Clara Belessiotis-Richards (Orcid ID: 0000-0001-6900-2678)

Naaheed Mukadam (Orcid ID: 0000-0001-8635-9521)

A cross-sectional study of potentially modifiable risk factors for dementia and cognitive function in India: a secondary analysis of 10/66, LASI, and SAGE data

Clara Belessiotis-Richards[1], Professor Gill Livingston[1] (MD), Louise Marston[2] (PhD), Naaheed Mukadam[1] (PhD)

[1]University College London (UCL) Department of Psychiatry, 6th Floor, Maple House, 149 Tottenham Court Road, London W1T 7NF

[2]UCL Department of Primary Care and Population Health, Upper Third Floor, UCL Medical School (Royal Free Campus), Rowland Hill Street, London NW3 2PF

Corresponding author details:
Dr Clara Belessiotis-Richards, MBBS MRCPsych
c.belessiotis@ucl.ac.uk
University College London (UCL) Department of Psychiatry, 6th Floor, Maple House, 149 Tottenham Court Road, London W1T 7NF

Word count: 3,570

Acknowledgements

ABSTRACT

Objectives

Dementia is rising globally, particularly in low-and-middle-income countries. India has almost four million people living with dementia, set to double by 2050. Targeting nine potentially modifiable risk factors (less education, hearing impairment, depression, physical inactivity, hypertension, obesity, smoking, diabetes, and social isolation) could possibly prevent or delay many dementias. We aimed for the first time to examine risk factors for dementia in India and their link with cognitive status and dementia, to inform prioritisation of public health interventions that could prevent or delay dementia.

Methods

We conducted a cross-sectional analysis using three studies: 10/66 Dementia Study (n= 2,004), Longitudinal Aging Study of India (n= 386), and Study of Global Ageing (n= 2,441). Our exposures were the nine risk factors above. We calculated a cognitive z-score within each study and used dementia diagnosis in 10/66. We adjusted for socioeconomic factors, age, and sex using multivariable linear for cognition and logistic regression for dementia.

Results

Less education, hearing impairment, depression, and physical inactivity were associated with lower z-scores and increased odds of dementia. Obesity was associated with higher z-

score and lower odds of dementia. Social isolation was associated with lower z-scores and decreased odds of dementia. Results for smoking, diabetes, and hypertension were inconsistent.

Conclusion

Our risk estimates were larger for less education, hearing impairment and physical inactivity compared to global estimates and should be intervention priorities. This study highlights the need for longitudinal studies to clarify the relationship between these potentially modifiable risk factors and dementia in India.

Word count: 250

Keywords: dementia prevention, public health, cognition, India, epidemiology

Key points:
- Age-specific incidence and prevalence of dementia has fallen in many higher income countries, leading to interest in targeting potentially modifiable risk factors to delay or prevent a large proportion of dementia cases, but little is known about the association between these risk factors and dementia risk in low-and-middle-income countries, especially in India.
- We looked at cognition and dementia in India in association with nine pre-specified potentially modifiable risk factors for dementia for the first time. We found that less education, hearing impairment, depression, and physical inactivity were linked with lower cognition and dementia in India. As expected, cross-sectional obesity and hypertension were not risks.
- The risks of dementia were larger than previously reported global estimates for people with less education, hearing impairment and those who were physically inactive. This is a good indication of where public health initiatives to prevent dementia in India should focus.

Main Text

I.   INTRODUCTION

Worldwide, the number of people living with dementia is rapidly increasing, from an estimated 50 million people in 2015 to an anticipated 152 million by 2050 [1]. 60% of people

with dementia already live in low-and-middle income countries (LMICs) and this is projected to increase to 80% by 2050 [2].

Many high-income countries (HICs) have reported a decline in age-specific dementia incidence, leading to increasing interest in the role of potentially modifiable risk factors for dementia [3]. The 2017 Lancet Commission on dementia prevention, intervention and care calculated that targeting nine established potentially modifiable risk factors (less education, mid-life hypertension, obesity, and hearing loss, and later-life diabetes, depression, social isolation, smoking, and physical inactivity) at specific times in the life course could potentially delay or prevent up to a third of dementias globally [1]. The addition of a further three factors (head injury, alcohol excess, and air pollution) increased this estimate to 40% but most data for meta-analysis on which the relative risks for these are calculated come from HICs with relatively little evidence from LMICs [4,5].

There are already a substantial number of individuals in India living with dementia (3·7 million in 2010) and this number is set to double by 2030 [6]. India is predicted to face the highest absolute number of deaths from non-communicable diseases (NCD) globally in the near future due to its high prevalence of illnesses such as cardiovascular disease and diabetes, large population (1·3 billion), and barriers to healthcare access. Rapid socioeconomic development, globalisation, and increasing incomes in parts of India have led to an increase in lifestyle risk factors such as smoking and obesity, but healthcare access remains a problem [7]. The population attributable fraction (PAF) of these nine potentially modifiable risk factors in India is estimated at 41%, which is higher than global estimates (35%) [5]. This calculation was based on local prevalence of risk factors; however, relative risk estimates from global studies were used and assumed to have the same impact on cognition in India as globally. We do not know whether this is true, though the higher frequency of some risk factors indicates a greater potential for dementia prevention in India [4].

There is an urgent need to increase our understanding of the role of potentially modifiable risk factors in LMICs and in India, in particular, so as to appropriately target and prioritise public health interventions that could prevent or delay dementia. Here, we aim to measure for the first time, to our knowledge, the association between the nine pre-specified potentially modifiable risk factors previously reported as worldwide risks in the Lancet Commission [1,5], cognitive performance, and dementia diagnosis, to better understand their contribution in this setting.

II.   METHODS

This is a secondary analysis of three pre-existing cross–sectional datasets.

1.1. *The 10/66 Dementia Research Group*

The 10/66 survey of individuals aged ≥65 years in 2003-2006 across urban and rural settings (n= 2,004) (Table 1) [2] used purposive site selection and door-to-door visits to identify eligible households (Figure 1). Response rate was 72% in urban India, and 98% in rural India. We received agreement to use this data on 3rd October 2019 and downloaded the data dictionary, questionnaires and assessment tools from the 10/66 website[8].

1.2. *The Longitudinal Aging Study in India (LASI)*

The LASI survey was of people in India aged ≥45 years in 2010 (Table 1). They used purposive sampling to select four states (n= 1,683) (Table 1, Figure 1), stratified by urban and rural location as detailed previously [9]. We only included those aged ≥65 (n=386). Response rate was 90·9%.

