Supplementary Material

Confirmed Synergy Between the ϵ 4 Allele of Apolipoprotein E and the Variant K of Butyrylcholinesterase as a Risk Factor for Alzheimer's Disease: A Systematic Review and Meta-Analysis

Search Strategies

For PubMed:

((ApoE) OR (Apo E) OR (Apo-E) OR (Apolipoprotein E Isoproteins) OR (Isoproteins, Apolipoprotein E) OR (Apo E Isoproteins) OR (Isoproteins, Apo E) OR (Apoproteins E) OR (Apoprotein E) OR (Apolipoprotein E) OR (Apolipoproteins E [MeSH])) AND ((Pseudocholinesterase) OR (Benzoylcholinesterase) OR (BCHE) OR (Butyrylthiocholinesterase) OR (Butyrylcholinesterase[MeSH])) AND ((Alzheimer Dementia) OR (Alzheimer Dementias) OR (Dementia, Alzheimer) OR (Alzheimer's Disease) OR (Dementia, Senile) OR (Senile Dementia) OR (Dementia, Alzheimer Type) OR (Alzheimer Type Dementia) OR (Alzheimer-Type Dementia (ATD)) OR (Alzheimer Type Dementia (ATD)) OR (Dementia, Alzheimer-Type (ATD)) OR (Alzheimer Type Senile Dementia) OR (Primary Senile Degenerative Dementia) OR (Dementia, Primary Senile Degenerative) OR (Alzheimer Sclerosis) OR (Sclerosis, Alzheimer) OR (Alzheimer Syndrome) OR (Alzheimer's Diseases) OR (Alzheimer Diseases) OR (Alzheimers Diseases) OR (Senile Dementia, Alzheimer Type) OR (Acute Confusional Senile Dementia) OR (Senile Dementia, Acute Confusional) OR (Dementia, Presenile) OR (Presenile Dementia) OR (Alzheimer Disease, Late Onset) OR (Late Onset Alzheimer Disease) OR (Alzheimer's Disease, Focal Onset) OR (Focal Onset Alzheimer's Disease) OR (Familial Alzheimer Disease (FAD)) OR (Alzheimer Disease, Familial (FAD)) OR (Familial Alzheimer Diseases (FAD)) OR (Alzheimer Disease, Early Onset) OR (Early Onset Alzheimer Disease) OR (Presenile Alzheimer Dementia) OR (Alzheimer[MeSH])).

For Embase:

#1 - apoe OR (apo AND e) OR 'apo e' OR (apolipoprotein AND e AND isoproteins) OR (isoproteins, AND apolipoprotein AND e) OR (apolipoprotein AND e) OR (apo AND e AND isoproteins) OR (isoproteins, AND apo AND e) OR (apoproteins AND e) OR (apoproteins AND e) OR (apoproteins AND e) OR (apoproteins AND e/exp)

#2 - pseudocholinesterase OR benzoylcholinesterase OR BCHE OR butyrylthiocholinesterase OR'butyrylcholinesterase'/exp

#3 - alzheimer AND dementia OR (alzheimer AND dementias) OR (dementia, AND alzheimer) OR (alzheimer AND is AND disease) OR (dementia, AND senile) OR (senile AND dementia) OR (dementia, AND alzheimer AND type) OR (alzheimer AND type AND dementia) OR ('alzheimer type' AND dementia AND atd) OR (alzheimer AND type AND dementia AND atd) OR (dementia, AND 'alzheimer type' AND atd) OR (alzheimer AND type AND senile AND dementia) OR (primary AND senile AND degenerative AND dementia) OR (dementia, AND primary AND senile AND degenerative) OR (alzheimer AND sclerosis) OR (sclerosis, AND alzheimer) OR (alzheimer AND syndrome) OR (alzheimer AND is AND diseases) OR (alzheimer AND diseases) OR (alzheimers AND diseases) OR (senile AND dementia, AND alzheimer AND type) OR (acute AND confusional AND senile AND dementia) OR (senile AND dementia, AND acute AND confusional) OR (dementia, AND presenile) OR (presenile AND dementia) OR (alzheimer AND disease, AND late AND onset) OR (late AND onset AND alzheimer AND disease) OR (alzheimer AND is AND disease, AND focal AND onset) OR (focal AND onset AND alzheimer AND is AND disease) OR (familial AND alzheimer AND disease AND fad) OR (alzheimer AND disease, AND familial AND fad) OR (familial AND alzheimer AND diseases AND fad) OR (alzheimer AND disease, AND early AND onset) OR (early AND onset AND alzheimer AND disease) OR (presenile AND alzheimer AND dementia) OR alzheimer Final Research - #1 AND #2 AND #3

For Scopus:

(TITLE-ABS-KEY (apoe) OR TITLE-ABS-KEY (apo AND e) OR TITLE-ABS-KEY (apo-e) OR TITLE-ABS-KEY (apolipoprotein AND e AND isoproteins) OR TITLE-ABS-KEY (isoproteins, AND apolipoprotein AND e) OR TITLE-ABS-KEY (apoproteins AND e) OR TITLE-ABS-KEY (apoproteins AND e) OR TITLE-ABS-KEY (apoproteins AND e) OR TITLE-ABS-KEY (apoprotein AND e) OR TITLE-ABS-KEY (apolipoprotein AND e)) AND (TITLE-ABS-KEY (alzheimer AND dementia) OR TITLE-ABS-KEY (alzheimer AND dementias) OR TITLE-ABS-KEY (alzheimer AND dementia, AND alzheimer) OR TITLE-ABS-KEY (alzheimer's AND disease) OR TITLE-ABS-KEY (dementia, AND alzheimer AND type) OR TITLE-ABS-KEY (senile AND dementia) OR TITLE-ABS-KEY (dementia, AND alzheimer AND type) OR TITLE-ABS-KEY (dementia) OR TITLE-ABS-KEY (demen

