RESEARCH ARTICLE

A lifecourse approach to the relationship between lung function and cognition function in late life: findings from the Mysore studies of Natal effect on Ageing and Health (MYNAH) in South India [version 1; peer review: awaiting peer review]

Murali Krishna^{1,2}, Sumanth Majgi^{id}³, Bharath DU^{id}², Gattu V. Krishnaveni^{id}¹, Sargoor R. Veena¹, Martin Prince^{id}⁴, Kalyanaraman Kumaran^{1,5}, Samuel Christaprasad Karat¹, Mohan Kumar¹, Mahesh Padukundru^{id}⁶, Santhosh Nagaraj¹, Caroline H.D. Fall^{id}⁵

¹CSI Holdsworth Memorial Hospital, Mandimohalla, Mysore, Karnataka, India

²Foundation for Research and Advocacy in Mental Health, Mysore, Karnataka, India

³Mysore Medical College and Research Institute, Mysore, Karnataka, India

⁴Institute of Psychiatry, Kings College London, London, UK

⁵Medical Research Council Life Course Epidemiology Unit, Southampton, UK

⁶Jss Medical College, Mysore, 570015, India

V1 First published: 27 Jan 2022, 7:25
<https://doi.org/10.12688/wellcomeopenres.16981.1>
Latest published: 27 Jan 2022, 7:25
<https://doi.org/10.12688/wellcomeopenres.16981.1>

Open Peer Review

Approval Status AWAITING PEER REVIEW

Any reports and responses or comments on the article can be found at the end of the article.

Abstract

Background: Emerging evidence from high income settings indicates that lung function may be an independent determinant of cognitive abilities in late life. Despite a high burden of chronic lung disorders and neurocognitive disorders, there are limited data exploring the relationship between lung and cognitive function in later life in low- and middle-income (LMIC) settings.

Methods: Between 2013 and 2016, 721 men and women from the Mysore Birth Records Cohort in South India, aged 55-80 years, were retraced and underwent standardised assessments for sociodemographic characteristics, cardiometabolic risk factors, lung function, cognitive function and mental health. Approximately 20 years earlier, a subset of them had assessments for cardiometabolic risk factors (n=522) and lung function (n=143).

Results: Forced Expiratory Volume at one second (FEV1) and six seconds (FEV6) were higher among men than women. Women had higher immediate and delayed recall scores compared to men. Multivariate models indicated that those with lower FEV1 (lts) and FEV1/FEV6 ratio in late life had lower composite cognitive score (SD, standard deviation), independent of growth and environment in early life and childhood, attained education, socioeconomic position,

cardiometabolic disorders in mid-and late life and lifestyle factors (0.29 SD per litre 95% confidence interval [CI] (0.10, 0.50) $p=0.006$ for FEV1 and 1.32 SD (0.20, 2.50) $p=0.02$ for FEV1/FEV6 ratio). Lung function in midlife was unrelated to cognitive outcomes in late life.

Conclusions: Causality cannot be inferred from cross sectional associations. Therefore, causality is best explored in longitudinal studies with serial, but contemporaneous measurements of both lung and cognitive function. Mechanistic studies that examine the role of shared risk factors like environmental pollutants and biomass exposure on this relationship are urgently required in LMICs.

Keywords

lung function, cognitive function, lifecourse, ageing, low-and middle-income countries (LMICs).

This article is included in the [Wellcome Trust/DBT India Alliance](#) gateway.

Corresponding author: Murali Krishna (muralidoc@gmail.com)

Author roles: **Krishna M:** Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Majgi S:** Data Curation, Formal Analysis, Investigation, Methodology, Software, Writing – Review & Editing; **DU B:** Writing – Review & Editing; **Krishnaveni GV:** Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing; **Veena SR:** Data Curation, Investigation, Project Administration, Resources, Validation; **Prince M:** Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Kumaran K:** Conceptualization, Data Curation, Funding Acquisition, Methodology, Project Administration, Validation, Visualization; **Christaprasad Karat S:** Formal Analysis, Investigation, Resources, Software, Validation; **Kumar M:** Data Curation, Formal Analysis, Investigation, Writing – Original Draft Preparation, Writing – Review & Editing; **Padukundru M:** Conceptualization, Methodology, Supervision; **Nagaraj S:** Data Curation, Formal Analysis, Investigation, Methodology, Resources, Writing – Original Draft Preparation, Writing – Review & Editing; **Fall CHD:** Formal Analysis, Funding Acquisition, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: This study was supported by the Wellcome DBT India Alliance [IA/E/11/1/500517, Early Career Fellowship grant awarded to Dr Murali Krishna].

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Copyright: © 2022 Krishna M *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Krishna M, Majgi S, DU B *et al.* **A lifecourse approach to the relationship between lung function and cognition function in late life: findings from the Mysore studies of Natal effect on Ageing and Health (MYNAH) in South India [version 1; peer review: awaiting peer review]** Wellcome Open Research 2022, 7:25 <https://doi.org/10.12688/wellcomeopenres.16981.1>

First published: 27 Jan 2022, 7:25 <https://doi.org/10.12688/wellcomeopenres.16981.1>

Introduction

Neurocognitive disorders are associated with high rates of dependence, disability and mortality in later life, and they disproportionately contribute to burden on health services and society^{1,2}. This burden is particularly high in low and middle income countries (LMICs) like India due to a steady increase in the proportion of older adults, combined with changes in family structures and restricted social care provisions, which presents with health, social and economic challenges to policy makers in these settings^{3,4}.

Health and disease in late life (above 60 years) are best explored through lifecourse approaches. Physiological processes intrinsic to aging are related to each other in a complex manner, and to functional outcomes in multiple ways^{5,6}. For example, age-related decline is observed in both pulmonary function and cognitive abilities⁷ and a growing body of evidence from cross-sectional studies indicate lower lung function as predictor of lower cognitive function among young adults, in mid-life and also in later life^{8–20}. This is often due to multiple reasons: shared risk factors (e.g. smoking and hypertension), direct result of lower lung function (e.g. hypoxemia and sleep disturbances) and/or its limitations (e.g. physical inactivity and reduced social activity)²¹.

A systematic review by Duggan and colleagues identified seven studies exploring the long-term relationship between lung and cognitive function in later life. All studies were from high income countries (HICs), with contemporaneous measurements of lung and cognitive function, and duration of follow-up varied from 5 to 28 years²². While in some studies a decline in pulmonary function was directly related to lower cognitive function in later life^{23–26}, no such relationship was observed in others^{15,27}. There are several plausible explanations for these associations between lung function and cognitive outcomes that unrelated to aging, like differences in early life environment and childhood growth which are not adequately explored in earlier studies. We have therefore conducted a lifecourse epidemiology study to explore the relationship between lung function with cognitive outcomes in late life in the Mysore studies of Natal effect on Ageing and Health (MYNAH), a birth cohort in South India. There are limited data exploring the lung-cognition relationship in LMIC settings.

