Supplementary material: further methods and full results of narrative review

Methods
Search Strategy

A search was performed of the PubMed Database and Cochrane Database of Systematic Reviews using the keywords “Dementia”, “Cognitive Impairment” or “Cognitive Dysfunction” AND “COPD”, “COAD”, “Chronic Obstructive Pulmonary Disease” or “Chronic Obstructive Airway Disease”. Databases were searched for papers published any time between January 2010 and January 2015. Dodd et al. (2010) was read and relevant references from this examined using the inclusion and exclusion criteria as detailed.

Inclusion and Exclusion Criteria

We included only peer reviewed articles published in English in the medical literature that were clinical trials, epidemiological studies, observational studies, cohort studies, review articles or case-control studies exploring a direct link between COPD and CI. Book chapters, grey-literature, animal studies, qualitative research papers and studies where full-text was not available were excluded. Studies which based on the title or abstract were clearly irrelevant (e.g investigating lung transplantation in COPD, investigating inhaler use in CI), did not measure CI as a specific outcome or did not specifically investigate a link between COPD and CI were excluded.

Figure S1: Prisma Diagram of Study
Supplementary Results – Narrative Findings of the Review

A full review of results is provided in supplementary table 1.

Biomarkers related to CI in COPD

Patients with COPD are known to have increased levels of systemic inflammatory markers such as C-reactive Protein and interleukin-6 (1,2). These may contribute to cognitive dysfunction via a direct neurotoxic effect or by contributing to cerebral atherosclerosis (3) with studies suggesting a dose-response relationship (1).

Clusterin is a glycoprotein expressed in the majority of human tissues (4). Previous studies state peripheral levels of clusterin are raised in CI and neuronal inflammation (5). The concentrations increased in the mild-moderate and severe COPD groups compared with controls (both p<0.01), being significantly higher in the severe COPD group compared to the mild-moderate group (p<0.01) as well. Level of cognitive dysfunction, reflected by the MMSE score, was correlated with clusterin levels in COPD (r=0.33, p<0.01). While this study showed an association between COPD severity, levels of peripheral clusterin and cognitive dysfunction a direct link has not yet been proven. Although age, BMI, sex and education levels were matched, other factors such as co-morbidity could have confounded.

S100B is a calcium-binding protein expressed mainly by astrocytes. Chronic neurodegenerative conditions such as Alzheimer’s disease have been shown to lead to peripherally increased levels of this protein. It is also used as a marker for CI; levels negatively correlated with MMSE scores (6)(7) measured the serum S100B levels across three groups. Serum S100B levels increased significantly in the mild-to-moderate (p<0.01) and severe COPD (P<0.01) groups compared with the control group. In addition, the serum S100B concentration was significantly higher in the severe COPD group than that in the mild-to-moderate COPD group (P<0.01). The study concluded that further investigation is needed to address the underlying mechanisms. This is in keeping with increased systemic markers, such as S100B in Alzheimer’s, being related to the level of cognitive dysfunction. Further investigation of this is required to establish if there are specific inflammatory markers mediating CI unique to COPD.

Differences in brain structure in COPD

The hippocampus forms part of the limbic system in the medial temporal lobe. It plays a role in memory, spatial awareness and is particularly vulnerable to hypoxemia (7). Magnetic Resonance Imaging (MRI) studies have found that atrophy of the hippocampal region is consistent with mild CI and Alzheimer’s disease (8).

Li et al. (2013)(7) investigated effects of hypoxaemia on hippocampal volume. Findings showed chronic hypoxaemia correlated with decreased hippocampal volume in COPD patients, leading to hippocampal atrophy resulting in CI. Of note, there were no significant differences of hippocampal volumes between mild-moderate and severe COPD groups. The study hypothesized that the cumulative loss of neurons and their connections results
in hippocampal atrophy in the early stage of the disease, while the structural change converts to the functional deterioration in later stages. The mechanisms of these structural changes are poorly understood, however a possible explanation is that hypoxaemia has particularly adverse effects on the hippocampus, and possibly the wider limbic system. Further research specifically comparing hippocampal volume in COPD and non-COPD patients would be of value.

