Risk factors for dementia with Lewy bodies

A case-control study

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ABSTRACT

Objective: To determine the risk factors associated with dementia with Lewy bodies (DLB).

Methods: We identified 147 subjects with DLB and sampled 2 sex- and age-matched cognitively normal control subjects for each case. We also identified an unmatched comparison group of 236 subjects with Alzheimer disease (AD). We evaluated 19 candidate risk factors in the study cohort.

Results: Compared with controls, subjects with DLB were more likely to have a history of anxiety (odds ratio; 95% confidence interval) (7.4; 3.5–16; $p < 0.0001$), depression (6.0; 3.7–9.5; $p < 0.0001$), stroke (2.8; 1.3–6.3; $p = 0.01$), a family history of Parkinson disease (PD) (4.6; 2.5–8.6; $p < 0.0001$), and carry *APOE* ε4 alleles (2.2; 1.5–3.3; $p < 0.0001$), but less likely to have had cancer (0.44; 0.27–0.70; $p = 0.0006$) or use caffeine (0.29; 0.14–0.57; $p < 0.0001$) with a similar trend for alcohol (0.65; 0.42–1.0; $p = 0.0501$). Compared with subjects with AD, subjects with DLB were younger (72.5 vs 74.9 years, $p = 0.021$) and more likely to be male (odds ratio; 95% confidence interval) (5.3; 3.3–8.5; $p < 0.0001$), have a history of depression (4.3; 2.4–7.5; $p < 0.0001$), be more educated (2.5; 1.1–5.6; $p = 0.031$), have a positive family history of PD (5.0; 2.4–10; $p < 0.0001$), have no *APOE* ε4 alleles (0.61; 0.40–0.93; $p = 0.02$), and to have had an oophorectomy before age 45 years (7.6; 1.5–39; $p = 0.015$).

Conclusion: DLB risk factors are an amalgam of those for AD and PD. Smoking and education, which have opposing risk effects on AD and PD, are not risk factors for DLB; however, depression and low caffeine intake, both risk factors for AD and PD, increase risk of DLB more strongly than in either. *Neurology*® 2013;81:833–840

GLOSSARY

AD = Alzheimer disease; **DLB** = dementia with Lewy bodies; **OR** = odds ratio; **PD** = Parkinson disease.

Dementia with Lewy bodies (DLB) is the second most common dementia syndrome, representing 10% to 15% of cases. Knowledge of risk factors for DLB may provide clues to the underlying pathophysiology, yet the only known risk factors are advanced age, male sex,[1] and a family history of dementia.[2] We compared the frequency of Alzheimer disease (AD) and Parkinson disease (PD) risk factors among subjects with DLB to age- and sex-matched controls, and to subjects with AD. Risk factors driving amyloid pathology should be present in AD and, to a lesser extent, in DLB. In contrast, risk factors driving Lewy body pathology should be found in DLB, but not AD or control subjects.

METHODS

Standard protocol approvals, registrations, and patient consents. All protocols were approved by our institutional review board, and consent was obtained from subjects and carers.

Subjects. Subjects were recruited into 3 longitudinal studies at Mayo Clinic, Rochester, MN. The Alzheimer Disease Patient Registry (1985–2004)[3] and Alzheimer Disease Research Center Study (1999–present) recruited patients with incident dementia and age- and sex-matched controls. The Mayo Clinic Study of Aging (2004–present) follows all community-dwelling persons aged 70 to 89 years.[4] No major recoding was required to harmonize the data between the studies.

Supplemental data at www.neurology.org

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Cases were diagnosed as clinically probable DLB or AD by experienced behavioral neurologists on the basis of published criteria.[5,6] DLB was defined as dementia with 2 or more core features (fluctuations, parkinsonism, or visual hallucinations), or by one core feature plus one or more suggestive features (neuroleptic sensitivity, reduced dopamine uptake on functional imaging, or REM sleep behavior disorder).[5] These features, and risk factor exposure, were ascertained as part of a standardized enrollment protocol; cases were then followed prospectively. At enrollment, a clinician obtains a medical history and performs a neurologic examination, a study coordinator interviews the subject and their informant, and a neuropsychologist administers a comprehensive test battery. The clinician, study coordinator, and neuropsychologist independently evaluate or diagnose the subject before a weekly consensus meeting. Further details on recruitment, subjects, procedures, and data definitions are provided elsewhere.[3,4] Individuals with structural brain lesions were excluded. Each subject with DLB was matched to 2 age-matched (±5 years) and sex-matched controls from the cohort studies. The control subjects underwent an extensive cognitive and medical evaluation, did not have evidence of cognitive impairment, movement disorder, stroke, head injury, or other neurologic disease, and saw the physician in the same month as a clinical subject was diagnosed. Control subjects who were subsequently diagnosed with DLB or AD remained in the control group for the purposes of the analysis. Pathologic confirmation of the diagnosis was obtained when possible.

