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Prevalence of Apolipoprotein E4 Genotype and Homozygotes (APOE e4/4) among Patients Diagnosed with Alzheimer's Disease: A Systematic Review and Meta-Analysis

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Key Words
Alzheimer's disease · Apolipoprotein E · Meta-analysis · Prevalence · Epidemiology

Abstract
Background: Population allele frequencies of apolipoprotein E (APOE) vary by geographic region. The purpose of this study is to summarize and evaluate published estimates for the prevalence of APOE e4 carrier status among the population diagnosed with Alzheimer's disease (AD) by geographic region and country. ***Methods:*** A systematic review of English-language publications from January 1, 1985, through May 31, 2010, was conducted. Studies reporting APOE e4 status for patients diagnosed with AD were included in the analysis; trials and autopsies were excluded. APOE e4 data were pooled, and prevalence and 95% confidence intervals (CIs) were calculated. ***Results:*** Pooled estimates for APOE e4 carrier prevalence data were derived from 142 independent samples: 48.7% (95% CI: 46.5–51.0), and from 73 samples for e4/4 (homozygotes): 9.6% (95% CI: 8.4–10.8). The highest estimates were in Northern Europe: 61.3% (95% CI: 55.9–66.7), e4/4 prevalence: 14.1% (95% CI: 12.2–16.0). The lowest estimates were in Asia and Southern Europe. Substantial heterogeneity of these prevalence estimates was observed. ***Conclusions:*** APOE e4 genotype prevalence varies among AD patients by region and within each country. Further exploration is warranted to better understand the substantial heterogeneity of these prevalence estimates.

Introduction

Alzheimer's disease (AD) is the most common form of dementia, and recent prevalence estimates suggest it impacts the lives of 4.4% of the population over 65 years old [1]. Apolipoprotein E (APOE) e4 has been recognized as a genetic risk factor for developing late-onset AD for over two decades [2–4]. Carriers of two APOE e4 alleles (homozygotes, e4/4) have a higher risk and also earlier onset of AD than heterozygous carriers (e4/–) [2, 4]. However, late-onset AD is believed to be caused by multiple other genetic and environmental factors that are not yet completely identified, and the interactions between these are not yet well understood [5]. Some researchers have suggested contemporary environmental conditions may have led APOE e4 carriers to have an increased suscepti-

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bility to developing AD, such as high intake of carbohydrates and fat, low fiber, and reduced physical activity [6].

The APOE gene is polymorphic, with three common alleles (e2, e3, e4), and in studies of the general population, a substantial amount of variation has been consistently observed by geographic location in the six genotypes: 3/3, 4/3, 3/2, 4/4, 4/2, and 2/2 [7]. APOE e3 is the most frequent [7]. APOE e4 is consistently observed to be more common in the general population residing in Northern Europe than in the Mediterranean regions of France and Italy, or in Asia [6–8]. The purpose of conducting this literature review is to summarize the published evidence on the prevalence of the APOE e4 genotype (e4/–) and homozygotes (e4/4) among patients diagnosed with AD. Specifically, published estimates of APOE e4 homozygote and heterozygote prevalence in observational studies were tabulated and reported for each country. Estimates for APOE e4 carrier prevalence were then derived for Asia, Europe (Central, North, and South/Mediterranean), North America, and South America.

Methods

A protocol was developed and followed for each of the steps of this review, and the methods used for this review followed current practices for conducting systematic reviews and meta-analyses of the literature. The data source for this project was the literature published between January 1, 1985, and May 31, 2010. The literature search was performed using both electronic and manual components. MEDLINE (via PubMed) and EMBASE were searched to identify English-language studies published within the past 25 years. The searches were conducted using a combination of search terms and key words for apolipoproteins, APOE4, and AD and terms related to the study design, such as observational, community-based, population, cross-section, epidemiological, longitudinal, prospective, cohort studies, and cross-sectional studies. Case reports, letters, commentaries, editorials, reviews, clinical trials, meta-analyses, practice guidelines, and in vitro studies were excluded. The search terms and strategies were developed in consultation with a medical librarian, and each search strategy was adapted to the idiosyncrasies of each of these databases by using the appropriate index structures (e.g. Medical Subject Headings – MeSH in MEDLINE and EMTREE in EMBASE). The searches included limits for English language and human subjects. A manual check of the bibliographies of each of the articles included in the analysis was also performed to identify additional potentially relevant material and supplement the electronic searches.

Citations and abstracts of all studies identified in the searches were downloaded and the duplicates removed; study selection was based on 2 levels of screening. Initially, the title and abstract of each citation were screened based on the prespecified inclusion and exclusion criteria in the protocol. Articles deemed potentially eligible were then retrieved, and the full text was screened by 2 independent reviewers to determine whether it met the eligibility criteria. All disagreements were resolved by consensus.

The eligible articles were observational studies (clinic or community-based samples) with 30 or more adults diagnosed with AD reporting APOE e4 genotype data at the baseline of a cohort study, case-control study, or cross-sectional survey. Autopsy studies were excluded. Accepted articles describing the same AD population ('kin studies') were identified by reviewing the method section, geographic location, sample sizes, and author or institution names, and a single citation for each independent sample of patients diagnosed with AD was included in the analysis to avoid double-counting the results from the same population.

Data were extracted by one researcher and verified by another, and any differences were resolved by consensus. Information was extracted from each included study on country, geographic location, sources of cases (clinic, community, other), study design (cross-sectional, case control, or cohort), AD case definition, subclasses (early, late onset, sporadic, familial, mixed), and demographics (gender, race, age). The frequency of the APOE e4 genotype and, when reported, e4/4 status stratified by AD case definitions were extracted for each study.

APOE e4 and e4/4 Prevalence

Study characteristics and subject level data were first summarized using SAS version 9.1 (SAS Institute, Cary, N.C., USA) to calculate basic descriptive statistics organized by country and geographic region. The prevalences of ApoE e4 (%) and e4/4 (%) were computed using restricted-maximum likelihood variance-weighted random effects meta-analyses [9, 10] that were conducted on the APOE e4 carrier and e4/4 proportions overall and by AD case definition. For this analysis, the term 'probable AD cases' is applied only to the samples specifically reported as meeting the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for 'probable' AD. AD cases were defined as possible when reported as 'possible' by the authors, identified as AD patients with no additional criteria, or reported as a mixed population of 'possible' and 'probable' cases.

