Centre for Healthy Brain Ageing (CHeBA)
COSMIC: Cohort Studies of Memory in an International Consortium

NEWSLETTER | March 2019

Dear COSMIC collaborators,

Welcome to our inaugural COSMIC newsletter. Since its inception 5 years ago, COSMIC has grown to 37 member studies from 29 countries in 6 continents. We currently have 13 projects at various stages of development or completion, from data requests to papers being under review at journals including Neurology, JAMA Neurology and PLOS Medicine. Published papers from COSMIC collaborators are already attracting much attention, and we frequently receive requests for the participation of COSMIC studies in grant applications. This newsletter briefly describes our projects, as well as other matters like the COSMIC meeting being planned for during the AAIC in Los Angeles in July, where we look forward to seeing all of you able to attend.

Scientia Professor Perminder Sachdev AM (Co-Director, CHeBA)

Dr Darren Lipnicki (Study Co-ordinator, COSMIC)

Active projects

1. Determinants of cognitive performance and decline in diverse ethno-regional groups (Darren Lipnicki, CHeBA)
   - Rejected by NEJM, JAMA, and JAMA Neurology.
   - Submitted to PLOS Medicine (Feb 27), currently under review.
2. BMI and cognitive decline (Steve Makkar, CHeBA)
   - Submitted to Neurology (Feb 15), currently under review.
3. How age and sex interactions influence the effects of APOE*4 on cognitive decline (Steve Makkar, CHeBA)
   - Submitted to JAMA Neurology (Feb 24), currently under review.
4. Relationship between education, APOE*4 and risk of cognitive impairment (Steve Makkar, CHeBA)
   - Abstract submitted for AAIC (attached).
   - Draft sent to COSMIC co-authors (deadline for feedback: Mar 15).
   - Intended for American Journal of Epidemiology.
5. MINDSED: The effects of sedentary behavior on cognitive function and cognitive decline in older persons without dementia (Rene Melis, Radboud University, The Netherlands).
   - Rejected by JAMA.
   - Submitted to PLOS Medicine (March 3).
6. Common and unique factors associated with odour identification in Indonesians and white Australians (Yuda Turana, Atma Jaya Catholic University, Indonesia).
   - Rejected by JAGS, Journal of Gerontology: Medical Sciences, and Chemical Senses.
   - Submitted to PLOS One (Mar 5).
7. The prevalence of subjective cognitive decline in and across different geographical and ethno-cultural regions (Susanne Roehr, University of Leipzig, Germany).
   - Draft in preparation.
   - Presentation accepted for IFPE Congress, April 2019.
   - Abstract submitted for AAIC (attached).
8. Reproductive history follow-up on nullipara and number of children and dementia (Jong Bin Bae, Seoul National University, South Korea)
   - Paper being written using data from 8 studies, and will include Gothenburg H70 once data agreement is finalised.
9. Risk factor clustering (Ruth Peters, NeuRA)
   - Abstract submitted for AAIC (attached).
10. Depression in the pre-clinical phase of AD: trajectories and determinants (Karen Ritchie, INSERM, France; Simone Reppermund, CHeBA)
    - Data provided for 13 studies.
    - Working to refine anti-depression medication use data.
11. Interactive effects of diabetes and apolipoprotein E ε4 on cognitive decline in elderly adults (Steve Makkar, CHeBA)
    - Data request sent to 14 studies (deadline April 1).
12. Decline in verbal and visual memory in mild cognitive impairment: predictors of AD and associations with biomarkers (Javier Oltra Cucarella).
    - Collating data.

13. The relationship between alcohol use trajectories and health, mortality and cognition in older adults (Louise Mewton, CHeBA)
    • Data request sent (deadline May 6).

AAIC 2019

14. COSMIC meeting: 2-hours followed by dinner on Tuesday July 16.
    • Around 18 people (not including CHeBA personnel) have registered interest in attending.
15. IALSA workshop on dementia risk models.
    • Exploring a supplemental NIA grant to fund travel and accommodation.

New projects

16. Physical activity and cognitive decline (Steve Makkar, CHeBA)
    • Will first try to apply a more comprehensive harmonization protocol to existing physical activity data (initially using Sydney MAS data).
17. Murali Krishna (MYNAH) is interested in lung functioning and cognition.
18. Ken Rockwood (CSHA) and PhD student possibly interested in a project on frailty.
19. Interest from EAS in projects on imaging, as well as occupational history.
20. Proposal on "Sleep, Mild Cognitive Impairment, and Dementia in Elderly Cohorts with Ethnoracial Diversity" received from Seung Wan Suh (KLOSCAD).