Candidate risk factors. We confined our risk factor assessment to 19 demographic, genetic, or disease characteristics associated with DLB, AD, or PD and for which data were available from the studies: age,[5] sex,[5] family history of dementia[2,7,8] or PD,[9,10] *APOE* ε4 status (any ε4 alleles vs none),[11,12] history of anxiety[13] or depression,[14,15] smoking (ever vs never in lifetime),[16,17] alcohol (ever vs never)[18,19] and caffeine consumption (ever vs never),[20,21] cancer (excluding nonmelanoma skin cancer),[22,23] diabetes mellitus,[24,25] education (9 or more years vs less than 9),[26,27] head injury,[28,29] number of children in men (more than one vs zero or one child),[30] occupation as a physician (vs all other occupations),[27] oophorectomy (uni- or bilateral, with or without hysterectomy),[31,32] oophorectomy at or before age 45,[32,33] and stroke.[34,35] Data definitions are in table e-1 on the *Neurology*® Web site at www.neurology.org. We also verified risk factor exposure interview responses by reviewing the relevant patient data in the unique resource medical records linkage system of the Rochester Epidemiology Project.[36] If the data sources conflicted, the risk factor was marked as present on the presumption that errors of omission are more likely than errors of commission. To minimize recall bias, anxiety and depression data were generated solely from the medical history section of the medical record. Missing values were excluded case-wise from analyses except in the case of oophorectomy, whereby missing values were coded as not present.

Statistical analyses. Associations for potential risk factors were assessed with univariate conditional logistic regression analyses comparing DLB and control subjects; these were powered ($\beta = 90\%$) to detect an odds ratio (OR) of 2.5 if the risk factor was present in 10% of cases. We adjusted for age and sex in unconditional logistic regression analyses of DLB vs AD. The number of children was considered only in men because a previous study in PD identified a link only among men.[30] This is the first analysis of multiple risk factors for DLB; we therefore chose to report results without correcting for multiple comparisons. However, we did repeat the analyses controlling for false discovery rate, and list the findings that did not survive correction.

In addition to the single-variable models, we examined all candidate risk factors found to be significant in the univariate analyses, and for which we had data on at least 90% of subjects, in multivariable logistic regression models adjusted for age and sex differences. We did this in order to identify the collection of features that displayed differences between study groups while controlling for the effects of the others. We omitted oophorectomy and number of children data from these multivariate models.

Sensitivity analyses. We analyzed the data to determine whether the DLB diagnostic criteria, changes in diagnosis during follow-up, or changing diagnostic practices over time affected our findings. Details can be found in the e-Methods.

RESULTS There were 147 subjects with DLB, 294 controls, and 236 subjects with AD (table 1). The DLB group contained more males and was younger at diagnosis than the AD group. Risk factor frequencies are shown in table 2. To facilitate a comparison of risk factor profiles for each disease, the risk estimates from published studies on AD and PD are compared with the OR estimates from this study in table 3. Comparing DLB and age- and sex-matched normal controls, subjects with DLB were more likely to have anxiety, depression, stroke, *APOE* ε4 alleles, and a family history of PD. Cancer and caffeine provided estimates of association that were suggestive of protective effects. Comparing DLB with AD, male sex, long education, depression, family history of PD, oophorectomy, and no *APOE* ε4 alleles were observed significantly more often in DLB than in AD.

