Respiratory disease and lower pulmonary function as risk factors for subsequent 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). By meta-analysing existing studies, we tested the hypothesis that lower pulmonary function and respiratory illness are linked to an elevated risk of dementia.

Aims: To review the best available evidence, taken from longitudinal studies, for pulmonary function and respiratory disease as risk factors 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 studied both). The lowest quartile of lung function measure Forced Expiratory Volume in one second (FEV_1) compared with the highest was associated with a 1.5-fold (1.51, 95%CI 0.94-2.42) increased dementia risk (N_{total}=127,710, 3 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 are at increased risk of dementia. The extent to which the association between poor pulmonary function and dementia is causal remains unclear.

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

INTRODUCTION

The considerable public health and care burden of dementia is 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) Recent studies have provided promising findings for pulmonary function as a potential modifiable risk factor for late-life dementia. Pulmonary function affects the oxygen supply to the brain. Low pulmonary function and pulmonary disease, in turn, are associated with exposure to multiple insults across the full life course – notably smoking, illness, and socioeconomic deprivation, stunting – suggesting that they may capture a number of dementia risk factors.(6, 7) As the number of studies on pulmonary function and dementia increases, 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.

METHODS

In accordance with the PRISMA guidelines,(8) 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. The review

protocol was registered with PROSPERO (https://www.crd.york.ac.uk/prospero/; CRD42019130376).

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, method of dementia ascertainment, and covariates included in the adjusted models. The methodology of each study informed an assessment of 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: 0-94%) 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 1**). Of these, 25 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, and one study had no comparator) with the remaining 21 being included in further analyses. We considered the results for studies recording pulmonary function (N=11) and

72 respiratory illness (N=11) separately (one study reported both pulmonary function and
73 respiratory illness).
74
75 **Pulmonary function as a risk factor for dementia**
76 We identified eleven prospective cohort studies that have been used to examine the association
77 between pulmonary function and later dementia (**Table 1**). Mean age of participants when
78 respiratory function was measured varied between 40 and 65 in eight studies(9-16) and was over
79 65 in three studies.(17-19) In these studies investigators used one of several spirometric measures
80 as the exposure of interest (risk factor): peak expiratory flow (PEF) refers to the maximum speed
81 of forced expiration (in litres per second); Forced Expiratory Volume (FEV) denotes the volume
82 of air (in litres) which can be expired in a specified period of time, usually in one second (FEV_1);
83 and Forced Vital Capacity (FVC) captures the total volume of air which can be expired. Maximal
84 inspiration is required before each measurement and many studies allow a defined number of
85 attempts and record the best performance. These measures of pulmonary function correlate
86 closely with each other(14) suggesting that associations seen for one measure with
87 dementia/cognitive impairment are likely to be replicated in the other measures.
88
89 A range of methods were used to ascertain dementia, some in combination: death
90 certification,(10, 14, 18, 19) linkage to electronic medical records (e.g., hospital discharge
91 records),(12, 15-17, 19, 20) and clinical assessment.(9, 11, 13, 16, 19) A number of these studies
92 were originally instigated to investigate risk factors for cardiovascular disease(10-12, 16, 18) or
93 the menopause(9) and then repurposed to include dementia follow-up as study participants aged;
94 only two were specifically set up to study diseases of ageing.(13, 19) Duration of follow up
95 ranged from 12 to 40 years.(10, 14)
96

Figure 2 shows two meta-analyses of studies on FEV and dementia risk – one for categories of FEV and one for a unit change. Only three studies (127,710 adults, 1905 dementia cases) compared the lowest quartile of FEV_1 with the highest quartile;(12, 14, 16) pooling these results in a meta-analysis gave a HR of 1.51 (95% CI 0.94, 1.64; P=0.092; I^2=47.0%). 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=79.3%; N=67,505, 2280 dementia cases). One of these studies standardised FEV_1 by dividing by height^2(13) but a sensitivity analysis excluding this transformation gave a similar pooled result (1.24, 0.92-1.68).(9, 11, 14, 16).

