BJPsych | The British Journal of Psychiatry
1–12. doi: 10.1192/bjp.bp.114.148403

Review article

Longitudinal course of behavioural and psychological symptoms of dementia: systematic review

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Background
More information about the pattern of behavioural and psychological symptoms of dementia (BPSD) in the course of dementia is needed to inform patients and clinicians and to design future interventions.

Aims
To determine the persistence and incidence of BPSD and their relation to cognitive function, in individuals with dementia or in cohorts investigated for dementia onset.

Method
A systematic literature review analysed the baseline prevalence, persistence and incidence of 11 symptoms. The review was conducted according to established guidelines with the exception that we could not exclude the possibilities of bias in the studies examined.

Results
The 59 included studies showed considerable heterogeneity in their objectives and methods. The symptoms hyperactivity and apathy showed high persistence and incidence; depression and anxiety low or moderate persistence and moderate incidence; and psychotic symptoms low persistence with moderate or low incidence.

Conclusions
Despite heterogeneity across studies in terms of setting, focus and length of follow-up, there were clinically relevant differences in the longitudinal courses of different BPSD. Apathy was the only symptom with high baseline prevalence, persistence and incidence during the course of dementia.

Declaration of interest
None.

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Behavioural and psychological symptoms of dementia (BPSD) include affective symptoms, psychotic symptoms, non-aggressive agitation, irritability, wandering, elation and sleep problems.[1] They have a high prevalence in dementia and nearly all people with dementia have at least one of these symptoms during the course of the disease.[2] Such symptoms have negative effects on the quality of life of both patients and caregivers and are associated with increased costs of care.[3,4] Better treatment and management of the symptoms are important, particularly as there is no effective treatment to alter the course of the underlying cognitive and functional decline. In order to design and conduct clinical trials for the treatment of BPSD, more information about the pattern of these symptoms in the different stages of dementia is needed to identify the best stage to intervene. In addition, insights into the extent to which BPSD occur over the course of dementia will help patients and care providers to plan for the future. Cross-sectional studies have shown that BPSD can occur at any time during the development of dementia. Their prevalence may increase from mild to severe dementia, whereas other studies suggest a non-linear course with the highest prevalence seen in the intermediate stages of disease.[5,6] Symptoms may persist or be episodic over time, and this may differ between symptoms. Evidence from longitudinal studies is limited and has not been brought together systematically. Two reviews on the course of BPSD specifically in care-home residents have been published recently.[7,8] They included a small number of studies (28 and 18) and concluded that the course of BPSD varied considerably between studies and between individual symptoms.

Our aim was to determine the longitudinal course of BPSD in individuals with dementia or in cohorts studied for dementia onset. We also investigated the persistence and incidence of symptoms and how persistence of BPSD over time relates to cognitive function. This review builds on five previous reviews by some of the same authors.[9–13]

Method

Studies were eligible for inclusion if they reported the persistence, incidence or association with cognitive function of one or more BPSD in older adults (i.e. majority of participants aged at least 65 years) with dementia or cognitive impairment, and measured symptoms at three or more time points. Observational studies or intervention studies where there was a control group were included. The symptoms included were apathy, depressive symptoms, anxiety, irritability or aggression, non-aggressive agitation, hallucination, delusion, misidentification, sleep problems, wandering and elation. No language restriction was applied. Studies with inadequate descriptions of the sampling of the population or measurement of BPSD were excluded. The review protocol was not registered.

Search method

Electronic searches of PubMed, EMBASE, Cinahl and PsycINFO databases were undertaken to identify potentially relevant articles published before March 2013. Search terms included text and MeSH terms for BPSD, dementia and longitudinal study (see online Fig. DS1). Two authors (R.v.d.L. and B.S.) independently searched titles and abstracts for potentially relevant articles. Following this, full text selection was completed by two authors: R.v.d.L. and A.M.P. (or B.S.). References of included studies were

searched backwards and forwards, using the literature database Scopus.

Data synthesis

Data were extracted independently and in duplicate (R.v.d.L. and B.S. or E.E.). Details extracted from each paper included setting, participant recruitment method, number of participants, follow-up time, BPSD and their measurement, number of BPSD measurements, population age (mean and range), baseline Mini-Mental State Examination (MMSE) score,[14] baseline BPSD prevalence, statistical methods used, covariates taken into account and findings on the persistence, incidence and association of BPSD with cognitive function. Risk of bias was not formally assessed in a quality assessment. Findings were divided by dementia severity and BPSD. Dementia severity was defined using MMSE categories based on clinical practice guidelines from the National Institute for Health and Care Excellence (NICE): mild dementia (MMSE score 21–26), moderate dementia (MMSE 15–20), moderately severe dementia (MMSE 10–14) and severe dementia (MMSE <10).[15] When no MMSE score was reported, equivalent cut-off scores from the Cambridge Cognitive Examination (CAMCOG), modified MMSE, Clinical Dementia Rating (CDR) scale and the Alzheimer's Disease Assessment Scale (ADAS) were used.[16–22] By use of results from factor analyses and cluster analysis reported in the literature,[10] symptoms were grouped into affective symptoms (comprising depression, anxiety and apathy), psychosis (comprising delusions and hallucinations), hyperactivity (comprising irritability, agitation and wandering), elation and sleep problems.

Where possible the persistence of symptoms was reported as the percentage of people with a certain symptom at baseline who also had the symptom at the next measurement or for whom the symptom persisted during the entire follow-up period. Incidence was reported as the percentage of people without symptoms at baseline who had developed new symptoms at the next measurement or during the entire follow-up period. Results from a multistate model were reported when available. Studies investigating the association between BPSD and cognitive function were summarised by reporting the analysis methods (e.g. Cox proportional hazards model, latent class linear mixed model or logistic regression model), covariates taken into account, BPSD score and results, including hazard ratios, β coefficients and *F* or *P* values.

Baseline BPSD prevalence, persistence, incidence and association with cognitive impairment were compared for each of the symptoms in the studies that included several BPSD. Prevalence, persistence and incidence were summarised as 'low' if the majority of studies found that the results were lower than that of most of the other symptoms included, 'high' if the majority found that results were higher than for most of the other symptoms and 'moderate' if the results were intermediate or mixed. The range of the results was reported for each symptom.

Results

Owing to considerable heterogeneity in study objectives and methods, inclusion criteria were revised *post hoc*. The following exclusion criteria were added: a follow-up period of less than 3 months; reporting only the prevalence at different time points; symptom measurement through retrospective caregiver report (retrospective studies using medical records were included); and measuring pure major depression or clinical depression only. Studies reporting on minor depression or depressive symptoms only or depression as part of BPSD were included (as discussed in two previous publications).[9,11] From 5923 identified articles 48 were selected for inclusion after the abstract and full-text selection stages. Cross-referencing resulted in an additional 11 studies. In total 59 studies were included.

Study design

Characteristics of the studies included are shown in Table 1 and online Table DS1. The majority of studies recruited participants from psychiatric services including memory and dementia clinics (31 studies out of 59). Participants in these studies typically had moderate dementia (16 studies) and a younger mean age (in 20 studies participants had a mean age below 75 years). Other studies recruited participants from the population (8 studies), primary care (7 studies) or institutional care (8 studies), or recruited volunteers from other settings (4 studies). One study retrospectively reviewed medical records. The 8 studies that reported on care-home residents mostly included older participants (mean age 75 years or over) with moderately severe or severe dementia. Studies recruiting participants without dementia (10 studies) were found for depression only and most of these recruited from the general population (6 studies). Overall, most studies were from the USA or Canada (27 studies) and Europe (29 studies). Follow-up times ranged from 3 months to 14 years: 8 studies had a follow-up period of 1 year or less, 24 studies a follow-up period of 1–5 years and 26 had a follow-up period of 5 years or more.

Symptoms

Included symptoms are shown in Table 1 and their baseline prevalence is summarised in Fig. 1. Full details of each symptom, its definition, the instrument used for its measurement and the baseline prevalence can be found in online Table DS2. Affective symptoms were the most frequently studied (37 studies), with 24 studies reporting on depression only. Anxiety was studied in 11 studies, apathy in 4, and 2 studies reported on a factor of affective symptoms. Psychotic symptoms were studied in 26 studies (delusions in 20, hallucinations in 21, misidentifications in 1, psychosis symptoms combined in 5). Hyperactivity symptoms, including irritability (16 studies), non-aggressive agitation (often including pacing or wandering) (16 studies), wandering (4 studies) or a factor of hyperactivity symptoms (6 studies), were studied in 30 studies. Elation was measured in only 5 studies and sleep problems in 9. Many different instruments exist to measure and define BPSD,[12] and 28 different instruments were used across the included studies. The Neuropsychiatric Inventory (NPI) was used in 8 studies.[23] Five studies used the total score of a BPSD instrument, rather than presenting individual symptom profiles.

Prevalence

The baseline prevalence varied widely across the studies (see Fig. 1). Generally, higher baseline prevalence was reported by studies that included a population with moderate or moderately severe dementia than by studies that included those with severe dementia only. A higher prevalence of symptoms was also seen in studies that recruited participants from psychiatric settings rather than from the population or institutional care settings (e.g. for depression: psychiatric settings 20–57%, institutional care 8–20%, population 22%). Studies with a younger mean age typically showed a higher symptom prevalence (e.g. for delusion: <75 years 24–40%, 75+ years 9–22%). There may also be differences by BPSD instrument. For example, studies that measured symptoms using the BEHAVE-AD typically showed a higher prevalence than studies using the NPI.

Table 1 Sample characteristics of included studies[a]

	No dementia		Mild dementia (MMSE 21–26)		Moderate dementia (MMSE 15–20)		Moderately severe dementia (MMSE 10–14)		Severe dementia (MMSE 0–9)	
Age, years: mean	<75	75+	<75	75+	<75	75+	<75	75+	<75	75+
Studies of persistence and/or incidence of symptoms										
Population-based	52 ●			75 ●						
Primary care								30 ● ● ● ●		
								89 ●		
								50 ● ●		
								36 ●		
Institutional care								76 ● ● ●		31 ● ● ● ● ●
										64 ●
										87 ● ●
Psychiatric services			28 ● ● ● ●	34 ●	39 ● ● ●	32 ● ● ● ●	25 ●	41 ●		
					29 ● ● ● ●	26 ● ● ● ● ●	27 ● ● ●	47 ●		
					88 ● ● ●	70 ● ● ● ● ●	44 ●			
					40 ● ● ●	42 ●				
					35 ● ●	51 ● ● ● ● ●				
					45 ●					
					92 ●					
					46 ●					
					43 ●					
					33 ●					
Volunteers/other								24 ● ●		
Studies of association with cognitive function										
Population-based	52 ●									
	58 ●									
	57 ●									
	54 ●									
	55 ●									
	59 ●									
Primary care								89 ●		
								50 ● ●		
								68 ●		
Institutional care						72 ●				64 ●
Psychiatric services	61 ●		65 ● ●		69 ●	70 ● ● ● ● ●	60 ●	63 ●		
					35 ● ●		67 ●			
					43 ●					
Volunteers/other	53 ●									
	56 ●									
	62 ●									

MMSE, Mini Mental State Examination; NPI, Neuropsychiatric Inventory.
Key:
● Investigated depression, anxiety and/or apathy.
● Investigated delusion, hallucination and/or misidentification.
● Investigated irritability, agitation and/or wandering.
● Investigated elation.
● Investigated sleep problems.
● NPI total score only.
a. Studies identified by reference number. See online Table DS1 for more details.

Symptom persistence and remission

The persistence and stability of symptoms or the change in symptom scores over time were considered for each of the five symptom domains separately. Figure 2 summarises the results of studies investigating the persistence of depression, hallucination and irritability (see online Fig. DS2 for the persistence of all symptoms). Detailed findings are available in online Table DS3

Depression, anxiety and apathy

A large variation in persistence of affective symptoms was seen, with great intra-individual variability.[24,25] Aalten *et al* reported a relatively low persistence of depression, anxiety and apathy,[26] whereas Haupt *et al* reported a persistence of depression of up to 59% over a 2-year period.[27] Anxiety and apathy may be more persistent over time than depressive symptoms,[26,28,29] although two studies reported that anxiety was less persistent than depression.[27,30] Wetzels *et al* (study not included in the figures because it described only the persistence over each observation) found that resolution of anxiety was consistently higher than persistence of symptoms, whereas apathy showed a variable course.[31] Where change was modelled statistically, affective symptoms were generally found to be stable without significant change over time.[32–34]

Delusions, hallucinations and misidentifications

The persistence of psychotic symptoms was mostly below 30% (5 studies), although one study reported that the 6-month persistence of delusions was 59% and hallucinations 52%.[18] Further, multistate models by Eustace *et al* showed delusions were persistent over 12 months in 65%.[28] Generally, hallucinations were less persistent than symptoms of delusion,[18,26,28,35] although one study found similar results for delusions and hallucinations,[27] and two studies found hallucinations were more persistent than delusions.[30,31]

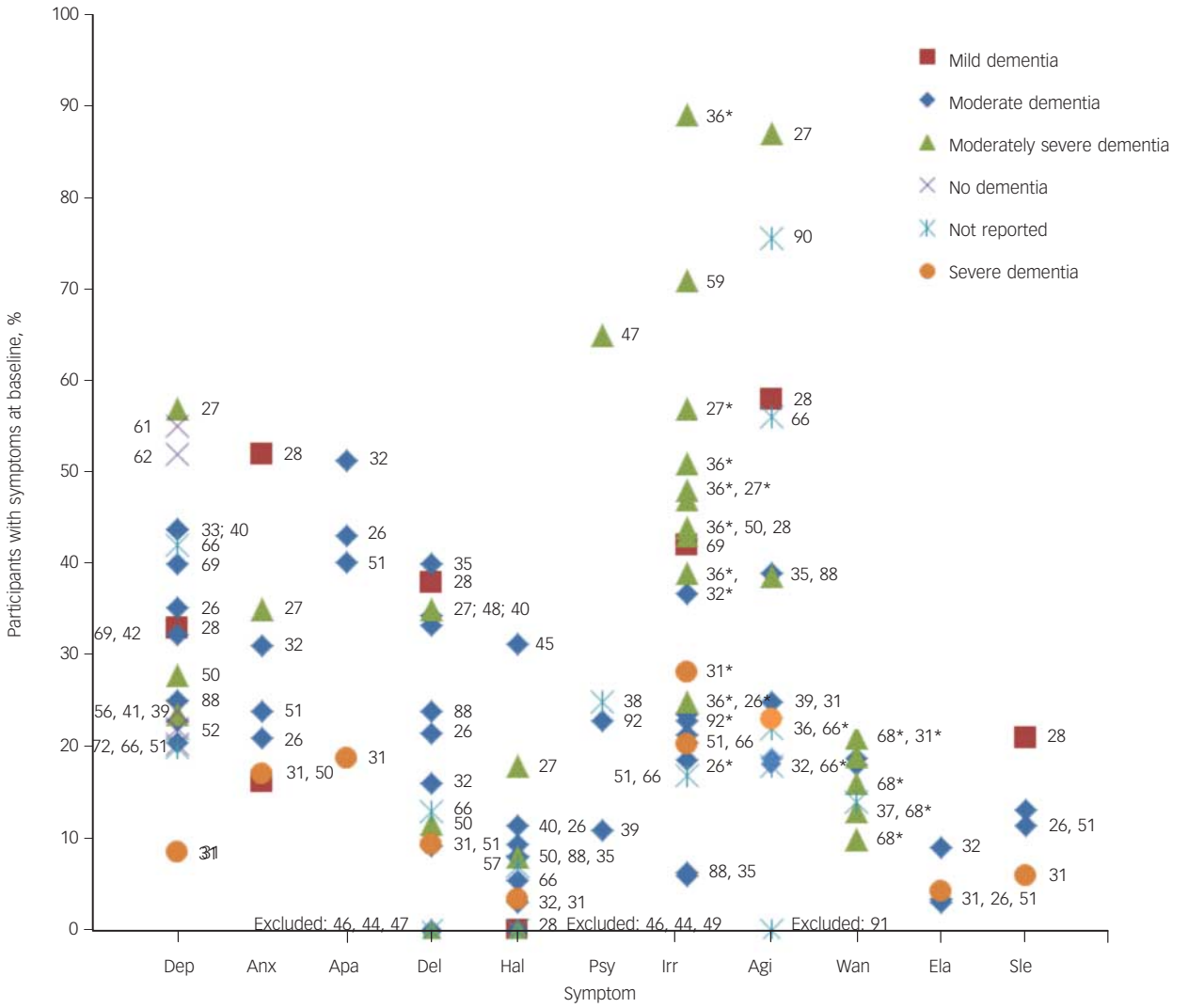

Fig. 1 Baseline prevalence of behavioural and psychological symptoms; see online Table DS2 for more details. Numbers are the reference numbers of the included studies. 'Excluded' indicates that the study excluded participants with a particular symptom at baseline (i.e. the prevalence was 0%). Twenty-six studies that did not report baseline prevalence or reported on a population already included in the figure are omitted. Dep, depression; Anx, anxiety; Apa, apathy; Del, delusions; Hal, hallucinations; Psy, psychosis; Irr, irritability; Agi, agitation; Wan, wandering; Ela, elation; Sle, sleep problems. *Subsymptom reported separately.

Irritability, agitation and wandering

Hyperactivity symptoms were mostly persistent, with one study showing that up to 76% of individuals had persistent symptoms of agitation over 2 years.[27] Studies that investigated several hyperactivity symptoms found that agitation was more persistent than irritability.[18,26,27] A study investigating several symptoms of irritability found that verbal aggression was the most common and longest-lasting form of aggressive behaviour, whereas aggressive resistance and physical aggression were most likely to persist until death.[36] King-Kallimanis *et al* found that wandering status was more likely to change from wandering to non-wandering rather than the reverse and that wandering was a temporary phase for approximately half of care-home residents who were admitted as wanderers.[37] Several authors analysed the course of hyperactivity over time using repeated measures analysis or a latent class linear mixed model. Garre-Olmo *et al* reported that over a 2-year period hyperactivity symptoms were mostly low and smoothly increasing (this pattern was found in two-thirds of participants).[32] Cohen-Mansfield *et al* found that aggressive behaviours increased over time whereas physically non-aggressive behaviours did not change significantly.[38]

Elation

The persistence of elation was investigated in only two studies. Wetzels *et al* found in severe dementia that, for each two consecutive assessments at 0–6 months, 6–12 months, 12–18 months and 18–24 months, symptoms were stable in 39%, 18%, 3% and 3% respectively.[31] Over a total follow-up period of 2 years Aalten *et al* found in moderate dementia that symptoms were stable over a 6-month period in 2%, whereas for none of the participants did symptoms persist over 12 months, 18 months or 24 months.[26] Therefore, these results suggest that elation is not persistent.

Sleep problems

Most studies that investigated sleep problems (4 studies) reported low persistence,[26,29,30] or a fluctuating course.[31] In only one study were sleep symptoms reported to be persistent.[28]

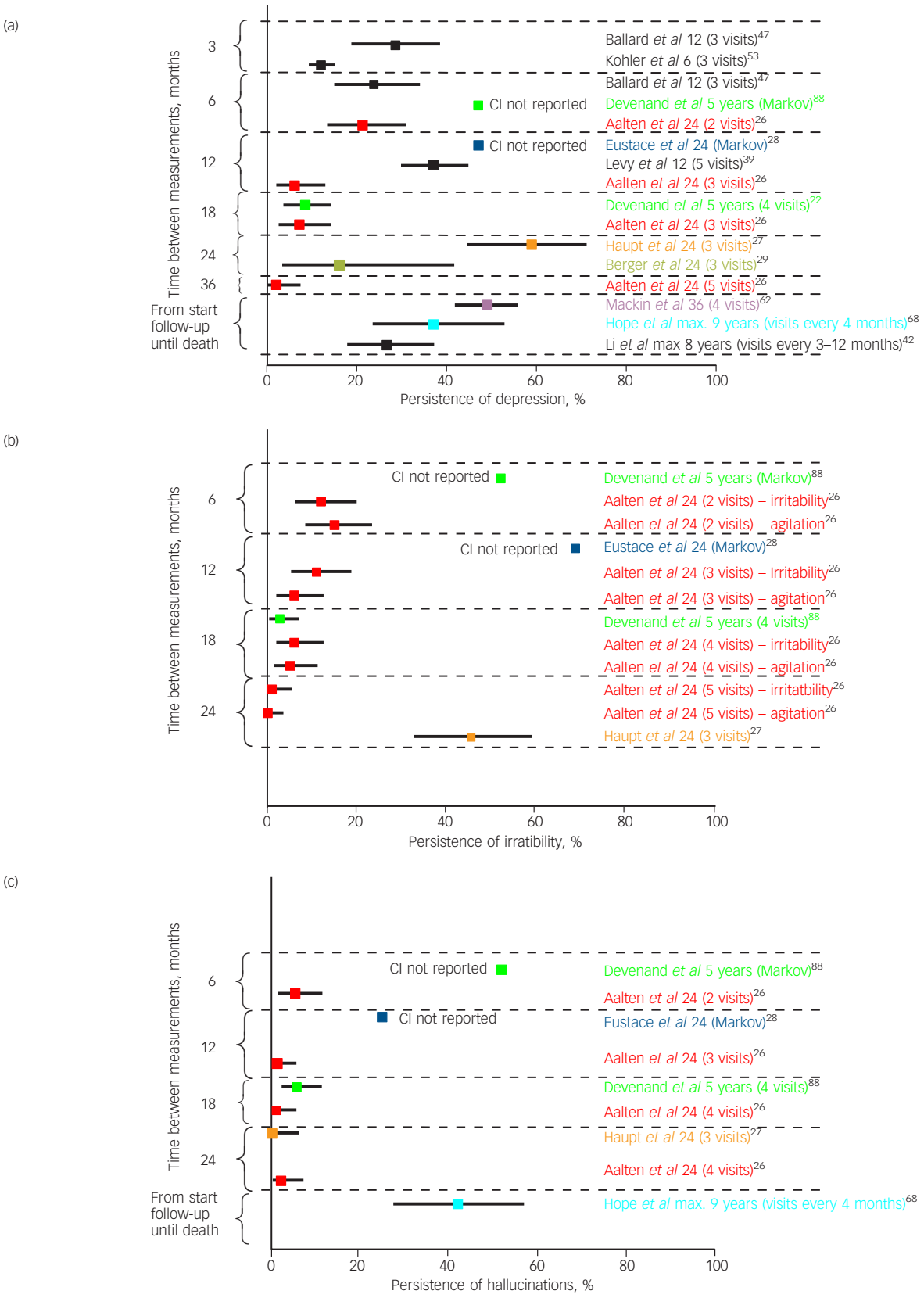

Fig. 2 Persistence of (a) depression, (b) irritability and (c) hallucinations.Squares indicate the reported percentage where the symptom persisted over the measurement period and the lines indicate 95% confidence intervals. The name of the first author is given next to the corresponding findings. If the study reported the persistence over several intervals, it is included in the figure more than once. Next to the name of the author the total follow-up time (in months unless specified) and the number of visits are reported. For example, Aalten *et al* measured symptoms at 5 visits over 24 months and reported on the percentage of participants with depression present at any consecutive period of 6 months (depression present at 2 visits), 12 months (present at 3 visits), 18 months (present at 4 visits) or 24 months (present at 5 visits).

