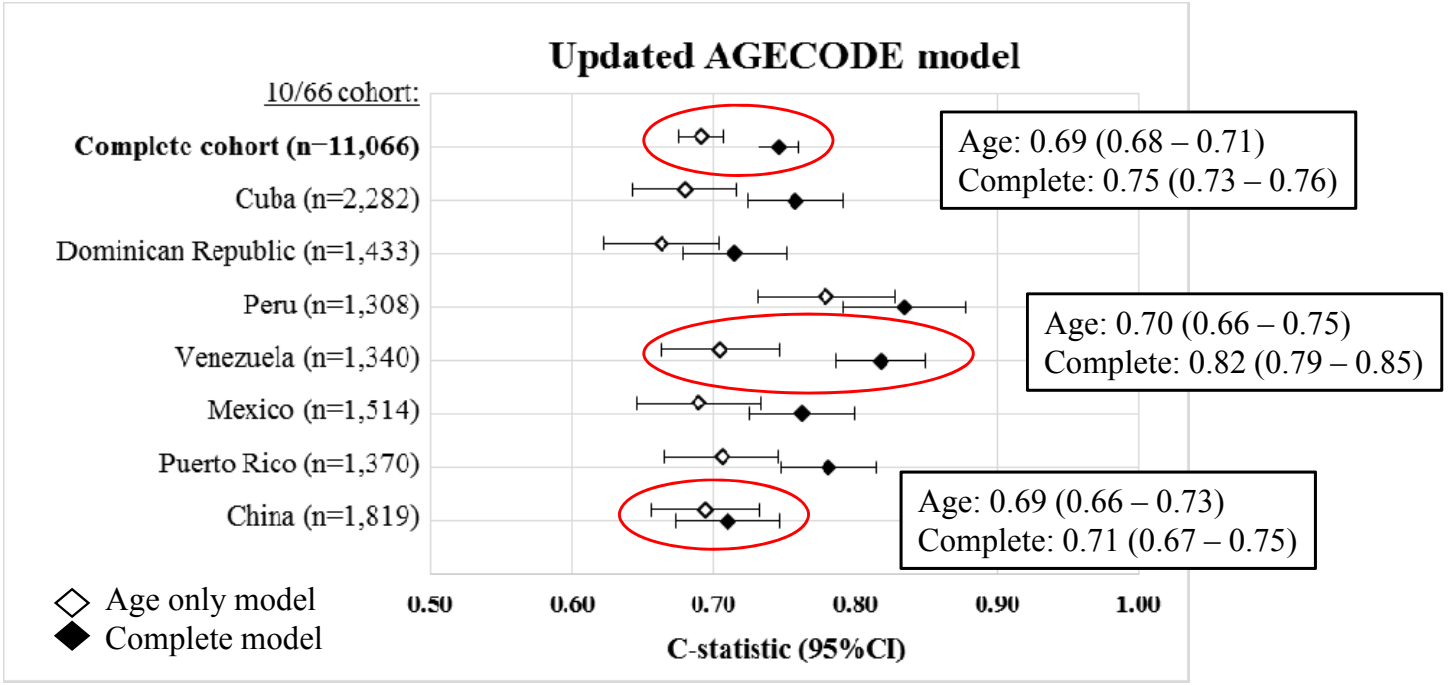
Harrell's C statistic and 95%CI



Development sample: 0.84 (0.80 – 0.88)
Test sample: 0.79 (0.74 – 0.84)

Complete score: 0.65 (0.63 – 0.67)
Age only score: 0.57 (0.56 – 0.59)

Updated AGECODE model



Re-calculation AGECODE risk scores

		AGECODE	Full cohort	Cuba	DR	Peru	Venezuela	Mexico	Puerto Rico	China
		score	score	score	score	score	score	score	score	score
GMS SMI scale	**0 points**	0	0	0	0	0	0	0	0	0
	0 - 3 points	2	0	1	0	1	1	0	0	2
	≥ 3 points	4	1	1	0	1	2	0	0	3
Animal naming	**< 18 named**	4	2	2	2	2	2	3	2	1
Delayed recall	**≥ 7 recall**	0	0	0	0	0	0	0	0	0
	5 - 7 recall	2	1	2	2	4	5	0	2	0
	0 - 5 recall	4	2	2	4	8	7	3	4	1
	CDR ≥ 0.5	4	2	3	1	2	2	3	3	-1
	ADL / IADL	2	1	1	1	0	2	0	1	1

Summary results

- The ANU-ADRI score performed well in the 10/66 cohort.
  - However, the performance of the score was primarily determined by the factor age.