Supplementary Figure 1 shows pooled results for FVC: lowest-to-highest quartile HR 1.63 (95% CI 1.14-2.32; P=0.007; I^2=49.3%; five studies, N=145,409, 2456 dementia cases);(10, 12, 14, 16, 18) 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).(9, 11, 14, 16) 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 high 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%.(11)

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);(14, 17) 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).(9, 14)

Four 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

123 FEV_2 and VC) was associated with an increased risk of dementia (multivariable-adjusted HR per
124 litre decrease in FEV_1 1.13, 95% CI 1.09-1.18).(15) This finding was replicated in stratified
125 analyses for smokers and non-smokers. Investigators in the Seven Countries Studies found that
126 men with greater FVC were less likely to die with dementia than men with lower FVC
127 (multivariable-adjusted hazard ratio for highest quartile [Q4] vs lowest quartile [Q1] 0.54, 95% CI
128 0.30-0.98) but the association observed in this study did not follow a dose-response gradient
129 (HR, 95% CI: Q3 vs Q1 1.03, 0.63-1.68; Q2 vs Q1 0.77, 0.46-1.28).(10) An Australian study
130 found an association between lower PEF and increased risk of subsequent hospitalisation with
131 dementia (adjusted HR lowest vs highest tertile 1.98, 95% CI 1.42-2.75).(17) Finally, of 484 men
132 and women from the Lothian Birth Cohort 1936, 106 adjudicated dementia diagnoses were
133 identified from multiple sources, including face-to-face clinical assessment.(19) No robust
134 evidence was found to suggest that FEV_1 measured at age 79 years would be associated with
135 developing dementia (multivariable-adjusted HR per litre/second increase 1.30, 95% CI 0.74-
136 2.30).
137
138 **Respiratory disease as a risk factor for dementia**
139 We identified eleven prospective studies in which investigators had explored the association
140 between respiratory disease and later dementia (**Table 2**). Mean age at which disease was
141 ascertained varied from 50.6 to 82.9 years but was over 65 years in six of the 11 studies.(21-26)
142 Investigators identified pulmonary disease using a National Health Insurance database,(21, 22,
143 25, 27, 28) hospitalisation data,(24) or self-report.(16, 23, 26, 29, 30) Dementia was ascertained
144 from the Taiwanese insurance database in five studies,(21, 22, 25, 27, 28) face-to-face
145 assessement by a clinician in four studies,(16, 23, 24, 30), cognitive test score in one,(26) and
146 linkage to hospital discharge and death certificate data in one.(29)
147

148 **Figure 2** shows a meta-analysis of these 11 studies with a total of 288,641 individuals and 15,898
149 dementia cases giving a pooled HR of 1.54 (95% CI 1.30-1.81; P<0.001; I^2=92.4%). Although
150 the study-specific estimates were heterogeneous, they all favoured risk factor status. Excluding a
151 study which investigated the association between atopic illnesses(29) (asthma, eczema, or rhinitis
152 – only one of which is likely to have a substantial effect on pulmonary function) and dementia
153 reduced the magnitude of the effect observed (1.28, 1.03, 1.60) as well as heterogeneity
154 (I^2=78.2%) but did not alter our conclusion.
155
156 **DISCUSSION**
157 Our main finding from the 21 articles included in this quantitative review is that individuals with
158 poorer pulmonary function (whether impaired function or overt respiratory disease), particularly
159 in midlife, are at an increased risk of developing dementia in later life. Comparing the group who
160 performed poorest on spirometry with the best performers was associated with a 1.5-fold
161 increase in risk of dementia. The presence of a respiratory illness was associated with a similar
162 magnitude of increased risk.
163
164 The effect size we found is comparable to other accepted risk factors for dementia as reported in
165 comprehensive meta-analyses in the World Alzheimer Report 2014(31) (**Figure 3**) where lower
166 educational attainment, for example, was found to be associated with an 1.8-fold increased risk
167 of incident dementia (effect estimate combining adjusted odds ratios and HRs, 95% CI 1.83,
168 1.63-2.05; 31 studies). Pooling 31 studies revealed that depression was associated with around a
169 doubling in the risk of incident dementia (unadjusted effect estimate, 1.97, 95% CI 1.67-2.02)
170 relative to people who were free of this psychological disorder, and having diabetes in late life
171 was associated with a 1.5-fold increase in the risk of developing dementia of any type (1.50, 1.33-
172 1.70) and a doubling of risk of developing vascular dementia (2.39, 1.92-2.98). The recent Lancet
173 commission on dementia prevention, intervention and care similarly reported approximately 1.5-

fold increased relative risk of dementia for individuals with midlife obesity, hypertension or later life smoking (**Figure 3**).(32)