Antonelli-Incalzi et al (2003)(9) investigated cerebral perfusion using Single Photon Emission Computed Tomography (SPECT) and compared to neuropsychological assessment scores in normal, hypoxaemic COPD, non-hypoxaemic COPD and known Alzheimer’s Disease (AD) patients. COPD groups scored less than controls in the domains of verbal attainment, attention and deductive thinking. SPECT scanning identified anterior cerebral hypoperfusion; the authors suggested this could precede frontal-type cognitive decline in hypoxaemic patients.

Forced Expiratory Volume in 1 Second (FEV1)

The FEV1 is used as a measure of severity of COPD; the lower the FEV1 percentage the greater the severity as defined by the GOLD criteria in 2010. FEV1 has been explored in relation to CI in COPD. Cleutjens et al (2014)(10) found worsening prospective memory and numeric short-term memory were associated with worsening FEV1. However Frohnhofen et al. (2011)(11) found that only 78% of their cohort and 47% of those with CI could adequately complete lung function testing. Therefore, it is difficult to accurately assess any association of CI and FEV1 if CI patients cannot perform spirometry.

Limitations of this review

A limitation of the SR is that only two databases were searched, and expert authors in the field were not contacted to identify relevant papers or identify the grey literature. As such the review may have been subject to selection bias and publication bias. The review was limited to 2010-2015 as a high quality systematic review of the subject was published in 2012 (5) and a large scale review was published by Dodd in 2010(12); we intended to build on and add to the literature regarding this subject to contextualise the background for the cross-sectional study.
| Study                                      | Design               | N   | N (COPD) | Diagnosis of COPD                  | Age (years)                          | Cognitive Test(s) Used and Cut-off score for defining impairment | Domains of Cognition Tested                                                                 | Percentage of CI in COPD cases (if calculable) | Main findings                                                                                                                                                                                                 |
|-------------------------------------------|----------------------|-----|----------|-----------------------------------|--------------------------------------|---------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ambrosino, Bruletti & Scala et al (2002)(13) | Controlled Cohort study | 97  | 63 (64.9%) undergoing severe exacerbation | American Thoracic Society criteria(14) | Exacerbation of COPD group mean age: 68 +/- 7 years Stable COPD Control Group mean age: 67 +/- 7 years | Mini Mental State Examination (MMSE) <24 used as threshold for CI | Global: Specifically spatial and temporal orientation, short-term and long-term verbal memory, attention, calculation, verbal attainment and praxic abilities | 43% of exacerbation group showed significantly worse mean scores in MMSE (p<0.00002) 3% of stable controls at discharge from hospital COPD exacerbation group showed significantly worse mean scores in MMSE (p<0.00002) Individual domain scores not reported. Significantly higher rates of CI in exacerbating COPD cases, but prevalence of CI became similar at 6 months after discharge. |
| Antonelli-Incalzi, Corsonello & Trojano et al (2007) (15) | Observational       | 149 | 149 (100%) | American Thoracic Society criteria(14) | Mean age 69.3 +/- 8.5 years | MMSE <24 used as threshold for CI Mental Deterioration Battery (MDB) Score <4 threshold for “dementia” | Global MDB: Visuospatial skills, verbal fluency, long and short term verbal memory, constructional ability, immediate visual memory, verbal expression | 34.2-35.5% Domain scores not individually compared to non-COPD patients. MMSE and a 5-item ADL score can be used to exclude but not detect CI in COPD patients. |                                                                                                                                                                                                 |
| Study                          | Design                  | Sample Size | COPD Cases | AD Cases | Controls | Case-Control Study | Cognitive Function Tests | Findings                                                                 |
|-------------------------------|-------------------------|-------------|------------|----------|----------|--------------------|----------------------------|--------------------------------------------------------------------------|
