

## Amyloid Deposition in Parkinson's Disease and Cognitive Impairment: A Systematic Review

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**ABSTRACT: Background:** Varying degrees of cortical amyloid deposition are reported in the setting of Parkinsonism with cognitive impairment. We performed a systematic review to estimate the prevalence of Alzheimer disease (AD) range cortical amyloid deposition among patients with Parkinson's disease with dementia (PDD), Parkinson's disease with mild cognitive impairment (PD-MCI) and dementia with Lewy bodies (DLB). We included amyloid positron emission tomography (PET) imaging studies using Pittsburgh Compound B (PiB).

**Methods:** We searched the databases Ovid MEDLINE, PubMed, Embase, Scopus, and Web of Science for articles pertaining to amyloid imaging in Parkinsonism and impaired cognition. We identified 11 articles using PiB imaging to quantify cortical amyloid. We used the metan module in Stata, version 11.0, to calculate point prevalence estimates of patients with "PiB-positive" studies, that is, patients showing AD range cortical A $\beta$ -amyloid deposition. Heterogeneity was assessed. A scatterplot was used to assess publication bias.

**Results:** Overall pooled prevalence of "PiB-positive" studies across all three entities along the spectrum of Parkinson's disease and impaired cognition (specifically PDD, PD-MCI, and DLB) was 0.41 (95% confidence interval [CI], 0.24-0.57). Prevalence of "PiB-positive" studies was 0.68 (95% CI, 0.55-0.82) in the DLB group, 0.34 (95% CI, 0.13-0.56) in the PDD group, and 0.05 (95% CI, -0.07-0.17) in the PD-MCI group.

**Conclusions:** Substantial variability occurs in the prevalence of "PiB-positive" studies in subjects with Parkinsonism and cognitive impairment. Higher prevalence of PiB-positive studies was encountered among subjects with DLB as opposed to subjects with PDD. The PD-MCI subjects showed overall lower prevalence of PiB-positive studies than reported findings in non-PD-related MCI. © 2015 International Parkinson and Movement Disorder Society

**Key Words:** Parkinson's disease; PDD; DLB; MCI; systematic review

Parkinson's disease (PD) is the second most common neurodegenerative disorder and is characterized by progressive motor and cognitive impairments. The risk of

developing dementia in the setting of PD is two to six times higher than in the general population, corresponding to lifetime risk estimates of 30% to 80%.<sup>1,2</sup>

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Parkinson's disease with dementia (PDD) is related closely to dementia with Lewy bodies (DLB), which is the second most common neurodegenerative dementia, accounting for up to 20% of dementia cases.<sup>3,4</sup> The key similarity between PDD and DLB is the requirement for synucleinopathy in characteristic regional depositions in the context of dementia. Distinction between the two entities is based on the "1-year rule," with subjects presenting with dementia before or within 1 year of developing parkinsonism classified as DLB and those developing dementia more than 1 y after PD diagnosis classified as PDD.<sup>5</sup> Although the PDD-DLB clinical classification was hoped to improve diagnostic homogeneity and highlight

distinctions between the two syndromes, subsequent studies have shown substantial overlap of PDD and DLB phenotypes in a number of clinical and neuropathological investigations.<sup>6-9</sup>

Recently developed molecular imaging approaches permit the detection of pathological accumulations of A $\beta$ -amyloid plaques.<sup>10</sup> Amyloid plaques are demonstrated commonly in both PDD and DLB on neuropathological examinations.<sup>6,8,11,12</sup> A number of amyloid positron emission tomography (PET) imaging studies have been performed in the setting of PD, PDD, and DLB.<sup>13-23</sup> Although a wide range of amyloid deposition and relatively few subjects are present in most individual studies, the overall impression is that higher levels of neocortical amyloid deposition (similar to those encountered in the setting of Alzheimer's disease [AD]) are more frequent in DLB than PDD. Potentially more interesting is the impression that higher levels of amyloid deposition are less frequent in PD with mild cognitive impairment (MCI) compared with frequencies reported in cognitively normal elderly subjects.<sup>16,19,21,23</sup> Delineating the frequency of AD-range amyloid deposition in patients with parkinsonism and cognitive impairment, specifically in the context of individual clinical subtypes (ie, PDD, DLB, and PD with mild cognitive impairment [PD-MCI]), is a prerequisite for understanding the role of amyloid in the multisystem neurodegeneration of PD. Prior amyloid imaging studies of PD and DLB are largely smaller series with relatively heterogeneous subject populations and varying imaging methods.