Heterogeneity (between-study inconsistency) was investigated and measured using Cochran's Q statistic and the I^2 statistic [11]. Cochran's Q, distributed as a χ^2 statistic, estimates heterogeneity as the weighted sum of squared differences in effects across pooled studies. I^2 estimates what percentage of interstudy variability is due to heterogeneity rather than to chance. As significant heterogeneity was present, the variation was investigated further by conducting stratified analyses and meta-regression. First, stratified analyses were performed by region and by country and AD case definition where there were at least 3 studies to pool. Next, age, AD case definition (probable AD vs. other), sample population source (community vs. other), and study design (case control vs. other), as predictors for regional APOE e4 and e4/4 prevalence, were explored using random effects meta-regression [12]. For countries with adequate numbers of studies, the impact of sampling from AD populations residing in different areas within the country was also explored. If there were too few studies within a given region or country, meta-regression was not performed. Each variable was converted to binary categories and modeled simultaneously. The age category was defined as below or above the age in the lowest quartile of the average age of all the studies. Variables found to explain heterogeneity were also applied individually to regional and country estimates to explain variance.

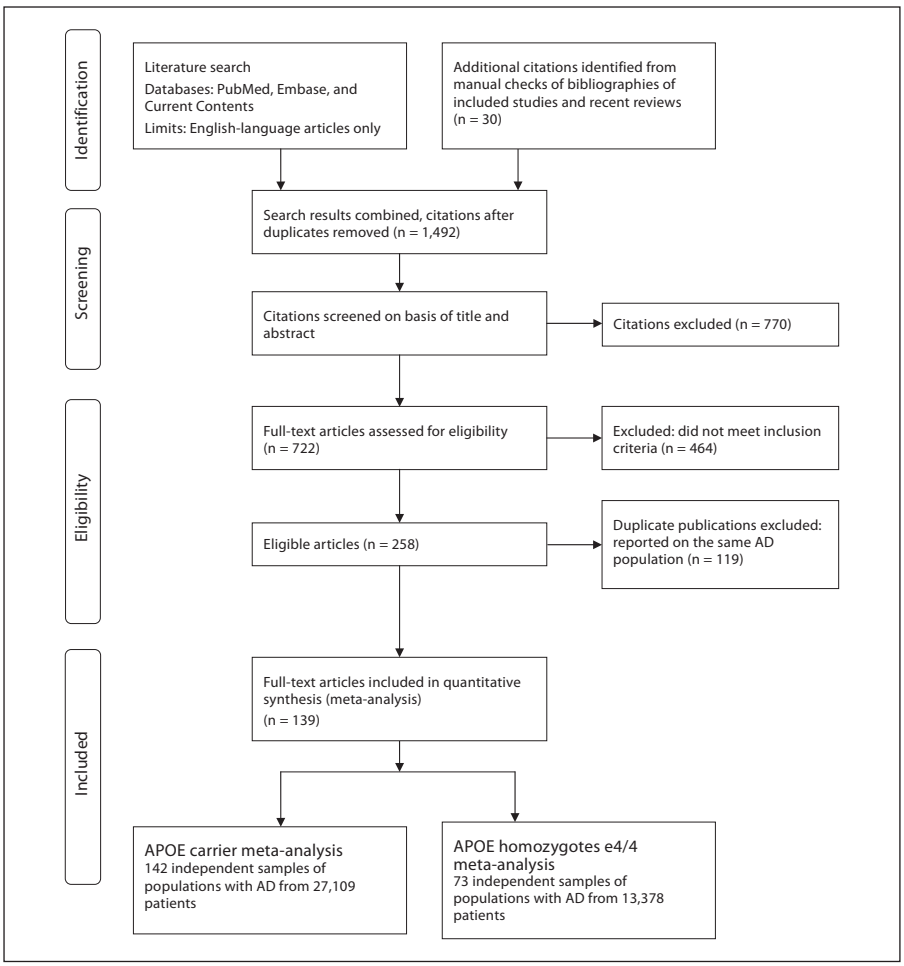

Fig. 1. Flow diagram of study selection.

Results

Study Selection

Titles and abstracts from a total of 1,492 articles were screened, and 722 full-text articles were reviewed (see fig. 1 for additional details on each step). The reasons for exclusion were no APOE data reported or not reported separately for adult AD patients, study sample size fewer than 30 subjects, or autopsy study. A total of 258 articles met our eligibility criteria, of which 139 were identified as reporting APOE e4 data from 142 independent samples of patients diagnosed with AD. Four studies reported on more than 1 patient population; these groups, as well as the 'parent' studies, were considered as 2 distinct populations for the purpose of analysis. The full study listing of the 139 articles reporting the data included in the analysis is provided in the Appendix. In addition, 73 of these independent samples of patients diagnosed with AD also provided data on the prevalence of APOE e4/4.

Study Characteristics

The studies analyzed included a combined 27,109 individuals with a mean age of 75.2 years (range: 63.0–89.0); 64.1% were female. Fifty-eight percent (15,773 participants) were diagnosed as 'probable' AD cases. Thirty-one were described clearly as community-based samples (4,040 individuals), the majority were clinic- or hospital-based samples (18,500 individuals), and the others were not possible to classify or were a combination. The analysis was conducted with separate estimation of the prevalence for 6 predefined geographic regions: Asia, Europe (Central, North, and South/Mediterranean), North America, and South America. As the region Oceania only included 1 country, Australia, this is reported with other country-specific analyses. Information from each study included in the analyses is provided for each region in tables 1–3.