We downloaded the data and questionnaires from the Gateway to Global Ageing website[10] on 15th August 2019.

1.3. *Study of Global AGEing (SAGE)*

The World Health Organisation (WHO) conducted SAGE, a multi-country survey for individuals aged ≥50 years. We used Wave 1 data from 2006-2007. The study selected six representative states in India (Table 1, Figure 1), using a multistage, stratified sampling design to select a final population (n= 12,198) [11]. We analysed those aged ≥65 (n=2,441) (Table 1).

Response rate was 68% [11]. We received approval for access to the SAGE data via the WHO website [12]; we downloaded the Phase 1 dataset and questionnaires on 19th September 2019.

2. Outcome Measures

2.1. Primary: cognitive function

The studies used differing cognitive tasks. To maximise comparability between datasets we used the three validated tasks which were present in all datasets to create a cognitive index (Table 2): verbal fluency in one minute, ten-word learning and ten-word delayed recall (Supplementary).

The final cognitive index had a total possible score of 27 (Table 2), with an approximately normal distribution in each dataset (Supplementary). Overall cognitive testing, defined as a pre-calculated cognitive score in 10/66 and the sum of other tasks in SAGE and LASI, showed good concurrent validity with our cognitive index (Spearman's rho 0·84 SAGE, 0·61 10/66, 0·94 LASI, all p<0·0001).

As in a previous study, we standardised cognitive tests to a continuous z-score by subtracting individual results from the study-specific means and dividing by the standard deviation (SD) [13]. This allowed direct comparison of cognition between datasets.

2.2. Secondary: dementia diagnosis

The 10/66 study gave dementia by an algorithm developed by 10/66 and Diagnostic and Statistical Manual (DSM) IV research criteria. The algorithm has a specificity of 94%, a sensitivity of 94%, and a 92% predictive validity in India [14].

In our sample, 17 individuals met DSM criteria and 181 the 10/66 algorithm criteria for dementia. 80% of our sample were not given a specified subtype of dementia and we therefore used 'any dementia' diagnosis, defined either by 10/66 or DSM criteria, as our outcome.

3. Exposure Variables

Exposures were the nine potentially modifiable risk factors for dementia identified in the 2017 Lancet Commission [1]. They were measured in each dataset using face-to-face interviews and anthropometric measurements. Table 3 shows the harmonised exposure variables, enabling comparison between studies. We were not able to include the three additional variables of head injury, alcohol excess, or air pollution, in the Lancet 2020 commission[4] due to a lack of data.

4. Adjusted variables

We controlled for four prespecified confounders: age, socioeconomic position (SEP), locality (urban or rural), and sex. We used total annual household income and food insecurity as measures of SEP, as in a previous study [15].

5. Statistical Analysis

5.1. Missing data

We conducted a complete case analysis. In SAGE and 10/66, the maximum amount of missing data across variables was 3% (for obesity). In LASI, less than 9% of data were missing for any variable, except for the Centre for Epidemiologic Studies Depression Scale (CESD) (17%), where we used individual mean score imputation for those with four or fewer missing items and excluded those with more than four missing items, in line with a previous paper [16]. Missing data did not appear random (e.g. people with missing anthropometric measurements had lower z-scores), so we judged that using complete case analysis would be more accurate than imputed values, with the exception of the CESD in LASI.

5.2. Regression analyses

SAGE and LASI provided individual level weights in their dataset to account for clustering and sampling strategy, which we used for all analyses. 10/66 assigned equal weight to each individual.

For both outcomes, we carried out regression analyses using a minimally-adjusted model, adjusted for age and sex, and a fully-adjusted model, adjusted for age, sex, locality and SEP. We used multivariable linear and logistic regression with cognitive z-score and dementia as the outcome, respectively.

6. RESULTS

6.1. Demographics

Table 1 describes the populations in our study. We used data from 2,004 people in 10/66, 386 in LASI and 2,441 in SAGE. As expected, mean z-score was inversely associated with increasing age in all three datasets (Table 4), with lowest mean z-score in the oldest groups

(80+ years), and odds of dementia increased with increasing age. Women had lower mean z-scores than men in all three datasets and almost twice the odds of dementia.

6.2. Early life

6.2.1. Less education

Those with less than secondary education (79-92% of participants in each study) had a lower mean z-score than those with at least secondary education: -0·35 to -0·08, compared to 0·38 to 0·98 (Table 4). On multivariable analysis, there was a strong association between lower z-scores and less education (Table 5). Those with less education were almost three times more likely to have dementia, but this association had wide confidence intervals (Table 6).

6.3. Mid-life

6.3.1. Hypertension

Prevalence of hypertension was lower in LASI (26%) and SAGE (33%) than in 10/66 (51%). Participants with current hypertension tended to have a higher mean z-score than those without in 10/66 and LASI: 0·14 to 0·19 compared to -0·05 to -0·09 (Table 4). In linear regression models, hypertension was associated with better cognitive function, except in SAGE (Table 5). Hypertension was associated with increased odds of dementia (Table 6).

6.3.2. Obesity

The prevalence of obesity ranged from 6-15%. Obese individuals tended to have a higher z-score than non-obese people: 0·19 to 0·36 compared to 0·00 (Table 4). Current obesity was associated with better performance on cognitive testing across all three datasets (Table 5) and with approximately 50% lower odds of dementia (Table 6).

6.3.3. Hearing loss

Hearing loss prevalence ranged from around 10% (10/66 and SAGE) to 47% (LASI). Participants with hearing impairment had a lower mean z-score than those with normal hearing: -0·89 to -0·10 compared to 0·05 to 0·10 (Table 4). After adjustment, hearing loss was associated with lower cognitive function in all datasets (Table 5) and those with hearing impairment had 3·5 times the odds of dementia than those without (Table 6).

6.4. LATE LIFE

6.4.1. Smoking

Frequency of self-reported smoking was 16% in 10/66, 21% in LASI and 48% in SAGE. Mean z-scores were around 0 for smokers and non-smokers (Table 4). In adjusted analyses across all datasets, smoking was associated with worse cognitive performance (Table 5) but lower odds of dementia in 10/66 (Table 6). Confidence intervals were wide for all findings.

