Respiratory disease and lower pulmonary function as risk factors for dementia: a systematic review with meta-analysis

Short title: Pulmonary function and dementia

Tom C. Russ PhD MRCPsych,[1-4 *] Mika Kivimäki FMedSci,[5] G. David Batty DSc[1,2,5,6]

[1] Alzheimer Scotland Dementia Research Centre, University of Edinburgh, UK
[2] Centre for Cognitive Ageing & Cognitive Epidemiology, University of Edinburgh, UK
[3] Edinburgh Dementia Prevention, University of Edinburgh, UK
[4] Division of Psychiatry, Centre for Clinical Brain Sciences, University of Edinburgh, UK
[5] Department of Epidemiology and Public Health, University College, London, UK
[6] School of Biological & Population Health Sciences, Oregon State University, USA

* Correspondence to: Dr Tom C. Russ, Alzheimer Scotland Dementia Research Centre, University of Edinburgh, 7 George Square, Edinburgh, EH8 9JZ, UK
Telephone: +44 (0)131 650 4340; Email: T.C.Russ@ed.ac.uk

Manuscript statistics: article body word count of 3886 plus an abstract of 201 words, 5 figures, 2 tables, and 3 supplementary figures.

Contributions: TCR and GDB generated the idea for the present manuscript. TCR conducted the literature search, extracted the results, and carried out the meta-analyses. TCR drafted the manuscript which was revised by GDB and MK. TCR is the guarantor of the article.

Funding: The present manuscript received no direct funding. TCR was supported by the Alzheimer Scotland Marjorie MacBeath fellowship from 2015-16 and is now employed in the UK National Health Service. TCR and GDB are members of the Alzheimer Scotland Dementia Research Centre which is funded by Alzheimer Scotland. GDB is supported by the UK Medical Research Council (MR/P023444/1) and the US National Institute on Aging (1R56AG052519-01; 1R01AG052519-01A1). MK is supported by the Medical Research Council, UK (S011676, R024227), NordForsk, the Nordic Research Programme on Health and Welfare (grant #75021), the Academy of Finland (311492), and the Helsinki Institute of Life Science. All researchers are independent of their funders.

Conflicts of interest: None declared.

Selected aspects of the present manuscript were presented in preliminary form as a poster at the 2017 Alzheimer's Association International Conference, London.

ABSTRACT

Background: In addition to affecting the oxygen supply to the brain, pulmonary function is a marker of multiple insults throughout life (including smoking, illness, and socioeconomic deprivation). In this meta-analysis of existing longitudinal studies, we tested the hypothesis that lower pulmonary function and respiratory illness are linked to an elevated risk of dementia.

Method: We conducted a systematic review of longitudinal studies using PubMed until April 1st, 2019 and, where possible, pooled results in random-effects meta-analyses.

Results: We identified eleven studies relating pulmonary function to later dementia risk, and eleven studies of respiratory illness and dementia (including one which assessed both). The lowest quartile of Forced Expiratory Volume in one second (FEV_1) compared with the highest was associated with a 1.4-fold (1.46, 95%CI 0.77-2.75) increased dementia risk (N_{total}=62,209, two studies). An decrease of one standard deviation in FEV_1 was associated with a 28% increase in dementia risk (1.28, 95%CI 1.03-1.60; N_{total}=67,505; six studies). Respiratory illness was also associated with increased dementia risk to a similar degree (1.54, 1.30-1.81, N_{total}=288,641, 11 studies).

Conclusions: Individuals with poor pulmonary function experience increased risk of dementia. The extent to which the association between poor pulmonary function and dementia is causal remains unclear and requires examination.

Key words: Dementia, Alzheimer's disease, pulmonary function, epidemiology, life course

INTRODUCTION

The considerable public health and care burden of dementia has been well documented.[1] While the age-standardised prevalence and incidence of dementia may be declining,[2-4] because of population ageing, the absolute number of people with dementia worldwide is projected to triple from approximately 44 million in 2013 to 135 million by 2050.[5]

The disappointing results from trials evaluating treatment modalities for dementia[6] has brought into sharp focus the need to identify modifiable risk factors for this neuropsychiatric disorder. Although by no means universal observations, some evidence suggest that lower mental ability, educational achievement, socioeconomic status, hypertension, and diabetes are linked to an increased occurrence of dementia.[7-15] Pulmonary function and respiratory disease have also been advanced as risk markers for dementia.[16] Mechanisms of effect include diminished supply of oxygen to the brain, resulting in low level but sustained hypoxia,[17] and the notion that both pulmonary function and respiratory disease may capture multiple environmental insults across the lifespan, notably smoking, socioeconomic deprivation, and physical stunting,[18-20] all of which have been linked with dementia in their own right.[7]

With the number of studies on pulmonary function and dementia increasing (**Figure 1**), to the best of our knowledge, we provide the first aggregation of these results by conducting a systematic review and meta-analysis of the evidence from longitudinal studies to examine the hypothesis that low pulmonary function and pulmonary disease are risk factors for later dementia. Additionally, we place our findings into context by comparing our aggregated results with those from reviews of other plausible risk factors for dementia.

METHODS

The review protocol was registered with PROSPERO (https://www.crd.york.ac.uk/prospero/; CRD42019130376). In accordance with the PRISMA guidelines,[21] we searched PubMed for articles reporting longitudinal (cohort) studies linking pulmonary function or respiratory illness with dementia occurrence from the inception of the database (1951) until 1st April 2019. The search strategy combined the terms dementia OR alzheimer* AND "forced expiratory volume" OR "expiratory volume" OR FEV OR "forced vital capacity" OR "vital capacity" OR FVC OR "peak expiratory flow" OR "peak flow" OR PEF OR ((pulmonary OR lung OR respiratory) AND function) OR asthma OR COPD OR "respiratory disease" or COAD or "airways disease" OR "lung disease" OR pneumonia AND longitudinal OR prospective OR cohort. We also scrutinised the reference sections of retrieved papers and searched our own files. TCR screened the search results using Covidence (https://www.covidence.org/) and extracted data from included articles.

We included studies that were published in English; had a prospective cohort study design with individual level exposure and outcome data, including an appropriate exposure comparator; examined the effect of pulmonary function or pulmonary disease; reported dementia as an outcome; and reported either estimates of relative risk (RR), odds ratios (OR), or hazard ratios (HR) with 95% CIs, or provided sufficient results to calculate these estimates.

We extracted the following information from each eligible article: name of the first author, start of the follow-up for dementia (year), study location (country), number of participants, number of dementia events, mean follow-up time, mean age of participants, proportion of women, measure of pulmonary function used and mean (SD) values or respiratory illness measured; age at which exposure was measured; covariables included in most-adjusted model; method of dementia ascertainment, and covariates included in the adjusted models. An assessment of risk of bias for

each study was carried out by one reviewer using pre-defined bespoke criteria – including the population studied, recruitment methods used, measurement of exposure, availability of relevant covariates, and method of determining the outcome – and was classified as low, medium, or high. We conducted sensitivity analyses including just the studies found to be at lower risk of bias. Meta-analyses were conducted using R for Windows 3.4.0 and the metafor and forestplot packages. In preliminary analyses, heterogeneity measured by the I^2 statistic was not consistently low (range: 0-92%) and so random effects models were used.

RESULTS

Our search returned 673 articles of which 627 were discarded after review of their abstract and/or title; 46 were read in full (**Figure 2**). Of these, 26 studies were excluded (eight did not focus on pulmonary function or disease, six were cross-sectional, six did not have dementia as an outcome, two were ongoing studies and no results had been published, three articles were commentaries, one had been superceded by a more recent report, and one study had no comparator) with the remaining 20 being included in further analyses. We considered the results for studies recording pulmonary function (N=10) and respiratory illness (N=11) separately (one study reported both pulmonary function and respiratory illness).

Pulmonary function as a risk factor for dementia

We identified ten prospective cohort studies that have been used to examine the association between pulmonary function and later dementia (**Table 1**). Mean age of participants when respiratory function was measured varied between 40 and 65 in seven studies[16,22-27] and was over 65 in three studies.[28-30] In these studies, investigators used one of several spirometric measures as the exposure of interest (risk factor): peak expiratory flow (PEF) refers to the maximum speed of forced expiration (in litres per second); Forced Expiratory Volume (FEV) denotes the volume of air (in litres) which can be expired in a specified period of time, usually in one second (FEV_1);

and Forced Vital Capacity (FVC) captures the total volume of air which can be expired. Maximal inspiration is required before each measurement and many studies allow a defined number of attempts and record the best performance. These measures of pulmonary function correlate closely with each other[16] suggesting that associations seen for one measure with dementia/cognitive impairment are likely to be replicated in the other measures.

A range of methods were used to ascertain dementia, some in combination: death certification,[16,23,29,30] linkage to electronic medical records (e.g., hospital discharge records),[25,26,28,30,31] and clinical assessment.[22,24,26,27,30] A number of these studies were originally instigated to investigate risk factors for cardiovascular disease[23,26,27,29] or the menopause[22] and then repurposed to include dementia follow-up as study participants aged; only two were specifically set up to investigate diseases of ageing.[24,30] Duration of follow up ranged from 12 to 40 years.[16,23] A wide variety of covariables were included in the studies (**Table 1**) but the possibility of residual confounding remains.

Figure 3 shows two meta-analyses of studies on FEV and dementia risk – one for categories of FEV and one for a unit change. Only two studies (62,209 adults, 1800 dementia cases) compared the lowest quartile of FEV_1 with the highest quartile;[16,26] pooling these results in a meta-analysis gave a HR of 1.46 (95% CI 0.77, 2.75; P=0.092; I^2=69.3%). Pooling the five studies which reported the effect of one standard deviation decrease (disadvantage) in FEV_1 resulted in a HR of 1.28 (1.03-1.60; P=0.028; I^2=78.2%; N=67,505, 2280 dementia cases). One of these studies standardised FEV_1 by dividing by height[224] but a sensitivity analysis excluding this transformation gave a similar pooled result (1.24, 0.92-1.68).[16,22,26,27]. A further sensitivity analysis using data only from the three studies deemed to have a low risk of bias[22,24,26] resulted in a similar pooled result (1.25, 1.00-1.56).[26]

Supplementary Figure 1 shows pooled results for FVC: lowest-to-highest quartile HR 1.58 (95% CI 1.07-2.33; P=0.021; I^2=57.6%; four studies, N=78,995, 2352 dementia cases);[16,23,26,29] per standard deviation disadvantage 1.21 (0.97-1.51; P=0.086; I^2=70.7%; four studies, N=63,840, 1992 dementia cases).[16,22,26,27] One study included in the latter meta-analysis reported an interaction between *APOE* status and the association between FEV/FVC and dementia which contributed to the substantial heterogeneity observed here; excluding this study did not affect the results of the meta-analysis but reduced the heterogeneity slightly to I^2=65.1%.[27]

Supplementary Figure 2 shows the result of pooling two studies which compared dementia risk in the lowest vs highest quartiles of PEF, giving a HR of 2.21 (95% CI 1.73-2.82; P<0.001; I^2=0.0%; N=50,830, 678 dementia cases);[16,28] combining the two studies which reported the association between one standard deviation decrease in PEF and dementia gave a HR of 1.39 (1.24-1.56; P<0.001; I^2=10.6%; N=49,316, 540 dementia cases).[16,22]

Three studies could not be pooled in meta-analyses because of the manner in which the results were reported. A study of 27,387 Kaiser Permanente Northern California members, of whom 7519 developed dementia over more than 28 years follow up, concluded that poorer FEV_1 (plus FEV_2 and VC) was associated with an increased risk of dementia (multivariable-adjusted HR per litre decrease in FEV_1 1.13, 95% CI 1.09-1.18).[25] This finding was replicated in stratified analyses for smokers and non-smokers. Investigators in the Seven Countries Studies found that men with greater FVC were less likely to die with dementia than men with lower FVC (multivariable-adjusted hazard ratio for highest quartile [Q4] vs lowest quartile [Q1] 0.54, 95% CI 0.30-0.98) but the association observed in this study did not follow a dose-response gradient (HR, 95% CI: Q3 vs Q1 1.03, 0.63-1.68; Q2 vs Q1 0.77, 0.46-1.28).[23] Finally, of 484 men and women from the Lothian Birth Cohort 1936, 106 adjudicated dementia diagnoses were identified from multiple sources, including face-to-face clinical assessment.[30] No robust evidence was found to suggest

that FEV_1 measured at age 79 years would be associated with developing dementia (multivariable-adjusted HR per litre/second increase 1.30, 95% CI 0.74-2.30).

