Familial Coaggregation of Alzheimer's Disease and Parkinson's Disease: Systematic Review and Meta-Analysis

Adina L. Feldman^a Anna L.V. Johansson^a Paul C. Lambert^{a, c} Johanna Sieurin^a
Fei Yang^a Nancy L. Pedersen^{a, d} Karin Wirdefeldt^{a, b}

Departments of ^aMedical Epidemiology and Biostatistics and ^bClinical Neuroscience, Karolinska Institutet, Stockholm, Sweden; ^cDepartment of Health Sciences, University of Leicester, Leicester, UK; ^dDepartment of Psychology, University of Southern California, Los Angeles, Calif., USA

Key Words

Alzheimer disease · Parkinson disease · Familial aggregation · Systematic review · Meta-analysis

Abstract

Background: Familial aggregation has been shown for Alzheimer's disease (AD) and Parkinson's disease (PD) separately, and it has been hypothesized that these diseases also co-aggregate in families. **Methods:** The authors investigated familial coaggregation of AD and PD by conducting a systematic review and meta-analysis. PubMed was searched for relevant studies published through the end of October 2012. Three independent investigators screened publications and extracted data. Relative risk estimates of AD risk associated with family history of PD or parkinsonism, or PD risk associated with family history of AD or dementia, were summarized into metaestimates using random effects models. Heterogeneity and publication bias were tested using Higgins' and Egger's tests, respectively. **Results:** We included 16 studies in the review, with 14 included in any meta-analysis. AD risk associated with family history of PD yielded a summary hazard ratio of 1.18 (95% CI: 1.00–1.39) based on 5 reconstructed cohort studies and a summary odds ratio (OR) of 1.40 (95% CI: 0.92–2.12) based on 7 case-control studies. PD

risk associated with family history of AD yielded a summary OR of 0.75 (95% CI: 0.49–1.16) based on 3 studies. There was no significant heterogeneity among studies, nor significant publication bias. **Conclusions:** There may be familial coaggregation of AD and PD, although the association was modest and only apparent when studying AD risk associated with family history of PD.

© 2013 S. Karger AG, Basel

Introduction

Alzheimer's disease (AD) and Parkinson's disease (PD) are aging-related progressive neurodegenerative conditions affecting cognition and motor function, respectively. Although different parts of the brain are initially affected and different primary pathological protein aggregates are associated with each disease, there is widespread comorbidity of the clinical syndromes dementia and parkinsonism in conditions such as PD dementia [1], Lewy body dementia [2] and progressive supranuclear palsy [3]. Familial aggregation has been shown for AD and PD separately, and it has been hypothesized that these diseases also coaggregate in families. The relative risk of PD associated with having a first-degree relative

with PD is estimated at 2.9 (95% CI: 2.2–3.8) [4], and the relative risk of AD associated with having a first-degree relative with AD is estimated at 3.5 (95% CI: 2.6–4.6) [5]. If familial coaggregation exists between AD and PD, shared genetic and/or familial environmental risk factors may also contribute to comorbidity of dementia and parkinsonism.

In 1991, van Duijn et al. [5] performed a meta-analysis of 2 early case-control studies [6, 7] that examined familial coaggregation of AD and PD by studying AD risk associated with family history of PD and found evidence for familial coaggregation of these diseases (pooled odds ratio, OR: 2.4; 95% CI: 1.0–5.8). Since then, an increasing number of studies have examined familial coaggregation of AD or dementia with PD or parkinsonism using both case-control and reconstructed cohort designs.

The aim of this study was to examine whether there is evidence for familial coaggregation of AD and PD and, if so, to determine the magnitude of the association between risk of AD or PD and family history of the other disease. We systematically reviewed studies published on this topic and summarized results into pooled metaestimates.

Method

We followed the MOOSE (Meta-Analysis of Observational Studies in Epidemiology) reporting guidelines [8].

Search Strategy

We searched PubMed for peer-reviewed articles published through the end of October 2012. The following search terms were used in combination: 'Parkinson and Alzheimer' or 'Parkinson and dementia' with 'risk' or 'epidemiology' and 'family history', 'familial aggregation', 'familial risk', 'relative', 'sibling', 'twin' or 'parent'. Records found in the search were first screened for eligibility based on the title and abstract and secondly assessed for inclusion based on the full text. We also manually searched reference lists of included articles and reviews, and considered articles referred to us.

Eligibility Criteria

We considered published observational epidemiological studies that met the following criteria:

- (1) Study design was case-control, cohort, reconstructed cohort or cross-sectional
- (2) Exposure was family history of PD, parkinsonism, AD or dementia; defined as ever/never disease status among 1 or any first-degree relative (sibling, parent or offspring)
- (3) Outcome was disease status (incident or prevalent) of the opposite disease (e.g. if exposure was family history of PD, outcome was AD, or vice versa)
- (4) To be included in the quantitative analysis (meta-analysis), the studies also had to include a crude or adjusted effect estimate of association such as an OR, hazard ratio (HR)/incidence rate

ratio or standardized incidence ratio (SIR), with an SE or 95% CI, or enough data allowing a crude effect estimate to be calculated, such as the number of exposed and unexposed among cases and controls in a case-control study

Data Extraction

From each study included we extracted data on: study setting, year and design (including outcome, family history exposure, comparison groups and inclusion criteria for participants); exposure and outcome ascertainment; covariates in analyses such as sex and age; numbers of study persons and events, and estimates of association with 95% CI or SE. If we were unable to identify relevant data to be extracted from the publication, we contacted the corresponding author for clarification.