ABS-KEY (alzheimer AND type AND dementia) OR TITLE-ABS-KEY (alzheimer-type AND dementia AND atd) OR TITLE-ABS-KEY (alzheimer AND type AND dementia AND atd) OR TITLE-ABS-KEY (dementia, AND alzheimer-type AND atd) OR TITLE-ABS-KEY (alzheimer AND type AND senile AND dementia) OR TITLE-ABS-KEY (primary AND senile AND degenerative AND dementia) OR TITLE-ABS-KEY (dementia, AND primary AND senile AND degenerative) OR TITLE-ABS-KEY (alzheimer AND sclerosis) OR TITLE-ABS-KEY (sclerosis, AND alzheimer) OR TITLE-ABS-KEY (alzheimer AND syndrome) OR TITLE-ABS-KEY (alzheimer's AND diseases) OR TITLE-ABS-KEY (alzheimer AND diseases) OR TITLE-ABS-KEY (alzheimers AND diseases) OR TITLE-ABS-KEY (senile AND dementia, AND alzheimer AND type) OR TITLE-ABS-KEY (acute AND confusional AND senile AND dementia) OR TITLE-ABS-KEY (senile AND dementia, AND acute AND confusional) OR TITLE-ABS-KEY (dementia, AND presenile) OR TITLE-ABS-KEY (presenile AND dementia) OR TITLE-ABS-KEY (alzheimer AND disease, AND late AND onset) OR TITLE-ABS-KEY (late AND onset AND alzheimer AND disease) OR TITLE-ABS-KEY (alzheimer's AND disease, AND focal AND onset) OR TITLE-ABS-KEY (focal AND onset AND alzheimer's AND disease) OR TITLE-ABS-KEY (familial AND alzheimer AND disease AND fad) OR TITLE-ABS-KEY (alzheimer AND disease, AND familial AND fad) OR TITLE-ABS-KEY (familial AND alzheimer AND diseases AND fad) OR TITLE-ABS-KEY (alzheimer AND disease, AND early AND onset) OR TITLE-ABS-KEY (early AND onset AND alzheimer AND disease) OR TITLE-ABS-KEY (presenile AND alzheimer AND dementia)) AND (TITLE-ABS-KEY (pseudocholinesterase) OR TITLE-ABS-KEY (benzoylcholinesterase) OR TITLE-ABS-KEY (butyrylthiocholinesterase) OR TITLE-ABS-KEY (bche) OR TITLE-ABS-KEY (butyrylcholinesterase))

For Web of Science, which needed an adaptation, due to the limit of terms, APOE, BCHE and the synonyms of both were used, the result of the return that did not include Alzheimer's disease was later excluded:

(ALL=(bche) OR ALL=(butyrylthiocholinesterase) OR ALL=(butyrylcholinesterase) OR ALL=(pseudocholinesterase) OR ALL=(benzoylcholinesterase)) AND (ALL=(apoe) OR ALL=(apo e) OR ALL=(apolipoprotein e isoproteins) OR ALL=(isoproteins, apolipoprotein e) OR ALL=(apoproteins) OR ALL=(apoproteins) OR ALL=(apoproteins) OR ALL=(apolipoproteins))

N.	Year - Tittle - Fist author	Decision and reason why was excluded			
1.	1997 - Synergy between the genes for butyrylcholinesterase K variant and apolipoprotein E4 in late-onset confirmed Alzheimer's disease - Lehmann	Included			
2.	1998 - The butyrylcholinesterase K variant is not associated with Alzheimer's disease - Helbecque	Excluded, found only the abstract, full study not available.			
3.	1998 - Age influences the synergy between butyrylcholinesterase K variant and apolipoprotein E epsilon 4 in late-onset Alzheimer's disease - Lehmann	Excluded, found only the abstract, full study not available.			
4.	1998 - K variant of butyrycholinesterase and late-onset Alzheimer's disease - Russ	In this study it was necessary to evaluate the third reviewer who decided: "Excluded, the way of presenting the data makes it impossible to extract and analyze".			
5.	1998 - No association between the K variant of the butyrylcholinesterase gene and pathologically confirmed Alzheimer's disease - Sigleton	In this study it was necessary to evaluate the third reviewer who decided: "Included. Plausible data for interpretation and insertion".			
6.	1998 - Analysis of the butyrylcholinesterase gene and nearby chromosome 3 markers in Alzheimer disease - Brindle	Excluded, due to making a separation between younger than 70 years old (<70) and older than 70 years old (>70) and used as a control group people with a mean age of 63.4 years while the AD group was 75.4 years old.			
7.	1998 - Butyrylcholinesterase K variant and apolipoprotein E4 genes do not act in synergy in Finnish late-onset Alzheimer's disease patients - Hiltunen	Excluded, this study presented data referring to E4 carriers and their relationship with BCHE-K and wild type, but it did not show this relationship in non-E4 carriers, this lack of data caused its exclusion.			
8.	1998 - The butyrylcholinesterase gene is neither independently nor synergistically associated with late-onset AD in clinic- and	Included.			