Respiratory disease as a risk factor for dementia

We identified eleven prospective studies in which investigators had explored the association between respiratory disease and later dementia (**Table 2**). Mean age at which disease was ascertained varied from 50.6 to 82.9 years but was over 65 years in six of the 11 studies.[32-37] Investigators identified pulmonary disease using three modes of data collection: National Health Insurance database,[32,33,36,38,39] hospitalisation data,[35] and self-report.[26,34,37,40,41] The specific pulmonary conditions most commonly ascertained at baseline were chronic obstructive pulmonary disorder, asthma, and pneumonia, the latter in only one study.[35] In all cases, the comparison was with individuals without the illness in question.

Dementia was ascertained from the Taiwanese insurance database in five studies,[32,33,36,38,39] face-to-face assessement by a clinician in four studies,[26,34,35,41], cognitive test score in one,[37] and linkage to hospital discharge and death certificate data in one.[40] Again, a wide variety of covariables were included in the studies (**Table 2**) but the possibility of residual confounding remains.

Figure 3 shows a meta-analysis of these 11 studies with a total of 288,641 individuals and 15,898 dementia cases giving a pooled HR of 1.54 (95% CI 1.30-1.81; P<0.001; I^2=92.4%). Although the study-specific estimates were heterogeneous, they all favoured risk factor status. Excluding a study which investigated the association between atopic illnesses[40] (asthma, eczema, or rhinitis – only one of which is likely to have a substantial effect on pulmonary function) and dementia reduced the magnitude of the effect observed (1.28, 1.03, 1.60) as well as substantial heterogeneity (I^2=78.2%) but did not alter our conclusion. A sensitivity analysis excluding the

one study assessed as having a high risk of bias[37] unsurprisingly gave a similar pooled result (1.52, 1.28-1.80), as did including only the two studies with a low risk of bias[26,35] (1.53, 0.75-3.13).

DISCUSSION

The main finding from our systematic review and meta-analysis of cohort studies is that people with poorer pulmonary function and those with overt respiratory disease (some of whom may nevertheless have pulmonary function in the normal range), particularly in midlife, experience a moderately elevated risk of later dementia These effects were apparent across different countries and research groups, were seen in men and women, and appeared to be robust to the statistical adjustment of a range of confounding factors.

Comparision with other risk markers

The effect size we found is comparable to other accepted risk factors for dementia as reported in comprehensive meta-analyses in the World Alzheimer Report 2014[42] (**Figure 4**) where both lower educational attainment and depression, for example, was found to be associated with around a doubling of dementia risk (effect estimate combining adjusted odds ratios and HRs, 95% CI 1.83, 1.63-2.05; 31 studies). A diagnosis of diabetes in late life was related to a 1.5-fold increase in the risk of developing dementia of any type (1.50, 1.33-1.70) and a doubling of risk of developing vascular dementia (2.39, 1.92-2.98). The recent Lancet commission on dementia reported similar effects for midlife obesity, hypertension, or later life smoking (**Figure 4**).[7]

In a related field, the authors of a recent systematic review of four longitudinal studies on the association between pulmonary function and cognitive performance,[43] while critical of the methodological quality of the studies they included, found a cross-sectional association between poorer lung function and lower levels of cognitive function. That there was little evidence for a longitudinal association may provide some suggestion for reverse causality or, aternatively, it may

239 reflect different mechanisms of cognitive performance and neurological pathology underlying
240 dementia as seems to be the case with other risk factors, such as vitamin D levels.[44,45]
241
242 **Review limitations and strengths**
243 The comprehensive search strategy used is likely to have identified practically all relevant
244 published studies. The inclusion of only longitudinal studies would seemingly strengthen the
245 robustness of our conclusions since, while such studies still only describe associations, the
246 temporal association between exposure and outcome is clearer than in case-control and cross-
247 sectional studies for instance. This notwithstanding, we cannot completely rule out reverse
248 causality; that is, the extended prodromal phase for dementia may have led to the outcome
249 influencing the two exposures, particularly in those studies which shorter duration of follow-up.
250 This has been demonstrated in other contexts; for instance, both body mass index and physical
251 activity in the aetiology of dementia.[46,47] The pooling of results, where possible, in random effects
252 meta-analyses provides a quantitative summary of the evidence that has more utility than a
253 narrative overview of results from individual studies.
254
255 There are several limitations to our work. Any review of scientific evidence is only as strong as
256 the studies on which it draws. The substantial statistical heterogeneity between studies is
257 matched by methodological heterogeneity and – importantly – variation in the specific measure
258 of pulmonary function used, though the correlation between different measures of pulmonary
259 function – FEV, FVC, and PEF – in population-based studies is typically high.[16] The respiratory
260 illnesses considered were varied and may have exerted different impacts on dementia risk. It
261 may be that, for instance, chronic exposure, characterised by conditions such as chronic
262 obstructive pulmonary disorder, would be more strongly related to dementia than the more acute
263 but shorter-lived pneumonia. Given a greater abundance of studies and therefore data, it would

have been desirable to explore the association of different types of respiratory disease on dementia risk.

Supplementary Figure 3 shows the funnel plots and results of Egger's regression (all $p \geq 0.05$) suggesting that publication bias has not influenced our findings, but the number of studies included in some of the comparisons is very small. Furthermore, not all of the identified studies could be pooled in the meta-analyses which may have further influenced our results, but it would not be expected that all such studies would have influenced our results in a particular direction.

The methodology used for dementia ascertainment is a potentially important limitation for individual studies. Face-to-face assessment by a clinician combined with brain imaging is a robust method to ascertain incident dementia cases, but is resource-intensive and differential participation in the screening process by different groups can introduce bias.[48] Linkage to electronic medical records has been shown to identify only a proportion of people known to be experiencing dementia, particularly those with mild symptoms.[16,49] Death certification has been criticised as a methodology for identifying dementia cases but reporting of dementia on death certificates seems to be becoming increasingly comprehensive: for instance, a recent investigation found that, in a memory clinic cohort, of all the patients with diagnosed dementia who died during the follow-up, death certification correctly identified the diagnosis in as large a proportion as 70% of deceased patients.[50] Furthermore, investigators studying the association between body mass index and dementia found their results were similar whether dementia was ascertained solely from mortality data or whether other methods were also used.[51]

Plausible mechanisms

A number of lines of research, in combination with the disappointing results from preventive interventions of dementia implemented at older ages,[52,53] provide circumstantial support for

aetiological process acting from earlier in the life course than previously thought.[54-58] First, recent diagnostic criteria for Alzheimer disease acknowledge a long induction period for dementia such that an asymptomatic 'preclinical' phase is now part of the classification.[59] Second, this accords with findings from pathological and epidemiological studies suggesting that dementia has its origins earlier in life than previously thought. For example, autopsy series demonstrate that Alzheimer-type pathology begins to develop decades before the clinical onset of symptoms.[60-62] Third, among persons without dementia, measurements of the Alzheimer biomarker, cerebral amyloid pathology, suggest a 20- to 30-year interval between first development of amyloid positivity and onset of clinial dementia.[63] Fourth, although not a universal finding,[9,11] there is some evidence from prospective cohort studies that cardiovascular disease risk factors measured in midlife are associated with later dementia risk.[23,41,64-66] Related, in a recent analysis of the Atherosclerosis Risk in Communities study, midlife hypertension and elevated measurements of midlife systolic blood pressure predicted accelerated cognitive decline during 20 years of follow-up.[67] That cardiovascular disease risk factors 'track' from early life into adulthood[68,69] – for example, there is a correlation between blood pressure measured in childhood and again later life[70] – is consistent with the long-term influence of exposures occurring in childhood. Fifth, a recent observational study linked early life cardiorespiratory fitness with later young-onset dementia,[71] though a similar association was not observed between cardiovascular disease risk factors and late-onset dementia mortality elsewhere.[72]

In the present context, these processes– the life course paradigm in dementia aetiology – are perhaps most relevant to pulmonary function rather than respiratory disease. There are at least three plausible mechanisms for the observed association between poorer pulmonary function and subsequent dementia: (i) pulmonary function may serve as a proxy for other exposures earlier in the life course which increase dementia risk; (ii) the association may result from the shared aetiology between pulmonary, cardiovascular disease and dementia; and (iii) hypoxic

damage to the brain resulting from poorer pulmonary function, i.e. impaired pulmonary function may be a true risk factor for dementia. These conceptual relationships are summarised, in simplified form, in **Figure 5**. These mechanisms will now be considered in turn.

First, similarly to physical stature with which it is correlated, lung function may reflect life course exposures which modify an individual's risk of dementia.[18,56,73,74] As alluded to above, the life course paradigm in epidemiology hypothesises that exposures at different points in the life course could influence the risk of developing dementia, either through an accumulation of risk or through exposure at critical/sensitive periods.[56-58] Researchers from the Age, Gene/Environment Susceptibility study in Reykjavik, Iceland, for example, reported that smaller birth size (considered a measure of intrauterine experience) was related to poorer cognitive function at the age of 75, providing the first evidence that even the time before birth is relevant to cognitive ageing.[75] Other potentially relevant factors which could influence lung function include: impaired growth leading to reduced maximal lung function; exposure to environmental factors affecting lung function and development, such as tobacco smoke (direct or indirect);[76] illness, such as childhood lower respiratory tract infections[77] and airway hyperresponsiveness;[78] socioeconomic factors (poverty, educational failure, and less-advantaged social class,[79-85]; environmental factors affecting lung function, such as atmospheric pollution[80] and local exposure to traffic.[86,87]

Second, both Alzheimer disease and vascular dementia may share some aetiology with cardiovascular disease and this overlap in the conditions might explain the association, independent of smoking.[88-90] It has been hypothesised that oxidative stress, inflammation, and amyloid deposition may link these two important conditions.[91,92] In particular, oxidative stress and synaptic dysfunction appear to be closely linked[93] and brain ischaemia – which could result from cerebral atherosclerosis and stroke – leading to oxidative stress-mediated damage.[94] This

may possibly be exacerbated by the pro-inflammatory function of *APOE*, but this effect is controversial.[95 96]

Third, the hypoxia theory proposes that poor pulmonary function is not only a risk marker but also a possible risk factor for dementia through its effects on the brain's oxygen supply. Indeed, most dementia cases in old age do not fall into 'pure' diagnostic categories, but rather manifest mixed pathologies including both vascular disease and Alzheimer-type pathology. For example, the hippocampus – an area of the brain selectively affected in Alzheimer disease – is particularly vulnerable to ischaemic damage,[97] although animal models of chronic hypoperfusion demonstrate impairment of spatial working memory and slowly evolving white matter abnormalities but no neuropathological changes in the hippocampus.[98] Future analyses of magnetic resonance imaging in large prospective cohort studies, such as UK Biobank[99] or the European Prevention of Alzheimer's Disease (EPAD) Longitudinal Cohort Study[100] could help interrogate more closely the putative influence of hypoxia on the hippocampus and other areas of the brain.

