Workstream 2.1

Development of accurate and simple tools to identify individuals at high risk of dementia

WS2: Dementia Risk Prediction Models and Dementia Screening

The Overall objective of WS2 is to develop simple tools to identify people at high risk of developing dementia and those with undetected dementia:

- WS2.1 – Develop tools for predicting future dementia application to LMIC
- WS2.2 – Develop tools to identify undetected dementia cases in LMICs.

WS2.1 Deliverables

1) Update systematic review of dementia risk prediction models
2) Undertake systematic review of MCI operationalization and prevalence in LMIC
3) Submit data request to the 10/66 Study Data Management Committee
4) Undertake dementia risk prediction model analysis – 10/66 Study data
5) Undertake external model validation using data from Malaysia and Tanzania

WS2.1 Deliverables

	YEAR 1 (1/8/2017 to 21/7/2018)												YEAR 2 (1/8/2018-31/7/2019)							
	AUG	SEP	OCT	NOV	DEC	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	JAN	FEB	MAR
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Deliverables																				
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WS2.1 Deliverables – current status

1) Update systematic review of dementia risk prediction models (completed)
2) Submit data request to the 10/66 Study Data Management Committee (completed)
3) Undertake dementia risk prediction model analysis – 10/66 Study data (in progress)
4) Undertake external model validation using data from Malaysia and Tanzania (in preparation)
5) Undertake systematic review of MCI operationalization and prevalence in LMIC (in progress)

What is a risk prediction model?

A model that use variables measured at one time point to estimate the probability of an outcome occurring within a given time in the future.

How do we evaluate risk prediction models?

Discrimination = to the ability of the model to separate individuals who develop events from those who do not. In time-to event settings, discrimination is the ability of the model to predict who will develop an event earlier and who will develop an event later or not at all.

Calibration = a measure on how accurate the model's predictions match overall observed event rates

C statistics – a global measure of model discrimination

- The probability that, given 2 individuals (one who experiences the outcome of interest and the other who does not or who experiences it later), the model will yield a higher risk for the first patient than for the second. It is a measure of concordance (hence, the name “C statistic”) between model-based risk estimates and observed events.

- C statistics measure the ability of a model to rank patients from high to low risk but do not assess the ability of a model to assign accurate probabilities of an event occurring (that is measured by the model’s calibration). C statistics generally range from 0.5 (random concordance) to 1 (perfect concordance).

WS2.1 Deliverables – current status

1) Update systematic review of dementia risk prediction models (completed)

Why is risk prediction model important for dementia?

There is yet no cure for dementia, and therefore risk reduction and prevention are the only way to reduce the current number of people who get dementia, delay its onset or mitigate its impact.

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 strategies for this condition are developed. Various dementia prediction mo including clinic-based criteria for mild cognitive impairment, and more-broac 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 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

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Learning objectives

Upon completion of this activity, participants should be able to:

1 Identify the criteria for mild cognitive impairment (MCI) and the role of MCI in predicting dementia.
2 Assess use of prognostic models to predict dementia and their utility in supplementing MCI.
3 Describe the utility of multifactor models for predicting dementia.

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 perso the promise of futu expected increase i early and accurate at a high risk of de research priority. incorporate know proposed to achiev tive utility of such 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 no who have not dev perfect prediction values of 100%; how observed unless the ultrasound for ab population-based (>90%) of both ser to ensure that misc such threshold valu in disease prevale 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 Brayn J. Launer[9], Blossom C. M. Stephan[1]

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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 t 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 an ity, specificity or the area under the curve (AUC) or c-statisti

Findings

In total, 1,234 articles were identified from the search; 21 ar 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

OPEN ACCESS

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

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Editorial

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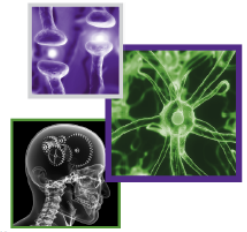
Neurodegenerative Disease Management



Dementia risk assessment tools: an update

Eugene Yee Hing Tang*[,1,2], Louise Robinson[1,2] & Blossom Christa Maree Stephan[1,2]
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"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."