Incidence and absence of symptoms

Online Table DS4 and Fig. DS3 show the incidence of symptoms and the percentage of participants who did not have symptoms during the follow-up period. A summary is shown in Fig. 3.

Depression, anxiety and apathy

Affective symptoms commonly develop in people with dementia. Over a 1-year period a high or moderate depression incidence of up to 37% was reported by eight studies,[26-28,31,39–42] whereas in others the onset of depression was low compared with other symptoms.[18] The incidence of apathy has been reported to be particularly high: 64% over 2 years,[26] and 14–27% over a 6-month period.[31]

Delusions, hallucinations and misidentifications

In four studies the probability of new-onset hallucinations was reported to be low,[18,27,28,31] whereas in another four incidence was reported to be moderate or high.[26,41,43,44] Other psychotic symptoms including delusions showed a consistently moderate incidence (11 studies).[18,26,27,39,40,44–49]

Irritability, agitation and wandering

All included studies that compared the incidence of hyperactivity with other symptoms (9 studies) concluded that the incidence of hyperactivity was high or moderate.[18,26–28,31,39,40,50,51] Although the incidence of agitation might be particularly high,[18,27,35] wandering might develop less often.[37]

Elation

The incidence of elation was investigated by three studies that used the NPI. Aalten *et al* reported a cumulative incidence over a 2-year period in 5%,[26] Wetzels *et al* reported that for each 6 months of observation new symptoms were seen in 3–4%,[31] and Gillette-Guyonnet *et al* reported that new symptoms developed during a maximum follow-up of 4 years in 8%.[51] These results suggest the incidence of elation is low.

Sleep problems

The probability of the onset of sleep problems was reported in four studies. No consistent findings were reported: at each 6-month period the incidence in one study was 15%,[28] and in another 2–8%,[31] whereas over a total follow-up of 2 years symptoms developed in 31%,[26] and over 4 years in 11%.[51]

Association with cognitive function

The results of studies investigating the association between the course of BPSD and cognitive function (25 studies) are summarised in online Table DS5.

BPSD and subsequent cognitive function

Eight studies investigated the association between depression and subsequent cognitive decline or development of dementia in those without dementia at baseline.[52–59] Those with persistent depression showed significant decline over time in global cognitive function, memory, processing speed, recall and attention.[52,53,58] Some found a slight increase in depression score before dementia diagnosis compared with those who did not develop dementia,[55,59] whereas others did not find a significant change in depression before dementia diagnosis.[56,57] In those with dementia, associations with progression of cognitive function were found for psychosis,[45,60] hyperactivity,[43] and depression.[33] Two studies investigated the link between BPSD and mild cognitive impairment. In one study persistence of depression was associated with progression to dementia,[61] whereas another reported no difference in persistence between those who were cognitively stable and those who progressed to dementia.[62]

Cognitive function and BPSD development

In individuals with dementia, psychosis, hyperactivity, agitation and physical aggression were associated with greater cognitive impairment.[26,35,38,63–65] In contrast, Marin *et al* found no association in dementia between cognitive impairment and depression, delusion, agitation and irritability.[66] Four studies found that symptoms increased with cognitive decline in the early stages of dementia and were most commonly seen in moderate dementia, followed by a declining or stable course in the final stages of dementia.[35,63,64,67] Cognitive function at onset of wandering was found to differ by type of wandering behaviour; for example, results suggested that excessive walking was more common in mild dementia, whereas in severe dementia getting lost was more likely.[68] No association was found between cognitive function and depressive symptoms in those with dementia,[69,70] whereas in those without dementia and without depression at baseline, cognitive impairment at baseline was associated with an increase of depressive symptoms over time.[54] In those aged 70 years and over cognitive function was found to be associated with initial scores for depression and anxiety, but not with symptom change over time.[71] Baseline dementia diagnosis was not significantly associated with severity of depression at follow-up.[72]

Comparison of symptoms

We summarised the studies investigating several BPSD to compare baseline prevalence, stability, incidence and association with cognitive function for each of the symptoms (Table 2). Some symptoms were studied more often than others, and evidence is lacking for infrequently studied symptoms such as wandering (included in only one study investigating several BPSD),[30] and apathy and elation (included in only four studies).[26,31,32,51] Depressive symptoms were most often studied (included in 12 of the 13 studies investigating several BPSD).[18,26–32,39,40,50,51] Compared with other symptoms, the results suggest that the persistence and incidence of depressive symptoms are moderate. Anxiety seems to be less prevalent and was reported to have a moderate persistence and incidence.[26–31,51] The few studies investigating apathy suggest a high prevalence, persistence and incidence of symptoms.[26,31,32,51] The prevalence, persistence and incidence of psychotic symptoms were suggested to be low to moderate, and may be particularly low for hallucinations.[18,26–32,35,39,40,50,51] Symptoms of hyperactivity were most frequently seen and the majority of studies reported a higher persistence and incidence compared with other symptoms.[18,26–29,31,32,35,39,40,50,51]

Discussion

This systematic review confirms that BPSD are common and relatively persistent in individuals with dementia. The results suggest there are differences between symptoms: hyperactivity and apathy showed high persistence and incidence; depression and anxiety low or moderate persistence and moderate incidence; and psychotic symptoms low persistence and a moderate or low incidence. Studies of the association between BPSD and cognitive function suggest that in those without dementia the presence of depression is associated with subsequent cognitive decline. In

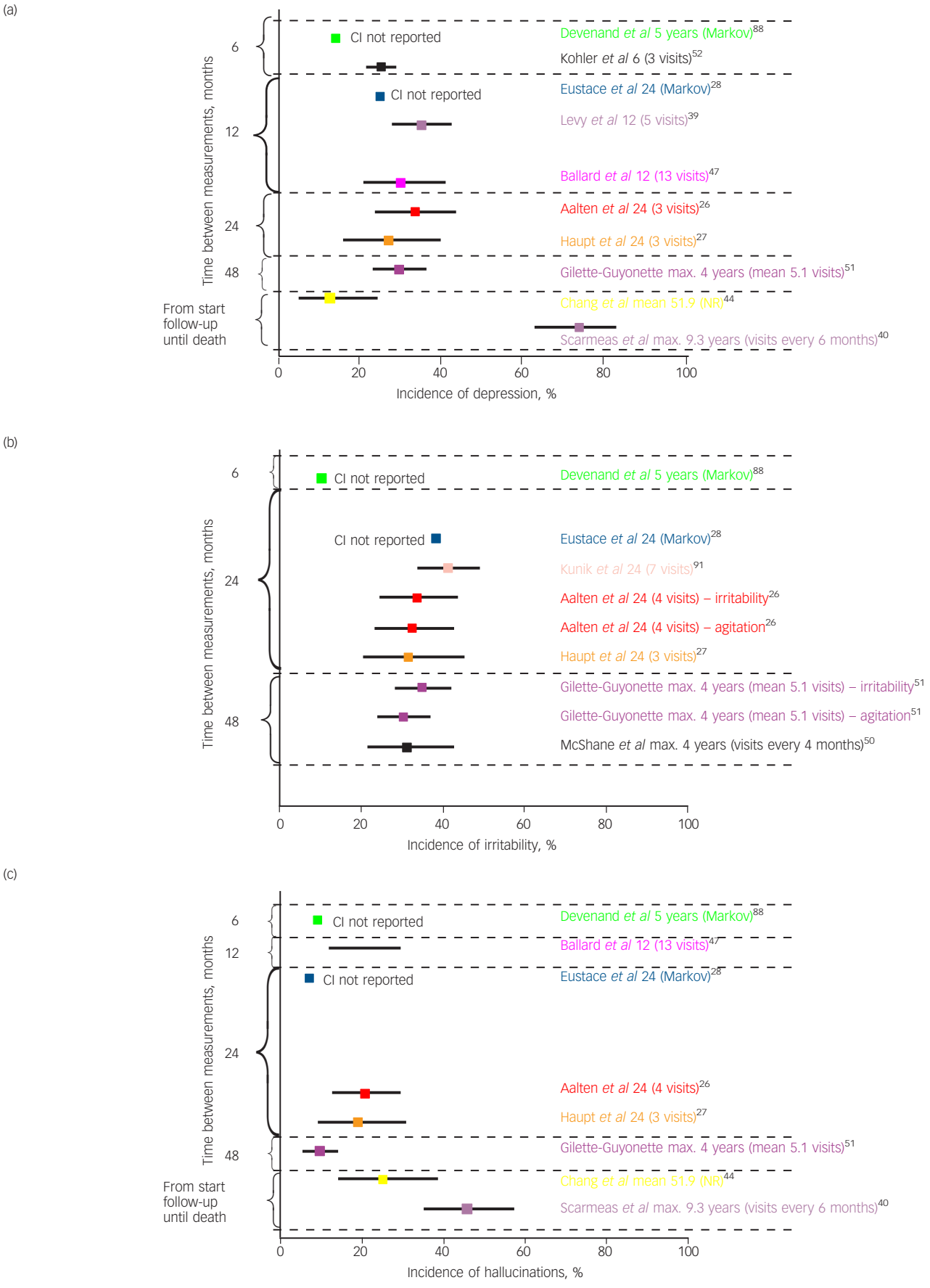

Fig. 3 Incidence of (a) depression, (b) irritability and (c) hallucinations. See Fig. 2 for an explanation of the symbols. NR, not reported.

Table 2 Results of 13 studies reporting at least two behavioural and psychotic symptoms of dementia

Symptoms	Number of studies	Baseline prevalence (%) 11 studies	Persistence (%)[a] 10 studies	Incidence (%)[b] 9 studies
Affective	12	High	Moderate	Moderate
Depression	12	High (8–57%)	Moderate (16–70)	Moderate (10–73)
Anxiety	8	High (17–52%)	Moderate (17–52)	Moderate (12–38)
Apathy	4	High (19–51)	High (20–55)	High (27–64)
Psychosis	13	Low	Moderate	Moderate
Delusions	10	Moderate (9–40)	Low (0–82)	Moderate (5–84)
Hallucinations	11	Low (0–18)	Low (0–52)	Low (4–45)
Hyperactivity	12	High	High	High
Irritability	9	High (6–57)	Moderate (12–80)	High (10–69)
Agitation	7	High (18–87)	Moderate (21–77)	High (19–80)
Wandering	1	NR	High (60)	NR
Elation	4	Low (3–9)	Low (2–39)	Low (4–5)
Sleep problems	7	Moderate (6–11)	Low (10–57)	Low (8–31)

NR, not reported.
a. Percentage of symptoms persistent over 3 months or more.
b. Percentage incidence over 3 months or more.

those with dementia, psychosis, hyperactivity, agitation and physical aggression were associated with greater cognitive impairment.

Strengths and limitations

Standardised procedures were used for the literature search and data extraction, including double reading to ensure quality. However, no established search term for BPSD exists and therefore relevant studies may have been missed. The reference lists of included articles and reviews were searched to minimise the number of missed articles. The review included studies with a high degree of heterogeneity in study design and population characteristics, including large differences in the period over which the persistence and incidence was reported (1 month to 4 years), the total follow-up time (3 months to 14 years), the instrument and cut-off score used to measure symptoms, the number of symptoms measured, dementia severity, recruitment setting and mean age. This made cross-study comparisons difficult and a meta-analysis was not possible. We were not able to investigate whether the course of BPSD differs between types of dementia as only five of the 59 studies reported findings by dementia type. We adhered to most of the items of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (see online Table DS6).[73] Although we have reported on a range of factors that might influence the quality of the study, risk of bias was not formally assessed in a quality assessment. Our review therefore does not meet items 12, 15, 19 and 22 of the guidelines. Bias in the included studies may have led to an overestimate of persistence (e.g. participants remained under medical attention) or to an underestimate of persistence (e.g. gaps in the follow-up period or attrition through death or care-home admission). In addition, the review protocol was not registered.

Study differences

Many different instruments exist to measure BPSD,[74] and 28 different instruments were used by the studies included in this review. However, the increasing use of the NPI might improve comparability of future studies.[13] The NPI was used by eight studies. In these studies the baseline prevalence seemed lower than that reported by studies using other instruments (e.g. for irritability, NPI rates were 19–37%, Present Behavioural Examination (PBE)[93] 25–89% and BEHAVE-AD[94] 42–57%). The total score on the NPI significantly increased over time,[26,34,75] and symptoms were mostly shown to be persistent,[26,31] stable or increasing.[32,76] The incidence reported by the studies using the NPI was low or moderate compared with studies using other instruments.[26,31,51]

Loss to follow-up is a challenge in longitudinal studies, and we have reported the number of participants at the end of the follow-up period for the included studies (online Table DS1). There was large variation in follow-up completion (24–100%, although often not reported) and reasons for leaving the study were often not reported. Persistence of BPSD may be associated with mortality and with refusal to participate in follow-up interviews, and differences in follow-up completion may have influenced the results. Furthermore, we have used study baseline as a proxy for disease and symptom onset and this may have affected the findings on the persistence of symptoms. Symptom course may be influenced by pharmacological or non-pharmacological interventions. Although there was large variation in medication use between study populations, in the majority of studies that included a sensitivity analysis the results were not altered when taking into account medication use. As we are not aware of a formal definition of high prevalence, persistence or incidence, we summarised the findings as 'low' if the majority of studies found that the results were lower than that of most of the other symptoms included, 'high' if the majority found that results were higher than for most of the other symptoms and 'moderate' if the results were intermediate or mixed.

Interpretation of findings

Prevalence

The prevalence of symptoms varied across the studies and between symptoms. Depression, apathy, irritability, agitation and wandering showed a high prevalence, whereas the prevalence of anxiety, hallucination and elation was low. Some studies consistently reported a relatively low prevalence of symptoms,[18,26,31,66] whereas others consistently reported a relatively high prevalence.[27,28,32] Differences might be due to variability in study design, population characteristics or measurement of symptoms. Indeed, a higher prevalence of symptoms was generally seen in studies that recruited participants with less severe dementia, in studies that recruited from psychiatric settings rather than from the population or institutional care settings, and in studies with a younger mean age. There may also be differences due to the BPSD instrument used.

Persistence

Large differences in persistence were seen across symptom groups and individual symptoms. Affective symptoms (including depression, anxiety and apathy) generally showed a moderate persistence, although a limited number of studies reported persistence of apathy to be high and in one study it was reported to be higher than for any other symptom.[26] Persistence of psychosis was low to moderate. In contrast, hyperactivity symptoms showed a high persistence. This is an issue of concern as these symptoms are among those most problematic for caregivers.[77,78] A low persistence was seen for elation and sleep problems. Differences in symptom persistence may reflect the nature of the symptom or might be explained by factors such as more widely available treatment options for depression and anxiety. Differences in dementia severity and baseline BPSD prevalence are likely to have affected results on persistence of symptoms. Persistence may be higher in those with more severe cognitive impairment at baseline,[32,35,38,46] and a higher BPSD prevalence.[32,39] However, associations between study characteristics and results could not be tested because of the large degree of heterogeneity in study design and population characteristics.

Incidence

The results suggest that affective symptoms and hyperactivity symptoms commonly develop in people with dementia. Large differences in reported incidence were seen between studies. For example, the reported incidence of depression ranged from 12% over a mean follow-up period of 52 months,[44] to 73% over a maximum follow-up period of 9.3 years.[40] Differences in study design and differences in baseline prevalence of symptoms are likely to have influenced the results. For example, the reported incidence might be higher in studies that reported a high baseline prevalence,[27] compared with studies with a low baseline prevalence,[18,28] although no formal analysis of the association between study characteristics and incidence was possible.

Role of cognition

The presence of depression before the onset of dementia was associated with subsequent cognitive decline.[52,53,58] In dementia, psychosis, hyperactivity, agitation and physical aggression were associated with greater cognitive impairment.[35,38,63–65,70] Symptoms may be most common in moderate dementia, followed by a declining or stable course in the final stages of dementia.[35,63,64] However, heterogeneity in the pattern of findings across studies investigating the associations between BPSD and cognitive function prevented us from drawing more specific conclusions. The heterogeneity of results does, however, suggest that BPSD do not solely arise secondary to cognitive impairment.

Study implications

The results from this systematic review suggest that some symptoms such as hyperactivity are more persistent than others such as elation and sleep problems. In particular apathy, irritability, agitation and wandering showed a high persistence. These symptoms should be targeted in clinical trials to improve management and intervention. Clinical trials typically follow participants with more severe dementia over a short period.[79,80] However, results presented here show that symptoms may persist over long periods until death,[18,30,42] and may be most common in moderate dementia.[35,63,64,67] Clinical trials focusing on the earlier stages of dementia with a long follow-up time might therefore be particularly informative. Results could also inform patients and care providers about which symptoms are most likely to recur, so that measures can be put in place to reduce their impact. Recommendations for monitoring of patients and symptom management interventions are outlined in guidance by the Alzheimer's Society.[81]

Future research

The heterogeneity in methods and results emphasises the importance of clearly reporting the study design, population characteristics and symptom definitions. Table 1 shows that studies typically included younger populations with moderate dementia, whereas studies recruiting those with mild or moderate dementia from the population or from primary care settings were lacking. As BPSD patterns may differ in these populations, they should be the focus of future studies. In addition, all included studies were conducted in high-income countries and the findings may therefore not be applicable outside these settings. Apathy was infrequently studied, and as the limited results suggest that it may have a high persistence and incidence, we recommend that this symptom should be the focus of future studies on symptom course.

These methodological issues reiterate the findings from several of our previous reviews. A review of reviews showed a focus on individual symptoms (particularly depression), raised the question how best to define and measure BPSD within and across populations, and recommended reporting more clearly the characteristics of the population, the inclusion and exclusion criteria and how BPSD were defined and measured.[9] Two reviews concluded that there were many instruments to measure BPSD,[12,13] of which the NPI – a short, informant-based questionnaire measuring ten symptoms – has been cited most frequently and should form the core of any battery, although researchers choosing instruments should carefully address any gaps in its content with regard to their research question. In a guest editorial we discussed that the populations used in studies of depression and BPSD are often not quite comparable and that the results therefore cannot be readily extrapolated.[11] Finally, we showed that studies investigating symptom groups show relatively consistent results, although there remains a large amount of individual variability.[10]

Studying covariates that may be associated with higher persistence of BPSD, including impairment in activities of daily living,[27,32,64] as well as medication use,[38,46] could improve understanding of potential mechanisms involved in the presence and persistence of BPSD. Environmental factors such as overstimulation and a person's surroundings, as well as physical factors such as pain and dehydration, are recognised as important triggers for BPSD.[5,82–85] These factors are often difficult to capture and have not been investigated in the studies included here.

Clinical implications

Our findings underscore the existing evidence that BPSD are common in dementia and that they are also relatively persistent. Different symptoms have a variable course over time: for example, psychotic symptoms have relatively low persistence – that is, they may resolve during the course of the dementia. In contrast, apathy emerged as the only individual symptom with high baseline prevalence, high persistence and also a high incidence during the course of the dementia. Thus, increased interest in apathy as a possible early sign of dementia, as a marker for underlying brain changes and as a sign of progression of dementia seems entirely warranted.[86] Although hyperactivity as a whole also had high baseline prevalence, high persistence and high incidence over time, the various symptoms subsumed under hyperactivity mean that it

is not a unitary phenomenon. These findings are relevant to clinicians as they indicate which symptoms may be expected to persist or to occur anew, and therefore give a better understanding of the natural history of BPSD which, in turn, can influence approaches to management and treatment.

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First received 18 Mar 2014, final revision 19 Dec 2015, accepted 27 Feb 2016

Funding

R.v.d.L. received a studentship from the National Institute for Health Research Collaborations for Leadership in Applied Health Research and Care for Cambridgeshire & Peterborough. A.M.P. was supported by the Medical Research Council (MRC RG56433 and MR/K021907/1).