- Update of the models to the 10/66 dataset suggest that:
  - Next to age, primarily factors associated with the dementia disease pathway are good predictors for the risk developing dementia, in elderly from LMICs.
  - However, the AGECODE model, incorporating these variables, did not performed well across **all** 10/66 countries.

Discussion

- Dementia diagnosed by 10/66 algorithm
- Missing data
- Not able to test al types of dementia models

Conclusion

- Currently, there is no robust dementia risk prediction model that performs well across the different countries in the 10/66 cohort.

- More research is needed to develop a dementia model that is able to identify high risk dementia cases across culturally and economically diverse settings.

Next steps?

1. Dementia risk model development in the 10 / 66 cohort:
   - Identify feasible, and robust, predictors for the risk of developing dementia across the different countries in the 10/66 cohort.

2. External validation of the new model in cohorts from LMICs:
   - The Ibadan Study from Nigeria
   - The Epidemiology of Dementia in Central Africa Study from Congo (EPIDEMCA-FU)
   - The Mexican Health and Aging Study (MHAS)
   - Chinese longitudinal Healthy Longevity Survey (CLHLS)

Systematic review

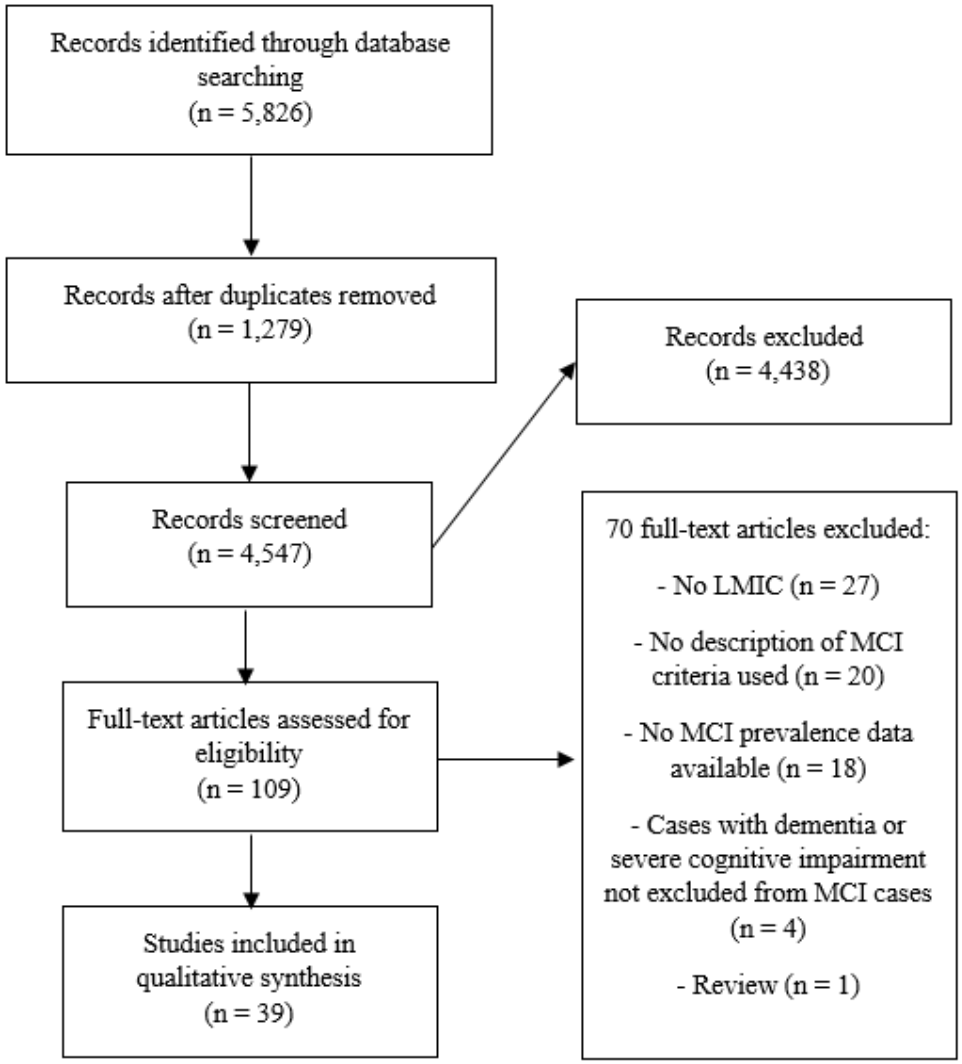
MILD COGNITIVE IMPAIRMENT (MCI) OPERATIONALISATION AND PREVALENCE IN LOW AND MIDDLE INCOME COUNTRIES.

