Supplementary Material

Confirmed Synergy Between the ε4 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 (apoprotein AND e) OR (apolipoproteins 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 (apo AND e AND isoproteins) OR TITLE-ABS-KEY (isoproteins, AND apo 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 (dementia, AND alzheimer) OR TITLE-ABS-KEY (alzheimer's AND disease) OR TITLE-ABS-KEY (dementia, AND senile) OR TITLE-ABS-KEY (senile AND dementia) OR TITLE-ABS-KEY (dementia, AND alzheimer AND type) OR TITLE-

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=(apo e isoproteins) OR ALL=(isoproteins, apo e) OR ALL=(apoproteins e) OR ALL=(apoprotein e) OR ALL=(apolipoprotein e) OR ALL=(apolipoproteins))

Supplementary Table 1. Exclusion List

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.

	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 without 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

Study	Pre-intervention		During the intervention	Post-intervention				General risk of bias
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

[1]This study was high because it did not present the mean age of the control group nor clearly that of the group with AD.
[2]At first, it was thought that data could be extracted from a healthy control group, but it was not possible, increasing the risk of bias.
[3]Study 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.
[4]Did not provide age data for sure.
[5]The 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							Summary of findings		
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)
							With Controll	With Alzheimer	
General population									
580 cases 165 controls (21 observational studies)	not serious	not serious	not serious	serious[a]	none	⨁⨁⨁◯ Moderate	580 cases 165 controls		**OR 3.43** (2.61 to 4.52)
Population younger than 65 years									
26 cases 19 controls (3 observational studies)	not serious	not serious	not serious	serious[a]	none	⨁⨁⨁◯ Moderate	26 cases 19 controls		**OR 1.32** (0.68 to 2.55)
Population aged 65 to 75 years									
138 cases 42 controls (9 observational studies)	not serious	not serious	not serious	serious[a]	none	⨁⨁⨁◯ Moderate	138 cases 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	not serious	serious[a]	none	⨁⨁⨁◯ Moderate	150 cases 32 controls		**OR 4.15** (2.71 to 6.36)

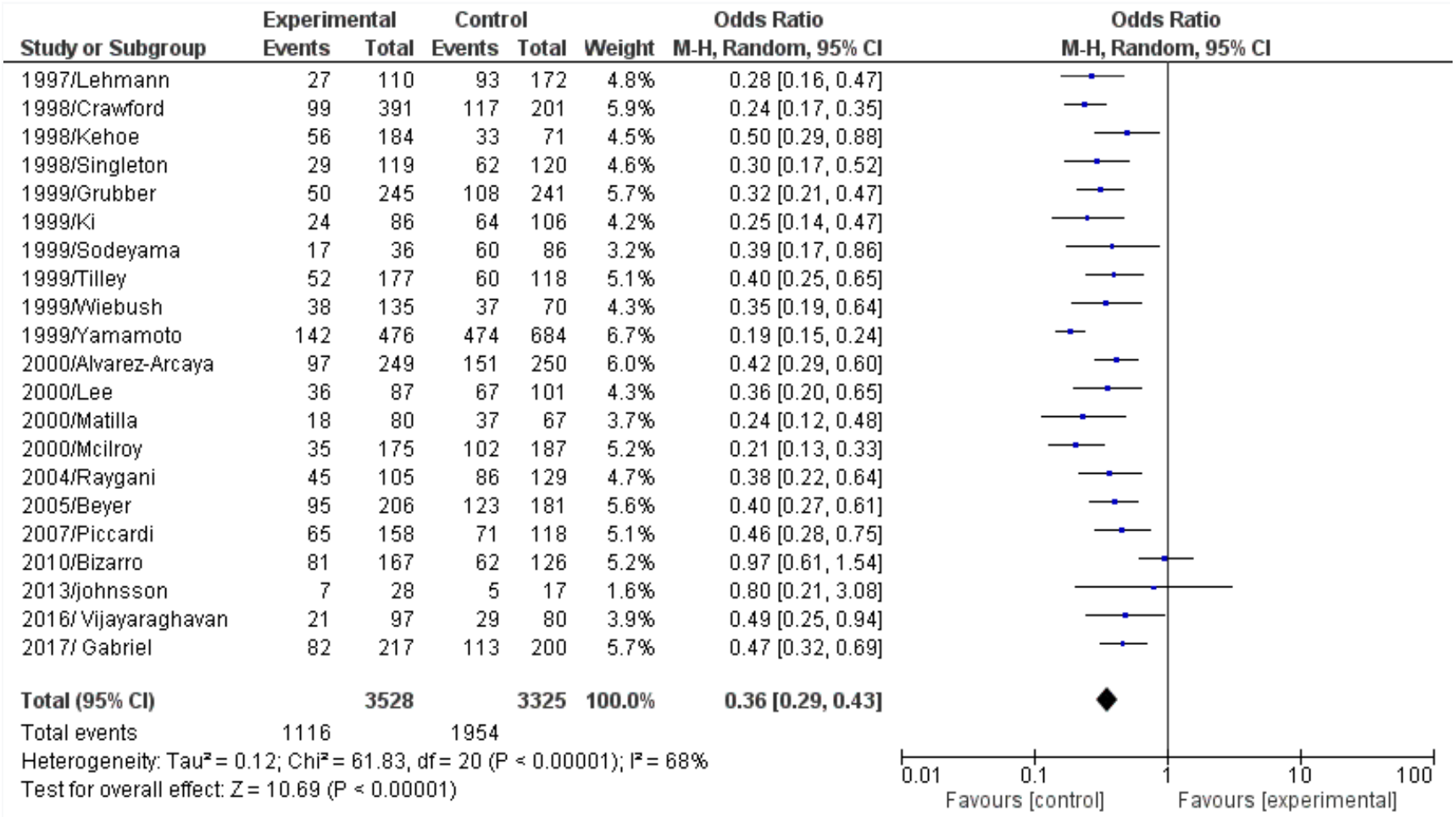
CI: confidence interval; **OR:** odds ratio

