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

Short title: Pulmonary function and dementia

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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 (FEV₁) compared with the highest was associated with a 1.4-fold (1.46, 95% CI 0.77-2.75) increased dementia risk (N\text{total}=62,209, two studies). An decrease of one standard deviation in FEV₁ was associated with a 28% increase in dementia risk (1.28, 95% CI 1.03-1.60; N\text{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\text{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.\textsuperscript{1} While the age-standardised prevalence and incidence of dementia may be declining,\textsuperscript{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.\textsuperscript{5}

The disappointing results from trials evaluating treatment modalities for dementia\textsuperscript{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.\textsuperscript{7-15} Pulmonary function and respiratory disease have also been advanced as risk markers for dementia.\textsuperscript{16} Mechanisms of effect include diminished supply of oxygen to the brain, resulting in low level but sustained hypoxia,\textsuperscript{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,\textsuperscript{18-20} all of which have been linked with dementia in their own right.\textsuperscript{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, 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 (FEV1);
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\textsuperscript{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,\textsuperscript{16,23,29,30} linkage to electronic medical records (e.g., hospital discharge records),\textsuperscript{25,26,28,30,31} and clinical assessment.\textsuperscript{22,24,26,27,30} A number of these studies were originally instigated to investigate risk factors for cardiovascular disease\textsuperscript{23,26,27,29} or the menopause\textsuperscript{22} and then repurposed to include dementia follow-up as study participants aged; only two were specifically set up to investigate diseases of ageing.\textsuperscript{24,30} Duration of follow-up ranged from 12 to 40 years.\textsuperscript{16,21} 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\textsubscript{1} with the highest quartile;\textsuperscript{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\textsuperscript{2}=69.3\%). Pooling the five studies which reported the effect of one standard deviation decrease (disadvantage) in FEV\textsubscript{1} resulted in a HR of 1.28 (1.03-1.60; P=0.028; I\textsuperscript{2}=78.2\%; N=67,505, 2280 dementia cases). One of these studies standardised FEV\textsubscript{1} by dividing by height\textsuperscript{24} but a sensitivity analysis excluding this transformation gave a similar pooled result (1.24, 0.92-1.68).\textsuperscript{16,22,26,27} A further sensitivity analysis using data only from the three studies deemed to have a low risk of bias\textsuperscript{22,24,26} resulted in a similar pooled result (1.25, 1.00-1.56).\textsuperscript{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; I²=57.6%; four studies, N=78,995, 2352 dementia cases);\textsuperscript{16,23,26,29} per
standard deviation disadvantage 1.21 (0.97-1.51; P=0.086; I²=70.7%; four studies, N=63,840,
1992 dementia cases).\textsuperscript{16,22,26,27} One study included in the latter meta-analysis reported an
interaction between \textit{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 I²=65.1%.\textsuperscript{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;
I²=0.0%; N=50,830, 678 dementia cases);\textsuperscript{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; I²=10.6%; N=49,316, 540 dementia cases).\textsuperscript{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\textsubscript{1} (plus
FEV\textsubscript{2} and VC) was associated with an increased risk of dementia (multivariable-adjusted HR per
litre decrease in FEV\textsubscript{1}; 1.13, 95% CI 1.09-1.18).\textsuperscript{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).\textsuperscript{21} 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.\textsuperscript{30} No robust evidence was found to suggest
that FEV₁ 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,⁵⁵ 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 assessment 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; I²=92.4%). Although the study-specific estimates were heterogeneous, they all favoured risk factor status. Excluding a study which investigated the association between atopic illnesses⁴⁰ (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 (I²=78.2%) but did not alter our conclusion. A sensitivity analysis excluding the
one study assessed as having a high risk of bias\textsuperscript{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\textsuperscript{36,38} (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.