6.4.2. Depression

Frequency of concurrent depressive features was 18% in LASI and 35% in 10/66. 21% of participants in SAGE reported a history of depression. Participants with depressive features had a lower mean z-score than those without: -0·45 to -0·11 compared to 0·03 to 0·10 (Table 4). There was a strong association between lower cognitive performance and depressive features in 10/66 and LASI, but not with depression over the past year in SAGE (Table 5). There were increased odds of dementia for those with depressive features (Table 6).

6.4.3. Physical inactivity

Physical inactivity levels varied across datasets (15-58%). Those with low levels of physical activity had a lower mean z-score than those who were active: -0·49 to -0·18 compared to 0·09 to 0·24 (Table 4). There was an association between worse cognitive performance and low physical activity in all models (Table 5). Those who were physically inactive also had almost 2·5 times the odds of having dementia than those who were active (Table 6).

6.4.4. Social isolation

Social isolation frequency ranged from 11-60% across datasets. Socially isolated participants had a lower mean z-score than those who were not isolated in LASI and SAGE (-0·36 to -0·15 compared to -0·16 to 0·21) but not in 10/66 (Table 4). After full adjustment, socially isolated participants performed worse on cognitive testing across all three datasets (Table 5). There were decreased odds of dementia in those with social isolation, but these results had wide confidence intervals (Table 6).

6.4.5. Diabetes

The prevalence of self-reported diabetes was 8-13% across the three datasets and participants with diabetes had a higher mean z-score than those without diabetes: 0·10 to 0·19 compared to -0·02 to -0·01 (Table 4). In adjusted multivariable linear analyses, diabetes was associated with better cognitive performance in LASI and SAGE but not in 10/66 (Table 5). There was no evidence of an association between self-reported diabetes and dementia (Table 6).

7. DISCUSSION

To our knowledge our study is the first to examine the association of nine pre-specified potentially modifiable risk factors with cognitive function and dementia in India. We found that less than secondary school education, hearing impairment, depression, and physical inactivity were associated with worse cognition and increased odds of dementia. When compared to HICs data [4] we found larger risk estimates for less education, hearing impairment and physical inactivity, and similar associations for depression, with dementia. Our findings were generally consistent with results from HICs but the relative contribution of these risk factors in India was different, with several risk factors being more common than in HICs, such as less education, hypertension, and physical inactivity.

Participants with less education performed between 0·5 and 0·9 SDs below those with more education, in keeping with a previous study [17], despite the selected tasks not being dependent on education. The frequency of leaving school before secondary education in India was higher across all three studies than worldwide (40%) estimates [1] and the odds of dementia were higher than global estimates (Table 6), suggesting that its relative contribution is greater here. This may be because the cut-point for education was lower than worldwide estimates in our study: less than secondary compared to middle of secondary school. Education has been estimated to have a PAF for dementia of 14% in India, based on relative risk estimates from HICs [5]. Less education is thought to increase the risk of subsequent dementia through a lack of development of cognitive reserve at a crucial time in the life-course [1], which reduces individuals' ability to maintain cognition despite neuropathological changes [18], and by being more socioeconomically deprived as an adult, however we controlled for socioeconomic factors. This study is in keeping with findings that less education is strongly associated with incident dementia in other LMICs [19].

Hearing impairment was associated with worse cognitive function and dementia, as in a previous study [22]. The mechanism of hearing impairment on dementia is not fully understood, though there is evidence of improved cognition after hearing aid use [23]. Our risk estimate was higher than previous global estimates, possibly due to low rates of hearing correction when compared to HICs. Hearing impairment is an important risk factor in India given its high frequency, strong association with dementia, and the potential for intervention, which may also be cost saving [24]. In our cross-sectional data it is possible that hearing impairment compromised cognitive testing, though this doesn't account for the strong association with dementia.

Physical inactivity was associated with worse cognitive performance and dementia to a greater degree than global estimates [4]. Similarly, a case-control study in Delhi found those who exercised less were more likely to have dementia [26]. There may be a differential effect of inactivity in people of South Asian ethnicity similar to the increased risk of hypertension and arterial stiffening in this group, or this may represent cultural expectations of domestic life, such that women may be less likely to keep physically inactive, especially in rural environments. The mechanism of physical inactivity on dementia in this setting is not clear and warrants further investigation. This finding may represent both a causal association, either directly or through mediators such as obesity, hypertension and diabetes, or reverse causation: as cognitive function declines, physical activity levels drop.

Where depression was concurrently assessed using validated tools in 10/66 and LASI (Table 3) it was associated with poorer cognitive performance. Depression was substantially more prevalent across all three of our datasets than the 5·2% estimated in a previous study [5], suggesting that this could be an important target for public health intervention. However, the size of the effect was smaller than global risk estimates [4] and may not be clinically meaningful. Depression can be a feature of early neurodegeneration, as well as a risk factor for later dementia development [1]. In our cross-sectional data, concurrent depressive symptoms may have affected cognitive performance leading to an artificially low result or may be evidence of a dementia 'prodrome'. In most HIC clinical settings, assessment for depression would be an important step before diagnosing dementia.

Hypertension and obesity, which are mid-life risk factors, are known to fall as dementia develops. These showed expected paradoxical associations with cognition in our study: in older people maintaining obesity or hypertension means you are unlikely to be developing dementia [4]. Hypertension has been previously associated with better cognition in LASI [20]. Hypertension was, however, associated with increased odds of dementia, contrasting with a previous study showing a positive linear association between hypotension and dementia [21], but confidence intervals were wide and we had no data on changes in blood pressure over time.

We found that being socially isolated was generally associated with worse cognitive function but with lower odds of dementia. This is in keeping with a study showing that community participation and increased social structure are associated with higher cognitive function in India [25]. We postulated that social isolation might be associated with reduced cognitive performance due to less cognitive stimulation, but that individuals who are sufficiently

impaired to receive a diagnosis of dementia may see an increase in social support from concerned relatives and friends due to the reduced function associated with this illness. Given the change in effect estimates seen between minimally and fully adjusted models for cognition in 10/66, there may also be socio-cultural dimensions to this risk factor that have yet to be explored.

Our results regarding diabetes and smoking were inconsistent. Previous estimates of diabetes prevalence in India in those above 65 years range from 15·4 to 18·8% [27], which is higher than self-reported diabetes history seen here. In contrast with global risk estimates, smoking showed slightly lower odds of dementia, which may relate to earlier smoking-related mortality obscuring increased dementia risk, but this result had wide confidence intervals [4]. Smoking prevalence was also lower than global risk estimates in two out of three of our datasets.