Supplementary Table 1. Exclusion List

	community-based populations - Crawford				
9.	1998 - Long-term tacrine treatment in three mild Alzheimer patients: effects on nicotinic receptors, cerebral blood flow, glucose metabolism, EEG, and cognitive abilities - Nordberg	Excluded, did not do bche genotyping.			
10.	1998 - The butyrylcholinesterase K variant and susceptibility to Alzheimer's disease - Kehoe	Included.			
11.	1998 - Butyrylcholinesterase K variant and cerebral amyloid angiopathy - Yamada	*This article was excluded at this stage, as it did not present data from the control group, but later these data were extracted from paper to complete the data of the study by Sodeyama, 1999, which are part of the same research group.			
12.	1999 - Further evidence for a synergistic association between APOE epsilon 4 and BCHE-K in confirmed Alzheimer's disease - Wiebusch	Included.			
13.	1999 - No association between the genes for butyrylcholinesterase K variant and apolipoprotein E4 in late- onset Alzheimer's disease - Ki	Included.			
14.	1999 - Butyrycholinesterase K variant and Alzheimer's disease - Panegyres	Included.			
15.	1999 - Evidence that the butyryl-cholinesterase K variant can protect against late-onset Alzheimer's disease - Laws	Excluded, found only the abstract, full study not available.			
16.	1999 - Analysis of association between Alzheimer disease and the K variant of butyrylcholinesterase (BCHE-K) - Grubber	Included, data hidden in the text, but extractable.			
17.	1999 - Failure to confirm a synergistic effect between the K- variant of the butyrylcholinesterase gene and the epsilon 4 allele	Included, data hidden in the text, but extractable.			

	of the apolipoprotein gene in Japanese patients with Alzheimer's disease - Yamamoto	
18.	1999 - Evaluation of polymorphisms in the presenilin-1 gene and the butyrylcholinesterase gene as risk factors in sporadic Alzheimer's disease - Tilley	Included.
19.	1999 - Association between butyrylcholinesterase K variant and the Alzheimer type neuropathological changes in apolipoprotein E epsilon 4 carriers older than 75 years - Sodeyama	Included.
20.	2000 - Association of butyrylcholinesterase K variant with cholinesterase-positive neuritic plaques in the temporal cortex in late-onset Alzheimer's disease - Lehman	Excluded, does not show data for other apoe alleles.
21.	2000 - Butyrylcholinesterase K variant is genetically associated with late onset Alzheimer's disease in Northern Ireland - McIlroy	Included.
22.	2000 - No association between butyrylcholinesterase K-variant and Alzheimer disease in Chinese - Lee	Included.
23.	2000 - Dipeptidyl carboxypeptidase 1 (DCP1) and butyrylcholinesterase (BCHE) gene interactions with the apolipoprotein E epsilon4 allele as risk factors in Alzheimer's disease and in Parkinson's disease with coexisting Alzheimer pathology - Mattila	Included.
24.	2000 - Candidate genes showing no evidence for association or linkage with Alzheimer's disease using family-based methodologies - Bertram	Excluded, did not show data regarding APOE.
25.	2000 - The butyrylcholinesterase K variant is a protective factor for sporadic Alzheimer's disease in women - Alvarez-Arcaya	Included.

26.	2001 - Neither the butyrylcholinesterase K variant nor transferrin C2 variant confers a risk for Alzheimer's disease in Koreans - Kim	Excluded, the way in which the APOE data is presented makes it impossible to extract it.			
27.	2002 - Age-dependent association between butyrylcholinesterase K-variant and Alzheimer disease-related neuropathology in human brains - Ghebremedhin	Excluded, did not show APOE data.			
28.	2004 - Analysis of association between butyrylcholinesterase K variant and apolipoprotein e genotypes in Alzheimer's disease - Raygani	Included.			
29.	2005 - Age at onset: an essential variable for the definition of genetic risk factors for sporadic Alzheimer's disease - Beyer	Included, data hidden in the text, but extractable.			
30.	2006 - Effect of age on response to rivastigmine or donepezil in patients with Alzheimer's disease - Bullock	Excluded, study design did not include people withou AD.			
31.	2006 - Differential CSF butyrylcholinesterase levels in Alzheimer's disease patients with the ApoE epsilon 4 allele, in relation to cognitive function and cerebral glucose metabolism - Darreh-Shori	Excluded, there is no presence of a group without AD.			
32.	2007 - Susceptibility groups for Alzheimer's disease (OPTIMA): Integration of gene variants and biochemical factors - Corder	Excluded, the way of presenting the data prevents the purification and extraction of the same.			
33.	2007 - Alzheimer's disease: case-control association study of polymorphisms in ACHE, CHAT, and BCHE genes in a Sardinian sample - Piccardi	Included.			
34.	2007 - Butyrylcholinesterase, ApoE and Alzheimer's disease in a population from the Canary Islands (Spain) - Deniz-Naranjo	Included.			
35.	2008 - Epistasis of butyrylcholinesterase wt/wt and APOE e4	Excluded, data are presented in p*, making it impossible			