**Compaision 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\textsuperscript{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).\textsuperscript{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,\textsuperscript{41} 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, alternately, it may
reflect different mechanisms of cognitive performance and neurological pathology underlying dementia as seems to be the case with other risk factors, such as vitamin D levels.\textsuperscript{44,45}

**Review limitations and strengths**

The comprehensive search strategy used is likely to have identified practically all relevant published studies. The inclusion of only longitudinal studies would seemingly strengthen the robustness of our conclusions since, while such studies still only describe associations, the temporal association between exposure and outcome is clearer than in case-control and cross-sectional studies for instance. This notwithstanding, we cannot completely rule out reverse causality; that is, the extended prodromal phase for dementia may have led to the outcome influencing the two exposures, particularly in those studies which shorter duration of follow-up. This has been demonstrated in other contexts; for instance, both body mass index and physical activity in the aetiology of dementia.\textsuperscript{46,47} The pooling of results, where possible, in random effects meta-analyses provides a quantitative summary of the evidence that has more utility than a narrative overview of results from individual studies.

There are several limitations to our work. Any review of scientific evidence is only as strong as the studies on which it draws. The substantial statistical heterogeneity between studies is matched by methodological heterogeneity and – importantly – variation in the specific measure of pulmonary function used, though the correlation between different measures of pulmonary function – FEV, FVC, and PEF – in population-based studies is typically high.\textsuperscript{16} The respiratory illnesses considered were varied and may have exerted different impacts on dementia risk. It may be that, for instance, chronic exposure, characterised by conditions such as chronic obstructive pulmonary disorder, would be more strongly related to dementia than the more acute 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≥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. 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. 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. 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.

Plausible mechanisms

A number of lines of research, in combination with the disappointing results from preventive
interventions of dementia implemented at older ages, provide circumstantial support for
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. 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. 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 clinical dementia. Fourth, although not a universal finding, there is some evidence from prospective cohort studies that cardiovascular disease risk factors measured in midlife are associated with later dementia risk. 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. That cardiovascular disease risk factors ‘track’ from early life into adulthood – for example, there is a correlation between blood pressure measured in childhood and again later life – 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, though a similar association was not observed between cardiovascular disease risk factors and late-onset dementia mortality elsewhere.

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. 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. 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. 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); illness, such as childhood lower respiratory tract infections and airway hyperresponsiveness; socioeconomic factors (poverty, educational failure, and less-advantaged social class; environmental factors affecting lung function, such as atmospheric pollution and local exposure to traffic.

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. It has been hypothesised that oxidative stress, inflammation, and amyloid deposition may link these two important conditions. In particular, oxidative stress and synaptic dysfunction appear to be closely linked and brain ischaemia – which could result from cerebral atherosclerosis and stroke – leading to oxidative stress-mediated damage.
may possibly be exacerbated by the pro-inflammatory function of APOE, but this effect is controversial.

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, 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. Future analyses of magnetic resonance imaging in large prospective cohort studies, such as UK Biobank or the European Prevention of Alzheimer’s Disease (EPAD) Longitudinal Cohort Study 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.

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 an age-dependent association with stronger links seen for midlife than old age respiratory function and respiratory disease. 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\textsuperscript{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\textsuperscript{101} and decline,\textsuperscript{102} although there is less evidence for prediction of dementia.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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


Figure 1. PubMed publication counts for pulmonary function and dementia, 1969-2018
Figure 2. PRISMA flowchart

673 studies screened

46 studies assessed for full-text eligibility

20 studies included

627 studies excluded

26 studies excluded:
- 8 not pulmonary function/disease
- 6 cross-sectional
- 5 wrong outcome
- 2 ongoing study
- 3 commentary
- 1 duplicate study population
- (more recent report included)
- 1 no comparator
Figure 3. The relation of forced expiratory volume and respiratory illness with dementia — meta-analysed results

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<td>Yeh et al., 2018</td>
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<td>1920</td>
<td>1.43 (1.20, 1.69)</td>
</tr>
<tr>
<td>Peng et al., 2015</td>
<td>63855</td>
<td>2337</td>
<td>1.27 (1.15, 1.41)</td>
</tr>
<tr>
<td>Liao et al., 2015</td>
<td>61257</td>
<td>2553</td>
<td>1.27 (1.19, 1.35)</td>
</tr>
<tr>
<td>Shah et al., 2013</td>
<td>5888</td>
<td>3602</td>
<td>2.24 (1.62, 3.10)</td>
</tr>
<tr>
<td>Summary</td>
<td>288641</td>
<td>18898</td>
<td>1.64 (1.30, 1.81)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV (low:high quartile)</td>
<td>1.46 (0.77, 2.75)</td>
</tr>
<tr>
<td>FEV (1SD disadvantage)</td>
<td>1.28 (1.03, 1.60)</td>
</tr>
<tr>
<td>Respiratory illness</td>
<td>1.54 (1.30, 1.81)</td>
</tr>
</tbody>
</table>