Explanations

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

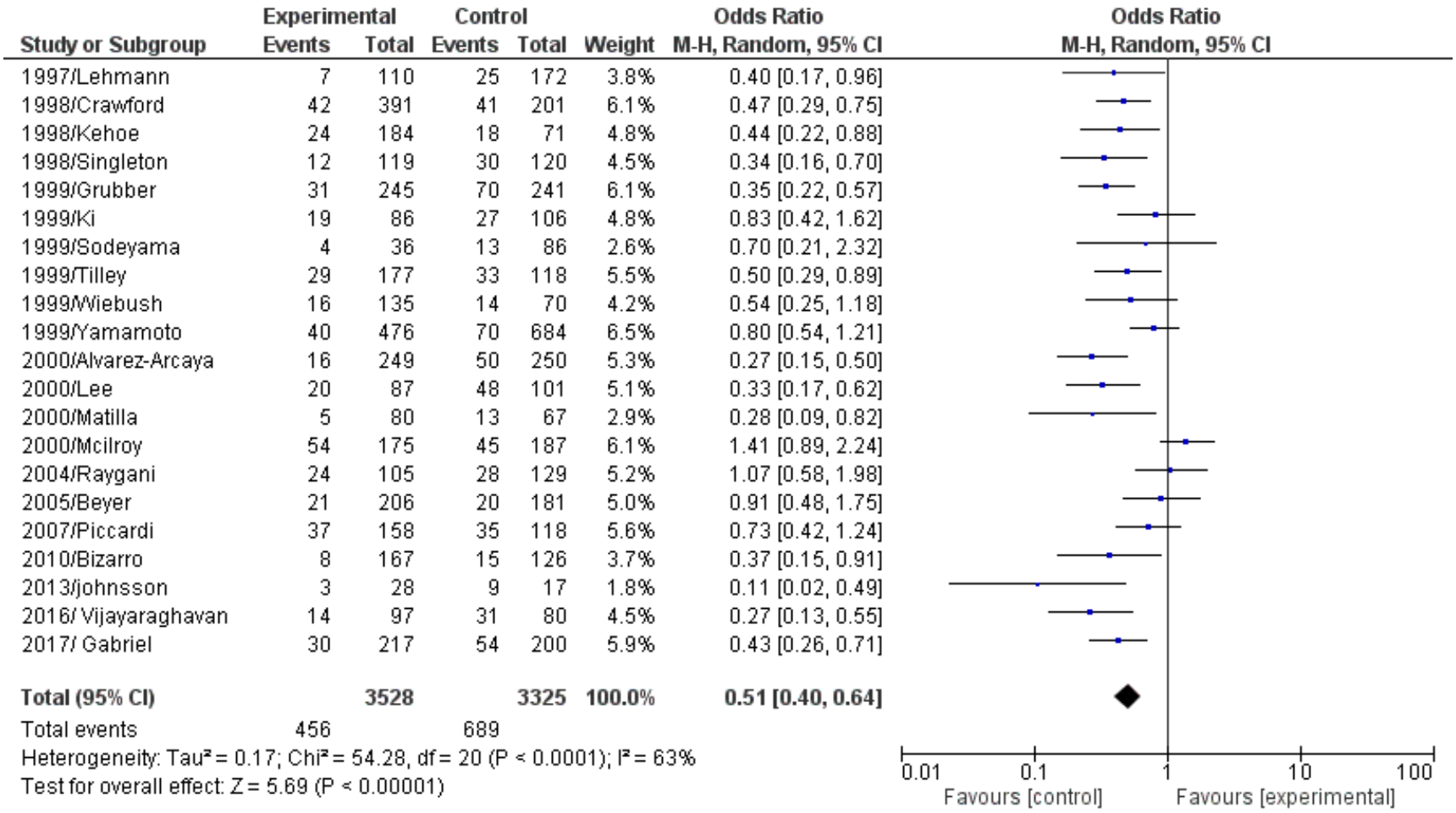
Ativar

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



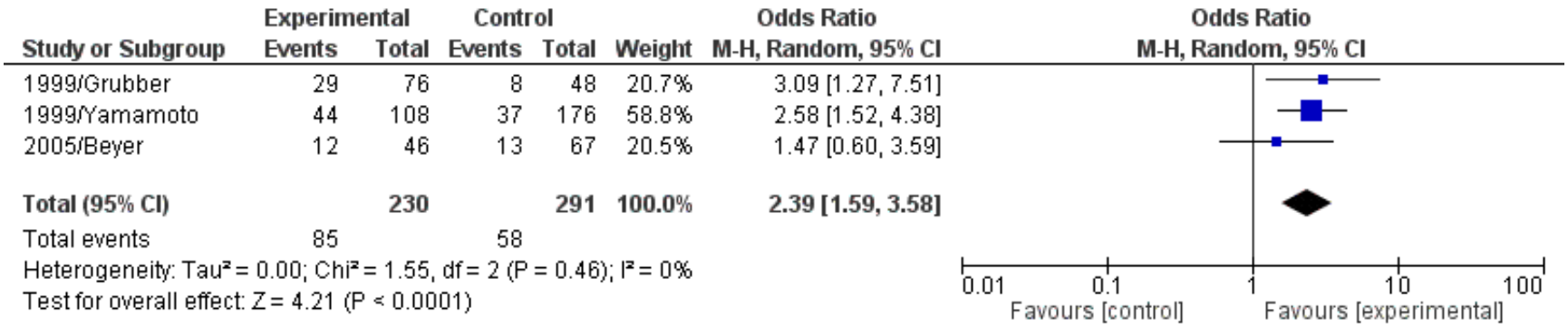
APOE4(-), non-carrier of allele E4 of apolipoprotein E; *BCHE-K* (-), non-carrier of variant K of butyrylcholinesterase.

Supplementary Figure 3. Forest plot of the comparison between people *APOE4*(-)/*BCHE-K*(+) with Alzheimer's disease and control in population without age separation.