The strengths of our study include that we compared results from three studies across diverse areas and populations in India, using large datasets. We validated our results for cognition against a formal diagnosis of dementia. We were able to calculate z-scores using similar cognitive measures and thus to compare datasets. This is the first time to our knowledge that less education has been examined as a risk factor in this population; most previous studies have adjusted for education. We also adjusted for socioeconomic factors that are particularly relevant in LMICs. As cognitive function tends to deteriorate with age, we controlled for age.

Our study had a number of limitations, most notably the challenge of interpreting cross-sectional data for mid-life risk factors such as hypertension and obesity, which were measured in late life in our cross-sectional study. Though we have classified our risk factors according to life stage in our tables, the prevalence of these has been measured in late life. While response rates were very high in 10/66 and LASI they were lower at 68% in SAGE. The datasets had less than 10% of data missing but these were not missing at random; for example, weight was more likely to be missing in those who were unable to stand on scales. We used odds ratios, which are not directly comparable to previously calculated global risk measures using relative risks, although for rare outcomes such as dementia the two measures would be similar. Our datasets may have underestimated the prevalence of self-reported risk factors, such as diabetes. Self-report is not only affected by participant recall bias but underestimates the true rate of non-communicable diseases in LMICs, due to restricted healthcare access [7]. The conflict in results between cognition and dementia that we saw with hypertension, smoking, social isolation, and diabetes is likely due to cognitive

tests not equating to a formal dementia diagnosis. In most cases, this clinical diagnosis incorporates collateral information of decline as well as other factors. In addition, our cognitive z-score was made up of a subset of tests to maximise comparability between datasets, which limited the number of cognitive domains covered by the score. It's possible that different constructs were measured in each dataset despite our harmonisation efforts. We had less power to detect differences in rarer risk factors (eg. obesity) in smaller samples such as LASI and particularly small numbers of individuals with more education in our samples, leading to wide confidence intervals. The sampling strategies aimed to achieve a representative final sample, however we excluded a significant proportion of younger people from SAGE and LASI.

Our results highlight the importance of public health strategies for dementia targeted to particular settings and outline potential priorities in India. The importance of less education, hearing loss and physical inactivity in India has already been highlighted and we found that they appeared to have a larger effect in our study than global estimates [5], which suggests these should be considered public health priorities. Though we could not infer direction of causality in our study, our findings reinforce these results and add depression and social isolation as potential targets to modify cognitive function in India. Longitudinal studies, using objective measures and with sufficiently long follow-up to distinguish between the early stages of dementia and risk factors that pre-date the condition, are needed to better understand the contribution of these potentially modifiable factors to dementia in LMICs. For governments and the research community to rise to the public health challenge of dementia, global collaborative efforts to harmonise large scale longitudinal studies across HICs and LMICs will be needed.

REFERENCES

1.   Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet* 2017; **390**(10113): 2673-734.
2.   Prince M, Ferri CP, Acosta D, et al. The protocols for the 10/66 dementia research group population-based research programme. *BMC Public Health* 2007; **7**: 165.
3.   Wolters FJ, Chibnik LB, Waziry R, et al. Twenty-seven-year time trends in dementia incidence in Europe and the United States: The Alzheimer Cohorts Consortium. *Neurology* 2020; **95**(5): e519-e31.
4.   Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet* 2020; **396**(10248): 413-46.
5.   Mukadam N, Sommerlad A, Huntley J, Livingston G. Population attributable fractions for risk factors for dementia in low-income and middle-income countries: an analysis using cross-sectional survey data. *Lancet Glob Health* 2019; **7**(5): e596-e603.

6.   India AsRDSo. The Dementia India Report: prevalence, impact, costs and services for Dementia: Executive Summary. New Delhi: ARDSI, 2010.

7.   Vellakkal S, Subramanian SV, Millett C, Basu S, Stuckler D, Ebrahim S. Socioeconomic inequalities in non-communicable diseases prevalence in India: disparities between self-reported diagnoses and standardized measures. *PLoS One* 2013; **8**(7): e68219.

8.   Group DR. The 10/66 Public Data Archive. 2020. https://www.alz.co.uk/1066/1066_public_archive_baseline.php2019).

9.   P. Arokiasamy DB, Jinkook Lee, Kevin Feeney, and Marija Ozolins. Longitudinal Aging Study in India: Vision, Design, Implementation, and Preliminary Findings. Washington (DC): National Research Council (US) Panel on Policy Research and Data Needs to Meet the Challenge of Aging in Asia, 2012.

10.   Data GtGA. LASI Downloads. https://g2aging.org/?section=page&pageid=262019).

11.   P. Arokiasamy SP, T. V. Sekher, H. Lhungdim. Study on global AGEing and adult health (SAGE) Wave 1 India National Report: International Institute for Population Sciences, 2013.

12.   (WHO) WHO. WHO Study on global AGEing and adult health (SAGE). https://www.who.int/healthinfo/sage/en/.

13.   Lipnicki DM, Makkar SR, Crawford JD, et al. Determinants of cognitive performance and decline in 20 diverse ethno-regional groups: A COSMIC collaboration cohort study. *PLoS Med* 2019; **16**(7): e1002853.

14.   Jotheeswaran AT, Williams JD, Prince MJ. The predictive validity of the 10/66 dementia diagnosis in Chennai, India: a 3-year follow-up study of cases identified at baseline. *Alzheimer Dis Assoc Disord* 2010; **24**(3): 296-302.

15.   Guerra M, Ferri CP, Sosa AL, et al. Late-life depression in Peru, Mexico and Venezuela: the 10/66 population-based study. *Br J Psychiatry* 2009; **195**(6): 510-5.

16.   Bono C, Ried LD, Kimberlin C, Vogel B. Missing data on the Center for Epidemiologic Studies Depression Scale: a comparison of 4 imputation techniques. *Res Social Adm Pharm* 2007; **3**(1): 1-27.

17.   Sosa AL, Albanese E, Prince M, et al. Population normative data for the 10/66 Dementia Research Group cognitive test battery from Latin America, India and China: a cross-sectional survey. *BMC Neurol* 2009; **9**: 48.

18.   Stern Y, Arenaza-Urquijo EM, Bartres-Faz D, et al. Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance. *Alzheimers Dement* 2020; **16**(9): 1305-11.

19.   Prince M, Acosta D, Ferri CP, et al. Dementia incidence and mortality in middle-income countries, and associations with indicators of cognitive reserve: a 10/66 Dementia Research Group population-based cohort study. *Lancet* 2012; **380**(9836): 50-8.