	state in subcortical vascular dementia and Alzheimer's disease - Almos	to extract.		
36.	2008 - Synergistic effect of apolipoprotein E epsilon 4 and butyrylcholinesterase K-variant on progression from mild cognitive impairment to Alzheimer's disease - Lane	In this study it was necessary to evaluate the third reviewer who decided: "Included, the MCI Group is used as a control, as in the 2020 study. There is a comparison group - can be used and then parenthesis. The study is very well done, and presents relevant information for a review"		
37.	2010 - BuChE K variant is decreased in Alzheimer's disease not in fronto-temporal dementia - Bizarro	Included.		
38.	2011 - Impact of butyrylcholinesterase k genotype on glial and proinflammatory markers in CSF of patients with Alzheimer's disease - Darreh-Shori	Excluded, APOE genotyping was not performed and the data are presented as p*, precluding their inclusion.		
39.	2011 - Apolipoprotein E4 affect phenotype of butyrylcholinesterase in CSF of patients with Alzheimer's disease - Darreh-Shori	Excluded, no group presence without DA.		
40.	2011 - The apolipoprotein E epsilon 4 allele plays pathological roles in AD through high protein expression and interaction with butyrylcholinesterase - Darreh-Shori	Excluded, no group presence without DA.		
41.	2011 - BCHE and CYP2D6 genetic variation in Alzheimer's disease patients treated with cholinesterase inhibitors - Chianella	Excluded, no group presence without DA.		
42.	2011 - Effect of apolipoprotein E and butyrylcholinesterase genotypes on cognitive response to cholinesterase inhibitor treatment at different stages of Alzheimer's disease - Patterson	Excluded, no group presence without DA.		
43.	2012 - Apolipoprotein epsilon 4 Modulates Phenotype of Butyrylcholinesterase in CSF of Patients with Alzheimer's Disease - Darreh-Shori	Excluded, no group presence without DA.		

44.	2013 - Cerebrospinal fluid (CSF) 25-hydroxyvitamin D concentration and CSF acetylcholinesterase activity are reduced in patients with Alzheimer's disease - Johansson	Included.		
45.	2013 - Interaction effects of butyrylcholinesterase K and apolipoprotein E genotypes related to gray matter volume differences in AD and MCI - Yoo	Excluded, no group presence without DA.		
46.	2014 - Effect of rivastigmine or memantine add-on therapy is affected by butyrylcholinesterase genotype in patients with probable Alzheimer's disease - Han	Excluded, no group presence without DA.		
47.	2014 - Butyrylcholinesterase K and Apolipoprotein epsilon 4 Affect Cortical Thickness and Neuropsychiatric Symptoms in Alzheimer's Disease - Yoo	Excluded, no group presence without DA.		
48.	2015 - Effect of rivastigmine or memantine add-on therapy is affected by butyrylcholinesterase genotype in patients with probable Alzheimer's disease - Han	Excluded, data presented in a way that makes it impossible to extract		
49.	2015 - Role of butyrylcholinesterase-K genotype in alzheimer's disease and lewy body dementia - Vijayaraghavan	Excluded, the study published by the same group in 2016 presents very similar data, due to the possibility of duplicating data and compromising the quality of the evidence, we decided to exclude one of them, keeping only the 2016 study.		
50.	2016 - Association of Butyrylcholinesterase-K Allele and Apolipoprotein E epsilon 4 Allele with Cognitive Decline in Dementia with Lewy Bodies and Alzheimer's Disease - Vijayaraghavan	Included.		
51.	2016 - Butyrylcholinesterase K and Apolipoprotein E-epsilon 4 Reduce the Age of Onset of Alzheimer's Disease, Accelerate Cognitive Decline, and Modulate Donepezil Response in Mild	Excluded, no group presence without DA.		

	Cognitively Impaired Subjects - De Beamount	
52.	2017 - The ApoE and bche genes interact to increase risk of incident Alzheimer's disease in the Baltimore study of aging - Chuang	Excluded, there is no presence of a group without AD and the form of data presentation (P*) makes it impossible to extract data.
53.	2017 - Association between butyrylcholinesterase and cerebrospinal fluid biomarkers in Alzheimer's disease patients - Gabriel	Included.
54.	2020 - Interaction between Apolipoprotein E and Butyrylcholinesterase Genes on Risk of Alzheimer's Disease in a Prospective Study - Chuang	In this study it was necessary to evaluate the third reviewer who decided: "Genotypes are presented. Included and they do not change lengthwise".
55.	2021 - Risk Variants in Three Alzheimer's Disease Genes Show Association with EEG Endophenotypes - Macedo	Excluded, did not present data on bche genotyping

