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

Martin Prince, Daisy Acosta, Cleusa P Ferri, Mariella Guerra, Yueqin Huang, Juan J Llibre Rodriguez, Aquiles Salas, Ana Luisa Sosa, Joseph D Williams, Michael E Dewey, Isaac Acosta, Amuthavalli T Jotheeswaran, Zhaorui Liu

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Centre for Global Mental Health, Health Service and Population Research Department, Institute of Psychiatry, King's College London, London, UK (Prof M Prince MD, C P Ferri PhD, Prof M E Dewey PhD); **Universidad Nacional Pedro Henriquez Ureña (UNPHU), Internal Medicine Department, Geriatric Section, Santo Domingo, Dominican Republic** (D Acosta MD); **Instituto de la Memoria y Desordenes Relacionados, Lima, Perú** (M Guerra PhD); **Peking University, Institute of Mental Health, Beijing, China** (Prof Y Huang PhD, Z Lui MPH); **Facultad de Medicina Finley-Albarran, Medical University of Havana, Havana, Cuba** (Prof J J Llibre Rodriguez PhD); **Medicine Department, Caracas University Hospital; Faculty of Medicine, Universidad Central de Venezuela, Caracas, Venezuela** (A Salas MD); **National Institute of Neurology and Neurosurgery of Mexico, Autonomous National University of Mexico, Delegacion Tlalpan, Mexico City, Mexico** (A L Sosa PhD, I Acosta MSc); **Voluntary Health Services, Taramani, Chennai, India** (J D Williams MD); **and Public Health Foundation for India, New Delhi, India** (A T Jotheeswaran MSc)

Correspondence to:
Prof Martin J Prince, Institute of Psychiatry, King's College London, Health Service and Population Research Department, London SE5 8AF, UK
martin.prince@kcl.ac.uk

Summary

Background Results of the few cohort studies from countries with low incomes or middle incomes suggest a lower incidence of dementia than in high-income countries. We assessed incidence of dementia according to criteria from the 10/66 Dementia Research Group and Diagnostic and Statistical Manual of Mental Disorders (DSM) IV, the effect of dementia at baseline on mortality, and the independent effects of age, sex, socioeconomic position, and indicators of cognitive reserve.

Methods We did a population-based cohort study of all people aged 65 years and older living in urban sites in Cuba, the Dominican Republic, and Venezuela, and rural and urban sites in Peru, Mexico, and China, with ascertainment of incident 10/66 and DSM-IV dementia 3–5 years after cohort inception. We used questionnaires to obtain information about age in years, sex, educational level, literacy, occupational attainment, and number of household assets. We obtained information about mortality from all sites. For participants who had died, we interviewed a friend or relative to ascertain the likelihood that they had dementia before death.

Findings 12 887 participants were interviewed at baseline. 11 718 were free of dementia, of whom 8137 (69%) were reinterviewed, contributing 34 718 person-years of follow-up. Incidence for 10/66 dementia varied between 18·2 and 30·4 per 1000 person-years, and were 1·4–2·7 times higher than were those for DSM-IV dementia (9·9–15·7 per 1000 person-years). Mortality hazards were 1·56–5·69 times higher in individuals with dementia at baseline than in those who were dementia-free. Informant reports suggested a high incidence of dementia before death; overall incidence might be 4–19% higher if these data were included. 10/66 dementia incidence was independently associated with increased age (HR 1·67; 95% CI 1·56–1·79), female sex (0·72; 0·61–0·84), and low education (0·89; 0·81–0·97), but not with occupational attainment (1·04; 0·95–1·13).

Interpretation Our results provide supportive evidence for the cognitive reserve hypothesis, showing that in middle-income countries as in high-income countries, education, literacy, verbal fluency, and motor sequencing confer substantial protection against the onset of dementia.

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Introduction

Most studies of the incidence of dementia from countries with low incomes or middle incomes report rates that are substantially lower than those from countries with high incomes.[1–4] Results of the 10/66 Dementia Research Group population-based studies[5] in Latin America, India, and China suggested that dementia prevalence might be underestimated when the widely used Diagnostic and Statistical Manual of Mental Disorders (DSM) IV diagnostic criteria are applied, particularly in rural and less developed sites; 10/66 dementia prevalences, derived from a cross-culturally calibrated and validated probabilistic algorithm,[6] were higher than were DSM-IV prevalences and more consistent with those in countries with high incomes.[7] A comprehensive cross-cultural comparison requires estimation of incidence rates and absolute and relative mortality risks for people with dementia.

Elderly people in developing countries often have little formal education, and occupational status and literacy levels tend to be low. Education and occupational attainment have been posited to lead to advantages in brain structure or function, or both, that modify the effect of neurodegenerative brain damage in late-life.[8] Termed cognitive reserve, this construct is complex and difficult to measure. Results from tests of crystallised intelligence and executive function have been proposed as proximal indicators.[8–10] Despite some inconsistency in cohort studies in developed countries, higher levels of education and occupational attainment are associated with a lower incidence of dementia than are limited education and a manual or unskilled profession.[11]

If cognitive reserve is less stimulated in countries with low incomes and middle incomes, then a higher incidence of dementia might be expected in these settings than in high-income countries. However, because normative roles and responsibilities for older adults vary across cultures, so might the cognitive meta-skills needed to maintain them against the challenge of neurodegeneration. Education and occupational attainment based on hierarchies from developed countries might be less relevant, and hence less clearly associated with dementia risk. The effects of occupational attainment and of literacy independent of education have not been tested.

We aimed to assess incidence of dementia according to both 10/66 and DSM-IV criteria, and the effect of dementia at baseline on mortality. We also aimed to examine independent effects of age, sex, socioeconomic position, and indicators of cognitive reserve (educational level, occupational attainment, literacy, and executive function) on dementia incidence.