Clinical and public health implications

In terms of prevention, the possibility that the association between pulmonary function and cognition might reflect a cause-and-effect relation is particularly important. To date, however, plausible mechanisms linking pulmonary function to dementia include both causal and non-causal explanations and further research on this issue is therefore needed.[22]

The point in time at which risk factors are measured seems to be important for their ability, or lack of it, to predict later dementia or cognitive decline: There was some evidence of be an age-dependent association with stronger links seen for midlife than old age respiratory function and respiratory disease.[30] Further research is needed to clarify whether this reflects the longer

exposure period among younger individuals or a critical period in which poor respiratory function is particularly damaging.

Future directions

Pulmonary function alone is likely to have relatively low sensitivity and specificity as a predictor of cognitive decline and dementia and therefore may not be a useful predictor of dementia in the absence of a range of other predictive factors. Further research is needed to examine this. One way forward is examination of pulmonary function and pathology as a contributor to risk factor algorithms – such as the modified CAIDE risk score[66] – given the reported associations between pulmonary function and dementia which remained after adjustment for cardiovascular risk factors. To date, there is some evidence to suggest that such risk scores predict cognitive function[101] and decline,[102] although there is less evidence for prediction of dementia.[103] Therefore there is, as yet, no risk score including lung function which can be used in clinical practice.

In addition to risk stratification and early identification of risk groups, further work is also required to confirm or refute the importance of pulmonary function as a risk factor amenable to modification and thus a target for prevention. Extended follow up of studies where the initial focus was treating respiratory illness might be a pragmatic place to start. It would be difficult to conduct a sufficiently powered randomised, controlled trial on this topic given the long follow-up from mid-life into later life needed and the large sample size required to obtain a sufficient number of incident dementia cases. These caveats notwithstanding, long-term surveillance of participants in smoking cessation trials, which are likely to have led to improvements in lung function, might have utility.[104] In the meantime, another means of reducing confounding and reverse causation bias, Mendelian randomization studies with genetic variants related to lung function as an instrument would provide one avenue to pursue.[105,106]

Further mechanistic research is also warranted in order to test in depth plausible pathways linking pulmonary function and dementia, such as the hypoxia and vascular damage hypotheses. The global public health importance of dementia is such that researchers should pursue this promising line of research on pulmonary function.

REFERENCES

1. Prince M, Wimo A, Guerchet M, Ali G-C, Wu Y-T, Prina M. *World Alzheimer Report 2015. The Global Impact of Dementia: An analysis of prevalence, incidence, cost and trends.* London: Alzheimer's Disease International; 2015.
2. Matthews FE, Arthur A, Barnes LE, et al. A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II. *Lancet (London, England).* 2013;382(9902):1405-1412.
3. Qiu C, von Strauss E, Bäckman L, Winblad B, Fratiglioni L. Twenty-year changes in dementia occurrence suggest decreasing incidence in central Stockholm, Sweden. *Neurology.* 2013;80(20):1888-1894.
4. Matthews F, Stephan B, Robinson L, et al. A two decade dementia incidence comparison from the Cognitive Function and Ageing Studies I and II. *Nature Communications.* 2016;7.
5. Prince M, Guerchet M, Prina M, Alzheimer's Disease International. *Policy Brief for Heads of Government: The Global Impact of Dementia 2013–2050.* London: Alzheimer Disease International; 2013.
6. Gauthier S, Albert M, Fox N, et al. Why has therapy development for dementia failed in the last two decades? *Alzheimer's & Dementia.* 2016;12(1):60-64.
7. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet (London, England).* 2017;390(10113):2673-2734.
8. Russ TC, Stamatakis E, Hamer M, Starr JM, Kivimaki M, Batty GD. Socioeconomic status as a risk factor for dementia death: individual participant meta-analysis of 86 508 men and women from the UK. *The British journal of psychiatry : the journal of mental science.* 2013;203(1):10-17.
9. Batty GD, Russ TC, Starr JM, Stamatakis E, Kivimaki M. Modifiable cardiovascular disease risk factors as predictors of dementia death: pooling of ten general population-based cohort studies. *Journal of negative results in biomedicine.* 2014;13:8.
10. McCartney G, Russ TC, Walsh D, et al. Explaining the excess mortality in Scotland compared with England: pooling of 18 cohort studies. *J Epidemiol Community Health.* 2015;69(1):20-27.
11. Russ TC, Lee IM, Sesso HD, Muniz-Terrera G, Batty GD. Five-decade trajectories in body mass index in relation to dementia death: follow-up of 33,083 male Harvard University alumni. *International journal of obesity (2005).* 2019;43(9):1822-1829.
12. Russ TC, Hannah J, Batty GD, Booth CC, Deary IJ, Starr JM. Childhood Cognitive Ability and Incident Dementia: The 1932 Scottish Mental Survey Cohort into their 10th Decade. *Epidemiology (Cambridge, Mass.).* 2017;28(3):361-364.
13. Calvin CM, Batty GD, Der G, et al. Childhood intelligence in relation to major causes of death in 68 year follow-up: prospective population study. *BMJ (Clinical research ed.).* 2017;357:j2708.
14. Cadar D, Lassale C, Davies H, Llewellyn DJ, Batty GD, Steptoe A. Individual and Area-Based Socioeconomic Factors Associated With Dementia Incidence in England: Evidence From a 12-Year Follow-up in the English Longitudinal Study of Ageing. *JAMA psychiatry.* 2018;75(7):723-732.
15. Chatterjee S, Peters SA, Woodward M, et al. Type 2 Diabetes as a Risk Factor for Dementia in Women Compared With Men: A Pooled Analysis of 2.3 Million People Comprising More Than 100,000 Cases of Dementia. *Diabetes care.* 2016;39(2):300-307.
16. Russ TC, Starr JM, Stamatakis E, Kivimäki M, Batty GD. Pulmonary function as a risk factor for dementia death: an individual participant meta-analysis of six UK general population cohort studies. *Journal of Epidemiology and Community Health.* 2015;69:550-556.
17. Yaffe K, Laffan AM, Harrison SL, et al. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. *JAMA.* 2011;306(6):613-619.

18. Batty GD, Gunnell D, Langenberg C, Smith GD, Marmot MG, Shipley MJ. Adult height and lung function as markers of life course exposures: associations with risk factors and cause-specific mortality. *Eur J Epidemiol.* 2006;21(11):795-801.
19. Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. *Int J Epidemiol.* 2002;31(2):285-293.
20. Batty GD, Shipley MJ, Kvaavik E, et al. Biomarker assessment of tobacco smoking exposure and risk of dementia death: pooling of individual participant data from 14 cohort studies. *J Epidemiol Community Health.* 2018;72(6):513-515.
21. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS med.* 2009;6(7):e1000097.
22. Guo X, Waern M, Sjögren K, et al. Midlife respiratory function and Incidence of Alzheimer's disease: A 29-year longitudinal study in women. *Neurobiol Aging.* 2007;28(3):343-350.
23. Alonso A, Jacobs Jr DR, Menotti A, et al. Cardiovascular risk factors and dementia mortality: 40 years of follow-up in the Seven Countries Study. *J Neurol Sci.* 2009;280(1):79-83.
24. Vidal JS, Aspelund T, Jonsdottir MK, et al. Pulmonary function impairment may be an early risk factor for late-life cognitive impairment. *Journal of the American Geriatrics Society.* 2013;61(1):79-83.
25. Gilsanz P, Mayeda ER, Flatt J, Glymour MM, Quesenberry CP, Jr., Whitmer RA. Early Midlife Pulmonary Function and Dementia Risk. *Alzheimer disease and associated disorders.* 2018;32(4):270-275.
26. Lutsey PL, Chen N, Mirabelli MC, et al. Impaired Lung Function, Lung Disease and Risk of Incident Dementia. *American journal of respiratory and critical care medicine.* 2019;199(11):1385-1396.
27. Giltay EJ, Nissinen A, Giampaoli S, Kromhout D. Apolipoprotein E genotype modifies the association between midlife lung function and cognitive function in old age. *Dement Geriatr Cogn.* 2009;28(5):433-441.
28. Simons LA, Simons J, McCallum J, Friedlander Y. Lifestyle factors and risk of dementia: Dubbo Study of the elderly. *The Medical journal of Australia.* 2006;184(2):68-70.
29. Newman AB, Sachs MC, Arnold AM, et al. Total and cause-specific mortality in the cardiovascular health study. *The journals of gerontology. Series A, Biological sciences and medical sciences.* 2009;64(12):1251-1261.
30. Sibbett RA, Russ TC, Allerhand M, Deary IJ, Starr JM. Physical fitness and dementia risk in the very old: a study of the Lothian Birth Cohort 1921. *BMC psychiatry.* 2018;18(1):285.
31. Defina LF, Willis BL, Radford NB, et al. The association between midlife cardiorespiratory fitness levels and later-life dementia: a cohort study. *Annals of internal medicine.* 2013;158(3):162-168.
32. Liao KM, Ho CH, Ko SC, Li CY. Increased Risk of Dementia in Patients With Chronic Obstructive Pulmonary Disease. *Medicine.* 2015;94(23):e930.
33. Liao WC, Lin CL, Chang SN, Tu CY, Kao CH. The association between chronic obstructive pulmonary disease and dementia: a population-based retrospective cohort study. *European journal of neurology.* 2015;22(2):334-340.
34. Minami Y, Tsuji I, Fukao A, et al. Physical status and dementia risk: a three-year prospective study in urban Japan. *The International journal of social psychiatry.* 1995;41(1):47-54.
35. Shah FA, Pike F, Alvarez K, et al. Bidirectional relationship between cognitive function and pneumonia. *American journal of respiratory and critical care medicine.* 2013;188(5):586-592.