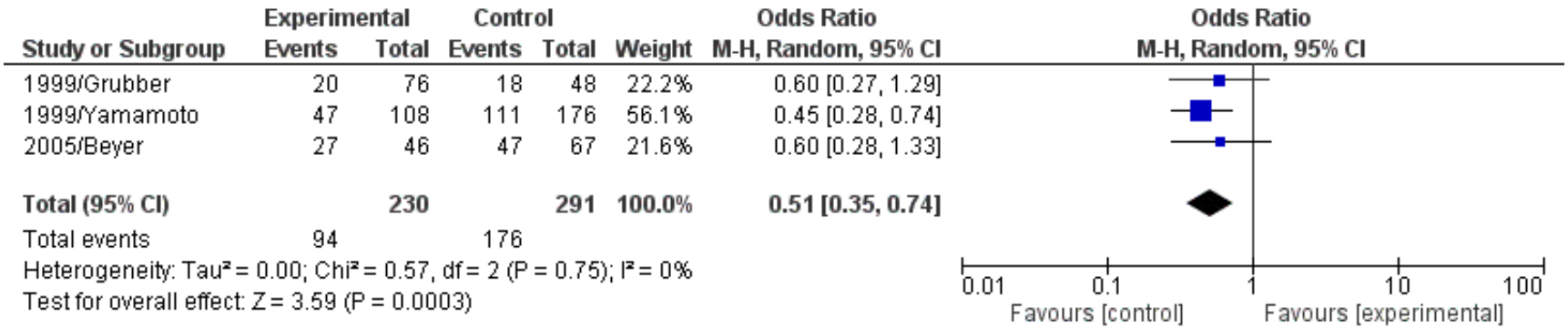
APOE4(-), non-carrier of allele E4 of apolipoprotein E; *BCHE-K* (+), carrier of variant K of butyrylcholinesterase.

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



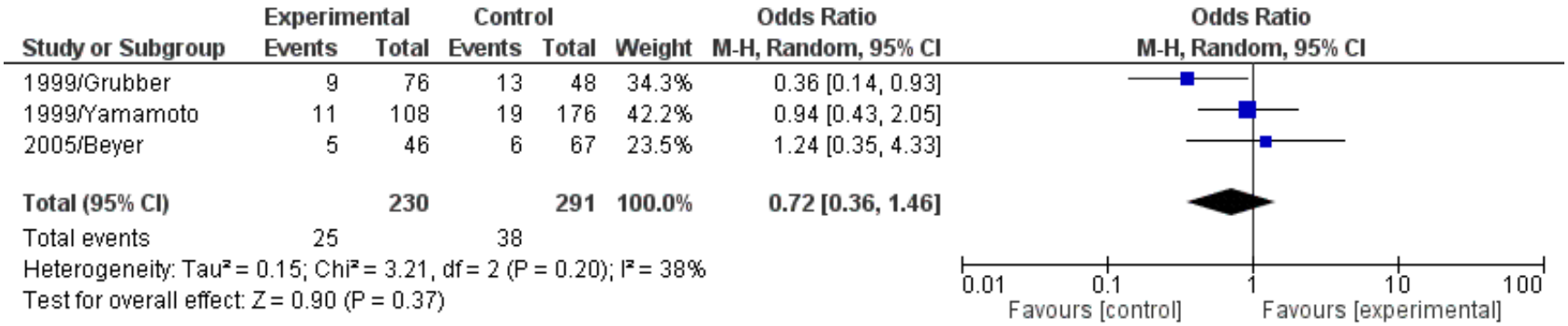
APOE4(+), carrier of allele E4 of apolipoprotein E; *BCHE-K* (-), non-carrier of variant K of butyrylcholinesterase.

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.