When cases were defined with more specific criteria[37] or by final diagnosis, the patterns of association were unchanged, except that alcohol use became statistically significant in the DLB vs control comparison (table e-2). In the DLB vs AD comparison, alcohol and caffeine reached statistical significance, but oophorectomy before age 45 lost significance, when the specific, but not final, diagnosis was used (table e-3). Only 7 of 677 subjects' diagnosis was changed to or from DLB during follow-up or at autopsy. Education in the DLB vs AD comparison was the only factor that did not retain statistical significance when included in a multivariate model. Only one variable interacted with enrollment date: in the DLB vs control comparison, the OR for cancer was greater among subjects enrolled later in the study (interaction $p = 0.03$). Redefining missing values of anxiety and depression as the absence of the feature did not alter significance of any comparison (data not shown).

None of the findings in the DLB vs control comparison lost significance after controlling the false discovery rate. In the DLB vs AD comparison, education and *APOE* ε4 lost significance after this adjustment. Neuropathologic confirmation was obtained in 27 of 94 DLB cases (18%) and 28 of 236 AD cases (12%). There were no significant risk factor differences between these groups, likely reflecting the

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Table 1 Demographic data

	Controls (n = 294), n (%) or mean (SD; range)	AD (n = 236), n (%) or mean (SD; range)	DLB (n = 147), n (%) or mean (SD; range)	DLB vs controls, OR estimate (95% CI, *p* value)	DLB vs AD, OR estimate (95% CI, *p* value)[a]
Male	226 (76.9)	90 (38.1)	113 (76.9)	NA	5.31 (3.3–8.5, <0.0001)
Age at diagnosis, y	NA	74.9 (10.1; 49–94)	72.5 (7.3; 51–90)	NA	0.97 (0.95–1.0, 0.021)
Age at death, y	84.5 (6.6; 66–98)	82.6 (7.9; 54–96)	77.9 (6.7; 52–94)	0.86 (0.81–0.90, <0.0001)	0.9 (0.86–0.95, <0.0001)

Abbreviations: AD = Alzheimer disease; CI = confidence interval; DLB = dementia with Lewy bodies; NA = not applicable; OR = odds ratio; PD = Parkinson disease.
[a] Adjusted for age and sex.

lack of statistical power (table e-3). There were insufficient control subjects with autopsy data (7/294; 2%) for meaningful statistical comparisons.

DISCUSSION In this retrospective study, we examined the frequency of 19 possible risk factors associated with the likelihood of DLB, AD, and normal aging. Our findings were consistent with risk factors for DLB being similar to those already identified for AD and PD, with additive effects seen in risk factors common to both (e.g., depression, cancer risk) and reduced effects on opposing risk factors such as smoking and education. A clinical diagnosis of DLB was associated with a greater likelihood of having a history of depression or anxiety, a family history of PD, history of stroke, and having *APOE* ε4 alleles. Prior caffeine use and history of cancer were associated with a reduced likelihood of an eventual DLB diagnosis. When considering whether a patient has DLB or AD, the presence of the following features are

Table 2 Risk factor frequencies for DLB compared with controls and unmatched subjects with AD

	Controls				AD				DLB			
Risk factor	**Yes**	**No**	**Missing**	**Yes, %[a]**	**Yes**	**No**	**Missing**	**Yes, %[a]**	**Yes**	**No**	**Missing**	**Yes, %[a]**
Family history												
PD	18	276	0	6	14	216	6	6	35	112	0	24
Dementia	81	213	0	28	83	147	6	36	57	90	0	39
Medical history												
Anxiety	14	273	7	5	29	106	101[b]	22	23	63	61	27
Depression	58	232	4	20	64	99	73[b]	27	78	54	15	59
Stroke	14	273	7	5	18	148	70[b]	11	13	90	44[b]	13
Cancer	123	169	2	42	60	172	4	26	31	116	0	21
Diabetes	55	239	0	19	28	208	0	12	18	128	1	12
Oophorectomy	21	46	1	31	10	120	16	8[c]	10	24	0	29
Oophorectomy ≤45 y	5	55	8[b]	8[c]	1	57	88[b]	2[c]	4	11	19[b]	27[c]
Head injury	33	255	6	12	30	138	68[b]	18	18	83	46[b]	18
Genetic												
***APOE* ε4 mean alleles, no. missing (SD)**	0.3		2	(0.48)	0.7		105[b]	(0.70)	0.5		11	(0.61)
Social history												
Alcohol	207	86	1	71	142	94	0	61	90	57	0	61
Smoking	193	101	0	66	107	125	4	46	89	58	0	61
Caffeine	257	19	18[b]	93	95	18	123[b]	84	75	20	52[b]	79
≥9 y of education	276	18	0	94	200	35	1	85	138	9	0	94
>1 child (fathers)	206	18	2	92	71	9	10[b]	89	105	5	3	96
Physician occupation	3	291	0	1	7	229	0	3	5	142	0	3