| Antonelli-Incalzi, Marra & Girordano (2003) | Case Control | 68          | 33 (48.5%) COPD | 15 (22.1%) AD | 10 (14.7%) control | American Thoracic Society criteria(14) | Control: mean 68.4 Years, SD 6.2 years                       | MDB: Visuospatial skills, verbal fluency, long and short term verbal memory, constructional ability, immediate visual memory, verbal competence Additional Tests: verbal attainment, immediate verbal memory, delayed verbal memory, visual attention, visual-spatial intelligence, visual-spatial memory, constructive function, executive function, deductive thinking, inductive thinking. Not individually assessed AD cases were significantly more cognitively impaired than COPD cases; dramatically worse in verbal memory scores. Groups did not differ in tests assessing: visual-spatial intelligence, visual attention, constructive functions, visual memory, selected mechanisms of secondary memory Compared to matched controls, Non-hypoxaemic and Hypoxaemic COPD patients scored less on tests exploring verbal memory, attention and deductive thinking. |
| Chang, Chen, McAvay & Tinteeti 2012 | Multicenter longitudinal cohort | 3693 | 431/3693 = 11.67 % | All ≥65years | Modified MMSE >1.5sd below the mean for education and race | Global | 6.3% of those with COPD had CI. Of those with CI, 20.3% had COPD. COPD and CI increased respiratory-related and all-cause hospitalizations and mortality. Individual domain scores not reported. |
| Cleutjens, Spruit & Ponds et al (2014) | UK Biobank Cohort | 43,039 | 5764 (13.4%) | COPD: 59.0 years +/- 7.6 Non-COPD: 56.0 years +/- 8.3 | GOLD criteria (18) | Five cognitive functioning tests were performed using a touch screen system: (1) the prospective memory test (2) the fluid intelligence test assesses (3) the pairs-matching test assesses visual spatial skills (4) Numeric memory test is used to measure numeric short-term memory and assesses the | (1)Prospective memory (2) fluid intelligence and cognitive functioning, (3) Visuospatial Memory (4) Numeric short term memory (5) Cognitive processing speed | Not assessed COPD group had significantly worse scores in prospective memory, visuospatial memory, numeric short term memory and cognitive processing speed than Non-COPD. |
| Study                                                                 | Design            | N       | GOLD Criteria | MMSE Age | TMT & Clock Test | MMSE | TMT & Clock Test | MMSE | TMT & Clock Test |
|----------------------------------------------------------------------|-------------------|---------|---------------|----------|------------------|------|------------------|------|------------------|
| Dal Negro, Bonadiman, Tognella, Bricolo & Turco (2014) (8)          | Case-control      | 402 (274M) | 229 (56.9%)   | 65.6 +/- 15.1 years | MMSE: Global | 16.6% using clock-drawing test | 16.6% using clock-drawing test | 16.6% using clock-drawing test |
|                                                                     |                   |          |               |           | TMT A/B (TMT A)  | TMTB - >283secs | TMTB - >283secs | TMTB - >283secs |
|                                                                     |                   |          |               |           | TMT A <94secs   | TMTB <283secs  | TMTB <283secs  | TMTB <283secs  |
|                                                                     |                   |          |               |           | Clock-Drawing   | Memory & Symbolic Representation |
|                                                                     |                   |          |               |           | test            |                |
| Dodd, Charlton, van den Broek & Jones (2013) (19)                    | Case-control      | 110 (50M) | 80 comprising: | 70 +/- 11 years | MMSE: Global | 20% COPD-E worse than controls in all cognitive measures. | 20% COPD-E worse than controls in all cognitive measures. | 20% COPD-E worse than controls in all cognitive measures. |
|                                                                     |                   |          | 30 exacerbating COPD inpatients (COPD-E), 50 stable COPD cases | Rey-complex figure tests WMS-III UK word lists Delis-Kaplan verbal Fluency & Trail Making Tests (DKVF, DKTMT) Wechler Adult Intelligence Scale (WAIS) – III UK | Rey Complex Figure Tests: Visuospatial, construction, memory: visual memory delayed and immediate recall, memory: verbal delayed and immediate recall, WMS-III UK word lists: Immediate and delayed verbal memory | 20% COPD-E had pathological loss of processing speed and scores were in the |
|                                                                     |                   |          |               |           | WTMAR |                |                 |                 |