WORLD ALZHEIMER REPORT 2014

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low educational attainment</td>
<td>1.83 (1.63, 2.05)</td>
</tr>
<tr>
<td>Depression</td>
<td>1.97 (1.67, 2.20)</td>
</tr>
<tr>
<td>Diabetes (all dementia)</td>
<td>1.50 (1.33, 1.70)</td>
</tr>
<tr>
<td>Diabetes (vascular dementia)</td>
<td>2.39 (1.92, 2.98)</td>
</tr>
</tbody>
</table>

LANCET COMMISSION 2017

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less education in early life</td>
<td>1.60 (1.26, 2.01)</td>
</tr>
<tr>
<td>Midlife hypertension</td>
<td>1.60 (1.16, 2.24)</td>
</tr>
<tr>
<td>Midlife obesity</td>
<td>1.60 (1.34, 1.92)</td>
</tr>
<tr>
<td>Midlife hearing loss</td>
<td>1.90 (1.38, 2.73)</td>
</tr>
<tr>
<td>Later life smoking</td>
<td>1.60 (1.15, 2.20)</td>
</tr>
<tr>
<td>Later life depression</td>
<td>1.90 (1.55, 2.33)</td>
</tr>
<tr>
<td>Later life physical inactivity</td>
<td>1.40 (1.16, 1.67)</td>
</tr>
<tr>
<td>Later life social isolation</td>
<td>1.60 (1.32, 1.85)</td>
</tr>
<tr>
<td>Later life diabetes</td>
<td>1.50 (1.33, 1.79)</td>
</tr>
</tbody>
</table>
Figure 5. Conceptual model of proposed potential relationships between impaired pulmonary function and dementia
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of participants</th>
<th>Number of dementia cases</th>
<th>Measurement of pulmonary function</th>
<th>Pulmonary function</th>
<th>Age at which pulmonary function was measured</th>
<th>Covariates included in most-adjusted model</th>
<th>Follow up</th>
<th>Findings</th>
<th>Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lutsey et al. (2018)</td>
<td>14,184 (5889 assessed clinically) male and female participants in the Atherosclerosis Risk in Communities (ARIC) study</td>
<td>1407 people developed dementia, identified by clinical assessment (N=298) and diagnostic codes recorded on hospitalisation.</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; and FVC expressed as a percentage of age-, race-, and sex-specific predicted values</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; 2.82 (0.77) or FEV&lt;sub&gt;1&lt;/sub&gt; 3.80 (0.99) or FVC 85% (14.6) of predicted</td>
<td>54.2 (5.8)</td>
<td>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</td>
<td>Median 23.0 years</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; (low) vs Q&lt;sub&gt;4&lt;/sub&gt; (high) 1.09 (95% CI 0.73, 1.65), Q&lt;sub&gt;2&lt;/sub&gt; vs Q&lt;sub&gt;5&lt;/sub&gt; (high) 0.77 (0.50, 1.18), Q&lt;sub&gt;5&lt;/sub&gt; vs Q&lt;sub&gt;3&lt;/sub&gt; (high) 0.30 (0.18, 0.50), OR per SD change in FEV&lt;sub&gt;1&lt;/sub&gt; 1.03 (0.89, 1.20). N=5889: Weighted, maximally-adjusted HR Q&lt;sub&gt;1&lt;/sub&gt; vs Q&lt;sub&gt;4&lt;/sub&gt; (low) vs Q&lt;sub&gt;5&lt;/sub&gt; (high) 1.11 (0.93, 1.32), OR per SD change in FEV&lt;sub&gt;1&lt;/sub&gt; 1.05 (0.98, 1.11). Results for FVC in both sets of analyses were similar.</td>
<td>Low</td>
</tr>
<tr>
<td>Gilsanz et al. (2018)</td>
<td>27,387 men and women who were members of Kaiser Permanente Northern California</td>
<td>7519 dementia diagnoses ascertained from inpatient and outpatient electronic medical records</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, FEV&lt;sub&gt;2&lt;/sub&gt;, and VC</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; 2.7 (0.8), FEV&lt;sub&gt;2&lt;/sub&gt; 3.3 (1.0), VC 3.5 (1.0)</td>