Abbreviations: AD = Alzheimer disease; DLB = dementia with Lewy bodies; PD = Parkinson disease.
[a] Percent of nonmissing values.
[b] Missing data for >5% of sample.
[c] Missing values coded as not present; see Methods.

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Table 3 Risk factors for AD, PD, and DLB[a]

Risk factor	Published risk estimate (95% CI)						OR estimate in this study (95% CI, *p* value)			
	AD vs controls			PD vs controls			DLB vs controls		DLB vs AD	
Family history										
PD	RR[9]	2.4	(1.0–5.8)	OR[10]	2.2	(1.2–4.0)	4.6	(2.5–8.6, <0.0001)	5.0	(2.4–10, <0.0001)
Dementia	RR[7]	3.5	(2.6–4.6)	HR[8]	1.4	(1.03–1.8)	1.4	(0.89–2.1, 0.15)	0.98	(0.61–1.6, 0.91)
Medical history										
Anxiety	ND	ND	ND	OR[13]	2.2	(1.4–3.4)	7.4	(3.5–16, <0.0001)	1.7	(0.83–3.4, 0.15)
Depression	OR[14]	2.0	(1.8–2.3)	HR[15]	2.2	(1.7–2.9)	6.0	(3.7–9.5, <0.0001)	4.3	(2.4–7.5, <0.0001)
Stroke	HR[34]	1.3[b]	(0.73–2.4)	OR[35]	1.7	(1.5–2.0)	2.8	(1.3–6.3, 0.01)	1.4	(0.6–3.2, 0.43)
Cancer	HR[22]	0.72	(0.52–1.00)	RR[23]	0.69	(0.62–0.78)	0.44	(0.27–0.70, 0.0006)	0.78	(0.48–1.3, 0.37)
Diabetes	RR[24]	1.4	(1.2–1.7)	OR[25]	0.75	(0.50–1.1)	0.64	(0.36–1.1, 0.13)	1.8	(0.87–3.9, 0.11)
Oophorectomy	HR[31]	1.07[b]	(1.01–1.1)	HR[32]	1.5	(0.86–2.8)	0.96	(0.38–2.4, 0.92)	4.2	(1.6–10.8, 0.003)
Oophorectomy ≤45 y	HR[33]	1.9[b]	(1.4–2.6)	HR[32]	1.8[c]	(0.98–3.5)	4.3[d]	(0.97–19, 0.056)	7.6	(1.5–39, 0.015)
Head injury	OR[28]	1.6	(1.2–2.1)	OR[29]	1.1	(0.9–1.3)	1.4	(0.7–2.6, 0.33)	0.89	(0.44–1.8, 0.75)
Genetic										
***APOE* ε4**	OR[11]	3.8	(3.6–4.1)	OR[12]	1.0	(0.91–1.1)	2.2	(1.5–3.3, <0.0001)	0.61	(0.40–0.93, 0.02)
Social history										
Alcohol	RR[18]	0.66	(0.47–1.3)	RR[19]	0.76	(0.45–1.3)	0.65[d]	(0.42–1.0, 0.0501)	0.73	(0.46–1.2, 0.20)
Smoking	RR[16]	1.45	(1.16–1.80)	RR[17]	0.51	(0.43–0.61)	0.84	(0.55–1.3, 0.43)	1.0	(0.62–1.6, 0.98)
Caffeine	RR[20]	0.73	(0.58–0.92)	RR[21]	0.69	(0.59–0.80)	0.29	(0.14–0.57, 0.0003)	0.53	(0.24–1.2, 0.12)
≥9 y of education	OR[26]	0.15	(0.05–0.40)	OR[27]	2.0	(1.1–3.6)	0.74	(0.31–1.7, 0.48)	2.5	(1.1–5.6, 0.031)
>1 child (fathers)	ND	ND	ND	OR[30]	2.0	(0.8–5.0)	1.7	(0.60–5.0, 0.30)	2.3	(0.72–7.2, 0.16)
Physician occupation	ND	ND	ND	OR[27]	3.7	(1.0–13)	3.1	(0.69–14, 0.14)	0.48	(0.14–1.6, 0.23)

Abbreviations: AD = Alzheimer disease; CI = confidence interval; DLB = dementia with Lewy bodies; HR = hazard ratio; ND = no data; OR = odds ratio; PD = Parkinson disease; RR = relative risk.