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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

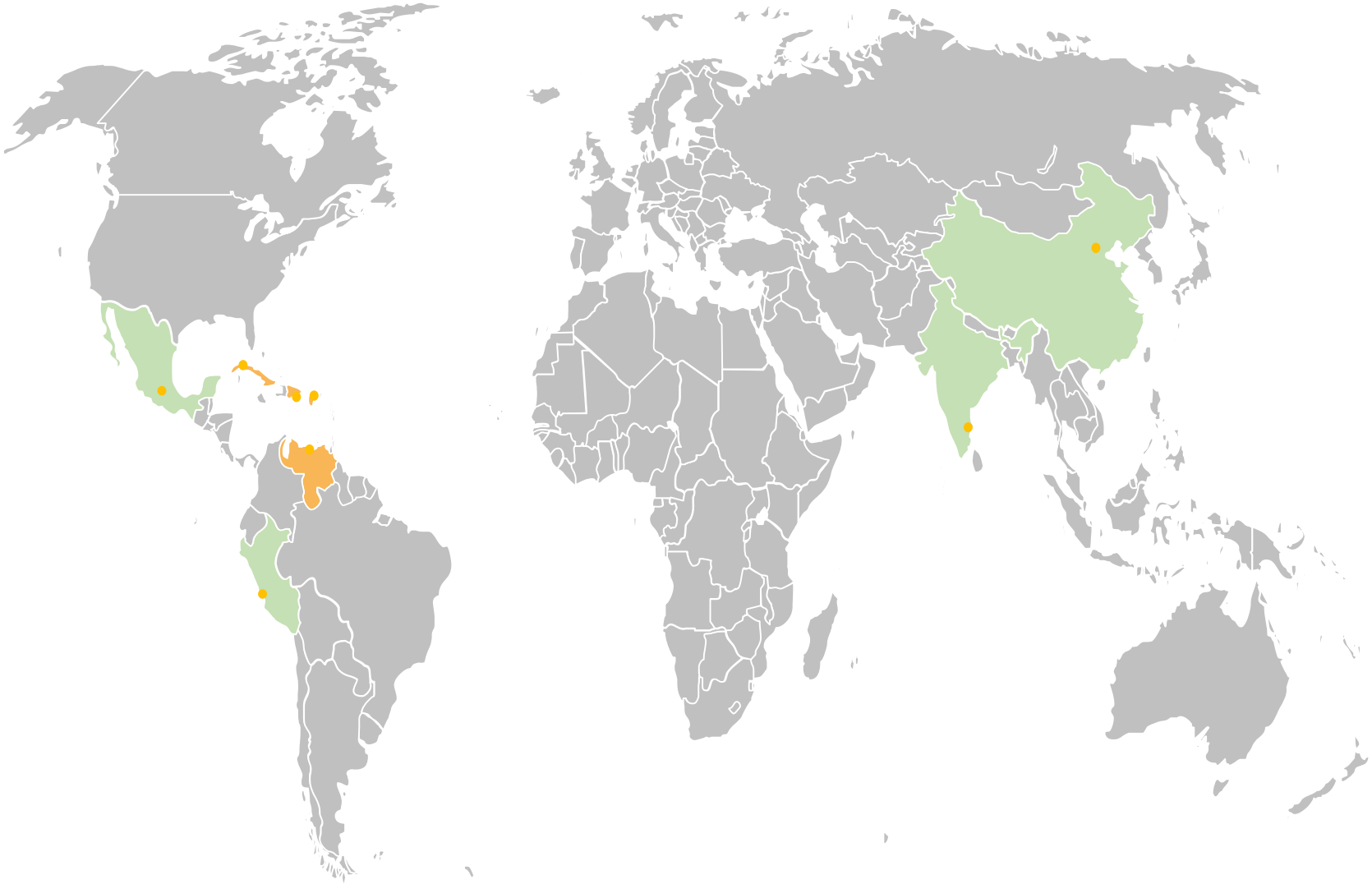
Future Medicine

WS2.1 Deliverables – current status

1) Update systematic review of dementia risk prediction models (completed)