Methods

Participants and procedures

The protocol for the 10/66 baseline and incidence waves is detailed elsewhere.[12] We did one-phase population-based surveys (2003–07) of all people aged 65 years and older living in geographically defined catchment areas from seven countries (urban sites in Cuba, the Dominican Republic, and Venezuela, and urban and rural sites in Mexico, Peru, China, and India).[12]

The baseline survey consisted of a clinical interview, an informant interview, and a physical examination. It generated information about dementia diagnosis, mental disorders, physical health, anthropometry, demographics, risk factors for dementia and chronic diseases, disability, use of health services, and care arrangements. Incidence waves were subsequently completed in all countries other than India (where for reasons of funding, follow-up was limited to individuals with dementia or cognitive impairment[13]) and a mortality screen was done on the whole baseline sample.[14]

In the incidence wave (2007–10), we sought to trace and reinterview all participants. Assessment protocols and procedures were identical for dementia ascertainment, and much the same in other respects. We revisited the participant's residence at baseline on up to four occasions. When the participant was no longer resident we sought information about vital status and current residence from up to three non-coresident friends or family members, the contact details for whom we recorded at baseline. When participants had moved away, we sought to reinterview them, even outside the catchment area, by telephone if necessary. In case of death, we recorded the date, and completed an informant verbal autopsy, including evidence of cognitive and functional decline suggestive of onset of dementia between baseline assessment and death.

Participation was on the basis of written informed consent. When participants were illiterate, their verbal consent was independently witnessed. Studies were approved by local ethical committees and by the King's College London research ethics committee.

Measures

Only assessments relevant to the present analyses are detailed in this Article. Sociodemographic information was collected at baseline. We obtained information about age in years, sex, educational level (coded 1=none, 2=did not complete primary, 3=completed primary, 4=completed secondary, 5=tertiary education), and number of household assets (car, television, refrigerator, telephone, mains water, mains electricity, plumbed toilet). Occupational attainment was ascertained from the question "What was the best job you ever had?", grouped into four categories (1=professional [manager or administrator, professional, associate professional], 2=clerical or trade [clerical worker or shop keeper], 3=skilled or semi-skilled manual worker, 4=unskilled labourer [labourer or agricultural worker]). Literacy was assessed by self-report, with the question "Can you read a newspaper?"

Dementia diagnosis was made according to 10/66[6] and DSM-IV[5] criteria. The algorithms have been reported[6,15] and validated.[6,13,15] The appendix pp 1–3 provides details of the main features of the two approaches. 10/66 dementia cases score above a cutpoint of predicted probability for dementia, calculated with coefficients derived from a logistic regression equation based on cognitive test and informant report scores and diagnostic output from clinical interviews.[6] DSM-IV dementia cases must meet all four qualifying criteria; characteristic cognitive impairment, decline in social or occupational functioning, not accounted for by another mental disorder, and not occurring only during delirium.[5]

See Online for appendix

We obtained information to establish the diagnoses from: (1) cognitive tests, the Community Screening Instrument for Dementia (CSI'D', COGSCORE scale),[16] incorporating the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) animal-naming verbal fluency task, and the modified CERAD ten word list learning task with delayed recall;[17] (2) a structured clinical mental state interview, the Geriatric Mental State;[18] (3) informant interview, evidence of cognitive and functional decline from the CSI'D' informant interview (RELSCORE scale);[16] and for course and onset of dementia from the History and Aetiology Schedule–Dementia Diagnosis and Subtype (HAS-DDS);[19] and (4) a structured neurological examination including the Luria three step motor sequencing fist-edge-palm (FEP) test (coded as 0=five sequences correct, 1=five sequences completed with one mistake, 2=five sequences completed after one redemonstration, 3=unable to complete five sequences correctly).

For individuals who died between baseline and follow-up we diagnosed probable incident dementia by applying the following criteria: a score of more than two points on RELSCORE from the post-mortem informant interview,

with endorsement of either "deterioration in memory" or "a general deterioration in mental functioning", or both; an increase in RELSCORE of more than two points from baseline; and the onset of these signs noted more than 6 months before death. In the baseline phase of the study, the first criterion would have detected individuals with either DSM-IV or 10/66 dementia with 73% sensitivity and 92% specificity.

Statistical analysis

We used Stata version 11 for all analyses. The cohort for the analyses of 10/66 dementia incidence consisted of individuals who did not have any dementia (DSM-IV or 10/66) at baseline. Only those with DSM-IV dementia were excluded in estimation of DSM-IV dementia incidence. We describe outcomes (reinterviewed, deceased, refused, could not be traced or contacted) for the baseline sample, and outcomes and sociodemographic characteristics for the dementia-free cohort.

Person-years risk for the onset of dementia were calculated as the interval between baseline and follow-up assessment, or the midpoint of this interval for those who developed dementia. Age-specific incidence (with Poisson SEs and 95% CIs) was estimated for each country, by sex, and by age in 5-year groups by dividing numbers of cases by the person-years contributed in each age group. As a sensitivity analysis we computed, for each country, the incidence of probable dementia in those deceased for whom an informant was interviewed at follow-up, and estimated the effect on 10/66 dementia incidence if the same pattern of incidence had occurred across all those who died before follow-up. We used direct standardisation (applying age-specific incidence rates from each 10/66 site to person-years from the EURODEM multisite European incidence study[20]) to compare rates between 10/66 sites and with those previously recorded in EURODEM,[20] and with the whole 10/66 incidence sample as the standard population to compare rates of 10/66 dementia between sites, standardising for age, sex, education, and assets.

We used the whole baseline sample to estimate the effect of 10/66 dementia on mortality during the follow-up period, reporting mortality rates per 1000 person-years stratified by baseline dementia status, and used Cox's proportional hazards regression to estimate site-specific hazard ratios (HRs), controlling for age and sex, pooled with fixed effects meta-analysis. Survival times were censored on the date of death, or the date of follow-up for those who were reinterviewed, or the median date of follow-up interview in that site for those refusing interview.