[a] Risk factor estimates for AD and PD vs controls from published studies and risk factor OR estimates for DLB vs controls and AD from this study. DLB is compared with age- and sex-matched normal controls and with AD subjects (adjusted for age and sex). Except in circumstances in which the risk factor is rare, ORs overestimate the magnitude of risk associated with a factor when compared with HR and RR ratio. Published risk estimates were included on the following bases: a) risk estimate derived from a meta-analysis, large cohort, or prospective study, b) HR or risk ratios reported, c) risk ratios adjusted for possible confounds, d) results consistent with other reported risk estimates of equal quality, and e) risk factor criteria best match those of the current study.

[b] Risk of all-cause dementia, not AD after bilateral oophorectomy.

[c] Risk of parkinsonism, not PD.

[d] $0.05 < p < 0.10$.

suggestive of a diagnosis of DLB: male sex, early oophorectomy, a history of depression, family history of PD, longer education, and zero *APOE* ε4 alleles.

Prior diagnoses of anxiety and depression were more likely to be present in subjects diagnosed with DLB compared with controls. Prior diagnosis of depression was also more common in subjects with DLB than in those with AD. In DLB, anxiety and depression likely have many interacting causes that blur the distinction between risk factor and premorbid symptom. First, they may be caused by atrophy and/or dysfunction of pontomesencephalic-limbic emotional circuitry. In PD, premorbid anxiety disorders and depression are more common than in matched controls, but only the association with anxiety holds true for more than 5 years before diagnosis.[13] In AD, lifetime history of depression and especially late-life depression is a risk factor.[38] Second, anxiety and depression may be direct risk factors for DLB, may mediate behaviors that place a subject at risk, or reflect recall bias, referral bias, or natural emotional responses to incipient cognitive decline. Finally, premorbid anxiety and depression may unmask symptoms of DLB earlier than in subjects without such personality traits. The inverse of this ascertainment bias may explain why a history of anxiety and depression is less common in subjects with incidental Lewy body pathology at autopsy.[39] In some instances, late-life anxiety and depression may reflect preclinical α-synucleinopathy: further research is needed to determine the duration of anxiety and depression before DLB diagnosis, and to identify features that could facilitate predementia

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diagnosis of DLB. For example, some subjects with bradykinesia, hypomimia, and abulia may be misdiagnosed as depressed by family members and physicians.

Our DLB cohort contained a majority of males, as have numerous autopsy series.[1] PD is 1.5 times more common in men.[19] The sex effect may be driven by differential toxicant and head trauma exposure, mitochondrial dysfunction, X-linkage of genetic risk factors, or neuroprotection from α-synucleinopathy by estrogen. Although initial studies of postmenopausal estrogen replacement indicated a reduced risk of dementia, follow-up investigations revealed that the risk is dependent on the woman's age. Consistent with this, we observed a trend suggesting that oophorectomy increased the likelihood of DLB compared with control subjects, but the effect disappeared if oophorectomy occurred after 45 years of age. Notably, this is a pattern that has also been shown in parkinsonism, dementia, and cognitive impairment.[40] Compared with AD subjects, DLB subjects were 2.4 years younger at diagnosis and 4.7 years younger at death (table 1); earlier death may be attributable to earlier disease onset, more rapid progression, or reflect an interaction with male sex.

A family history of parkinsonism is a well-known risk factor for PD but not for AD.[10] In our study, a first-degree family history of PD was more common in DLB compared with AD and normal control subjects. It is not known whether these relatives also had accompanying dementia. Obtaining this information will determine whether the presence of dementia accompanying parkinsonism, or PD alone, is a risk factor for DLB.