Table 1. Study characteristics and meta-analysis estimates of the prevalence of APOE e4 carriers (e4/–) and e4/4 in Asia

First author, year	Country	AD case definition	Mean age years	e4/– n/N	APOE e4/– %	e4/4 n/N	APOE e4/4 %
Bi XH, 2009	China	NR	NR	161/386	41.7	NR	NR
Hu J, 2009	China	NR	76.1	78/344	22.7	NR	NR
Jiang H, 2005	China	NR	74.2	19/60	31.7	2/60	3.3
Tsai SJ, 2006	China	NR	74.9	63/175	36.0	NR	NR
Wang B, 2008	China	NR	77.6	58/207	28.0	NR	NR
Yang JD, 2003	China	NR	74.6	86/183	47.0	23/183	12.6
Zhao FG, 2005	China	NR	75.7	18/107	16.8	NR	NR
Zhou S, 2010	China	NR	71.6	29/106	27.4	NR	NR
Ma SL, 2005	China	possible	77.6	27/95	28.4	2/95	2.1
Chen L, 1999	China	probable	NR	73/196	37.2	9/196	4.6
Jiang H, 2009	China	probable	70.4	109/362	30.1	NR	NR
Shi, J, 2004	China	probable	NR	84/369	22.8	NR	NR
Tsai SJ, 2003	China	probable	75.8	85/234	36.3	NR	NR
Yu JT, 2008	China	probable	74.2	49/109	45.0	NR	NR
Zhang JW, 2005	China	probable	NR	81/192	42.2	NR	NR
Chandak GR, 2002	India	possible	NR	17/49	34.7	2/49	4.1
Raygani AV, 2006	Iran	probable	74.2	34/94	36.2	8/94	8.5
Namekata K, 1997	Japan	NR	NR	127/294	43.2	28/294	9.5
Shibata N, 2008	Japan	NR	67.4	75/180	41.7	NR	NR
Suzuki Y, 2004	Japan	NR	76.3	45/85	52.9	4/85	4.7
Yamagata Z, 1997	Japan	NR	81.6	79/163	48.5	9/163	5.5
Yoshida S, 2001	Japan	NR	72.6	17/32	53.1	NR	NR
Asada T, 2000	Japan	probable	77.5	38/62	61.3	NR	NR
Hu J, 1999	Japan	probable	73.7	52/131	39.7	14/131	10.7
Isoe K, 1996	Japan	probable	75.5	61/131	46.6	NR	NR
Kawamata J, 1994	Japan	probable	NR	17/53	32.1	4/53	7.5
Kimura M, 2000	Japan	probable	75.1	121/216	56.0	26/216	12.0
Kimura R, 2009	Japan	probable	72	214/437	49.0	NR	NR
Kuwano R, 2006	Japan	probable	NR	777/1,526	50.9	147/1,526	9.6
Matsubara-Tsutsui M, 2002	Japan	probable	NR	70/154	45.5	NR	NR
Muramatsu T, 1996	Japan	probable	76	56/101	55.4	NR	NR
Quan W, 2006	Japan	probable	NR	130/230	56.5	32/230	13.9
Tanaka N, 2010	Japan	probable	76.8	69/153	45.1	NR	NR
Toji H, 1999	Japan	probable	NR	69/117	59.0	12/117	10.3
Yoshizawa T, 1997	Japan	probable	74.1	36/82	43.9	NR	NR
Ponomareva NV, 2008	Russia	probable	65.2	33/50	66.0	11/50	22.0
Jo SA, 2006	South Korea	probable	73	157/316	49.7	NR	NR
Kim HC, 2000	South Korea	probable	71	13/30	43.3	1/30	3.3
Kim JM, 2002	South Korea	probable	76.5	18/52	34.6	1/52	1.9
Kim JM, 2002	South Korea	probable	77.4	27/52	51.9	1/52	1.9
Huang H, 2002	Taiwan	NR	76.3	32/99	32.3	6/99	6.1
Liu HC, 2005	Taiwan	NR	75.5	83/232	35.8	NR	NR
Senanarong V, 2001	Thailand	probable	NR	25/42	59.5	5/42	11.9
MA estimate (95% CI)				43 (8,288)	41.88 (38.48–45.27)*	21 (3,817)	7.70 (5.84–9.55)*
Test for heterogeneity							
I^2				89%		61.00%	
Square-root Tau				10.38		3.46	
Q p value				<0.001		<0.001	

* Significant heterogeneity at $p < 0.01$. NR = Not reported.

Table 2. Study characteristics and meta-analysis estimates of the prevalence of APOE e4 carriers (e4/–) and e4/4 in Europe