<td>41.8 (4.2)</td>
<td>Age, race/ethnicity, education, height, midlife health indicator (hypertension, BMI, smoking status) and late-life health indicator (stroke, diabetes, heart failure)</td>
<td>28+ years</td>
<td>Multivariable adjusted HR per litre decrease in FEV&lt;sub&gt;1&lt;/sub&gt; 1.13 (95% CI 1.09, 1.18). Dose response association observed – worst FEV&lt;sub&gt;1&lt;/sub&gt; quintile compared to best HR 1.24 (95% CI 1.10, 1.34). Results for FEV&lt;sub&gt;1&lt;/sub&gt; and VC similar, as were results stratified by smoking status.</td>
<td>Mod.</td>
</tr>
<tr>
<td>Sibbett et al. (2018)</td>
<td>484 men and women born in 1921 forming the Lothian Birth Cohort 1921</td>
<td>106 diagnoses of dementia obtained from clinical reviews, death certificates, and electronic medical records and adjudicated by a clinical panel</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>1.95 (0.59) in people with dementia vs 1.84 (0.62) in those without</td>
<td>79.04 (0.55) [Narrow age cohort]</td>
<td>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</td>
<td>16 years</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; measured at age 79 years was not associated with developing dementia (multivariable-adjusted HR per L/s lower FEV&lt;sub&gt;1&lt;/sub&gt; 1.30, 95% CI 0.74, 2.30)</td>
<td>Low</td>
</tr>
<tr>
<td>Russ et al. (2015)</td>
<td>54,671 men and women from six UK cohort studies</td>
<td>459 dementia deaths identified from death certificates</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, FVC and PEF</td>
<td>Cut-offs for FEV&lt;sub&gt;1&lt;/sub&gt; quartiles were 1.36, 1.81, and 2.35L</td>
<td>46.8 (17.6) [16-100]</td>
<td>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).</td>
<td>Mean (SD) 11.7 (3.7) years</td>
<td>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&lt;sub&gt;1&lt;/sub&gt; 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).</td>
<td>Mod.</td>
</tr>
<tr>
<td>Alonso et al. (2009)</td>
<td>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</td>
<td>160 dementia deaths identified from death certificates (up to four codes were examined)</td>
<td>FVC (categorised into quartiles because of measurement differences between studies)</td>
<td>4.8 (0.8)</td>
<td>49.2 (5.6) [40-59]</td>
<td>Age, study, cohort, occupation, height, smoking status, BMI, serum cholesterol, hypertension, and previous history of cardiovascular disease.</td>
<td>40 years</td>
<td>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&lt;sub&gt;max&lt;/sub&gt;=0.28)</td>
<td>Mod.</td>
</tr>
<tr>
<td>Study</td>
<td>Participants</td>
<td>Methods</td>
<td>Results</td>
<td></td>
<td></td>
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<tr>
<td>Newman et al. (2009)</td>
<td>6575 men and women aged ≥65 years at baseline in the Cardiovascular Health Cohort Study.</td>
<td>392 dementia deaths identified from death certificates</td>
<td>FVC</td>
<td>2.9 (0.9)</td>
<td>72.8 (5.6) [65+]</td>
<td>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.</td>
<td>Average 13 or 16 years for two waves of recruitment</td>
<td>Increasing FVC was associated with a lower risk of dementia death compared to the lowest group (&lt;2.06L): 2.06-2.54L HR, 95% CI 0.92, 0.67-1.28; 2.54-3L 0.98, 0.69-1.40; 3.0L-3.6L 0.79, 0.52-1.20; &gt;3.6L 0.71, 0.44-1.15.</td>