Quality Assessment

We assigned a methodological quality score to all studies included, regardless of whether they fulfilled the criteria for being included in the quantitative analysis, based on 4 study characteristics. For each characteristic, the study was given a score of 1 for 'more rigorous method', or 0 for 'less rigorous method'. The scores were summed to give a total score ranging from 0 to 4. The quality characteristics were:

- (1) Setting: whether the study participants could be considered to be sampled in a reasonably population-based manner (1) or not (0); e.g. using neighborhood controls was considered to be a reasonably population-based manner, whereas using spouse controls, hospital-based controls or only hospital-based cases with an unspecified catchment area was not
- (2) Diagnostic ascertainment in first-degree relatives: whether disease status of first-degree relatives was ascertained by family history interviews only (0) or whether confirmation by clinical examination or medical record review was sought in some or all instances (1)
- (3) Study design: whether the study was a case-control study that did not enumerate first-degree relatives (0) or a cohort or reconstructed cohort study that did enumerate first-degree relatives (1)
- (4) Inclusion criteria: whether the study excluded (0) or included (1) index cases with co-occurring dementia and parkinsonism, such as in PD dementia

The term 'index case' has a different meaning depending on the study design. In case-control studies of familial aggregation, the index cases are the unit of analysis along with the controls (they experience the outcome). In reconstructed cohort studies, which can be compared to matched cohort studies in design, the index cases provide the family history exposure, whereas the first-degree relatives of the index cases and controls are the unit of analysis who experience the outcome [9].

Three investigators with experience in neuroepidemiology conducted the literature search (A.L.F. and F.Y.) and data extraction/quality assessment (A.L.F. and J.S.). The investigators were blinded to each other's findings, and disagreements were resolved by consensus decisions.

Statistical Methods

Study-specific relative risk estimates were pooled into summarized metaestimates, using the random effects model of DerSimonian and Laird [10], and reported with 95% CI. Studies that reported the same measure of association (OR or HR/SIR) and had

Fig. 1. Flowchart illustrating how studies were included in the systematic review and meta-analyses.

the same outcome (AD/dementia or PD/parkinsonism) were analyzed together. For studies that reported subgroup-specific estimates but no overall estimate, we collapsed the subgroup estimates before entering them into the meta-analysis. Where possible, we calculated pooled estimates for some specific subgroups, such as first-degree relatives of young-onset index cases, sibling relationships and parent-offspring relationships. Heterogeneity among studies was evaluated with the Q-statistic from the inverse-variance fixed-effect model and with the Higgins test yielding the I^2 measure [11]. We constructed forest plots and funnel plots for each meta-analysis and assessed the presence of publication bias using Egger's test for funnel plot asymmetry [12]. Tests were two-sided and the significance level was 0.05. Analyses were performed using the 'metan', 'metafunnel' and 'metabias' commands in Stata version 12.1 [13].

Results

Studies Retrieved

The database search resulted in 405 studies that were screened for eligibility. No duplicates were found. After excluding 366 studies that were found to be ineligible based on the title and abstract, 39 remained to be assessed for inclusion. Following screening based on the full text of the remaining studies, a further 27 studies were excluded. Ultimately, 12 studies from the database search

were included in the qualitative review. An additional 4 studies were identified via references and referrals, leading to a total of 16 studies included (fig. 1; table 1).

The reasons for excluding 27 studies in the second screening are listed in online supplementary table 1 (see www.karger.com/doi/10.1159/000355452 for all online suppl. material). Briefly, 14 studies were about familial coaggregation between AD and/or PD and another outcome (such as amyotrophic lateral sclerosis, PD dementia, dementia with Lewy bodies, progressive supranuclear palsy or depression), 3 studies solely concerned the amyotrophic lateral sclerosis-PD complex of Guam, and 10 studies did not include a control group or were missing other crucial data.

Of the final 16 studies, 2 studies did not provide estimates from regression analyses but reported enough crude data that estimates could be calculated and included in the meta-analysis. Two studies fulfilled the criteria to be included in the systematic review, but they were excluded from the meta-analysis; 1 because it did not include enough relevant quantitative data [14] and 1 due to unclear results [15]. The latter study included SIR for AD risk associated with having a sibling with PD and SIR for PD risk associated with having a sibling with AD, but it was unclear from the published article which estimate