20.   Farron MR, Kabeto MU, Dey AB, Banerjee J, Levine DA, Langa KM. Hypertension and Cognitive Health Among Older Adults in India. *J Am Geriatr Soc* 2020; **68 Suppl 3**: S29-S35.

21.   Albanese E, Lombardo FL, Prince MJ, Stewart R. Dementia and lower blood pressure in Latin America, India, and China: a 10/66 cross-cohort study. *Neurology* 2013; **81**(3): 228-35.

22.   Prince M, Acosta D, Ferri CP, et al. The association between common physical impairments and dementia in low and middle income countries, and, among people with dementia, their association with cognitive function and disability. A 10/66 Dementia Research Group population-based study. *Int J Geriatr Psychiatry* 2011; **26**(5): 511-9.

23.   Amieva H, Ouvrard C. Does Treating Hearing Loss in Older Adults Improve Cognitive Outcomes? A Review. *J Clin Med* 2020; **9**(3).

24.   Mukadam N, Anderson R, Knapp M, et al. Effective interventions for potentially modifiable late-onset dementia risk factors: their costs and cost-effectiveness. *The Lancet Healthy Longevity* 2020.

25.   Jiang N, Wu B, Lu N, Dong T. Neighborhood-based social capital and cognitive function among older adults in five low- and middle-income countries: Evidence from the World Health Organization Study on global AGEing and adult health. *Int J Geriatr Psychiatry* 2020; **35**(4): 365-75.

26.   Tripathi M, Vibha D, Gupta P, et al. Risk factors of dementia in North India: a case-control study. *Aging Ment Health* 2012; **16**(2): 228-35.

27.   India State-Level Disease Burden Initiative Diabetes C. The increasing burden of diabetes and variations among the states of India: the Global Burden of Disease Study 1990-2016. *Lancet Glob Health* 2018; **6**(12): e1352-e62.

28.   Lloyd-Jones DM, Hong Y, Labarthe D, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation* 2010; **121**(4): 586-613.

29.   WHO. Waist circumference and waist-hip ratio. Report of a WHO expert consultation. Geneva, 8–11 December 2008. Geneva: World Health Organization, 2011.

30.   Vilagut G, Forero CG, Barbaglia G, Alonso J. Screening for Depression in the General Population with the Center for Epidemiologic Studies Depression (CES-D): A Systematic Review with Meta-Analysis. *PLoS One* 2016; **11**(5): e0155431.
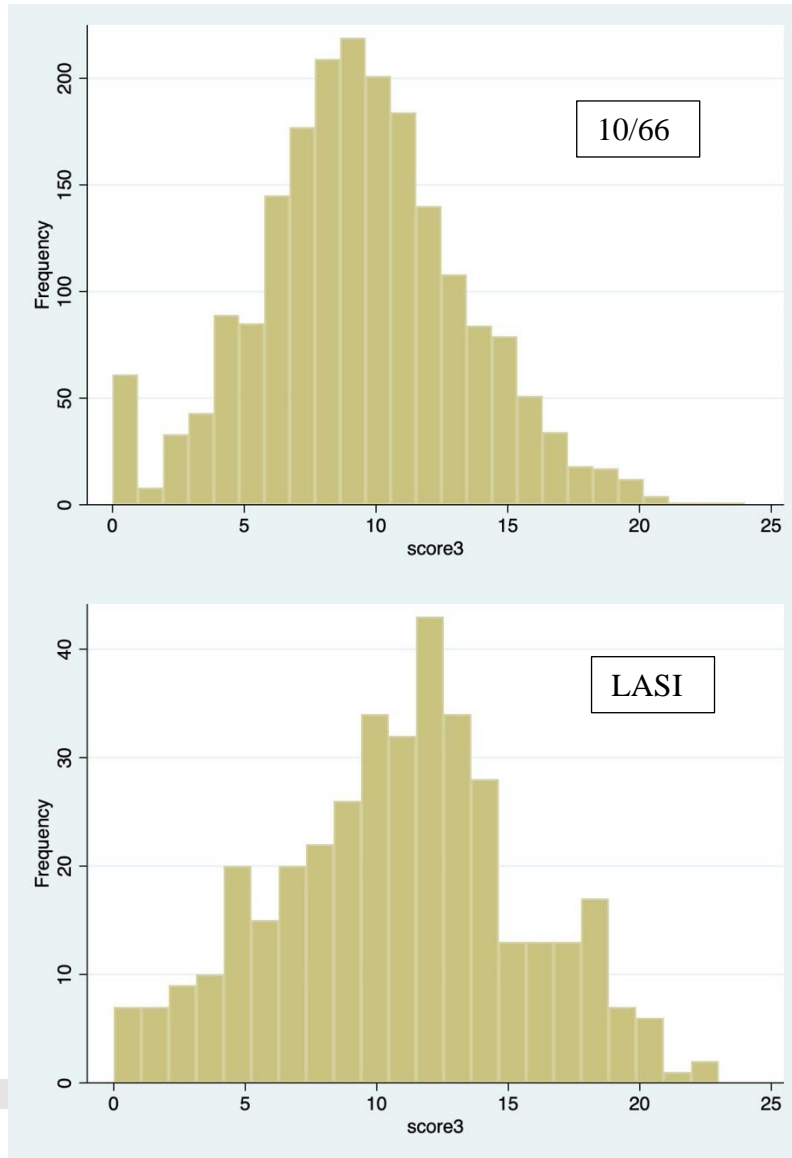
Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Appendix

Figure 1. Results of cognitive testing (score3) in each dataset.
Score3 denotes the sum score out of a possible total of 27 of three cognitive tasks: verbal fluency in one minute, ten-word learning and ten-word delayed recall
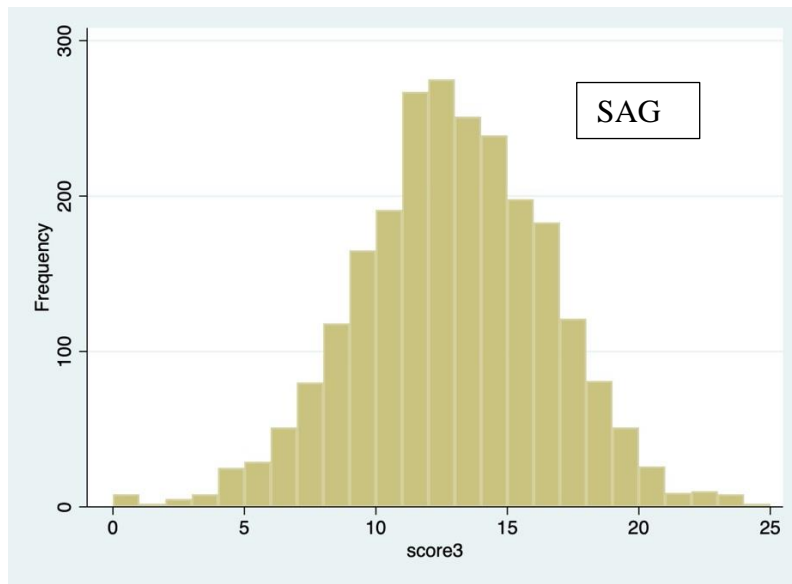
Table 1. List of words used for ten-word learning and delayed recall in each dataset.