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Fig. DS1 Overview of the search terms
Table DS1 Characteristics of included studies
Table DS2 Definition and baseline prevalence of BPSD
Fig. DS2 Persistence of BPSD reported in included studies
Table DS3 Persistence and remission of symptoms in those with symptoms at baseline
Table DS4 Incidence and absence of symptoms in those without symptoms at baseline
Fig. DS3 Incidence of BPSD reported in included studies
Table DS5 Association BPSD and cognitive function
Table DS6 Adherence to the PRISMA reporting guidelines
Online reference list of included studies

Fig DS1 Overview of the search terms

DEPRES	ANXIETY	APATHY	SLEEP	IRRITABI	PSYCHO	WANDER	ELATION	AGITATI	BPSD
MeSh Depressive disorder Depression	**MeSh** Anxiety disorders Anxiety	**MeSh** Apathy	**MeSh** Sleep disorders Sleep Sleep Apnea, Obstructive Sleep Initiation and Maintenance Disorders	**MeSh** Irritable mood	**MeSh** Psychotic disorders Delusions Paranoid behavior Hallucinations	**MeSh** Wandering behavior	**MeSh** Euphoria	**MeSh** Psychomotor agitation Aggression Anger	**Text[tiab]** "neuropsychiatric symptoms" "neuro-psychiatric symptoms" "psycho-behavioral symptoms" "psycho-behavioural Symptoms" "psychiatric symptoms" "Behavioral symptoms" "behavioural symptoms" "psychological symptoms" "disruptive behaviour" "disruptive behaviour" "noncognitive symptoms" "non-cognitive symptoms" "neuropsychological symptoms" "bpsd"
Text[ti ab] dysphoria depression depressive depressed	**Text[tiab]** anxiety anxious	**Text[tiab]** Apathy "lack of interest"	**Text[tiab]** Sleep	**Text[tiab]** irritability lability "mood change" "mood changes"	**Text[tiab]** psychosis psychotic delusion delusions delusional hallucination hallucinations misidentification	**Text[tiab]** wandering stalking "getting lost" Aberrant motor behaviour	**Text[tiab]** euphoria elation disinhibition laughter	**Text[tiab]** agitation agitated aggression rage "catastrophic reactions" anger angry complaining negativism screaming	
AND Dementia: Dementia [Mesh] OR dementia* [tiab] OR alzheimer* [tiab] OR "lewy body" [tiab] OR "lewy bodies"[tiab] OR frontotemporal [tiab]									
AND Longitudinal study: Longitudinal studies [Mesh] OR longitudinal[tiab] OR prospective[tiab] OR "follow-up study"[tiab]									

Depres: Depressive symptoms; Sleep: sleep problems; Irritabi: Irritability; Psycho: Psychosis; Wander: Wandering; Agitati: Agitation; BPSD=Behavioural and Psychological Symptoms of Dementia

Note: Shown are the search terms used in Pubmed, the Mesh terms used in the other literature databases may differ slightly.

Table DS1 Characteristics of included studies

	Author	Year	Setting	Details setting	Reports	Months follow-up	n BPSD measures	Time between measures (months)	n at baseline	n with complete follow-up	Baseline MMSE	Dementia type	Age minimum	Age mean	BPSD instrument	Interview	BPSD
Mild dementia (MMSE 21-26)																	
22	Eustace	2002	DC	National referral centre for people with memory disorders, Ireland	Per, Inc	24	3	12	216	52	21.6	AD	NR (SD 7.8)	73.3	BEHAVE-AD	INF	Dep, Anx, Irr, Agi/Wan, Hal, Del, Sle
16	Clare	2012	DC	Memory clinics in North Wales, UK	Per	20	3	8-12	101	51	24.2 (18+)	AD, VD, mixed		78.7	HADS; NPI	INF	Dep, Anx, Total score
52	Tschanz	2011	PB	Cache County Study, USA	Per	Mean 3.8 yrs., max 12.9 yrs.	Mean 1.9	NR	328	33%	21.9	AD		85.9	NPI	INF	Total score
Moderate dementia (MMSE 15-20)																	
39	Levy	1996	NR	NR (clinical trial), USA	Per, Inc	12	5	3	215	181	20	AD	51	70.8	ADAS	INF	Dep, Agi/Wan, Psy
8	Berger	2005	DC	Outpatient Memory Clinic of university, Germany	Per, Inc	24	5	3-6	45	18	20	NR	48	70.6	BEHAVE-AD	CLIN?	Dep, Anx, Hal, Del, Irr, Agi/Wan, Sle
29	Holtzer[1b]	2005	DC	3 sites in USA and 2 sites in Europe (Paris and Greece) (1b)	Cog	max: 14 yrs.	max: 28	6	536	130 (5 yrs.)	NR	AD		74	CUSPAD	INF	Dep
51	Scarmeas[1b]	2007	DC	See 1b	Per, Cog	max:14 yrs.	max:25	6	497	NR	16+	AD	49	74	CUSPAD	NR	Agi, Irr, Wan
50	Scarmeas[1b]	2002	DC	See 1b	Inc	max: 9.3 yrs. (mean 5.5 yrs.)	NR	6	87	NR	NR	AD		70.7	CUSPAD	INF	Dep, Behavioural (Agi, Wan, Irr) , Hal, Del
20	Devanand[1a]	1997	DC	3 medical centres, USA (1a)	Per, Inc	5 yrs. (mean 3 yrs.)	7	6	235	137	NR	AD	82.1% 65+	73.1	CUSPAD	INF	Dep, Irr, Agi/Wan, Hal,Del, Mis
28	Holtzer[1a]	2003	DC	See 1a	Per, Inc, Cog	5 yrs.	11	6	236	102	NR	AD		72.7	CUSPAD	INF	Irr, Agi/Wan, Hal, Del
24	Garre-Olmo	2010	DC	Memory Clinic of hospital, Spain	Per	24	5	6	491	253	NR	AD	48	75.2	NPI	INF	Apa, Dep, Anx, Irr, Agi/Wan, Hal, Del, Sle, Eat, Dis
1	Aalten[2]	2005	DC	Outpatients of Memory Clinic of University Hospital, or psychiatry clinic, The Netherlands (2)	Per, Inc	24	5	6	199	99	18.1	AD, VD, LBD, mixed	53	76.4	NPI	INF	Apa, Dep, Anx, Irr, Agi/Wan, Hal, Del, Sle, Ela, Eat, Dis

2	Aalten[2]	2005	DC	See 2	Per, Cog	24	5	6	199	99	18.1	AD, VD, LBD, mixed	53	76.4	NPI	INF	Apa, Dep, Anx, Irr, Agi/Wan, Del, Hal, Sle, Ela, Eat, Dis
25	Gillette-Guyonnet	2011	DC	16 memory clinics in France, community dwelling	Inc	max 48	mean 5.1	6	686	207	20.0 (10-26/30)	AD		77.9	NPI	INF	Apa, Dep, Anx, Irr, Agi/Wan, Sle, Hal, Del, Ela
59	Zahodne	2013	DC	Outpatient clinics and clinical research centres at 3 sites in USA and 1 in France	Per, Cog	5.5 yrs.	mean 10.1	6	509	167	NR	AD		74.2	CUSPAD	INF	Dep
49	Rosen	1991	DC	Ambulatory care setting, living in the community, USA	Per, Inc	6 yrs.	7	1 yr.	32	7 at least 3 assess-ments	15.5	AD	NR (SD 7.9)	70.3	DSMIII	INF + PAR	Hal, Del
48	Paulsen	2000	DC	Alzheimer's Disease Research Centre of University, USA	Inc	Until death, reported for 5 yrs.	5	1 yr.	329	NR	NR	AD	NR (SD 6.4-7.7.7)	72.6	DIS for the DSMIII	INF	Hal, Del
56	Wilkosz	2006	DC	Alzheimer disease research centre of University, USA	Inc	mean: 25.8	NR	1 yr.	NR	288 at least 1 follow-up	20.09	AD or MCI	38	74.3	CERAD	INF	Hal, Del
Moderately severe dementia (MMSE 10-14)																	
19	Deudon	2009	CH	Nursing homes in 2 regions, France	Per	3	3	1 or 2	132	114	12.1	Not reported	NR (SD 6.7)	86	CMAI, NPI and Observation Scale	INF	Agi, Irr, Psy, Hyperactivity (Wan, Ela, Irr)
23	Fauth	2006	NR	Community outreach and in-home respite programs (control group only), USA	Per	3	4	1	85	NR	13.3	Not reported	NR (SD 8.8)	79.6	Daily record of behaviour (DRB)	OBS	Dep, Agi/Wan, Irr, Sle, Total score
6	Ballard[3]	1996	CLIN/ DC	Old-age psychiatry services and a memory clinic, UK (3)	Per, Inc	12	12	1	124	89	NR	AD, VD, DLB	NR	79.7	Cornell scale	INF + PAR	Dep
5	Ballard[3]	1997	CLIN/ DC	See 3	Per, Inc	12	12	1	125	87	NR	AD, VD, DLB	NR	79.9	Burn's symptom checklist	NR	Psy
35	Keene[5]	1999	CLIN	Recruited through local general practitioners, community psychiatric nurses and consultant old-age psychiatrists, UK (5)	Per	max: 10 yrs.	30	4	99	NR (n=88 followed until death)	NR	AD, VD		NR	PBE	INF	Irr
31	Hope[5]	2001	CLIN	See 5	Cog	max: 9 yrs.	mean:10.5	4	86	NR (n=77 until death of which 75 >1yr)	NR	AD, VD		NR	PBE	INF	Wan
44	McShane[5]	1995	CLIN	See 5	Per, Cog	max: 5 yrs. (until death)	NR	4	98	41 (who had died)	13	AD		NR	PBE	INF	Hal
30	Hope[5]	1999	CLIN	See 5	Per	max: 9 yrs.	NR	4	100	48 (at least 1 yr.)	14	AD, VD, mixed, other	60	78	PBE and Past behavioural history	INF	Dep, Anx, Irr, Hal, Del, Sle, Wan, Eat

														interview		
45	McShane[5]	1998	CLIN	See 5	Inc, Cog	max: 4 yrs. (until death)	NR	4	86	80 (>4yrs or until death)	15	AD, VD, DLB, Other		77	PBE	INF	Dep, Anx, Irr, Hal, Del
4	Asada	1999	DC + VOL	Outpatients at clinic, voluntary patients whose caregivers were members of a self-help network and patients identified by formal service providers, Japan	Cog	5 yrs.	6	12	103	31	NR	AD	NR (SD 8.7)	79.4	Troublesome behaviour scale (TBS)	INF	Agi/Irr factor, Wan factor
47	Neundorfer	2001	DC	University hospitals, Alzheimer disease research centre, USA	Per	max:5 yrs.	max:10	12	353	NR	NR	AD, other	50	73	CERAD	INF	Dep
43	McCarty	2000	DC	Memory Disorders Clinic at University, USA	Cog	24	3	12	150	61	13.52	AD	56	74.2	Memory and Behaviour Problem Checklist-Revised	INF	Apa factor; Dep/Anx/Agi/Wan/Irr factor
26	Haupt[4]	1996	DC	Outpatient Clinic of University, Germany (4)	Cog	24	3	12	90	61	NR	AD	57	74.3	BEHAVE-AD	INF + PAR	Hal, Del
27	Haupt[4]	2000	DC	See 4	Per, Inc	24	3	12	90	60	13.5	AD	57	73.4	BEHAVE-AD	INF + PAR	Dep, Anx, Irr, Agi/Wan, Hal, Del
14	Chang	2004	DC	Memory clinic for veterans, Taiwan	Inc	mean: 51.9	NR	NR	56	NR (>1 visit)	NR	AD	NR (SD 8.8)	74.2	SCID DSM IIIR	INF + PAR	Dep, Hal, Del
Severe dementia (MMSE 0-9)																	
55	Wetzels	2010	CH	Dementia special care units from nursing homes, The Netherlands	Per, Inc	24	5	6	290	117	7.6	AD, VD	NR (SD 7.4)	81.7	NPI nursing home version	INF	Apa, Dep, Anx, Irr, Agi/Wan, Hal, Del, Sle, Ela, Eat, Dis
12	Burgio	2007	CH	Nursing homes, USA	Per, Cog	18	4	6	78	55	8	AD, VD, mixed, uncertain	59.8	82.2	Modified NHBPS and observation	INF + OBS	Irr

18	de Rooij	2012	CH	5 long-term care settings in The Netherlands and Belgium	Per	12	3	6	179	126	S-MMSE 6.1	Not reported	NR	85.9	QUALIDEM	INF	Dep, Agi
Normal cognitive function (MMSE 27+, no dementia)																

37	Kohler	2010	POP	Collaborative network of family practices, the Netherlands	Per, Inc, Cog	6	3	3	598	412	27.7 (MMSE<24 excluded)	Not reported	60	69.4	Symptom Checklist	NR	Dep
7	Becker	2009	POP	Non-institutionalised individuals from the Part A Medicare list, USA	Cog	max: 9 yrs.	9	12	441	288 (at least 3 measures)	NR (cognitively normal at baseline)	AD	70	77.5	CES-D	NR	Dep
53	Vinkers	2004	POP	Population-based study of all 85 year old inhabitants of city, The Netherlands	Cog	4 yrs.	5	12	500	298	27 (MMSE<19 excluded)	Not reported	All aged 85	85	GDS15	NR	Dep
3	Amieva	2008	POP	Population-based sample of community dwelling individuals, France	Cog	max: 14 yrs.	7	12-36	350 who developed AD and 350 control	25 AD and 24 control	NR Dementia free at baseline, those who developed dementia during follow-up compared to control.	AD	65	86.2	CES-D	NR	Dep
58	Wilson	2010	POP	Census of a geographically defined region of city, USA	Cog	max: 8-9 yrs.	mean:3.6/4.0	36	357+340	NR (100% / 90% "longitu-dinal data")	Initially dementia free; 20.4 at dementia diagnosis	AD	65	82.5	CES-D (10-item) and Hamilton Depression Rating Scale (0-35)	INF + PAR	Dep
9	Bielak	2011	POP	Electoral role Australian citizens, Australia	Cog	max: 15 yrs. (mean: 6.0 yrs.)	5	2-6yrs	1,206	NR	NR (without dementia)	Not reported	70	78.16	CES-D	PAR	Dep
32	Houde	2008	DC	Memory Clinic of university General Hospital, Canada	Cog	max: 10 (mean: 4.3 yrs.)	max:11	1	60	NR	27.2 (MCI)	MCI, AD	55	74.5	GDS	NR	Dep
21	Dotson	2008	VOL	Community dwelling generally healthy group of volunteers, USA	Cog	max 26 yrs. 9mean: 4.4 yrs.)	NR	24	1,586	NR	28.65 (without dementia)	Not reported	50	65.4	CES-D	PAR	Dep
41	Mackin	2011	VOL	Alzheimer's Disease Neuroimaging Initiative, USA and Canada	Per, Cog	3 yrs.	4	12	405	227	27.2 (MCI)	MCI	NR	74.9	GDS	NR	Dep
57	Wilson	2008	OTHER	Older Catholic nuns, priests and brothers, USA	Cog	max: 13 yrs.	mean:7.8	24	917	23 (13yrs; 5+yrs: 630)	27.4 No dementia at baseline, some developed	MCI, AD	65	74.8	CES-D	PAR	Dep

											AD during follow-up						
Comparing cognitive groups																	
33	Janzing	2000	CH	6 homes for the elderly in the specified region, The Netherlands	Cog	12	3	6	201	121 (49 dem)	18.2 (moderate dementia) and 26.7 (normal)	Not reported	NR (SD 5.3; 6.5)	86.6 (dem); 82.6 (normal)	GMS AGECAT	PAR?	Dep
10	Blansi	2005	DC	Memory Clinic of University Hospital and control sample, Switzerland	Cog	max: 3-4 yrs.	3-4	12	662 (217 dem)	36 (dem 4+ visits)	26.1 (AD, 24+); 28.8 (control)	AD	50	73.4	NOSGER	INF	Dep, Disturbing behaviour
40	Li	2001	DC + VOL	Cognitively impaired outpatients and cognitively normal volunteers, USA (76% treated with antidepressant medication)	Per, Inc	max 7.8 yrs. (mean 3.5 yrs.)	NR	3-12	294 (129 dem)	239 (3+ visits, 93 dem)	17 (moderate dementia); 29 (normal); 26.1 (MCI)	MCI, AD, VAD	50	76.5	HDRS	PAR	Dep
11	Bunce	2012	PB (community)	Aged 70 and over living in the community in Canberra or nearby, Australia	Cog	max: 12 yrs.	max 4	4yrs	837-870	95	NR	Not reported	70	76.6	Goldberg Depression and Anxiety Scales	PAR	Dep, Anx
	Dementia severity not reported																
36	King-Kalli-manis	2010	CH	Veterans Administration nursing homes, USA	Per, Inc	4 yrs. (mean 390/297 days)	mean:4	3	6,673	NR	NR	Not reported	24	72.5	Minimum dataset	NR	Wan
54	Volicer	2012	CH	8 nursing homes, The Netherlands (retrospective Minimum Dataset analysis)	Per	15	4	3	1101	1101	NR	AD, other, mixed	65	84.2	Minimum dataset	NR	Agi/Wan
46; 38	Morgan; Kunik	2012	DC	Veterans administration outpatient data files, flyers, radio and print advertisements and the primary care and geriatrics clinic (94% male), USA	Inc	24	7	4	171	NR	NR	Not reported	60	75.8	CMAI	INF	Irr

17	Cohen-Mans-field	1998	CH?	Community dwelling, senior day care centres in Maryland, USA	Per, Cog	24	5	6	200	104	NR	AD, VD, PD, unknown, no diagnosis	60	79.2	CMAI-C	INF	Irr, Agi
15	Chen	1991	DC	Patients presenting for evaluation of dementia in a clinical practice, USA	Inc	mean 5 yrs.	2 or more	6	72	NR (29 followed until death)	NR	AD	At onset AD: 64.1, mean duration at baseline: 3.0 years	NR	DSMIII-R	INF + PAR	Psy
34	Jost	1996	DC	Autopsy confirmed AD patients enrolled in a regional brain bank through a university geropsychiatry clinic and by clinicians and caregivers in surrounding communities, USA	Inc	Retrospective using medical records		Retrospective	Retrospective	100	NR	AD	NR	NR	Medical record review		Dep, Anx, Irr, Hal, Del, Sle
42	Marin	1997	DC	Alzheimer's disease Research Centre, USA	Cog	mean 37.1	mean:6.0	6	201	153 (12+ months)	NR	AD	50	86.6	ADAS	INF	Dep, Irr, Agi, Agi/Wan, Hal, Del, Total score
13	Caligiuri	2003	NR	NR, USA	Inc	24	3	12	54	NR	NR	AD	NR (SD 8.6)	77.1	BEHAVE-AD	INF	Hal, Del

Reference numbers refer to the Online Reference List

Papers from the same study groups:
1a Predictors study 1: Columbia Medical Centre, John Hopkins University School of Medicine, Massachusetts General Hospital, USA
1b Predictors study 2: 3 centres in USA (see 1a) and 2 centres in Europe (Paris and Greece)
2 Maasbed study
3 Ballard et al. (Psychiatry services in the West Midlands and a memory clinic in Bristol)
4 Haupt et al. (Outpatient clinic at the institute of psychiatry of the Technical University in Munich)
5 Hope et al. (Oxford)

Reports on:
Per=Persistence
Inc=Incidence
Cog=Association with cognitive function

Settings
DC=Dementia or memory clinic
POP=Population-based
CH=Care home
CLIN=Referred by clinicians
VOL=Volunteers
NR=Not reported

Data collection
INF=Informant-based
PAR=Participant-based
OBS=Observation

BPSD= behavioural and psychological symptoms of dementia
Apa=apathy
Dep=depression
Anx=anxiety
Irr=irritability/aggression
Agi=agitation
Hal=hallucination
Per=persecution
Mis=misidentification
Sle=sleep problems
Wan=wandering
Ela=elation

AD=Alzheimer's disease
VD=Vascular Dementia
DLB=Dementia with Lewy Bodies
MCI=Mild Cognitive Impairment
PD=Parkinson's Disease
NR=not reported
MMSE=Mini Mental State Examination

Table DS2 Definition and baseline prevalence of BPSD

Affective symptoms

	Author	Year	Instrument	Depression / Anxiety / Apathy	
				Definition	Prevalence (%)
Mild dementia (MMSE 21-26)					
22	Eustace	2002	BEHAVE-AD	**Dep:** Tearfulness and other depressed mood (e.g. death statements) with or without clear affective or physical components **Anx:** Anxiety about upcoming events, other anxieties, fear of being left alone, other phobias	Dep: 33 Anx: 52
16	Clare	2012	HADS; NPI total	**Dep:** 8 items including a loss of interest, laughing less, being less cheerful, being less optimism, and not being hopeful about the future **Anx:** 8 items including about feeling tense, worrying, panic attacks, feeling something awful is about to happen	NR
Moderate dementia (MMSE 15-20)					
39	Levy	1996	ADAS	**Dep:** Tearfulness and depression	Dep: 23
8	Berger	2005	BEHAVE-AD	**Dep:** Tearfulness and other depressed mood (e.g. death statements) with or without clear affective or physical components **Anx:** Anxiety about upcoming events, other anxieties, fear of being left alone, other phobias	Dep median 0.5 Anx median 0.0
29	Holtzer[1b]	2005	CUSPAD	**Dep:** Depressed mood (sad, depressed, blue, down in the dumps), difficulty sleeping and change in appetite	Dep: 40
50	Scarmeas[1a]	2002	CUSPAD	**Dep:** Depressed mood (sad, depressed, blue, down in the dumps), difficulty sleeping and change in appetite	Dep: 43.7
20	Devanand[1a]	1997	CUSPAD	**Dep:** Depressed mood (sad, depressed, blue, down in the dumps), difficulty sleeping and change in appetite	Dep: 25.1
24	Garre-Olmo	2010	NPI-10	**Dep:** Includes seeming sad or depressed, saying or acting as if sad or in low spirits **Anx:** Includes being very nervous, being worried, or frightened, being tense **Apa:** Loss of interest, more difficult to engage, apathetic or indifferent	Dep: 43.8 Anx: 31.2 Apa: 51.3
1	Aalten[2]	2005	NPI	**Dep:** Includes seeming sad or depressed, saying or acting as if sad or in low spirits **Anx:** Includes being very nervous, being worried, or frightened, being tense **Apa:** Loss of interest, more difficult to engage, apathetic or indifferent	Dep: 35.2 Anx: 21.1 Apa: 40.2
2	Aalten[2]	2005	NPI	**Mood/apathy cluster:** depression, apathy, night-time behaviour disturbances and eating abnormalities (See Aalten[2])	See Aalten[2]
25	Gillette-Guyonnet	2011	NPI	**Dep:** Includes seeming sad or depressed, saying or acting as if sad or in low spirits **Anx:** Includes being very nervous, being worried, or frightened, being tense **Apa:** Loss of interest, more difficult to engage, apathetic or indifferent	Dep: 20.6 Anx: 23.9 Apa: 43.0
59	Zahodne	2013	CUSPAD	**Dep:** Depressed mood (sad, depressed, blue, down in the dumps), difficulty sleeping and change in appetite	Mean 0.74 (0-4)
Moderately severe dementia (MMSE 10-14)					
23	Fauth	2006	Daily record of behaviour (DRB)	**Dep:** Mood, include crying and being tearful	NR
6	Ballard[3]	1996	Cornell scale	**Dep:** Sadness, sad expression, sad voice, tearfulness, lack of reactivity to pleasant events	Dep: minor 23.6; major 23.6
30	Hope[5]	1999	PBE and Past behavioural history interview	**Dep:** Apparent sadness, appearing to be particularly sad, miserable or depressed **Anx:** Anxiety or fearfulness (with physical symptoms)	NR
45	McShane[5]	1998	PBE	**Dep:** Apparent sadness, appearing to be particularly sad, miserable or depressed **Anx:** Anxiety or fearfulness (with physical symptoms)	Dep: 27.9 Anx: 16.3