We note a recent systematic review of four longitudinal studies on the association between pulmonary function and cognitive performance.(33) While critical of the methodological quality of the studies they included, the investigators found a cross-sectional association between poorer lung function and lower levels of cognitive function, but little evidence for a longitudinal association. This 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.(34, 35)

Limitations and strengths

The comprehensive search strategy used is likely to have identified practically all relevant published studies and the inclusion of only longitudinal studies strengthens the robustness of our conclusions since, while such studies still only describe associations and do not permit causal inferences to be drawn, the temporal association between exposure and outcome adds weight to the potential importance of any identified association. The pooling of results, where possible, in random effects meta-analyses provides a quantitative summary of the evidence being a more precise estimate and overview of the literature than narrating the results of the individual studies.

There are several limitations to our work. The substantial statistical heterogeneity between studies is matched by methodological heterogeneity and – importantly – variation in the specific measure of pulmonary function used. This limited the number of studies which could be pooled in meta-analyses which may have biased our results, though the direction of bias is unlikely to be consistent in all the excluded studies.

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.(36) Linkage to electronic medical records has been shown to identify only part of a known cohort of people with dementia, particularly if multiple sources are used, although mild and undiagnosed cases are not captured.(14, 37) 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.(38) Furthermore, investigators studying BMI and dementia found their results were similar whether dementia was ascertained solely from mortality data or whether other methods were also used.(39)

Plausible mechanisms

A number of lines of research, in combination with the disappointing results from preventive interventions of dementia implemented at older ages,(40, 41) provide circumstantial support for aetiological process acting from across the life course.(42-46) 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.(47) 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 studies of individuals of all ages demonstrate that Alzheimer-type pathology begins to develop decades before the clinical onset of symptoms.(48-50) 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.(51) Fourth, there is some evidence from prospective cohort studies that cardiovascular disease risk factors measured in midlife are associated with later dementia risk.(10, 30, 52-54) For example, in a recent analysis of the Atherosclerosis Risk in Communities (ARIC) study, midlife hypertension and elevated midlife systolic blood pressure predicted accelerated cognitive decline during 20 years of follow-up.(55) That cardiovascular disease risk factors 'track' from early life into adulthood(56, 57) – for example, there is a correlation between blood pressure measured in childhood and again later life(58) – 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,(59) though a similar association was not observed between cardiovascular disease risk factors and late-onset dementia mortality elsewhere.(60)

There are at least three plausible mechanisms for the observed association: (i) hypoxic damage to the brain resulting from poorer pulmonary function; (ii) pulmonary function may serve as a proxy for other exposures earlier in the life course which increase dementia risk; and (iii) the association may result from the shared aetiology between pulmonary, cardiovascular disease and dementia. These mechanisms will now be considered in turn.

First, 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 are with mixed pathologies including both vascular and neuronal damage. For example, the hippocampus – an area of the brain selectively affected in Alzheimer's disease – is particularly vulnerable to ischaemic damage,(61) 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.(62) Future analyses of magnetic resonance imaging in large prospective cohort studies, such as UK Biobank(63) or