First author, year	Country	AD case definition	Mean age years	e4/– n/N	APOE e4/– %	e4/4 n/N	e4/4 %
Northern Europe							
Kuusisto J, 1994	Finland	possible	NR	27/46	58.7	6/46	13.0
Tilvis RS, 1998	Finland	possible	NR	21/41	51.2	NR	NR
Vepsalainen S, 2007	Finland	probable	NR	312/424	73.6	NR	NR
Yasuda M, 1998	Finland	probable	74.5	116/178	65.2	23/178	12.9
Slooter AJC, 1998	The Netherlands	NR	84.1	43/129	33.3	7/129	5.4
van der Flier WM, 2008	The Netherlands	NR	69	175/251	69.7	38/251	15.1
van Duijn CM, 1994	The Netherlands	NR	63	92/175	52.6	29/175	16.6
Sando SB, 2008	Norway	possible	79.5	241/376	64.1	57/376	15.2
Lilius L, 1999	Sweden	NR	NR	44/94	46.8	NR	NR
Prince JA, 2004	Sweden	NR	77.4	367/563	65.2	70/563	12.4
Andreasen N, 1999	Sweden	probable	71.4	36/52	69.2	NR	NR
Landen M, 1996	Sweden	probable	NR	45/54	83.3	12/54	22.2
Lilius L, 1999	Sweden	probable	NR	130/175	74.3	NR	NR
Zetterberg M, 2008	Sweden	probable	75.8	548/800	68.5	135/800	16.9
Davidson Y, 2007	UK	NR	63.1	291/462	63.0	73/462	15.8
Holmes C, 1996	UK	possible	81.9	92/164	56.1	NR	NR
Craig D, 2005	UK	probable	78	221/404	54.7	49/404	12.1
McIlroy SP, 1999	UK	probable	77.7	86/175	49.1	NR	NR
MA estimate (95% CI)				18 (4,563)	61.25 (55.85–66.66)**	11 (3,438)	14.10 (12.19–16.02)*
Test for heterogeneity							
I^2				89.00%		51.00%	
Square-root Tau				10.96		2.31	
Q p value				<0.001		0.025	
Central Europe							
Grunblatt E, 2008	Austria	possible	NR	33/127	26.0	NR	NR
Bettens K, 2009	Belgium	probable	NR	286/555	51.5	NR	NR
Dupuy AM, 2001	France	NR	NR	22/50	44.0	4/50	8.0
Lambert JC, 1999	France	NR	72	348/600	58.0	NR	NR
Araria-Goumidi L, 2002	France	probable	72.3	276/451	61.2	64/451	14.2
Bickeboller H, 1996	France	probable	NR	233/417	55.9	54/417	12.9
Martinez M, 1998	France	probable	NR	162/290	55.9	46/290	15.9
Merched A, 1998	France	probable	77.9	58/118	49.2	NR	NR
Wavrant-DeVrieze F, 1997	France	probable	77.3	79/144	54.9	16/144	11.1
Drzezga A, 2009	Germany	NR	NR	18/32	56.3	NR	NR
Hong GS, 2009	Germany	NR	72.3	210/363	57.9	NR	NR
Czech C, 1994	Germany	possible	NR	23/40	57.5	6/40	15.0
Riemenschneider M, 2002	Germany	probable	69.3	91/207	44.0	NR	NR
Paragh G, 2002	Hungary	NR	64.3	19/30	63.3	6/30	20.0
Rakonczay Z, 2005	Hungary	possible	73.1	28/64	43.8	5/64	7.8
Gacia M, 2008	Poland	probable	72.1	136/217	62.7	NR	NR
Klimkowicz-Mrowiec, 2009	Poland	probable	75.8	173/332	52.1	21/332	6.3
Trebunova M, 2009	Slovakia	NR	73.26	32/69	46.4	NR	NR
Gold G, 2003	Switzerland	NR	79.9	33/82	40.2	NR	NR
MA estimate (95% CI)				19 (4,188)	51.74 (47.57–55.92)**	9 (1,818)	11.85 (9.10–14.60)**
Test for heterogeneity							
I^2				80.00%		61.00%	
Square-root Tau				8.08		3.09	
Q p value				<0.001		0.009	

Table 2 (continued)

First author, year	Country	AD case definition	Mean age years	e4/– n/N	APOE e4/– %	e4/4 n/N	e4/4 %
Southern/Mediterranean Europe							
Bowirrat A, 2006	Israel	NR	82.6	20/168	11.9	NR	NR
Folin M, 2005	Italy	NR	80.3	25/79	31.6	4/79	5.1
Ventriglia M, 2005	Italy	NR	72.0	90/227	39.6	NR	NR
Orsitto G, 2007	Italy	possible	79.8	35/82	42.7	5/82	6.1
Palumbo R, 1997	Italy	possible	NR	58/140	41.4	5/140	3.6
Terreni L, 2003	Italy	possible	76.4	103/256	40.2	NR	NR
Altamura C, 2007	Italy	probable	74.7	24/68	35.3	NR	NR
Bosco P, 2007	Italy	probable	NR	49/109	45.0	8/109	7.3
Bracco L, 2007	Italy	probable	70.9	40/85	47.1	11/85	12.9
Flex A, 2006	Italy	probable	77.3	80/183	43.7	NR	NR
Monastero R, 2003	Italy	probable	72.0	53/149	35.6	NR	NR
Orlacchio A, 2002	Italy	probable	NR	35/135	25.9	NR	NR
Panza F, 2003	Italy	probable	71.6	15/49	30.6	2/49	4.1
Piccardi M, 2007	Italy	probable	76.8	56/158	35.4	4/158	2.5
Poli M, 2003	Italy	probable	72.0	48/113	42.5	NR	NR
Scacchi R, 1995	Italy	probable	83.5	21/80	26.3	1/80	1.3
Spalletta G, 2007	Italy	probable	NR	48/99	48.5	7/99	7.1
Venturelli E, 2005	Italy	probable	NR	184/432	42.6	NR	NR
Zappia M, 2004	Italy	probable	71.3	64/148	43.2	NR	NR
Fernandes M, 1999	Portugal	probable	68.2	27/74	36.5	7/74	9.5
Blazquez L, 2007	Spain	NR	73.5	103/211	48.8	NR	NR
Clarimon J, 2003	Spain	possible	74.8	66/118	55.9	5/118	4.2
Deniz-Naranjo MC, 2008	Spain	probable	NR	138/282	48.9	NR	NR
Ezquerra M, 1997	Spain	probable	NR	76/174	43.7	NR	NR
Rodriguez-Rodriguez E, 2008	Spain	probable	75.7	223/414	53.9	NR	NR
Vazquez-Higuera JL, 2009	Spain	probable	76.8	221/408	54.2	NR	NR
Smach MA, 2010	Tunisia	probable	73.0	45/93	48.4	NR	NR
Aybeck H, 2007	Turkey	possible	73.3	24/62	38.7	2/62	3.2
Yokes MB, 2005	Turkey	possible	77.5	20/68	29.4	0/68	0.0
MA estimate (95% CI)				29 (4,664)	40.45 (36.77–44.13)**	13 (1,203)	4.56 (2.74–6.38)*
Test for heterogeneity							
I^2				84.00%		53.00%	
Square-root Tau				9.11		2.58	
Q p value				<0.001		0.012	

* Significant heterogeneity at $p < 0.10$; ** significant heterogeneity at $p < 0.01$. NR = Not reported.