36. Yeh JJ, Wei YF, Lin CL, Hsu WH. Effect of the asthma-chronic obstructive pulmonary disease syndrome on the stroke, Parkinson's disease, and dementia: a national cohort study. *Oncotarget.* 2018;9(15):12418-12431.
37. Xie F, Xie L. COPD and the risk of mild cognitive impairment and dementia: a cohort study based on the Chinese Longitudinal Health Longevity Survey. *International journal of chronic obstructive pulmonary disease.* 2019;14:403-408.
38. Chen MH, Li CT, Tsai CF, et al. Risk of dementia among patients with asthma: a nationwide longitudinal study. *Journal of the American Medical Directors Association.* 2014;15(10):763-767.
39. Peng YH, Wu BR, Su CH, et al. Adult asthma increases dementia risk: a nationwide cohort study. *Journal of epidemiology and community health.* 2015;69(2):123-128.
40. Eriksson UK, Gatz M, Dickman PW, Fratiglioni L, Pedersen NL. Asthma, eczema, rhinitis and the risk for dementia. *Dementia and geriatric cognitive disorders.* 2008;25(2):148-156.
41. Rusanen M, Ngandu T, Laatikainen T, Tuomilehto J, Soininen H, Kivipelto M. Chronic obstructive pulmonary disease and asthma and the risk of mild cognitive impairment and dementia: a population based CAIDE study. *Current Alzheimer research.* 2013;10(5):549-555.
42. Prince M, Albanese E, Guerchet M, Prina M. *World Alzheimer Report 2014, Dementia and Risk Reduction: An analysis of protective and modifiable factors* London: Alzheimer's Disease International; 2014.
43. Duggan EC, Graham RB, Piccinin AM, et al. A Systematic Review of Pulmonary Function and Cognition in Aging. *The Journals of Gerontology: Series B.* 2018:gby128-gby128.
44. Mokry LE, Ross S, Morris JA, Manousaki D, Forgetta V, Richards JB. Genetically decreased vitamin D and risk of Alzheimer disease. *Neurology.* 2016;87(24):2567-2574.
45. Maddock J, Zhou A, Cavadino A, et al. Vitamin D and cognitive function: A Mendelian randomisation study. *Scientific reports.* 2017;7(1):13230.
46. Kivimaki M, Luukkonen R, Batty GD, et al. Body mass index and risk of dementia: Analysis of individual-level data from 1.3 million individuals. *Alzheimers Dement.* 2018;14(5):601-609.
47. Kivimaki M, Singh-Manoux A, Pentti J, et al. Physical inactivity, cardiometabolic disease, and risk of dementia: an individual-participant meta-analysis. *BMJ (Clinical research ed.).* 2019;365:l1495.
48. Bermejo F, Gabriel R, Vega S, Morales JM, Rocca WA, Anderson DW. Problems and Issues with Door-To-Door, Two-Phase Surveys: An Illustration from Central Spain. *Neuroepidemiology.* 2001;20(4):225-231.
49. Russ TC, Gatz M, Pedersen NL, et al. Geographical variation in dementia: examining the role of environmental factors in Sweden and Scotland. *Epidemiology (Cambridge, Mass.).* 2015;26(2):263-270.
50. Russ TC, Batty GD, Starr JM. Cognitive and behavioural predictors of survival in Alzheimer disease: results from a sample of treated patients in a tertiary-referral memory clinic. *International Journal of Geriatric Psychiatry.* 2012;27(8):844-853.
51. Kivimäki M, Luukkonen R, Batty GD, et al. Body mass index and risk of dementia: Analysis of individual-level data from 1.3 million individuals. *Alzheimer's & dementia : the journal of the Alzheimer's Association.* 2018;14(5):601-609.
52. McGuinness B, Craig D, Bullock R, Passmore P. Statins for the prevention of dementia. *Cochrane Database of Systematic Reviews.* 2009;2:CD003160.
53. McGuinness B, Todd S, Passmore P, Bullock R. Blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairment and dementia. *Cochrane Database Syst Rev.* 2009;4:CD004034.

54. Kuh D, Ben-Shlomo Y, Lynch J, Hallqvist J, Power C. Life course epidemiology. *Journal of Epidemiology and Community Health.* 2003;57(10):778.
55. Ben-Shlomo Y, Mishra G, Kuh D. Life Course Epidemiology. In: Ahrens W, Pigeot I, eds. *Handbook of Epidemiology*: Springer New York; 2014:1521-1549.
56. Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. *International Journal of Epidemiology.* 2002;31(2):285-293.
57. Kuh D, Shlomo YB. *A life course approach to chronic disease epidemiology.* Oxford University Press; 2004.
58. Whalley LJ, Dick FD, McNeill G. A life-course approach to the aetiology of late-onset dementias. *Lancet Neurology.* 2006;5(1):87-96.
59. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia.* 2011;7(3):280-292.
60. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathologica.* 1991;82(4):239-259.
61. Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. *Neurobiology of Aging.* 1997;18(4):351-357.
62. Braak H, Thal DR, Ghebremedhin E, Del Tredici K. Stages of the Pathologic Process in Alzheimer Disease: Age Categories From 1 to 100 Years. *Journal of Neuropathology & Experimental Neurology.* 2011;70(11):960-969.
63. Jansen WJ, Ossenkoppele R, Knol DL, et al. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. *Jama.* 2015;313(19):1924-1938.
64. Whitmer R, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology.* 2005;64(2):277-281.
65. Daviglus ML, Bell CC, Berrettini W, et al. National Institutes of Health State-of-the-Science Conference statement: preventing Alzheimer disease and cognitive decline. *Ann Intern Med.* 2010;153(3):176-181.
66. Exalto LG, Quesenberry CP, Barnes D, Kivipelto M, Biessels GJ, Whitmer RA. Midlife risk score for the prediction of dementia four decades later. *Alzheimers Dement.* 2013;ePub.
67. Gottesman RF, Schneider AL, Albert M, et al. Midlife Hypertension and 20-Year Cognitive Change: The Atherosclerosis Risk in Communities Neurocognitive Study. *JAMA Neurology.* 2014;71(10):1218-1227.
68. Webber LS, Freedman DS, Cresanta JL. Tracking of cardiovascular disease risk factor variables in school-age children. In: Berenson GS, ed. *Causation of cardiovascular risk factors in children*. New York: Raven Press; 1986:42-64.
69. Strasser T. Prevention in childhood of major cardiovascular diseases of adults. In: Falkner F, ed. *Prevention in childhood of health problems in adult life*. Geneva: World Health Organisation; 1980.
70. Chen X, Wang Y. Tracking of blood pressure from childhood to adulthood a systematic review and meta–regression analysis. *Circulation.* 2008;117(25):3171-3180.
71. Nyberg J, Åberg MAI, Schiöler L, et al. Cardiovascular and cognitive fitness at age 18 and risk of early-onset dementia. *Brain.* 2014;137:1514-1523.
72. Batty GD, Galobardes B, Starr JM, Jeffreys M, Davey Smith G, Russ TC. Examining if being overweight really confers protection against dementia: Sixty-four year follow-up of participants in the Glasgow University alumni cohort study. *Journal of negative results in biomedicine.* 2016;15(1):19.
73. Beeri MS, Davidson M, Silverman JM, Noy S, Schmeidler J, Goldbourt U. Relationship between body height and dementia. *Am J Geriat Psychiat.* 2005;13(2):116-123.

74. Russ TC, Kivimäki M, Starr JM, Stamatakis E, Batty GD. Height in Relation to Dementia Death: Individual-participant Meta-analysis of Eighteen UK Prospective Cohort Studies. *British Journal of Psychiatry.* 2014;205:348-354.
75. Muller M, Sigurdsson S, Kjartansson O, et al. Birth size and brain function 75 years later. *Pediatrics.* 2014;134(4):761-770.
76. Cook DG, Strachan DP, Carey IM. Parental smoking and spirometric indices in children. *Thorax.* 1998;53(10):884-893.
77. Tennant PWG, Gibson GJ, Pearce MS. Lifecourse predictors of adult respiratory function: results from the Newcastle Thousand Families Study. *Thorax.* 2008;63(9):823-830.
78. Harmsen L, Ulrik CS, Porsbjerg C, Thomsen SF, Holst C, Backer V. Airway hyperresponsiveness and development of lung function in adolescence and adulthood. *Respiratory medicine.* 2014;108(5):752-757.
79. Bartley M, Kelly Y, Sacker A. Early life financial adversity and respiratory function in midlife: a prospective birth cohort study. *American journal of epidemiology.* 2012;175(1):33-42.
80. Mann SL, Wadsworth ME, Colley JR. Accumulation of factors influencing respiratory illness in members of a national birth cohort and their offspring. *Journal of Epidemiology and Community Health.* 1992;46(3):286-292.
81. Lawlor DA, Ebrahim S, Davey Smith G. Association between self-reported childhood socioeconomic position and adult lung function: findings from the British Women's Heart and Health Study. *Thorax.* 2004;59(3):199-203.
82. Tabak C, Spijkerman AMW, Verschuren WMM, Smit HA. Does educational level influence lung function decline (Doetinchem Cohort Study)? *European Respiratory Journal.* 2009;34(4):940-947.
83. Johannessen A, Eagan TML, Omenaas ER, Bakke PS, Gulsvik A. Socioeconomic risk factors for lung function decline in a general population. *European Respiratory Journal.* 2010;36(3):480-487.
84. Jackson B, Kubzansky LD, Cohen S, Weiss S, Wright RJ. A matter of life and breath: childhood socioeconomic status is related to young adult pulmonary function in the CARDIA study. *International Journal of Epidemiology.* 2004;33(2):271-278.
85. Ramsay SE, Whincup PH, Lennon LT, Morris RW, Wannamethee SG. Longitudinal associations of socioeconomic position in childhood and adulthood with decline in lung function over 20 years: results from a population-based cohort of British men. *Thorax.* 2011;66(12):1058-1064.
86. Gauderman WJ, Vora H, McConnell R, et al. Effect of exposure to traffic on lung development from 10 to 18 years of age: a cohort study. *Lancet (London, England).*369(9561):571-577.
87. Götschi T, Heinrich J, Sunyer J, Künzli N. Long-Term Effects of Ambient Air Pollution on Lung Function: A Review. *Epidemiology (Cambridge, Mass.).* 2008;19(5):690-701 610.1097/EDE.1090b1013e318181650f.
88. Schmidt R, Schmidt H, Curb JD, Masaki K, White LR, Launer LJ. Early inflammation and dementia: A 25-year follow-up of the Honolulu-Asia aging study. *Annals of Neurology.* 2002;52(2):168-174.
89. Sin DD, Wu LL, Man SFP. The Relationship Between Reduced Lung Function and Cardiovascular Mortality: A Population-Based Study and a Systematic Review of the Literature. *Chest.* 2005;127(6):1952-1959.
90. Stephan BC, Brayne C. Vascular factors and prevention of dementia. *International Review of Psychiatry.* 2008;20(4):344-356.