Supplementary	Table 2. ROBINS-I
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Supplementary Table 2	2. KUBINS-I		D · · · · ·					a	
Study	Pre-inte	rvention	During the intervention	During the Post-intervention					
Year/First Author	Bias due to confusion	Bias in the selection of participants	Intervention bias rating	bias due to deviations from intended interventions	bias due to lack of data	bias in measuring results	bias in the selection of the reported outcome	Low/moderate/ high/critical	
1997/Lehmann	Low	Moderate	Low	Low	Moderate	-	-	Moderate	
2000/Mcilroy	Low	Low	Low	Moderate	Moderate	-	-	Moderate	
1999/Tilley	Low	Moderate	Low	Low	Moderate	-	-	Moderate	
2000/Lee	Low	Moderate	Low	Low	Low	-	-	Moderate	
2007/Deniz-Naranjo	Moderate	Moderate	Low	Moderate	High	-	-	High ¹	
1999/Grubber	Low	Low	Low	Moderate	Moderate	-	-	Moderate	
1999/Ki	Low	Moderate	Low	Low	Moderate	-	-	Moderate	
1998/Singleton	Moderate	Moderate	Moderate	Low	Moderate	-	-	Moderate	
2010/Bizarro	Low	Low	Low	Moderate	Moderate	-	-	Moderate	
2005/Beyer	Moderate	Low	Low	Low	Moderate	-	-	Moderate	
1998/Crawford	Moderate	Low	Low	Moderate	Low	-	-	Low	
2004/Raygani	Low	Moderate	Low	Low	Moderate	-	-	Moderate	
2020/Chuang	High	High	Moderate	Moderate	Moderate	-	-	High ²	
2000/Alvarez-Arcaya	Moderate	Moderate	Moderate	Low	Moderate	-	-	Moderate	
1998/Kehoe	Moderate	Moderate	Low	Low	Moderate	-	-	Moderate	
2000/Mattila	Moderate	Moderate	Low	Low	Low	-	-	Low	
1999/Yamamoto	Moderate	Low	Low	Low	Low	-	-	Moderate	
2016/Vijayaraghavan	Moderate	Low	Low	Low	Moderate	-	-	Low	
1999/Sodeyama	Moderate	Moderate	Low	Moderate	Moderate	-	-	Moderate	
2008/Lane	Moderate	High	Moderate	Moderate	Moderate	-	-	High ³	
1999/Wiebush	Low	Moderate	Low	Moderate	Low	-	-	Moderate	

1999/Panegyres	Moderate	Moderate	Moderate	Low	High	-	-	High4
2013/Johansson	Low	Moderate	Moderate	Moderate	Low	-	-	Moderate
2017/Gabriel	Low	Low	Low	Low	Low	-	-	Low
2007/Piccardi	Moderate	Moderate	Low	Moderate	Low	-	-	Moderate
2019/Jasiecki	Moderate	High	Low	Moderate	Moderate	-	-	High5

¹This study was high because it did not present the mean age of the control group nor clearly that of the group with AD.

²At first, it was thought that data could be extracted from a healthy control group, but it was not possible, increasing the risk of bias.

³Study classified high due to being a longitudinal study, there was an attempt to adapt but even so, if the group that the researchers used as a comparator (MCI) were included, it would compromise the results.

⁴Did not provide age data for sure.

⁵The number of the AD group is almost four times greater than the control group (55x18), this may decrease the quality of the evidence so it was excluded due to high risk of bias.

Supplementary Figure 1. GRADE

Alzheimer compared to Controll for APOE4+ and BCHE-K+ Bibliography:

	Certainty assessment								ndings	
Participants	Diele of					Overall certainty of evidence	Study event rates (%)			
(studies) Follow-up	bias	Inconsistency	Indirectness	Imprecision	Publication bias		With Controll	With Alzheimer	(95% CI)	
General pop	Seneral population									
580 cases 165 controls (21 observational studies)	not serious	not serious	not serious	serious ^a	none	⊕⊕⊕O Moderate	580 cases 165 controls		OR 3.43 (2.61 to 4.52)	
Population y	younger t	han 65 years	i							
26 cases 19 controls (3 observational studies)	not s erious	not serious	not serious	serious ^a	none	⊕⊕⊕O Moderate	26 cases	19 controls	OR 1.32 (0.68 to 2.55)	
Population a	Population aged 65 to 75 years									
138 cases 42 controls	not serious	not serious	not serious	serious ^a	none	Moderate	138 cases	s 42 controls	OR 4.46 (2.64 to 7.54)	

Population older than 75 years

150 cases 32 controls (11 observational studies) not serious not serious	serious ^a	none	⊕⊕⊕O Moderate	150 cases 32 controls	OR 4.15 (2.71 to 6.36)
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Cl: confidence interval; OR: odds ratio

Explanations

(9 observational studies)