47	Neundorfer	2001	CERAD	**Dep:** Feelings of anxiety, sad appearance, hopelessness, crying, feelings of guilt, poor self-esteem and feelings that life is not worth living	NR
43	McCarty	2000	Memory and Behaviour Problem Checklist-Revised	**Apathy cluster**: forgetting the day, can't self-start activities, unable to keep busy, following people, spends time inactive, talking little or none, sad/depressed	mean 1.34 (0.66) of max 3.00
27	Haupt[4]	2000	BEHAVE-AD	**Dep:** Tearfulness and other depressed mood (e.g. death statements) with or without clear affective or physical components **Anx:** Anxiety about upcoming events, other anxieties, fear of being left alone, other phobias	Dep: 57 Anx: 35
14	Chang	2004	SCID DSM IIIR	**Dep:** SCID diagnosis	
Severe dementia (MMSE 0-9)					
55	Wetzels	2010	NPI nursing home version	**Dep:** Includes seeming sad or depressed, saying or acting as if sad or in low spirits **Anx:** Includes being very nervous, being worried, or frightened, being tense **Apa:** Loss of interest, more difficult to engage, apathetic or indifferent	Dep: 8.5 Anx: 17.1 Apa: 18.8
18	de Rooij	2012	QUALIDEM	**Dep:** negative affect	NR
Normal cognitive function (MMSE 27+, no dementia)					
37	Kohler	2010	Symptom Checklist	**Dep:** As in Symptom Checklist	Dep: 22 scored high
7	Becker	2009	CES-D	**Dep:** Includes depressed affect, positive affect, somatic complaint, interpersonal problem	NR
53	Vinkers	2004	GDS15	**Dep:** Satisfaction with life, dropping activities and interests, feeling life is empty, being bored, not being hopeful about future, being bothered by thoughts, not being in good spirits, being afraid, feeling less happy, feeling helpless, being restless, not going out, worrying, memory problems, feeling downhearted and blue, feeling worthless, being less excited, having less energy, feeling upset, crying, difficulty concentrating, not enjoying getting up, avoiding social gathering, being less decisive, not having a clear mind	Dep: Median score: 2, score 2 or less: 67%
3	Amieva	2008	CES-D	**Dep:** Includes depressed affect, positive affect, somatic complaint, interpersonal problem	NR
58	Wilson	2010	CES-D (10-item) and Hamilton Depression Rating Scale (0-35)	**Dep:** Includes depressed affect, positive affect, somatic complaint, interpersonal problem (CES-D) and depression, anxiety, insomnia, somatic complaint (HDRS)	Dep: Median CES-D score: 1.0; median HDRS score 2.0
9	Bielak	2011	CES-D	**Dep:** Includes depressed affect, positive affect, somatic complaint, interpersonal problem	Mean 50.1
32	Houde	2008	GDS	**Dep:** Satisfaction with life, dropping activities and interests, feeling life is empty, being bored, not being hopeful about future, being bothered by thoughts, not being in good spirits, being afraid, feeling less happy, feeling helpless, being restless, not going out, worrying, memory problems, feeling downhearted and blue, feeling worthless, being less excited, having less energy, feeling upset, crying, difficulty concentrating, not enjoying getting up, avoiding social gathering, being less decisive, not having a clear mind	Dep: 52
21	Dotson	2008	CES-D	**Dep:** Includes depressed affect, positive affect, somatic complaint, interpersonal problems	NR

41	Mackin	2011	GDS	**Dep:** Satisfaction with life, dropping activities and interests, feeling life is empty, being bored, not being hopeful about future, being bothered by thoughts, not being in good spirits, being afraid, feeling less happy, feeling helpless, being restless, not going out, worrying, memory problems, feeling downhearted and blue, feeling worthless, being less excited, having less energy, feeling upset, crying, difficulty concentrating, not enjoying getting up, avoiding social gathering, being less decisive, not having a clear mind	Dep: 55
57	Wilson	2008	CES-D	**Dep:** Includes depressed affect, positive affect, somatic complaint, interpersonal problems	Dep: 23.9 reporting 1, 9.7 reporting 2, 6.1 reporting 3 and 6.8 reporting 4 or more
Comparing cognitive groups					
33	Janzing	2000	GMS AGECAT	**Dep:** Subcase or depressive case	Dep: Dementia - Depressive case: 12.2, subcase 20.4
10	Blansi	2005	NOSGER	**Dep:** Mood	NR
40	Li	2001	HDRS	**Dep:** HDRS>7 and "motivationally related depressive symptoms", including loss of interest, fatigue, retardation, loss of energy and general somatic symptoms	Dep: AD: 32.4; VAD: 29.7
11	Bunce	2012	Goldberg depression and anxiety scale	**Dep:** 9 items including about energy, interest, confidence, hope, concentration, slowing, weight and waking **Anx:** 9 items including being on edge, worrying, being irritable, having difficulty relaxing, difficulty sleep, having headaches and physical symptoms	NR
Dementia severity not reported					
34	Jost	1996	Medical record review	**Dep:** Depression, mood change, social withdrawal, suicidal ideation (reported as separate symptoms) **Anx:** Anxiety	NR
42	Marin	1997	ADAS	**Dep**: tearfulness, depressed mood	Tearfulness - moderate/severe: 3, very mild or greater: 20 Depressed mood - moderate/severe: 5, very mild or greater: 42

Psychotic symptoms

	Author	**Year**	**Instrument**	**Delusion / Hallucination / Misidentification**	
				Definition	Prevalence (%)
Mild dementia (MMSE 21-26)					
22	Eustace	2002	BEHAVE-AD	**Hal:** Visual, auditory, olfactory and other hallucinations **Del:** Paranoid and delusional ideation (people are stealing things, one's house is not one's home, spouse or caregiver is imposter, abandonment, other)	Del: 38 Hal: 0
Moderate dementia (MMSE 15-20)					
39	Levy	1996	ADAS	**Psy:** Hallucination (visual, auditory, tactile) and delusion (belief in ideas that are almost certainly not true) combined in psychosis subscale	Psy: 11
8	Berger	2005	BEHAVE-AD	**Psy symptoms cluster**, Del: Paranoid and delusional ideation (people are stealing things, one's house is not one's home, spouse or caregiver is imposter, abandonment, other) Hal: Visual, auditory, olfactory and other hallucinations	Median 0.0

50	Scarmeas [1a]	2002	CUSPAD	**Hal:** Auditory, visual, tactile and olfactory illusions **Del:** General del (strange ideas or unusual beliefs), paranoid del (people are stealing things or unfaithful wife/husband or unfounded suspicions), abandonment del (accused caregiver of plotting to leave him/her), somatic del (false belief that the patient has cancer or other physical illness), misidentification (false belief that people are in the house when nobody is there, or that someone else is in the mirror, or that spouse/caregiver is an imposter, or that the patient's home is not home, or that the characters on TV are real) and a miscellaneous category. At least one of these.	Del: 33.3 Hal: 11.5
20	Devanand [1a]	1997	CUSPAD	**Hal:** Auditory, visual, tactile and olfactory **Del:** Paranoid del, misidentification (reported also separately), somatic and abandonment	Del: 23.9 Hal: 8.1
28	Holtzer [1a]	2003	CUSPAD	**Hal:** Auditory, visual, tactile and olfactory **Del:** Paranoid del, misidentification (reported also separately), somatic and abandonment	Del: 40 Hal: 8
24	Garre-Olmo	2010	NPI-10	**Hal:** Including visions, voices, experiencing things that are not present **Del:** Beliefs that are not true, believing people are not who they say they are, believing their house is their home	Del: 16.1 Hal: 5.5
1	Aalten [2]	2005	NPI	**Hal:** Including visions, voices, experiencing things that are not present **Del:** Beliefs that are not true, believing people are not who they say they are, believing their house is their home	Del: 21.6 Hal: 9.5
2	Aalten [2]	2005	NPI	**Psychosis cluster:** Hallucinations and delusion (See Aalten [2])	See Aalten [2]
25	Gillette-Guyonnet	2011	NPI	**Hal:** Including visions, voices, experiencing things that are not present **Del:** Beliefs that are not true, believing people are not who they say they are, believing their house is their home	Del: 9.3 Hal: 3.1
49	Rosen	1991	DSMIII	**Hal:** e.g. visual, auditory, olfactory **Del:** Various types e.g. paranoia, the belief that one's spouse is an impostor	Del: 34.4 Hal: 31.3
48	Paulsen	2000	DIS for the DSMIII	**Hal:** e.g. visual, auditory, olfactory **Del:** Various types e.g. paranoia, the belief that one's spouse is an impostor	Psy: 23
56	Wilkosz	2006	CERAD	**Hal:** Sensory perceptions for which there was no basis in reality **Del:** A persistent false belief based on incorrect inference about external reality, resistant to persuasion or contrary evidence, and not attributable to social or cultural mores	Del: 0 Hal: 0 (excluded those with symptoms at baseline)
Moderately severe dementia (MMSE 10-14)					
19	Deudon	2009	CMAI, NPI and Observation Scale	**NPI Psychotic subgroup:** Hal (Including visions, voices, experiencing things that are not present) and del (beliefs that are not true, believing people are not who they say they are, believing their house is their home)	mean 6.14 (severity x frequency of 2 symptoms)
5	Ballard [3]	1997	Burn's symptom checklist	**Hal:** If described by the patient or if clearly described to the informant by the patient **Del:** Beliefs that are false, firmly held and impervious to evidence to the contrary and that are not explained entirely by cognitive failure and that have been experienced at least twice, on occasions more than 1 week apart **Mis:** Included the categories of Capgras delusions, misidentification of house, misidentification of television, and misidentification of one's mirror image. Symptoms also had to fulfil the definition for a delusion	**Psy:** 65.0
44	McShane [5]	1995	PBE	**Hal:** Appears to have auditory or visual hallucinations	NR (31.7 at some point during the study)
30	Hope [5]	1999	PBE and Past behavioural history interview	**Hal:** Appears to have auditory or visual hallucinations **Del:** Persecutory ideas: expressed ideas that people were trying to harm him/her, plotting against him/her or stealing or damaging his/her property	NR
45	McShane [5]	1998	PBE	**Hal:** Appears to have auditory or visual hallucinations **Del:** Persecutory ideas: expressed ideas that people were trying to harm him/her, plotting against him/her or stealing or damaging his/her property	Del: 11.6, Hal: 8.1
26	Haupt [4]	1996	BEHAVE-AD	**Hal:** Visual, auditory, olfactory and other hallucinations **Del:** Paranoid and delusional ideation (people are stealing things,	**Del:** GDS 5: 48; GDS 6: 25; GDS 7: 14 **Hal:** GDS 5: 12;

				one's house is not one's home, spouse or caregiver is imposter, abandonment, other)	GDS 6: 25; GDS 7: 19
27	Haupt[4]	2000	BEHAVE-AD	**Hal:** Visual, auditory, olfactory and other hallucinations **Del:** Paranoid and delusional ideation (people are stealing things, one's house is not one's home, spouse or caregiver is imposter, abandonment, other)	Del: 35 Hal: 18
14	Chang	2004	SCID DSM IIIR	**Hal:** Formed visual hallucinations, non-formed visual hallucinations, auditory hallucinations or other hallucinations (olfactory or tactile)**Del:** Thoughts or experiences of systematic persecution, non-systematic persecution, theft, infidelity or jealousy	Del: 0 Hal: 0 Excluded
Severe dementia (MMSE 0-9)					
55	Wetzels	2010	NPI nursing home version	**Hal:** Including visions, voices, experiencing things that are not present **Del:** Beliefs that are not true, believing people are not who they say they are, believing their house is their home	Del: 9.4 Hal: 3.4
Dementia severity not reported					
15	Chen	1991	DSMIII-R	**Psy**: presence of persistent hallucinations, illusions or delusions	25
34	Jost	1996	Medical record review	Hallucinations, paranoia, accusatory behaviour, and delusions (reported as separate symptoms)	NR
42	Marin	1997	ADAS	**Hal:** visual, auditory, tactile hallucination **Del:** belief in ideas that are almost certainly not true	Del: moderate/severe: 4. very mild or greater: 13 Hal: moderate/severe: 1, very mild or greater: 7
13	Caligiuri	2003	BEHAVE-AD	**Hal:** Visual, auditory, olfactory and other hallucinations **Del:** Paranoid and delusional ideation (people are stealing things, one's house is not one's home, spouse or caregiver is imposter, abandonment, other)	Del: 0 Hal: 0 (excluded those with symptoms at baseline)

Hyperactivity symptoms

	Author	**Year**	**Instrument**	**Irritability / Agitation / Wandering**	
				Definition	Prevalence (%)
Mild dementia (MMSE 21-26)					
22	Eustace	2002	BEHAVE-AD	**Irr:** Verbal outbursts, physical threats and/or violence, other agitation **Agi/Wan:** activity disturbance, includes wandering and purposeless and inappropriate activities	Irr: 42 Agi/Wan: 58
Moderate dementia (MMSE 15-20)					
39	Levy	1996	ADAS	**Agi/Wan:** Pacing and increased motor activity	Agi/Wan: 25
8	Berger	2005	BEHAVE-AD	**Behavioural disturbances cluster** - aggressiveness, activity disturbances	Median 1.0
51	Scarmeas[1b]	2007	CUSPAD	**Agi/Wan:** Agitation/restlessness **Wan:** Wandering away from home or from the caregiver **Irr:** Verbal outbursts, physical threats, violence	NR
50	Scarmeas[1a]	2002	CUSPAD	**Behavioural symptoms**: wandering away from home, verbal outbursts, physical threats or violence, agitation or restlessness and sundowning	Behavioural symptoms: 56.3
20	Devanand[1a]	1997	CUSPAD	**Agi/Wan:** Agitation/restlessness **Irr:** Verbal outbursts, physical threats, violence	Agi/Wan: 38.7 Irr (physical aggression): 6.4%
28	Holtzer[1a]	2003	CUSPAD	**Agi/Wan:** Agitation/restlessness **Irr:** Verbal outbursts, physical threats, violence	Agi/Wan: 39 Irr: 6
24	Garre-Olmo	2010	NPI-10	**Agi/Wan**: Includes pacing, repetitive behaviour **Irr ("irritability")**: Includes getting irritated and easily disturbed; changeable moods, abnormally impatient; **Irr ("agitation")** refuses to cooperate or won't let people help	Agi/Wan: 18.9 Irr: 36.7; 23
1	Aalten[2]	2005	NPI	**Agi/Wan**: Includes pacing, repetitive behaviour **Irr ("irritability")**: Includes getting irritated and easily disturbed; changeable moods, abnormally impatient; **Irr ("agitation")** refuses to cooperate or won't let people help	Agi/Wan: 25.6 Irr: 23.6; 18.6

2	Aalten[2]	2005	NPI	**Hyperactivity cluster:** agitation, euphoria, irritability, disinhibition, aberrant motor behaviour.	See 2
25	Gillette-Guyonnet	2011	NPI	**Agi/Wan**: Includes pacing, repetitive behaviour **Irr ("irritability")**: Includes getting irritated and easily disturbed; changeable moods, abnormally impatient; **Irr ("agitation")** refuses to cooperate or won't let people help	Agi/Wan: 18.2 Irr: 20.6; 21.3
Moderately severe dementia (MMSE 10-14)					
19	Deudon	2009	CMAI, NPI and Observation Scale	**Agi**: non-aggressive agitation (verbal and non-verbal) **Irr:** aggressive agitation (verbal and non-verbal); observational scale including screaming, hitting, tearing things, biting **NPI Hyperactivity subgroup**: Includes agi/wan (pacing, repetitive behaviour) and irr (anger, uncooperative)	**Agi:** Physical non-aggressive: mean 1.80; Verbal non-aggressive: mean 1.89 **Irr:** Physical aggressive: mean 1.28; Verbal aggressive mean 2.32; Observation scale: mean 13.26 **Hyperactivity subgroup:** mean 35.68 (severity x frequency of 5 symptoms)
23	Fauth	2006	Daily record of behaviour (DRB)	**Agi/Wan:** Restless, pacing up and down **Irr:** Disruptive, physically aggressive behaviour, including hitting, kicking, biting, scratching, spitting, pushing, grabbing	NR
35	Keene[5]	1999	PBE	**Irr:** Physical aggression (e.g. hitting, kicking, scratching, pushing or spitting in an aggressive manner), aggressive resistance (resisting help or being uncooperative), physical threats (e.g. shaking a fist), verbal aggression (spoken in an aggressive or angry way, e.g. angry or cross tone or voice raised in anger), refusing to speak (wilful or uncooperative), destructive behaviour (damaged objects in anger or deliberately), general irritability (bad mood or likely to become irritable at the least provocation), avoiding aggressive behaviour (carer avoided something that might have resulted in aggressive behaviour)	Verbal aggression: 89; aggressive resistance: 71; physical aggression: 51; physical threats: 48; refusing to speak: 44; destructive behaviour: 25; general irritability: 39; avoiding aggressive behaviour: 89
31	Hope[5]	2001	PBE	**Wan:** Increased walking, walks distinctly more than normal; attempting to leave home, made attempts to leave the house that have been prevented; being brought back home, number of times being brought back home; trailing, tends to follow right behind carer for total of at least 30 minutes; aimless walking, walked about the house, garden or beyond without an obvious reason; pottering, tended to walk around the house trying to do household chores or potter around the garden trying to do odd jobs; inappropriate, walking around the house, garden or outside for a reason that seems odd to carer; excessive inappropriate, walked around the house, garden or outside for an appropriate reason but repeated this several times; night time walking, walked during the night, includes walking aimlessly, pottering and walking inappropriately or excessively	Increased walking: 16; Attempting to leave home: 10; Being brought back home: 13; Trailing: 21; Aimless walking: 21; Pottering: 19; Inappropriate or excessive appropriate: 10
30	Hope[5]	1999	PBE and Past behavioural history interview	**Wan:** Time spent walking; attempts to leave house; being brought back; trailing and checking; aimless walking **Irr:** Physical aggression towards others; aggressive resistance (i.e. resisting care during intimate care e.g. washing and dressing), verbal aggression (i.e. spoke in an aggressive or angry way)	NR
45	McShane[5]	1998	PBE	**Irr:** Verbal aggression (i.e. spoke in an aggressive or angry way)	Irr: 43
4	Asada	1999	Troublesome behaviour scale (TBS)	**Irritability factor:** false accusation, ill-natured denial and/or distortion, hiding and/or losing things, interfering with a happy home circle, being restless and/or noisy at night, physical and/or verbal aggression, repetition and/or clinging, pica. **Hyperactivity factor**: hiding and/or losing things, wandering, pica, rummaging, making the dwelling dirty, crying and/or screaming	NR

43	McCarty	2000	Memory and Behaviour Problem Checklist-Revised	**Emotional and impulsive behaviours cluster**: confusing past and present, wandering/lost, restless/agitated, constantly talkative, waking people, sad/depressed, anxious/worried, angry, striking out, destroying property, dangerous behaviour	mean 0.61 (0.57) of max 3.00
27	Haupt[4]	2000	BEHAVE-AD	**Irr:** Verbal outbursts, physical threats and/or violence, other agitation **Agi/Wan:** activity disturbance, includes wandering and purposeless and inappropriate activities	Agi: 87 Irr: 57/47
Severe dementia (MMSE 0-9)					
55	Wetzels	2010	NPI nursing home version	**Agi/Wan**: Includes pacing, repetitive behaviour **Irr ("irritability")**: Includes getting irritated and easily disturbed; changeable moods, abnormally impatient; **Irr ("agitation")** refuses to cooperate or won't let people help	Agi/Wan: 23.1 Irr: 28.2; 20.3
12	Burgio	2007	Modified NHBPS and observation	**Irr:** Including screaming, talking to self, moaning, cursing, complaining, repeated requests for attention, repetitive words, inappropriate disrobing, hitting, punching, spitting, pounding, banging objects, stomping feet, kicking, pushing, grabbing, scratching or throwing objects	Total score Staff report: 15.2 (of 56), observation: 18.0 (of 100)
18	de Rooij	2012	QUALIDEM	**Agi:** Restless behaviour	NR
Comparing cognitive groups					
10	Blansi	2005	NOSGER	Disturbing behaviour	NR
Dementia severity not reported					
36	King-Kallimanis	2010	Minimum dataset	**Wan:** Locomotion with no discernible, rational purpose	14
54	Volicer	2012	Minimum dataset	**Agi/Wan:** Periods of restlessness, repetitive physical movements, wandering, socially inappropriate/disruptive behaviour	75.6
46; 38	Morgan; Kunik	2012	CMAI	**Irr:** intent to harm through spitting, verbal aggression, hitting, kicking, grabbing, pushing, throwing, biting, scratching, hurting self/others, tearing things/destroying property, making inappropriate verbal sexual advances or making inappropriate physical sexual advances	Excluded at baseline
17	Cohen-Mansfield	1998	CMAI-C	**Agi:** Verbally non-aggressive behaviour; physically non aggressive behaviour **Irr:** Verbally aggressive behaviour and physically aggressive behaviour	NR
34	Jost	1996	Medical record review	**Irr**: mild irr and severe irr ("aggression")	NR
42	Marin	1997	ADAS	**Agi:** tremors **Agi/Wan:** pacing, increased activity **Irr:** uncooperativeness cluster	**Agi:** moderate/severe: 6, very mild or greater: 56 **Agi/Wan:** pacing - moderate/severe: 8, very mild or greater: 18 Increased activity - moderate/severe: 5, very mild or greater: 22 **Irr:** moderate/severe: 8, very mild or greater: 17