Methods

Setting

This study was carried out at the Epidemiology Research Unit, CSI Holdsworth Memorial Hospital (HMH), Mysore South India. The study was approved by the HMH Ethics and Research Committee (approval number-2012/ERU/5).

Recruitment

Between 1993 and 2001, 3427 men and women born during 1934–1966 at HMH were located by a house-to house survey of the area of Mysore city surrounding HMH, and matched to their birth records. The birth weight for each participant was extracted from their records. During the tracing process, information related to the education and occupation of

parents at the time of birth of the study participants was collected. Of these 3427 participants, 1069 were examined for cardiometabolic risk factors and a subset of them (286 out of 1069) had measurements of lung function with a turbine computerised spirometer (Microlab 3300, Micro Medical, and UK)²⁸. They were then aged 40–67 years [‘midlife’: mean 46.7 years SD (4.7)] and assessments carried at baseline are indicated by ** in [Table 1](#). These 1069 men and women constitute the MYNAH cohort and the cohort profile has been published elsewhere²⁹.

Between 2013–2016, 721 (408 men and 313 women born between 1934 and 1955) aged above 55 years were retraced through door to door survey by research assistants and recruited to this study after obtaining written informed consent ([Figure 1](#)), a detailed protocol of which has been published elsewhere³⁰.

Assessments

The interviews and physical assessments were carried out between 2011 and 2015 at Holdsworth Memorial Hospital, Mysore and are provided in [Table 1](#). If the participant was not able to provide accurate information (example after a stroke or due to cognitive impairment), we interviewed a reliable informant. Assessments of relevance to this study are described as follows.

A structured questionnaire developed and validated by the 10/66 Dementia Research Group collecting information on age, sex, marital status, level of education, employment, family structure and lifestyle factors like smoking, use of alcohol and physical activity³¹. Socioeconomic position was ascertained by administering the Standard of Living Index questionnaire³².

Cognitive assessment was conducted by using the 10/66 Dementia Research Battery in the local language (Kannada) administered by a trained clinical psychologist. This included a Community Screening Instrument for Dementia, a 32 item test assessing orientation, comprehension, memory, naming and language³³, an Animal naming task^{33,34} from the Centre for European Registry for Alzheimer’s Disease (CERAD) test for assessing verbal fluency (score of one point was given for each valid name generated in the space of a minute), a Word List Memory and Recall test (WLMR) adapted from the CERAD and used in the Indo-US Ballabgarh study to evaluate immediate and delayed recall respectively³⁵ and Community Screening Instrument for Dementia (CSID)^{36,37}.

In the learning phase of WLMR test a list of 10 words was read out to the participant who was then asked to recall straight away the words that they remembered. This process was repeated three times, giving the subject a score out of 30. Approximately five minutes later, the participant was again asked to recall the 10 words, giving a recall score out of 10 and total score of 40. CSID is an informant interview with a reliable informant for evidence of cognitive and functional decline. The frequency of six specific and characteristic memory lapses (forgetting where s/he has put things, where things are kept, names of friends, names of family, when s/he last saw the informant,

Table 1. Instruments, assessments and investigations in the Mysore studies of Natal effect on Ageing and Health (MYNAH) study.

Socioeconomic assessments[†]	i) Structured interview for socio-demographic information ii) Standard of Living Index**
Battery of cognitive tests	i) The Community Screening Instrument for Dementia (CSI'D') COGSCORE incorporating the CERAD animal naming verbal fluency task. (CERAD-Consortium to Establish a register for Alzheimer's Disease) ii) The modified CERAD 10-word list learning task with delayed recall iii) Informant interview, for evidence of cognitive and functional decline*
Instruments for diagnosis of dementia	i) Battery of cognitive tests (listed above) ii) A structured clinical mental state interview, the Geriatric Mental State, which applies a computer algorithm iii) An extended informant interview, the History and Aetiology Schedule- Dementia Diagnosis and subtype* iv) The NEUROEX, a brief fully structured neurological assessment, v) Behavioral and Psychological symptoms: assessed by Neuropsychiatric Inventory *
Health status and physical health assessment	i) Self-reported global health, diagnoses and treatments for these conditions by a structured interview [†] ii) A self-reported list of 12 commonly occurring physical impairments [†] iii) Activity limitation and participation restriction measured by the WHO-Disability Assessment Schedule II [†] iv) Rose Angina questionnaire** v) Direct physical assessments: pulse rate, systolic and diastolic resting blood pressure, weight, height, waist/hip ratio and 12 lead ECG for Minnesota coding** vi) Spirometry**
Blood tests and genetic assay.	Blood tests: glucose tolerance test and lipid profile (total cholesterol, triglycerides, LDL and HDL cholesterol) **

* Instruments administered to informants only in this study

** Instruments and investigations carried out at baseline and in this study

[†]Instruments administered to the informants ONLY if the participants had communication difficulties arising from cognitive problems, severe mental illness, deafness or mutism in this study

LDL: Low Density Lipoprotein HDL: High Density Lipoprotein

and what happened the day before) was obtained. If the subject was receiving care, the primary caregiver was considered as a reliable informant^{36,37}.

The Geriatric Mental State (GMS) Examination, a standardised structured interview for diagnosis of depression and other mental disorders was administered by a trained psychiatrist (MK)³⁸.

Spirometry: PiKo-6 micro-spirometry (nSpire Health Inc., Longmont, CO, USA) was performed by a trained research assistant. After a demonstration, all participants practiced blowing into the Piko-6 spirometer. They were instructed to inhale maximally, and exhale as fast and hard as possible into the Piko-6 mouthpiece until a beep after 6 seconds. Each participant was encouraged to carry out this procedure at least three times and the highest forced expiratory volumes at one and six seconds (FEV1 and FEV6) were obtained. From these values the FEV1/FEV6 ratio was calculated. The Piko-6 spirometer has an inbuilt automatic quality alert test and this

indicates any attempts that were not valid due to an abnormal blow or a cough. The Piko-6 spirometry has been validated for use in Indian population both in epidemiological and clinical settings³⁹.

Definitions

Diabetes mellitus was diagnosed if fasting plasma glucose was ≥ 7 mmol/l or 2-hour plasma glucose ≥ 11.1 mmol/l⁴⁰. Those who were known to have diabetes and were taking medication for diabetes were also classified as having diabetes.

Hypertension was defined as a systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg (International Diabetes Federation definition)⁴¹. Those who were known to have hypertension and were taking antihypertensive medication were also classified as having hypertension.

Metabolic syndrome was diagnosed using International Diabetes Federation criteria⁴¹ as follows: central obesity (defined as waist circumference ≥ 90 cms for South Asian men and

Figure 1. The Mysore Birth Records Cohort studies flow chart. HMH=Holdsworth Memorial Hospital, CHD= coronary heart disease.