We modelled the effect of covariates on 10/66 dementia incidence with a competing-risks regression derived from Fine and Gray's proportional subhazards model[21] (Stata stcrreg command). This model is based on a cumulative incidence function, indicating the probability of failure (ie, dementia onset) before a specific time, acknowledging the possibility of a competing event (ie, dementia-free death). In conventional Cox's proportional hazards regression, deaths would be right-censored with such individuals treated as no more or less likely to fail from the cause of interest than those still at risk. This type of censoring is inappropriate because, after death, failure from dementia is not merely unobservable, but no longer possible. Competing risks regression works by keeping individuals who have competing events at risk so that they can be counted as having no chance of failing. We used this approach to estimate mutually adjusted independent effects of age (per 5-year group), sex (men compared with women), education (per level), occupational attainment (per level), and assets (per asset) on 10/66 dementia incidence separately in each site, generating proportional sub-HRs with robust 95% CIs to take account of household clustering, and a fixed effects meta-analysis to combine them. We computed Higgins I^2, estimating the proportion of between-site variability in the estimates accounted for by heterogeneity, rather than sampling error; up to 40% heterogeneity is conventionally deemed negligible, whereas 40–60% is indicative of moderate heterogeneity.[22] Effects of literacy, verbal fluency, and Luria motor sequencing were tested separately in three additional models, controlling for all covariates in the first model.

Role of the funding source

The 10/66 Dementia Research Group's research has been funded by the Wellcome Trust Health Consequences of Population Change Programme (GR066133—prevalence phase in Cuba and Brazil; GR08002—incidence phase in Peru, Mexico, Argentina, Cuba, Dominican Republic, Venezuela, and China), WHO (India, Dominican Republic, and China), the US Alzheimer's Association (IIRG–04–1286—Peru, Mexico, and Argentina), and FONACIT/CDCH/UCV (Venezuela). The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

In all 12887 participants were interviewed in the six countries at baseline, of whom 11718 were free of dementia (table 1); 8137 (69%) were successfully traced and re-interviewed at follow-up, contributing 34718 person years of follow-up. Mortality at follow-up was highest in China, the Dominican Republic, and Cuba (partly a function of longer follow-up intervals), offset by low refusal rates. The highest proportions of participants lost to follow-up were in Venezuela and urban Peru. Median follow-up was shortest in urban Peru and Mexico, and longest in Venezuela, Cuba, the Dominican Republic, and China (table 1); this variation is explained by different timings of baseline data collection. Among the reinterviewed dementia-free cohort, mean age at follow-up ranged from 75·7 years (Venezuela) to 78·6 years (Dominican Republic). Women preponderated in all countries. Levels of education

were notably lower in Dominican Republic, Mexico, and rural China than in other sites. Sites with low levels of education also had a high prevalence of illiteracy (table 1).

Excluding losses to follow-up because of death, we recorded few differences in characteristics between those reinterviewed and others (appendix p 4). Older age was associated with loss to follow-up in Cuba, the Dominican Republic, and Venezuela. Men were more likely to be lost to follow-up than were women in Dominican Republic and rural Mexico. Participants with higher levels of education were more likely to be lost in Cuba than were those with little education, whereas those with lower occupational attainment were more likely to be lost to follow-up in urban Peru and Venezuela than were those with high occupational attainment. The effect sizes were modest (appendix p 4).

We identified 770 incident cases of 10/66 dementia, 284 of which also met criteria for DSM-IV dementia. 10/66 dementia incidence was lowest in Peru and highest in Mexico (table 2 and figure 1). Incidence tended to be higher in women than in men in all centres, and increased exponentially with increasing age (figure 1). For individuals aged 80 years and older, annual incidence per 1000 person-years was lowest in Cuba and highest in Venezuela (table 2). After age-standardising to the EURODEM incidence cohort (table 3) the incidence rate of 10/66 dementia varied between 20 and 30 per 1000 person-years in most sites, a little higher than the 18·4 per 1000 person-years incidence of DSM-III-R dementia recorded in EURODEM. However, age-standardised incidence of 10/66 dementia was substantially higher than that for DSM-III-R dementia in rural China,