<td></td>
</tr>
<tr>
<td>Gilat et al. (2007)</td>
<td>464 men from three cohorts of the Seven Countries Study, aged 45-64, from Finland and Italy</td>
<td>159 with questionable-to-mild dementia and 24 with moderate-to-severe dementia, based on the CDR for those who scored &lt;27 on the MMSE</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; and FVC</td>
<td>Q1 0.77 (0.12)</td>
<td>54.2 (5.6)</td>
<td>Age, sex, higher education, occupation class, midlife BMI and physical activity, depressive symptoms, COPD, CHD, hypertension, diabetes mellitus, and smoking habits.</td>
<td>25 years</td>
<td>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 [FVC&lt;sub&gt;1&lt;/sub&gt;]; 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 [FVC&lt;sub&gt;1&lt;/sub&gt;]; 1.59, 0.91–2.77 [FVC]; P&lt;sub&gt;interaction&lt;/sub&gt; &lt; 0.05)</td>
<td></td>
</tr>
<tr>
<td>Vidal et al. (2013)</td>
<td>3665 men and women from the AGES-RS, born between 1907 and 1935 (mean SD) age 52.3 [5.3] at baseline</td>
<td>288 cases of dementia based on cognitive screening, neuropsychological testing, informant interview, and neurological assessment. 128 people were identified to have mild cognitive impairment</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/height&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Q1 0.77 (0.12)</td>
<td>54.7 (5.6)</td>
<td>Age, sex, higher education, occupation class, midlife BMI and physical activity, depressive symptoms, COPD, CHD, hypertension, diabetes mellitus, and smoking habits.</td>
<td>23 years</td>
<td>Increasing pulmonary function was associated with a decreased risk of dementia (OR per SD increase in FEV&lt;sub&gt;1&lt;/sub&gt;/height&lt;sup&gt;2&lt;/sup&gt;; 95% CI 0.68, 0.55-0.84)</td>
<td></td>
</tr>
<tr>
<td>Simons et al. (2000)</td>
<td>2805 men and women aged ≥60 and living in the community in New South Wales, Australia</td>
<td>285 hospital admissions where dementia was recorded</td>
<td>PEF</td>
<td>Men 440 (120) Women 332 (83)&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Women 69.6 (7.3)</td>
<td>Age, alcohol intake, gardening, walking, depression, marital status, education, prior history of stroke, and activities of daily living.</td>
<td>16 years</td>
<td>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).</td>
<td></td>
</tr>
<tr>
<td>Guo et al. (2007)</td>
<td>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</td>
<td>147 dementia cases (96 AD) diagnosed clinically by neuropsychiatric examination and informant interview</td>
<td>PEF (in 1974-5), FEV&lt;sub&gt;1&lt;/sub&gt; and FVC (in 1980-1)</td>
<td>PEF 402 (79) FVC 3.2 (0.6) FEV&lt;sub&gt;1&lt;/sub&gt; 2.5 (0.5)</td>
<td>52 (6) [PEF 44-66 FVC/FEV&lt;sub&gt;1&lt;/sub&gt; 50-72]</td>
<td>Age, height, BMI, education, physical activity, smoking, asthma, chronic bronchitis, myocardial infarction, angina pectoris, and hypertension at baseline.</td>
<td>29,739 person-years</td>
<td>There was an association between better pulmonary function and a lower risk of dementia (HR per SD increase in [advantage] in PEF, 95% CI 0.77, 0.65-0.91; FEV&lt;sub&gt;1&lt;/sub&gt;, 0.75, 0.59-0.95; FVC, 0.72, 0.57-0.92). Similar patterns were observed for AD</td>
<td></td>
</tr>
</tbody>
</table>