≥ 80 cms for South Asian women) plus any two of the following four factors: raised triglyceride level (≥ 1.7 mmol/l), low high-density lipoproteins (HDL) cholesterol (<1.03 mmol/l in males and <1.29 mmol/l in females), raised blood pressure: systolic blood pressure ≥ 130 or diastolic blood pressure ≥ 85 mm Hg or treatment of previously diagnosed hypertension, or raised fasting plasma glucose (> 5.6 mmol/l) or previously diagnosed type-2 diabetes.

A diagnosis of coronary heart disease (CHD) was derived from an algorithm, drawing information from the Rose chest pain

questionnaire, Minnesota electrocardiogram (ECG) coding and a clinical history of cardiac revascularisation procedures. CHD was diagnosed if there was typical angina on the Rose chest pain questionnaire, or a history of cardiac revascularisation procedures, or the presence of Minnesota codes 1-1 or 1-2 (major Q waves) on the ECG.

The 10/66 protocol³¹ and Piko-6 spirometry were used for diagnosis of chronic obstructive pulmonary disease (COPD). COPD was diagnosed in people who responded 'yes' to the question 'do you usually cough phlegm from your chest first thing

in the morning?’ and whose answer to the question “for how many months of the year does this usually happen?” was 3 months or more and whose FEV1/FEV6 ratio was $<0.7^{31}$.

A diagnosis of stroke was made according to the 10/66 protocol based on symptoms and findings from a structured neurological examination. Stroke was coded only if there was a clear history of sudden onset of unilateral paralysis, loss of speech, or blindness lasting for more than 24 hours, hence excluding previous episodes of transient ischemic attack³¹.

A diagnosis of dementia was defined as a score above a cut-off point of predicted probability of Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV) Dementia Syndrome from the logistic regression equation of the 10/66 dementia diagnostic algorithm^{37,42}.

A diagnosis of depression was derived from the computerised algorithm of the Geriatric Mental State Examination (GMS)³⁸.

Indicators of the child environment

As study participants were not examined during their childhood, we have considered maternal educational level at the time of the participants’ birth and adult leg length as proxy indicators of the childhood milieu⁴³.

Statistical analyses

Continuous normally distributed variables are presented as mean and standard deviation, continuous skewed variables as median (inter-quartile range) and categorical variables as number and proportions. Independent t-tests were used to test for differences in means, and non-parametric tests for differences in median scores between groups (for example between men and women). The differences in proportions between the groups were compared using chi square tests. SPSS version 22 was used for analysis.

The 721 study participants were the offspring of 421 marriages and siblings were more similar in their standardised cognitive function score than those who were unrelated. The between-sibship variance of 0.203 was 3.5 times larger than its standard error (0.058, $p=0.0005$) and the intra-class correlation was 0.20. To account for the influence of sibship, mixed linear regression analyses, adjusting for sibship, were conducted to examine the associations of size at birth with continuous measures of cognitive function, and mixed logistic regression analyses for binary outcomes (dementia).

Results

Of the 721 (488 men and 313 women) examined in this study (Table 2), 716 were able to provide acceptable spirometry readings and all of them completed the cognitive assessments and baseline spirometry data [FEV1, Forced Vital Capacity (FVC) and Peak Expiratory Flow (PEF)] were available for 143 study participants (93 men and 50 women). FEV1 (<0.001), FEV6(<0.001) and FEV1/6 ratio in late life($p=0.004$) was higher among men than women. Metabolic syndrome ($p=0.01$), hypertension (0.001) and depression (<0.001) were more

Table 2. Characteristics of study participants according to sex.

	Men n=408		Women n=313		p
Demographic characteristics					
Age (yrs)*	62.0	(5.2)	62.8	(5.4)	0.25
Height (cms)*	164.1	(14.1)	150.3	(6.2)	<0.001
BMI (kg/m2)*	25.2	(4.6)	28.44	(5.5)	<0.001
Underweight n(%)	28	(7)	8	(3)	
Normal n(%)	184	(45)	76	(24)	<0.001
Overweight n(%)	136	(33)	120	(39)	
Obese n(%)	59	(15)	28.44	(5.5)	<0.001
Marital status n (%)					
Never married	12	(3)	11	(3)	
Married	370	(90)	189	(60)	0.30
Widowed	17	(4)	106	(34)	
Divorced	9	(3)	7	(3)	
Education n (%)					
Illiterate	7	(2)	15	(5)	
Primary	49	(12)	46	(15)	
Secondary	105	(26)	87	(28)	0.18
Pre-university	78	(19)	67	(21)	
Diploma	53	(13)	43	(14)	
Graduate	65	(16)	18	(6)	
Postgraduate	51	(12)	37	(11)	
SLI score*	37.3	(7.4)	36.4	(8.0)	0.10
Current occupation n (%)					
Unemployed	8	(2)	3	(1)	
House wife	5	(1)	207	(66)	0.64
Retired	146	(36)	53	(17)	
In paid employment	249	(61)	50	(16)	
Lifetime alcohol status n (%)					
Never drinker	235	(57)	303	(96)	
Ex-drinker	68	(17)	8	(3)	0.02
Current drinker	105	(26)	2	(1)	
Lifetime smoking status n (%)					
Never smoker	137	(33)	311	(98)	
Ex-smoker	137	(34)	1	(1)	<0.001
Current smoker	134	(33)	1	(1)	

	Men n=408	Women n=313	p
Physical activity n(%)			
Sedentary	2 (1)	1 (1)	
Mild	12 (3)	15 (5)	0.63
Moderate	319 (79)	267 (85)	
Strenuous	73 (27)	30 (9)	
Lung function*			
FEV at 1 second (lts)	1.66 (0.56)	1.51 (0.36)	<0.001
FEV at 6 seconds (lts)	1.76 (0.54)	1.19 (0.34)	<0.001
FEV1/FEV6 (ratio)	0.94 (0.08)	0.96 (0.06)	0.004
NCD characteristics n(%)			
Diabetes	192 (47)	149 (48)	0.79
Hypertension	231 (57)	214 (69)	0.001
Metabolic Syndrome	243 (60)	215 (69)	0.01
Coronary Heart Disease	104 (25)	95 (30)	0.15
Stroke	19 (5)	2 (1)	<0.001
Depression	54 (13)	84 (27)	<0.001
Dementia	12 (3)	10 (3)	0.84
COPD	10 (2)	2 (1)	0.06
Cognitive Function (scores)*			
Global cognition	28.7 (2.8)	28.9 (3.1)	0.81
Verbal fluency	13.4 (3.1)	13.5 (4.1)	0.84
Immediate recall	15.6 (3.8)	17.1 (4.1)	<0.001
Delayed recall	5.1 (1.9)	5.9 (2.1)	<0.001

* mean (SD); differences between the groups were examined using t-tests. Differences within categorical variables were examined using Chi-square tests. SLI: Standard Living Index NCD: Non-communicable disorders COPD: Chronic Obstructive Pulmonary Disease

common among women compared to men. Women had higher immediate ($p<0.0001$) and delayed recall scores ($p<0.001$) compared to men.