2) Submit data request to the 10/66 Study Data Management Committee (completed)

10/66 cohort



WS2.1 Deliverables – current status

1) Update systematic review of dementia risk prediction models (completed)
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3) Undertake dementia risk prediction model analysis – 10/66 Study data (in progress)

Model validation study

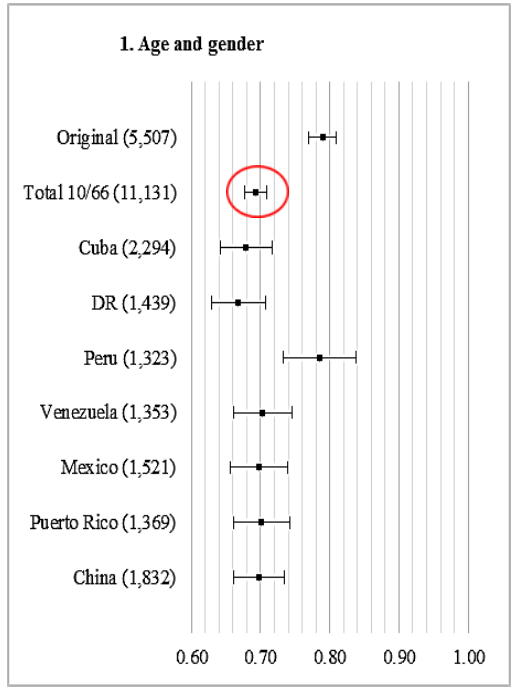
Dementia risk model validation in low and middle-income countries: The 10/66 Study

Description study

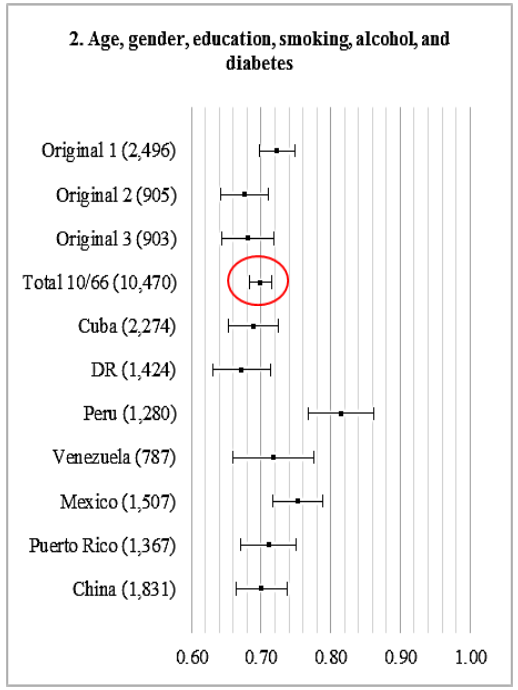
- Thirteen dementia risk prediction models selected
  - All developed in high income country cohorts.
  - Models incorporate demographics, disease status (e.g. diabetes), lifestyle (e.g. smoking), physical functioning (e.g. need help with money), and neurocognitive test performance variables.
- Models tested in 10 / 66 cohort using competing risk regression models.
- Discriminative performance tested with Harrell’s c-statistic.