a. There was data conversion, possibly not the same as the real data

	Experim	ental	Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1997/Lehmann	27	110	93	172	4.8%	0.28 [0.16, 0.47]	_ -
1998/Crawford	99	391	117	201	5.9%	0.24 [0.17, 0.35]	
1998/Kehoe	56	184	33	71	4.5%	0.50 [0.29, 0.88]	
1998/Singleton	29	119	62	120	4.6%	0.30 [0.17, 0.52]	_ _
1999/Grubber	50	245	108	241	5.7%	0.32 [0.21, 0.47]	
1999/Ki	24	86	64	106	4.2%	0.25 [0.14, 0.47]	
1999/Sodeyama	17	36	60	86	3.2%	0.39 [0.17, 0.86]	
1999/Tilley	52	177	60	118	5.1%	0.40 [0.25, 0.65]	
1999/Wiebush	38	135	37	70	4.3%	0.35 [0.19, 0.64]	_
1999/Yamamoto	142	476	474	684	6.7%	0.19 [0.15, 0.24]	-
2000/Alvarez-Arcaya	97	249	151	250	6.0%	0.42 [0.29, 0.60]	
2000/Lee	36	87	67	101	4.3%	0.36 [0.20, 0.65]	_
2000/Matilla	18	80	37	67	3.7%	0.24 [0.12, 0.48]	-
2000/Mcilroy	35	175	102	187	5.2%	0.21 [0.13, 0.33]	_ -
2004/Raygani	45	105	86	129	4.7%	0.38 [0.22, 0.64]	_ -
2005/Beyer	95	206	123	181	5.6%	0.40 [0.27, 0.61]	
2007/Piccardi	65	158	71	118	5.1%	0.46 [0.28, 0.75]	_ _
2010/Bizarro	81	167	62	126	5.2%	0.97 [0.61, 1.54]	-
2013/johnsson	7	28	5	17	1.6%	0.80 [0.21, 3.08]	
2016/ Vijayaraghavan	21	97	29	80	3.9%	0.49 [0.25, 0.94]	-
2017/ Gabriel	82	217	113	200	5.7%	0.47 [0.32, 0.69]	
Total (95% CI)		3528		3325	100.0%	0.36 [0.29, 0.43]	◆
Total events	1116		1954				
Heterogeneity: Tau ² = 0.	.12; Chi ^z =	61.83. (df = 20 (P	o.00 × ۱	001); P= 6	68%	
Test for overall effect: Z	= 10.69 (P	< 0.000)01)				U.U1 U.1 1 1U 1UU
	`		r				ravouis [control] ravouis [experimental]

Supplementary Figure 2. Forest plot of the comparison between people *APOE4(-)/BCHE-K(-)* with Alzheimer's disease and control in population without age separation.

Supplementary Figure 3. F	orest plot of the comparison	n between people APOE	4(-)/BCHE-K(+) with	Alzheimer's disease	and control
in population without age sep	paration.				

	Experim	ental	Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1997/Lehmann	7	110	25	172	3.8%	0.40 [0.17, 0.96]	
1998/Crawford	42	391	41	201	6.1%	0.47 [0.29, 0.75]	
1998/Kehoe	24	184	18	71	4.8%	0.44 [0.22, 0.88]	-
1998/Singleton	12	119	30	120	4.5%	0.34 [0.16, 0.70]	_
1999/Grubber	31	245	70	241	6.1%	0.35 [0.22, 0.57]	- -
1999/Ki	19	86	27	106	4.8%	0.83 [0.42, 1.62]	
1999/Sodeyama	4	36	13	86	2.6%	0.70 [0.21, 2.32]	
1999/Tilley	29	177	33	118	5.5%	0.50 [0.29, 0.89]	-
1999AViebush	16	135	14	70	4.2%	0.54 [0.25, 1.18]	- _
1999/Yamamoto	40	476	70	684	6.5%	0.80 [0.54, 1.21]	
2000/Alvarez-Arcaya	16	249	50	250	5.3%	0.27 [0.15, 0.50]	_
2000/Lee	20	87	48	101	5.1%	0.33 [0.17, 0.62]	_
2000/Matilla	5	80	13	67	2.9%	0.28 [0.09, 0.82]	
2000/Mcilroy	54	175	45	187	6.1%	1.41 [0.89, 2.24]	+
2004/Raygani	24	105	28	129	5.2%	1.07 [0.58, 1.98]	_
2005/Beyer	21	206	20	181	5.0%	0.91 [0.48, 1.75]	
2007/Piccardi	37	158	35	118	5.6%	0.73 [0.42, 1.24]	
2010/Bizarro	8	167	15	126	3.7%	0.37 [0.15, 0.91]	
2013/johnsson	3	28	9	17	1.8%	0.11 [0.02, 0.49]	
2016/ Vijayaraghavan	14	97	31	80	4.5%	0.27 [0.13, 0.55]	
2017/ Gabriel	30	217	54	200	5.9%	0.43 [0.26, 0.71]	
Total (95% CI)		3528		3325	100.0%	0.51 [0.40, 0.64]	◆
Total events	456		689				
Heterogeneity: Tau ² = 0.	.17; Chi ² =	54.28, (df = 20 (P	× 0.00	01); I² = 63	3%	
Test for overall effect: Z	= 5.69 (P «	• 0.0000)1) È				U.U1 U.1 1 1U 1UU
			-				ravours (control) ravours (experimental)

Supplementary Figure 4. Forest plot of the comparison between people *APOE4(+)/BCHE-K(-)* with Alzheimer's disease and control in population younger than 65 years.

	Experim	ental	Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1999/Grubber	29	76	8	48	20.7%	3.09 [1.27, 7.51]	
1999/Yamamoto	44	108	37	176	58.8%	2.58 [1.52, 4.38]	│
2005/Beyer	12	46	13	67	20.5%	1.47 [0.60, 3.59]	
Total (95% CI)		230		291	100.0%	2.39 [1.59, 3.58]	◆
Total events	85		58				
Heterogeneity: Tau² = Test for overall effect:	: 0.00; Chi² Z = 4.21 (F	° = 1.55, P < 0.00	df = 2 (P 01)	= 0.46)); I² = 0%		0.01 0.1 1 10 100 Favours [control] Favours [experimental]

Supplementary Figure 5. Forest plot of the comparison between people *APOE4(-)/BCHE-K(-)* with Alzheimer's disease and control in population younger than 65 years.



Supplementary Figure 6. Forest plot of the comparison between people *APOE4(-)/BCHE-K(+)* with Alzheimer's disease and control in population younger than 65 years.