91. Winblad B, Amouyel P, Andrieu S, et al. Defeating Alzheimer's disease and other dementias: a priority for European science and society. *The Lancet Neurology.* 2016;15(5):455-532.
92. Sweeney MD, Zhao Z, Montagne A, Nelson AR, Zlokovic BV. Blood-Brain Barrier: From Physiology to Disease and Back. *Physiological Reviews.* 2019;99(1):21-78.
93. Tonnies E, Trushina E. Oxidative Stress, Synaptic Dysfunction, and Alzheimer's Disease. *J Alzheimers Dis.* 2017;57(4):1105-1121.
94. Love S. Oxidative Stress in Brain Ischemia. *Brain Pathology.* 1999;9(1):119-131.
95. Jofre-Monseny L, Minihane AM, Rimbach G. Impact of apoE genotype on oxidative stress, inflammation and disease risk. *Molecular nutrition & food research.* 2008;52(1):131-145.
96. Guo L, LaDu MJ, Van Eldik LJ. A dual role for apolipoprotein E in neuroinflammation. *Journal of Molecular Neuroscience.* 2004;23(3):205-212.
97. Hatanpaa KJ, Raisanen JM, Herndon E, et al. Hippocampal sclerosis in dementia, epilepsy, and ischemic injury: differential vulnerability of hippocampal subfields. *Journal of Neuropathology and Experimental Neurology.* 2014;73(2):136-142.
98. Kitamura A, Saito S, Maki T, et al. Gradual cerebral hypoperfusion in spontaneously hypertensive rats induces slowly evolving white matter abnormalities and impairs working memory. *Journal of Cerebral Blood Flow & Metabolism.* 2016;36(9):1592-1602.
99. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS medicine.* 2015;12(3):e1001779.
100. Ritchie CW, Molinuevo JL, Truyen L, et al. Development of interventions for the secondary prevention of Alzheimer's dementia: the European Prevention of Alzheimer's Dementia (EPAD) project. *Lancet Psychiatry.* 2015;3(2):179-186.
101. Kaffashian S, Dugravot A, Nabi H, et al. Predictive utility of the Framingham general cardiovascular disease risk profile for cognitive function: evidence from the Whitehall II study. *European Heart Journal.* 2011:ehr133.
102. Kaffashian S, Dugravot A, Elbaz A, et al. Predicting cognitive decline A dementia risk score vs the Framingham vascular risk scores. *Neurology.* 2013;80(14):1300-1306.
103. Russ TC, Hamer M, Stamatakis E, Starr JM, Batty GD, Kivimaki M. Does the Framingham cardiovascular disease risk score also have predictive utility for dementia death? An individual participant meta-analysis of 11,887 men and women. *Atherosclerosis.* 2013;228(1):256-258.
104. Batty GD, Shipley MJ, Kivimaki M, Smith GD, West R. Impact of smoking cessation advice on future smoking behavior, morbidity, and mortality: up to 40 years of follow-up of the first randomized controlled trial of a general population sample. *Archives of internal medicine.* 2011;171(21):1950-1951.
105. Smith GD, Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol.* 2003;32(1):1-22.
106. Au Yeung SL, Borges MC, Lawlor DA. Association of Genetic Instrumental Variables for Lung Function on Coronary Artery Disease Risk: A 2-Sample Mendelian Randomization Study. *Circulation. Genomic and precision medicine.* 2018;11(4):e001952.
107. Simons LA, McCallum J, Friedlander Y, Simons J, Powell I, Heller R. Dubbo study of the elderly: sociological and cardiovascular risk factors at entry. *Australian and New Zealand journal of medicine.* 1991;21(5):701-709.

Figure 1. PubMed publication counts for pulmonary function and dementia , 1969-2018

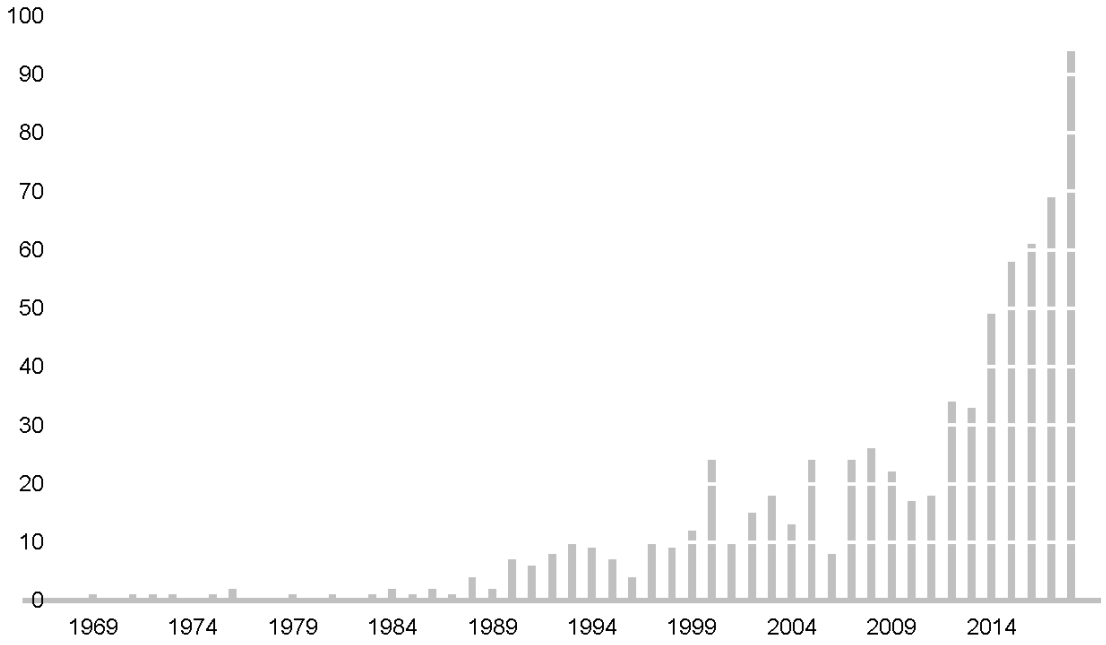


Figure 2. PRISMA flowchart

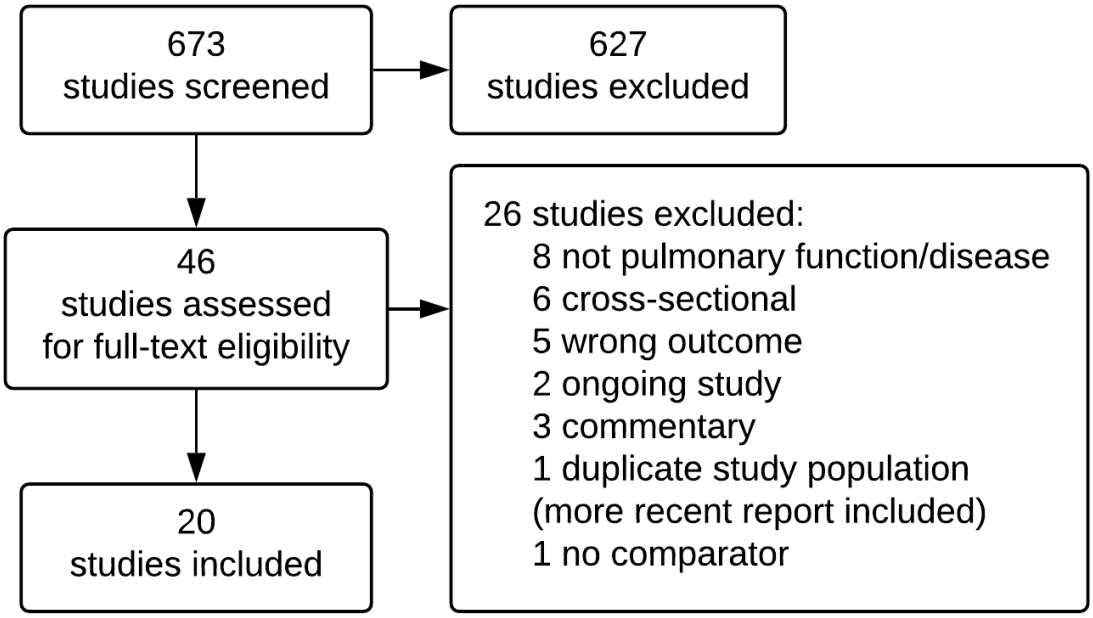


Figure 3. The relation of forced expiratory volume and respiratory illness with dementia — meta-analysed results

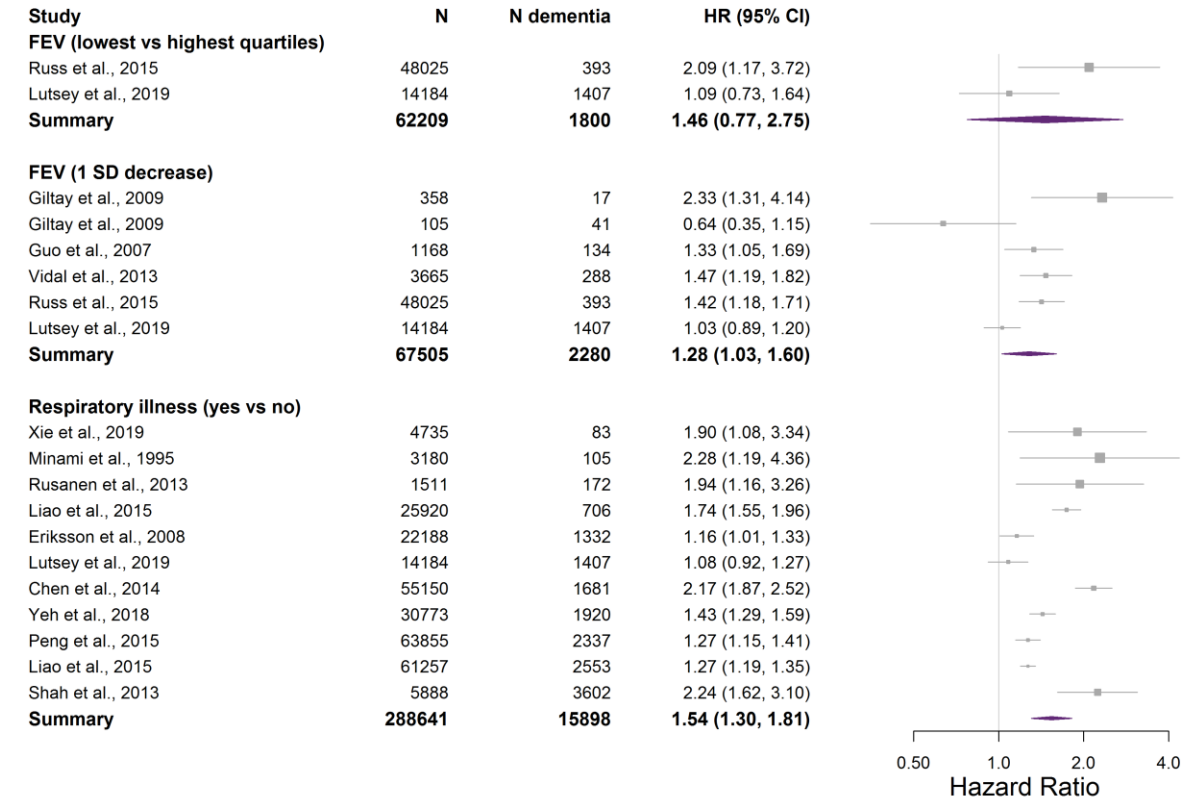


Figure 4. Comparison of meta-analytic findings with other potential risk factors for dementia in the World Alzheimer Report 2014[42] and Lancet Commission on dementia prevention, intervention, and care[7]