| Study                                          | Design       | Sample Size | COPD Group Characteristics                                                                 | Control Group Characteristics                                                                 |
|------------------------------------------------|--------------|-------------|-------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Fix, Golden & Daughton et al (1982) (20)       | Observational| 66          | Clinical diagnosis of COPD Not Available                                                   | Test scores were significantly related to PaO2 and degree of lung impairment. Patient who survived to 3-year follow-up had scored significantly higher on Neuropsychological Tests. |
| Grant, Heaton, McSweeny, Adams & Timms (1982) (21) | Case-control | 277         | Clinical diagnosis of COPD 65.5 +/- 8.4 years                                              | Significantly worse impairment in the COPD group in Halstead, Reitan and additional tests. Only low order significant inverse correlations were found between neuropsychologic impairment and PaO2, resting arterial oxygen saturations. COPD cases impaired in non-verbal memory, cognitive flexibility, complex perceptuo-motor manoeuvres, and... |
| Study                                      | Design               | COPD Cases | Controls | COPD Diagnosis | Control Mean Age | Clinical Test Battery | Global, Reported as 4 Main Factors | MMSE: | Prevalence |
|--------------------------------------------|----------------------|------------|----------|----------------|-------------------|------------------------|-----------------------------------|-------|------------|
| Grant, Prigratano & Heaton et al (1987)    | Case-control         | 401        |          | COPD           | 63.1 +/- 10.3     | Halstead-Reitan Battery (time, memory and localization,) Speech perception tests, Seashore rhythm test, Tapping test, TMT's, aphasia screening test, Perceptual examination, grip strength, WAIS, WMS, Rennick-lafayette repeatable battery | Verbal intelligence, Perceptual learning and problem solving, Alertness, attention Psychomotor Speed | MMSE: | 27% (mild hypoxaemia) 61% (severe hypoxaemia) 42% overall. |
|                                            |                      | 302        |          | COPD           | 64.3 +/- 8.2      |                         |                                   |       | Multivariate analyses revealed a significant relationship between the extent of hypoxaemia and CI. Patients with severe hypoxaemia functioned worse on most tests. Level of impairment appears related to level of hypoxaemia. Severe hypoxaemia worse scores in Perceptual learning, problem solving, alertness and psychomotor speed and simple motor tests. |
|                                            |                      | 1,424      |          | COPD           | 65.9 +/- 8.3      |                         |                                   |       |            |
| Frohnhofen, Heuer, Willschrei and Falkenhahn (2011) | Cross-sectional cases only | 1,424      | 1,424    | No dementia    | 80 +/- 8 years     | MMSE < 24 threshold to indicate cognitive impairment. |                                   |       | 30% mild dementia 22% moderate to severe dementia 30% of patients with obstructive airways disease had mild dementia (type not specified) 22% suffered from moderate-severe dementia (type not specified) Lung function testing feasibility significantly decreased with presence of dementia. |
|                                            |                      | (527M)     | (100%)   | COPD           | 81 +/- 7 years    |                         |                                   |       |            |
| Hjalmarsen, Waterloo & Dahl et al (1999)   | Case-control         | 10         | 10       | COPD group:    | 65.9 +/- 7.3 years | Seashore Rhythm Test (SRT)` TMTA` Simple Reaction Time and Complex Reaction Time Test Wechsler Memory Scale Revised' TMTB' Grooved Pegboard Test' | Attention, Psychomotor speed and speed of information processing. Memory Conceptual Functioning GPT - Motor Functioning | Prevalence not calculable due to study design. |       | COPD group had significantly lower scores compared to controls on Verbal and Visual Memory Tests, Trail Making Test A and B, Seashore Rhythm Test, and Complex Reaction Time Tests. A significant difference between the two groups was also |
|                                            |                      | (4M)       | (50%)    | COPD; CI       | 66.1 +/- 4.7 years |                         |                                   |       |            |