AD = Alzheimer’s disease; AGES-RS = Age, Gene/Environment Susceptibility – Reykjavik 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; FVC = 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of participants</th>
<th>Number of dementia cases</th>
<th>Respiratory disease</th>
<th>Age at which disease ascertained (Mean (SD)/Range)</th>
<th>Covariables included in most-adjusted model</th>
<th>Follow up</th>
<th>Findings</th>
<th>Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xie et al. (2019)</td>
<td>4735</td>
<td>83 people were newly identified as having dementia, presumably based on MMSE score</td>
<td>Self-reported COPD diagnosis</td>
<td>82.9 (9.7)</td>
<td>Age, gender, marital status, education level, alcohol drinking, current exercise, baseline BMI, smoking status, baseline hypertension, diabetes, and stroke</td>
<td>3 years</td>
<td>Maximally-adjusted HR COPD vs no COPD 1.00 (1.08–3.33). In current smokers, the same HR was 3.38 (1.09–10.5).</td>
<td>High</td>
</tr>
<tr>
<td>Lutsey et al. (2015)</td>
<td>14,184 (5889 assessed clinically male and female participants in the Atherosclerosis Risk in Communities (ARIC) study)</td>
<td>1407 people developed dementia, identified by clinical assessment (N=298) and diagnostic codes recorded on hospitalisation.</td>
<td>Participants were divided into four groups based on self-reported information and spirometry: normal, respiratory symptoms with normal spirometry, restrictive impairment pattern, and COPD</td>
<td>54.2 (5.8) [45-64]</td>
<td>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</td>
<td>Median 23.0 years Max. 27.1 years</td>
<td>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)</td>
<td>Low</td>
</tr>
<tr>
<td>Yeh et al. (2016)</td>
<td>30,773</td>
<td>1920 diagnoses of dementia</td>
<td>&gt;2 clinical contacts recording asthma-COPD</td>
<td>Asthma-COPD</td>
<td>Age, sex, comorbidity, inhaled corticosteroids, and oral steroids</td>
<td>10 years</td>
<td>Asthma-COPD was associated with an increased risk of subsequent dementia (multivariable-adjusted HR 1.43, 95% CI 1.29, 1.59)</td>
<td>Mod.</td>
</tr>
<tr>
<td>Peng et al. (2015)</td>
<td>12,771</td>
<td>2337 individuals identified from the Taiwan National Health Insurance database.</td>
<td>New diagnoses of asthma recorded on the National Health Insurance database.</td>
<td>Asthma</td>
<td>Age, sex, atrial fibrillation, hypertension, hyperlipidemia, diabetes, heart failure, stroke, head injury, annual outpatient visits, and inhaled corticosteroids used</td>
<td>11 years</td>
<td>Asthma was associated with an increased risk of dementia (adjusted HR, 95% CI 1.27, 1.15–1.41).</td>
<td>Mod.</td>
</tr>
<tr>
<td>Liao et al. (2015)</td>
<td>20,492</td>
<td>2553 individuals identified from the Taiwan National Health Insurance database.</td>
<td>New diagnoses of COPD recorded on the National Health Insurance database.</td>
<td>COPD</td>
<td>Age, sex, urbanization, and comorbidities Mean (SD)</td>
<td>COPD vs no COPD 1.90 (1.08–3.33)</td>
<td>COPD was associated with an increased risk of dementia (adjusted HR, 95% CI 1.27, 1.20–1.36).</td>
<td>Mod.</td>
</tr>
<tr>
<td>Chen et al. (2014)</td>
<td>11,030</td>
<td>1661 individuals identified from the Taiwan National Health Insurance database.</td>
<td>Asthma recorded on the National Health Insurance database.</td>
<td>60.88 (10.39)</td>
<td>Demographic data, health system utilization, medical comorbidities, and use of inhaled steroid and asthma as a binary variable</td>
<td>8.0±3.0 years</td>
<td>Having asthma was associated with a doubling of risk of developing dementia (adjusted HR, 95% CI 2.17, 1.87–2.52).</td>
<td>Mod.</td>
</tr>
<tr>
<td>Liao et al. (2015)</td>
<td>8640</td>
<td>706 individuals with AD or Parkinson’s disease identified from the Taiwan National Health Insurance database.</td>
<td>COPD recorded on the National Health Insurance database.</td>
<td>68.76 (10.74)</td>
<td>Age, gender, urbanization, coronary artery disease, stroke, hyperlipidemia, hypertension, diabetes, and head injury</td>
<td>Not stated</td>
<td>COPD was associated with an increased risk of dementia (adjusted HR, 95% CI 1.74, 1.55–1.96).</td>
<td>Mod.</td>
</tr>
<tr>
<td>Erikson et al. (2008)</td>
<td>22,188</td>
<td>1352 twins had a record of atopy from hospital discharge and death certificate data.</td>
<td>History of atopy (asthma, eczema, or rhinitis)</td>
<td>52.9 [57-71]</td>
<td>Age, sex, history of smoking, level of education, and myocardial infarction</td>
<td>22.6±7.7 years</td>
<td>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).</td>
<td>Mod.</td>
</tr>
<tr>
<td>Shah et al. (2013)</td>
<td>5888</td>
<td>3602 identified by two-phase screening, including clinical assessment</td>