10/66 used the list from the Hindi MMSE, adapted from The Consortium to Establish a Registry for Alzheimer's Disease (CERAD)[1], we could not identify the source for SAGE's published list[2], and LASI used three options of ten word lists from CERAD [3].

10/66	SAGE	LASI		
		List one	List two	List three
Butter	Arm	River	Monkey	Elephant
Arm	Bed	Tree	Car	Bike
Letter	Plane	Temple	Stone	Kite
Queen	Dog	School	Doctor	Teacher
Ticket	Clock	Hospital	Phone	House
Grass	Bike	Dog	Fire	Water
Corner	Ear	Cat	Road	Job
Stone	Hammer	Radio	Silver	Book
Book	Chair	Chair	Flower	Market
Stick	Cat	Gold	Cow	Baby

References

1.   Ganguli M, Chandra V, Gilby JE, et al. Cognitive test performance in a community-based nondemented elderly sample in rural India: the Indo-U.S. Cross-National Dementia Epidemiology Study. *Int Psychogeriatr* 1996; **8**(4): 507-24.
2.   Brionne Alvord Carroll PK, Nirmala Naidoo, Somnath Chatterji. Measuring cognitive status in older age in lower income countries: Results from
a pilot of the Study on global AGEing and Adult Health (SAGE). SAGE Working Paper No. 3.
20 Avenue Appia
CH-1211 Geneva 27
Switzerland World Health Organization 2012.

3.   Morris JC, Heyman A, Mohs RC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology* 1989; **39**(9): 1159-65.

Table 1: Description of datasets

Variables	1066	LASI	SAGE
N (65 years and over)	2,004	386	2,441
Dates of survey	2003-2006	2010	2007
Locations of survey	Tamil Nadu (Chennai and Vellore)	Kerala, Karnataka, Rajasthan, Punjab	Assam, Karnataka, Maharashtra, Rajasthan, Uttar Pradesh, West Bengal
Sampling strategy	Purposive, mapping of individual eligible households	Stratified, multistage sampling design based on the 2001 Indian national census	Probability of selection stratified multistage cluster sample design, based on the Indian 2001 Census
Mean age in years (standard deviation)	72 (6·0)	72 (6·5)	71 (6·4)
Sex distribution			
Number of males (%)	873 (44)	197 (51)	1,329 (54)
Number of females (%)	1,116 (56)	189 (49)	1,112 (46)
Rural/urban distribution			
Number of urban residents (%)	1005 (50)	101 (26)	628 (26)
Number of rural residents (%)	999 (50)	285 (74)	1,813 (74)
Median yearly income in rupees (inter-quartile range)	12,000 (0-36,000)	56,000 (12,000-134,900)	40,000 (19,000-90,000)
Number of people experiencing food insecurity (%)	348 (17)	12 (3)	429 (18)

Table 1: Variables contributing to the cognitive index

Variable	Score and categorisation	Notes
Verbal fluency	0 to 7, ordinal	Naming as many animals as possible within one minute. Re-categorized based on Addenbrooke's Cognitive Exam (ACE-III)
Registration	0 to 10, ordinal	A list of ten words is read out over three trials and participants repeat this
Delayed recall	0 to 10, ordinal	Participants recall the same ten words at a later point in the testing
TOTAL		
Cognitive index	0 to 27, ordinal	Total possible score of 27.

Table 1: exposure variable definitions

Risk factor definitions	10/66	SAGE	LASI
EARLY LIFE			
Low education level	Self-report of receiving less than secondary education		
MID-LIFE			
Hypertension	Average blood pressure of two readings of either ≥140 systolic or ≥90 diastolic, in keeping with the WHO and the American Heart Association (AHA) definitions [28]		Self-reported diagnosis of hypertension
Obesity	Waist circumference of ≥88 cm in women and ≥102 cm in men based on WHO guidelines [29]		BMI >30
Hearing impairment	Self-reported hearing impairment causing at least some difficulty	Interviewer assessed	Self-reported difficulty hearing
LATE LIFE			
Smoking	Self-reported history of inhaled tobacco. Smoking history defined as currently smoking or having quit in prior 12 months [28].		
Depression	Diagnosis of depression on stage 1 Geriatric Mental State (GMS) and computer algorithm (AGECAT), which delivers a predicted diagnosis based on a three-stage hierarchical differentiation of syndromes with organic disease at the top of the hierarchy	Self-report of any of loss of interest in usual activities, very low energy or tiredness, low mood, sadness or depression, for at least two weeks over the past 12 months	Score of ≥16 [30] on Centre for Epidemiologic Studies Depression Scale (CESD): a validated, short, self-report scale with 20 questions and a total score ranging from zero to 60, designed to examine the epidemiology of depressive symptoms in the general population
Physical inactivity	Self-report of being physically 'not very' active or 'not at all' active	Self-report of <150 minutes of moderate or <75 minutes of vigorous activity/week, based on AHA guidelines [28].	Self-report of being 'hardly ever' or 'never' active for either moderate or vigorous activity
Social isolation	< Monthly contact with neighbours, relatives, clubs, and friends as in Mukadam et al [5].	< Monthly contact with relatives, friends and attendance at clubs	< Monthly contact with friends and neighbours, attendance at clubs/societies, and being out of the house for social activities.
Diabetes	Self-reported diagnosis of diabetes		

Table 4

Number (N°) of individuals, frequency (%) of risk factors and mean cognitive performance (mean z-score) with 95% confidence interval (95% CI) for each risk factor in all three datasets.

Risk factors ordered by life-course.