252 the European Prevention of Alzheimer's Disease (EPAD) Longitudinal Cohort Study(64) could
253 help interrogate more closely the putative influence of hypoxia on the hippocampus and other
254 areas of the brain.
255
256 Second, similarly to physical stature with which it is correlated, lung function may reflect life
257 course exposures which modify an individual's risk of dementia.(6, 44, 65, 66) As alluded to
258 above, the life course paradigm in epidemiology hypothesises that exposures at different points
259 in the life course could influence the risk of developing dementia, either through an
260 accumulation of risk or through exposure at critical/sensitive periods.(44-46) Researchers from
261 the Age, Gene/Environment Susceptibility study in Reykjavik, Iceland, for example, reported
262 that smaller birth size (considered a measure of intrauterine experience) was related to poorer
263 cognitive function at the age of 75, providing the first evidence that even the time before birth is
264 relevant to cognitive ageing.(67) Other mechanisms includes: impaired growth leading to reduced
265 maximal lung function; exposure to environmental factors affecting lung function and
266 development, such as tobacco smoke (direct or indirect);(68) illness, such as childhood lower
267 respiratory tract infections(69) and airway hyperresponsiveness;(70) socioeconomic factors
268 (poverty, educational failure, and less-advantaged social class,(71-77); environmental factors
269 affecting lung function, such as atmospheric pollution(72) and local exposure to traffic.(78, 79)
270
271 Third, both Alzheimer's disease and vascular dementia may share some aetiology with
272 cardiovascular disease and this overlap in the conditions might explain the association,
273 independent of smoking.(80-82) It has been hypothesised that oxidative stress, inflammation,
274 and amyloid deposition may link these two important conditions.(83, 84) In particular, oxidative
275 stress and synaptic dysfunction appear to be closely linked(85) and brain ischaemia – which
276 could result from cerebral atherosclerosis and stroke – causes oxidative stress-mediated

277 damage.(86) This may possibly be exacerbated by the pro-inflammatory function of *APOE*, but
278 this effect is controversial.(87) (88)
279
280 **Clinical and public health implications**
281 In terms of prevention, the possibility that the association between pulmonary function and
282 cognition might reflect a cause-and-effect relation is particularly important. To date, however,
283 plausible mechanisms linking pulmonary function to dementia include both causal and non-
284 causal explanations and further research on this issue is therefore needed.(9)
285
286 The point in time at which risk factors are measured seems to be important for their ability, or
287 lack of it, to predict later dementia or cognitive decline: There was some evidence of be an age-
288 dependent association with stronger links seen for midlife than old age respiratory function and
289 respiratory disease. Further research is needed to clarify whether this reflects the longer exposure
290 period among younger individuals or a critical period in which poor respiratory function is
291 particularly damaging.
292
293 **Future directions**
294 Pulmonary function alone is likely to have relatively low sensitivity and specificity as a predictor
295 of cognitive decline and dementia and therefore may not be a useful predictor of dementia in the
296 absence of a range of other predictive factors. Further research is needed to examine this. One
297 way forward is examination of pulmonary function and pathology as a contributor to risk factor
298 algorithms – such as the modified CAIDE risk score(54) – given the reported associations
299 between pulmonary function and dementia which remained after adjustment for cardiovascular
300 risk factors. To date, there is some evidence to suggest that such risk scores predict cognitive
301 function(89) and decline,(90) although there is less evidence for prediction of dementia.(91)

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 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. Therefore, in order to reduce confounding and reverse causation bias, Mendelian randomization studies with genetic variants related to lung function as an instrument would provide one avenue to pursue.

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.