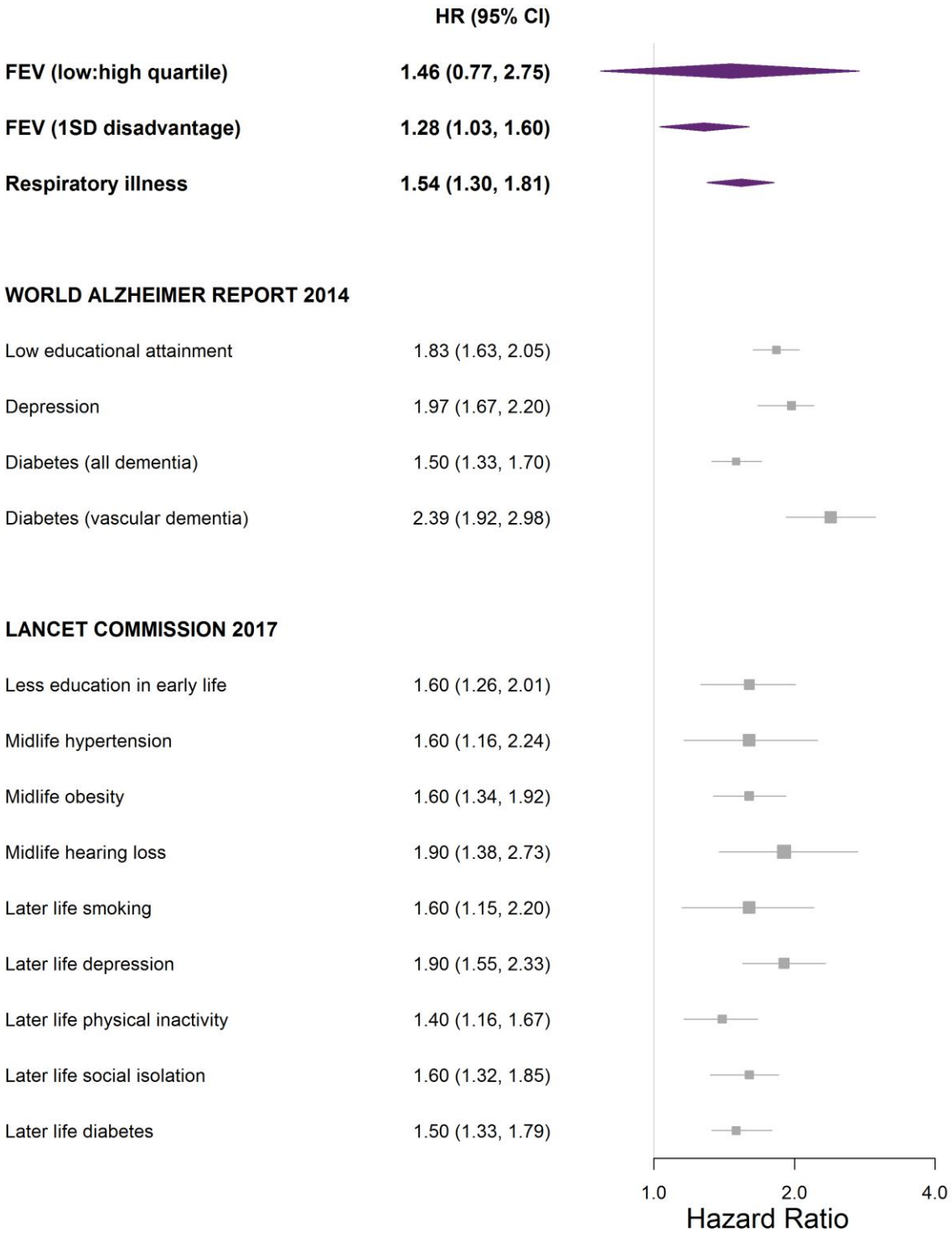


Figure 5. Conceptual model of proposed potential relationships between impaired pulmonary function and dementia

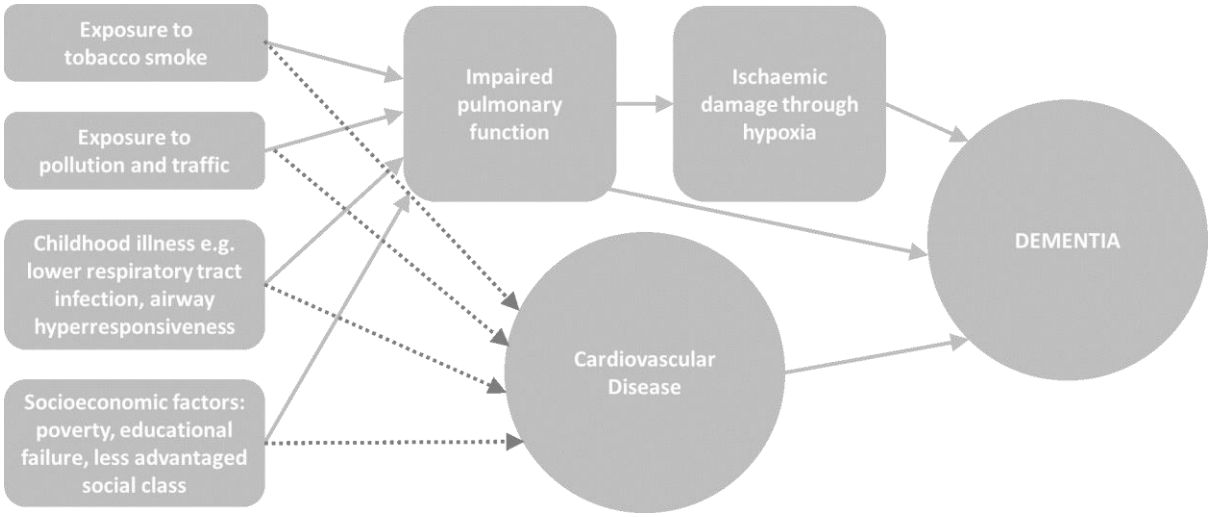


Table 1. Summary of longitudinal studies of the association between pulmonary function and dementia

Study	Number of participants	Number of dementia cases	Measurement of pulmonary function	Pulmonary function *Mean (SD)*	Age at which pulmonary function was measured *Mean (SD) [Range]*	Covariables included in most-adjusted model	Follow up	Findings	Risk of Bias
Lutsey et al. (2018)[26]	14,184 (5889 assessed clinically) male and female participants in the Atherosclerosis Risk in Communities (ARIC) study	1407 people developed dementia, identified by clinical assessment (N=298) and diagnostic codes recorded on hospitalisation.	FEV_1 and FVC expressed as a percentage of age-, race-, and sex-specific predicted values	FEV_1 2.82 (0.77) or 93.5% (17.0) of predicted FVC 3.80 (0.99) or 98.1% (14.6) of predicted	54.2 (5.8) [45-64]	Age, sex, study centre, education level, and race-centre, cigarette smoking and pack-years smoking, physical activity, BMI, systolic blood pressure, blood pressure medication use, diabetes, HDL cholesterol, LDL cholesterol, lipid-lowering medications, prevalent CHD, heart failure, stroke, *APOE* genotype, and fibrinogen	Median 23.0 years Max. 27.1 years	N=14,184: Maximally-adjusted OR Q_1 FEV_1 (low) vs Q_4 (high) 1.09 (95% CI 0.73, 1.65), Q_2 0.77 (0.50, 1.18), Q_3 0.90 (0.61, 1.33). OR per SD change in FEV_1 1.03 (0.89, 1.20). N=5889: Weighted, maximally-adjusted HR Q_1 FEV_1 (low) vs Q5 (high) 1.11 (0.93, 1.32). OR per SD change in FEV_1 1.05 (0.98, 1.11) Results for FVC in both sets of analyses were similar.	Low
Gilsanz et al. (2018)[25]	27,387 men and women who were members of Kaiser Permanente Northern California	7519 dementia diagnoses ascertained from inpatient and outpatient electronic medical records	FEV_1, FEV_2, and VC	FEV_1 2.7 (0.8) FEV_2 3.3 (1.0) VC 3.5 (1.0)	41.8 (4.2) [35-50]	Age, race/ethnicity, education, height, midlife health indicator (hypertension, BMI, smoking status) and late-life health indicator (stroke, diabetes, heart failure)	28+ years	Multivariable adjusted HR per litre decrease in FEV_1 1.13 (95% CI 1.09, 1.18). Dose response association observed – worst FEV_1 quintile compared to best HR 1.24 (95% CI 1.14, 1.34). Results for FEV_2 and VC similar, as were results stratified by smoking status.	Mod.
Sibbett et al. (2018)[30]	484 men and women born in 1921 forming the Lothian Birth Cohort 1921	106 diagnoses of dementia obtained from clinical reviews, death certificates, and electronic medical records and adjudicated by a clinical panel	FEV_1	1.95 (0.59) in people with dementia 1.84 (0.62) in those without	79.04 (0.55) [Narrow age cohort]	Age, sex, height, *APOE* genotype, age 11 IQ, history of hypertension, ever smoking, 6m walk time, grip strength, history of cardiovascular or cerebrovascular disease or diabetes	16 years	FEV_1 measured at age 79 years was not associated with developing dementia (multivariable-adjusted HR per L/s lower FEV_1 1.30, 95% CI 0.74, 2.30)	Low
Russ et al. (2015)[16]	54,671 men and women from six UK cohort studies	459 dementia deaths identified from death certificates	FEV_1, FVC and PEF	Cut-offs for FEV_1 quartiles were 1.36, 1.81, and 2.35L	46.8 (17.6) [16-100]	Age, sex, height, ethnicity, socioeconomic status (occupational social class and educational attainment), health behaviours (smoking, alcohol consumption, and BMI), and illness (self-rated general health and self-reported longstanding illness).	Mean (SD) 11.7 (3.7) years	There was a dose-response association between poorer lung function and a higher risk of dementia-related death. Controlling for height, socioeconomic status, smoking, and general health attenuated but did not remove the association (multivariable-adjusted HR compared to highest quartile of FEV_1, 95% CI: second quartile 1.15, 0.82-1.62; third quartile 1.37, 0.96-1.94; fourth quartile 2.09, 1.17-3.71).	Mod.
Alonso et al. (2009)[23]	10,211 men from 13 cohort studies of the Seven Countries Study (Finland, Greece, Italy, the Netherlands, Serbia and Croatia [formerly Yugoslavia], Japan and the USA) aged 40-59 at baseline	160 dementia deaths identified from death certificates (up to four codes were examined)	FVC (categorised into quartiles because of measurement differences between studies)	4.8 (0.8)	49.2 (5.6) [40-59]	Age, study, cohort, occupation, height, smoking status, BMI, serum cholesterol, hypertension, and previous history of cardiovascular disease.	40 years	Participants with poorer FVC (lowest quartile vs highest quartile) were at a lower risk of dementia death (0.54, 0.30-0.98) but there was no evidence of a dose-response association (P_{trend}=0.28)	Mod.