To help delineate important questions for future research, we undertook a systematic review meta-analysis of prior amyloid imaging studies of DLB, PDD, and PD-MCI. Because of the relatively small number of aggregate subjects and varying methods of imaging data analysis (discussed later), we selected high (AD-range) levels of neocortical amyloid deposition as the most robust endpoint for comparing amyloid deposition in the DLB, PDD, and PD-MCI groups.

The specific objective purpose of this systematic review is to estimate the frequency of "amyloid-positive" subjects among patients with DLB, PDD, and PD with MCI. We define "amyloid positive" as exhibiting AD-range cortical amyloid deposition on brain PET imaging performed with Pittsburgh compound B (PiB; hence the term "PiB-positive" also is used) with thresholds determined by the individual laboratories where each study was performed.

## METHODS

### Information Sources/Study Search Strategy

In February 2013, we systematically searched Ovid MEDLINE, PubMed, Embase, Scopus, and Web of

Science for articles pertaining to amyloid imaging in Parkinson's disease dementia. The MeSH and Emtree vocabularies were used whenever possible, along with keyword variations of the imaging and disease terms. The initial search was run in Ovid Medline and then translated to the other databases (see Supplemental Data for the complete Ovid MEDLINE strategy). In all searches, non-English studies were excluded from the results, but no other limits or restrictions were applied. The combined yield of all searches was 938 citations, of which 509 were identified as duplicates in Endnote X5 (Thomson Reuters). The resulting set of 429 unique citations were exported into Excel and distributed to the lead author for screening.

### Study Selection

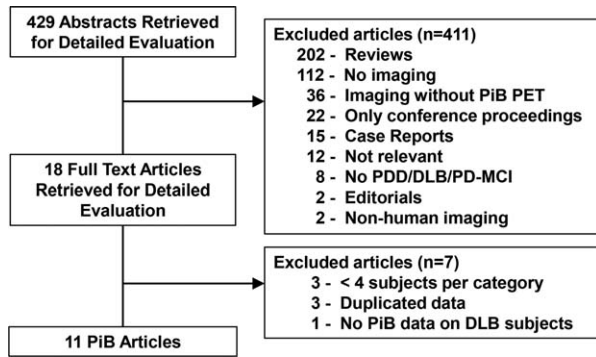
We included a study if it satisfied the following criteria: human studies using PiB for amyloid brain PET imaging in subjects with PDD or PD-MCI or DLB, more than three subjects/disease category, and subject mean ages included in the provided data. Studies involving duplicated data were identified, and the larger dataset only was included.

### Data Collection and Extraction

Two reviewers (M.P., B.R.F.) independently evaluated each abstract for inclusion. Next, we obtained full publications for further assessment and data extraction. The same reviewers independently reviewed each article and reached a final consensus for inclusion. These reviewers abstracted the information from the eligible articles: author, journal, year of publication, number of subjects, demographic and clinical characteristics of subjects, as well as the method of PiB PET image classification into positive versus negative (based on volume of distribution or based on standard uptake values measurements). Numbers of "PiB-positive" versus "PiB-negative" subjects per clinical classification group were the main outcome of interest extracted from the included studies.