Variable	Categories	N° (%)	Mean z-score (95% CI)	N° (%)	Mean z-score (95% CI)	N° (%)	Mean z-score (95% CI)
		10/66 (n= 2,004)		**LASI (n= 386)**		**SAGE (n=2, 441)**	
DEMOGRAPHICS							
Age group (years)	65-69	746/2,002 (37)	0·26 (0·19 to 0·33)	134/386 (35)	0·22 (0·06 to 0·38)	1,055/2,441 (43)	0·11 (0·01 to 0·20)
	70-74	669/2,002 (33)	-0·03 (-0·11 to 0·04)	121/386 (31)	0·01 (-0·16 to 0·18)	715/2,441 (29)	-0·06 (-0·19 to 0·07)
	75-79	321/2,002 (16)	-0·11 (-0·21 to -0·01)	66/386 (17)	0·10 (-0·14 to 0·35)	343/2,441 (14)	-0·15 (-0·29 to -0·02)
	80+	266/2,002 (13)	-0·51 (-0·63 to -0·39)	64/386 (16)	-0·63 (-0·89 to -0·37)	328/2,441 (13)	-0·50 (-0·66 to -0·34)
Sex	Male	873/1,989 (44)	0·16 (0·09 to 0·23)	197/386 (51)	0·22 (0·08 to 0·35)	1,329/2,441 (54)	0·10 (-0·00 to 0·20)
	Female	1,116/1,989 (56)	-0·13 (-0·19 to -0·07)	189/386 (49)	-0·23 (-0·38 to -0·08)	1,112/2,441 (46)	-0·25 (-0·35 to -0·16)
EARLY LIFE							
Less education (less than secondary)	No	157/2,002 (8)	0·98 (0·81 to 1·14)	82/386 (21)	0·58 (0·40 to 0·77)	422/2,441 (17)	0·38 (0·29 to 0·47)
	Yes	1,845/2,002 (92)	-0·08 (-0·12 to -0·04)	304/386 (79)	-0·16 (-0·27 to -0·05)	2,019/2,441 (83)	-0·35 (-0·39 to -0·31)
MID-LIFE							
Hypertension	No	962/1,975 (49)	-0·09 (-0·16 to -0·04)	283/382 (74)	-0·05 (-0·17 to 0·07)	1,579/2,391 (65)	0·04 (-0·01 to 0·09)
	Yes	1,013/1,975 (51)	0·14 (0·07 to 0·20)	99/382 (26)	0·19 (0·03 to 0·36)	812/2,391 (33)	-0·05 (-0·12 to 0·02)
Obesity	No	1,653/1,944 (85)	-0·00 (-0·05 to 0·04)	330/350 (94)	0·00 (-0·10 to 0·11)	2,059/2,348 (94)	-0·00 (-0·04 to 0·04)
	Yes	291/1,944 (15)	0·26 (0·15 to 0·38)	20/350 (6)	0·36 (-0·06 to 0·79)	289/2,348 (6)	0·19 (0·07 to 0·30)
Hearing impairment	No	1,829/2,002 (91)	0·08 (0·04 to 0·13)	202/384 (53)	0·10 (-0·03 to 0·23)	2,193/2,438 (90)	0·05 (0·00 to 0·09)
	Yes	173/2,002 (9)	-0·89 (-1·07 to -0·73)	182/384) (47)	-0·10 (-0·25 to 0·06)	245/2,438 (10)	-0·42 (-0·54 to -0·30)
LATE LIFE							
Smoking	No	1,669/1,996 (84)	-0·01 (-0·06 to 0·04)	303/384 (79)	0·02 (-0·09 to 0·14)	1,267/2,440 (52)	0·01 (-0·04 to 0·07)
	Yes	327 /1,996 (16)	0·04 (-0·05 to 0·13)	81/384 (21)	-0·07 (-0·26 to 0·11)	1,173/2,440 (48)	-0·02 (-0·07 to 0·04)
Depression	No	1,295/2,004 (65)	0·10 (0·04 to 0·16)	292/358 (82)	0·10 (-0·01 to 0·21)	1,933/2,440 (79)	0·03 (-0·02 to 0·07)
	Yes	709/2,004 (35)	-0·18 (-0·25 to -0·11)	66/358 (18)	-0·45 (-0·69 to -0·22)	507/2,440 (21)	-0·11 (-0·19 to -0·02)
Physical inactivity	No	1,690/1,996 (85)	0·09 (0·04 to 0·13)	162/386 (42)	0·24 (0·09 to 0·40)	1,384/2,440 (57)	0·16 (0·11 to 0·21)
	Yes	306/1,996 (15)	-0·49 (-0·61 to -0·38)	224/386 (58)	-0·18 (-0·30 to -0·05)	1,056/2,440 (43)	-0·21 (-0·27 to -0·15)
Social isolation	No	1,791/2,003 (89)	0·00 (-0·04 to 0·05)	154/383 (40)	0·21 (0·07 to 0·35)	1,677/2,438 (69)	-0·16 (-0·21 to -0·12)
	Yes	212/2,003 (11)	-0·03 (-0·15 to 0·09)	229/383 (60)	-0·15 (-0·29 to -0·01)	761/2,438 (31)	-0·36 (-0·43 to -0·29)
Diabetes	No	1,816/2,003 (91)	-0·01 (-0·06 to 0·03)	329/378 (87)	-0·01 (-0·12 to 0·09)	2,235/2,440 (92)	-0·02 (-0·06 to 0·02)
	Yes	187/2,003 (9)	0·11 (-0·03 to 0·25)	49/378 (13)	0·10 (-0·14 to 0·33)	205/2,440 (8)	0·19 (0·06 to 0·32)

Table 5
Linear regression analyses of the association between potentially modifiable risk factors for dementia and cognitive performance in three datasets.
Showing β association with z-score in minimally and fully adjusted models.
*Minimally adjusted (MA) models: adjusted for age, sex.
+Fully adjusted (FA) models: adjusted for age, sex, locality, and SEP.