Newman et al. (2009)[29]	6575 men and women aged ≥65 years at baseline in the Cardiovascular Health Cohort Study.	392 dementia deaths identified from death certificates	FVC	2.9 (0.9)	72.8 (5.6) [65+]	Age, sex, weight, smoking status (pack-years), physical activity, self-rated health, history of congestive heart failure or CHD at baseline, carotid stenosis, ankle-arm index, systolic blood pressure, using diuretics, fasting glucose, serum albumin and creatinine, CRP, *APOE* genotype, IL-6, IADL impairment, and DSST score	Average 13 or 16 years for two waves of recruitment	Increasing FVC was associated with a lower risk of dementia death compared to the lowest group (<2.06L): 2.06-2.54L HR, 95% CI 0.92, 0.67-1.28; 2.54-3L 0.98, 0.69-1.40; 3-3.6L 0.79, 0.52-1.20; >3.6L 0.71, 0.44-1.15.	Mod.
Giltay et al. (2009)[27]	646 men from three cohorts of the Seven Countries Study, aged 45-64, from Finland and Italy	159 with questionable-to-mild dementia and 24 with moderate-to-severe dementia, based on the CDR for those who scored <27 on the MMSE	$FEV_{0.75}$ and FVC	$FEV_{0.75}$ ε4- 3.1 (95% CI 3.1-3.2) ε4+ 3.1 (3.0-3.1) FVC ε4- 4.6 (4.6-4.7) ε4+ 4.5 (4.4-4.7)	ε4- 50.9 (4.4) ε4+ 51.4 (4.6) [45-64]	Country, age, chronic disease including COPD at baseline, socioeconomic status, job-related physical activity, marital status, smoking status, BMI, height, systolic blood pressure, and prevalent chronic disease at follow up (as a time-dependent variable).	25 years	Increasing pulmonary function was associated with a decreased risk of dementia both in *APOE* ε4 non-carriers (OR moderate-to-severe dementia, 95% CI 0.43, 0.24–0.76 [$FEV_{0.75}$]; 0.59, 0.32–1.08 [FVC]) but an increased risk of dementia in *APOE* ε4 carriers (OR questionable-to-severe dementia, 95% CI 1.57, 0.87–2.85 [$FEV_{0.75}$]; 1.59, 0.91–2.77 [FVC]; $P_{interaction}<0.05$)	Mod.
Vidal et al. (2013)[24]	3665 men and women from the AGES-RS, born between1907 and 1935 (mean [SD] age 52.3 [5.3] at baseline)	288 cases of dementia based on cognitive screening, neuropsychological testing, informant interview, and neurological assessment. 128 people were identified to have mild cognitive impairment	$FEV_1/height^2$	Q1 0.77 (0.12) Q2 0.95 (0.09) Q3 1.07 (0.09) Q4 1.24 (0.12)	Q_1 54.2 (5.6) Q_4 49.7 (5.2) [<70]	Age, sex, higher education, occupation class, midlife BMI and physical activity, depressive symptoms, COPD, CHD, hypertension, diabetes mellitus, and smoking habits.	23 years	Increasing pulmonary function was associated with a decreased risk of dementia (OR per SD increase in $FEV_1/height^2$, 95% CI 0.68, 0.55-0.84)	Low
Simons et al. (2006)[28]	2805 men and women aged ≥60 and living in the community in New South Wales, Australia	285 hospital admissions where dementia was recorded	PEF	Men 440 (120) Women 332 (83)s[107]	Women 69.6 (7.3) Men 68.6 (6.7) [60+]	Age, alcohol intake, gardeining, walking, depression, marital status, education, prior history of stroke, and activities of daily living.	16 years	Decreasing PEF was associated with an increased risk of dementia (tertile 2 vs 3 [highest] HR, 95% CI 1.58, 1.13-2.21; 1 [lowest] vs 3 1.98, 1.42-2.75).	Mod.
Guo et al. (2007)[22]	1291 women, born in 1908, 1914, 1918, 1922, or 1930, participating in the Prospective Population Study of Women in Gothenburg (Sweden) followed from 1974 to 2003	147 dementia cases (96 AD) diagnosed clinically by neuropsychiatric examination and informant interview	PEF (in 1974-5), FEV_1 and FVC (in 1980-1)	PEF 402 (79) FVC 3.2 (0.6) FEV_1 2.5 (0.5)	52 (6) [PEF 44-66 FVC/FEV_1 50-72]	Age, height, BMI, education, physical activity, smoking, asthma, chronic bronchitis, myocardial infarction, angina pectoris, and hypertension at baseline.	29,739 person-years	There was an association between better pulmonary function and a lower risk of dementia (HR per SD increase [advantage] in PEF, 95% CI 0.77, 0.65-91; FEV_1 0.75, 0.59-0.95; FVC 0.72, 0.57-0.92). Similar patterns were observed for AD	Low

AD = Alzheimer's disease; AGES-RS = Age, Gene/Environment Susceptibility – Rekyavik Study; *APOE* = Apolipoprotein E genotype; BMI = body mass index; CHD = coronary heart disease; CI = confidence interval; CRP = C-reactive protein; DSST = digit-symbol substitution test; FEV = Forced Expiratory Volume in a specified period; (F)VC = (Forced) Vital Capacity; HR = hazard ratio; IADL = instrumental activities of daily living; IL = interleukin; IQ = intelligence quotient; MCI = mild cognitive impairment; OR = odds ratio; PEF = Peak Expiratory Flow; SD = standard deviation

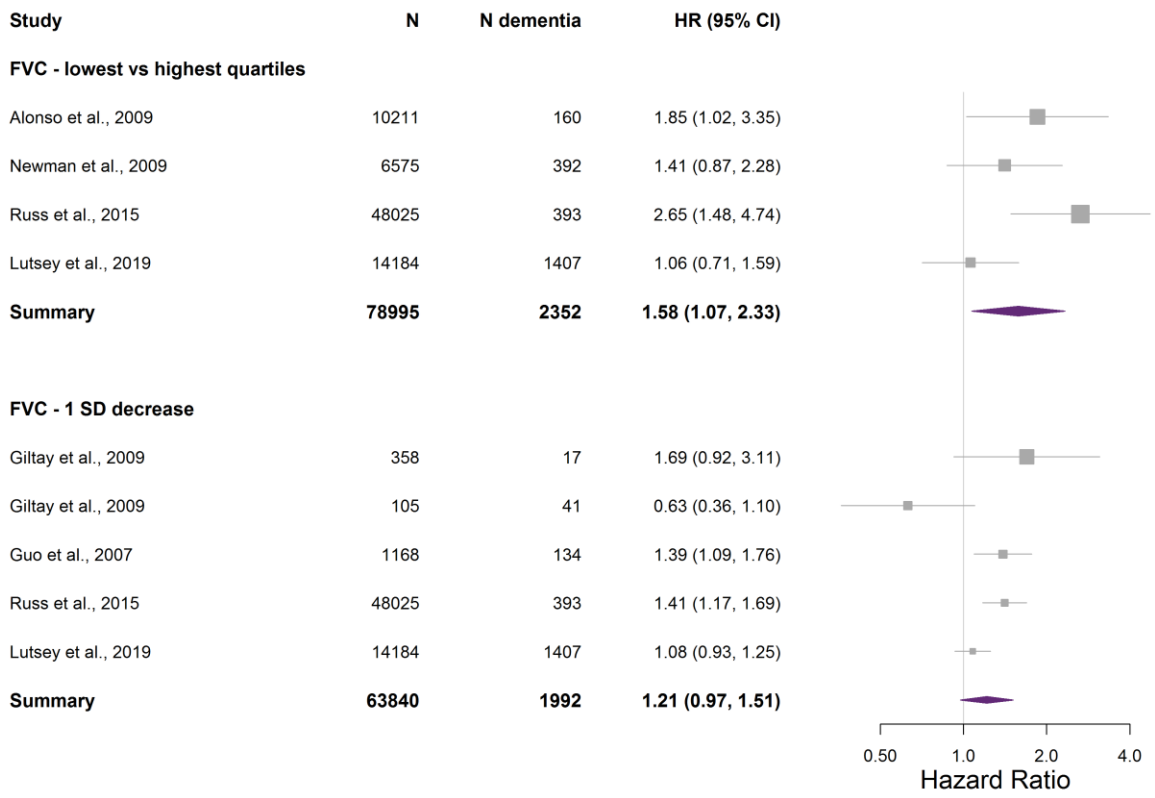
Table 2. Summary of longitudinal studies of the association between respiratory disease and dementia

Study	Number of participants	Number of dementia cases	Respiratory disease	Age at which disease ascertained *Mean (SD) [Range]*	Covariables included in most-adjusted model	Follow up	Findings	Risk of Bias
Xie et al. (2019)[37]	4735 participants in the Chinese Longitudinal Health Longevity Survey (CLHLS)	83 people were newly identified as having dementia, presumably based on MMSE score	Self-reported COPD diagnosis	82.9 (9.74)	Age, gender, marital status, education level, alcohol drinking, current exercise, baseline BMI, smoking status, baseline hypertension, diabetes, and stroke	3 years	Maximally-adjusted HR COPD vs no COPD 1.90 (1.08–3.33). In current smokers, the same HR was 3.38 (1.09–10.5).	High
Lutsey et al. (2018)[26]	14,184 (5889 assessed clinically) male and female participants in the Atherosclerosis Risk in Communities (ARIC) study	1407 people developed dementia, identified by clinical assessment (N=298) and diagnostic codes recorded on hospitalisation.	Participants were divided into four groups based on self-reported information and spirometry: normal, respiratory symptoms with normal spirometry, restrictive impairment pattern, and COPD	54.2 (5.8) [45-64]	Age, sex, study centre, education level, and race-centre, cigarette smoking and pack-years smoking, physical activity, BMI, systolic blood pressure, blood pressure medication use, diabetes, HDL cholesterol, LDL cholesterol, lipid-lowering medications, prevalent CHD, heart failure, stroke, *APOE* genotype, and fibrinogen	Median 23.0 years Max. 27.1 years	N=14,184: Maximally-adjusted HR COPD vs normal 1.08 (95% CI 0.92, 1.27) N=5889: Weighted, maximally-adjusted OR COPD vs normal 1.16 (95% CI 0.74, 1.82)	Low
Yeh et al. (2018)[36]	30,773 men and women from the Taiwanese National Health Insurance Research Database	1920 diagnoses of dementia	>2 clinical contacts recording asthma-COPD	Asthma-COPD 65.6 (11.8) No illness 65.5 (11.9)	Age, sex, comorbidity, inhaled corticosteroids, and oral steroids	10 years	Asthma-COPD was associated with an increased risk of subsequent dementia (multivariable-adjusted HR 1.43, 95% CI 1.29, 1.59	Mod.
Peng et al. (2015)[39]	12,771 people with asthma and 51,084 matched controls.	2337 individuals identified from the Taiwan National Health Insurance database.	New diagnoses of asthma recorded on the National Health Insurance database.	Asthma 53.8 (17.3) No illness 53.7 (17.4)	Age, sex, atrial fibrillation, hypertension, hyperlipidaemia, diabetes, heart failure, stroke, head injury, annual outpatient visits, and inhaled corticosteroids used	11 years	Asthma was associated with an increased risk of dementia (adjusted HR, 95% CI 1.27, 1.15-1.41).	Mod.
Liao et al. (2015)[33]	20,492 men and women with COPD and 40,765 matched controls.	2553 individuals identified from the Taiwan National Health Insurance database.	New diagnoses of COPD recorded on the National Health Insurance database.	COPD 67.0 (12.5) No illness 68.2 (12.4)	Age, sex, urbanization, and comorbidities	Mean (SD) 6.3 (3.5) years for cases, 6.9 (3.4) for controls	COPD was associated with an increased risk of dementia (adjusted HR, 95% CI 1.27, 1.20-1.36).	Mod.
Chen et al. (2014)[38]	11,030 adults aged >45 years with asthma and 44,120 age- and sex-matched controls.	1681 individuals identified from the Taiwan National Health Insurance database.	Asthma recorded on the National Health Insurance database.	60.88 (10.39)	Demographic data, health system utilization, medical comorbidities, and use of inhaled steroid and asthma as a binary variable	8.0±3.0 years	Having asthma was associated with a doubling of risk of developing dementia (adjusted HR, 95% CI 2.17, 1.87-2.52).	Mod.
Liao et al. (2015)[32]	8640 men and women ≥40 years hospitalized with COPD and 17,280 age-, sex-, and admission year-matched controls.	706 individuals with AD or Parkinson's disease identified from the Taiwan National Health Insurance database.	COPD recorded on the National Health Insurance database.	68.76 (10.74)	Age, gender, urbanization, coronary artery disease, stroke, hyperlipidemia, hypertension, diabetes, and head injury	Not stated	COPD was associated with an increased risk of dementia (adjusted HR, 95% CI 1.74, 1.55-1.96).	Mod.
Eriksson et al. (2008)[40]	22,188 twins in the population-based Swedish Twin Registry	1332 twins had a record of dementia from hospital discharge and death certificate data.	History of atopy (asthma, eczema, or rhinitis)	52.9 [37-71]	Age, sex, history of smoking, level of education, and myocardial infarction	22.6±7.7 years	History of atopy was associated with a modest increased risk of AD (HR, 95% CI 1.16, 0.98-1.37) or dementia (1.16, 1.01-1.33).	Mod.
Shah et al. (2013)[35]	5888 participants in the Cardiovascular Health Study	3602 identified by two-phase screening, including clinical assessment	Hospitalisation with pneumonia	72.8 (5.6)	Demographics, income, educational status, health behaviors (smoking history, alcohol use, and blocks walked per week), lung (percent predicted FEV1) and kidney function (estimated glomerular filtration rate), history of hypertension, atrial fibrillation, stroke, coronary heart disease, congestive heart failure, and diabetes.	10 years	Pneumonia was associated with an increased risk of later dementia (HR, 95% CI 2.24, 1.62-3.11).	Low