Table 1. Studies of familial coaggregation of AD and PD

Year	First author [reference]	Country	Study design	Comparison groups	Outcome	Family history exposure	Disease ascertainment in index cases ^a	Index cases with co-occurring dementia and parkinsonism included ^b	Disease ascertainment in FDR	Types of FDR included	Covariates
1986	Amaducci ^a [6]	Italy	CC	AD cases vs. matched controls	AD	PD	Clinical diagnosis of AD	No	Report of PD status in FDR from informants of the index AD cases and controls	N/A	Age, sex, region of residence
1988	Huff ^b [14]	USA	RC	FDR of AD cases vs. FDR of controls	PD	AD	Clinical diagnosis of AD	Yes	Report of PD status in FDR from informants of the index AD cases and controls	Siblings, parents	N/A
1989	Hofman [7]	The Netherlands	CC	AD cases vs. matched controls	AD	PD	Clinical diagnosis of AD	No	Report of PD status in FDR from informants of the index AD cases and controls (confirmed by medical records)	Siblings, parents	Age, sex, area of residence, number of FDR
1992	Li [25]	China	CC	AD cases vs. matched controls	AD	PD	Clinical diagnosis of AD	No	Report of PD status in FDR from informants of the index AD cases and controls	N/A	Age, sex, neighborhood of residence
1993	Fratiglioni [22]	Sweden	CC	AD cases vs. matched controls	AD	PD	Clinical diagnosis of AD	Yes	Report of PD status in FDR from informants of the index AD cases and controls	Siblings, parents	Age, sex, education, type of informant, age of parents at death, number of siblings
1994	Silverman ^c [26]	USA	CC	AD cases vs. spouse controls	AD	PD	Clinical diagnosis of AD	Yes	Report of PD status in all FDR from spouse controls (confirmed by medical records)	Siblings, parents, offspring	N/A
1997	Mickel ^d [19]	USA	RC	1. FDR of AD cases vs. FDR of spouse controls; 2. FDR of PD cases vs. FDR of spouse controls	AD, PD	AD, PD	Clinical diagnosis of AD or PD	Yes	Report of AD or PD status in all FDR from spouse controls (confirmed in medical records)	Siblings, parents	Age, sex, type of FDR
1999	Marder [18]	USA	RC	1. FDR of PDD cases vs. FDR of controls; 2. FDR of PDND cases vs. FDR of controls	AD	PD	Clinical diagnosis of PD	Yes ^{i,j}	Report of AD status in FDR from the index PD cases (or their informants) and controls, with additional information from informants of each FDR and some clinical diagnoses	Siblings, parents	Age, sex, ethnicity, the index PD case's/control's education and APOE-ε4 status
2002	Kockler [23]	Germany	RC	FDR of AD cases vs. FDR of controls	PD	AD	Clinical diagnosis of AD	Yes	Report of PD status in FDR from personal interviews or informants of the index AD cases and controls	N/A	Age, sex, source of information of relative disease status
2003	Kurz ^c [24]	Norway	CC	PD cases vs. controls	PD	Dementia	Clinical diagnosis of PD	Yes	Report of dementia status in FDR from the index PD cases and controls	Siblings, parents, offspring	N/A
2004	Levy [17]	USA	RC	FDR of PD cases vs. FDR of controls	AD	PD	Clinical diagnosis of PD	No	Report of AD status in FDR from the index PD cases and controls	Siblings, parents	Age, sex, education, ethnicity
2006	Hemminki ^c [15]	Sweden	C	1. FDR of AD cases vs. whole population; 2. FDR of PD cases vs. whole population	AD, PD	AD, PD	Hospital register record of AD or PD	Yes	Hospital register record of AD or PD	Siblings	Age, sex, calendar period, region, socioeconomic status

Table 1 (continued)

Year	First author [reference]	Country	Study design	Comparison groups	Outcome	Family history exposure	Disease ascertainment in index cases ^a	Index cases with co-occurring dementia and parkinsonism included ^b	Disease ascertainment in FDR	Types of FDR included	Covariates
2006	Suhanov [27]	Russia	CC	AD cases vs. matched controls	AD	Parkinsonism	Clinical diagnosis of AD	No	Report of parkinsonism status from informants of the index AD cases and controls (confirmed by medical records if available)	N/A	Age, sex, education, place of birth ⁱ
2007	Rocca [20]	USA	RC	FDR of PD cases vs. FDR of controls	Cognitive impairment or dementia	PD	Clinical diagnosis of PD	Yes	Report of dementia or cognitive status in FDR from personal interviews or from medical records (or from an informant of the FDR)	Siblings, parents, offspring	Age, sex, education, type of interview
2007	Rosen ^g [21]	USA	CC	1. AD cases; 2. PD cases; 3. AD/PD cases vs. controls	AD, PD, AD/PD	AD, PD	Clinical diagnosis of AD, PD or AD/PD	Yes ^j	Report of AD or PD status in FDR from the index PD cases and controls or from informants of the index AD or AD/PD cases	N/A	Age, sex, race
2010	Costello [16]	USA	RC	FDR of PD cases vs. FDR of controls	AD	PD	Clinical diagnosis of PD	No	Report of AD or dementia status in FDR from the index PD cases and controls	Siblings, parents, offspring	Age, sex, the index PD case's/control's education, minority status

APOE = Apolipoprotein E; C = cohort study; CC = case-control study; FDR = first-degree relatives; PDD = PD dementia; PDND = PD no dementia; RC = reconstructed cohort study.
^aThe study included 1 group of cases and 2 control groups, 1 hospital based and 1 population based. Only estimates from comparisons between the cases and the population-based controls are included in the quantitative analysis.

^bThe study was excluded from the quantitative analysis because there was no adjusted estimate of association reported, and neither were there enough data reported to be able to calculate a crude estimate.

^cNo adjusted estimate of association was reported, but enough data were included to calculate a crude estimate and to include the study in the quantitative analysis.

^dThe study investigated familial coaggregation in both directions, but an estimate of association was only reported for risk of AD among FDR of PD cases versus FDR of controls. For risk of PD among FDR of AD cases versus FDR of controls, not enough data were included to calculate a crude estimate, and thus this part of the study could only be included in the qualitative analysis.

^eThe study was excluded from the quantitative analyses because there were 2 reported estimated SIR for shared familial risk, 1 for risk of AD in siblings of PD cases and 1 for risk of PD in siblings of AD cases, but it was unclear which estimate was for which comparison.

^fThe study reported 2 estimates, 1 from a univariate model adjusted for age, sex, education and place of birth, and 1 from a multivariate model which was further adjusted for hypothyroidism and history of head trauma with the loss of consciousness. Only the estimate from the univariate model was included in the quantitative analysis.

^gThe study included a group of AD/PD cases, defined as persons with both parkinsonism and dementia. This group was treated as having both outcomes and, thus, included in quantitative analyses in both directions.

^hNote that in CC studies, the index cases are the unit of analysis (experience the outcome), whereas in C/RC studies the index cases provide the family history exposure (the FDR are the unit of analysis).

ⁱIndex cases with PDD were included, but if dementia preceded PD, they were excluded.