<td>Hospitalisation with pneumonia</td>
<td>72.8 (5.6)</td>
<td>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.</td>
<td>10 years</td>
<td>Pneumonia was associated with an increased risk of later dementia (HR, 95% CI 2.24, 1.62-3.11).</td>
<td>Low</td>
</tr>
<tr>
<td>Minami et al. (1995)</td>
<td>3180 people without dementia in Sendai, Japan, of whom 2461 were followed up.</td>
<td>105 individuals were clinically diagnosed with dementia at follow up.</td>
<td>Self-reported respiratory disease.</td>
<td>≥65 years</td>
<td>Sex and age-group</td>
<td>3 years</td>
<td>Respiratory disease was associated with a doubling of risk of dementia (adjusted OR, 95% CI 2.28, 1.19-4.36)</td>
<td>Mod.</td>
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<tr>
<td>Rusanen et al. (2013)</td>
<td>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</td>
<td>172 identified by screening and, for those screening positive, clinical examination</td>
<td>Self-reported diagnosis of COPD or asthma</td>
<td>50.6 (6.0) [39.2-64.1]</td>
<td>Age, sex, education, midlife smoking, APOE genotype, midlife physical activity, systolic blood pressure, BMI, total serum cholesterol, and late-life vascular disease.</td>
<td>Mean (SD) 25.5 (6.2) years</td>
<td>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).</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>N dementia</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FVC - lowest vs highest quartiles</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Alonso et al., 2005</td>
<td>10211</td>
<td>160</td>
<td>1.85 (1.02, 3.35)</td>
</tr>
<tr>
<td>Newman et al., 2009</td>
<td>6575</td>
<td>392</td>
<td>1.41 (0.87, 2.28)</td>
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<tr>
<td>Russ et al., 2015</td>
<td>48025</td>
<td>393</td>
<td>2.65 (1.48, 4.74)</td>
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<tr>
<td>Lutsey et al., 2019</td>
<td>14184</td>
<td>1407</td>
<td>1.06 (0.71, 1.59)</td>
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<tr>
<td><strong>Summary</strong></td>
<td>78995</td>
<td>2352</td>
<td><strong>1.58 (1.07, 2.33)</strong></td>
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</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>N dementia</th>
<th>HR (95% CI)</th>
</tr>
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<tr>
<td><strong>FVC - 1 SD decrease</strong></td>
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<tr>
<td>Gitay et al., 2009</td>
<td>358</td>
<td>17</td>
<td>1.69 (0.92, 3.11)</td>
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<tr>
<td>Gitay et al., 2009</td>
<td>105</td>
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<td>0.63 (0.36, 1.10)</td>
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<td>Guo et al., 2007</td>
<td>1188</td>
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<td>Russ et al., 2015</td>
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<td>1.41 (1.17, 1.69)</td>
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<td>Lutsey et al., 2019</td>
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<td><strong>Summary</strong></td>
<td>63840</td>
<td>1992</td>
<td><strong>1.21 (0.97, 1.51)</strong></td>
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Hazard Ratio
**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

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>N dementia</th>
<th>HR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td><strong>PEF - lowest vs highest quartiles</strong></td>
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<td></td>
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<td>Simone et al., 2006</td>
<td>2805</td>
<td>285</td>
<td>1.96 (1.42, 2.75)</td>
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<tr>
<td>Russ et al., 2015</td>
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<td>393</td>
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<td><strong>Summary</strong></td>
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<td>678</td>
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<tr>
<td><strong>PEF - 1 SD decrease</strong></td>
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</tr>
<tr>
<td>Guo et al., 2007</td>
<td>1291</td>
<td>147</td>
<td>1.30 (1.10, 1.54)</td>
</tr>
<tr>
<td>Russ et al., 2015</td>
<td>48025</td>
<td>393</td>
<td>1.46 (1.27, 1.67)</td>
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<tr>
<td><strong>Summary</strong></td>
<td>49316</td>
<td>540</td>
<td>1.39 (1.24, 1.56)</td>
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</tbody>
</table>

*Hazard Ratio*
**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:higher quartiles)

Illness vs no illness – p=0.050