	Cuba	Dominican Republic	Peru, urban	Peru, rural	Venezuela	Mexico, urban	Mexico, rural	China, urban	China, rural	All centres
Total baseline sample										
n	2813	2011	1381	552	1965	1003	1000	1160	1002	12 887
Deceased	608 (22%)	467 (23%)	98 (7%)	54 (10%)	200 (10%)	99 (10%)	110 (11%)	224 (19%)	291 (29%)	2151 (17%)
Refused	20 (1%)	42 (2%)	257 (19%)	32 (6%)	240 (12%)	64 (6%)	112 (11%)	24 (2%)	0	791 (6%)
Not traced	178 (6%)	305 (15%)	136 (10%)	45 (8%)	268 (14%)	91 (9%)	65 (7%)	171 (15%)	0	1259 (10%)
Reinterviewed	2007 (71%)	1197 (60%)	890 (64%)	421 (76%)	1257 (64%)	749 (75%)	713 (71%)	741 (64%)	711 (71%)	8686 (67%)
Dementia free cohort										
n	2517	1769	1251	516	1820	910	913	1076	946	11718
Deceased	449 (18%)	370 (21%)	61 (5%)	48 (9%)	161 (9%)	78 (9%)	88 (10%)	175 (16%)	251 (27%)	1681 (14%)
Refused	17 (<1%)	41 (2%)	248 (20%)	30 (6%)	221 (12%)	57 (6%)	106 (12%)	24 (2%)	0	744 (6%)
Not traced/uncontactable	159 (6%)	287 (16%)	120 (10%)	41 (8%)	246 (14%)	74 (8%)	63 (7%)	166 (15%)	0	1156 (10%)
Reinterviewed	1892 (75%)	1071 (61%)	822 (66%)	397 (77%)	1192 (66%)	701 (77%)	656 (72%)	711 (66%)	695 (74%)	8137 (69%)
Characteristics of dementia-free cohort who were reinterviewed										
Person years of follow-up	8679	5561	2434	1479	5269	2155	2009	3613	3496	34 695
Median follow-up (years; IQR)	4·5 (3·9–5·2)	5·1 (5·0–5·2)	2·9 (2·6–3·3)	3·7 (3·7–3·8)	4·3 (4·1–4·8)	3·0 (3·0–3·2)	3·0 (3·0–3·1)	5·1 (4·7–5·4)	5·0 (4·8–5·3)	4·4 (3·4–5·0)
Mean age at follow-up (SD)	78·1 (6·1)	78·6 (6·5)	77·0 (6·6)	77·0 (6·7)	75·7 (5·9)	76·4 (5·8)	76·2 (6·1)	77·7 (5·4)	76·0 (5·0)	77·1 (6·1)
Female sex	1249 (66%)	736/1069 (69%)	540 (66%)	211 (53%)	769/1190 (65%)	460 (66%)	411 (63%)	419 (59%)	394 (57%)	5189/8133 (64%)
Did not complete primary education	414/1889 (22%)	733/1068 (68%)	73/818 (9%)	151/392 (38%)	319/1185 (27%)	388/699 (55%)	536 (82%)	240 (34%)	465 (67%)	3319/8113 (41%)
Median assets (IQR)	6 (5–6)	5 (4–6)*	6 (6–6)	5 (4–6)	6 (6–7)	6 (6–7)	4 (3–6)	5 (5–6)†	6 (5–7)	6 (5–6)‡
Illiteracy	146/1888 (8%)	214/1068 (20%)	54/819 (7%)	103/394 (26%)	70/1187 (6%)	118/694 (17%)	177/654 (27%)	174/709 (24%)	403/641 (63%)	1459/8054 (18%)
Occupational attainment§										
Professional	581 (32%)	101 (9%)	283 (35%)	30 (8%)	320 (29%)	105 (15%)	15 (2%)	273 (38%)	23 (3%)	1731 (21%)
Trade	234 (13%)	112 (10%)	211 (26%)	16 (4%)	278 (25%)	116 (16%)	26 (4·0)	32 (5%)	2 (<1%)	1027 (13%)
Semi-skilled	547 (30%)	268 (25%)	244 (30%)	70 (18%)	431 (39%)	199 (28%)	165 (25%)	261 (37%)	6 (<1%)	2191 (27%)
Labourer	436 (24%)	582 (54%)	66 (8%)	280 (71%)	76 (6%)	280 (40%)	449 (68%)	144 (20%)	664 (96%)	2977 (37%)
Verbal fluency and motor sequencing										
Mean verbal fluency (SD)	16·8 (5·8)	14·3 (4·8)	17·7 (5·7)	16·0 (4·8)	18·7 (6·3)	15·9 (5·1)	13·9 (4·5)	16·9 (4·4)	15·4 (5·5)	16·4 (5·5)
Luria motor sequencing (five sequences, no errors)	622/1884 (33%)	184/1053 (18%)	418/811 (51%)	183/392 (46%)	275/955 (29%)	108/692 (15%)	86/653 (13%)	461/707 (65%)	530 (76%)	2867/7842 (37%)

Data are n (%) or n/N (%), unless otherwise specified. *Data for three participants are missing. †Data for one participant are missing. ‡Data for 11 participants are missing. §For occupational attainment, data for 94 participants are missing for Cuba, for eight participants are missing for the Dominican Republic, for 18 participants are missing for urban Peru, for one participant are missing for rural Peru and urban China, and for 87 participants are missing for Venezuela, with 209 values missing for this measure overall.

Table 1: **10/66 incidence wave data**

	Cuba		Dominican Republic		Venezuela		Peru		Mexico		China	
	Cases; PYR	Incidence (95% CI)	Cases; PYR	Incidence (95% CI)	Cases; PYR	Incidence (95% CI)	Cases; PYR	Incidence (95% CI)	Cases; PYR	Incidence (95% CI)	Cases; PYR	Incidence (95% CI)
Whole sample	170; 8078·5	21·0 (18·1–24·5)	118; 5217·3	22·6 (18·8–27·0)	135; 4973·9	27·1 (22·9–32·1)	69; 3798·9	18·2 (14·3–23·0)	121; 3978·4	30·4 (25·5–36·3)	161; 6696·9	24·0 (20·6–28·1)
By site												
Urban	170; 8078·5	21·0 (18·1–24·5)	118; 5217·3	22·6 (18·8–27·0)	135; 4973·9	27·1 (22·9–32·1)	42; 2370·4	17·7 (13·1–24·0)	41; 2092·1	19·6 (14·4–26·6)	84; 3395·4	24·7 (20·0–30·6)
Rural	..	..	..	..	..	..	27; 1428·5	18·9 (13·0–27·6)	80; 1886·3	42·4 (34·1–52·8)	77; 3301·5	23·3 (18·7–29·2)
By sex												
Male	50; 2723·5	18·4 (13·9–24·2)	27; 1671·1	16·2 (10·9–23·2)	42; 1787·7	23·5 (17·4–31·8)	22; 1497·5	14·7 (9·7–22·3)	42; 1413·6	29·7 (22·0–40·2)	54; 2853·7	18·9 (14·5–24·7)
Female	120; 5355·0	22·4 (18·7–26·8)	91; 3546·3	25·7 (20·8–31·4)	92; 3179·9	28·9 (23·6–35·5)	49; 2301·4	21·3 (16·1–28·2)	79; 2564·8	30·8 (24·7–38·4)	107; 3843·3	27·8 (23·0–33·6)
By age (years)												
65–69	7; 1656·7	4·2 (2·0–8·9)	7; 1069·9	6·5 (2·9–12·9)	13; 1861·6	7·0 (4·1–12·0)	1; 976·8	1·0 (0·1–7·3)	9; 1043·9	8·6 (4·2–16·6)	19; 1643·3	11·6 (7·4–18·1)
70–74	28; 2682·7	10·4 (7·2–15·1)	21; 1670·6	12·6 (8·0–18·9)	34; 1525·5	22·3 (15·9–31·2)	6; 1099·8	5·5 (2·5–12·1)	28; 1264·8	22·1 (15·3–32·1)	34; 2534·3	13·4 (9·6–18·8)
75–79	51; 2096·5	24·3 (18·5–32·0)	30; 1248·7	24·0 (16·5–33·9)	29; 929·9	31·2 (21·7–44·9)	16; 858·0	18·6 (11·4–30·4)	29; 887·6	32·7 (22·7–47·0)	39; 1630·9	23·9 (17·5–32·7)
≥80	82; 1834·4	44·7 (36·0–55·5)	60; 1227·5	48·9 (37·6–62·5)	59; 657·1	89·8 (59·6–115·9)	46; 864·3	53·2 (39·9–71·1)	55; 782·2	70·3 (54·0–91·6)	69; 888·4	77·7 (61·3–98·3)