Meta-data on the IALSA network (Maelstrom)

21. KLOSCAD, Bambui and MMAP have been added, more to come.
22. COSMIC also listed, and member studies are linked
    • https://www.maelstrom-research.org/mica/network/cosmic#/
23. Updating descriptions and/or requesting data dictionaries so variables can also be listed.
    • Study leaders will be contacted by Darren Lipnicki and Maelstrom Research as required.

Membership

24. Shanghai Aging Study are interested, though need to obtain IRB approval.

Data

25. Gothenburg data agreement being finalised.

26. New baseline and 1-year follow-up data from CLAS.

27. SPAH will send recently obtained APOE data.

28. MYNAH documents for sharing data need to be completed.

Ethics

29. We are working with our local ethics committee to improve the procedures for compliance (eg, not alerting all listed COSMIC personnel of changes to the list).

Data manager

30. We will be advertising for a CHeBA data manager to work on COSMIC and other consortia.
    - They will take over some of the data management currently done by Darren Lipnicki.

Website

31. We are working towards having an area of the COSMIC website (based on the UNSW SharePoint platform) that will include a forum for better communication between members, which includes allowing members to share files and leave comments.

Grant applications

32. COSMIC will be a contributing partner in an IALSA application for an R01 grant to NIA for advancing risk factor models in dementia.
    - There will be some financial support to us if the application is successful.
    - The usual principles of project approval etc. will remain the same.

Relationship between education, apolipoprotein epsilon 4 (APOE*4) and cognitive impairment in diverse ethno-regional groups: The COSMIC collaboration

Steve R. Makkar, Darren M. Lipnicki, John D. Crawford, Anbupalam Thalamuthu, Nicole A. Kochan, Henry Brodaty, Perminder S. Sachdev, for Cohort Studies of Memory in an International Consortium (COSMIC)

Background: Greater years of education are associated with a lower incidence of dementia and reduced magnitude of cognitive decline in late adulthood. Unclear is whether this association is linear or nonlinear, and whether there is a threshold level of educational attainment after which additional education yields no further protection against cognitive impairment. Also unclear is how gender, ethnicity, and carriage of the APOE*4 allele moderate the relationship between education and cognitive impairment.

Methods: Participants were 29,221 individuals (58.3% White, 20.1% Asian, 2% Black) aged 63-91 years from 17 studies participating in COSMIC (Cohort Studies of Memory in an International Consortium). We conducted a one-step individual participant data (IPD) meta-analysis using multilevel survival analysis to examine the association between education and cognitive impairment risk (i.e., Mini Mental State Examination ≤ 18), and moderation of these effects by age, sex, APOE*4 carriage and ethnicity. We analysed education as both continuous and categorical, where participants were assigned to one of the following educational levels based on cohort-specific cut-offs: Incomplete Primary; Primary; Middle-School; and High School and above.

Results: Years of education were related to reduced risk of cognitive impairment; this association was nonlinear, indicating a less pronounced reduction in risk at higher levels of education. In categorical analyses, cognitive impairment risk was lower for Middle-school versus Primary education (Fig 1A), and this association was stronger in women than men (Fig 1B), larger in Blacks than Whites (Fig 1C), and weakened with older baseline age. High school education did not reduce cognitive impairment risk relative to Middle-school or Primary education, except in Asians (Fig 1D). Finally, Middle-school education was related to a reduced risk of cognitive impairment in non-White APOE*4 carriers (Fig 2).