^jIndex cases with co-occurring dementia and parkinsonism (referred to as PDD cases in Marder et al. [18] and AD/PD cases in Rosen et al. [21]) were included as a separate group.

Table 2. Meta-analysis of relative risk of AD associated with family history of PD

Year	First author [reference]	Quality score	AD events among FDR with PD family history, n	AD events among FDR without PD family history, n	HR	95% CI	Weight, %
<i>Reconstructed cohort studies</i>							
1997	Mickel [19]	3	28 (625)	21 (675)	1.55	0.88–2.74	8.90
1999	Marder ^a [18]	3	61 (1,130)	164 (2,865)	1.00	0.73–1.36	29.60
2004	Levy [17]	2	61 (2,534)	52 (2,285)	1.1	0.7–1.6	16.80
2007	Rocca [20]	4	146 (1,019)	119 (858)	1.37	1.03–1.81	31.72
2010	Costello [16]	2	37 (2,980)	35 (2,981)	1.02	0.64–1.64	12.97
	Pooled HR				1.18	1.00–1.39	100.00
	p for heterogeneity				0.466		
	I ²				0.0%		
Year	First author [reference]	Quality score	AD cases with PD family history, n	Controls with PD family history, n	OR	95% CI	Weight, %
<i>Case-control studies</i>							
1986	Amaducci ^b [6]	0	5 (96)	3 (96)	1.67	0.10–27.57	2.14
1989	Hofman [7]	2	14 (198)	5 (198)	2.9	1.1–8.5	16.07
1992	Li ^c [25]	1	1 (64)	1 (128)	2.00	0.13–31.89	2.22
1993	Fratiglioni [22]	2	5 (85)	15 (245)	0.9	0.3–2.7	13.92
1994	Silverman ^d [26]	2	6 (118)	6 (118)	1.0	0.31–3.19	12.45
2006	Suhanov ^e [27]	1	12 (260)	3 (260)	4.2	1.1–18.7	8.37
2007	Rosen ^f [21]	2	46 (718)	40 (228)	1.06	0.57–1.95	44.82
	Pooled OR				1.40	0.92–2.12	100.00
	p for heterogeneity				0.414		
	I ²				1.3%		
<p>Values in parentheses denote total numbers. The pooled estimates are from random effects models. FDR = First-degree relatives; PDD = PD dementia; PDND = PD no dementia.</p> <p>^aThe HR was collapsed from 2 estimates reported separately, 1 for FDR of PDD cases versus FDR of controls, and 1 for FDR of PDND cases versus FDR of controls.</p> <p>^bCI calculated from reported p values.</p> <p>^cThere is an inconsistency in the crude numbers reported in the article; an alternative interpretation is that there were 66 cases and 132 controls (there is no effect on the interpretation of the study).</p> <p>^dCrude OR and CI were calculated from reported frequencies as there were no adjusted estimates reported.</p> <p>^eThe estimate included is from the reported univariate analysis (the estimate from the multivariate analysis was: OR = 4.2; 95% CI: 1.2–15.1).</p> <p>^fThe OR was collapsed from 2 estimates reported separately, 1 for AD cases versus controls, and 1 for AD/PD cases versus controls.</p>							

was for which comparison. We were in contact with the authors of the study but did not receive sufficient information to include it. Ultimately, the meta-analyses included estimates from 14 studies.

Of the 16 studies included, 7 investigated the coaggregation of AD and PD as their primary aim [7, 16–21], whereas 9 studies investigated the coaggregation of AD and PD as one of many aims [6, 14, 15, 22–27]. The relative risk estimates from the studies included in the meta-analysis could be divided into 4 groups: (1) reconstructed cohort studies estimating HR with AD or dementia as the outcome [16–20] (n = 5; table 2); (2) case-control studies

estimating OR with AD or dementia as the outcome [6, 7, 21, 22, 25–27] (n = 7; table 2); (3) reconstructed cohort studies estimating OR with PD or parkinsonism as the outcome [23] (n = 1), and (4) case-control studies estimating OR with PD or parkinsonism as the outcome [21, 24] (n = 2). We pooled all 3 studies on PD risk associated with family history of AD, even though the study designs differed, because they all estimated OR (table 4). Three studies included both AD and PD as outcomes [15, 19, 21], but only 1 of these reported enough quantitative data for both outcomes to be included in their respective meta-analyses [21].

Fig. 2. Forest plot of reconstructed cohort studies and case-control studies regarding risk of AD associated with family history of PD. Case-control studies estimate OR and reconstructed cohort studies estimate HR. Values in parentheses denote 95% CI.

Quality of Studies Included

The quality score assigned is listed next to each included estimate in tables 2, 3 and 4. Of the 16 studies included, most were assigned a score of 0–2, whereas 2 were given the highest possible quality score (4) [15, 20] (whereof 1 study [20] was included in the meta-analysis). Among the 3 studies given the second-highest possible quality score (3) [18, 19, 23], the reason for failing to reach the highest score was a non-population-based study population in 2 studies [18, 19], and exclusion of index cases with comorbid dementia and parkinsonism in 1 study [23].

Meta-Analyses of AD Risk Associated with First-Degree Family History of PD

Table 2 and figure 2 show the results of the meta-analysis of HR from 5 reconstructed cohort studies and of OR from 7 case-control studies on risk of AD or dementia associated with first-degree family history of PD. The pooled HR was 1.18 (95% CI: 1.00–1.39) and the pooled OR was 1.40 (95% CI: 0.92–2.12). One reconstructed cohort study and 2 case-control studies showed significant results in support of familial coaggregation of AD and PD, whereas the rest showed no association. Included relative risk estimates ranged from 0.9 to 4.2.