### Assessment of Methodologic Quality

Two reviewers (M.P., B.R.F.) independently assessed the quality of each study according to the Quality Assessment for Studies of Diagnostic Accuracy (QUADAS) criteria.<sup>24</sup> These criteria assessed adequacy of index test description, adequacy of reference standard likely to correctly classify disease, adequacy of reference standard test description, blinded interpretations of index tests, absence of differential verification bias, absence of incorporation bias, absence of partial verification bias, whether a representative spectrum of diseased patients will receive the test in practice, whether selection criteria were clearly described, whether there



**FIG. 1.** Flowchart illustrates the selection of studies. PiB, Pittsburgh compound B; PET, positron emission tomography; PDD, Parkinson’s disease with dementia; DLB, dementia with Lewy bodies; PD-MCI, Parkinson’s disease with mild cognitive impairment.

a short period occurred between index and reference and whether uninterpretable results were reported. Each of these criteria were scored as “yes,” “no,” or “unclear.” All studies classified subjects as having DLB based on the revised consensus criteria.<sup>5</sup> In five of six studies that included PDD subjects, diagnosis of PDD was based on the relative timing of dementia and parkinsonism. Diagnosis of PD in these subjects was based on the UK Parkinson Disease Society (UKPDS) brain bank criteria<sup>25</sup> in four of the studies and on criteria proposed by Larsen et al.<sup>26</sup> in one study.<sup>17</sup> Diagnosis of dementia was based on Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, criteria<sup>27</sup> in these five studies. In one of six studies including PDD subjects, neuropsychological testing outcomes were used to determine the presence of dementia<sup>23</sup> in the presence of PD. Determination of PD-MCI was more variable and based on neuropsychological testing outcomes. Representative disease spectrum was also determined on the basis of included range of neuropsychological testing outcomes. Any disagreements in abstracted results between the reviewers were resolved by discussion and consensus.

### Statistical Analysis

We used the metan module in Stata, version 11.0, to calculate the frequency estimates of PiB-positive studies among the PDD, PD-MCI, and DLB groups, using random effects modeling. The 95% confidence intervals for these also were calculated. Data were intrinsically weighed by using individual study variances.

### Assessment of Heterogeneity

Heterogeneity was assessed using the quantity  $I^2$  as defined by  $I^2 = 100\% \times (Q-df)/Q$ , where  $I^2$  is a measure of consistency across studies,  $Q$  is the Cochran’s heterogeneity statistic, and  $df$  is the degrees of freedom. Higgins et al.<sup>28</sup> propose describing  $I^2$  values of 25%, 50%, and 75% as low, moderate, and high, respec-

tively, between trial heterogeneity.<sup>28</sup> We obtained the  $I^2$  values as an output of the *metan* program.

### Testing for Publication Bias

A scatterplot of the estimated point prevalence versus the corresponding study’s standard error measurement was used to assess publication/small sample bias. The scatterplot should have a symmetric distribution when publication bias is not present. A linear regression of the point prevalence of PiB-positive subjects versus standard error measurement also was used for publication bias assessment, with  $P < 0.05$  indicating significant asymmetry.

## Results

### Study Selection

Numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusion at each stage, are given in Figure 1. The search yielded 429 literature citations for potential inclusion. We excluded a total of 389 studies because they were review-based articles, did not include imaging, did not specifically include PiB imaging, did not include subjects with DLB or PDD, did not include human subjects, or were case reports. Of the 40 studies that fulfilled criteria, only 18 were full-length publications; the rest of the studies were reported in abstracts included in conference proceedings. One of the 18 studies did not include PiB data on DLB patients, one of the studies only included one DLB subject, one study only included three PDD subjects, and one study included three DLB subjects. Three additional studies were excluded based on overlapping data with the included studies. A total of 11 studies were included in the analysis.

### Study Characteristics

The 11 included studies involved 74 subjects diagnosed with PDD, 99 subjects with DLB, and 60 subjects with PD and mild cognitive impairment. The studies were published between 2007 and 2013 (Table 1). Three studies were performed in Europe, six in North America, one in Asia, and one in Australia. Six studies determined “PiB-positive” versus “PiB-negative” status based on measures of volume of distribution. Five studies determined “PiB-positive/negative” status based on standard uptake value measurements of the radiotracer uptake.