Conclusions: Educational attainment beyond Middle-school did not yield significant reductions in cognitive impairment risk, except in Asians. Among APOE*4 carriers, Middle-school education was related to reduced risk of cognitive impairment only in non-Whites, implying that education may be a proxy for other dementia-related risk factors (e.g., economic deprivation) in non-White older adults. At a minimum, attainment of a Middle-school education may protect individuals against latelife cognitive impairment.
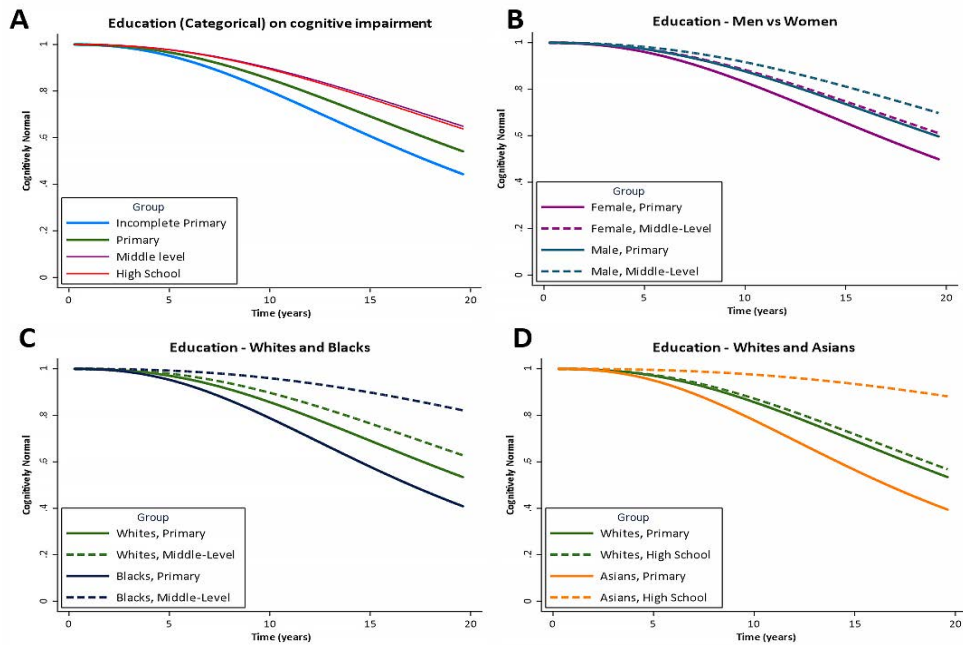
Figure 1. Relationship between education and risk of cognitive impairment (i.e., MMSE ≤ 18) treating education as categorical. A, Proportion of participants cognitively normal over time for participants with four educational levels: incomplete primary, primary, middle-level, and high school. B, Proportion of participants cognitively normal with either a middle-level or primary education in men and women separately. C, Proportion of participants cognitively normal among participants with a primary or high school education, in Whites and Asians. D, Proportion of participants cognitively normal among participants with a primary or middle-level education, in Whites and Blacks.
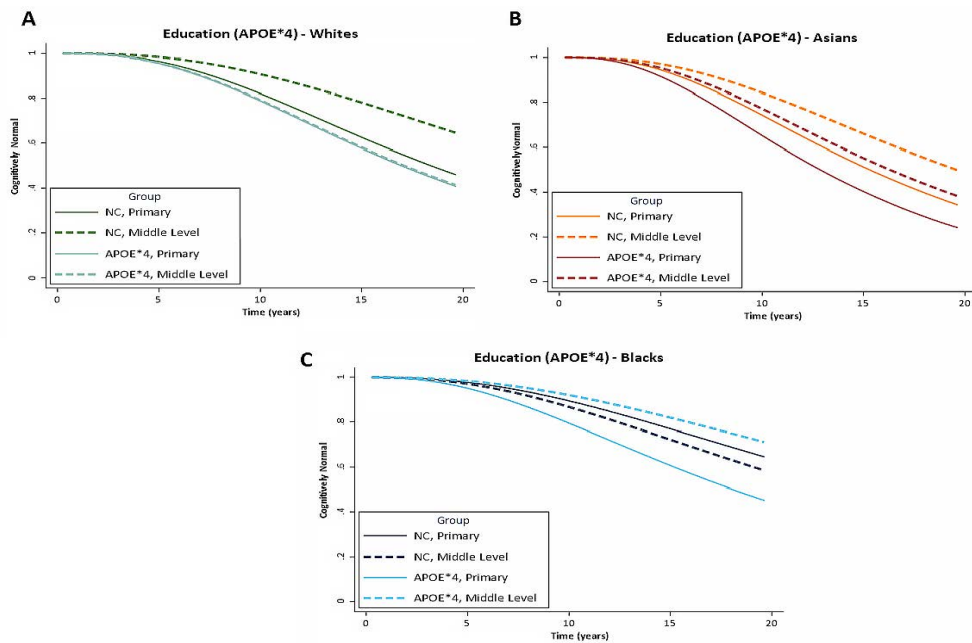

Figure 2. Interaction between educational level and carriage of APOE*4 on the risk of cognitive impairment in ethnoregional groups. A, Proportion of White participants cognitively normal with a primary or middle-level education in APOE*4 carriers and non-carriers. B, Proportion of Asian participants cognitively normal with a primary or middle-level education in APOE*4 carriers and non-carriers. C, Proportion of Black participants cognitively normal with a primary or middle-level education in APOE*4 carriers and non-carriers.