Variable	10/66				LASI				SAGE			
	MA β* (95% CI)	P-value	FA β+ (95% CI)	P-value	MA β* (95% CI)	P-value	FA β+ (95% CI)	P-value	MA β* (95% CI)	P-value	FA β+ (95% CI)	P-value
EARLY LIFE												
Less education (less than secondary)	-0·95 (-1·11 to -0·79)	<0·0001	-0·78 (-0·94 to -0·62)	<0·0001	-0·81 (-1·06 to -0·56)	<0·0001	-0·77 (-1·04 to -0·49)	<0·0001	-0·56 (-0·73 to -0·38)	<0·0001	-0·49 (-0·64 to -0·34)	<0·0001
MID-LIFE												
Hypertension	0·21 (0·13 to 0·30)	<0·0001	0·11 (0·03 to 0·19)	0·0081	0·39 (0·18 to 0·60)	0·0005	0·35 (0·12 to 0·59)	0·0038	-0·01 (-0·14 to 0·13)	0·9151	-0·01 (-0·14 to 0·12)	0·8809
Obesity	0·37 (0·25 to 0·49)	<0·0001	0·27 (0·16 to 0·39)	<0·0001	0·46 (-0·00 to 0·92)	0·0524	0·44 (-0·01 to 0·90)	0·0563	0·27 (0·10 to 0·45)	0·0022	0·22 (0·05 to 0·38)	0·0118
Hearing impairment	-0·83 (-0·97 to -0·68)	<0·0001	-0·70 (-0·84 to -0·55)	<0·0001	-0·26 (-0·52 to -0·01)	0·0430	-0·28 (-0·52 to -0·05)	0·0196	-0·19 (-0·37 to -0·02)	0·0316	-0·19 (-0·37 to -0·01)	0·0362
LATE LIFE												
Smoking	-0·15 (-0·27 to -0·02)	0·0227	-0·07 (-0·19 to 0·05)	0·2834	-0·15 (-0·37 to 0·08)	0·1991	-0·12 (-0·35 to 0·12)	0·3289	-0·15 (-0·29 to -0·01)	0·0323	-0·12 (-0·24 to 0·01)	0·0651
Depression	-0·26 (-0·35 to -0·17)	<0·0001	-0·23 (-0·32 to -0·15)	<0·0001	-0·43 (-0·71 to -0·16)	0·0028	-0·41 (-0·68 to -0·15)	0·0030	-0·07 (-0·20 to 0·06)	0·2891	-0·03 (-0·16 to 0·09)	0·5782
Physical inactivity	-0·48 (-0·59 to -0·36)	<0·0001	-0·44 (-0·55 to -0·32)	<0·0001	-0·33 (-0·58 to -0·09)	0·0092	-0·33 (-0·58 to -0·09)	0·0091	-0·31 (-0·44 to -0·18)	<0·0001	-0·31 (-0·44 to -0·19)	<0·0001
Social isolation	-0·04 (-0·17 to 0·10)	0·5971	-0·40 (-0·54 to -0·25)	<0·0001	-0·30 (-0·52 to -0·08)	0·0090	-0·31 (-0·53 to -0·09)	0·0074	-0·20 (-0·35 to -0·06)	0·0053	-0·22 (-0·36 to -0·08)	0·0026
Diabetes	0·08 (-0·07 to 0·22)	0·3117	-0·00 (-0·14 to 0·14)	0·9566	0·20 (-0·04 to 0·45)	0·1032	0·15 (-0·13 to 0·42)	0·3006	0·35 (0·08 to 0·63)	0·0121	0·29 (0·03 to 0·55)	0·0314

Table 6
Number of individuals (N) and frequency (%) of dementia according to each risk factor in 10/66. Risk factors ordered by life-course. Logistic regression analysis between dementia diagnosis and risk factor variables in 10/66, showing odds ratios (ORs) as effect estimates for each variable (age as continuous). Previously calculated global relative risk (RR) estimates shown for comparison.
*Minimally adjusted (MA) model: adjusted for age and sex
+Fully-adjusted (FA) model: adjusted for age, sex, income, rural or urban locality, and food insecurity

Variable	Categories	N of people with dementia (%)	MA OR* (95% CI)	P-value	FA OR+ (95% CI)	P-value	Global RR estimates (95% CI) [4]
DEMOGRAPHICS							
Age group (years)	65-69	38 (5)	1		1		
	70-74	60 (9)	1·84 (1·21 to 2·80)	0·0046	1·77 (1·16 to 2·70)	0·0082	
	75-79	28 (8)	1·86 (1·12 to 3·10)	0·0165	1·81 (1·08 to 3·02)	0·0232	
	80+	57 (21)	5·50 (3·53 to 8·56)	<0·0001	5·37 (3·44 to 8·38)	<0·0001	
Sex	Male	57 (6)	1		1		
	Female	126 (11)	1·96 (1·41 to 2·74)	0·0001	1·92 (1·37 to 2·69)	0·0001	
EARLY LIFE							
Less education (less than secondary)	No	4 (3)	1		1		
	Yes	179 (10)	2·92 (1·05 to 8·09)	0·0393	2·18 (0·77 to 6·19)	0·1422	1·6 (1·3 to 2·0)
MID-LIFE							
Hypertension	No	78 (8)	1		1		
	Yes	95 (9)	1·22 (0·88 to 1·68)	0·2285	1·32 (0·95 to 1·84)	0·0959	1·6 (1·2 to 2·2)
Obesity	No	146 (9)	1		1		
	Yes	18 (6)	0·51 (0·30 to 0·87)	0·0133	0·56 (0·33 to 0·95)	0·0301	1·6 (1·3 to 1·9)
Hearing impairment	No	135 (7)	1		1		
	Yes	48 (28)	3·60 (2·42 to 5·35)	<0·0001	3·56 (2·35 to 5·38)	<0·0001	1·9 (1·4 to 2·7)
LATE LIFE							
Smoking	No	164 (10)	1		1		
	Yes	18 (6)	0·76 (0·44 to 1·33)	0·3351	0·71 (0·40 to 1·24)	0·2259	1·6 (1·2 to 2·2)
Depression	No	104 (8)	1		1		
	Yes	79 (11)	1·40 (1·02 to 1·92)	0·0373	1·38 (1·00 to 1·91)	0·0518	1·9 (1·6 to 2·3)
Physical inactivity	No	123 (7)	1		1		
	Yes	60 (20)	2·43 (1·71 to 3·44)	<0·0001	2·42 (1·69 to 3·46)	<0·0001	1·4 (1·2 to 1·7)
Social isolation	No	170 (9)	1		1		
	Yes	13 (6)	0·57 (0·31 to 1·02)	0·0600	0·74 (0·39 to 1·39)	0·3464	1·6 (1·3 to 1·9)
Diabetes	No	167 (9)	1		1		
	Yes	16 (9)	1·04 (0·60 to 1·80)	0·8814	1·13 (0·65 to 1·97)	0·6569	1·5 (1·3 to 1·8)

Figure legends

Figure 1: Sites for each study