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Figure 1. PRISMA flowchart

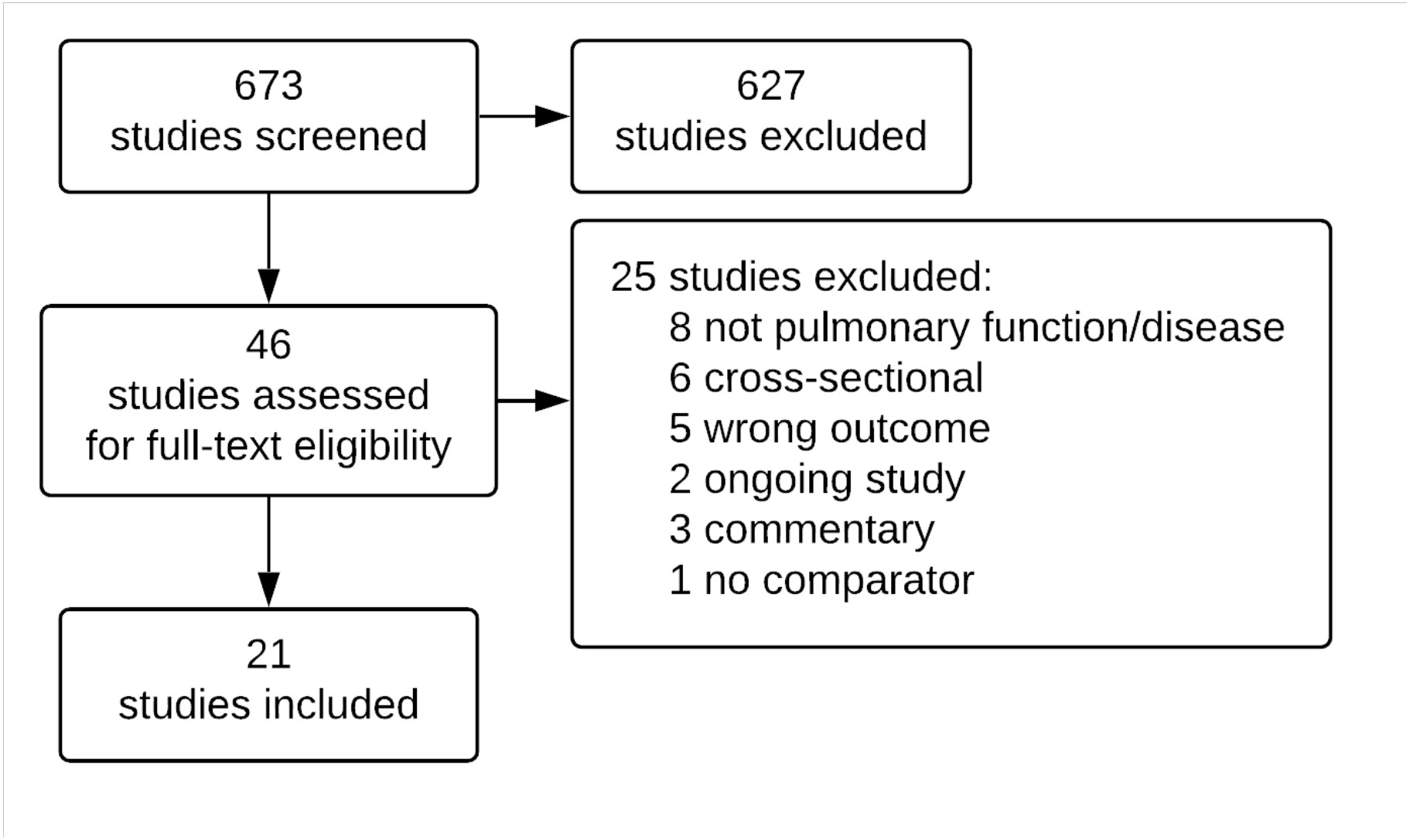


Figure 2. The relation of forced expiratory volume and respiratory illness with dementia — meta-analysed results

STUDY	N	N dementia	HR (95% CI)
FEV – lowest vs highest quartiles			
Pathan et al., 2011	65501	105	1.83 (0.71, 4.70)
Russ et al., 2015	48025	393	2.09 (1.17, 3.72)
Lutsey et al., In press	14184	1407	1.09 (0.73, 1.64)
Summary	**127710**	**1905**	**1.51 (0.94, 2.42)**
FEV – 1 SD decrease			
Giltay et al., 2009	358	17	2.33 (1.31, 4.14)
Giltay et al., 2009	105	41	0.64 (0.35, 1.15)
Guo et al., 2007	1168	134	1.33 (1.05, 1.69)
Vidal et al., 2013	3665	288	1.47 (1.19, 1.82)
Russ et al., 2015	48025	393	1.42 (1.18, 1.71)
Lutsey et al., In press	14184	1407	1.03 (0.89, 1.20)
Summary	**67505**	**2280**	**1.28 (1.03, 1.60)**
Respiratory illness – yes vs no			
Xie et al., 2019	4735	83	1.90 (1.08, 3.34)
Minami et al., 1995	3180	105	2.28 (1.19, 4.36)
Rusanen et al., 2013	1511	172	1.94 (1.16, 3.26)
Liao et al., 2015	25920	706	1.74 (1.55, 1.96)
Eriksson et al., 2008	22188	1332	1.16 (1.01, 1.33)
Lutsey et al., In press	14184	1407	1.08 (0.92, 1.27)
Chen et al., 2014	55150	1681	2.17 (1.87, 2.52)
Yeh et al., 2018	30773	1920	1.43 (1.29, 1.59)
Peng et al., 2015	63855	2337	1.27 (1.15, 1.41)
Liao et al., 2015	61257	2553	1.27 (1.19, 1.35)
Shah et al., 2013	5888	3602	2.24 (1.62, 3.10)
Summary	**288641**	**15898**	**1.54 (1.30, 1.81)**