There was no indication of significant heterogeneity among studies.

One study [15] reported 2 estimates for coaggregation of AD and PD – SIR 10.9 (95% CI: 1.5–45.5) and SIR 8.3 (95% CI: 1.1–34.6) – but it was unclear which of the estimates was for AD as the outcome, and thus this study could not be included in the meta-analysis. As a sensitivity analysis, we pooled both SIR from this study and entered it in the meta-analysis with the reconstructed cohort studies listed in table 2. The resulting pooled estimate was HR 1.32 (95% CI: 0.97–1.80), with $p = 0.011$ for heterogeneity and $I^2 = 66.2\%$, indicating that the added study was significantly different from the other studies as there had been no indication of heterogeneity before including it. The weight of the additional study was 5.42%.

A funnel plot illustrating the relationship between study size (expressed as SE) and effect estimate in all studies of AD risk associated with family history of PD is included as online supplementary figure 1. Egger's test of funnel plot asymmetry revealed no indication of publication bias ($p = 0.244$).

Table 3 shows the results from meta-analyses of subgroup estimates for parents/offspring, siblings and first-

Table 3. Meta-analysis of relative risk of AD associated with family history of PD from reconstructed cohort studies, according to FDR type or age at onset of index PD case

Year	First author [reference]	Quality score	AD cases among FDR with PD family history, n	AD cases among FDR without PD family history, n	HR	95% CI	Weight, %
<i>Parent-offspring relationships</i>							
1999	Marder ^a [18]	3	39 (461)	102 (1,516)	1.13	0.77–1.65	28.22
2004	Levy [17]	2	50 (868)	41 (762)	1.1	0.7–1.6	26.96
2007	Rocca [20]	4	57 (226)	28 (176)	2.84	1.62–5.00	21.76
2010	Costello [16]	2	29 (742)	29 (796)	1.03	0.61–1.74	23.06
	Pooled HR				1.34	0.89–2.02	100.00
	p for heterogeneity				0.026		
	I ²				67.7%		
<i>Sibling relationships</i>							
1999	Marder ^a [18]	3	22 (669)	62 (1,349)	0.98	0.10–9.93	1.89
2004	Levy [17]	2	10 (1,013)	10 (863)	1.1	0.5–2.8	13.67
2007	Rocca [20]	4	83 (463)	85 (432)	1.07	0.76–1.52	84.44
	Pooled HR				1.07	0.78–1.47	100.00
	p for heterogeneity				0.995		
	I ²				0.0%		
<i>FDR of young-onset PD cases</i>							
2004	Levy [17] (50 years) ^b	2	42 (1,543)	52 (2,285)	1.0	0.6–1.7	33.10
2007	Rocca [20] (66 years) ^b	4	52 (349)	119 (858)	1.73	1.21–2.46	40.59
2010	Costello [16] (60 years) ^b	2	11 (553)	35 (2,981)	2.86	1.44–5.71	26.31
	Pooled HR				1.65	0.99–2.74	100.00
	p for heterogeneity				0.049		
	I ²				66.9%		
<i>Parent-offspring relationships, restricted to FDR of young-onset PD cases</i>							
2007	Rocca [20] (66 years) ^b	4	24 (94)	28 (176)	3.04	1.51–6.11	50.69
2010	Costello [16] (60 years) ^b	2	11 (162)	29 (796)	2.42	1.19–4.91	49.31
	Pooled HR				2.72	1.65–4.47	100.00
	p for heterogeneity				0.653		
	I ²				0.0%		

Values in parentheses denote total numbers, unless specified otherwise. The pooled estimates are from random effects models. FDR = First-degree relatives; PDD = PD dementia; PDND = PD no dementia.

^a The HR was collapsed from 2 estimates reported separately, 1 for FDR of PDD cases versus FDR of controls, and 1 for FDR of PDND cases versus FDR of controls.

^b Study-specific age cutoff for ‘young onset’.

degree relatives of young-onset cases as well as parents/offspring of young-onset cases from 4 reconstructed cohort studies on AD risk associated with first-degree family history of PD. Compared with the overall meta-analysis for all first-degree relatives (table 2), pooled estimates were higher for parent-offspring relationships and for first-degree relatives of young-onset PD cases, although there was considerable heterogeneity among studies in both analyses. For siblings of PD cases there was no indication of an increased risk of AD in any of the 3 studies included. However, there was a strongly significant asso-

ciation between AD risk and family history of young-onset PD in a parent or offspring in a meta-analysis based on 2 studies.

Meta-Analysis of PD Risk Associated with First-Degree Family History of AD

Table 4 shows the result from the meta-analysis of OR from 2 case-control studies and 1 reconstructed cohort study of PD risk associated with first-degree family history of AD. The pooled OR showed no association, with little heterogeneity among studies.

Table 4. Meta-analysis of relative risk of PD associated with family history of AD

Year	First author [reference]	Quality score	PD cases with AD family history, n	Controls with AD family history, n	OR	95% CI	Weight, %
2003	Kurz [24]	1	22 (245)	12 (100)	0.72	0.34–1.52	33.77
2007	Rosen ^a [21]	2	92 (711)	40 (228)	0.80	0.44–1.44	53.33
2002	Kockler ^b [23]	3	1 (4)	1,054 (1,891)	0.64	0.19–2.12	12.90
Pooled OR					0.75	0.49–1.16	100%
p for heterogeneity					0.944		
I ²					0.0%		

Values in parentheses denote total numbers. The pooled estimate is from a random effects model.

^a The OR was collapsed from 2 estimates reported separately, 1 for PD cases versus controls, and 1 for AD/PD cases versus controls.