### Point Prevalence Estimates

Figure 2 shows the forest plot of the point prevalence values. The overall pooled prevalence of PiB-positive studies in the setting of PD and cognitive impairment is 0.41 (95% CI, 0.24-0.57). The pooled

**TABLE 1.** Individual study characteristics

Study Number	Author	Year	Origin	Age of Subjects
1	Burke	2011	USA	DLB: 72 (54-90)
2	Edison	2008	UK	DLB: 72 (62-80) PDD: 69 (56-80) PD-MCI: 68 (58-73)
3	Foster	2010	USA	DLB: 71 PDD: 75 PD-MCI: 73
4	Gomperts	2012	USA	DLB: 72 PDD: 73 PD-MCI: 69
5	Gomperts	2013	USA	PD-MCI: 67
6	Jokinen	2010	Finland	PDD: 72 (56-79)
7	Kantarci	2012	USA	DLB: 73 (60-87)
8	Maetzler	2009	Germany	DLB: 69 (62-75) PDD: 70 (62-80)
9	Petrou	2012	USA	PDD: 70 (60-84) PD-MCI: 70 (60-84)
10	Rowe	2007	Australia	DLB: 72 (63-81)
11	Shimada	2013	Japan	DLB: 73

Abbreviations: PDD, Parkinson's disease with dementia; DLB, dementia with Lewy bodies; PD-MCI, Parkinson's disease with mild cognitive impairment.

prevalence of PiB-positive scans among the DLB group is 0.68 (95% CI, 0.55-0.82). The pooled prevalence of PiB-positive scans among the PDD group is 0.34 (95% CI, 0.13-0.56). The pooled prevalence of PiB-positive scans among the PD-MCI group is 0.05 (95% CI, -0.07-0.17).

**Assessment of Methodological Quality**

Study quality scores ranged from 7 to 10 out of a possible score of 11 (Fig. 3). Overall, study quality scores were high. Almost 40% of the studies do not include a representative disease spectrum in terms of disease severity, with most demented subjects only having mild disease. This likely reflects the difficulties in performing imaging studies in patients with moderate and severe dementia. Most studies did not explicitly state whether the interpretation of the index test was blinded or whether a short time elapsed between the reference and the index testing.

**Assessment of Heterogeneity**

The point prevalence estimates for the 11 studies demonstrated a high level of heterogeneity using the mixed-model analysis ( $I^2 = 90\%$ ;  $P < 0.001$ ). The sub-analyses of the point prevalence for the DLB and PDD subgroups demonstrated a much higher level of heterogeneity ( $I^2 = 72\%$ ;  $P < 0.001$  and  $I^2 = 73\%$ ;  $P < 0.001$ , respectively) compared with the PD-MCI subgroup ( $I^2 = 0\%$ ;  $P = 0.95$ ). These findings highlight the heterogeneity in these clinical syndromes, especially as the diseases evolve beyond the initial MCI stage.