FEV1 and FEV6 in late life were directly associated with scores across all domains of cognitive function and composite cognitive score (Table 3 and Table 4). FEV1/FEV6 in late life was directly related to global cognition, delayed recall and composite cognitive score, but was unrelated to verbal fluency and immediate recall. Indicators of lung function in midlife were unrelated to cognitive outcomes late life. Indicators of lung function in mid- and late life were unrelated to dementia.

Correlations between potential confounders (Table 5) influencing the relationship between lung and cognitive function were examined to inform the construction of multivariate

models (Table 6). Adult height was strongly correlated with FEV1 and FEV6 (correlation coefficient = 0.6 and $p<0.001$ for both), and adult leg length (correlation coefficient= 0.9 and $p<0.001$).

The models were serially adjusted for: indicators of growth and environment in prenatal period indicated by birth weight (model one), childhood environment indicated by maternal educational level at the time of participants' birth and adult leg length (model two), standard of living index (SLI) and education in adult life (model three) and for BMI, physical activity, smoking, alcohol, marital status and depression in late life (model four). Adult leg length was chosen as an indicator of growth in childhood, to avoid multiple adjustments. The regression models were not further adjusted for adult height, and the overall model structure and results remained unchanged when adult leg length was replaced by adult height.

The effect size of the associations of FEV1, FEV6 and FEV1/FEV6 with composite cognitive score in late life progressively reduced with serial adjustments but remained statistically significant in model four for FEV1 and FEV1/FEV6; and was of borderline significance for FEV6. Further adjustments for cardiometabolic disorders: diabetes, hypertension, metabolic syndrome and stroke in mid- and late life (data not shown) did not change the effect size or significance levels observed in model four. These models indicated that those with lower FEV1 and FEV1/FEV6 in late life had lower composite cognitive score, independent of growth and environment in early life and childhood, attained education, socioeconomic position, cardiometabolic disorders in mid-and late life and lifestyle factors. The multivariate models when stratified by different age groups or by sex did not differ in effect sizes or statistical significance. As an example, we have further illustrated the influence of these factors on the relationship between FEV1 and composite cognitive score in a mixed effects lifecourse model (Table 7) along with an estimate of variance from predictors adjusted in each of the models.

There was an interaction of borderline significance ($p=0.07$ for the interaction variable) between FEV1 and smoking pack years for composite cognitive score in late life. There were no significant interactions between the indicators of lung function (in mid-and late life) and the following: sex, birth weight, education, socioeconomic position and physical activity for composite cognitive score in late life.

Discussion

To the best of our knowledge, this is the first birth cohort study to examine lung-cognition relationship in a LMIC setting. In this urban cohort, among those aged 55–80 years higher FEV1 and FEV1/FEV6 ratio were directly related to higher cognitive function. However, these associations were cross-sectional and do not infer causality. Our finding is similar to reports from several other cross sectional studies and share similar methodological issues related to exploring multivariate relationships across a broad age range. The observed associations could be due to 'directional decline' (e.g. decline in cognitive

Table 3. Associations of lung function in mid- and late life with cognitive outcomes in late life.

Predictor	n	Global cognition (score) B (95%CI)* P	Verbal fluency (score) B (95%CI)* P	Immediate recall (score) B (95%CI)* P	Delayed recall (score) B (95%CI)* P	Composite cognitive score(SD) B (95%CI)* P	Dementia (yes/no) OR (95% CI)* P
FEV1 (late life) (lts)	717	1.21 (0.76, 1.65) <0.001	1.22 (0.53, 1.92) 0.001	1.48 (0.82, 2.14) <0.001	0.54 (0.20, 0.87) 0.002	0.45 (0.28, 0.61) <0.001	0.47 (0.16,1.40) 0.18
FEV6 (late life) (lts)	717	0.98 (0.56, 1.39) <0.001	0.91 (0.27, 1.55) 0.005	1.26 (0.65, 1.87) <0.001	0.40 (0.09, 0.71) 0.01	0.35 (0.20, 0.51) <0.001	0.52 (0.18,1.50) 0.23
FEV1/FEV6 ratio	717	3.06 (0.42, 5.69) 0.02	1.83 (-2.19, 5.86) 0.37	2.40 (-1.46, 6.27) 0.22	2.05 (0.11, 3.99) 0.04	0.99 (0.01, 1.96) 0.05	0.16 (0.00, 15.3) 0.43
FEV1 (midlife) (ltr)	143	0.01 (-0.85, 0.87) 0.99	-0.24 (-1.78, 1.31) 0.76	0.99 (-0.57, 2.54) 0.21	0.41 (-0.34, 1.16) 0.28	0.13 (-0.21, 0.47) 0.45	1.01 (0.99, 1.02) 0.16
PEF (midlife) (ltr/min)	143	-0.00 (-0.00, 0.00) 0.70	0.00 (-0.01, 0.01) 0.91	0.01 (-0.01, 0.01) 0.76	0.00 (-0.00, 0.01) 0.24	0.00 (-0.00, 0.00) 0.78	0.96 (0.91, 1.00) 0.17
FVC (midlife) (ltr)	143	-0.11 (-0.85, 0.62) 0.76	-0.30 (-1.62, 1.01) 0.65	1.22 (-0.11, 2.55) 0.07	0.51 (-0.13, 1.45) 0.12	0.15 (-0.14, 0.44) 0.31	0.89 (0.73,1.08) 0.23

CI: confidence interval FEV1: Forced Expiratory Volume at 1second FEV6: Forced Expiratory Volume at 6seconds

PEF: Peak Expiratory Flow FVC: Forced Vital Capacity

*Mixed effects models adjusted for age, sex and sibship

Table 4. Associations of lung function in late life with cognition function.