Supplementary Figure 7. Forest plot of the comparison between people *APOE4*(+)/*BCHE-K*(-) with Alzheimer's disease and control in population between 65 to 75 years old.

	Experim	ental	Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1997/Lehmann	34	74	30	104	13.9%	2.10 [1.12, 3.91]	- _
1999/Grubber	66	125	22	143	14.8%	6.15 [3.46, 10.92]	
1999/Ki	23	69	10	74	10.5%	3.20 [1.39, 7.36]	—
1999/Wiebush	16	46	8	43	8.7%	2.33 [0.88, 6.21]	+
1999/Yamamoto	171	298	72	400	19.4%	6.13 [4.35, 8.65]	
2000/Mcilroy	24	58	11	79	10.6%	4.36 [1.91, 9.95]	
2004/Raygani	13	61	7	53	8.4%	1.78 [0.65, 4.86]	
2005/Beyer	42	92	10	73	11.2%	5.29 [2.42, 11.58]	
2013/johnsson	14	28	1	17	2.5%	16.00 [1.86, 137.61]	· · · · · · · · · · · · · · · · · · ·
Total (95% CI)		851		986	100.0%	3.98 [2.77, 5.72]	•
Total events	403		171				
Heterogeneity: Tau² =	= 0.15; Chi [≥]	= 17.19	9, df = 8 (F	P = 0.03	3); I² = 53	%	
Test for overall effect:	Z = 7.44 (F	° < 0.00	001)				Favours [control] Favours [experimental]

Supplementary Figure 8. Forest plot of the comparison between people *APOE4(-)/BCHE-K(+)* with Alzheimer's disease and control in population between 65 to 75 years old.

	Experim	ental	Contr	ol		Odds Ratio	Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl		
1997/Lehmann	5	74	15	104	7.5%	0.43 [0.15, 1.24]			
1999/Grubber	14	125	39	143	18.7%	0.34 [0.17, 0.66]	_ -		
1999/Ki	14	69	19	74	13.6%	0.74 [0.34, 1.62]			
1999/Wiebush	5	46	11	43	6.3%	0.35 [0.11, 1.12]			
1999/Yamamoto	21	298	42	400	27.7%	0.65 [0.37, 1.12]			
2000/Mcilroy	9	58	22	79	11.2%	0.48 [0.20, 1.13]			
2004/Raygani	4	61	4	53	4.1%	0.86 [0.20, 3.62]			
2005/Beyer	6	92	10	73	7.4%	0.44 [0.15, 1.27]			
2013/johnsson	3	28	9	17	3.6%	0.11 [0.02, 0.49]			
Total (95% CI)		851		986	100.0%	0.48 [0.36, 0.65]	◆		
Total events	81		171						
Heterogeneity: Tau ² =	0.00; Chi ^a	² = 8.05,	df = 8 (P	= 0.43)); I ² = 1 %		0.01 0.1 1 10 100		
Test for overall effect:	Z = 4.90 (F	- < 0.00	001)				Favours [control] Favours [experimental]		

Supplementary Figure 9. Forest plot of the comparison between people *APOE4(-)/BCHE-K(-)* with Alzheimer's disease and control in population between 65 to 75 years old.

	Experimental Control				Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1997/Lehmann	17	74	57	104	11.4%	0.25 [0.13, 0.48]	_ - -
1999/Grubber	19	125	65	143	13.4%	0.22 [0.12, 0.39]	_
1999/Ki	18	69	42	74	10.5%	0.27 [0.13, 0.55]	_ -
1999/Wiebush	14	46	22	43	7.7%	0.42 [0.18, 0.99]	
1999/Yamamoto	75	298	276	400	23.5%	0.15 [0.11, 0.21]	
2000/Mcilroy	14	58	43	79	9.7%	0.27 [0.13, 0.56]	_
2004/Raygani	29	61	41	53	8.5%	0.27 [0.12, 0.60]	_
2005/Beyer	36	92	51	73	11.7%	0.28 [0.14, 0.53]	_ -
2013/johnsson	7	28	5	17	3.6%	0.80 [0.21, 3.08]	
Total (95% CI)		851		986	100.0%	0.24 [0.19, 0.32]	•
Total events	229		602				
Heterogeneity: Tau ² = Test for overall effect:	0.05; Chi [≇] 7 = 10 23	² = 11.70 (P < 0.0	6, df = 8 (F 0001)	P = 0.1	6); I² = 32'	%	
restrict system should	2 .0.20	v. 0.0	00017				Favours (control) Favours (experimental)

Supplementary Figure 10. Forest plot of the comparison between people *APOE4*(+)/*BCHE-K*(-) with Alzheimer's disease and control in population older 75 years.