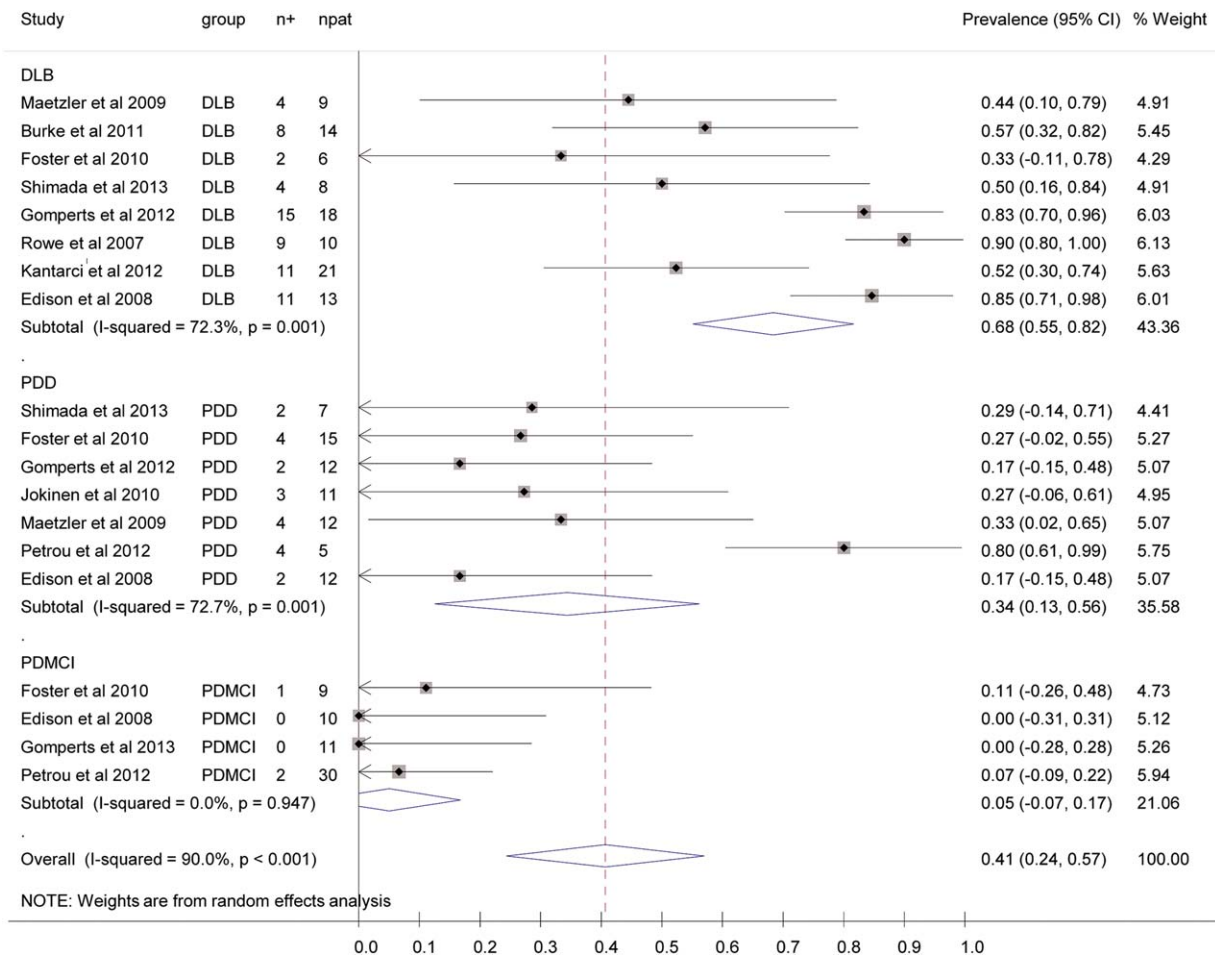
**Publication Bias**

As seen in the scatterplot (Fig. 4), an asymmetric distribution of the data was seen, with a tendency of the studies with a lower standard of error to have higher point prevalence. Regression analysis demonstrated a significant publication bias (bias coefficient = -4.82;  $P < 0.001$ ). Again, the findings indicate the significant heterogeneity of the investigated diseases and associated effects of small samples on estimates of the frequency of AD-range amyloidopathy.

**Discussion**

Relative timing and severity of cognitive impairment in the setting of Parkinsonism is used to assign the diagnoses of PD-MCI, PDD, and DLB. Despite the acknowledged central role of amyloid plaques in AD and a general impression that amyloid deposition is an important contributor to cognitive impairments in synucleinopathies, relatively few in vivo imaging studies have been performed of Aβ-amyloid deposition in dementias associated with synucleinopathy. Therefore, our systematic review of the existing, smaller studies in this setting is pertinent. Our results indicate substantial variability in AD-range cortical amyloid deposition, as determined by PiB PET imaging positivity among patients with Parkinsonism and cognitive impairment classified clinically as PDD, PD-MCI, and DLB. To frame the potential significance of this analysis, a brief summary of the relationship of Aβ-amyloid deposition in the more common setting of AD follows.