PYR=person-years.

Table 2: **Incidence (per 1000 person-years) for 10/66 dementia, by country, site, sex, and age**

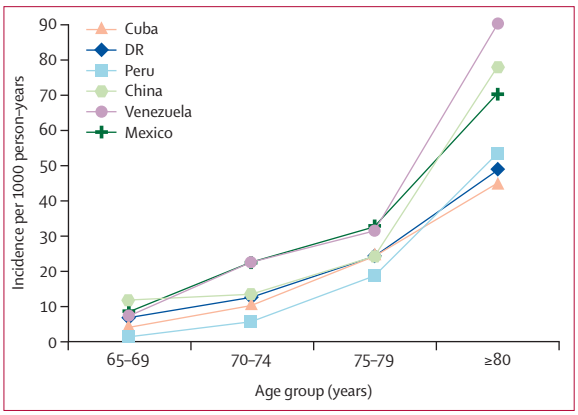

Figure 1: **Incidence of 10/66 dementia, by age group and country**
DR=Dominican Republic.

	Standardised for age (EURODEM incidence cohort)	Standardised for age, sex, education, and household assets (entire 10/66 Dementia Research Group incidence cohort)
Cuba	21·9 (19·0–25·1)	17·2 (14·6–20·1)
Dominican Republic	24·1 (20·3–28·5)	18·9 (15·6–22·9)
Peru, urban	20·1 (15·3–25·9)	23·1 (17·8–29·2)
Peru, rural	22·8 (16·5–30·8)	19·4 (13·6–26·7)
Venezuela	40·1 (35·0–45·8)	30·0 (25·7–35·0)
Mexico, urban	21·3 (16·1–27·7)	16·9 (12·5–22·7)
Mexico, rural	50·7 (41·7–61·0)	34·2 (27·1–42·7)
China, urban	31·2 (25·8–37·1)	23·5 (18·9–28·7)
China, rural	37·5 (31·5–44·1)	20·4 (16·3–25·4)
EURODEM[21] (DSM-III-R dementia)	18·4	..

Data are incidence (95% CI). DSM-III-R=Diagnostic and Statistical Manual of Mental Disorders, third edition revised.

Table 3: **Directly standardised incidence (per 1000 person-years) for 10/66 dementia, by site**

Venezuela, and rural Mexico (table 3). The extent of the variation was reduced after standardisation for for sex, education, and household assets (table 3).

In the sensitivity analysis, we identified 142 cases of probable dementia among the 1282 deaths for which informant interviews were completed. The crude incidence of probable dementia among those who had died before follow-up was 38·3 per 1000 person-years (95% CI 29·4–49·9) in Cuba compared with 21·0/1000 person-years (18·1–24·5) for 10/66 dementia among those alive and reinterviewed, 50·1 (38·5–65·2) versus 22·6 (18·8–24·5) in Dominican Republic, 47·2 (28·0–84·4) versus 18·2 (14·3–23·0) in Peru, 60·6 (41·4–89·2) versus 27·1 (22·9–32·1) in Venezuela, 49·7 (30·8–76·8) versus 30·4 (25·5–36·3) in Mexico, and 32·8 (25·1–47·8) versus 24·0 (20·6–28·1) in China. Pooling 10/66 dementia incidence among individuals who were alive and reinterviewed and probable dementia among those who were deceased, the overall crude incidence of dementia would be 11% higher in Cuba (23·3 per 1000 person-years; 95% CI 20·5–26·5), 19% higher in Dominican

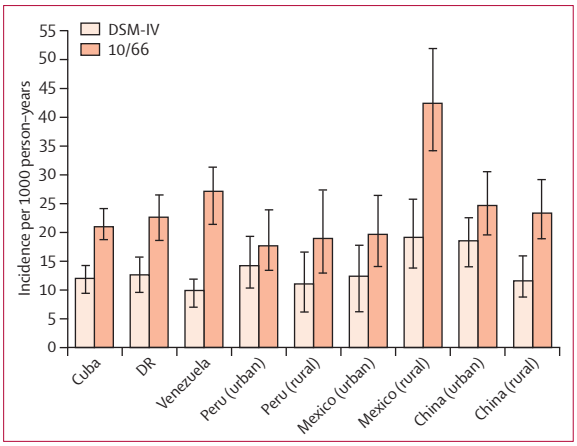

Figure 2: **Crude incidence of 10/66 dementia and DSM-IV dementia, per 1000 person-years, by site**
Error bars are 95% CI. DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, fourth edition. DR=Dominican Republic.