	Original model							Mapping in the 10/66 dataset
	Author, year	Country	Sample size	Age at baseline	Follow-up	Outcome	Variables	Variables
1	Verhaaren, 2013	NL	5507	45 - 99 years	10 years	Alzheimer	Age (in years) Gender (male/female)	Age (in years) Gender (male/female)
2	Anstey, 2014	(1) USA (2) Sweden (3) USA	(1) 2496 (2) 905 (3) 903	(1) ≥ 62 years (2) ≥ 74 years (3) ≥ 54 years	(1) 3,5 years (2) 6 years (3) 6 years	Dementia	**ANU-ADRI score of different variables:** Age (<65/65-69/70-74/75-79/80-84/85-89/≥90) Gender (male/female) Education (>11 year/8 to 11 year/<8 year) Smoking status (current/former/never) **Alcohol intake (no/light to moderate)** Diabetes (yes/no)	Age (65-69/70-74/75-79/80-84/85-89/≥90) Gender (male/female) Education[1] (categories) Smoking status (current/former/never) **Hazardous drinker (yes/no)** Diabetes (yes/no)
3	Kivipelto, 2006	Finland	1409	39 - 64 years	20 years	Dementia	**CAIDE score:** Age (<47/47-53/>53) Gender (male/female) Education (≥10 years, 7-9 years, 0-6 years) Physical activity (active/inactive) **BMI (≤30/>30)** Systolic blood pressure (above or below 140) Total cholesterol (≤6.5, >6.5)	Age (65-69/70-74/75-79/≥80) Gender (male/female) Education (categories) Physical activity (active/inactive) **WC (women >88cm, men >102cm)** Systolic BP (above or below 140) Total cholesterol (≤6.5, >6.5)
4	Jorm, 2005	Hawaii	3734	71 - 93 years	3 - 6 years	Dementia	Age (in years) Education (in years) **CASI episodic memory (continuous)** **CASI visual construction (continuous)** Subjective memory (5 categories from 'definitely improved' to definitely deteriorated')	Age (in years) Education (categories) **World list learning (continuous)** **Copy circle correct (yes/no) and copy pentagon correct (yes/no)** Subjective memory impairment (yes/no)

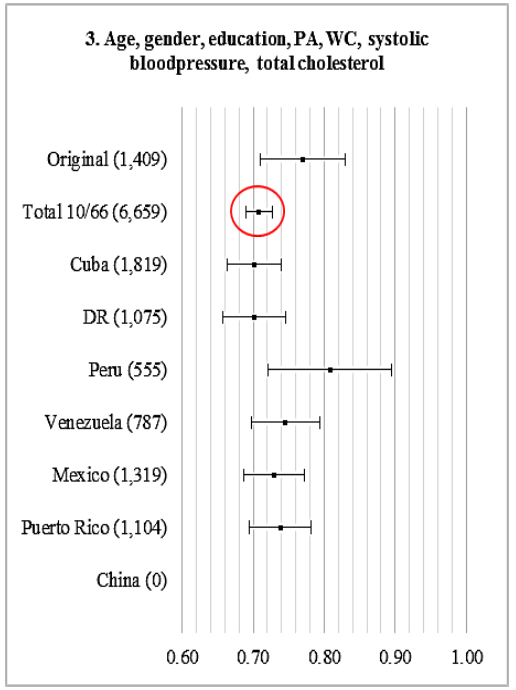
Harrell's C statistic and 95%CI for dementia risk prediction models



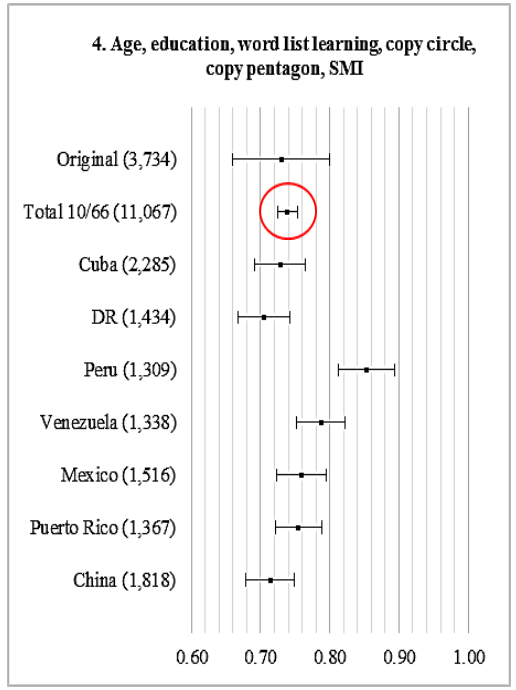
Original:
0.79 (0.77 – 0.81), n=5,507
10 / 66:
0.69 (0.68 – 0.71), n=11,131.