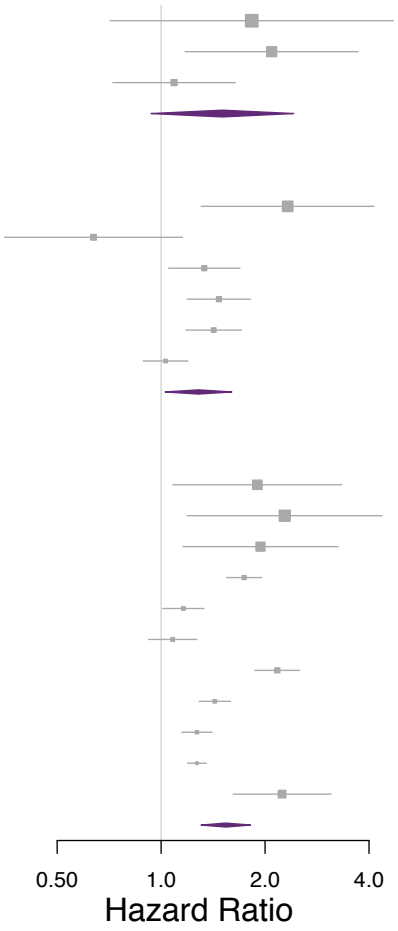


Figure 3. Comparison of meta-analytic findings with accepted risk factors for dementia in the World Alzheimer Report 2014(31) and Lancet Commission on dementia prevention, intervention, and care(32)