	Mortality rate per 1000 person-years (95% CI)		Age and sex adjusted mortality hazard ratios (95% CI)
	No dementia	Dementia cases	
Cuba	44·8 (40·9–49·0)	195·4 (166·6–227·8)	3·20 (2·61–3·92)
Dominican Republic	54·5 (49·3–60·1)	148·3 (120·8–180·3)	2·22 (1·75–2·81)
Peru, urban	18·7 (14·7–23·4)	139·3 (104·0–184·4)	5·69 (3·33–9·73)
Peru, rural	28·9 (22·3–37·6)	59·5 (24·1–123·8)	1·74 (0·68–4·44)
Venezuela	24·3 (21·0–28·2)	98·4 (71·0–133·3)	2·27 (1·42–3·62)
Mexico, urban	31·6 (25·7–38·9)	114·4 (71·8–173·5)	2·70 (1·56–4·67)
Mexico, rural	36·6 (30·1–44·4)	89·7 (61·5–132·4)	1·56 (0·94–2·59)
China, urban	40·7 (35·3–46·9)	168·1 (126·6–215·4)	3·02 (2·13–4·28)
China, rural	57·0 (50·5–64·2)	216·1 (156·5–291·4)	3·59 (2·47–5·21)
India, urban	62·5 (53·1–73·7)	171·6 (113·5–249·6)	2·33 (1·48–3·67)
Meta-analysed effect*	..	..	2·77 (2·47–3·10)

*Test for heterogeneity p=0·01. Higgins I^2=58% (95% CI 15–79).

Table 4: **Effect of baseline 10/66 dementia on subsequent mortality**

Republic (26·8; 23·3–31·0), 7% higher in Peru (19·4; 15·7–24·0), 8% higher in Venezuela (29·2; 25·1–34·0), 4% higher in Mexico (31·7; 26·8–37·1), and 7% higher in China (25·6; 22·4–29·1).

The incidence of DSM-IV dementia was around half that of 10/66 dementia (figure 2, appendix p 5). The incidence of DSM-IV dementia was particularly high in individuals with 10/66 dementia not meeting criteria for DSM-IV dementia at baseline (147·2/1000 person-years [95% CI 125·4–171·7] overall, ranging from 96·0 to 247·9 by site; appendix p 6).

Mortality rates for individuals with dementia at baseline varied between 59·5 and 216·1 per 1000 person years, and were substantially higher than those for participants who were free of dementia at baseline (table 4). After controlling for age and sex in a Cox's proportional hazards regression, hazard of death was 1·56–5·69 times higher in those with dementia (meta-analysed HR 2·77, 95% CI 2·47–3·10). The meta-analysis suggested moderate heterogeneity between sites; the absolute and relative risk of death was much lower in rural than in urban Latin American sites, but the opposite was the case in China (table 4).

Older age was independently associated with 10/66 dementia incidence in all sites (table 5). After meta-analysis, the incidence of 10/66 dementia tended to be lower in men than in women (table 5), and education tended to be inversely associated with the incidence of 10/66 dementia (table 5). Occupational attainment was not associated with 10/66 dementia incidence, in any sites, nor when meta-analysed. Having more assets were associated with a lower incidence after meta-analysis than was having few assets, but with substantial heterogeneity between sites. Even after controlling for educational level, occupational attainment, and household assets, literacy was independently associated with a reduced incidence of 10/66 dementia in four sites, and overall (table 5). Higher verbal fluency scores were associated with a lower incidence of dementia in seven sites and overall than were low scores (table 5), and worse performance on motor sequencing task was associated with a higher incidence in five sites and overall than was good performance (table 5).

Discussion

In this study of more than 12 800 individuals, incidence rates for 10/66 dementia were roughly 1·5–2·5 times higher than those for DSM-IV dementia. Mortality hazards were higher in individuals with dementia at baseline than in dementia-free individuals. Informant reports suggested a high incidence of dementia before death; overall incidence could be between 4% and 19% higher if these data were included. 10/66 dementia incidence was independently associated with increased age, female gender, and low education, but not with occupational attainment.

This is one of the largest studies of dementia incidence. The EURODEM pooled analysis from four prospective studies (in Denmark, France, the Netherlands, and the UK) consisted of 528 incident dementia cases and 28 768 person-years of follow-up.[20] Other than a large national cohort study from Mexico (333 incident cases with 12 980 person-years),[23] incidence studies in countries with low or middle incomes have been modest in scale—eg, Ballabgarh, India (nine incident cases with