Original:
(1) 0.72 (0.70 – 0.75), n=2,496
(2) 0.68 (0.64 – 0.71), n=905
(3) 0.68 (0.64 – 0.72), n=903
10 / 66:
0.70 (0.68 – 0.72), n=10,470.

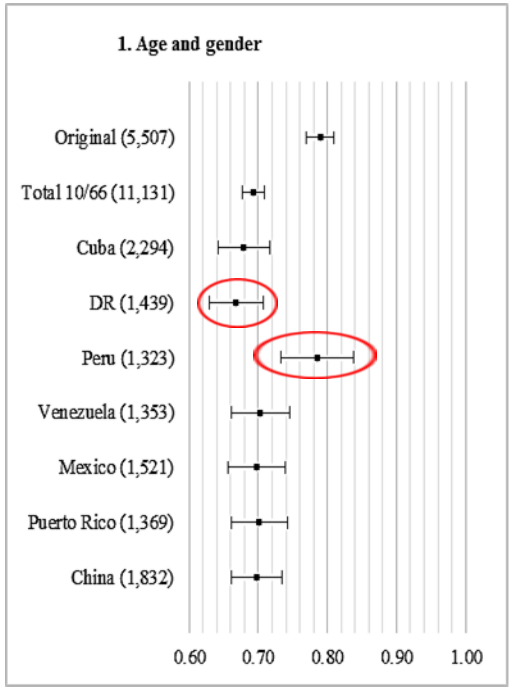


Original:
0.77 (0.71 – 0.83), n=1,409
10 / 66:
0.71 (0.69 – 0.73), n=6,659

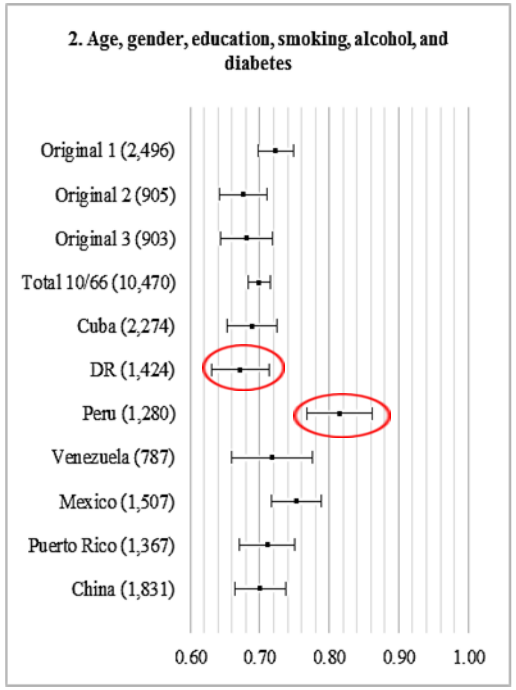


Original:
0.73 (0.66 – 0.80), n=3,734
10 / 66:
0.74 (0.72 – 0.75), n=11,067

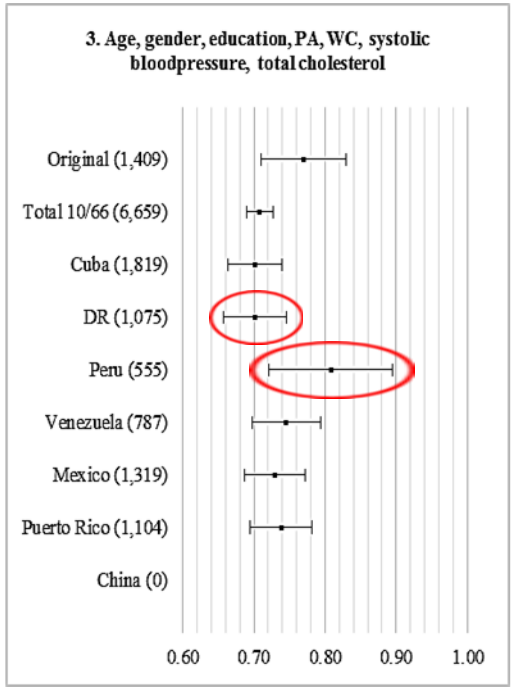
Harrell's C statistic and 95%CI for dementia risk prediction models