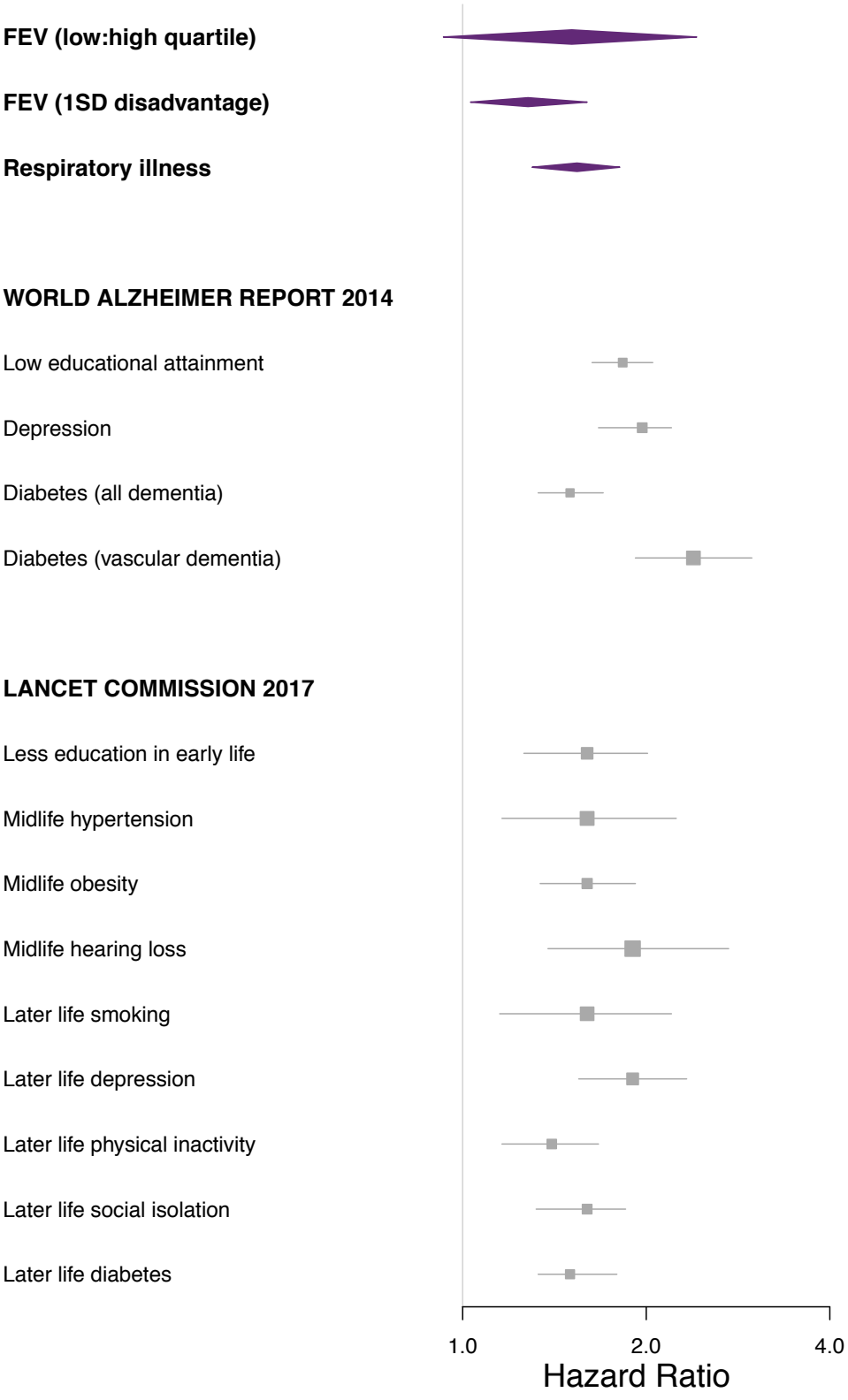


Table 1. Summary of longitudinal studies of the association between pulmonary function and dementia

Study	Number of participants	Number of dementia cases	Measurement of pulmonary function	Age at which pulmonary function was measured *Mean (SD) [Range]*	Follow up	Findings	Risk of Bias
Lutsey et al. (2018)(16)	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	54.2 (5.8) [45-64]	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)(15)	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	41.8 (4.2) [35-50]	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)(19)	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	79.04 (0.55) [Narrow age cohort]	16 years	FEV_1 measured at age 79 years was not associated with developing dementia (multivariable-adjusted HR 1.30, 95% CI 0.74, 2.30)	Low
Russ et al. (2015)(14)	54,671 men and women from six UK cohort studies	459 dementia deaths identified from death certificates	FEV_1, FVC and PEF	46.8 (17.6) [16-100]	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)(10)	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)	49.2 (5.6) [40-59]	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)(18)	6575 men and women aged ≥65 years at baseline in the Cardiovascular Health Cohort Study.	392 dementia deaths identified from death certificates	FVC	72.8 (5.6) [65+]	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)(11)	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	ε4- 50.9 (4.4) ε4+ 51.4 (4.6) [45-64]	25 years	Increasing pulmonary function was associated with a decreased risk of dementia both in *APOE* □ 4 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* □ 4 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.
Pathan et al. (2011)(12)	9837 men and women, aged 45-64 in 1987-9, who attended in the second visit (1990-2) of the ARIC study in four areas of the USA for whom hospitalisation data were available	205 hospital admissions where dementia was recorded	FEV_1 and FVC	Q_1 59.1 (5.5) Q_4 54.1 (4.8) [47-70]	Median 14.1 years	Being in the lowest quartile compared to the highest quartile of FEV_1 (1.6, 0.9-2.3) and FVC (2.1, 1.2-3.7) was associated with dementia hospitalisation but the FEV_1/FVC ratio was not. The authors conclude that a restrictive ventilatory pattern is associated with dementia, rather than obstructive or mixed patterns	Mod.
Vidal et al. (2013)(13)	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/height²	Q_1 54.2 (5.6) Q_4 49.7 (5.2) [<70]	23 years	Increasing pulmonary function was associated with a decreased risk of dementia (OR, 95% CI 0.68, 0.55-0.84)	Low
Simons et al. (2006)(17)	2805 men and women aged ≥60 and living in the community in New South Wales, Australia	285 hospital admissions where dementia was recorded	PEF	Women 69.6 (7.3) Men 68.6 (6.7) [60+]	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)(9)	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)	52 (6) [PEF 44-66 FVC/FEV_1 50-72]	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; CI = confidence interval;
FEV = Forced Expiratory Volume in a specified period; (F)VC = (Forced) Vital Capacity; HR = hazard ratio; MCI = mild cognitive impairment; OR = odds ratio;
PEF = Peak Expiratory Flow; SD = standard deviation