MCI review

- MCI is an intermediate stage of cognitive function between normal age related changes and dementia.

- MCI could potentially be used to identify individuals with a high risk of developing dementia in the near future.

- Study selection criteria:
  - Mild Cognitive Impairment (MCI) prevalence in LMICs.
  - No restriction in definition of MCI and / or population characteristics.
  - Literature search up to January 2018


Records identified through database searching
(n = 5,826)
Records after duplicates removed
(n = 1,279)
Records excluded
(n = 4,438)
Records screened
(n = 4,547)
70 full-text articles excluded:
- No LMIC (n = 27)
- No description of MCI criteria used (n = 20)
- No MCI prevalence data available (n = 18)
- Cases with dementia or severe cognitive impairment not excluded from MCI cases (n = 4)
- Review (n = 1)
Full-text articles assessed for eligibility
(n = 109)
Studies included in qualitative synthesis
(n = 39)

Study characteristics

- Data available from 22 countries including:
  - Brazil, Bulgaria, Central African Republic, China, Columbia, Cuba, Dominican Republic, Egypt, Ghana, India, Iran, Malaysia, Mexico, Nigeria, Peru, Philippines, Puerto Rico, Republic of Congo, Russia, South-Africa, Tanzania, Venezuela.

- Sample size ranged from 99 to 32,715 participants.

- All studies were conducted in a elderly population (at least ≥ 50 years), except one study, which studied MCI prevalence in middle age cardiac surgery patients.

MCI criteria

- Criteria used:
  - Original Mayo-clinic / Petersen criteria, 1999
  - International Working Group (IWG) on MCI criteria, 2004
  - European Consortium on Alzheimer's disease criteria, 2006
  - NIA-AA criteria, 2011
  - DSM-V criteria, 2013

- In addition:
  - CIND criteria
  - Study specific criteria
  - Cut-off scores for neuropsychological assessment tools (e.g. MMSE)

Name MCI criteria, year of publication	**Summary of core MCI criteria**				
	Cognitive complaint	**Global cognitive function**	**Cognitive impairment**	**Physical functioning**	**Dementia**
1) Original Mayo-clinic / Petersen criteria, 1999	Memory complaint	Normal	Abnormal memory for age	Normal ADL	Not demented
2) International Working Group (IWG) on MCI criteria, 2004	Report of cognitive decline	N/A	Cognitive decline over time, or cognitive deficits (+ subjective report of cognitive decline)	ADL preserved, and IADL are either intact or minimally impaired	Not demented
3) European Consortium on Alzheimer's disease criteria, 2006	Report of cognitive complaints + cognitive decline	N/A	Impairment in any of the cognitive domains	Absence of major repercussions on daily life	Not demented
4) NIA-AA criteria, 2011	Report of concern cognitive decline	N/A	Impairment in any of the cognitive domains	Preserved functional abilities.	Not demented
5) DSM-V criteria, 2013	Report of concern mild cognitive decline	N/A	Modest impairment in any of the cognitive domains	Cognitive deficits do not interfere with capacity for independence in everyday activities	N/A