	Base model (mutually adjusted)					Extensions to the base model*		
	Older age, per 5 year group	Sex, men *vs* women	Higher education, per level†	Lower occupational attainment, per level‡	More assets, per asset	Animal naming, per word	Luria fist-edge-palm sequencing test	Literacy, literate *vs* illiterate
Cuba	1·52 (1·32–1·75)	0·79 (0·55–1·11)	0·89 (0·74–1·06)	0·98 (0·82–1·17)	1·17 (0·96–1·42)	0·92 (0·89–0·95)	1·33 (1·15–1·54)	1·34 (0·77–2·34)
Dominican Republic	1·60 (1·36–1·88)	0·57 (0·37–0·88)	1·10 (0·87–1·40)	1·00 (0·83–1·21)	1·01 (0·89–1·15)	0·94 (0·90–0·98)	1·05 (0·87–1·28)	0·51 (0·33–0·78)
Peru, urban	2·78 (1·79–4·33)	0·68 (0·35–1·31)	0·72 (0·51–1·02)	1·17 (0·87–1·58)	0·60 (0·43–0·83)	0·88 (0·83–0·93)	2·51 (1·74–3·63)	0·46 (0·22–0·99)
Peru, rural	2·68 (1·80–3·98)	0·47 (0·20–1·11)	0·65 (0·40–1·06)	1·20 (0·70–2·07)	1·23 (0·92–1·63)	0·97 (0·91–1·05)	0·91 (0·62–1·33)	0·68 (0·25–1·87)
Venezuela	1·84 (1·55–2·18)	0·80 (0·55–1·16)	1·05 (0·84–1·31)	1·14 (0·92–1·42)	0·90 (0·77–1·05)	0·93 (0·90–0·96)	1·59 (1·29–1·95)	0·91 (0·47–1·76)
Mexico, urban	1·47 (1·12–1·92)	0·50 (0·24–1·07)	0·79 (0·57–1·09)	1·19 (0·85–1·66)	0·94 (0·70–1·25)	0·89 (0·84–0·94)	1·64 (1·12–2·39)	0·43 (0·19–0·96)
Mexico, rural	1·80 (1·45–2·23)	0·98 (0·62–1·57)	0·76 (0·50–1·16)	1·18 (0·76–1·84)	0·86 (0·76–0·97)	0·89 (0·84–0·94)	1·13 (0·88–1·45)	0·51 (0·28–0·92)
China, urban	1·54 (1·22–1·94)	0·98 (0·61–1·59)	0·71 (0·57–0·88)	0·91 (0·72–1·14)	1·07 (0·72–1·58)	0·98 (0·93–1·03)	1·15 (0·90–1·48)	1·35 (0·71–2·55)
China, rural	1·59 (1·29–1·95)	0·42 (0·25–0·72)	1·13 (0·84–1·52)	0·89 (0·53–1·51)	0·82 (0·70–0·97)	0·98 (0·94–1·02)	0·65 (0·38–1·11)	0·42 (0·18–0·96)
Meta-analysed effects	1·67 (1·56–1·79)	0·72 (0·61–0·84)	0·89 (0·81–0·97)	1·04 (0·95–1·13)	0·93 (0·88–1·00)	0·93 (0·91–0·94)	1·28 (1·18–1·38)	0·68 (0·55–0·84)
p for heterogeneity	0·05	0·23	0·04	0·79	0·005	0·009	<0·0001	0·03
Higgins I^2 % (95% CI)	49% (0–76)	25% (0–64)	50% (0–77)	0% (0–65)	63% (24–82)	61% (19–81)	76% (54–88)	53% (1–78)

Data are hazard ratio (95% CI) unless otherwise stated. *Further indicators of cognitive reserve—adjusted for base model, but not for each other. †Educational level: 1=none, 2=did not complete primary, 3=completed primary, 4=completed secondary, 5=tertiary education. ‡Occupational attainment: 1=professional (manager or administrator, professional, associate professional), 2=clerical or trade (clerical worker or shop keeper), 3=skilled or semi-skilled manual worker, 4=unskilled labourer (labourer or agricultural worker).

Table 5: **Associations with incident 10/66 dementia**

1160 person-years);[2] Cantanduva, Brazil (50 incident cases with 3623 person-years);[3] Ibadan, Nigeria (70 incident cases with 2459 at risk);[1] and Beijing, China (13 incident cases with 825 at risk).[4] We are therefore able to compare the incidence of dementia across rural and urban sites in Latin America, the Caribbean, and China, and estimate prospective associations with indicators of cognitive reserve with reasonable precision. Loss to follow-up is the main challenge to validity, but was modest in most sites, and generally non-differential with respect to the risk exposures studied; however, a relatively high loss to follow-up in urban Peru and Venezuela, which was more substantial in those with higher levels of education, might have led to overestimation of dementia incidence in these sites.

The incidence of 10/66 dementia, when age standardised to the age distribution of the EURODEM cohort, was consistently higher than that for DSM-III-R dementia in Europe. Incidence might have been between 4% and 19% higher still, had probable incident cases in individuals who died before reinterview been included. Post-mortem interviews with collateral informants is a valid approach for detection of cases.[24] This source of underestimation is rarely alluded to in published work,[3] and we are not aware that it has been addressed in other studies. In a large multisite population-based cohort study in the UK,[25] the prevalence of dementia in the year before death was 30% for those interviewed within this interval, with International Classification of Disease 10 dementia coded on death certificates also taken as evidence.

DSM-IV dementia incidence was around half that of 10/66 dementia, although the discrepancy was larger in Venezuela and smaller in urban Peru and urban China than in other sites. The DSM-IV dementia criterion identifies a severe form of dementia with high diagnostic reliability, but findings from our previous work[7,13,15] suggests systematic underestimation, particularly in low-income and middle-income countries where awareness of dementia is lower than in high-income countries, and where older people are routinely supported in many core and instrumental activities of daily living. The validity of the 10/66 dementia diagnosis is supported through its cross-cultural development, calibration, and validation in a 25 centre pilot study in Latin America, Africa, India, China, and southeast Asia,[6] and, in the context of our population-based studies, by showing concurrent validity against local clinician judgment in Cuba,[15] and of its predictive validity in Chennai, India.[13] In our study, individuals with 10/66 dementia but not meeting criteria for DSM-IV dementia at baseline had a very high incidence of DSM-IV dementia during the follow-up period, further supporting the validity of 10/66 dementia and clarifying the relation between the two diagnoses.

Mortality in those with 10/66 dementia at baseline was increased in all sites (pooled HR 2·77, 95% CI 2·47–3·10), with moderate heterogeneity. Effect sizes from studies in countries with low or middle incomes have tended to be higher than those indicated by a meta-analysis of studies mainly from countries with high incomes (relative risk 2·63, 95% CI 2·17–3·21);[26] with an HR of 2·83 (95% CI 1·10–7·27) in Nigeria,[27] and 5·16 (95% CI 3·74–7·12) in Brazil.[28] Therefore a relatively high incidence of dementia in less developed countries might be balanced (with respect to effect on prevalence), by a high case mortality.