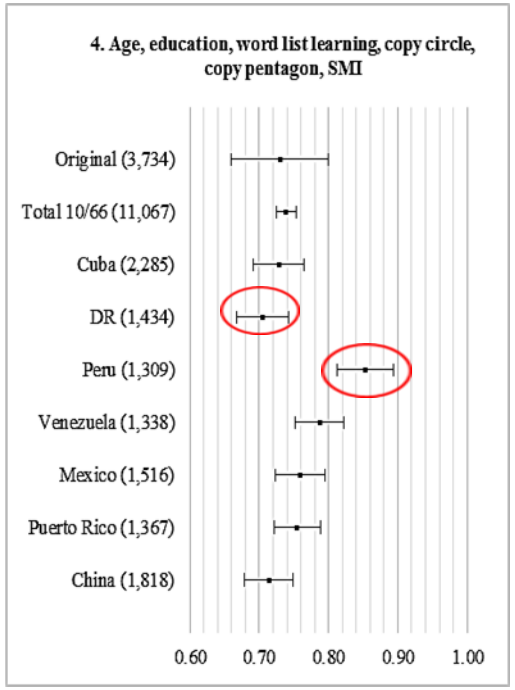
DR: 0.67 (0.62 - 0.71), n=1,439
Peru: 0.79 (0.73 - 0.84), n=1,323