Predictor (late life)	Word List Immediate Recall score mean (SD)	Word List Delayed Recall score mean (SD)	Verbal Fluency score Mean (SD)	Global Cognition score mean (SD)
FEV 1 (lts)				
< 1	15.69 (4.34)	5.36 (2.03)	13.04 (4.13)	27.77 (3.36)
1 to 1.5	16.44 (4.21)	5.49 (2.14)	13.14 (3.80)	28.31 (2.43)
1.5 to 2	16.00 (3.62)	5.24 (1.83)	14.00 (4.05)	28.71 (2.07)
2 to 2.5	16.63 (3.81)	5.53 (1.92)	14.08 (4.46)	28.56 (3.03)
> 2.5	18.47 (2.62)	6.12 (1.83)	14.24 (4.28)	29.72 (1.60)
FEV6 (lts)				
< 1	15.60 (4.38)	5.25 (2.07)	13.15 (4.33)	24.55 (3.58)
1 to 1.5	16.40 (4.20)	5.51 (2.10)	13.04 (3.75)	25.27 (2.47)
1.5 to 2	16.15 (3.81)	5.33 (1.92)	13.98 (4.07)	28.67 (2.04)
2 to 2.5	16.39 (3.50)	5.37 (1.88)	13.91 (4.28)	28.83 (2.68)
> 2.5	17.31 (3.77)	5.75 (1.86)	14.19 (4.13)	28.97 (2.35)
FEV1/FEV6 (ratio)				
< 0.7	14.38 (3.10)	4.69 (1.80)	12.69 (4.03)	28.20 (1.84)
> 0.7	16.28 (4.02)	5.43 (2.01)	13.49 (4.04)	28.38 (2.64)

SD: Standard deviation FEV1: Forced Expiratory Volume at 1 second FEV6: Forced Expiratory Volume at 6 seconds

Table 5. Correlations between variables related to cognitive function in the Mysore studies of Natal effect on Ageing and Health (MYNAH) cohort.

Variables		Birth weight (kgs)	Maternal Education*	Adult Leg Length (cms)	Education level of subject*	SLI (score)	BMI (score)	Physical activity**	Alcohol (units/week)	Depression (0=no, 1=yes)	Marital status (0=married, 1=others)
Birth weight (kgs)	Pearson Correlation	1.00	0.11	0.25	0.12	0.13	0.09	0.05	0.03	-0.08	-0.03
	p		<0.001	<0.001	<0.001	<0.001	0.02	0.15	0.36	0.04	0.41
Maternal Education*	Pearson Correlation		0.10	0.10	0.49	0.25	0.06	-0.01	0.02	-0.01	-0.08
	p			0.01	<0.001	<0.001	0.10	0.80	0.69	0.01	0.04
Adult leg length (cms)	Pearson Correlation			1.00	0.25	0.14	-0.25	0.14	0.12	-0.20	-0.32
	Sig. (2-tailed)				<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Education level of subject*	Pearson Correlation				1.00	0.45	0.05	0.03	-0.01	-0.19	-0.15
	p					<0.001	0.18	0.44	0.84	<0.001	<0.001
SLI (score)	Pearson Correlation					1.00	0.24	0.01	-0.06	-0.21	-0.16
	Sig. (2-tailed)						<0.001	0.73	0.14	<0.001	<0.001
BMI (score)	Pearson Correlation						1.00	-0.08	-0.15	-0.01	.05
	Sig. (2-tailed)							0.05	<0.001	0.86	0.19
Physical Activity**	Pearson Correlation							1.00	0.01	-0.14	-0.04
	Sig. (2-tailed)								.858	<0.001	.327
Alcohol (units/week)	Pearson Correlation								1.00	-0.00	-0.04
	Sig. (2-tailed)									.962	.343
Depression (0=no, 1=yes)	Pearson Correlation									1.00	0.19
	Sig. (2-tailed)										<0.001
Marital status (0=married, 1=others)	Pearson Correlation										1.00
	Sig. (2-tailed)										

* Education:0=illiterate 1=primary 2=secondary 3=preuniversity 4=college 5=graduate 6=postgraduate.

**Physical activity: 0=sedentary 1=mild 2=moderate 3=strenuous. SLI: Standard of Living Index BMI: Body Mass Index

Table 6. Associations of lung function in mid and late life with composite cognitive scores in late life in the Mysore studies of Natal effect on Ageing and Health (MYNAH) cohort.

Predictor		Composite Cognitive Function (SD)				
Indicators of Lung function	n	Unadjusted B (95%CI) p	Model 1 B (95%CI) p	Model 2 B (95%CI) p	Model 3 B (95%CI) p	Model 4 B (95%CI) p
FEV1 (lts) (late life)	716	0.26 (0.11, 0.40) <0.001	0.41 (0.24, 0.60) <0.001	0.30 (0.14, 0.46) <0.001	0.15 (-0.00, 0.30) 0.05	0.29 (0.10, 0.50) 0.006
FEV6 (lts) (late life)	716	0.18 (0.05, 0.31) 0.10	0.32 (0.17, 0.50) <0.001	0.25 (0.10, 0.40) 0.002	0.10 (-0.04, 0.24) 0.15	0.20 (-0.07, 0.31) 0.06
FEV1/FEV6 (ratio) (late life)	716	1.51 (0.53, 2.50) 0.003	0.99 (0.02, 1.95) 0.04	1.01 (0.10, 1.91) 0.03	0.70 (-0.15, 1.50) 0.11	1.32 (0.17, 2.47) 0.02
FEV1 (lts) (midlife)	143	-0.20 (-0.44, 0.10) 0.13	0.10 (-0.25, 0.44) 0.60	-0.02 (-0.40, 0.32) 0.90	-0.02 (-0.40, 0.32) 0.91	-0.02 (-0.40, 0.32) 0.91
PEF (lts) (midlife)	143	-0.00 (-0.00, 0.00) 0.80	0.00 (-0.00, 0.00) 0.92	-0.00 (-0.00, 0.00) 0.40	-0.00 (-0.00, 0.00) 0.50	-0.01 (-0.02, 0.00) 0.21
FVC (lts) (midlife)	143	-0.20 (-0.40, 0.05) 0.13	0.12 (-0.20, 0.42) 0.43	0.02 (-0.30, 0.32) 0.90	-0.02 (-0.30, 0.32) 0.90	-0.01 (-0.30, 0.28) 0.94

CI: confidence interval FEV1: Forced Expiratory Volume PEF: Peak Expiratory Flow FVC: Forced Vital Capacity SD: Standard deviation

Model 1: Mixed effects model adjusted for age, sex and sibship, and birth weight

Model 2: Mixed effects model adjusted for age, sex and sibship, birth weight and childhood factors (maternal education and leg length)

Model 3: Mixed effects model adjusted for age, sex and sibship, birth weight, childhood, and adult factors (education and SLI). Further adjustment for lung function indicators in midlife did not change the effect size or p value of this model.

Model 4: Mixed effects model adjusted for age, sex and sibship, birth weight, childhood, adult life and late life factors (BMI, physical activity, smoking, alcohol, marital status and depression). Further adjustment for other NCDs (diabetes, hypertension, metabolic syndrome and stroke did not change the effect size or p value of model 4)

Table 7. A mixed effects lifecourse model for cognitive function in late life in the Mysore studies of Natal effect on Ageing and Health (MYNAH) cohort.