CI: Clinical Impairment; COPD: Chronic Obstructive Pulmonary Disease; MMSE: Mini-Mental State Examination; TMT: Trail Making Test; SRT: Seashore Rhythm Test; |
pulmonary tuberculosis

Hung, Wiskinevsky and Siu et al (2009) (24) Cohort Study 4150 498 (12%) Self-reported history of COPD 62.6 years +/- 1.7 (controls) 62.6 years +/-1.8 years (non-severe COPD) 62.9 years +/- 1.8 years (severe COPD) Validated 35-point cognition score testing including elements of MMSE and telephone interview cognitive screening. Scored form 0-35, with 35 being best score. No threshold for impairment specified. Global, domains not specifically described. Not specifically described. Obtained on the Wechsler Adult Intelligence Scale (WAIS) subtest Block Design.

Antonelli-Incalzi, Gemma & Marra et al (1993) (25) Case-control 139 36/139 = 25.8% American Thoracic Society criteria(14) Age 69 +/- 10 years (COPD) 69 +/- 7 years (normal adults) 78 +/- 2 years (elderly adults) 72 +/- 6 years Alzheimer’s disease 70 +/- 8 years (multi-infarct dementia) Mental Deterioration Battery (MDB) 10 further tests MBD – Global Other tests specifically: verbal ability, verbal memory, visuospatial intelligence, constructive functions, visual memory, visual attention, abstract thinking, visuo-spatial memory. 48.5% of COPD patients had specific pattern of cognitive impairment. 48.5% COPD group had specific pattern of CI characterize by impairment in verbal fluency and verbal memory tasks, well preserved visual attention and worsening (diffuse) of other functions. Compared with matched controls, COPD showed diffuse cognitive deterioration, less severe than the AD group. MDB score significantly higher in both control groups compared to COPD group. Significant association of increasing CI with Increasing age (p<0.05) and longer duration of
| Author(s) | Study Type | N | Description | Age | MMSE | Global | Notes |
|-----------|-------------|---|-------------|-----|------|--------|-------|
| Incalzi, Chiappini, Fuso, Torrice & Gemma (1998) (26) | Consecutive cohort study | 84 | 84 (100%) hypoxemic COPD on continuous oxygen therapy. | Age 68+/- 9.8 years (Group A – completed study) 68+/- 11 years (Group B – died) 73 years +/- 9 years (Group C lost to follow-up) | MMSE (<24 threshold for impairment) Geriatric Depression Scale (GDS) Activities of Daily Living (ADLs) | Global | Not assessed as individual outcome. More than half (44/84) died or were lost to follow-up. These were analysed as sub-groups. Significant deterioration from baseline to 1 year and 2 year assessments. Two-year changes in MMSE inversely correlated with GDS scores. Decline is faster in the presence of airway obstruction, and parallels the worsening affective status of patients receiving oxygen therapy. |
| Isoaho, Puolijoki & Huhti et al (1996) (27) | Case-control | 82 with COPD 246 controls | 82/328=25% | Clinical diagnosis +/- spirometry FEV1/FVC <0.65 | 64 years and over | MMSE (<24 threshold) | Global | 17% of men with COPD 5% of women with COPD No difference in MMSE scores in COPD group or age matched controls. No significant differences detected in any domains of cognition. |
| Kozora, Filley & Julian et al (1999) (28) | Case-control | 94 (32 COPD group, 31 mild AD group and 31 control group.) | 32/94 =33% | Clinical diagnosis | Mean age COPD group 70.3 years Mean age AD group 72.7 years Mean age controls 69.9 years. | Wechsler Memory Scale- Revised Digit Span Subtest, logical memory and visual reproduction, Verbal Pair associates TMTB Controlled oral word association test Animal naming test Boston Naming Test (BNT) | Immediate auditory attention, Immediate and delayed verbal recall. TMTB: global cognitive efficiency Animal naming & Oral word association: verbal fluency BNT: naming to confrontation. | Threshold for CI not used, cumulative analyses. COPD group had significantly worse verbal fluency than controls, but not clinically impaired as a group. COPD group were not impaired in attention, visuomotor abilities, immediate and delayed verbal recall, verbal fluency or confrontational naming. Patients with COPD, controls and AD can be distinguished based on patterns of |
| Study | Design | Participants | Gender | Age | GOLD Criteria | MMSE | Cognitive Impairment | Comment |
|-------|--------|--------------|--------|-----|---------------|------|----------------------|---------|