^b Note that this is a reconstructed cohort study that reported an OR, which is why we included it in a meta-analysis among case-control studies. Translated to reconstructed-cohort terms, there was 1 PD case among 1,055 persons with AD family history, and 3 PD cases among 840 persons without PD family history.

Review of Studies Which Could Not Be Included in Meta-Analyses

Three cohort/reconstructed cohort studies investigated the PD risk associated with family history of AD but could not be included in a meta-analysis; 1 cohort study was excluded due to unclear results [15] (see above), and 2 reconstructed cohort studies were excluded as they only reported crude counts of affected first-degree relatives of cases and controls, but neither rates nor estimates of association [14, 19]. We could not include these 2 studies because the data were not suitable for calculating crude OR (as we were able to do with several case-control studies) and not enough data were reported to calculate crude HR. Mickel et al. [19] reported 5 PD events among 628 first-degree relatives of AD cases and 6 PD events among 644 first-degree relatives of spouse controls ($p = 0.64$ from log rank test), and Huff et al. [14] reported 1 PD event among 250 first-degree relatives of AD cases (lifetime risk: 1.0%; SD: 1.0%) and 4 PD events among 232 first-degree relatives of controls (lifetime risk: 3.9%; SD: 2.0%; $p > 0.05$ from test of differences in proportions).

Discussion

The finding from this systematic review is of a modest familial coaggregation between AD and PD, indicating some shared familial risk for the diseases. This conclusion is supported by several facts: (1) the only 2 studies [15, 20] that reached the highest possible quality score showed significant associations in support of familial coaggregation; (2) although pooled metaestimates from case-control and

reconstructed cohort studies of AD risk associated with family history of PD were, respectively, nonsignificant and borderline significant, they were in the same direction and of similar magnitude; and (3) despite considerable variation in estimates and quality scores, there was little heterogeneity among the studies included in the main meta-analyses, which supports the validity of the results.

The quality score reflected several sources of possible bias. An example of information bias is when index cases (or their proxies) are more likely to report a family history of a disease than controls. Relying on proxy reports in studies of familial risk of PD has been shown to be prone to information bias [28]. This kind of bias may be reduced by confirming diagnoses in first-degree relatives and by enumerating all first-degree relatives, and consider each individually instead of broadly ascertaining all first-degree relatives together ('any' family history). In studies of familial coaggregation of diseases which assume a direct effect of one disease on the other within the same person (e.g. an association between PD and risk of comorbid dementia), conditioning on one of the diseases, for instance by adjusting for it in a statistical model or by stratification (exclusion of comorbid cases), may induce a biased estimate [29]. In studies of familial coaggregation of AD or dementia with PD or parkinsonism, this type of conditioning is analogous to excluding either index cases or first-degree relatives with co-occurring parkinsonism and dementia. Other types of bias include selection and ascertainment biases, which may be reduced by adhering to a population-based study design. Similar to our results, a previous meta-analysis of familial aggregation of PD showed that summary estimates from case-control stud-

ies were higher with broader CI compared with estimates from reconstructed cohort studies [4]. That study also found that non-population-based studies yielded higher estimates than population-based studies, presumably because they were more biased. Even when disregarding the quality characteristic pertaining to study design in the present review, case-control studies typically had lower quality scores than reconstructed cohort studies, which indicates that the higher summary estimate obtained from case-control studies may be more biased than that from reconstructed cohort studies.

Co-occurrence of dementia and parkinsonism is exceedingly common; the relative risk of developing dementia in PD cases compared with PD-free individuals is estimated to be between 1.7 and 5.9 [1]. It is notable that the association between dementia risk and PD appears much stronger than the association between AD risk and having a first-degree relative with PD, indicating that there must be other causes of dementia in PD besides the familial risk shared between AD and PD. Indeed, there is evidence from *in vitro* and *in vivo* studies that downstream effects from expression of risk genes for PD lead to dementia [30, 31], and this is further supported by the observation that more advanced neuropathological stage according to Braak et al. [32] in PD is associated with cognitive decline [33].

As this study has shown, shared familial risk for AD and PD is possibly a contributing, albeit minor, cause of the co-occurrence of parkinsonism and dementia. However, what constitutes this shared familial risk is unknown. There is little support for shared familial risk for AD and PD outside epidemiological studies. Few environmental risk factors that may be familial are known for either AD or PD, with the possible exception of the protective effect of smoking on PD [34] and the protective effect of higher education on AD [35]. Interestingly, neither of these risk factors have similar effects in AD and PD; education may even have the opposite effect in PD [36]. Furthermore, there has been no evidence of overlap between genetic risk factors for AD and PD from genome-wide scans thus far [37–39].

One case-control study [21] and 1 reconstructed cohort study [18] used the same control group/same group of unexposed first-degree relatives in subgroup estimates, which could lead to an underestimate of the SE when pooling the subgroup estimates before entering them into the overall meta-analysis. Consequently, it could be argued that these 2 studies deserve lower weights than what was assigned to them in the random effects model. In both studies, the estimates included were closer to the null than the final pooled metaestimate, and thus the metaestimates present-

ed in table 2 may in fact be somewhat higher than what was found, further strengthening the conclusion that there is an association between AD risk and family history of PD.

The evidence from the subgroup analyses was not consistent but still revealed some interesting findings. Based on 2 studies [16, 20], it seems that there may be a strong association between AD risk and family history of PD for all first-degree relatives or parents/offspring of young-onset PD cases, although a third study [17] deviated from this finding. Age at onset was defined differently in each study, which makes it hard to draw firm conclusions from this finding, although it could indicate that a shared familial risk for AD and PD may share genetic causes with early-onset PD.