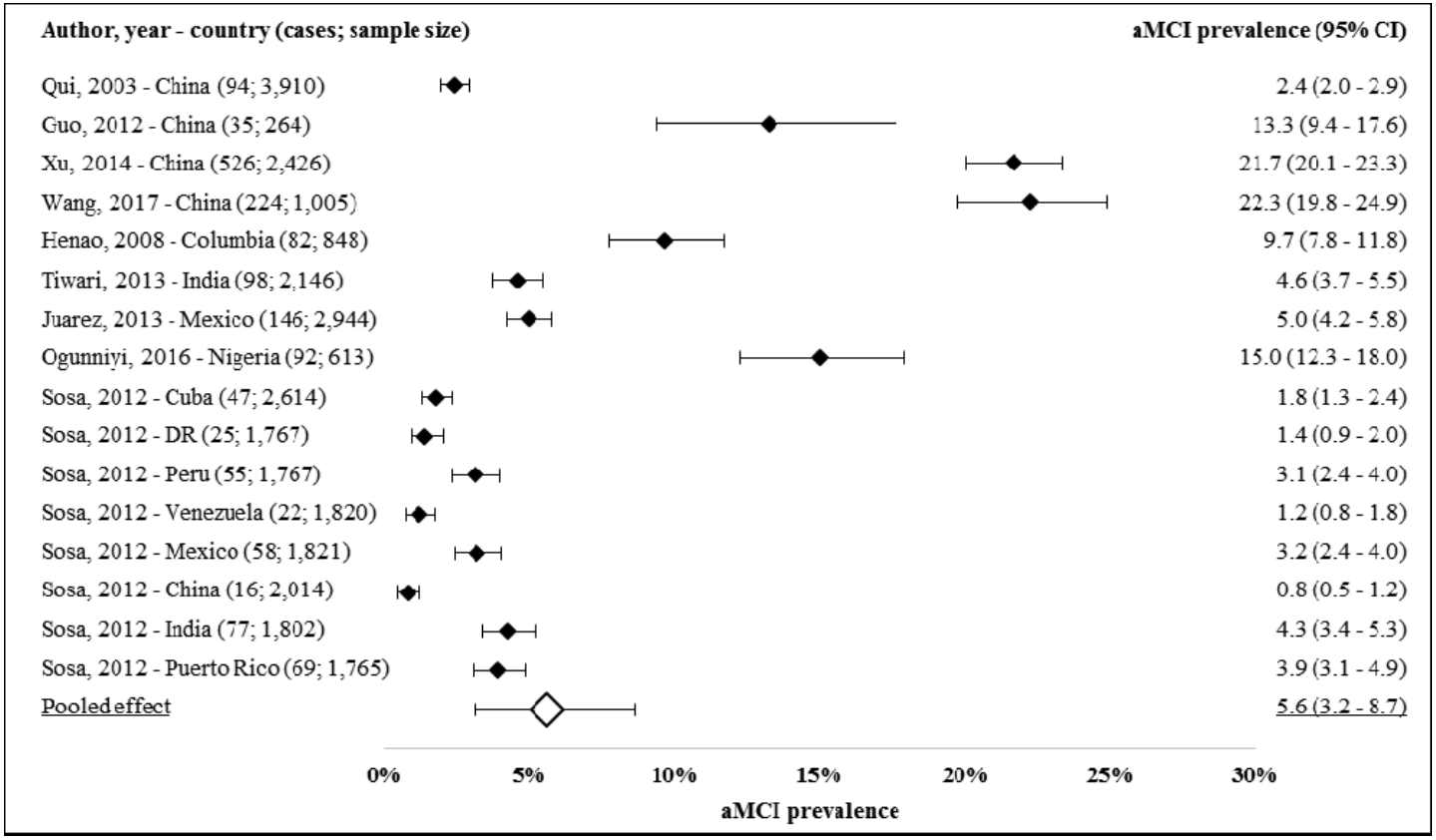


Figure 1A Forest plot of aMCI prevalence according to Petersen's criteria (1999).