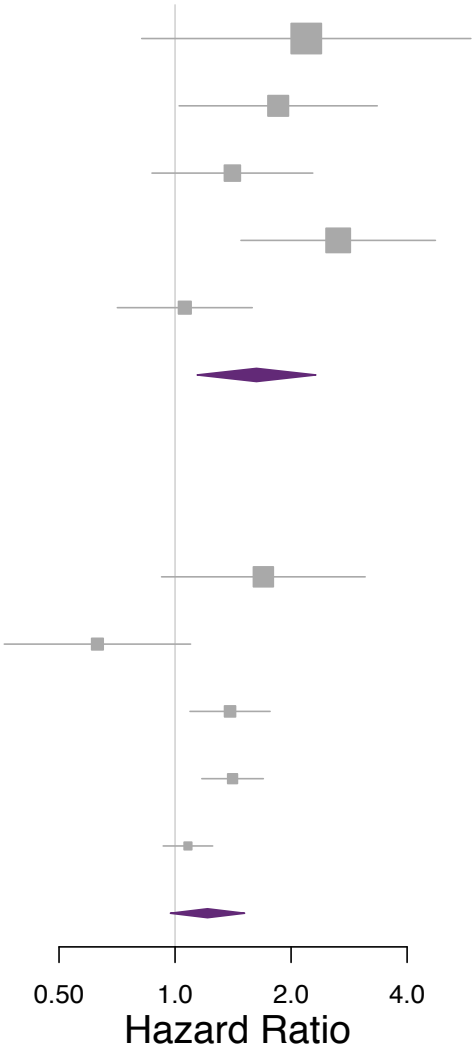
Table 2. Summary of longitudinal studies of the association between respiratory disease and dementia

Study	Number of participants	Number of dementia cases	Respiratory disease	Age at which disease ascertained *Mean (SD) [Range]*	Follow up	Findings	Risk of Bias
Xie et al. (2019)(26)	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)	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)(16)	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]	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)(25)	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)	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)(28)	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)	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)(22)	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)	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)(27)	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)	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)(21)	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)	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)(29)	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]	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)(24)	5888 participants in the Cardiovascular Health Study	3602 identified by two-phase screening, including clinical assessment	Hospitalisation with pneumonia	72.8 (5.6)	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)(23)	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	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)(30)	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]	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

STUDY	N	N dementia	HR (95% CI)
FVC – lowest vs highest quartiles			
Pathan et al., 2011	66414	104	2.19 (0.82–5.85)
Alonso et al., 2009	10211	160	1.85 (1.02–3.35)
Newman et al., 2009	6575	392	1.41 (0.87–2.28)
Russ et al., 2015	48025	393	2.65 (1.48–4.74)
Lutsey et al., In press	14184	1407	1.06 (0.71–1.59)
Summary	**145409**	**2456**	**1.63 (1.14–2.32)**
FVC – 1 SD decrease			
Giltay et al., 2009	358	17	1.69 (0.92–3.11)
Giltay et al., 2009	105	41	0.63 (0.36, 1.10)
Guo et al., 2007	1168	134	1.39 (1.09–1.76)
Russ et al., 2015	48025	393	1.41 (1.17–1.69)
Lutsey et al., In press	14184	1407	1.08 (0.93–1.25)
Summary	**63840**	**1992**	**1.21 (0.97–1.51)**



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