Lifestyle and cardiovascular risk factor clusters and cognitive decline

Ruth Peters, Kim M Kiely, Darren M. Lipnicki, Marie-Laure Ancelin, Kaarin J Anstey, Henry Brodaty, Erico Costa, Antonio Guaita, Mary Haan, Mindy J. Katz, Ki Woong Kim, Richard B Lipton, Juan J Llibre Rodriguez, Karen Ritchie, Nikolaos Scarmeas and Perminder S. Sachdev.

Background: Modifiable risk factors for cognitive decline are well established. However, to date, the literature has typically focused on the relationship between individual risk factors and later cognitive outcome. Despite this, we know that risk factors co-occur. We examined the impact of concomitant risk factor clusters on cognitive function in harmonised multi-cohort longitudinal data from the Cohort Studies of Memory in an International Consortium (COSMIC).

Method: Those without prevalent dementia, with a baseline Mini-Mental State Exam (MMSE)>23 and cognitive follow-up assessment were included. Four concomitant risk factor clusters were derived a-priori based on prior research (fig 1). Linear mixed models with two-stage individual participant meta-analysis and logistic regression (pooled data) were used to examine the impact of the clustered risk factors on (1) change in MMSE and (2) incident cognitive decline (present/absent) (using the Reliable Change Index applied to the MMSE) adjusted for age, sex and education, and stratified by age (≤65/>65), sex and region.

Result: There were 11,928 eligible individuals drawn from 10 cohorts across the Americas, Europe, Asia and Australia. Mean age 70 years (SD=6.7, range:54-100), 54% female, mean follow-up 2.5 years (SD=1.4, range:0.5-15). Mean baseline MMSE was 28.1 (SD=1.7) and 8% (965) had incident cognitive decline. There were 651 (5.5%) participants identified with high lifestyle and cardiovascular risk, 38% with high cardiovascular risk only, 5% with high lifestyle risk only, 51% were low risk. Only the cardiovascular group was associated with greater rates of decline in MMSE scores (B=-0.13,95%CI=-0.24:-0.02) (fig 2). Neither the lifestyle (OR=1.03(95%CI=0.77:1.38)), nor the cardiovascular (OR=1.07(95%CI=0.93:1.24)) group was associated with an increased risk of incident cognitive decline compared to the low risk group. Having both lifestyle and cardiovascular risk resulted in an OR=1.10 (95%CI=0.83:1.46). The impact of risk factor clusters varied by outcome, region, study, and key socio-demographic groups (age, sex).

Conclusion: There were no robust relationships between a priori defined modifiable risk factor clusters and cognitive decline. Limitations include use of binary risk factors, and missing or uncollected risk factor data. The next step may be to examine the potential role of continuous risk factor data and data driven risk factor clusters.

Fig 1 Risk factor clusters

Cardiovascular risk group	Lifestyle, mental health risk group
Hypertension* plus at least one other risk factor from high cholesterol, cardiovascular disease, diabetes mellitus, prior stroke	Low physical activity* plus at least one other risk factor from current smoking, obesity, depressive symptomology
High risk group	**Low risk group**
Meeting criteria for both cardiovascular and lifestyle risk	Neither meeting cardiovascular nor lifestyle risk categories

*Modifiable risk factors with highest prevalence.