APOE e4 and e4/4 Prevalence Estimates

Summary Estimates

The meta-analyses reported in table 4 are the pooled estimates for APOE e4 carrier prevalence: 48.7% (95% confidence interval, CI: 46.5–51.0) and e4/4 prevalence: 9.6% (95% CI: 8.4–10.8). Strong evidence of heterogeneity was observed for these overall estimates, and also when stratified by AD case definitions (table 4).

Regional Estimates

An overview of the variation across 6 geographic regions is presented graphically in figure 2. The meta-analysis estimates and tests for heterogeneity are provided in tables 1–3. As has been observed in the general population, the prevalence varied by geographic location, with the lowest regional estimates for the prevalence of e4 carriers in Asia: 41.9% (95% CI: 38.5–45.3); e4/4 prevalence: 7.7% (95% CI: 5.8–9.6) or Southern Eu-

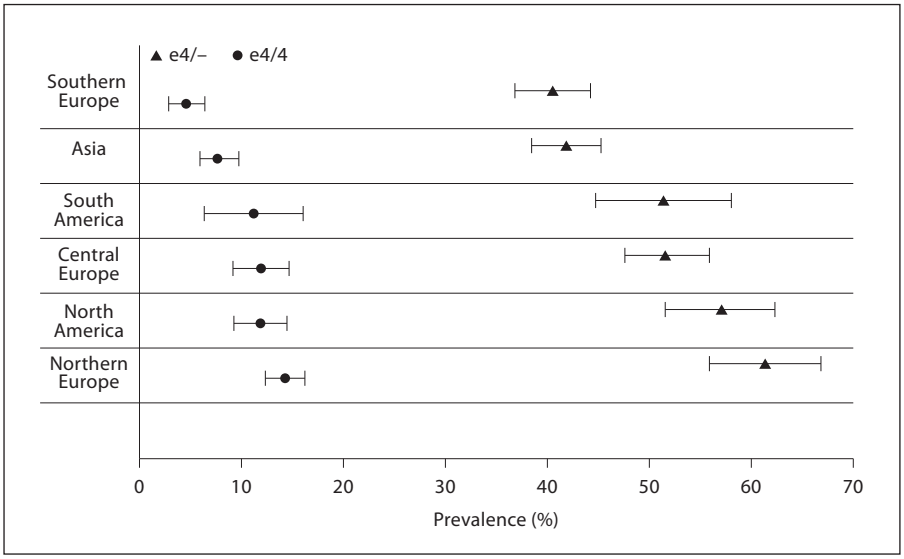

Fig. 2. APOE e4 carrier (heterozygotes or homozygotes) and homozygote e4/4 prevalence in the AD population, stratified by region (T bars indicate 95% CI).

rope/Mediterranean: 40.5% (95% CI: 36.8–44.1); e4/4 prevalence: 4.6% (95% CI: 2.7–6.4). The highest were in Northern Europe: 61.3% (95% CI: 55.9–66.7); e4/4 prevalence: 14.1% (95% CI: 12.2–16.0). However, substantial heterogeneity of these prevalence estimates was observed, as indicated by a value of I^2 greater than 50% for each region. The meta-analysis results for each region, stratified by AD case definition, are provided in table 5. The probable cases generally had higher estimates within each region, albeit with substantial heterogeneity in the results from each study.

Country-Specific Estimates

Fifteen countries had more than 3 studies and, for these 15 countries, the data were pooled for each country (table 6). Substantial within-region variation was evident; for example, in Asia the point estimate and 95% CI for Japan were 48.9% (95% CI: 45.9–51.9), and for China they were 32.8% (95% CI: 28.3–37.3). Substantial heterogeneity of the majority of these country-specific prevalence estimates was observed, as indicated by a value of I^2 greater than 50% for all the countries except 4 – Canada, France, South Korea, and Spain. Subgroup analyses were conducted to explore sources of heterogeneity by AD case definition (table 7). The probable cases generally had higher estimates within each country, although there was substantial heterogeneity in the study results.

Variation within Countries

Analyses were also conducted to explore sources of heterogeneity within Italy, Japan, and the USA, as adequate numbers of studies, >3 per area within the country, were available to support exploring estimates obtained from different areas within each of these countries. For example, estimates for Italy from 6 studies (948 patients) conducted in the North (42.51%; 95% CI: 39.33–45.68) were similar to 10 studies (1,351 patients) in the South (39.35%; 95% CI: 36.42–42.27). For Japan, estimates from 3 studies (349 patients) conducted in the North were higher (55.59%; 95% CI: 50.36–60.81) than 13 studies (2,092 patients) in the South (48.05%; 95% CI: 44.34–51.76). For the USA, the variation in pooled estimates by location was explored further by assigning studies to 4 groups – the pooled estimates from 5 studies (374 patients) conducted in the West (67.10%; 95% CI: 62.29–71.91) and 3 studies (593 patients) in the South (66.61%; 95% CI: 62.81–70.41) were higher than 6 studies (2,092 patients) in the Northeast (50.34%; 95% CI: 39.63–61.06) and 3 studies (480 patients) in the central states (40.97%; 95% CI: 26.48–55.47).

Meta-Regression

As significant heterogeneity was present, the variation in each geographic region was explored using meta-regression. Although meta-regression can adjust for the effect of study level characteristics on the results, the factors should be commonly reported at the study level, and this limits the factors that can be considered in these analyses. In the meta-regression analyses for APOE e4 carrier prevalence in Asia and North America, the AD case definition significantly contributed to the heterogeneity of the regional results, although this was not ob-

Table 3. Study characteristics and meta-analysis estimates of the prevalence of APOE e4 carriers (e4/–) and e4/4 in America and Oceania