In the presence of familial coaggregation of AD and PD, we would generally expect the magnitude of the association to be similar regardless of which disease is the outcome and which disease the family history exposure in the study. There was no significant association between PD risk and family history of AD in any of the 3 studies included in the meta-analysis [21, 23, 24], nor in 2 studies only included in the qualitative review [14, 19], with the exception of the 1 study excluded from the meta-analysis due to unclear results [15]. Although the results of this systematic review and meta-analysis support a modest familial coaggregation of AD and PD, further studies of the association between PD risk and family history of AD are needed.

This study has several strengths. The comprehensive screening of retrieved studies and data extraction/quality assessment were carried out in duplicate by independent researchers. We were able to systematically study the hypothesis of familial coaggregation of AD and PD in several different epidemiological study designs. Limitations of this study are that few studies included reported separate estimates for siblings or parent-offspring relationships, making it difficult to interpret those subgroup summary findings. Among the studies included in the meta-analyses, there was only 1 study that fulfilled all 4 quality characteristics.

In conclusion, there is some evidence of familial coaggregation of AD and PD. However, the modest effect was only present when studying AD risk associated with family history of PD. Nevertheless, the familial coaggregation of AD and PD appears to be of a much smaller magnitude than the familial aggregation within each of these diseases separately, and this supports previous findings that co-occurrence of dementia and parkinsonism is primarily caused by factors other than shared familial risk.

Acknowledgments

This study was supported by: the Swedish Research Council (grant No. 2005-3296, 2008-7483 and 2010-2579); Karolinska Institutet; the Swedish Parkinson Foundation; the Swedish Medical Society, and the Swedish Society for Medical Research.

Disclosure Statement

No conflict of interest is declared for any author.

References

- 1 Aarsland D, Kurz MW: The epidemiology of dementia associated with Parkinson disease. *J Neurol Sci* 2010;289:18–22.
- 2 McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA, Salmon DP, Lowe J, Mirra SS, Byrne EJ, Lennox G, Quinn NP, Edwardson JA, Ince PG, Bergeron C, Burns A, Miller BL, Lovestone S, Collerton D, Jansen EN, Ballard C, de Vos RA, Wilcock GK, Jellinger KA, Perry RH: Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the Consortium on DLB International Workshop. *Neurology* 1996;47:1113–1124.
- 3 Litvan I, Agid Y, Calne D, Campbell G, Dubois B, Duvoisin RC, Goetz CG, Golbe LI, Grafman J, Growdon JH, Hallett M, Jankovic J, Quinn NP, Tolosa E, Zee DS: Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. *Neurology* 1996;47:1–9.
- 4 Thacker EL, Ascherio A: Familial aggregation of Parkinson's disease: a meta-analysis. *Mov Disord* 2008;23:1174–1183.
- 5 van Duijn CM, Clayton D, Chandra V, Fratiglioni L, Graves AB, Heyman A, Jorm AF, Kokmen E, Kondo K, Mortimer JA, Rocca WA, Shalat SL, Soininen H, Hofman A, et al: Familial aggregation of Alzheimer's disease and related disorders: a collaborative re-analysis of case-control studies. *Int J Epidemiol* 1991;20(suppl 2):S13–S20.
- 6 Amaducci LA, Fratiglioni L, Rocca WA, Fieschi C, Livrea P, Pedone D, Bracco L, Lippi A, Gandolfo C, Bino G, et al: Risk factors for clinically diagnosed Alzheimer's disease: a case-control study of an Italian population. *Neurology* 1986;36:922–931.
- 7 Hofman A, Schulte W, Tanja TA, van Duijn CM, Haaxma R, Lameris AJ, Otten VM, Saan RJ: History of dementia and Parkinson's disease in 1st-degree relatives of patients with Alzheimer's disease. *Neurology* 1989;39:1589–1592.
- 8 Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB: Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-Analysis of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;283:2008–2012.
- 9 Susser E, Susser M: Familial aggregation studies: a note on their epidemiologic properties. *Am J Epidemiol* 1989;129:23–30.
- 10 DerSimonian R, Laird N: Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–188.
- 11 Higgins JP, Thompson SG: Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–1558.
- 12 Egger M, Davey Smith G, Schneider M, Minder C: Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–634.
- 13 StataCorp: Stata: statistical software, release 12. College Station, StataCorp, 2011.
- 14 Huff FJ, Auerbach J, Chakravarti A, Boller F: Risk of dementia in relatives of patients with Alzheimer's disease. *Neurology* 1988;38:786–790.
- 15 Hemminki K, Sundquist K, Li X: Familial risks for main neurological diseases in siblings based on hospitalizations in Sweden. *Twin Res Hum Genet* 2006;9:580–586.
- 16 Costello S, Bordon Y, Bronstein J, Ritz B: Familial associations of Alzheimer disease and essential tremor with Parkinson disease. *Eur J Neurol* 2010;17:871–878.
- 17 Levy G, Louis ED, Mejia-Santana H, Côté L, Andrews H, Harris J, Waters C, Ford B, Frucht S, Fahn S, Ottman R, Marder K: Lack of familial aggregation of Parkinson disease and Alzheimer disease. *Arch Neurol* 2004;61:1033–1039.
- 18 Marder K, Tang MX, Alfaro B, Mejia H, Côté L, Louis E, Stern Y, Mayeux R: Risk of Alzheimer's disease in relatives of Parkinson's disease patients with and without dementia. *Neurology* 1999;52:719–724.
- 19 Mickel SF, Broste SK, Hiner BC: Lack of overlap in genetic risks for Alzheimer's disease and Parkinson's disease. *Neurology* 1997;48:942–949.
- 20 Rocca WA, Bower JH, Ahlsgog JE, Elbaz A, Grossardt BR, McDonnell SK, Schaid DJ, Maraganore DM: Risk of cognitive impairment or dementia in relatives of patients with Parkinson disease. *Arch Neurol* 2007;64:1458–1464.
- 21 Rosen AR, Steenland NK, Hanfelt J, Factor SA, Lah JJ, Levey AI: Evidence of shared risk for Alzheimer's disease and Parkinson's disease using family history. *Neurogenetics* 2007;8:263–270.
- 22 Fratiglioni L, Ahlborn A, Viitanen M, Winblad B: Risk factors for late-onset Alzheimer's disease: a population-based, case-control study. *Ann Neurol* 1993;33:258–266.
- 23 Kockler M, Nitardy A, Papassotiropoulos A, Ptak U, Maier W, Heun R: Physical disorders and causes of death in relatives of Alzheimer's disease patients. *Int J Geriatr Psychiatry* 2002;17:335–342.
- 24 Kurz M, Alves G, Aarsland D, Larsen JP: Familial Parkinson's disease: a community-based study. *Eur J Neurol* 2003;10:159–163.
- 25 Li G, Shen YC, Li YT, Chen CH, Zhou YW, Silverman JM: A case-control study of Alzheimer's disease in China. *Neurology* 1992;42:1481–1488.
- 26 Silverman JM, Raiford K, Edland S, Fillenbaum G, Morris JC, Clark CM, Kukull W, Heyman A: The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part VI. Family history assessment: a multi-center study of first-degree relatives of Alzheimer's disease probands and nondemented spouse controls. *Neurology* 1994;44:1253–1259.
- 27 Suhanov AV, Pilipenko PI, Korczyn AD, Hofman A, Voevoda MI, Shishkin SV, Simonova GI, Nikitin YP, Feigin VL: Risk factors for Alzheimer's disease in Russia: a case-control study. *Eur J Neurol* 2006;13:990–995.
- 28 Elbaz A, McDonnell SK, Maraganore DM, Strain KJ, Schaid DJ, Bower JH, Ahlsgog JE, Rocca WA: Validity of family history data on PD: evidence for a family information bias. *Neurology* 2003;61:11–17.
- 29 Hudson JI, Javara KN, Laird NM, VanderWeele TJ, Pope HG Jr, Hernán MA: A structural approach to the familial coaggregation of disorders. *Epidemiology* 2008;19:431–439.
- 30 Crews L, Tsigelny I, Hashimoto M, Masliah E: Role of synucleins in Alzheimer's disease. *Neurotox Res* 2009;16:306–317.
- 31 Ono K, Takahashi R, Ikeda T, Yamada M: Cross-seeding effects of amyloid β -protein and α -synuclein. *J Neurochem* 2012;122:883–890.
- 32 Braak H, del Tredici K, Rüb U, de Vos RA, Jansen Steur EN, Braak E: Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 2003;24:197–211.
- 33 Braak H, Rüb U, del Tredici K: Cognitive decline correlates with neuropathological stage in Parkinson's disease. *J Neurol Sci* 2006;248:255–258.