Composite Cognitive Score in late life (SD)					
Predictor	Unadjusted/univariate) B (95%CI) p	Model 1 B (95%CI) p	Model 2 B (95%CI) p	Model 3 B (95%CI) p	Model 4 B (95%CI) p
Age	-0.03 (-0.04, -0.02) <0.001	-0.03 (-0.04, -0.01) <0.001	-0.03 (-0.004, -0.13) <0.001	-0.02 (-0.04, -0.02) <0.001	-0.02 (0.04, -0.02) <0.001
Sex (0= men 1= women)	0.27 (0.12, 0.41) <0.001	0.52 (0.36, 0.69) <0.001	0.67 (0.48, 0.85) <0.001	0.58 (0.41, 0.76) <0.001	0.65 (0.38, 0.93) <0.001
FEV1 (lts) (latelife)	0.26 (0.11, 0.40) <0.001	0.41 (0.24, 0.60) <0.001	0.30 (0.14, 0.46) <0.001	0.15 (-0.00, 0.30) 0.05	0.29 (0.10, 0.50) 0.006
Birth weight (kgs)	0.28 (0.10, 0.45) 0.002	0.27 (0.10, 0.44) 0.002	0.14 (-0.03, 0.30) 0.10	0.12 (-0.03, 0.27) 0.12	0.18 (-0.04, 0.40) 0.20
Maternal Education*	0.26 (0.20, 0.32) <0.001		0.14 (0.17, 0.28) <0.001	0.08 (0.02, 0.13) 0.01	0.10 (0.02, 0.18) 0.01
Leg length (cms)	0.01 (-0.02, 0.02) 0.10		0.02 (0.01, 0.04) 0.001	0.01 (-0.00, 0.03) 0.07	0.01 (-0.01, 0.03) 0.37
Education* (per level)	0.29 (0.25, 0.33) <0.001			0.21 (0.17, 0.26) <0.001	0.20 (0.14, 0.27) <0.001

Composite Cognitive Score in late life (SD)					
Predictor	Unadjusted/univariate B (95%CI) p	Model 1 B (95%CI) p	Model 2 B (95%CI) p	Model 3 B (95%CI) p	Model 4 B (95%CI) p
SLI (score)	0.04 (0.03, 0.05) <0.001			0.02 (0.01, 0.03) 0.001	0.01 (-0.01, 0.02) 0.58
BMI (score)	0.03 (0.02, 0.05) <0.001				-0.01 (0.01, 0.03) 0.49
Physical Activity**	0.23 (0.06, 0.39) 0.01				0.19 (-0.01, 0.39) 0.01
Smoking pack years (years)	-0.01 (-0.01, 0.04) <0.001				-0.01 (0.01, -0.04) <0.001
Alcohol (units/week)	-0.00 (-0.01, 0.01) 0.60				0.00 (0.01, 0.01) 0.50
Marital status (0=married 1=others)	-0.26 (-0.43, 0.01) 0.004				0.10 (0.15, 0.36) 0.42
Depression (0=no 1=yes)	-0.51 (-0.70, -0.33) <0.001				-0.15 (-0.40, 0.10) 0.21
Estimate of the variance explained by the predictors in each model		0.09	0.21	0.34	0.46

* Education:0=illiterate 1=primary 2=secondary 3=preuniversity 4=college 5=graduate 6=postgraduate.

**Physical activity: 0=sedentary 1=mild 2=moderate 3=strenuous. CI: confidence interval FEV1: Forced Expiratory volume at 1 second. SLI: Standard of Living Index BMI: Body Mass Index

Model 1: Adjusted for age, sex and sibship, and birth weight

Model 2: Adjusted for age, sex and sibship, birth weight and childhood factors (maternal education and adult leg length)

Model 3: Adjusted for age, sex and sibship, birth weight, childhood, and adult factors (education and SLI). Adjustment for midlife lung function did not change the model.

Model 4: Adjusted for adjusted for age, sex and sibship, birth weight, childhood, adult life and late life factors (BMI, physical activity, smoking, marital status and depression), Further adjustment for other NCDs (diabetes, hypertension, metabolic syndrome and stroke) in late life did not change the models.

function as a result of decline in lung function or the reverse), shared risk factors and causal pathways (e.g. exposure to air pollutants resulting in inflammation in lungs and brain; smoking and sedentary lifestyle) or due to normal aging process across all physiological systems^{44,45}. Therefore, this relationship is best explored in longitudinal studies with serial, but contemporaneous measurements of both lung and cognitive function.

A direct relationship has been observed between indicators of lung function in mid-life and cognitive outcomes at follow-up across several longitudinal studies^{17,46–51}. However in our study, midlife lung function was unrelated to cognitive outcomes measured approximately 20 years later. Besides issues related to power, non-availability of cognitive measurements in midlife and different methods of spirometry (a turbine computerised spirometer in midlife and Piko-6 microspirometry in late life) limited us from conducting structural equation modelling to explore causal pathways of this relationship. Structural equation modelling would adequately account for pulmonary

reserve and cognitive reserve, which are important latent pathway variables.

We have for the first time demonstrated that the direct association of lung function in late life with cognitive outcomes was independent of: growth and development in early life and childhood; lung function, cardiometabolic disorders socioeconomic position and BMI in midlife; and cardiometabolic disorders, lifestyle factors and depression in late life, indicating that lung function may be an important determinant of cognitive function in late life. However we were unable to explore casual pathways due to the same reasons listed above.

A major strength of the study is the completeness of the lung and cognitive function data in late life for analyses. In addition, the cohort is unique for a LMIC setting with availability of data from early and midlife allowing us to examine the risk factors across the lifecourse on lung-cognition relationship in later life. When a participant was receiving care, a reliable

informant was always interviewed to capture information related to cognitive function and decline. Standardised assessments were carried out for diagnosing NCDs.

Only a small proportion of study participants were diagnosed with COPD and dementia in this cohort. Therefore lack of observed associations of lung function with dementia, and COPD with cognitive outcomes is most likely due to insufficient power. Different spirometers (in mid and late life) were used to measure lung function and bronchodilators were not administered before spirometry. Caution should also be exerted in generalising findings beyond the study setting, because those who participated in this study were a small proportion of older adults who were born and matched to their birth records from one hospital in Mysore, India. When compared to the original cohort members, those who were retraced and examined in this study were of higher socioeconomic position, had higher levels of attained education, higher lung function and had lower rates of NCDs²⁹.

Conclusions

Despite several limitations, this study has highlighted the importance of lifecourse approaches to exploring complex relationship between lung function and cognitive function. Mechanistic studies, particularly which examine the role of shared risk factors like environmental pollutants and biomass exposure on this relationship are urgently required in LMICs where the burden of both chronic lung diseases and neurocognitive disorders is higher than HICs^{52,53}.

Data availability

Data are available subject to Health Ministry Screening Committee (HMSC), India and Institutional Ethics Committee approval. Access may be granted for research purposes only. For further information contact the corresponding author Dr Murali Krishna via email: muralidoc@gmail.com.