Moderate to high levels of Aβ-amyloid plaque density are required for pathological diagnosis of AD.<sup>29</sup> Recent in vivo imaging studies of fibrillary amyloid deposition with PiB and related tracers confirm that high percentages of clinically diagnosed probable AD patients are amyloid positive.<sup>30</sup> The minor fractions that are amyloid negative are probably attributable to clinical misclassification of frontotemporal dementias or of pure DLB as probable AD,<sup>13</sup> with the intriguing and recently described phenomenon of suspected non-amyloid pathology an additional potential contributor.<sup>31</sup> Comparative amyloid imaging and pathological confirmatory studies support for the most part the image-based classification of individual subject amyloid status.<sup>32,33</sup> The necessary role of high-level cortical amyloid deposition in AD (cascade hypothesis) is supported by the frequency of PiB-positive findings in MCI without PD and the significant although lower frequency of PiB positivity in asymptomatic normal elderly subjects.<sup>34-37</sup> Recent study of monogenic AD indicates onset of amyloid deposition more than a decade before symptomatic cognitive deficits, supporting the concept that initial amyloid deposition predates significant neurodegeneration and symptom onset.<sup>38</sup> Similarly, recent imaging data suggest that cortical



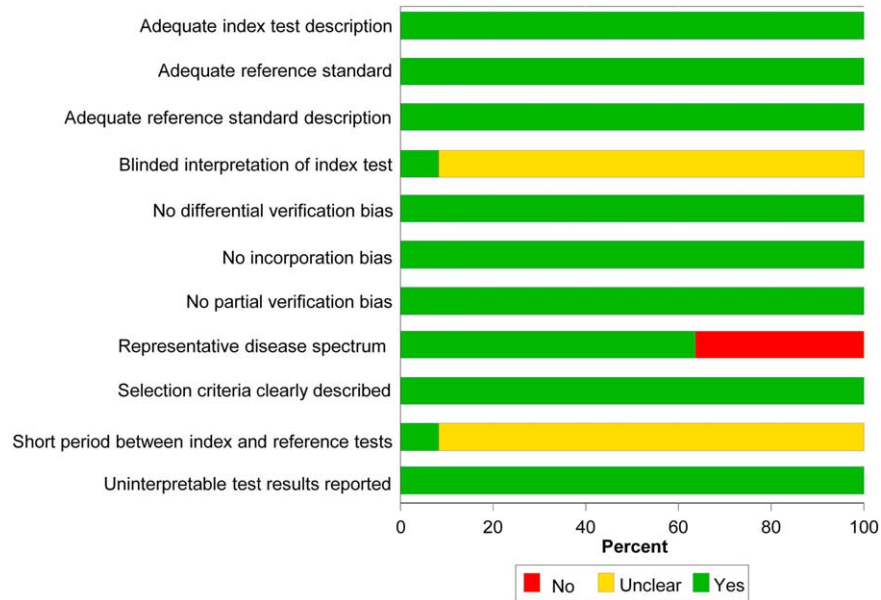
**FIG. 2.** Forest plot of point prevalence of PiB-positive studies among the three entities encompassed by parkinsonism and cognitive impairment, specifically PDD, DLB, and PD-MCI. The center point represents the estimated point prevalence for the respective study and the horizontal line, the 95% confidence interval for the respective study. The vertical broken line represents the pooled point prevalence, and the boundaries of the hollow diamond represents the 95% CI of the pooled results. PDD, Parkinson’s disease with dementia; DLB, dementia with Lewy bodies; PD-MCI, Parkinson’s disease with mild cognitive impairment; n+, number of subjects positive for amyloid; npat, total number of patients in each study. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

amyloid deposition plateaus at high levels before onset of cognitive impairment in AD.<sup>39</sup> Against this background, our findings in synucleinopathy subjects are significantly divergent.