Fig 2: Forest plots showing study and pooled estimates of the difference in change in MMSE for risk groups vs low-risk group.
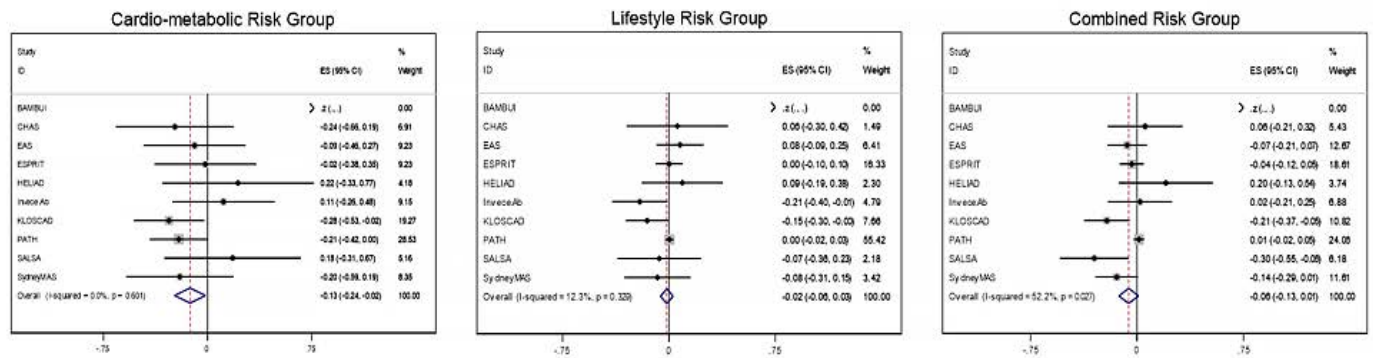
Subjective cognitive decline in and across international cohort studies of ageing: The COSMIC collaboration

Susanne Roehr; Alexander Pabst; Steffi G. Riedel-Heller; Marie-Laure Ancelin; Kaarin J. Anstey; Carol Brayne; Henry Brodaty, Mary Ganguli; Maëlenn Guerchet; Antonio Guaita; Mindy J. Katz; Ki Woong Kim; Sebastian Koehler; Shuzo Kumagai; Richard Lipton; Antonio Lobo; Tze Pin Ng; Pierre-Marie Preux; Karen Ritchie; Suzana Shahar; Yuda Turana; Martin van Boxtel; Darren M. Lipnicki; Perminder S. Sachdev; for Cohort Studies of Memory in an International Consortium (COSMIC)

Background: Subjective cognitive decline (SCD), i.e. a self-experienced decline in cognitive ability in the absence of objective cognitive impairment, is recognized as the first notable cognitive syndrome in the preclinical stage of Alzheimer's disease (AD) and other dementias. However, estimates on the prevalence of SCD are scarce. Therefore, we aimed to estimate SCD prevalence based on consensus research criteria for SCD in and across international cohort studies of ageing.

Method: Analyses were based on the combined baseline data for 16 international cohort studies from 15 different countries. All studies were members of COSMIC (Cohort Studies of Memory in an International Consortium). Qualitative/semantic and quantitative (item response theory/IRT) approaches were used to a) harmonize SCD items across studies and b) derive SCD prevalence estimates, applying a uniform operationalization algorithm based on current SCD research criteria and implementation guidelines according to Jessen et al. (2014) and Molinuevo et al. (2017); i.e. endorsement of a self-experienced decline in cognitive functioning; unimpaired cognitive performance operationalized as less than 1.5 SD below the age-, sex-, and education adjusted study-based mean of Mini-Mental Status Examination scores; preserved ability to perform instrumental activities of daily living; exclusion of major depressive and anxiety symptomatology.

Result: The total sample comprised 44,228 dementia-free individuals at least 60 years of age (mean age: M = 73.3 years; SD = 7.2 years); 58.1% were women. Variety of SCD items was high between studies; however, qualitative and quantitative harmonization approaches both robustly suggested an age- and sex-standardized SCD prevalence of one third across study populations. Individuals from high-income countries as well as individuals with educational levels above primary education tended to show lower SCD prevalence rates compared to individuals from middle- and low-income countries and individuals with low education, respectively.

Conclusion: SCD is frequent in ageing populations around the globe, as estimated across 16 international cohorts. However, SCD measurement still largely varies in the absence of standardized instruments. Therefore, estimates on SCD prevalence may be associated with some inaccuracy. Nevertheless, the frequent occurrence of SCD warrants further investigation of its significance as a cognitive syndrome in preclinical AD as well as in non-AD dementia, specifically in conjunction with early neuropsychiatric symptoms. This may lead to improved strategies for early identification and secondary prevention of dementia.

References:

Jessen F, Amariglio RE, van Boxtel M, et al. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. Alzheimers Dement. 2014;10:844-852.

Molinuevo JL, Rabin LA, Amariglio R, et al. Implementation of subjective cognitive decline criteria in research studies. Alzheimers Dement. 2017;13:296-311.

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