- 34 Wirdefeldt K, Adami HO, Cole P, Trichopoulos D, Mandel J: Epidemiology and etiology of Parkinson's disease: a review of the evidence. *Eur J Epidemiol* 2011;26(suppl 1):S1–S58.
- 35 Sharp ES, Gatz M: Relationship between education and dementia: an updated systematic review. *Alzheimer Dis Assoc Disord* 2011;25: 289–304.
- 36 Frigerio R, Elbaz A, Sanft KR, Peterson BJ, Bower JH, Ahlskog JE, Grossardt BR, de Andrade M, Maraganore DM, Rocca WA: Education and occupations preceding Parkinson disease: a population-based case-control study. *Neurology* 2005;65:1575–1583.
- 37 Bertram L, McQueen MB, Mullin K, Blacker D, Tanzi RE: Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database. *Nat Genet* 2007;39: 17–23.
- 38 Lill CM, Roehr JT, McQueen MB, Kavvoura FK, Bagade S, Schjeide BM, Schjeide LM, Meissner E, Zauft U, Allen NC, Liu T, Schilling M, Anderson KJ, Beecham G, Berg D, Biernacka JM, Brice A, DeStefano AL, Do CB, Eriksson N, Factor SA, Farrer MJ, Foroud T, Gasser T, Hamza T, Hardy JA, Heutink P, Hill-Burns EM, Klein C, Latourelle JC, Maraganore DM, Martin ER, Martinez M, Myers RH, Nalls MA, Pankratz N, Payami H, Satake W, Scott WK, Sharma M, Singleton AB, Stefansson K, Toda T, Tung JY, Vance J, Wood NW, Zabetian CP, Young P, Tanzi RE, Khoury MJ, Zipp F, Lehrach H, Ioannidis JP, Bertram L: Comprehensive research synopsis and systematic meta-analyses in Parkinson's disease genetics: the PDGene database. *PLoS Genet* 2012;8:e1002548.
- 39 Moskvina V, Harold D, Russo G, Vedernikov A, Sharma M, Saad M, Holmans P, Bras JM, Bettella F, Keller MF, Nicolaou N, Simón-Sánchez J, Gibbs JR, Schulte C, Durr A, Guerreiro R, Hernandez D, Brice A, Stefansson H, Majamaa K, Gasser T, Heutink P, Wood N, Martinez M, Singleton AB, Nalls MA, Hardy J, Owen MJ, O'Donovan MC, Williams J, Morris HR, Williams NM: Analysis of genome-wide association studies of Alzheimer disease and of Parkinson disease to determine if these 2 diseases share a common genetic risk. *JAMA Neurol* 2013, E-pub ahead of print.