In the three studies so far that have compared dementia with other health and sociodemographic factors affecting mortality in countries with low or middle incomes, dementia was the leading contributor.[14,27,28]

Previous evidence for cognitive reserve in less developed countries was limited and inconclusive (panel). In a national cohort study in Mexico,[23] education was inversely associated with dementia incidence, particularly among younger age groups. Investigators of two small cohort studies, in urban settings in China and Brazil, reported non-significant trends towards a protective effect of literacy[3,4] and education.[3] Our findings regarding indicators of cognitive reserve and the incidence of dementia suggest that the protective effect of education extends to middle-income country settings. We identified an additional independent effect of literacy, perhaps because literacy is an important indicator of the quality of education,[29] which, in many settings, does not correlate well with years of education. The absence of association with occupational attainment contrasts with studies in countries with high incomes, where nine of 12 studies showed a statistically significant protective effect (pooled odds ratio 0·56, 95% CI 0·49–0·65).[11] The reason for this discrepancy is not immediately clear. Only one of the positive studies in the systematic review[11] controlled for education; however, inspection of our models showed that controlling for education did not account for the null effect.

Both the animal naming verbal fluency task and the Luria FEP motor sequencing task were independently associated with dementia incidence, after adjustment for age, sex, education, and occupational attainment. Other population-based studies have shown predictive associations with category fluency for long periods before dementia onset.[30–32] Semantic processing could be an important underlying mechanism,[30,33] which is also relevant to effective performance of the Luria FEP task, according to findings from functional neuroimaging studies.[34–36] Such processes are susceptible to neurodegeneration, but are hard-wired through educational and other lifetime experiences, as shown by research that fails to discriminate clearly between measures of executive function and either crystallised intelligence[9] or latent traits of cognitive reserve.[10] Ultimately, to distinguish between cognitive reserve and the long clinical prodrome for dementia as alternative explanations for prospective associations with dementia onset is difficult. The activation of disparate cortical areas when doing seemingly simple motor tasks such as the Luria FEP task[34–36] attests to important functional connections between language, verbal and non-verbal semantic knowledge, and praxis. The development of neural networks fit for this purpose might be an important component of cognitive reserve, stimulated through education and the acquisition of literacy.[37]

In conclusion, the incidence of dementia in middle-income countries might be as high, if not higher than that recorded in countries with high incomes, offset, with respect to prevalence, by a high case mortality. Our studies provide supportive evidence for the cognitive reserve hypothesis, showing that, in settings with diverse cultures and lifestyles, and much greater variance in levels of education and literacy than occurs nowadays in countries with high incomes, these variables, together with better performance on verbal fluency and motor sequencing tasks, confer substantial protection against the onset of dementia. To answer the question "Why is there not an epidemic of dementia in countries with very low levels of education?" will probably need a much better understanding of what constitutes cognitive reserve, and how its indicators might vary across cultures.

Panel: Research in context

Systematic review

We searched Ovid and Medline databases for studies of the incidence of dementia since 1980, with the search terms ["Dementia"[Mesh] AND ("incidence"[Mesh] OR "epidemiology"[Mesh])]. We identified 1718 abstracts but only five previous studies from countries with low or middle incomes. We also searched for evidence of population-based cohort studies assessing evidence of education as a potential protective factor for the incidence of dementia or Alzheimer's disease, with the search terms [("dementia"[Mesh] OR "Alzheimer disease"[Mesh]) AND "educational Status"[Mesh] AND ("risk factors"[Mesh] OR "etiology"[Subheading])], (354 abstracts), and for occupational attainment by substituting the Mesh term "occupations", which indentified (52 abstracts). In the course of these searches we identified a systematic review of brain reserve (the effects of education, occupation, premorbid IQ, and mental activities) and the incidence of dementia or Alzheimer's disease covering work published up to 2004; all the studies were done in high-income countries.[10] Our own searches identified only three relevant studies done in countries with low or middle incomes, from Brazil examining the effects of literacy and education,[3] from China examining the effects of literacy,[4] and from Mexico investigating years of education.[11]

Interpretation

Our study suggests that the incidence of dementia in six urban and three rural catchment area sites in Latin America and China might be much the same as that typically recorded in countries with high incomes, when using our cross-culturally calibrated and validated 10/66 dementia diagnosis. DSM-IV dementia incidence is lower than that with 10/66 criteria, probably because mild to moderate cases are missed. Our findings confirm that incidence increases exponentially with age, and is higher in women than in men. The protective effects of education seem to extend to settings where many older people have had little or no formal education, and literacy confers an additional independent benefit. These findings, together with evidence of protective effects of better baseline executive function, support the notion that cognitive reserve might counter the effects of neurodegeneration in later life.

Contributors

All the authors worked collectively to develop the protocols and methods described in this report. MP led the research group and CF was the research coordinator. JLR (Cuba), DA (Dominican Republic), MG (Peru), AS (Venezuela), ALS (Mexico), JDW (India), and YH (China) were principal investigators responsible for the fieldwork in their respective countries. MP wrote the first draft and did the analyses with statistical support from Michael Dewey. Other authors reviewed the report, and provided further contributions and suggestions. All authors read and approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest. The 10/66 Dementia Research Group works closely with Alzheimer's Disease International (ADI), the non-profit federation of 77 Alzheimer associations around the world. ADI is committed to strengthening Alzheimer associations worldwide, raising awareness regarding dementia and Alzheimer's disease, and advocating for more and better services for people with dementia and their caregivers. ADI is supported in part by grants from GlaxoSmithKline, Novartis, Lundbeck, Pfizer, and Eisai.

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