Family history of dementia was not more common in DLB compared with control or AD subjects, in contrast to positive findings in an autopsy-confirmed DLB series.[2] Recall and selection bias in that series may have overestimated risk. More work is needed to clarify whether a family history of dementia poses a greater risk of the development of DLB. Taken together, these findings support the view that positive family history for PD reflects risk of α-synucleinopathy. Further investigation is needed to determine whether a family history of dementia is associated with a greater risk of amyloid deposition or mixed pathology.

Similarly, *APOE* ε4 was more frequent in our subjects with DLB compared with controls. It was less frequent when DLB was compared with AD dementia, although this result lost significance when we controlled the false discovery rate. The results likely reflect the mixed synuclein/AD pathology seen in most DLB cases. The presence of one or more *APOE* ε4 alleles is a well-known risk factor for AD[10] but it is unrelated to PD.[19]

Studies indicate that the risk of PD,[19] and possibly AD,[20] is reduced among coffee and caffeine users. In this study, caffeine use was associated with a reduced likelihood of DLB when compared with normal controls. Similar sized, significant associations with a dose effect are seen in PD after adjusting for education, smoking, and alcohol with almost all of the effect in that study attributed to men and younger-onset PD.[19]

Some studies show a protective effect of moderate alcohol intake on risk of AD but others do not.[18] There has been no consistent effect on PD risk.[19] In our study, there was a trend for reduced risk of DLB in alcohol users compared with normal controls ($p = 0.0501$), but not compared with AD.

Smoking was not associated with DLB in our study. In contrast, studies have demonstrated a 30% to 60% smoking-related risk reduction with a dose effect for PD[17] but a risk increase, again with a dose effect, for AD.[16] Many DLB cases have dual α-synuclein and AD pathology, therefore the lack of association of smoking with DLB may reflect opposing influences on these pathologies canceling out. Alternatively, it may reflect a unique difference between PD and DLB, or an unknown secondary or confounding association. Secondary associations may be responsible for the links between caffeine, alcohol, and smoking and many neurodegenerative syndromes. For example, socioeconomic or personality features, or prodromal manifestations of disease, might curtail substance use.

Longer duration of education reduces risk of AD[26] but increases risk of PD.[27] In our study, more than 9 years of education was more common in subjects with DLB compared with subjects with AD, but this distinction did not survive adjustment for the false discovery rate. Education level did not distinguish DLB from controls.

Education level and occupation are highly correlated, and physicians have 6.8 times increased risk of incidental Lewy body disease[39] and 3.7 times increased risk of PD.[27] Higher complexity of work has been inversely associated with AD risk, or at least time to the development of the dementia. Current results show that physician occupation was not associated with a greater likelihood of developing DLB, although this may reflect a restricted sample. In this and previous studies, there have been only 4 to 11 affected physicians per group. The data are particularly subject to ascertainment and surveillance bias: physicians may be more prone to see a specialist and participate in research.[27]

AD[22] and PD[23] have been associated with reduced risk of cancer. We also demonstrated that a history of cancer was less likely among those with DLB compared with normal controls, but not compared with AD subjects. This adds to the growing body of evidence supporting an inverse correlation between cancer and neurodegenerative disease, perhaps mediated by inherited immune protective factors.

In our study, history of stroke was more common in subjects with DLB vs controls, but this effect was

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not seen in the AD comparison. Drawing inferences is difficult because symptoms due to stroke are listed as exclusionary criteria for DLB, AD, and PD. Stroke, a risk factor for PD[35] and dementia, is not itself an established risk factor for AD,[34] although vascular risk factors such as midlife hypertension, diabetes, and hypercholesterolemia increase risk of AD. Their relationship to PD is unclear, although premorbid blood pressure can be affected by prodromal α-synuclein–induced dysautonomia. Diabetes did not alter risk in this study. Head injury has been associated with AD[28]; its association with PD is likely attributable to reverse causation.[19] It was not a risk factor for DLB. Fathering more than one child, a PD but not AD risk factor,[30] did not affect DLB risk.

We minimized selection and incidence/prevalence bias with stringent recruitment methods, and minimized recall and surveillance bias by verifying patient and carer reports in the medical record. Misclassification bias was reduced by use of more specific diagnostic criteria, but this remains an important limitation of our study. Pathologic confirmation of the clinical diagnoses supported the significance of associations suggested by the study; however, this was available for only a small subset of subjects.