Elation

	Author	**Year**	**Instrument**	**Elation**	
				Definition	Prevalence (%)
Moderate dementia (MMSE 15-20)					
24	Garre-Olmo	2010	NPI-10	Too cheerful or too happy, abnormally good mood, finds humour where others do not	9
1	Aalten[2]	2005	NPI	Too cheerful or too happy, abnormally good mood, finds humour where others do not	3.5
2	Aalten[2]	2005	NPI		

25	Gillette-Guyonnet	2011	NPI	Too cheerful or too happy, abnormally good mood, finds humour where others do not	3.1
Severe dementia (MMSE 0-9)					
55	Wetzels	2010	NPI nursing home version	Too cheerful or too happy, abnormally good mood, finds humour where others do not	4.3

Sleep problems

	Author	**Year**	**Instrument**	**Sleep problems**	
				Definition	Prevalence (%)
Mild dementia (MMSE 21-26)					
22	Eustace	2002	BEHAVE-AD	Diurnal rhythm disturbances	21
Moderate dementia (MMSE 15-20)					
8	Berger	2005	BEHAVE-AD	Diurnal rhythm disturbance	Median 0.0
1	Aalten[2]	2005	NPI	Difficulty sleeping, up at night, wander at night	13.1
2	Aalten[2]	2005	NPI	Difficulty sleeping, up at night, wander at night	
25	Gillette-Guyonnet	2011	NPI	Difficulty sleeping, up at night, wander at night	11.5
Moderately severe dementia (MMSE 10-14)					
23	Fauth	2006	Daily record of behaviour (DRB)	Woke caregiver up during the night	NR
30	Hope[5]	1999	PBE and Past behavioural history interview	Disturbed diurnal rhythm: evidence of sever disruption of diurnal rhythm	NR
Severe dementia (MMSE 0-9)					
55	Wetzels	2010	NPI nursing home version	Difficulty sleeping, up at night, wander at night	6
Dementia severity not reported					
34	Jost	1996	Medical record review	Diurnal change	NR

Reference numbers refer to the Online Reference List

Papers from the same study groups:
1a Predictors study 1: Columbia Medical Centre, John Hopkins University School of Medicine, Massachusetts General Hospital, USA
1b Predictors study 2: 3 centres in USA (see 1a) and 2 centres in Europe (Paris and Greece)
2 Maasbed study
3 Ballard et al. (Psychiatry services in the West Midlands and a memory clinic in Bristol)
4 Haupt et al. (Outpatient clinic at the institute of psychiatry of the Technical University in Munich)
5 Hope et al. (Oxford)

Apa=apathy
Dep=depression
Anx=anxiety
Irr=irritability/aggression
Agi=agitation
Hal=hallucination
Per=persecution
Mis=misidentification
Sle=sleep problems
Wan=wandering
Ela=elation

Fig. DS2 Persistence of BPSD reported in included studies

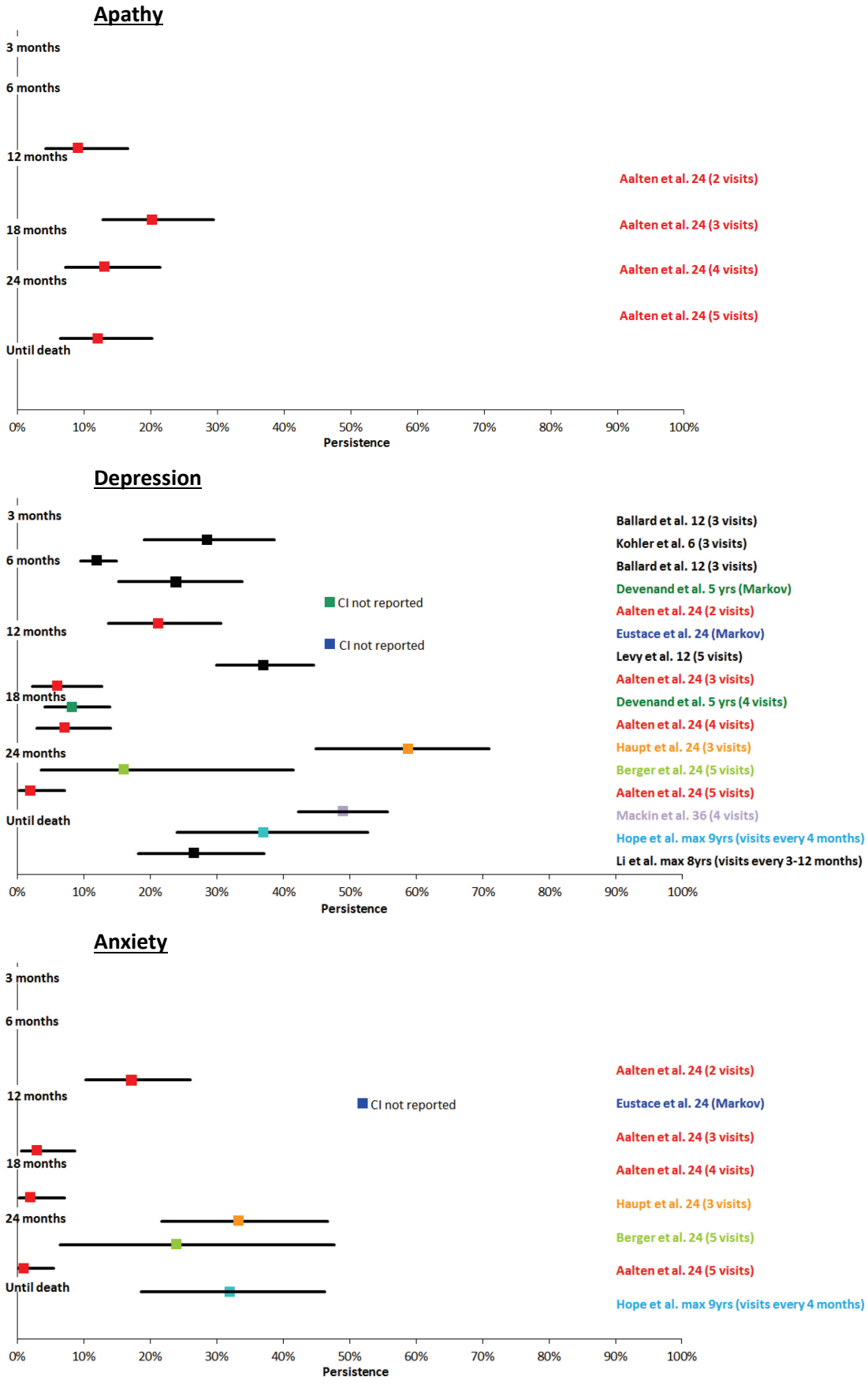
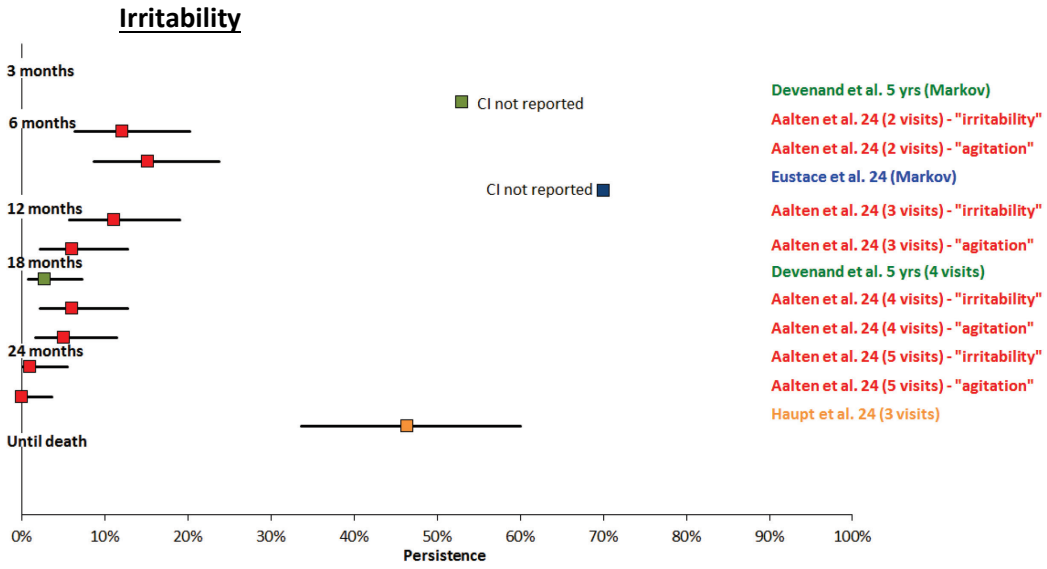
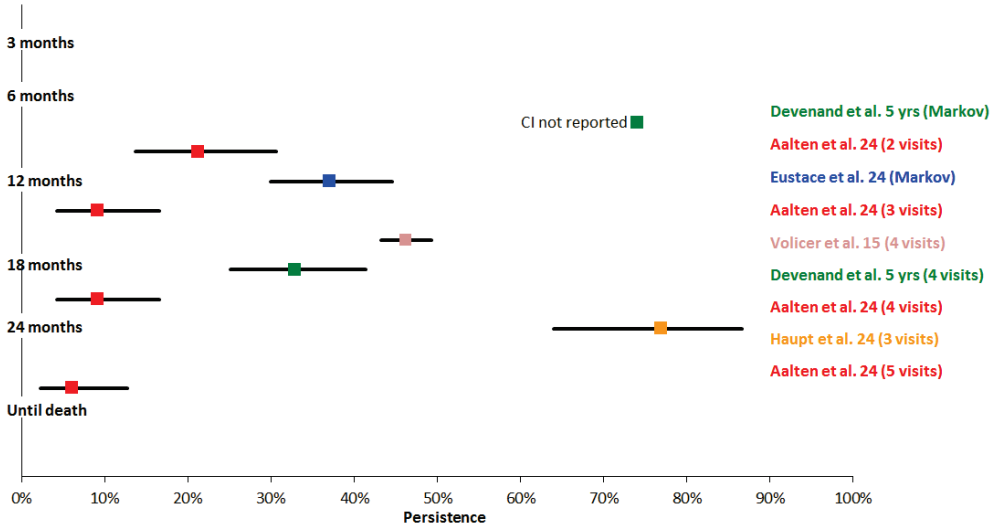
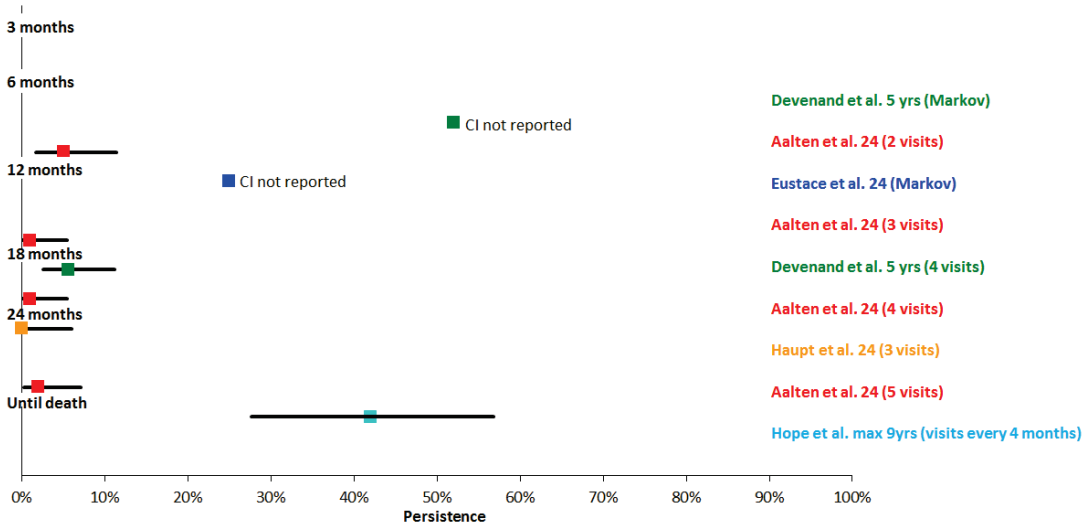


Fig. DS2 continued







The figures show the percentage of participants in which the symptom persisted over the period indicated on the y-axis, and the 95% confidence interval. For each figure, a legend shows the author name, the duration of the total follow-up in months and the number of visits.

Table DS3 Persistence and remission of symptoms in those with symptoms at baseline

Affective symptoms

	Author	Year	Setting	Months follow-up	n BPSD measures	Time between measures (months)	Details	Depression / Anxiety / Apathy		
								Per measurement (%)	Over total follow-up (%)	Fluctuating (%)
Mild dementia (MMSE 21-26)										
22	Eustace	2002	DC	24	3	12	Transition probabilities (Markov model).	Dep: 47 Anx: 52		
16	Clare	2012	DC	20	3	8-12	Random effects regression analysis.			Dep, anx: No significant change over time
Moderate dementia (MMSE 15-20)										
39	Levy	1996	NR	12	5	3	No model; Present at all five visits when present at baseline.	Dep: 49-59	37	
8	Berger	2005	DC	24	5	3-6	Total: each measurement time over 2 year period. Fluctuation: Present at 50% or more / less than 50% of measurement time over 2 yr. period.		Dep: 16 Anx: 24	Dep: 38; 22 Anx: 31; 18
20	Devanand[1a]	1997	DC	5 yrs. (mean 3 yrs.)	7	6	Per obs: Markov model; Total: present at any 4 visits; Fluctuating: present at 1 2 or 3 visits of any 4 visits.	Dep: 47	Dep: 8.3	Dep: 23.9; 17.2; 9.4
24	Garre-Olmo	2010	DC	24	5	6	Linear and quadratic growth mixture models.			Factor score: Low and stable: 80.2%, High and decreasing: 9.0%, Low and increasing: 10.8%
1	Aalten[2]	2005	DC	24	5	6	Present at any consecutive period of 6, 12, 18, 24 months.		Dep: 21.2; 6.1; 7.1; 2 Anx: 17.2; 3; 2; 1 Apa: 9.1; 20.2; 13.1; 12.1	

2	Aalten[2]	2005	DC	24	5	6	Repeated measure analysis between symptoms and baseline and follow-up, adjusted for MMSE and duration of illness.		Mood/apa: F=14.2, p<0.001 (also associated with baseline NPI total, hyperactivity and psy)	
59	Zahodne	2013	DC	5.5 yrs.	mean 10.1	6	Latent growth curve modelling.		No significant change - stable over time	
Moderately severe dementia (MMSE 10-14)										
23	Fauth	2006	NR	3	4	1	Latent growth curve modelling. A linear model of symptom change over time was compared to a model with a quadratic component and the fixed and random growth curve parameters of initial level, linear slope and quadratic slope were estimated. Log BPSD (frequency × duration +10) Covariates: MMSE score, use of neuroleptic medication, use of cholinesterase inhibitor, age, use of in-home respite care, relationship caregiver.		Mood: Quadratic model. Significant intra-individual variability in rate of change	
6	Ballard[3]	1996	CLIN/DC	12	12	1	Percentage with minor dep at baseline that had 3 or more months dep; 6 or more months.		Dep: 28.6; 23.8	
30	Hope[5]	1999	CLIN	9 yrs.	NR	4	Percentage with a single episode that persists until the last interview before death; Fluctuating: A single episode ending before death, more than one discrete episode, the behaviour may or may not persist until death.		Dep: 37 Anx: 32	Dep: 47; 16 Anx: 57; 11

47	Neundorfer	2001	DC	max: 5yrs	max:10	12	Hierarchical modelling or multilevel analysis.		Dep: Changes over time within patients and differences between patients.	
27	Haupt[4]	2000	DC	24	3	12	% of those with symptoms at baseline with symptoms after 1 and 2 years; Fluctuating: % with symptoms after 1 or 2 yrs.; % symptoms absent.		Dep: 58.8 Anx: 33.3	Dep: 26.5; 14.7 Anx: 28.6; 38.1
Severe dementia (MMSE 0-9)										
55	Wetzels	2010	CH	24	5	6	No model. For each observation 0-1, 1-2, 2-3, 3-4 months.	Dep: 70.0, 37.5, 12.4, 0.0 Anx: 39.8, 42.9, 24.8, 31.4 Apa: 54.8, 36.0, 51.9, 39.4		
Normal cognitive function (MMSE 27+, no dementia)										
37	Kohler	2010	POP	6	3	3	Stability defined as a score within the upper quartile group on 2 consecutive assessments: highly depressed at baseline only (fluctuating), highly depressed at follow-up only (fluctuating) and persistently highly depressed (total).		Dep: 12	Dep: 8; 25
41	Mackin	2011	VOL	3 yrs.	4	12	Proportion of individuals who remained stable, declined, improved, or fluctuated over 3 years was calculated and compared between groups using Fisher's exact test.		Dep: 49 stable	Dep: 16 worsening, 8 improved, 27 fluctuations
Comparing cognitive groups										
40	Li	2001	DC + VOL	93.6	NR	3-12	Persistent: All HDRS scores during follow-up >7 Improved (fluctuating): All HDRS scores during follow-up <7 Fluctuating: HDRS scores at follow-up >7 or <7.		Dep: AD 26.6; VAD 66.7; MCI 60.0	Dep: AD 66.7, 6.7; VAD 22.2, 11.1; MCI 20.0, 20.0

Psychotic symptoms

	Author	Year	Setting	Months follow-up	n BPSD measures	Time between measures (months)	Details	Delusion / Hallucination / Misidentification		
								Per measurement (%)	Over total follow-up (%)	Fluctuating (%)
Mild dementia (MMSE 21-26)										
22	Eustace	2002	DC	24	3	12	Transition probabilities (Markov model).	Del: 65 Hal: 25		
Moderate dementia (MMSE 15-20)										
39	Levy	1996	NR	12	5	3	No model; Present at all five visits when present at baseline.	Psy: 68-82	Psy: 57	
8	Berger	2005	DC	24	5	3-6	Total: each measurement time over 2 year period; Fluctuation: Present at 50% or more / less than 50% of measurement time over 2 year period.		Psy: 24	Psy: 20; 27
20	Devanand[1a]	1997	DC	5 yrs. (mean 3yrs)	7	6	Per obs: Markov model; Total: present at any 4 visits; Fluctuating: present at 1; 2; 3 of any 4 visits.	Del: 59 (includes mis) Hal: 52	Del: 12.8 Hal: 5.6	Del: 20; 17.8; 18.9 Hal: 18.9; 11.1; 4.4
28	Holtzer[1a]	2003	DC	5 yrs.	11	6	Markov model. By mMMSE 39-57, 33-38, 26-32, 14-25, 0-13.	Del: 76, 75, 78, 82, 64 Hal: 14, 42, 30, 50, 43		
24	Garre-Olmo	2010	DC	24	5	6	Linear and quadratic growth mixture models.			Factor score: Moderate and stable: 6.9%, Fluctuating: 6.9%, Low and stable 86.2%
1	Aalten[2]	2005	DC	24	5	6	Present at any consecutive period of 6, 12, 18, 24 months.		Del: 11.1; 3; 4; 4 Hal: 5.1; 1; 1; 2	

2	Aalten[2]	2005	DC	24	5	6	Repeated measure analysis between symptoms and baseline and follow-up, adjusted for MMSE and duration of illness.		Psy: F=28.3, p<0.001. Also associated with baseline NPI total and hyperactivity, not mood/apathy)	
49	Rosen	1991	DC	6 yrs.	7	1yr	Percentage remission of those with at least one follow-up visit after onset symptom (n=6).			Psy: 33
Moderately severe dementia (MMSE 10-14)										
19	Deudon	2009	CH	3	3	1 or 2	Mixed linear model with random effect. Covariates: age.		NPI psychosis factor: beta= 0.03 (0.604)	
5	Ballard[3]	1997	CLIN/DC	12	12	1	Resolution of symptoms in those followed-up for a yr.			Psy: 53 Del: 73 Hal: 61 Mis: 65
44	McShane[5]	1995	CLIN	5 yrs.	NR	4	Proportion of interviews were hallucinations were present.	Hal: With cortical Lewy bodies: 0.44 (SEM<0.15); without cortical Lewy bodies: 0.06 (SEM 0.03)		
30	Hope[5]	1999	CLIN	9 yrs.	NR	4	Percentage with a single episode that persists until the last interview before death; Fluctuating: A single episode ending before death; More than one discrete episode, the behaviour may or may not persist until death.		Del: 23 Hal: 42	Del: 68; 9 Hal: 42; 17
27	Haupt[4]	2000	DC	24	3	12	% of those with symptoms at baseline with symptoms after 1 and 2 years; Fluctuating: % with symptoms after 1 or 2 years; % symptoms absent.		Del: 0 Hal: 0	Del: 42.9; 57.1 Hal: 72.7; 27.3
Severe dementia (MMSE 0-9)										
55	Wetzels	2010	CH	24	5	6	No model. For each observation 0-1, 1-2, 2-3, 3-4.	Del: 36.2, 28.3, 12.5, 28.3 Hal: 50.0, 25.0, 50.0, 50.0		