First author, year	Country	AD case definition	Mean age years	e4/– n/N	APOE e4/– %	e4/4 n/N	e4/4 %
North America							
Gauthier E, 2000	Canada	possible	NR	41/68	60.3	NR	NR
Percy M, 2008	Canada	probable	74.1	37/54	68.5	5/54	9.3
Wood PL, 2010	Canada	probable	NR	26/40	65.0	9/40	22.5
He J, 2009	USA	NR	77.8	44/68	64.7	NR	NR
Johnston J, 2000	USA	NR	82.8	29/102	28.4	NR	NR
Morris MC, 2000	USA	NR	NR	86/216	39.8	NR	NR
Sheu KFR, 1999	USA	NR	89.0	68/179	38.0	NR	NR
Zhan J, 2009	USA	NR	76.8	95/181	52.5	NR	NR
Adak S, 2004	USA	possible	71.9	26/39	66.7	NR	NR
Devi G, 1999	USA	possible	78.0	106/312	34.0	NR	NR
Grubber J, 1999	USA	possible	72.7	164/245	66.9	NR	NR
Harwood DB, 2004	USA	possible	NR	457/960	47.6	58/960	6.0
Murrell JR, 2006	USA	possible	83.8	88/162	54.3	21/162	13.0
Nielson K, 1996	USA	possible	74.1	30/42	71.4	6/42	14.3
Town T, 1998	USA	possible	NR	126/190	66.3	21/190	11.1
Weiner MF, 1999	USA	possible	72.4	105/158	66.5	20/158	12.7
Bretsky PM, 1999	USA	probable	80.5	57/80	71.3	6/80	7.5
Chuu JYJ, 2006	USA	probable	NR	100/146	68.5	NR	NR
Dal Forno G, 1996	USA	probable	NR	70/101	69.3	14/101	13.9
Gomez-Isla T, 1996	USA	probable	77.8	222/359	61.8	59/359	16.4
Moceri VM, 2000	USA	probable	78.0	178/393	45.3	NR	NR
Sunderman EE, 2007	USA	probable	NR	20/38	52.6	NR	NR
Tsai MS, 1994	USA	probable	80.5	45/77	58.4	9/77	11.7
MA estimate (95% CI)				23 (4,210)	56.83 (51.45–62.21)**	11 (2,223)	11.82 (9.18–14.46)**
Test for heterogeneity							
I^2				91.00%		78.00%	
Square-root Tau				12.26		3.28	
Q p value				<0.001		<0.001	
South America							
Souza DRS, 2003	Brazil	NR	71.5	31/68	45.6	3/68	4.4
Bahia VS, 2008	Brazil	probable	75.2	61/120	50.8	13/120	10.8
Quiroga P, 1999	Chile	possible	NR	59/95	62.1	17/95	17.9
Jacquier M, 2001	Colombia	possible	73.3	32/83	38.6	7/83	8.4
Arboleda GH, 2001	Colombia	probable	72.4	35/61	57.4	10/61	16.4
Forero DA, 2006	Colombia	probable	73.3	56/106	52.8	NR	NR
Jacquier M, 2001	Colombia	probable	NR	19/39	48.7	5/39	12.8
MA estimate (95% CI)				6 (533)	51.29 (44.66–57.92)*	5 (427)	11.14 (6.34–15.95)*
Test for heterogeneity							
I^2				57.00%		57.00%	
Square-root Tau				6.32		4.29	
Q p value				0.039		0.055	

Table 3 (continued)

First author, year	Country	AD case definition	Mean age years	e4/– n/N	APOE e4/– %	e4/4 n/N	e4/4 %
Oceania							
Yang JG, 1996	Australia	NR	NR	26/30	86.7	6/30	20.0
Ellis KA, 2009	Australia	possible	78	133/211	63.0	NR	NR
Martins RN, 1995	Australia	probable	NR	72/142	50.7	19/142	13.4
Taddei K, 2002	Australia	probable	NR	147/280	52.5	19/280	6.8
MA estimate (95% CI)				4 (663)	62.44 (47.23–77.65)**	3 (452)	11.61 (4.88–18.34)*
Test for heterogeneity							
I^2				84.00%		77.00%	
Square-root Tau				14.84		4.88	
Q p value				<0.001		0.014	

* Significant heterogeneity at $p < 0.10$; ** significant heterogeneity at $p < 0.01$.

Table 4. APOE e4 carrier and homozygote (e4/4) prevalence, percentage, and 95% CI in the AD population combined estimate, stratified by AD case definition

Outcome	AD population	Studies, n (patients)	Prevalence, % (95% CI)	I^2, %	Square-root Tau	Q p value
APOE e4/–	All studies	142 (27,109)	48.74 (46.50–50.98)*	92.00	12.81	<0.001
	Possible	66 (11,375)	46.83 (43.25–50.41)*	93.00	14.01	<0.001
	Probable	77 (15,773)	50.38 (47.64–53.12)*	91.00	11.42	<0.001
APOE e4/4	All studies	73 (13,378)	9.62 (8.43–10.81)*	74.00	4.4	<0.001
	Possible	34 (5,551)	8.87 (7.09–10.65)*	76.00	4.52	<0.001
	Probable	40 (7,866)	10.34 (8.78–11.90)*	71.00	4.15	<0.001

* Significant heterogeneity at $p < 0.01$.

served for all regions. In the analyses of North America, AD case definition, community studies, and age ≤75 years contributed to the heterogeneity. None of the variables included in these analyses consistently explained the heterogeneity among all the APOE e4 regional results.

As significant heterogeneity was present, the variation in estimates from Italy, Japan, and the USA was explored using meta-regression and included location within a country (e.g. North vs. South). None of the variables for different areas within a country included in these analyses explained the heterogeneity among the results in these 3 countries.

In the meta-regression analyses for APOE e4/4, none of the variables included in these analyses explained the heterogeneity in any of the geographic regions or in Italy, Japan, and the USA.