DR: 0.67 (0.63 - 0.71), n=1,424
Peru: 0.82 (0.77 - 0.86), n=1,280

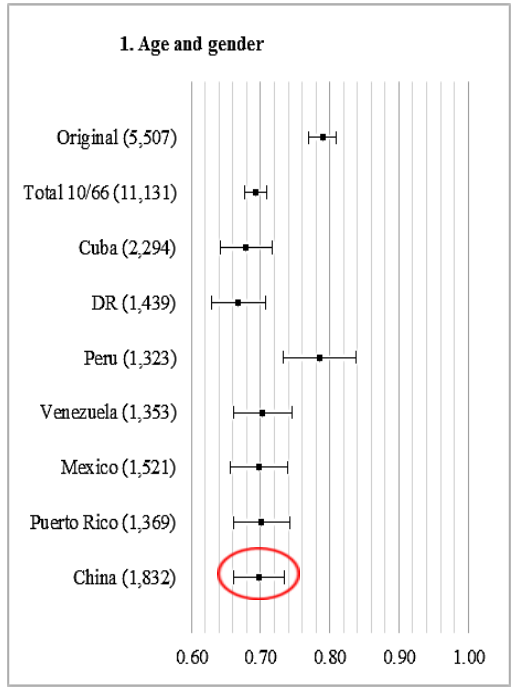


DR: 0.70 (0.66 - 0.75), n=1,075
Peru: 0.80 (0.72 - 0.89), n=555

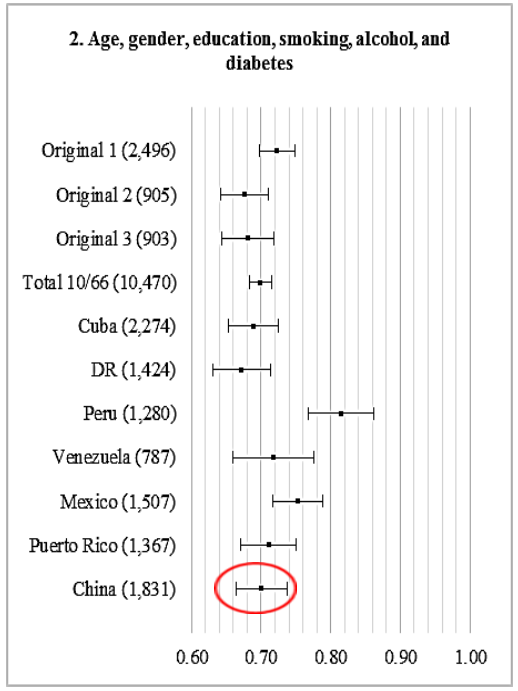


DR: 0.71 (0.67 - 0.74), n=1,434
Peru: 0.85 (0.81 - 0.89), n=1,309

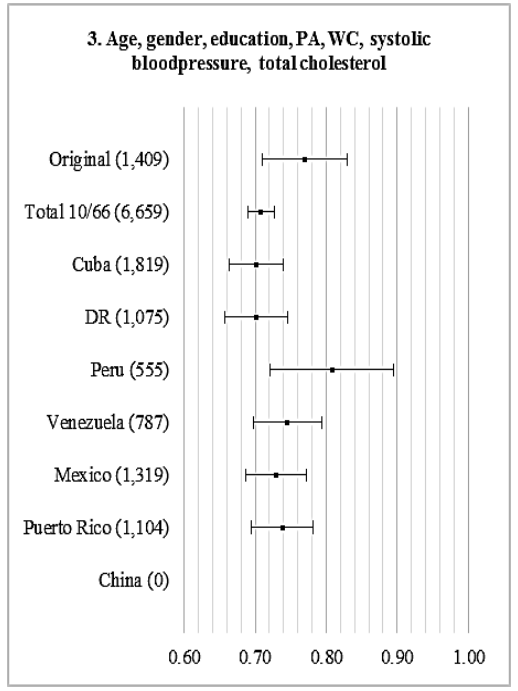
Harrell's C statistic and 95%CI for dementia risk prediction models



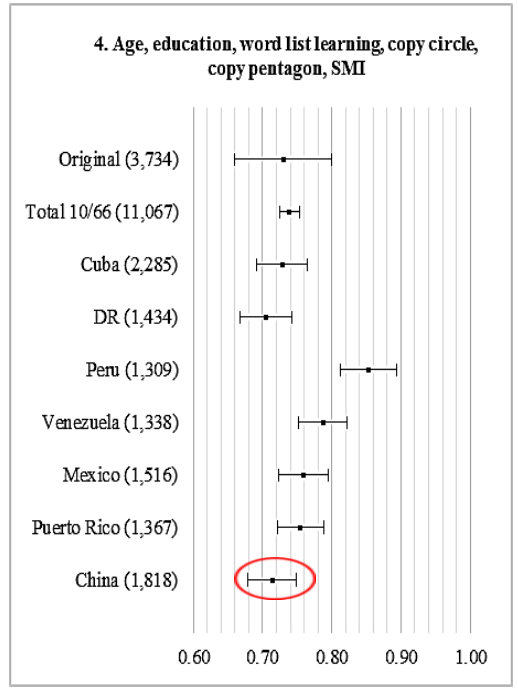
0.70 (0.66 - 0.73), n=1,832



0.70 (0.67 - 0.74), n=1,831



n=0



0.71 (0.68 - 0.75), n=1,818

Preliminary conclusion

- Some dementia risk prediction models developed in HIC appear to translate well in 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.

Next steps

1. Dementia risk model development in the 10 / 66 cohort:
   - Possibly detect new predictors of dementia.
   - Identify best performing cognitive performance scores.
   - Focus on feasibility of use of the model in LMICs.

2. External validation of new model in cohorts from LMICs:
   - The Ibadan study (Nigeria)?
   - MHAS study (Mexico)?
   - Chinese Longitudinal Healthy Longevity Survey (CLHLS)?
   - Cuban Health and Alzheimer Study (CHAS)?