Hyperactivity symptoms

	Author	Year	Setting	Months follow-up	n BPSD measures	Time between measures (months)	Details	Irritability / Agitation / Wandering		
								Per measurement (%)	Over total follow-up (%)	Fluctuating (%)
Mild dementia (MMSE 21-26)										
22	Eustace	2002	DC	24	3	12	Transition probabilities (Markov model).	Irr: 70		
Moderate dementia (MMSE 15-20)										
39	Levy	1996	NR	12	5	3	No model; Present at all five visits when present at baseline.	Agi/Wan: 65-67	Agi/Wan: 37	
8	Berger	2005	DC	24	5	3-6	Total: each measurement time over 2 year period Fluctuation: Present at 50% or more / less than 50% of measurement time over 2 year period.		Behavioural disturbances, aggressiveness, activity disturbances: 44	Behavioural disturbances, aggressiveness, activity disturbances: 31; 16
51	Scarmeas[1b]	2007	DC	NR	14yrs	max:25	Generalised estimating equation model. Disruptive behavioural symptoms.			Symptoms increase by 0.07 for every year of follow-up (p<0.001)
20	Devanand[1a]	1997	DC	5 yrs. (mean 3 yrs.)	7	6	Per obs: Markov model; Total: present at any 4 visits; Fluctuating: present at 1; 2; 3 of any 4 visits.	Agi/Wan: 74 Irr: 53	Agi/Wan: 32.8 Irr: 2.8	Agi/Wan: 14.4; 16.7; 21.7 Irr: 14.4; 12.8; 8.9
28	Holtzer[1a]	2003	DC	5 yrs.	11	6	Markov model. By mMMSE 39-57, 33-38, 26-32, 14-25, 0-13.	Agi/Wan: 54, 59, 72, 81, 80 Irr: 27, 20, 22, 59, 69		
24	Garre-Olmo	2010	DC	24	5	6	Linear and quadratic growth mixture models.			Factor score: Low and smooth increasing: 66.6%, High and increasing: 4.3%, Moderate and stable: 17.5%, Low and sharp increasing: 11.6%

1	Aalten[2]	2005	DC	24	5	6	Present at any consecutive period of 6, 12, 18, 24 months.		Agi/Wan: 21.2; 9.1; 9.1; 6.1; Irr ("irritability"): 12.1; 11.1; 6.1; 1 Irr ("agitation"): 15.2; 6.1; 5.1; 0	
2	Aalten[2]	2005	DC	24	5	6	Repeated measure analysis between symptoms and baseline and follow-up, adjusted for MMSE and duration of illness.		Hyperactivity: F=4.8n p<0.05, Also associated with baseline NPI total, mood apathy and hyperactivity, but not psy	
Moderately severe dementia (MMSE 10-14)										
19	Deudon	2009	CH	3	3	1 or 2	Mixed linear model with random effect. Covariates: age.		Global CMAI: beta=0.02 (0.797) Physically non-aggressive behaviour: beta=-0.003 (0.368), verbally non-aggressive behaviour: beta=0.001 (0.832) NPI hyperactivity factor: beta=0.35 (0.091) Physically aggressive behaviour: beta=0.004 (0.11), verbally aggressive behaviour: beta=-0.001 (0.776). Observation scale: beta=-0.16 (0.17)	

23	Fauth	2006	NR	3	4	1	Latent growth curve modelling. A linear model of symptom change over time was compared to a model with a quadratic component and the fixed and random growth curve parameters of initial level, linear slope and quadratic slope were estimated. Log BPSD (frequency × duration +10) Covariates: MMSE score, use of neuroleptic medication, use of cholinesterase inhibitor, age, use of in-home respite care, relationship caregiver.		Disruptive problems: Quadratic model. Disruptive behaviour: Significant intra-individual variability in rate of change Restlessness: linear model. Significant variability of people's baseline scores.	
35	Keene[5]	1999	CLIN	10 yrs.	30	4	Persistence: Percentage with a single episode that persists until the last interview before death; Fluctuating: A single episode ending before death; More than one discrete episode, the behaviour may or may not persist until death.		Irr: verbal aggression: 54; aggressive resistance 60; physical aggression 51; physical threats 29; refusal to speak 17; destructive behaviour 28; general irritability 14; carer avoids aggression 44 (Same population as Hope et al. ref 43)	Irr: verbal aggression: 25; 21 aggressive resistance 18; 22 physical aggression 33; 16 physical threats 46; 25 refusal to speak 72; 11 destructive behaviour 68; 4 general irritability 73; 14 carer avoids aggression 40; 16

30	Hope[5]	1999	CLIN	9 yrs.	NR	4	Percentage with a single episode that persists until the last interview before death; Fluctuating: A single episode ending before death; More than one discrete episode, the behaviour may or may not persist until death.		Wan: Trailing and checking: 33; aimless walking: 35; being brought back 22; attempts to leave home 22; walking more 35; Irr: verbal aggression: 58; aggressive resistance 64; physical aggression 60	Wan: Trailing and checking: 60; 7 aimless walking: 57; 9 being brought back 70; 9 attempts to leave home 50; 28 walking more 50; 15 Irr: verbal aggression: 24; 18; aggressive resistance 18; 18 physical aggression 30; 10
27	Haupt[4]	2000	DC	24	3	12	% of those with symptoms at baseline with symptoms after 1 and 2 years; Fluctuating: % with symptoms after 1 or 2 years; % symptoms absent.		Agi: 76.9; Irr: 46.4	Agi: 21.2; 1.9
Severe dementia (MMSE 0-9)										
55	Wetzels	2010	CH	24	5	6	No model. For each observation 0-1, 1-2, 2-3, 3-4.	Irr (“agitation”): 51.4, 51.9, 37.6, 56.1 Irr (“irritability”): 54.1, 55.2, 62.4, 52.9 Agi/Wan: 63.0, 58.1, 41.9, 59.0		

12	Burgio	2007	CH	18	4	6	Multilevel analysis. Restricted maximum likelihood estimation method with a specification of the unstructured covariance. Analysed linear and curvilinear time effects.		Staff: Agitation changed little over the 18 month period; Obs: Both linear and quadratic effect were statistically significant ($p<0.05$) indicating that the trajectory of agitation had a decreasing trend linearly but the rate of decrease lessened over time.	
18	de Rooij	2012	CH	12	3	6	Changes across time within Dutch and Belgian traditional and small-scale settings.		Netherlands: coefficient -0.85; Belgium: -0.24	
Dementia severity not reported										
36	King-Kallimanis	2010	CH	4 yrs. (mean 390/297 days)	mean: 4	3	Total: Wan at admission and for the duration of the study Fluctuating: Wan at admission and one change to a non-wan; Wan at admission and changed to wan and back to wan; Wan at admission and fluctuated multiple times. (% of all wan at baseline).	Wan: 49	Wan: 43; 5; 3	
54	Volicer	2012	CH	15	4	3	Four groups: agi lower on first than last assessment (declined); higher agi score on first than last (improved), agi on both first and last (stable), not agi on first or last (no agi). In all second and third assessment intermediate between first and last.		Agi: increased 19.6, decreased 16.7, stable 46.2, no agi 17.3	

17	Cohen-Mansfield	1998	CH	24	5	6	Repeated measures multivariate analyses of variances (MANOVA) CMAI syndrome scores: mean of behaviours comprising each type of agitation.	Verbally non-aggressive behaviour increased F=270, p=0.03; Physical non-aggressive behaviour NS Verbally aggressive behaviour increased over time F=3.83, p<0.01, Physically aggressive behaviour increased over time F=4.43, p<0.01		

Elation

	Author	**Year**	**Setting**	**Months follow-up**	**n BPSD measures**	**Time between measures (months)**	**Details**	**Elation**		
								Per measurement (%)	Over total follow-up (%)	Fluctuating (%)
Moderate dementia (MMSE 15-20)										
1	Aalten[2]	2005	DC	24	5	6	Present at any consecutive period of 6, 12, 18, 24 months.		2, 0, 0, 0	
Severe dementia (MMSE 0-9)										
55	Wetzels	2010	CH	24	5	6	No model. For each observation 0-1, 1-2, 2-3, 3-4.	39.5, 17.6, 33.3, 20.9		

Sleep problems

	Author	Year	Setting	Months follow-up	n BPSD measures	Time between measures (months)	Details	Sleep problems		
								Per measurement (%)	Over total follow-up (%)	Fluctuating (%)
Mild dementia (MMSE 21-26)										
22	Eustace	2002	DC	24	3	12	Transition probabilities (Markov model).	68		
Moderate dementia (MMSE 15-20)										
8	Berger	2005	DC	24	5	3-6	Total: each measurement time over 2 year period; Fluctuation: Present at 50% or more / less than 50% of measurement time over 2 year period.		9	18; 29
1	Aalten[2]	2005	DC	24	5	6	Present at any consecutive period of 6, 12, 18, 24 months.		10.1; 1; 1; 1	
Moderately severe dementia (MMSE 10-14)										
23	Fauth	2006	NR	3	4	1	Latent growth curve modelling. A linear model of symptom change over time was compared to a model with a quadratic component and the fixed and random growth curve parameters of initial level, linear slope and quadratic slope were estimated. Log BPSD (frequency × duration +10) Covariates: MMSE score, use of neuroleptic medication, use of cholinesterase inhibitor, age, use of in-home respite care, relationship caregiver.		Linear model. Significant variability of people's baseline scores. Intra-individual variability NS	

30	Hope[5]	1999	CLIN	9 yrs.	NR	4	Percentage with a single episode that persists until the last interview before death; Fluctuating: A single episode ending before death; More than one discrete episode, the behaviour may or may not persist until death.		23	68; 10
Severe dementia (MMSE 0-9)										
55	Wetzels	2010	CH	24	5	6	No model. For each observation 0-1, 1-2, 2-3, 3-4.	Sle: 56.7, 50.0, 0.0, 20.9		

Total BPSD score

	Author	**Year**	**Setting**	**Months follow-up**	**n BPSD measures**	**Time between measures (months)**	**Details**	**Total score**
Mild dementia (MMSE 21-26)								
16	Clare	2012	DC	20	3	8-12	Random effects regression analysis.	Significant increase over time (lope 0.17, p<0.001), no significant change in severity
52	Tschanz	2011	PB	Mean 3.8 yrs., max 12.9 yrs.	NR	NR	Linear effects models, annual rate of change in NPI total.	Increase of total NPI score over time: intercept: 2.5, time 3.1 (p=0.002)
Moderate dementia (MMSE 15-20)								
2	Aalten[2]	2005	DC	24	5	6	Repeated measure analysis between symptoms and baseline and follow-up, adjusted for MMSE and duration of illness.	NPI: F=16.5, p<0.001 Also associated with baseline mood/apathy, hyperactivity and psy

Moderately severe dementia (MMSE 10-14)								
23	Fauth	2006	NR	3	4	1	Latent growth curve modelling. A linear model of symptom change over time was compared to a model with a quadratic component and the fixed and random growth curve parameters of initial level, linear slope and quadratic slope were estimated. Log BPSD (frequency × duration +10) Covariates: MMSE score, use of neuroleptic medication, use of cholinesterase inhibitor, age, use of in-home respite care, relationship caregiver.	No fixed or linear quadratic parameters were significant - on *average* no significant change over time for any domain, BPSD stable over 3 months

Reference numbers refer to the Online Reference List

Papers from the same study groups:
1a Predictors study 1: Columbia Medical Centre, John Hopkins University School of Medicine, Massachusetts General Hospital, USA
1b Predictors study 2: 3 centres in USA (see 1a) and 2 centres in Europe (Paris and Greece)
2 Maasbed study
3 Ballard et al. (Psychiatry services in the West Midlands and a memory clinic in Bristol)
4 Haupt et al. (Outpatient clinic at the institute of psychiatry of the Technical University in Munich)
5 Hope et al. (Oxford)

Settings
DC=Dementia or memory clinic
POP=Population-based
CH=Care home
CLIN=Referred by clinicians
VOL=Volunteers
NR=Not reported

BPSD= behavioural and psychological symptoms of dementia
Apa=apathy
Dep=depression
Anx=anxiety
Irr=irritability/aggression
Agi=agitation
Hal=hallucination
Per=persecution
Mis=misidentification
Sle=sleep problems
Wan=wandering
Ela=elation

MMSE=mini mental state examination; mMMSE=modified mini mental state examination; SEM=standard error of the mean

Table DS4 Incidence and absence of symptoms in those without symptoms at baseline

Affective symptoms

	Author	Year	Setting	Months follow-up	n BPSD measures	Time between measures (months)	Details	Depression / Anxiety / Apathy		
								Per measurement (%)	Over total follow-up (%)	Absent (%)
Mild dementia (MMSE 21-26)										
22	Eustace	2002	DC	24	3	12	Markov model. Transition probability for onset over 2 yr. period.	Dep: 25 Anx: 28		
Moderate dementia (MMSE 15-20)										
39	Levy	1996	NR	12	5	3	Rate of new appearance of a symptom during the observation period in patients who had not reported the symptom at study onset.		Dep:35	
8	Berger	2005	DC	24	5	3-6	Absent at each measurement time over the 2 yr. period.			Dep: 24 Anx: 31
50	Scarmeas[1a]	2002	NR	9.3 yrs.	NR	6	Manifesting incident symptoms at any follow-up visit. Calculated from manifesting symptom at follow-up and no symptom at first visit.		Dep: 73.5	
20	Devanand[1a]	1997	DC	5 yrs. (mean 3 yrs.)	7	6	Markov model. Absent: Of participants that completed 4 consecutive periods of 6 months: present at none of the 4 visits.	Dep: 14		Dep: 41.1
1	Aalten[2]	2005	DC	24	5	6	Cumulative incidence: the proportion of patients who were symptom free at baseline but developed the specific symptom at next assessments.		Dep: 33.4 Anx: 27.5 Apa: 63.9	

25	Gillette-Guyonnet	2011	DC	max 48	mean 5.1	6	Incidence of NPI 4 or higher per 100 person years and % events during 4 year follow-up in those without the symptom at baseline (between brackets).		Dep: 16.5 (29.5) Anx: 19.6 (33.9) Apa: 41.7 (55.7)	
Moderately severe dementia (MMSE 10-14)										
6	Ballard[3]	1996	CLIN	12	12	1	Without major or minor depression at baseline interview		Dep: 29.8 minor; 10.6 major	
27	Haupt[4]	2000	DC	24	3	12	Absent at baseline and present after 1 or 2 years / 1 and 2 years (% without symptoms at baseline). Absent: absent at baseline and after 1 or 2 years (% without symptom at baseline).	Dep: 26.9; 26.9 Anx: 38.5; 7.7		Dep: 50.0 Anx: 53.8
14	Chang	2004	DC	mean: 51.9	NR	NR	Symptoms developed during follow-up period, those with symptoms at baseline excluded.		Dep: 12.5	
Severe dementia (MMSE 0-9)										
55	Wetzels	2010	CH	24	5	6	No model. For each observation 0-1, 1-2, 2-3, 3-4.	Dep: 8.4, 9.8, 3.0, 3.4 Anx: 6.2, 9.7, 11.9, 8.5 Apa: 13.7, 17.4, 27.2, 18.8		
Normal cognitive function (MMSE 27+, no dementia)										
37	Kohler	2010	POP	6	3	3	Those who had symptoms at follow-up visits only Absent: never highly depressed.		Dep: 25	Dep:55

Comparing cognitive groups										
40	Li	2001	DC + VOL	93.6	NR	3-12	Annual incidences of new-onset depressive symptoms among non-depressed subjects at baseline. No model. Calculated by dividing cumulative numbers of subjects showing new onset depressive symptoms (HDRS>7) by mean interval of follow-up years.	Dep: AD - 15 per 100 person years (8/26) MCI 11.7 (5/13) VAD 26.8 (13/23)		
Dementia severity not reported										
34	Jost	1996	DC	Retro-spective using medical records	Retro-spective	Retro-spective	Documentation of onset of symptoms in medical records.		Dep: 72	

Psychotic symptoms

	Author	**Year**	**Setting**	**Months follow-up**	**n BPSD measures**	**Time between measures (months)**	**Details**	**Delusion / Hallucination / Misidentification**		
								Per measurement (%)	Over total follow-up (%)	Absent (%)
Mild dementia (MMSE 21-26)										
22	Eustace	2002	DC	24	3	12	Markov model. Transition probability for onset over 2 yr. period.	Del: 35 Hal: 7		

Moderate dementia (MMSE 15-20)										
39	Levy	1996	NR	12	5	3	Rate of new appearance of a symptom during the observation period in patients who had not reported the symptom at study onset.		Del: 25	
8	Berger	2005	DC	24	5	3-6	Absent at each measurement time over the 2 year period.			Psy: 29
50	Scarmeas[1a]	2002	NR	9.3 yrs.	NR	6	Manifesting incident symptoms at any follow-up visit. Calculated from manifesting symptom at follow-up and no symptom at first visit.		Del: 84.5 Hal: 45.5	
20	Devanand[1a]	1997	DC	5 yrs. (mean 3 yrs.)	7	6	Markov model. Absent: Of participants that completed 4 consecutive periods of 6 months: present at none of the 4 visits.	Del: 17 Hal: 9		Del: 30.6 Hal: 60
28	Holtzer[1a]	2003	DC	5 yrs.	11	6	Markov model. By mMMSE 39-57, 33-38, 26-32, 14-25, 0-13.	Del: 76, 75, 78, 82, 64 Hal: 14, 42, 30, 50, 43		
1	Aalten[2]	2005	DC	24	5	6	Cumulative incidence: the proportion of patients who were symptom free at baseline but developed the specific symptom at next assessments.		Del: 34 Hal: 20.5	
25	Gillette-Guyonnet	2011	DC	max 48	mean 5.1	6	Incidence of NPI 4 or higher per 100 person years and % events during 4 year follow-up in those without the symptom at baseline (between brackets).		Del: 8.2 (16.5) Hal: 4.4 (9.4)	
49	Rosen	1991	DC	6 yrs.	7	1 yr.	Emerging of psychosis by MMSE score.		82.4 (n=14 of total n=32 of which n=15 with symptoms during course)	

48	Paulsen	2000	DC	4 yrs.	5	1 yr.	The cumulative incidence for hallucinations or delusions in patients with a clinical diagnosis of probable AD		20.1% at 1 year, 36.1% at 2 years, 49.5% at 3 years, and 51.3% at 4 years	
56	Wilkosz	2006	DC	mean: 25.8	NR	1 yr.	Only numbers and incidence rate given, I calculated percentages from this using n=288.		Psy: 28.5 Del: 8.7 Mis: 16.0	
Moderately severe dementia (MMSE 10-14)										
5	Ballard[3]	1997	DC	12	12	1	Percentage without symptoms at baseline that developed symptoms during follow-up.		Psy: 47 Del: 30 Hal: 20 Mis: 17	
27	Haupt[4]	2000	DC	24	3	12	Absent at baseline and present after 1 or 2 yrs. / 1 and 2 yrs. (% without symptoms at baseline). Absent: absent at baseline and after 1 or 2 years (% without symptom at baseline).		Del: 29.7; 0 Hal: 18.8; 2.1	Del: 7 Hal: 79.2
14	Chang	2004	DC	mean: 51.9	NR	NR	Symptoms developed during follow-up period, those with symptoms at baseline excluded.		Del: 32.1 Hal: 25	
Severe dementia (MMSE 0-9)										
55	Wetzels	2010	CH	24	5	6	No model. For each observation 0-1, 1-2, 2-3, 3-4.	Del: 2.9, 5.4, 5.5, 4.3 Hal: 1.8, 2.7, 0.0, 5.1		
Dementia severity not reported										
15	Chen	1991	DC	5 yrs.	2 or more	6	Incidence during follow-up period.		Psy: 29.6	
34	Jost	1996	DC	Retro-spective using medical records	Retro-spective	Retro-spective	Documentation of onset of symptoms in medical records.		Psy: 45	
13	Caligiuri	2003	DC? NR	24	3	1 yrs.	Incidence rate over 2 yrs. for new onset psychosis (those with symptoms at baseline excluded).		Psy: 32.5	

Hyperactivity symptoms

	Author	Year	Setting	Months follow-up	n BPSD measures	Time between measures (months)	Details	Irritability / Agitation / Wandering		
								Per measurement (%)	Over total follow-up (%)	Absent (%)
Mild dementia (MMSE 21-26)										
22	Eustace	2002	DC	24	3	12	Markov model. Transition probability for onset over 2 yr. period.	Irr: 38		
Moderate dementia (MMSE 15-20)										
39	Levy	1996	NR	12	5	3	Rate of new appearance of a symptom during the observation period in patients who had not reported the symptom at study onset.		Agi/Wan: 39	
8	Berger	2005	DC	24	5	3-6	Absent at each measurement time over the 2 year period.			9 (behavioural disturbance, aggressiveness, activity disturbance)
50	Scarmeas[1a]	2002	NR	9.3 yrs.	NR	6	Manifesting incident symptoms at any follow-up visit. Calculated from manifesting symptom at follow-up and no symptom at first visit.		Behavioural symptoms (wandering and irritability): 94.7	
20	Devanand[1a]	1997	DC	5 yrs. (mean 3 yrs.)	7	6	Markov model. Absent: Of participants that completed 4 consecutive periods of 6 months: symptom present at none of the 4 visits.	Agi/Wan: 31 Irr: 10		Agi/Wan: 14.4; Irr: 61.1
28	Holtzer[1a]	2003	DC	5 yrs.	11	6	Markov model. By mMMSE 39-57, 33-38, 26-32, 14-25, 0-13.	Agi/Wan: 54, 59, 72, 81, 80 Irr: 27, 20, 22, 59, 69		

1	Aalten[2]	2005	DC	24	5	6	Cumulative incidence: the proportion of patients who were symptom free at baseline but developed the specific symptom at next assessments.		Agi/Wan: 48.7 Irr ("irritability"): 33.5 Irr ("agitation"): 32.1	
25	Gillette-Guyonnet	2011	DC	max 48	mean 5.1	6	Incidence of NPI 4 or higher per 100 person years and % events during 4 year follow-up in those without the symptom at baseline (between brackets).		Agi/Wan: 21.4 (36.5) Irr ("irritability"): 20.6 (34.7) Irr ("agitation"): 17.1 (30.1)	
Moderately severe dementia (MMSE 10-14)										
45	McShane[5]	1998	CLIN	4 yrs.	NR	4	Newly developed behaviours during 3 year period (association with symptoms in first year also reported).		Irr: 31; Agi: 16.7	
27	Haupt[4]	2000	DC	24	3	12	Absent at baseline and present after 1 or 2 years / 1 and 2 years (% without symptoms at baseline). Absent: absent at baseline and after 1 or 2 years (% without symptom at baseline).		Agi: 28.6; 71.4 Irr: 31.3; 18.8	Agi: 0 Irr: 50
Severe dementia (MMSE 0-9)										
55	Wetzels	2010	CH	24	5	6	No model. For each observation 0-1, 1-2, 2-3, 3-4.	Irr (“agitation”): 9.5, 20.6, 15.3, 23.1Irr (“agitation”): 17.2, 18.2, 16.5, 23.1 Agi/Wan: 15.6, 15.1, 10.5, 18.8		