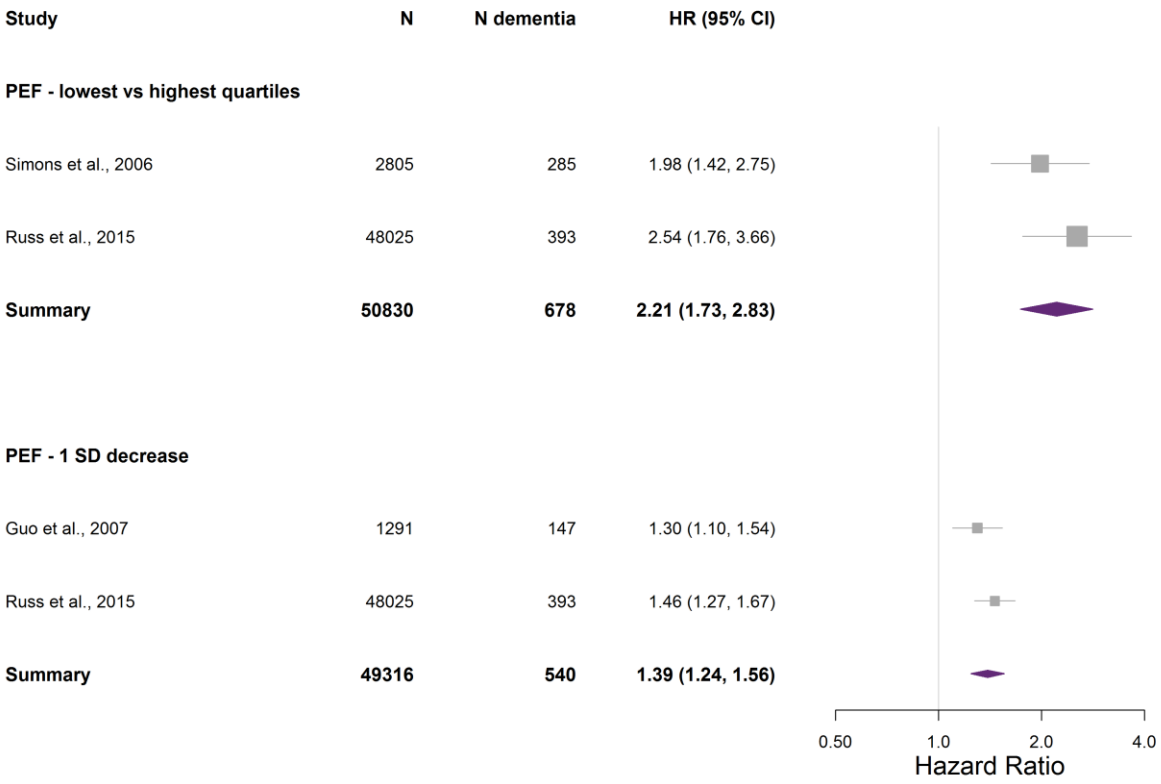
Minami et al. (1995)[34]	3180 people without dementia in Sendai, Japan, of whom 2461 were followed up.	105 individuals were clinically diagnosed with dementia at follow up.	Self-reported respiratory disease.	≥65 years	Sex and age-group	3 years	Respiratory disease was associated with a doubling of risk of dementia (adjusted OR, 95% CI 2.28, 1.19-4.36)	Mod.
Rusanen et al. (2013)[41]	1511 male and female participants, aged 39.2-64.1 years at baseline, followed up at either of two points (1998 and/or 2005-8) from a random sample of 2000 (at baseline: 1972, 1977, 1982 or 1987) from four cohort studies in Eastern Finland	172 identified by screening and, for those screening positive, clinical examination	Self-reported diagnosis of COPD or asthma	50.6 (6.0) [39.2-64.1]	Age, sex, education, midlife smoking, *APOE* genotype, midlife physical activity, systolic blood pressure, BMI, total serum cholesterol, and late-life vascular disease.	Mean (SD) 25.5 (6.2) years	Pulmonary disease at baseline was associated with an increased risk of later dementia (HR, 95% CI 1.94, 1.16-3.27). Pulmonary disease in 1998 was associated with a decreased risk of dementia in 2005-8 (0.42, 0.19-0.93).	Mod.

AD = Alzheimer's disease; CI = confidence interval; COPD = Chronic Obstructive Pulmonary Disease; HR = hazard ratio; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; SD = standard deviation

Supplementary Figure 1. The association between Forced Vital Capacity – lowest quartile compared to highest quartile and one standard deviation decrease – and dementia with meta-analysed results

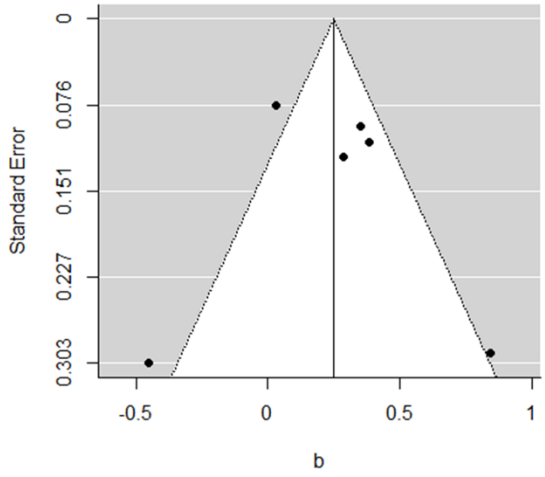


Supplementary Figure 2. The association between Peak Expiratory Flow – lowest quartile compared to highest quartile and one standard deviation decrease – and dementia with meta-analysed results

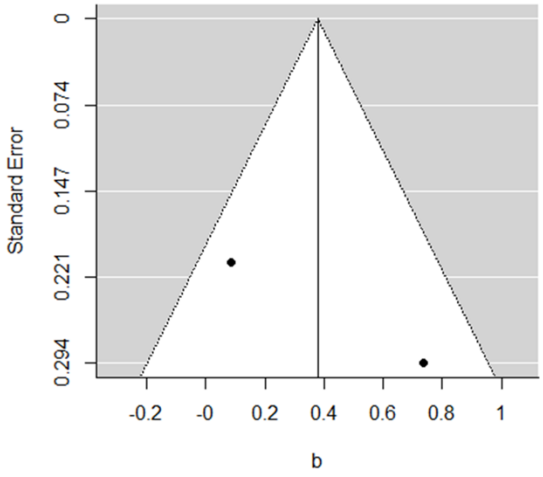


Supplementary Figure 3. Egger plots to explore publication bias with regression test for asymmetry, where it is possible to calculate

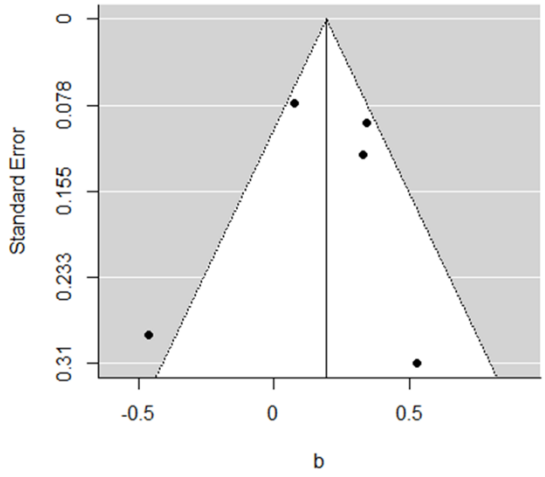
FEV (1 SD change) – p=0.92



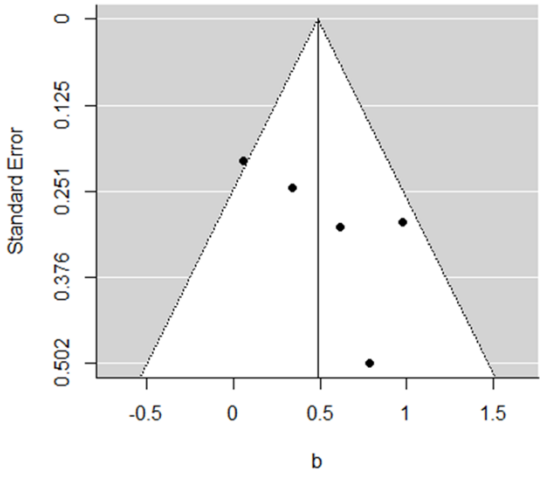
FEV (lowest:highest quartiles)



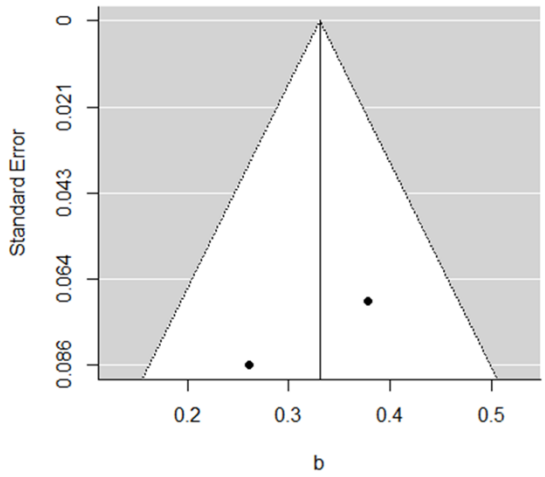
FVC (1 SD change) – p=0.62



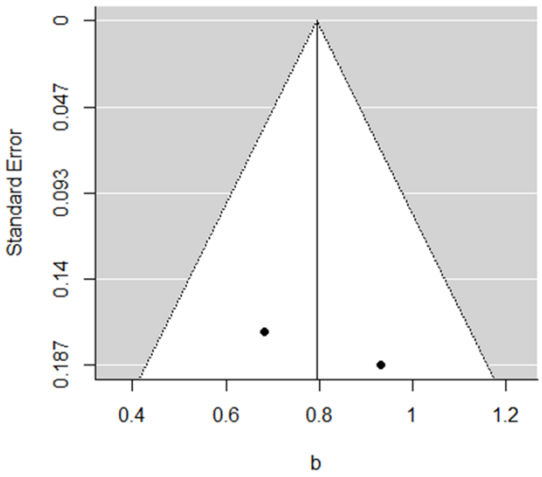
FVC (lowest:highest quartiles) – p=0.067



PEF (1 SD change)



PEF (lowest:highest quartiles)



Illness vs no illness – p=0.050