We were unable to include several factors in the multivariate model because of missing data. Missing data are disproportionately found in the AD group because data for some risk factors began to be collected partway through the AD cohort study. Only one of 19 risk factor associations interacted with date of enrollment, suggesting that this historical fact should not affect our conclusions. Our findings on education and *APOE* ε4 status in the DLB vs AD comparison did not survive correction for multiple comparisons: they may represent type I errors. For some factors (e.g., caffeine, smoking, and alcohol), we have only binary data and thus cannot determine the degree of exposure. Two of the 3 cohorts that contributed subjects to the study were convenience samples, and ascertainment bias might have affected the results, particularly in the AD vs DLB comparison. Other suspected risk factors for DLB were not assessed in this study, including toxin exposure, well-water consumption, non-*APOE* genetic factors (e.g., *GBA*), hypercholesterolemia, obesity, cognitive and physical inactivity, and attention deficit and hyperactivity disorder, as information on these was not captured in the 3 Mayo Clinic studies on which this analysis was based. We excluded others because of mixed evidence in α-synucleinopathy: nonphysician occupation[19,27] and hypertension. Nor did we include many prodromal α-synucleinopathy symptoms, including REM sleep behavior disorder, olfactory dysfunction, dysautonomia, and repeated falls.

Comment: Epidemiology of dementia with Lewy bodies—The Alzheimer-Parkinson overlap

Dementia with Lewy bodies (DLB) is viewed by many as a condition that combines features of Alzheimer disease (AD) and Parkinson disease (PD). Autopsy in DLB discloses both amyloid and synuclein deposition, and the relative degree of each may determine the clinical phenotype.[1] Despite being the second most common form of dementia, risk factors of DLB have never been systematically studied. The current report by Boot et al.[2] therefore represents a considerable advance. Relying on data from 3 separate cohorts, the authors found that the risk factor profile of DLB appeared to combine aspects of AD and PD. Known risk factors for PD, such as nonuse of caffeine, anxiety, depression, and family history of PD were present in DLB. Similarly, AD risk factors such as *APOE* status, depression, and stroke were also present in DLB. Smoking, a protective factor for PD and a risk factor for AD, was not associated with DLB, perhaps suggesting that the risk factors "canceled out." However, when risk factors were common between conditions (depression and caffeine use), the relationship in DLB appeared to be stronger than for AD or PD individually, suggesting additive risks. Although the risk factors were not always comprehensively assessed and diagnosis was clinical in the majority of cases (albeit with broadly similar results in the subgroup with autopsy confirmation), the study is well-designed and comprehensively analyzed. In addition to providing for the first time a broad picture of risk factors for DLB, the study reinforces the close interactions among DLB, PD, and AD, and points to the potential importance of multiple interacting pathologies in determining clinical disease.

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AUTHOR CONTRIBUTIONS

Dr. Boot and Dr. Orr: drafting/revising the manuscript for content, including medical writing for content, study concept or design, analysis or interpretation of data, acquisition of data, and statistical analysis. Dr. Ahlskog, Dr. Knopman, and Dr. Boeve: drafting/revising the manuscript for content, including medical writing for content, study concept or design, and study supervision or coordination. Dr. Pankratz and J.A. Aakre: analysis or interpretation of data, and statistical analysis. Dr. Ferman, Dr. Roberts, Dr. Geda, Dr. Dickson, Dr. Parisi, and Dr. Petersen: drafting/revising the manuscript for content.

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This Week's *Neurology*® Podcast

Risk factors for dementia with Lewy bodies: A case-control study (See p. 833)

This podcast begins and closes with Dr. Robert Gross, Editor-in-Chief, briefly discussing highlighted articles from the August 27, 2013, issue of *Neurology*. In the second segment, Dr. David Geldmacher talks with Dr. Brendon Boot about his paper on risk factors for dementia with Lewy bodies. Dr. Adam Numis then reads the e-Pearl of the week about reversible cerebral vasoconstriction syndrome. In the next part of the podcast, Dr. Brandy Matthews focuses her interview with Dr. Bill Seeley on therapeutics and future directions in frontotemporal degeneration. Disclosures can be found at www.neurology.org.

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