Not surprisingly, and consistent with pathological studies, a significant fraction of DLB and PDD subjects had subthreshold amyloid levels, indicating that the neurodegeneration secondary to synucleinopathy is driving cognitive decline in these individuals. Second, substantial differences are seen in PiB-positive prevalence among PDD and DLB subjects, with minimal overlap in the 95% confidence intervals. An overall lower frequency of PiB positivity was found in PDD than in DLB subjects. A plausible explanation for this observation is a cumulative effect of two major pathologies; the majority of previously asymptomatic subjects with high neocortical amyloid burden and significant synucleinopathy will present with dementia and therefore be classified as having DLB (or AD if parkinsonism is not yet clinically evident). This

“classification” bias inherent to the 1-y rule of relative timing of dementia and parkinsonism could explain the differential rates of PiB-positive studies among different diagnostic groups. Frequency of amyloidopathy in PDD/DLB may be related to patient age as well as disease duration. For example, the Sydney Multicenter Study of PD showed that longer duration of disease is increasingly accompanied by comorbid AD pathology, especially after 5 y.<sup>40</sup>

We find a low frequency of PiB positivity in PD-MCI compared not only with DLB and PDD but also as compared with reports in non-PD-associated MCI. Furthermore, the mean prevalence of amyloid positivity in PD-MCI is lower than mean values reported in cognitively normal elderly controls, although overlap in confidence intervals is seen with those reported in series of normal elderly with no diagnosis of neurologic disease. High neocortical amyloid deposition in MCI and normal elderly controls is inferred to be part of a sequential cascade leading to AD with the

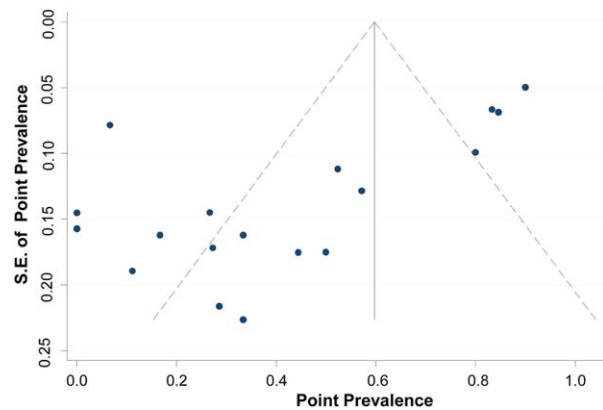


**FIG. 3.** Study Quality Scores. Graph illustrates study quality based on QUADAS criteria, expressed as a percentage of studies meeting each criterion. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

presence of high amyloid deposition on PET imaging associated with high increase of risk for ultimate progression to AD. One possible explanation of this marked discrepancy is a strong form of the selection phenomenon suggested previously to account for the differential frequency of high neocortical amyloid deposition in PDD versus DLB. Another intriguing possibility is that the PD brain is less hospitable to the generation of fibrillar amyloid. Recent data suggest that changes in neurotransmitter systems influence amyloid precursor protein metabolism significantly.<sup>41,42</sup>

Our study has limitations. None of the reviewed reports used the true gold standard for PDD/DLB, autopsy. Variability was seen in the degree of cognitive impairment of subjects between reports, and PD-MCI, in particular, is a heterogeneous clinical syndrome with variable definitions. Patients with severe dementia were not included in most of the studies, presumably because of inability to cooperate with the imaging protocol. Furthermore, the age distribution, with mean ages of approximately 70 years, is not fully representative of the PD population as a whole. Given expected age-associated increases in amyloid deposition, interrogating amyloidopathy at younger ages within the disease spectrum may limit confounding age effects and provide more insight into the role of amyloid deposition in synucleinopathy-associated cognitive impairments. Classification of dementia may be based on varying degrees of prospective/retrospective data in different centers. Apolipoprotein E status, which is known to affect amyloid deposition, was not reported in most of these studies and therefore was not part of the analysis.<sup>43</sup> All studies reviewed came

from tertiary referral centers, and subject recruitment is subject to referral biases. Definite heterogeneity is found in the PiB imaging and image processing protocols across different laboratories, reflecting technical imaging preferences and practices. Our analysis is based on the presence of AD-range cortical A $\beta$ -amyloid deposition, because this was the criterion used to classify subjects as “PiB positive” and reported in the collection of studies summarized in this systematic review. Our pragmatic approach of accepting