Discussion

This study summarizes the APOE e4/4 homozygote and e4/– carrier prevalence data published since 1985, and pools the genetic data collected from 27,109 patients diagnosed with AD residing in 33 countries. Prevalence estimates are reported for AD populations worldwide, including populations residing in Europe (North, Central,

Table 5. APOE e4 carrier and homozygote e4/4 prevalence and 95% CI, stratified by region and AD case definition

Region	APOE e4/–		APOE e4/4	
	studies, n (patients)	prevalence, % (95% CI)	studies, n (patients)	prevalence, % (95% CI)
Asia	43 (8,288)	41.88 (38.48–45.27)**	21 (3,817)	7.70 (5.84–9.55)**
Possible	17 (2,797)	36.17 (31.30–41.03)**	8 (1,028)	6.14 (3.63–8.64)*
Probable	26 (5,491)	45.61 (41.52–49.69)**	13 (2,789)	8.82 (6.26–11.38)**
Europe				
Northern	18 (4,563)	61.25 (55.85–66.66)**	11 (3,438)	14.10 (12.19–16.02)*
Possible	10 (2,301)	56.60 (49.77–63.42)**	7 (2,002)	13.50 (10.74–16.25)*
Probable	8 (2,262)	66.95 (59.46–74.44)**	4 (1,436)	14.95 (11.69–18.21)*
Central	19 (4,188)	51.74 (47.57–55.92)**	9 (1,818)	11.85 (9.10–14.60)**
Possible	10 (1,457)	48.82 (41.36–56.29)**	4 (184)	11.40 (6.29–16.51)
Probable	9 (2,731)	54.39 (50.69–58.09)**	5 (1,634)	11.99 (8.58–15.40)**
Southern/Mediterranean	29 (4,664)	40.45 (36.77–44.13)**	13 (1,203)	4.56 (2.74–6.38)*
Possible	10 (1,411)	37.93 (30.21–45.66)**	6 (549)	3.82 (2.21–5.43)
Probable	19 (3,253)	41.96 (38.16–45.77)**	7 (654)	5.81 (2.80–8.82)*
America				
North America	23 (4,210)	56.83 (51.45–62.21)**	11 (2,223)	11.82 (9.18–14.46)**
Possible	14 (2,922)	53.60 (46.13–61.06)**	5 (1,512)	10.49 (7.04–13.95)**
Probable	9 (1,288)	62.07 (55.75–68.38)**	6 (711)	13.39 (9.79–17.00)
South America	6 (533)	51.29 (44.66–57.92)*	5 (427)	11.14 (6.34–15.95)*
Possible	3 (246)	48.91 (34.94–62.89)**	3 (246)	9.92 (2.29–17.56)*
Probable	4 (326)	52.45 (47.02–57.89)	3 (220)	12.73 (8.30–17.16)

Regions include studies from the following countries: Asia: China, India, Iran, Japan, Russia, South Korea, Taiwan, Thailand; North America: Canada, USA; South America: Brazil, Chile, Colombia; Central Europe: Austria, Belgium, France, Germany, Hungary, Poland, Slovakia, Switzerland; Northern Europe: Finland, The Netherlands, Norway, Sweden, UK; Southern Europe/Mediterranean: Israel, Italy, Portugal, Spain, Tunisia, Turkey.

* Significant heterogeneity at $p < 0.10$; ** significant heterogeneity at $p < 0.01$.

Table 6. APOE e4 carrier and homozygote e4/4 prevalence and 95% CI, stratified by country

Country	APOE e4/–		APOE e4/4	
	studies, n (patients)	prevalence, % (95% CI)	studies, n (patients)	prevalence, % (95% CI)
Australia	4 (663)	62.44 (47.23–77.65)**	3 (452)	11.61 (4.88–18.34)*
Canada	3 (162)	64.20 (56.79–71.61)	–	
China	15 (3,125)	32.78 (28.26–37.31)**	4 (534)	5.52 (1.05–9.99)**
Colombia	3 (250)	49.37 (38.42–60.32)*	–	
Finland	4 (689)	64.14 (54.87–73.41)**	–	
France	7 (2,070)	56.36 (53.54–59.18)	5 (1,352)	13.61 (11.77–15.44)
Germany	4 (642)	53.04 (44.85–61.24)*	–	
Italy	18 (2,592)	39.08 (36.21–41.95)**	9 (881)	5.07 (2.99–7.14)*
Japan	18 (4,147)	48.92 (45.91–51.93)**	9 (2,815)	9.69 (8.07–11.32)
The Netherlands	3 (555)	52.04 (31.42–72.65)**	3 (555)	12.26 (5.33–19.19)**
South Korea	4 (450)	46.25 (38.95–53.55)	3 (134)	2.24 (0.00–4.75)
Spain	6 (1,607)	51.15 (47.88–54.41)	–	
Sweden	6 (1,738)	67.88 (58.78–76.99)**	3 (1,417)	15.71 (11.36–20.06)*
UK	4 (1,205)	56.16 (50.43–61.90)**	–	
USA	20 (4,048)	55.84 (49.90–61.78)**	9 (2,129)	11.47 (8.74–14.21)**

* Significant heterogeneity at $p < 0.10$; ** significant heterogeneity at $p < 0.01$.

and South/Mediterranean), Asia, North America, and South America. Enough studies have been conducted in 9 countries (Australia, China, France, Germany, Japan, Italy, Spain, the UK, and the USA) to also develop country-specific estimates.

The meta-analysis results suggest that heterogeneity within geographic locations and AD definitions is not fully explained by variation in the source of the patient sample, study design, or mean age of the individual study population. The potential for selection bias has to be considered, as the frequency of the APOE e4 allele has been observed to be lower in community-based AD patient samples than in research clinics, trials, or autopsy studies [13, 14]. This review excluded trials and autopsy studies, but it should be noted that almost two thirds of the participants included in the analysis were recruited while attending a clinic. This analysis also could not consider the factors influencing why some patients volunteer for this genetic test. There can be genetic heterogeneity within areas of a country, and some studies may select a specific or non-representative population; for example, Bowirrat et al. [15] conducted a door-to-door survey of elderly Arabs residing in a certain area of Israel (Wadi Ara). Although differences in AD case definitions contribute to the substantial heterogeneity of published prevalence estimates within each region, the variables included in these analyses could not explain the heterogeneity observed in the published estimates. Meta-regression can adjust for the effect of study level characteristics on the results, but relatively few factors were commonly reported at the study level, and this limited the factors able to be considered in this analysis. For example, race was not recorded in many studies, and the ability to fully explore age was limited to the mean age reported in the publications. Although the reasons for the substantial heterogeneity were not possible to elucidate from this review, caution is warranted when attempting to infer regional or country-specific estimates of the ApoE e4 allele frequency. Such differences may arise from small-area variations in allele frequency, environmental risks that vary between regions, methodologic differences, or a combination. The heterogeneity limits the ability to incorporate allele frequencies into models forecasting AD incidence and prevalence estimates and may hinder health policy planning efforts related to allele frequency.