| Li & Fei (2013) | Prospective case-control | 116 (37 mild to moderate COPD, 48 severe COPD and 31 controls) | 85/116 (73.2%) | COPD: 68.4 +/- 8.0 years Controls: 66.5 +/- 7.0 years | MMSE: <24 threshold for impairment | MMSE: Global | MMSE score was significantly lower in the mild-moderate and severe COPD groups than controls (p<0.01). Significantly lower MMSE score in severe COPD group compared to mild-moderate COPD group. (p<0.01). Cognitive domains not individually assessed. Lower PaO$_2$ significantly associated with lower MMSE scores in all COPD groups. |
| Li, Huang & Fei (2013) | Case-Control | 89 (63M) 27 mild-moderate COPD, 35 severe COPD and 27 control. | 62 (69.7%) | Control: 66.3 +/- 7.08 years Mild-moderate COPD 70.48 +/- 7.75 Severe COPD group: 68.20 +/- 7.82 years | MMSE: <24 threshold for impairment | MMSE: Global (Specifically spatial and temporal orientation, short-term and long-term verbal memory, attention, calculation, verbal attainment and praxic abilities$^{[43]}$) | MMSE is an independent risk factor for cognitive impairment. MMSE significantly lower in mild-moderate (p<0.001) and severe (p<0.001) COPD group. In mild-moderate and severe COPD groups, MMSE score significantly correlated with serum clusterin level and with PaO$_2$. Serum clusterin level may be a relevant biomarker of CI in COPD patients. |
| Study Authors and Year | Study Type | Sample Size | CI Prevalence | Age Range | Tests Used | Cognitive Performance | Findings |
|------------------------|------------|-------------|---------------|-----------|-------------|-----------------------|----------|
| Liesker, Postma, Beukema et al (2004) (30) | Case-Control | 50 | 30/50 =60% | American Thoracic Society criteria | Stroop Colour Word Test (SCWT) | COPD group significantly worse than healthy volunteers on TMTB, digit symbol of the Wechsler Adult Intelligence Scale, Addition subtest of Groningen Intelligence test and Story Recall | Lower scores on MMSE and SCWT in COPD group. |
| Martin, Bradley, Buick, Crossan & Elborn (2011) (31) | Interventional Study | 10 | 100% | Clinical diagnosis defined as a history of tobacco exposure and airflow limitation (FEV1 <0.7) | WTAR Trail Making Tests | Cognitive performance maintained in all tests when PaO2<6.6 kPa in COPD | No significant difference in cognitive performance. |
| Pimenta, Bicalho, Romano-Silva, Moraes, Rezende (2013) (32) | Cross-sectional + control | 424 | 12.2% (n not stated) | Clinical diagnosis (from medical records) | MMSE | Prevalence not calculable due to study design | Lower scores on MMSE in COPD patients. |
| Singh, Parsaik & Mielke (2013) (4) | Cohort Study | 1,927 | 288 (14.94%) | Age range 70-89 | Short Test of Mental Status | Higher prevalence of CI in patients with COPD (27.1% vs 14.6% P<0.001) | Odds ratio of CI was almost two-times higher in COPD cases (OR=1.90). |
Singh, Mielke & Parsaik et al (2014) (33) | Prospective cohort | 1425 (715M) | 171 (12%) | Automated digital algorithms and medical records of clinical diagnosis | Age range 70-89 years CI group median 82.08 years, non-CI group median 78.33 years. | Short test of Mental Statusb Domain Specific Score of <1SD below age specific population mean represented possible CI. Diagnosis was based on professional consensus, considering test results. | Memory Language Executive Function Visuospatial Skills | 14.05% had COPD and cognitive impairment at baseline. COPD almost doubled risk of developing non-amnesic MCI (Confidence interval 1.04-3.23; Hazard Ratio 1.83) Increased risk if COPD > 5 years. Dose-response relationship between length of COPD and risk of CI. |
---|---|---|---|---|---|---|---|---|
Thakur, Blanc & Julian et al (2010) (3) | Matched case-referent analysis | 1504 | 1202 (79.92%) | Clinical Diagnosis of COPD | Mean age 58.2years (COPD group) Mean age 58.5years (Reference group) | MMSEa <24 points suggested impairment | MMSE: Global | 5.5% in COPD group 2.0% in non-COPD group Significantly higher rate of CI in COPD subjects (p<0.0051) No discussion of individual domains. Low baseline oxygen saturations were strongly related to CI, dose response relationship demonstrated. |
Villeneuve, Pepin, Rahayel et al 2012 (34) | Case-control | 90 (36M) | 45 (47.37%) | GOLD criteria(29) | range 40-90 MMSEa <26 indicates impairment MoCA cut-off threshold was 26, with <25 indicating impairment | MMSE: Global MoCA: Global (specifically, short tem memory recall, visuospatial abilities, executive function, phonemic fluency, attention, concentration and working memory, language, verbal fluency) | 36% CI significantly more likely in COPD, mainly in nonamnesic domain, with predominant attention and executive dysfunction. Second most commonly affected areas were verbal learning and memory. |

List of abbreviations used in table:
M= Male
Review studies not included in table.
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