Acknowledgments

We are grateful to participants and their families for their cooperation and participation in this study. We acknowledge the contributions of the present and previous staff at Holdsworth Memorial Hospital, Mysore. They include: Dr Sona Rao, Saroja A, Somashekara R, Malathi MP, Pavithra Rani HD, Tony Gerald, Jayakumar MN, Geetha S, Annamma, Chachyamma, Tony Gerald Lawrence, Tony Clifford Onslow, Swaranagowri MN, Sulekha, Gopal Singh, Shylaja, Harini, Shobha, Poornima, Srinivas and Stephen Justine Manohar. We are thankful to the late Professor David JP Barker for his support in establishing the cohort and the research centre at CSI Holdsworth Memorial Hospital. We also thank other members of the MRC Lifecourse Epidemiology Unit, University of Southampton, UK, who have contributed to the Mysore Birth Records Cohort studies including Claudia Stein who created the cohort by tracing people born in HMH in 1993–1995.

The thesis this paper is based on is available online at [eprints.soton.ac.uk \(https://eprints.soton.ac.uk/435570/1/Murali_Krishna_PhD_copy_to_university.pdf\)](https://eprints.soton.ac.uk/435570/1/Murali_Krishna_PhD_copy_to_university.pdf).

References

- Lim SS, Vos T, Flaxman AD, *et al.*: **A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010.** *Lancet*. 2012; **380**(9859): 2224–2260. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Prince M, Albanese E, Guerchet M, *et al.*: **World Alzheimer Report 2014: Dementia and risk reduction: An analysis of protective and modifiable risk factors.** Published online September 21, 2014. Accessed June 9, 2021. [Reference Source](#)
- Bhatia R: **Elderly in India –Profile and Programmes, 2006.** 103. [Reference Source](#)
- Situation analysis of the elderly in India.** India Environment Portal | News, reports, documents, blogs, data, analysis on environment & development | India, South Asia. Accessed June 9, 2021. [Reference Source](#)
- Clouston SAP, Brewster P, Kuh D, *et al.*: **The dynamic relationship between physical function and cognition in longitudinal aging cohorts.** *Epidemiol Rev*. 2013; **35**(1): 33–50. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Spiro A III, Brady CB: **Integrating Health Into Cognitive Aging Research and Theory: Quo Vadis?** In: *Handbook of Cognitive Aging: Interdisciplinary Perspectives*. SAGE Publications, Inc.; 2008; 260–283. [Publisher Full Text](#)
- Lara J, Cooper R, Nissan J, *et al.*: **A proposed panel of biomarkers of healthy ageing.** *BMC Med*. 2015; **13**: 222. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Albert MS, Jones K, Savage CR, *et al.*: **Predictors of cognitive change in older persons: MacArthur studies of successful aging.** *Psychol Aging*. 1995; **10**(4): 578–589. [PubMed Abstract](#) | [Publisher Full Text](#)
- Anstey KJ, Windsor TD, Jorm AF, *et al.*: **Association of Pulmonary Function with Cognitive Performance in Early, Middle and Late Adulthood.** *Gerontology*. 2004; **50**(4): 230–234. [PubMed Abstract](#) | [Publisher Full Text](#)
- Cerhan JR, Folsom AR, Mortimer JA, *et al.*: **Correlates of cognitive function in middle-aged adults. Atherosclerosis Risk in Communities (ARIC) Study Investigators.** *Gerontology*. 1998; **44**(2): 95–105. [PubMed Abstract](#) | [Publisher Full Text](#)
- Chyou PH, White LR, Yano K, *et al.*: **Pulmonary function measures as predictors and correlates of cognitive functioning in later life.** *Am J Epidemiol*. 1996; **143**(8): 750–6. [PubMed Abstract](#) | [Publisher Full Text](#)
- Cook NR, Evans DA, Scherr PA, *et al.*: **Peak expiratory flow rate in an elderly population.** *Am J Epidemiol*. 1989; **130**(1): 66–78. [PubMed Abstract](#) | [Publisher Full Text](#)
- Deary IJ, Whalley LJ, Batty GD, *et al.*: **Physical fitness and lifetime cognitive change.** *Neurology*. 2006; **67**(7): 1195–1200. [PubMed Abstract](#) | [Publisher Full Text](#)
- Emery CF, Huppert FA, Schein RL: **Do pulmonary function and smoking behavior predict cognitive function? findings from a british sample.** *Psychology & Health*. 1997; **12**(2): 265–275. [Publisher Full Text](#)
- Emery CF, Pedersen NL, Svartengren M, *et al.*: **Longitudinal and genetic effects in the relationship between pulmonary function and cognitive performance.** *J Gerontol B Psychol Sci Soc Sci*. 1998; **53**(5): P311–317. [PubMed Abstract](#) | [Publisher Full Text](#)
- Min JY, Min KB, Paek D, *et al.*: **The association between neurobehavioral performance and lung function.** *Neurotoxicology*. 2007; **28**(2): 441–444. [PubMed Abstract](#) | [Publisher Full Text](#)
- Pathan SS, Gottesman RF, Mosley TH, *et al.*: **Association of lung function with**