The pooled estimate for APOE e4 carrier prevalence was 48.7% (95% CI: 46.5–51.0), and homozygote (e4/4) prevalence was 9.6% (95% CI: 8.4–10.8). However, there was substantial heterogeneity in these prevalence estimates. In 1997, Farrer et al. [4] published somewhat high-

Table 7. Prevalence of APOE e4 and e4/4, meta-regression coefficients by region

Region/country	t (n)	Intercept	Probable AD vs. possible	Community sample vs. others	Case-control study vs. others	Age ≤75 vs. >75 years	Area vs. others[1]
Asia	43 (8,288)	0.37 (0.31–0.43)	0.09 (0.03–0.16)**	–0.05 (–0.12 to 0.03)	0.15 (–0.08 to 0.38)	0.00 (–0.06 to 0.07)	–
Northern Europe	18 (4,563)	0.56 (0.45–0.67)	0.11 (–0.02 to 0.25)*	0.00 (–0.18 to 0.18)**	–0.06 (–0.21 to 0.08)	0.05 (–0.08 to 0.18)*	–
Central Europe	19 (4,188)	0.44 (0.36–0.53)	0.06 (–0.02 to 0.15)	–0.04 (–0.24 to 0.16)	0.07 (–0.07 to 0.21)	0.08 (–0.01 to 0.17)	–
Southern Europe/ Mediterranean	29 (4,664)	0.40 (0.32–0.48)	0.01 (–0.07 to 0.10)	–0.07 (–0.22 to 0.07)	–0.03 (–0.12 to 0.06)	0.02 (–0.05 to 0.10)	–
North America	23 (4,210)	0.56 (0.47–0.65)	0.10 (0.02–0.18)	–0.13 (–0.21 to –0.05)	0.01 (–0.07 to 0.09)	0.12 (0.01–0.22)	–
South America	6 (533)	0.38 (0.12–0.64)	0.13 (–0.06 to 0.32)	0.24 (–0.07 to 0.56)	–	0.04 (–0.18 to 0.26)	–
Country							
Italy	16 (2,299)	0.41 (0.34–0.48)	0.00 (–0.07 to 0.07)	–	0.05 (–0.02 to 0.12)	0.00 (–0.07 to 0.07)	–0.03 (–0.10 to 0.03)
Japan	16 (2,441)	0.54 (0.44–0.65)	0.02 (–0.06 to 0.10)	–0.08 (–0.15 to 0.00)*	–	–0.05 (–0.13 to 0.03)	–0.04 (–0.13 to 0.05)
USA	19 (3,971)	0.56 (0.50–0.62)	0.07 (–0.03 to 0.16)	–0.17 (–0.25 to –0.10)**	–	0.12 (0.02–0.23)*	0.06 (–0.03 to 0.15)

[1] Italy and Japan: northern region (vs. southern region); USA: west vs. other.
* Significant heterogeneity at $p < 0.10$; ** significant heterogeneity at $p < 0.01$.

er prevalence estimates (e4/–: 58.5% and e4/4: 14.8%) from a pooled analysis of data, provided by 40 research teams, that had been collected from 5,107 'Caucasian' patients diagnosed with probable or definite AD. The lower estimates in the current study could perhaps be anticipated as approximately one third of the cases are from Asia, where APOE e4 prevalence is lower in the general population, and autopsy studies were excluded.

The lowest regional estimates for e4 carrier status were observed in Asia (41.9%; 95% CI: 38.5–45.3) and Southern Europe (40.5%; 95% CI: 36.8–44.1), where the majority of AD cases were not APOE e4 carriers. In marked contrast, the majority of cases in Northern Europe were carriers (61.3%; 95% CI: 55.9–66.7). Similar patterns were observed for APOE e4/4 estimates. These trends are consistent with general population studies in which the APOE e4 frequencies were observed to be higher in Northern than in Southern Europe or Asia, and to be lowest in Italy, Japan and Korea [6–8]. Substantial heterogeneity of the estimates was observed within each region and remained when additional analyses pooled the estimates by country or, in some cases, by areas within each country.

When the analyses were stratified by AD case definition, graphically there was a general trend within each region for a higher prevalence in the studies selecting 'probable' AD cases. In the meta-regression analysis for Asia, North America, and Australia, the case definition contributed to the heterogeneity of these regional results, although this was not observed for all regions. For this analysis, the term 'probable' AD case is applied only to the samples specifically reported as meeting the NINCDS-ADRDA criteria. The differences in AD case definitions are therefore likely to be contributing to the heterogeneity observed in the published prevalence estimates, especially as not all the studies specified the criteria applied. This review identified studies conducted in this field during the last 25 years, and each of the researchers applied the current clinical diagnostic criteria for AD; however, in the future, biomarkers for AD will increasingly be used to support diagnoses in research settings [16], and this has the potential to improve the design of studies in this field.

Genotyping results stratified by familial AD, sporadic AD, early-onset AD, and late-onset AD were extracted when reported. However, the number of studies reporting these specific categories was insufficient to conduct analyses by region. Although differences in the genetic susceptibility for these different clinical presentations of AD may explain in part the substantial amount of inter-study heterogeneity demonstrated across every analysis, this could not be explored in this project.

Although APOE e4 is a well-studied genetic risk factor for developing AD, in some regions most patients do not carry this genotype, and additional research is needed to be able to understand both other genetic and environmental risk factors. Currently, genetic testing of APOE e4 carrier status is not routinely considered in clinical practice. However, if the mechanism of action of new products for preventing the progression of AD is contingent on a patient's APOE e4 carrier status, then there may be regions where testing could be essential to consider both during drug development and postmarketing.

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Appendix

Included Studies

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