Dementia severity not reported										
36	King-Kallimanis	2010	CH	4 yrs. (mean 390/297 days)	mean:4	3	Of non-wan at admission, changed to wan and remained wan; Of non-wan at admission, changed to wan and back to non-wan; Of non-wan at admission, changed to wan and fluctuated Absent: Of non-wan at admission, % that remained non wan for the duration of the study or until discharge.		Wan: 3;2; 1	Wan: 94
46; 38	Morgan; Kunik	2012	DC	24	7	4	Incidence during follow-up period (incidence in first 5 months excluded in Morgan 2012, included in Kunik 2010).		Agg: 38 (Morgan); 41 (Kunik)	
34	Jost	1996	DC	Retro-spective using medical records	Retro-spective	Retro-spective	Documentation of onset of symptoms in medical records.		Irr: 77 Wan: 43	

Elation

	Author	**Year**	**Setting**	**Months follow-up**	**n BPSD measures**	**Time between measures (months)**	**Details**	**Elation**		
								Per measurement (%)	Over total follow-up (%)	Absent (%)
Moderate dementia (MMSE 15-20)										
1	Aalten[2]	2005	DC	24	5	6	Cumulative incidence: the proportion of patients who were symptom free at baseline but developed the specific symptom at the next assessments.		4.6	

25	Gillette-Guyonnet	2011	DC	max 48	mean 5.1	6	Incidence of NPI 4 or higher per 100 person years and % events during 4 year follow-up in those without the symptom at baseline (between brackets).		3.9 (8.2)	
Severe dementia (MMSE 0-9)										
55	Wetzels	2010	CH	24	5	6	No model. For each observation 0-1, 1-2, 2-3, 3-4 .	3.6, 4.5, 2.7, 2.7		

Sleep problems

	Author	**Year**	**Setting**	**Months follow-up**	**n BPSD measures**	**Time between measures (months)**	**Details**	**Sleep problems**		
								Per measurement (%)	Over total follow-up (%)	Absent (%)
Mild dementia (MMSE 21-26)										
22	Eustace	2002	DC	24	3	12	Markov model. Transition probability for onset over 2 year period.	15		
Moderate dementia (MMSE 15-20)										
8	Berger	2005	DC	24	5	3-6	Absent at each measurement time over the 2 year period.			44
1	Aalten[2]	2005	DC	24	5	6	Cumulative incidence: the proportion of patients who were symptom free at baseline but developed the specific symptom at next assessments.		30.6	
25	Gillette-Guyonnet	2011	DC	max 48	mean 5.1	6	Incidence of NPI 4 or higher per 100 person years and % events during 4 year follow-up in those without the symptom at baseline (between brackets).		11.2 (21.5)	
Severe dementia (MMSE 0-9)										
55	Wetzels	2010	CH	24	5	6	No model. For each observation 0-1, 1-2, 2-3, 3-4.	1.8, 6.3, 4.7, 8.5		

Dementia severity not reported										
34	Jost	1996	DC	Retrospective using medical records	Retrospective	Retrospective	Documentation of onset of symptoms in medical records.		56%	

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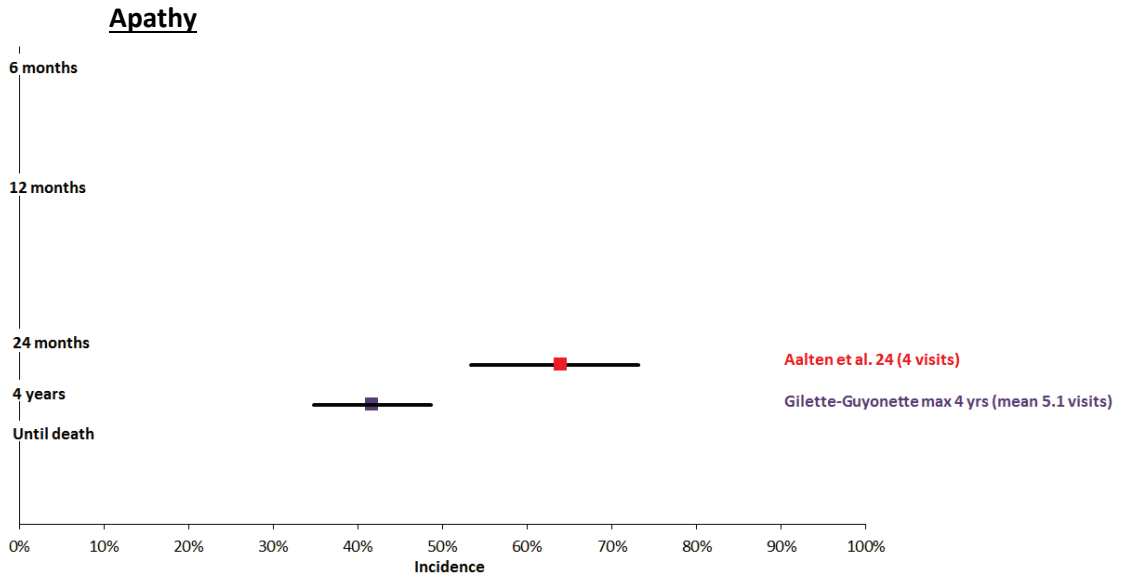
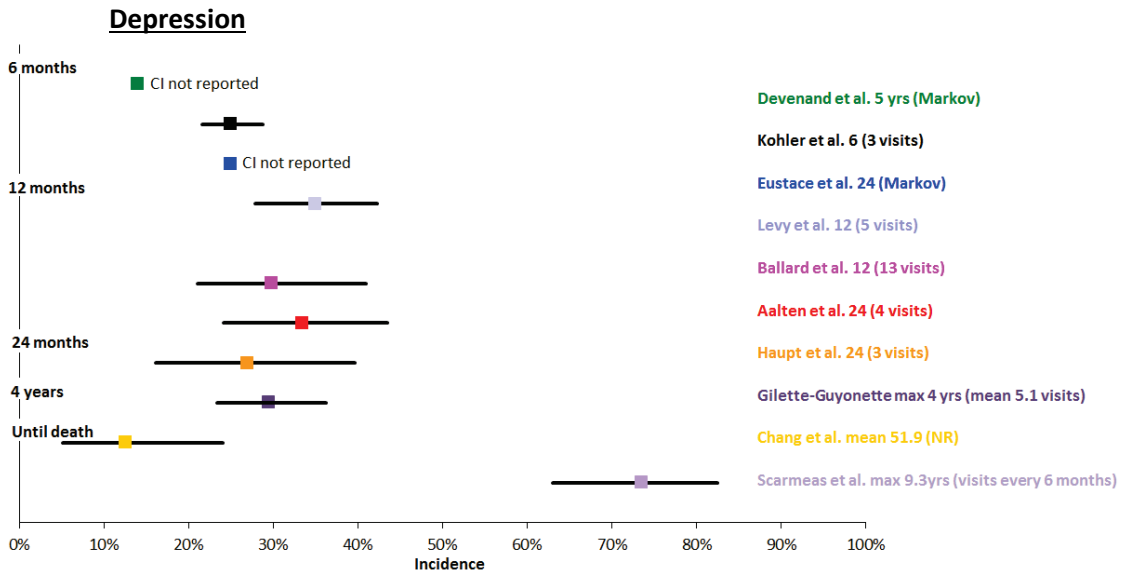
Agi=agitation
Hal=hallucination
Per=persecution
Mis=misidentification
Sle=sleep problems
Wan=wandering
Ela=elation

Fig. DS3 Incidence of BPS reported in included studies





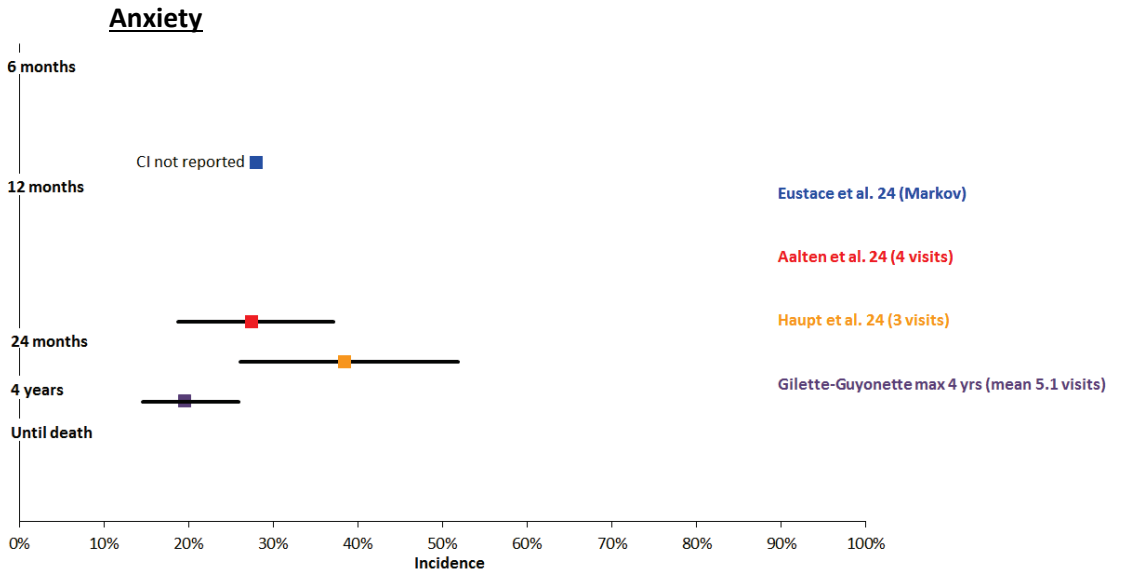


Fig. DS3 continued

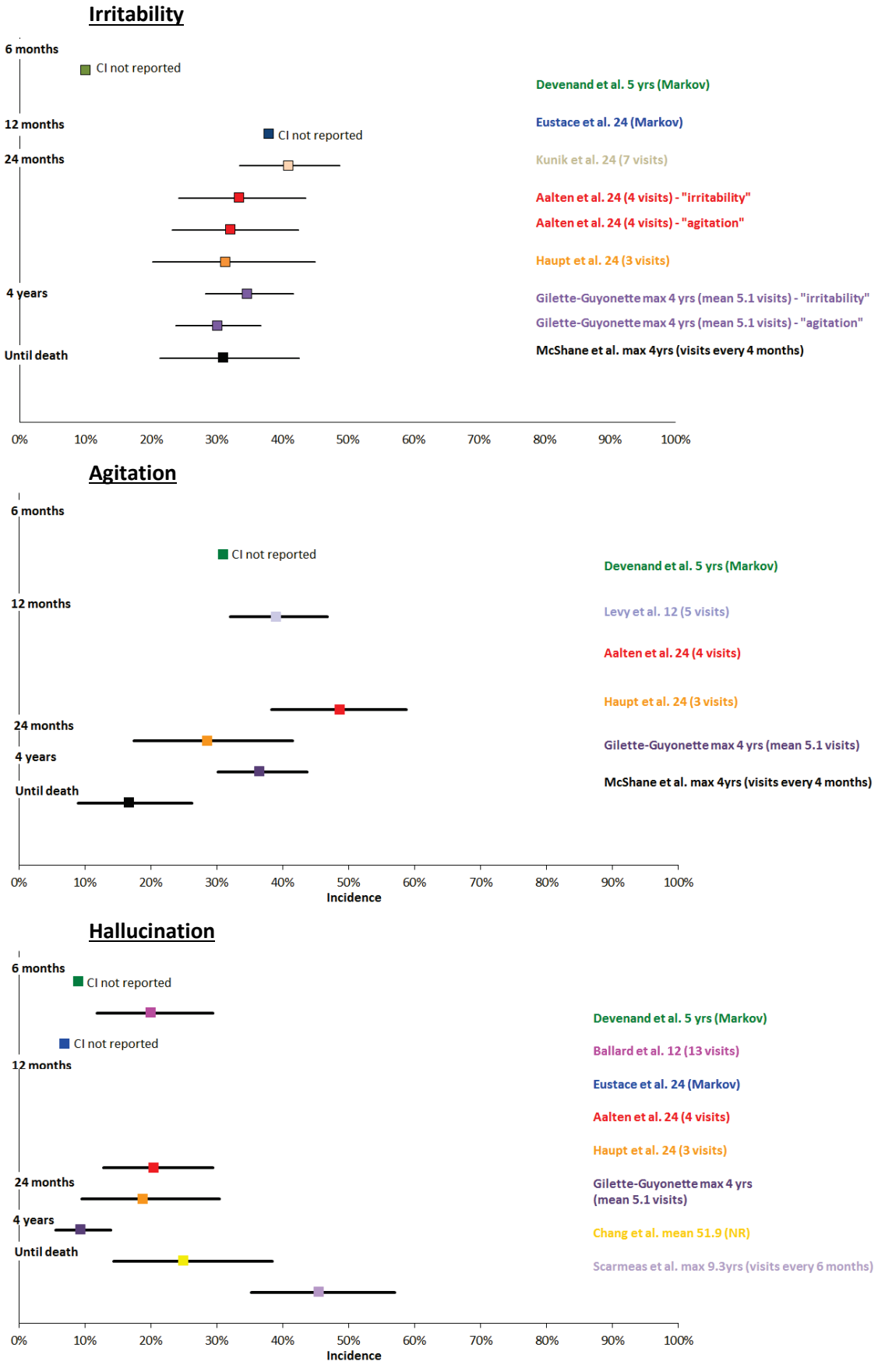
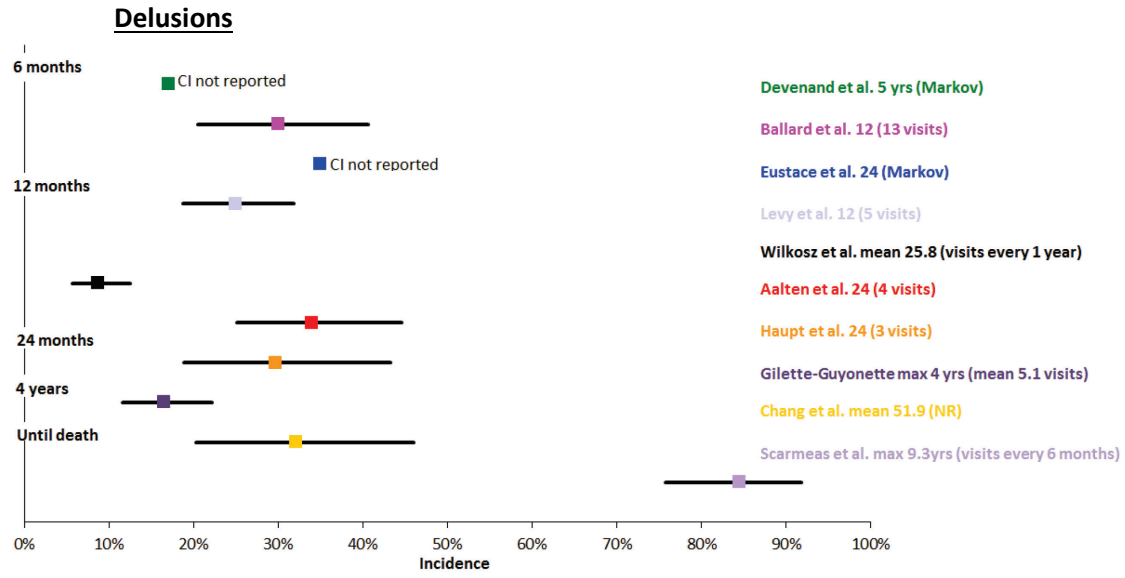
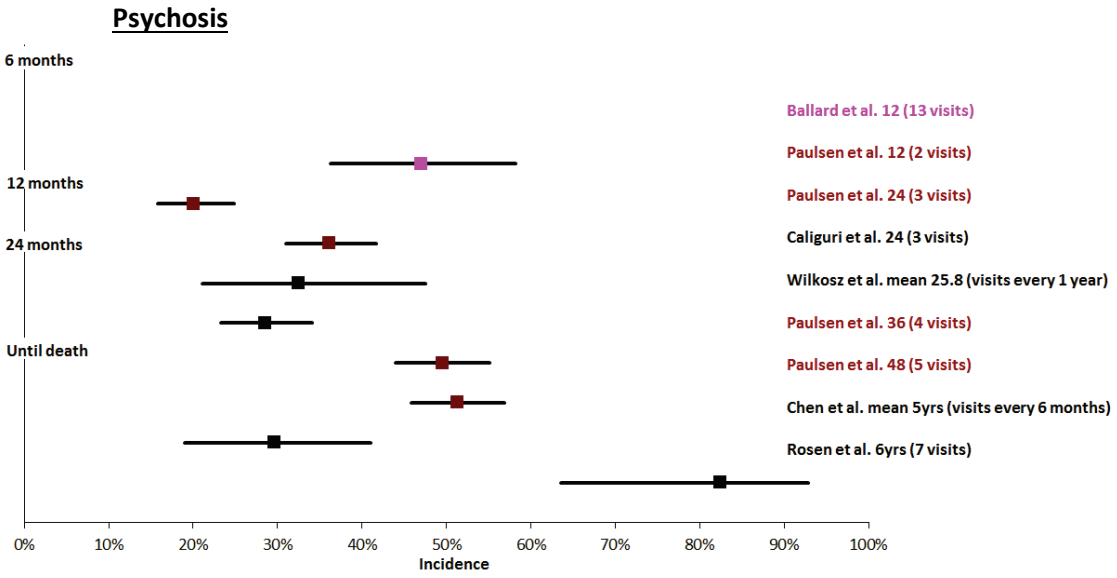


Fig. DS3 continued





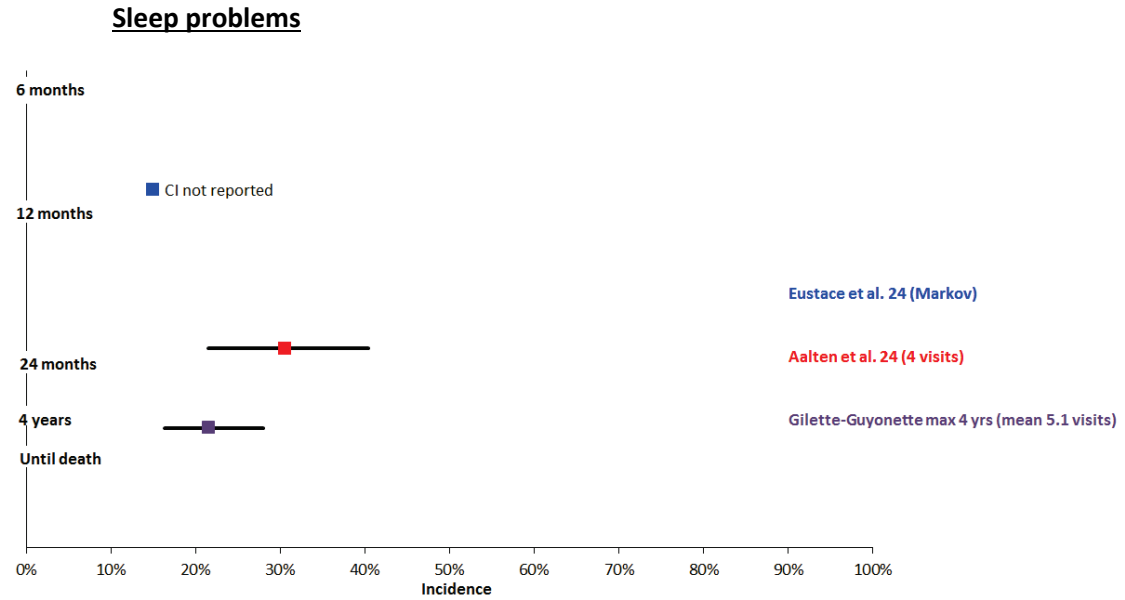
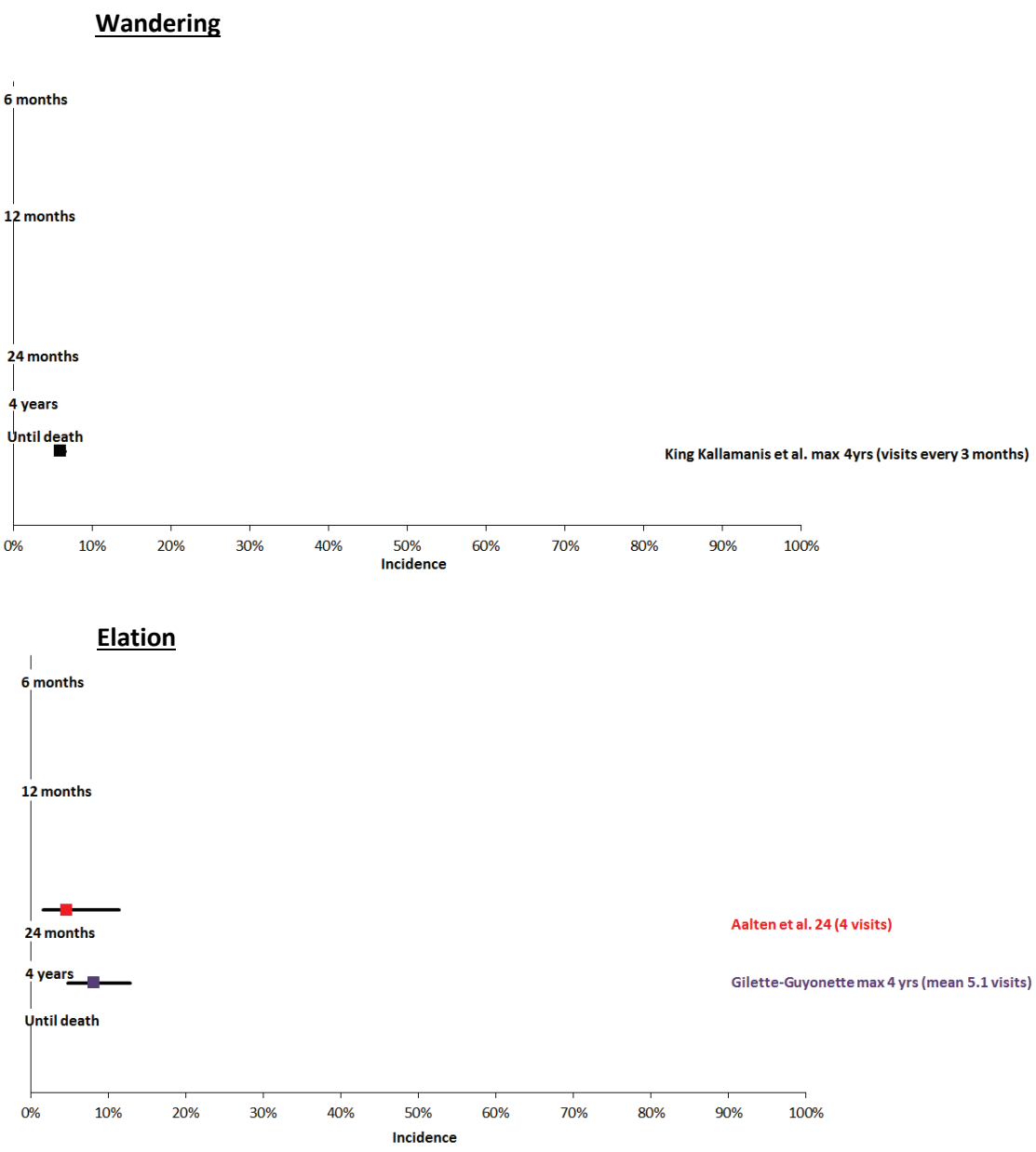


Fig. DS3 continued



The figures show the percentage of participants in which new symptoms developed during the period indicated on the y-axis, and the 95% confidence interval. For each figure, a legend shows the author name, the duration of the total follow-up in months and the number of visits.