	Experim	ental	Contr	ol		Odds Ratio	Odds Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl			
1997/Lehmann	14	36	21	68	10.0%	1.42 [0.61, 3.31]				
1998/Singleton	41	92	7	70	9.8%	7.24 [2.99, 17.49]				
1999/Grubber	15	44	4	50	8.1%	5.95 [1.80, 19.69]				
1999/Ki	4	17	1	32	4.1%	9.54 [0.97, 93.72]				
1999/Sodeyama	12	36	11	86	9.5%	3.41 [1.33, 8.71]				
1999/Tilley	62	177	16	118	11.2%	3.44 [1.87, 6.33]	_			
1999/Wiebush	26	89	8	27	9.4%	0.98 [0.38, 2.52]				
1999/Yamamoto	37	70	11	108	10.3%	9.89 [4.53, 21.58]				
2000/Mcilroy	25	117	23	108	11.0%	1.00 [0.53, 1.90]				
2004/Raygani	3	44	6	64	6.9%	0.71 [0.17, 2.99]				
2005/Beyer	20	68	10	41	9.8%	1.29 [0.53, 3.12]				
Total (95% CI)		790		772	100.0%	2.60 [1.48, 4.54]	◆			
Total events	259		118							
Heterogeneity: Tau ² =	= 0.63; Chi ^a	$^{2} = 40.76$	6, df = 10	(P ≤ 0.)	0001); I ^z =	= 75%				
Test for overall effect	Z= 3.34 (P = 0.00	108)				Favours [control] Favours [experimental]			

	Experim	ental	Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1997/Lehmann	2	36	10	68	6.4%	0.34 [0.07, 1.65]	
1998/Singleton	9	92	20	70	10.1%	0.27 [0.11, 0.64]	- _
1999/Grubber	8	44	18	50	9.5%	0.40 [0.15, 1.03]	
1999/Ki	5	17	8	32	7.6%	1.25 [0.34, 4.65]	
1999/Sodeyama	4	36	13	86	8.2%	0.70 [0.21, 2.32]	
1999/Tilley	29	177	33	118	11.7%	0.50 [0.29, 0.89]	
1999/Wiebush	11	89	3	27	7.4%	1.13 [0.29, 4.38]	
1999/Yamamoto	8	70	9	108	9.3%	1.42 [0.52, 3.87]	-
2000/Mcilroy	45	117	23	108	11.6%	2.31 [1.28, 4.18]	
2004/Raygani	20	44	12	64	10.1%	3.61 [1.52, 8.57]	
2005/Beyer	10	68	4	41	8.1%	1.59 [0.47, 5.46]	
Total (95% CI)		790		772	100.0%	0.93 [0.53, 1.62]	•
Total events	151		153				
Heterogeneity: Tau ² =	: 0.61; Chi ^z	= 37.37	7, df = 10	(P < 0.0	0001); I ? =	= 73%	
Test for overall effect:	Z=0.27 (F	P = 0.79)				Favours [control] Favours [experimental]

Supplementary Figure 11. Forest plot of the comparison between people *APOE4(-)/BCHE-K(+)* with Alzheimer's disease and control in population older 75 years.

Supplementary Figure 12. Forest plot of the comparison between people *APOE4(-)/BCHE-K(-)* with Alzheimer's disease and control in population older 75 years.

	Experim	ental	Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1997/Lehmann	10	36	36	68	7.8%	0.34 [0.14, 0.82]	
1998/Singleton	21	92	35	70	10.5%	0.30 [0.15, 0.58]	
1999/Grubber	11	44	25	50	7.7%	0.33 [0.14, 0.80]	
1999/Ki	6	17	22	32	4.6%	0.25 [0.07, 0.86]	
1999/Sodeyama	17	36	60	86	8.7%	0.39 [0.17, 0.86]	_
1999/Tilley	52	177	60	118	14.2%	0.40 [0.25, 0.65]	_ - _
1999/Wiebush	24	89	15	27	7.5%	0.30 [0.12, 0.72]	
1999/Yamamoto	20	70	87	108	10.0%	0.10 [0.05, 0.20]	_
2000/Mcilroy	21	117	59	108	11.8%	0.18 [0.10, 0.33]	_ - _
2004/Raygani	16	44	45	64	8.4%	0.24 [0.11, 0.55]	
2005/Beyer	32	68	25	41	8.8%	0.57 [0.26, 1.25]	
Total (95% CI)		790		772	100.0%	0.28 [0.21, 0.38]	◆
Total events	230		469				
Heterogeneity: Tau ² =	0.10; Chi ^z	= 17.18	3, df = 10	(P = 0.)	07); I² = 4	2%	
Test for overall effect:	Z = 8.30 (F	P < 0.00	001)				Favours [control] Favours [experimental]

Supplementary Figure 13. Funnel plot of the comparison between people *APOE4*(-)/*BCHE-K*(+) with Alzheimer's disease and control in population without age separation.



APOE4(-), non-carrier of allele E4 of apolipoprotein E; BCHE-K (+), carrier of variant K of butyrylcholinesterase.

Supplementary Figure 14. Funnel plot of the comparison between people *APOE4(-)/BCHE-K(-)* with Alzheimer's disease and control in population without age separation.



APOE4(-), non-carrier of allele E4 of apolipoprotein E; BCHE-K (-), non-carrier of variant K of butyrylcholinesterase.

Supplementary Figure 15. Funnel plot of the comparison between people *APOE4*(+)/*BCHE-K*(+) with Alzheimer's disease and control in population without age separation.



APOE4(+), carrier of allele E4 of apolipoprotein E; BCHE-K (+), carrier of variant K of butyrylcholinesterase.

Supplementary Figure 16. Funnel plot of the comparison between people APOE4(+)/BCHE-K(-) with Alzheimer's disease and control in population without age separation.



APOE4(+), carrier of allele E4 of apolipoprotein E; BCHE-K (-): non-carrier of variant K of butyrylcholinesterase