WS2.1 Deliverables – current status

1) Update systematic review of dementia risk prediction models (completed)
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Model validation outside of 10/66

We’re currently considering options including:

EPIDEMCA (Central African Republic and Republic of Congo)

CHARLS (China Health and Retirement Longitudinal Study)

MHAS (Mexican Health and Aging Study)

Any other options?

WS2.1 Deliverables – current status

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5) Undertake systematic review of MCI operationalization and prevalence in LMIC (in progress)

Systematic review

Mild Cognitive Impairment (MCI) operationalisation and prevalence in low and middle income countries.

Systematic review MCI prevalence in LMICs

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

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

Study characteristics

- Data available from 18 countries including:
  - Bulgaria, Russia, China, India, Malaysia, Nigeria, Tanzania, Central African Republic, Republic of Congo, Burkina Faso, South-Africa, Brazil, Mexico, Venezuela, Puerto Rico, Peru, Dominican Republic and Cuba.

- Sample size ranged from 108 to 32,715 participants.

- Only studies in older population (range: ≥50 and ≥ 80 years).

Criteria MCI

- Heterogeneity in diagnostic criteria for MCI.

- Majority of studies used one of the Petersen criteria.
  - Amnestic MCI
  - Non-amnestic MCI
  - Single domain MCI
  - Multi domain MCI

- Six used CIND criteria
  - Cognitive Impairment No Dementia

- Remaining studies slightly deviating criteria.

Example criteria MCI

Definitions	Original Mayo Clinic [6]	Expanded/ Key Symposium [7, 8]
Criteria		
Self- or informant-reported memory complaint	x	
Self- or informant-reported cognitive complaint		x
Objective memory impairment	x	
Objective cognitive impairment		x
Essentially preserved general cognitive functioning	x	
Preserved independence in functional abilities	x	x
No dementia	x	x

Petersen, Ronald C., Barbara Caracciolo, Carol Brayne, Serge Gauthier, Vesna Jelic, and Laura Fratiglioni. "Mild cognitive impairment: a concept in evolution." Journal of internal medicine 275, no. 3 (2014): 214-228.

Operationalisation criteria MCI

- Also, heterogeneity in operationalisation of criteria.

- For example:
  - Cognitive function was assessed by 17 different tools
    - e.g. MMSE, CERAD, and CSI-D.
  - Dementia diagnosis:
    - DSM-IV criteria;
    - Low score cognitive assessment tool; or
    - 10/66 dementia algorithm.

MCI prevalence in LMICs

- Range prevalence 0.6% and 49.1%.

- Prevalence rates differed significantly between criteria (p=0.008)
  - Median prevalence
    - Petersen’s criteria: 13.9% = 23 countries
    - CIND: 26.5% = 6 countries
    - Other criteria: 23.1% = 5 countries

Example MCI prevalence

- 10/66 study (Sosa, 2012):
  - Cuba, Dominican Republic, Peru, Mexico, Venezuela, Puerto Rico, China, and India.
  - Individuals aged 65+ (N=15,376)
  - **A-MCI prevalence between 0.6% and 4.6%.**

- WHO SAGE study (Vancampfort, 2017):
  - China, Ghana, India, Mexico, Russia, and South Africa.
  - Individuals aged 50+ (N=32,715)
  - **MCI prevalence 15.3%**

	SMC	**Global Function**	**Memory**	**Non-memory**	**Physical Functioning**	**Dementia**
10/66 cohort	Summing items scores from relevant questions of the GMS.	N/A	- Composite memory score from the memory subscale of the CSI 'D'. - Immediate and delayed word recall scores from the modified CERAD ten-word list [1.5 SD age and education cut-off)	N/A	- CSI 'D' informant interview on ADL and IADL. - Very mild or no impairment in carrying out: household chores, pursuing hobbies, using money, feeding, dressing, or toileting	10/66 dementia algorithm and DSM-IV criteria
WHO SAGE	Self-reported	N/A	CERAD 10-word learning list (-1SD cut-off)	WAIS digit span test, and animal naming task (-1SD cut-off)	ADL deficiency	Severe levels of cognitive impairment.

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)

Future steps?