Table DS5 Association BPSD and cognitive function

Affective symptoms

	Author	Year	Setting	Months follow-up	n BPSD measures	Time between measures (months)	Details	Covariates	Score	Depression / Anxiety / Apathy
Moderate dementia (MMSE 15-20)										
29	Holtzer[1b]	2005	DC	14yrs	28	6	Time-dependent Cox analysis to evaluate if cognitive status predicted the first episode of dep during follow-up. General estimating equation with cognitive status, functional activity and disease duration as predictors, taking into account the multiple visits per patient as well as the likelihood that an individual's characteristics correlate with each other over time. Dichotomous depression outcome, also results for categorical and continuous outcomes in paper.	Time, age, sex, education, cohort, antidepressant medication, Charlson comorbidity index.	1 Depression dichotomous exclusive of physical symptoms, 2 frequency of depression exclusive of physical symptoms (5 level scale), 3 total depression scores inclusive of physical symptoms.	Dep: Time dependent Cox analysis: mMMSE NS. GEE analysis with dichotomous outcome 1: mMMSE: 0.003 (0.000-0.006) (p=0.03), Time: -0.0022 (-0.037-0.007) (p=0.004), BDRS 0.002 (0.001-0.002) (p<0.001); mMMSE NS using other 2 depression outcomes.
2	Aalten[2]	2005	DC	24	5	6	Analyses of variance with repeated measures, overall between effects. MMSE at baseline and course of BPSD.	Age, sex, SES, MMSE and GDS at baseline. Also symptoms at baseline and duration of illness.	Three subsyndrome factors and NPI total score.	Dep: NR (both MMSE and GDS)
59	Zahodne	2013	DC	5.5yrs	mean 10.1	6	Latent growth curve modelling.	Cognitive decline and function.	CUSPAD dep, continuous.	Dep: higher level of dep was associated with worse initial functioning and faster subsequent cognitive and functional decline.
Moderately severe dementia (MMSE 10-14)										
43	McCarty	2000	DC	24	3	1	Mean response of the items that loaded on each factor. Test-retest correlations and mixed model analyses.	By 4 severity levels based on initial MMSE score.	BEHAVE-AD, total score 18 (6 questions with maximum score 3).	The patterns are similar for all factors (including Emotional/impulsive behaviours and apathy). Those with initial MMSE scores ranging from 11 to 30 (severity levels 1 and 2) tended to show increased memory and behavioural problems across time, whereas those with initial MMSE scores ranging from 1 to 10 (severity 3) tended to show stable scores across time.

Normal cognitive function (MMSE 27+, no dementia)										
37	Kohler	2010	POP	6	3	3	Linear mixed-model analysis was used to measure the association between depressive symptom severity and cognitive decline from baseline to 3- and 6-year follow-up.	Age, sex, education and baseline cognition scores. .	Stability of depression was defined as a score within the upper quartile group on 2 consecutive assessments (baseline or follow-up (F1 or F2). This produced four groups: highly depressed at baseline only, highly depressed at follow-up only and persistently highly depressed.	Participants who were persistently highly depressed over time showed a widespread pattern of decline, including memory (p<0.001), processing speed (p=0.002), and global cognition (p=0.0) when compared to participants who were never highly depressed. They also performed lower on baseline measures of processing speed (p=0.04) and attention and executive function (p<0.001).
7	Becker	2009	POP	9yrs	9	12	Association between dep and cognitive function scores 1992-1999 which was then examined as a predictor of the development of dementia between 2002-2007. Cox proportional hazard models.	Age, ventricular grade.	CESD score or correlation variable of CESD and 3MSE scores.	No significant associations between non-dep/transiently dep/persistently dep in 1994-1998 and dementia after 1998-1999
53	Vinkers	2004	POP	4yrs	5	1	Separate linear mixed models. Additional annual increase of dep score per SD of cognitive function test score at baseline in those without dep at baseline (GDS15=<2) (p).	Sex and educational level.	Total GDS-15 score.	Dep: Global cognitive function: -0.06 (0.17); Attention: 0.08 (0.05); Processing speed:-0.03 (0.42); Immediate recall: -0.17 (0.01); Delayed recall: -0.10 (0.02).
3	Amieva	2008	POP	4yrs	7	12-36	Longitudinal analyses were done using a semiparametric extension of the mixed-effects linear model. The mean changes of the scores are assumed to be smooth curves, approximated by cubic splines.		Total CES-D score.	Dep: CES-D score over time before diagnosis of dementia / control: Slight increase in score with some minor fluctuation. The score increased slightly but regularly in the pre-dementia group until the diagnosis and between 8 and 7 years before diagnosis the curve of the predementia group became distinguishable from that of the control subjects.
58	Wilson	2010	POP	8-9yrs	mean: 3.6	36	Change in depression scores using GEE models. The models included a term for time in years since baseline, indicators for MCI and AD, interactions of indicators with time. Also reported for depressive domains.	Age, sex, race, education.	CES-D score ranging from 0-10. Rate of 0.04 units per year equals 1 symptom per 25 years. Also Hamilton Depression Rating Scale, ranging from 0-235.	Dep: CES-D - Prediagnosis of AD: 0.04 (0.004); postdiagnosis of AD: -0.00 (0.913) Hamilton - scores did not change in any of the groups.

57	Wilson	2008	OTHER	13yrs	mean:7.8	24	Generalised estimating equation models to analyse change in depressive symptoms before the diagnosis of AD (compared to those who never developed dementia) during the study period, with a logit-link function and a binomial error. Because preliminary analyses with quadratic terms for time showed no evidence of nonlinear change, all analyses are of linear change.	Age, sex, education and interactions.	Treating the number of reported symptoms as a proportion of the 10 possible symptoms.	Dep: The rate of change in depressive symptoms in the incident AD subgroup did not differ from the rate in unaffected persons before the AD diagnosis (p=0.64) or after it (p=0.62). There was no systematic change in depressive symptoms in the unaffected subgroup or in the affected subgroup before (p=0.92) or after (p=0.16) the initial MCI diagnosis.
32	Houde	2008	DC	max:10	max:11 (unsure)	1	Cox proportional hazard of the association of symptoms and covariates with progression to dementia.	Age, education, MMSE score, Apoe E4 status.	GDS score.	Dep: Persistent dep associated with progression to AD. MCI individuals who remained MCI: depression tended to improve in the first two years of follow-up. MCI who progressed to dementia: persistence of depression until the year prior to diagnosis as AD. After diagnosis, depression improved.
21	Dotson	2008	VOL	max 26yrs	NR	24	Linear mixed models using the PROC MIXED procedure in SAS. Yields information on the unique effects of each predictor, including both fixed and random effects.	Baseline age, time interval and interval and interactions. Sex, self-reported race, educations and scores on the primary mental abilities vocabulary test.	Continuous CES-D score.	Dep: Higher average depressive symptoms were associated with poorer performance on TMT-A and TMT-B. Individuals with higher average CES-D scores showed greater longitudinal decline on CVLT-A, long delay free recall, BIMCS and MMSE. Some interaction effects. See table 5 and figure 3.
41	Mackin	2011	VOL	3yrs	4	12	Participants were classified 'MCI converters' if they were diagnosed with dementia within 3 years of their baseline evaluation or 'MCI cognitively stable' if they did not progress to dementia during this interval.			Dep: no difference in stability between cognitively stable and those who progressed to dementia.
9	Bielak	2011	POP	15yrs	5	2-6yrs	Bivariate dual change score models.	Age, education, baseline general cognitive ability and self-reported health.		Dep: the data best fit the hypothesis that depressive symptoms predict subsequent change in perceptual speed. More depressive symptoms predicted subsequently stronger declines in perceptual speed over time lags of 1 year.

Comparing cognitive groups										
33	Janzing	2000	CH	12	3	6	Logistic regression of dep and dementia.	Age, sex, physical illness and somatic complaints.		Subjects with and without dementia had comparable baseline prevalences of depressive caseness (12.2% compared to 11.1, ns) and depression subcaseness (20.4% compared to 28.9%, ns). This remained stable during 12 month follow-up.
10	Blansi	2005	DC	3-4yrs	3-4	12	Linear and quadratic curves were fitted to repeated symptom and MMSE measurements for each patient. Linear (increasing) or quadratic (inverse U-shaped) course as a function of MMSE scores.	Age, years of education and gender.		Dep: Sign test for the analysis of a linear course (increasing) was significant p<0.01; Quadratic (inverse U shaped) not significant.
11	Bunce	2012	PB	max 12yrs	max 4	4 yrs.	Latent growth models estimating the intercept and slope of dep and anx symptoms.	Cognitive measures.		Dep: Higher initial scores of dep significantly associated with poorer initial performance on SLMT, verbal fluency and episodic memory, dep slope NS Anx: Higher initial scores of anx associated with poorer verbal fluency, anx slope NS.
Dementia severity not reported										
17	Cohen-Mansfield	1998	CH?	24	5	6	Repeated measures multivariate analyses of variances (MANOVA).		CMAI syndrome scores: mean of behaviours comprising each type of agitation.	
42	Marin	1997	NR	mean 37.1	mean:6.0	6	Matched sample t-tests.			Dep: NS for any year.

Psychotic symptoms

	Author	Year	Setting	Months follow-up	n BPSD measures	Time between measures (months)	Details	Covariates	Score	Delusion / Hallucination / Misidentification
Moderate dementia (MMSE 15-20)										
28	Holtzer[1a]	2003	DC	5yrs	11	6	GEE analyses to calculate the odds of having each of the psychopathological behaviours as a function of cognitive status in the entire sample with all available patient visits.	Controlled for age, education and sex.		Del: mMMSE 39-57: ref; 33-38:1.4 (0.0314); 26-32: 2.3 (<0.0001); 14-25: 2.4 (<0.0001); 0-13: 1.1 (0.8356) Hal: mMMSE 39-57: ref; 33-38:2.0 (0.0287); 26-32: 2.6 (0.0009); 14-25: 3.3 (0.0001); 0-13: 2.6 (0.0059).
2	Aalten[2]	2005	DC	24	5	6	Analyses of variance with repeated measures, overall between effects. MMSE at baseline and course of BPSD.	Age, sex, social class, MMSE and GDS at baseline. Also symptoms at baseline and duration of illness.	Three subsyndrome factors and NPI total score.	MMSE at baseline related to higher level of psychosis at follow-up, F=3.5, p=0.034 - GDS NR.

49	Rosen	1991	DC	6yrs	7	1 yr.	Cognitive decline during entire follow-up for those who developed symptoms compared to those that did not.			Patients who developed psychosis exhibited a more rapid rate of cognitive decline on average during the entire follow-up period than those who did not develop psychosis (p<0.03).
Moderately severe dementia (MMSE 10-14)										
44	McShane[5]	1995	CLIN	4yrs	NR	4	Analysis of covariance.	Cortical Lewy bodies, visual problems, interaction term.	Proportion of all interviews at which hallucinations had been rated positively.	Hal: Cortical Lewy bodies associated with persistent hallucinations. Those who had ever had hallucinations (even if at only one interview) had significantly lower MMSE scores at their last interview (8.5 vs. 3.5, p=0.005); Cognitive decline did not have a significant independent effect on proportion of interviews with hallucinations, sum of squares 0.010, F=0.19, p=0.67.
26	Haupt[4]	1996	DC	24	3	1	Association of psychotic symptoms with rate of cognitive decline, multiple stepwise regression.	None	BEHAVE-AD, total score 18 (6 questions with maximum score 3).	Del: 12 months change - CAMCOG: 0.03 (NS), MMSE: 0.02 (NS), 24 months change - CAMCOG: 0.27 (significant), MMSE: 0.13 (NS) Hal: 12 months change - CAMCOG: 0.03 (NS), MMSE: 0.04 (NS), 24 months change - CAMCOG: 0.01 (NS), MMSE: 0.01 (NS)

Hyperactivity symptoms

	Author	Year	Setting	Months follow-up	n BPSD measures	Time between measures (months)	Details	Covariates	Score	Irritability / Agitation / Wandering
Moderate dementia (MMSE 15-20)										
51	Scarmeas[1b]	2007	NR	14yrs	max:25	6	Cox models predicting cognitive function by disruptive behavioural symptoms as time-dependent covariates. Also sundowning, also unadjusted results reported.	Controlled for cohort, recruitment centre, age, sex, education, baseline MMSE, baseline blessed dementia rating scale score, comorbidity index, use of cholinesterase inhibitors and use of neuroleptics.	Disruptive behavioural symptoms.	Agi: HR=1.64 (1.16-2.33) Wan: NS Irr: NS Total score: Sum (0-5): HR=1.21 (1.07-1.36); Any (0-1) HR=1.45 (1.03-2.03).
28	Holtzer[1a]	2003	DC	5yrs	11	6	GEE analyses to calculate the odds of having each of the psychopathological behaviours as a function of cognitive status in the entire sample with all available patient visits.	Controlled for age, education and sex.		Wan: mMMSE 39-57: ref; 33-38:1.5 (0.0568); 26-32: 2.0 (0.0064); 14-25: 3.3 (<0.0001); 0-13: 4.2 (<0.0001) Irr: mMMSE 39-57: ref; 33-38:3.5 (0.0016); 26-32: 3.1 (0.0001); 14-25: 3.6 (<0.0001); 0-13: 9.0 (<0.0001).
2	Aalten[2]	2005	DC	24	5	6	Analyses of variance with	Age, sex, SES, MMSE	Three subsyndrome factors	Hyperactivity - Significant interaction between time and

							repeated measures, overall between effects. MMSE at baseline and course of BPSD.	and GDS at baseline. Also symptoms at baseline and duration of illness.	and NPI total score.	GDS, F=4.9, p=0.008 - MMSE NR.
Moderately severe dementia (MMSE 10-14)										
31	Hope[5]	2001	CLIN	Cog	9yrs	mean:10.5	MMSE score at onset of behaviour and at death in participants included in the study for more than one year.	Period with dementia.		Lower MMSE score and death associated with wan ($p<0.05$). Median MMSE scores at onset suggests progression from excessive but appropriate walking, attempts to leave the home and pottering, through to clear hyperactivity that becomes increasingly aimless and inappropriate.
45	McShane[5]	1998	CLIN	4yrs	NR	4	Relationship between symptoms and cognitive function in first year using Pearson X^2 or student's t statistics as appropriate.			MMSE in year after entry lower in those with physical aggression than in those without (8.1 compared to 15.7, $p<0.003$) and in those with hyperactivity than in those without (9.2 compared to 16.0, $p=0.001$).
4	Asada	1999	DC + VOL	5yrs	6	1	Symptom change by baseline CDR stage: Repeated measurement analysis with the PROC MIXED program based only on the data for the subjects who completed all six assessments. Four candidate models were proposed: constant correlation, correlation declining exponentially with time, no mathematical pattern and no relation. Association symptom change and level of global impairment.		Behavioural factor score.	See figure 1 and 2 Hyperactivity: CDR 2 and 3: slopes of the lines for hyperactivity showed a significant downward trend. Factor score reached its peak during the CDR 2 stage and followed a linear downward trend thereafter. Agitation: CDR 2 Significant downward trend, CDR 3 NS.
Severe dementia (MMSE 0-9)										
12	Burgio	2007	CH	18	4	6	Examined cognitive status modelling time as a regression variable to compare cognitive status at specific times.			Irr: Staff: no difference; Obs: profoundly impaired (MMSE=<7) changed little, moderately impaired (MMSE>7) symptoms improved slightly up to 12 months and worsened at the 18 month point.
Comparing cognitive groups										
10	Blansi	2005	DC	3-4yrs	3-4	12	Linear and quadratic curves were fitted to repeated symptom and MMSE measurements for each patient. Linear (increasing) or quadratic (inverse U-shaped) course as a function of MMSE scores.	Age, years of education and gender.		Agi: Disturbing behaviour: Linear and quadratic not significant.

Dementia severity not reported										
17	Cohen-Mansfield	1998	CH?	24	5	6	Repeated measures multivariate analyses of variances (MANOVA)			Agi: Physical non-aggressive behaviour: those with moderate or severe impairment increased twice as much as those who were cognitively intact at baseline, average increases were 0.30, 0.35 and 0.14. Verbally non-aggressive behaviour: all groups showed relatively constant levels over time, with the group with moderate levels of impairment manifesting consistently higher levels of agitation. Irr: Both types of aggressive behaviours show increases over time, not significantly influenced by cognitive function
42	Marin	1997	NR	mean 37.1	mean:6.0	6	Matched sample t-tests			Agi: NS for any year Pacing: Significant yearly change from baseline to year 1 (0.39 points, p=0.003) Irr: NS for any year

Elation

No results

Sleep problems

No results

Total BPSD score

	Author	Year	Setting	Months follow-up	n BPSD measures	Time between measures (months)	Details	Covariates	Score	Total score
Moderate dementia (MMSE 15-20)										
2	Aalten[2]	2005	DC	24	5	6	Analyses of variance with repeated measures. MMSE at baseline and course of BPSD	Age, sex, SES, MMSE and GDS at baseline. Also symptoms at baseline and duration of illness	Three subsyndrome factors and NPI total score	Significant interaction between time and GDS score and the NPI total score, F=4.9, p=0.008. Severe dementia: scores decreased, mild dementia: scores increased - MMSE NR
Dementia severity not reported										
42	Marin	1997	NR	mean 37.1	mean:6.0	6	Matched sample t-tests			Total scores did not worsen significantly during any study year (year 1: p>-.05, year 2: p>0/1, year 3: p>0.1, year 4: p>0.1, year 5: p>0.1)

Reference numbers refer to the Online Reference List

Papers from the same study groups:
1a Predictors study 1: Columbia Medical Centre, John Hopkins University School of Medicine, Massachusetts General Hospital, USA
1b Predictors study 2: 3 centres in USA (see 1a) and 2 centres in Europe (Paris and Greece)
2 Maasbed study
3 Ballard et al. (Psychiatry services in the West Midlands and a memory clinic in Bristol)
4 Haupt et al. (Outpatient clinic at the institute of psychiatry of the Technical University in Munich)
5 Hope et al. (Oxford)

Settings
DC=Dementia or memory clinic
POP=Population-based
CH=Care home
CLIN=Referred by clinicians
VOL=Volunteers
NR=Not reported

BPSD= behavioural and psychological symptoms of dementia
Apa=apathy
Dep=depression
Anx=anxiety
Irr=irritability/aggression
Agi=agitation
Hal=hallucination
Per=persecution
Mis=misidentification
Sle=sleep problems
Wan=wandering
Ela=elatio

Table DS6 Adherence to the PRISMA reporting guidelines

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	According to journal guidelines
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction section
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Not relevant.
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not available
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Methods – eligibility criteria
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Methods – search methods
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	eFigure1

Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Methods – data synthesis
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Methods – data synthesis
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Methods – data synthesis
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Not assessed
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Methods – data synthesis
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Not applicable
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Not assessed
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not applicable
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Results – characteristics – search results (text box)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	eTable 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Not assessed
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	No interventions. Results Figure 2 and Figure 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not applicable

Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Not assessed
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Acknowlegements Abstract

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**

Online reference list of included studies

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3. Amieva H, Le Goff M, Millet X, Orgogozo JM, Peres K, Barberger-Gateau P, Jacqmin-Gadda H, Dartigues JF. 2008. Prodromal Alzheimer's disease: Successive emergence of the clinical symptoms. *Ann Neurol* 64: 492-498.

4. Asada T, Kinoshita T, Morikawa S, Motonago T, Kakuma T. 1999. A prospective 5-year follow-up study on the behavioral disturbances of community-dwelling elderly people with Alzheimer disease. *Alzheimer Dis Assoc Disord* 13: 202-208.

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Longitudinal course of behavioural and psychological symptoms of dementia: systematic review

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BJP published online August 4, 2016 Access the most recent version at DOI: 10.1192/bjp.bp.114.148403

Supplementary Material	Supplementary material can be found at: http://bjp.rcpsych.org/content/suppl/2016/07/25/bjp.bp.114.148403.DC1.html
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Downloaded from	http://bjp.rcpsych.org/ on August 21, 2016 Published by The Royal College of Psychiatrists

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