- cognitive decline and dementia: the Atherosclerosis Risk in Communities (ARIC) Study.** *Eur J Neurol.* 2011; **18**(6): 888–898.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
18. Russ TC, Starr JM, Stamatakis E, *et al.*: **Pulmonary function as a risk factor for dementia death: An individual participant meta-analysis of six UK general population cohort studies.** *J Epidemiol Community Health.* 2015; **69**(6): 550–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
 19. Sachdev PS, Anstey KJ, Parslow RA, *et al.*: **Pulmonary Function, Cognitive Impairment and Brain Atrophy in a Middle-Aged Community Sample.** *Dement Geriatr Cogn Disord.* 2006; **21**(5–6): 300–308.
[PubMed Abstract](#) | [Publisher Full Text](#)
 20. Singh-Manoux A, Dugravot A, Kauffmann F, *et al.*: **Association of lung function with physical, mental and cognitive function in early old age.** *Age (Dordr).* 2011; **33**(3): 385–392.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 21. Dodd JW: **Lung disease as a determinant of cognitive decline and dementia.** *Alzheimers Res Ther.* 2015; **7**(1): 32.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 22. Duggan EC, Graham RB, Piccinin AM, *et al.*: **Systematic Review of Pulmonary Function and Cognition in Aging.** *Gutchess A ed. J Gerontol B Psychol Sci Soc Sci.* 2020; **75**(5): 937–952.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 23. Emery CF, Finkel D, Pedersen NL: **Pulmonary Function as a Cause of Cognitive Aging.** *Psychol Sci.* 2012; **23**(9): 1024–1032.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 24. MacDonald SWS, DeCarlo CA, Dixon RA: **Linking Biological and Cognitive Aging: Toward Improving Characterizations of Developmental Time.** *J Gerontol B Psychol Sci Soc Sci.* 2011; **66** Suppl 1(Suppl 1): i59–70.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 25. Finkel D, Reynolds CA, Emery CF, *et al.*: **Genetic and environmental variation in lung function drives subsequent variation in aging of fluid intelligence.** *Behavior Genetics.* 2013; **43**(4): 274–285.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 26. Weuve J, Glymour MM, Hu H, *et al.*: **Forced expiratory volume in 1 second and cognitive aging in men.** *J Am Geriatr Soc.* 2011; **59**(7): 1283–1292.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 27. Richards M, Strachan D, Hardy R, *et al.*: **Lung function and cognitive ability in a longitudinal birth cohort study.** *Psychosom Med.* 2005; **67**(4): 602–608.
[PubMed Abstract](#) | [Publisher Full Text](#)
 28. Stein CE, Kumaran K, Fall CH, *et al.*: **Relation of fetal growth to adult lung function in south India.** *Thorax.* 1997; **52**: 895–899.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 29. Krishna M, Kalyanaraman K, Veena SR, *et al.*: **Cohort Profile: The 1934–66 Mysore Birth Records Cohort in South India.** *Int J Epidemiol.* 2015; **44**(6): 1833–1841.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 30. Krishna M, Kumar GM, Veena SR, *et al.*: **Birth size, risk factors across life and cognition in late life: protocol of prospective longitudinal follow-up of the MYNAH (Mysore studies of Natal effects on Ageing and Health) cohort.** *BMJ Open.* 2017; **7**(2): e012552.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 31. 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.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 32. **National Family Health Survey.** Accessed June 9, 2021.
[Reference Source](#)
 33. Hall KS, Gao S, Emsley CL, *et al.*: **Community screening interview for dementia (CSI 'D'); performance in five disparate study sites.** *Int J Geriatr Psychiatry.* 2000; **15**(6): 521–531.
[PubMed Abstract](#) | [Publisher Full Text](#)
 34. 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): 1159–1165.
[PubMed Abstract](#) | [Publisher Full Text](#)
 35. 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): 507–524.
[PubMed Abstract](#) | [Publisher Full Text](#)
 36. Hendrie HC, Osuntokun BO, Hall KS, *et al.*: **Prevalence of Alzheimer's disease and dementia in two communities: Nigerian Africans and African Americans.** *Am J Psychiatry.* 1995; **152**(10): 1485–1492.
[PubMed Abstract](#) | [Publisher Full Text](#)
 37. Prince M, Acosta D, Chiu H, *et al.*: **Dementia diagnosis in developing countries: a cross-cultural validation study.** *Lancet.* 2003; **361**(9361): 909–917.
[PubMed Abstract](#) | [Publisher Full Text](#)
 38. Copeland JR, Dewey ME, Griffiths-Jones HM: **A computerized psychiatric diagnostic system and case nomenclature for elderly subjects: GMS and AGECAT.** *Psychol Med.* 1986; **16**(1): 89–99.
[PubMed Abstract](#) | [Publisher Full Text](#)
 39. Thorat YT, Salvi SS, Kodgule RR: **Peak flow meter with a questionnaire and mini-spirometer to help detect asthma and COPD in real-life clinical practice: a cross-sectional study.** *NPJ Prim Care Respir Med.* 2017; **27**(1): 32.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 40. World Health Organization, International Diabetes Federation: **Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycaemia : Report of a WHO/IDF Consultation.** World Health Organization. 2006; Accessed June 13, 2021.
[Reference Source](#)
 41. Alberti KGMM, Zimmet P, Shaw J: **Metabolic syndrome—a new world-wide definition. A Consensus Statement from the International Diabetes Federation.** *Diabet Med.* 2006; **23**(5): 469–480.
[PubMed Abstract](#) | [Publisher Full Text](#)
 42. **Diagnostic and Statistical Manual of Mental Disorders Source Information.** Accessed June 9, 2021.
[Reference Source](#)
 43. Wadsworth MEJ, Hardy RJ, Paul AA, *et al.*: **Leg and trunk length at 43 years in relation to childhood health, diet and family circumstances; evidence from the 1946 national birth cohort.** *Int J Epidemiol.* 2002; **31**(2): 383–390.
[PubMed Abstract](#) | [Publisher Full Text](#)
 44. Hofer SM, Flaherty BP, Hoffman L: **Cross-Sectional Analysis of Time-Dependent Data: Mean-Induced Association in Age-Heterogeneous Samples and an Alternative Method Based on Sequential Narrow Age-Cohort Samples.** *Multivariate Behav Res.* 2006; **41**(2): 165–187.
[PubMed Abstract](#) | [Publisher Full Text](#)
 45. Kraemer HC, Yesavage JA, Taylor JL, *et al.*: **How can we learn about developmental processes from cross-sectional studies, or can we? Am J Psychiatry. 2000; **157**(2): 163–171.
[PubMed Abstract](#) | [Publisher Full Text](#)**
 46. Aiken-Morgan AT, Gamaldo AA, Wright RS, *et al.*: **Stability and change in cognitive status classification of black older adults.** *J Am Geriatr Soc.* 2018; **66**(1): 179–183.
[PubMed Abstract](#) | [Publisher Full Text](#)
 47. Infurna FJ, Gerstorf D: **Linking perceived control, physical activity, and biological health to memory change.** *Psychol Aging.* 2013; **28**(4): 1147–1163.
[PubMed Abstract](#) | [Publisher Full Text](#)
 48. Koster A, Penninx BWJH, Bosma H, *et al.*: **Socioeconomic differences in cognitive decline and the role of biomedical factors.** *Ann Epidemiol.* 2005; **15**(8): 564–571.
[PubMed Abstract](#) | [Publisher Full Text](#)
 49. Swan GE, LaRue A, Carmelli D, *et al.*: **Decline in cognitive performance in aging twins: Heritability and biobehavioral predictors from the National Heart, Lung, and Blood Institute Twin Study.** *Arch Neurol.* 1992; **49**(5): 476–481.
[PubMed Abstract](#) | [Publisher Full Text](#)
 50. Vidal JS, Aspelund T, Jonsdottir MK, *et al.*: **Pulmonary function impairment may be an early risk factor for late-life cognitive impairment.** *J Am Geriatr Soc.* 2013; **61**(1): 79–83.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 51. Whitfield KE, Seeman TE, Miles TP, *et al.*: **Health indices as predictors of cognition among older African Americans: MacArthur studies of successful aging.** *Ethn Dis.* 1997; **7**(2): 127–136.
[PubMed Abstract](#)
 52. Soriano JB, Kendrick PJ, Paulson KR, *et al.*: **Prevalence and attributable health burden of chronic respiratory diseases, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017.** *Lancet Respir Med.* 2020; **8**(6): 585–596.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 53. GBD 2016 Dementia Collaborators: **Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016.** *Lancet Neurol.* 2019; **18**(1): 88–106.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)