Studies excluded from the meta-analysis if only the very old elderly were included in the study (Hai, 2012), the same study cohort was used twice (Wang, 2015), or if aMCI prevalence was studied in a very specific study population (Gao, 2016). Pooled effect was calculated according to random model analysis with the MetaXL software. 95%CI Confidence Interval. aMCI Amnestic Mild Cognitive Impairment. DR Dominican Republic.

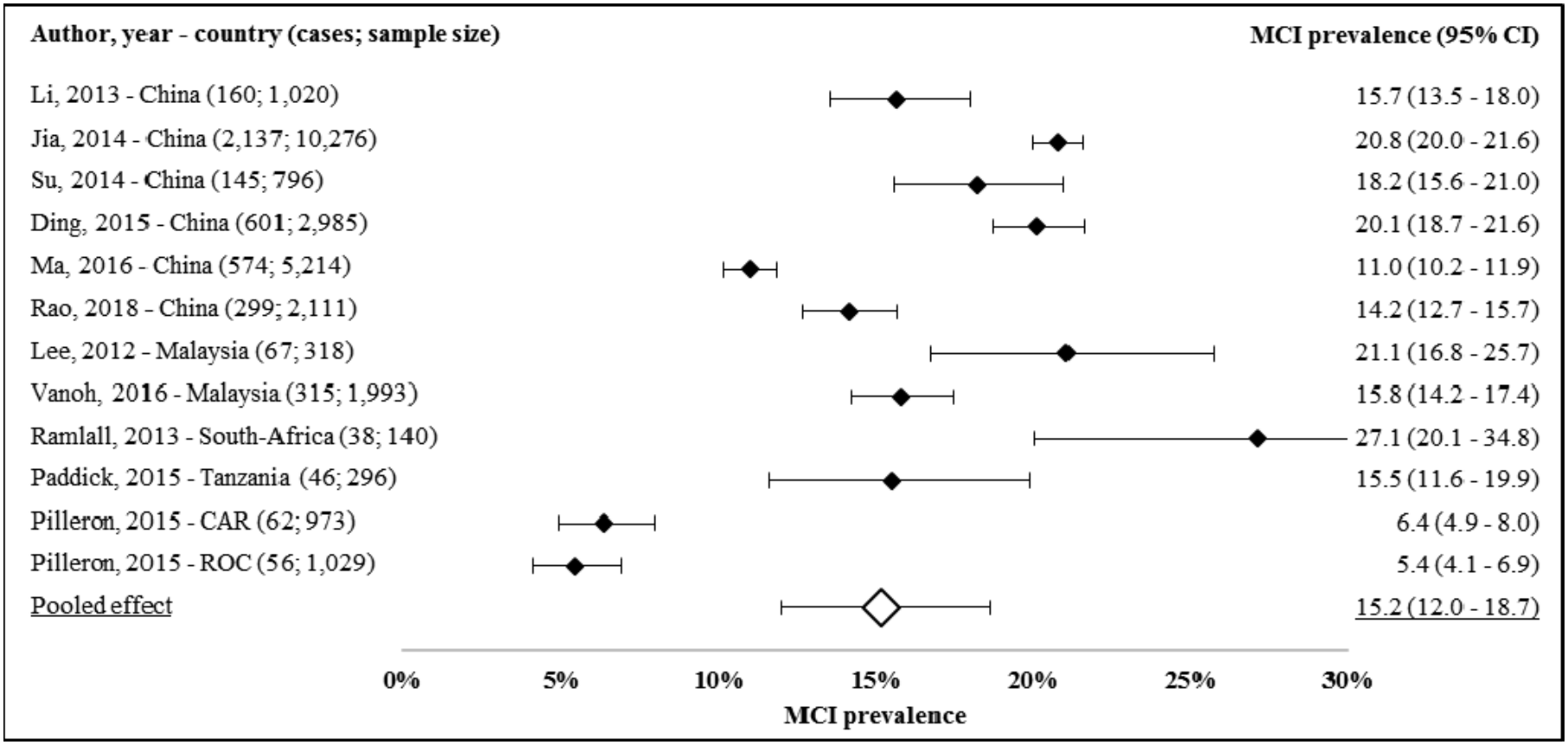


Figure 1B Forest plot of MCI prevalence according to the International Working Group (IWG) criteria (2004).

Study excluded from the meta-analysis, as the same study cohort was used twice (Shahar, 2013). Pooled effect was calculated according to random model analysis with the MetaXL software. 