**FIG. 4.** Assessing Publication Bias. The funnel plot horizontal axis expresses treatment effect, in this instance, measured by point prevalence. The vertical axis expresses study size, as measured by standard error (SE). Studies with larger standard errors have a wider confidence interval (CI) caused by smaller sample size. The graphed vertical line represents the point prevalence, and the dashed lines represent the 95% confidence limits for the expected distribution for published studies. The points represent the observed distribution of the published studies. Visual inspection of the plot demonstrates the presence of publication bias, with many studies outside the 95% confidence limits. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

each laboratory's classification of PiB imaging studies into "positive" or "negative" based on laboratory-specific determination of this categorical outcome attempts to moderate these technical differences between facilities, but it is associated with inherent limitations. One of the limitations of bridging differences between laboratories via a categorical approach to cortical amyloid quantification analysis is the inability to assess the significance of cortical amyloid levels *below* the AD range. Such an endeavor would involve treating cortical amyloid as a continuous variable, which is not possible given the differences between imaging and postprocessing parameters and associated reported outcomes. Although PiB PET has a finite detection threshold and cases with amyloid plaques at biopsy or autopsy occupying less than 2% of the microscopic field are classed as PiB negative, this is unlikely to confound our analysis based on AD-range cortical amyloid deposition.

Levels of A $\beta$ -amyloid deposition *below* AD-range thresholds may have clinical salience in Lewy body diseases, in which a multisystem neurodegenerative process takes place. Our own data suggest a significant correlation between lower than AD-range levels of neocortical A $\beta$ -amyloid deposition and cognitive function in PD patients at risk for dementia.<sup>23</sup> Further supporting this notion of an "amplified" effect on cognition of low levels of cortical amyloid in the setting of a synucleinopathy are the neuropathologic findings by Compta et al<sup>11</sup> suggesting that the combination of cortical amyloid deposits and presence of cortical Lewy bodies may be the best predictor of cognitive decline in Parkinson's disease patients. Our group also has shown that neocortical A $\beta$ -amyloid deposition and cholinergic degeneration are independent predictors of impaired cognition in the setting of Parkinson's disease. This further supports the idea of a lower symptomatic threshold for effects of amyloidopathy than the levels defined in the AD population—a concept consistent with the selection effects raised here.

The studies reviewed contained relatively small numbers of subjects, constraining the analytic power of our review and explaining the significant publication/small sample size bias. We aggregated the results of the relatively small numbers of subjects from individual amyloid imaging studies to provide a more robust quantitative estimate of the prevalence of amyloid deposition in these subject groups. Our analysis suggests substantial variability in AD-range cortical A $\beta$ -amyloid deposition across the entire spectrum of patients with synucleinopathy and impaired cognition. Establishing the prevalence and understanding the role of amyloidopathy in parkinsonian patients with cognitive impairment is important because emerging targeted amyloid-related interventions may be applicable

to these patient populations. This analysis exposes the need for prospective, systematic, larger studies employing uniform recruitment, clinical, and imaging characterization protocols and concurrent evaluation of vulnerable neuronal populations in synucleinopathies to clarify the roles of amyloidopathy in synucleinopathy-related cognitive impairments. Analysis of early PD and PD-MCI populations may be particularly interesting because confirmation of lower cortical amyloid deposition in these populations may provide clues into the modulation of amyloid precursor protein metabolism and deposition *in vivo*. ■

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## Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.