95%CI Confidence Interval. CAR Central African Republic. MCI Mild Cognitive Impairment. ROC Republic of Congo.

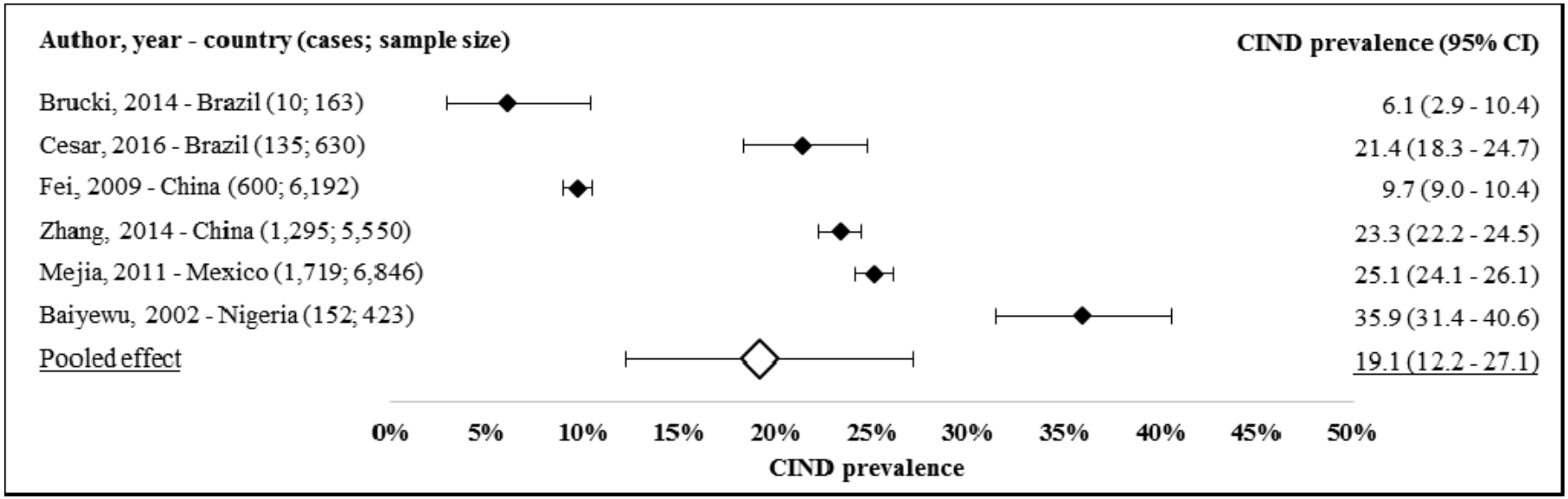


Figure 1B Forest plot of CIND prevalence.

Study excluded from the meta-analysis, because the same study cohort was used twice (Shahar, 2013). Pooled effect was calculated according to random model analysis with the MetaXL software. 95%CI Confidence Interval. CIND Cognitive Impairment No Dementia.

Summary results: MCI prevalence in LMICs

- Heterogeneity in criteria and operationalisation of MCI.
- Variability in MCI prevalence.
- Future work to look at whether MCI is predictive of dementia in LMIC settings
  - Next planned systematic review

THANK YOU