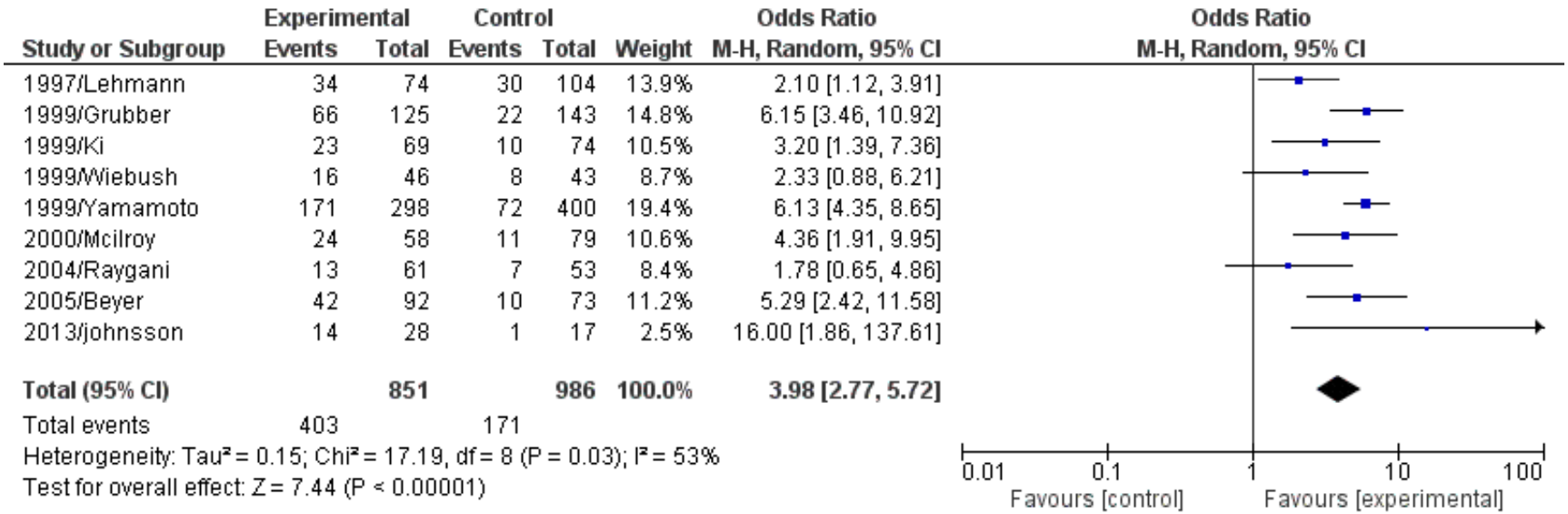
APOE4(+), carrier of allele E4 of apolipoprotein E; *BCHE-K* (-), non-carrier of variant K of butyrylcholinesterase.

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.



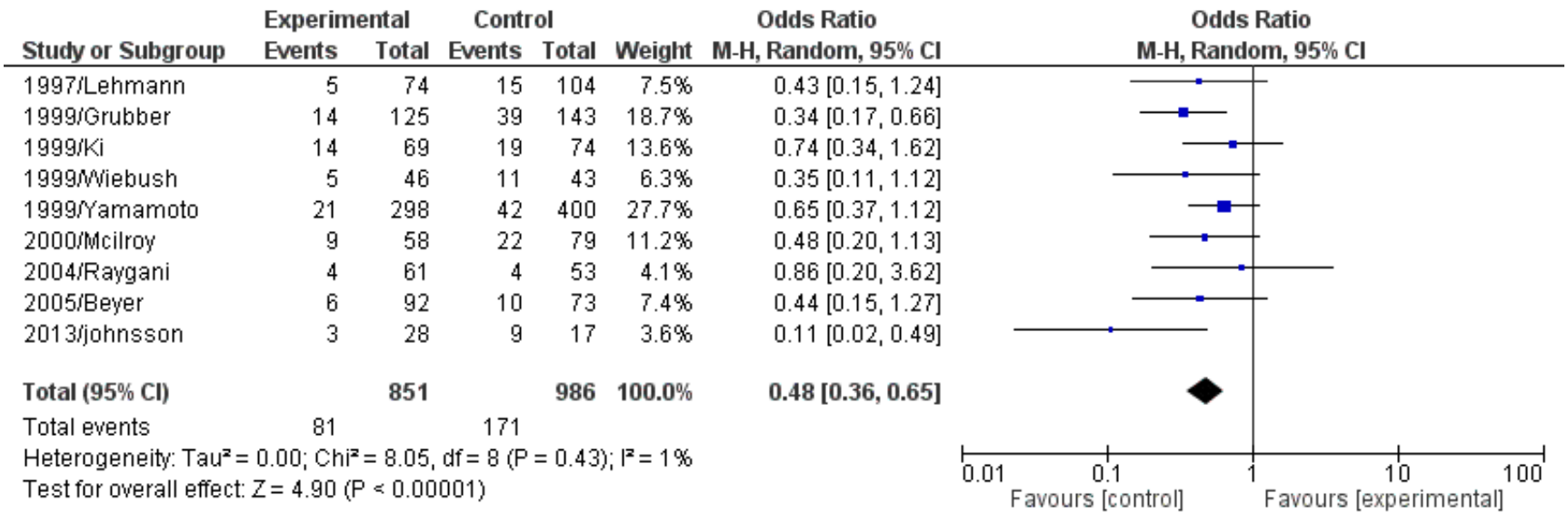
APOE4(-), non-carrier of allele E4 of apolipoprotein E; *BCHE-K* (+), carrier of variant K of butyrylcholinesterase.

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.



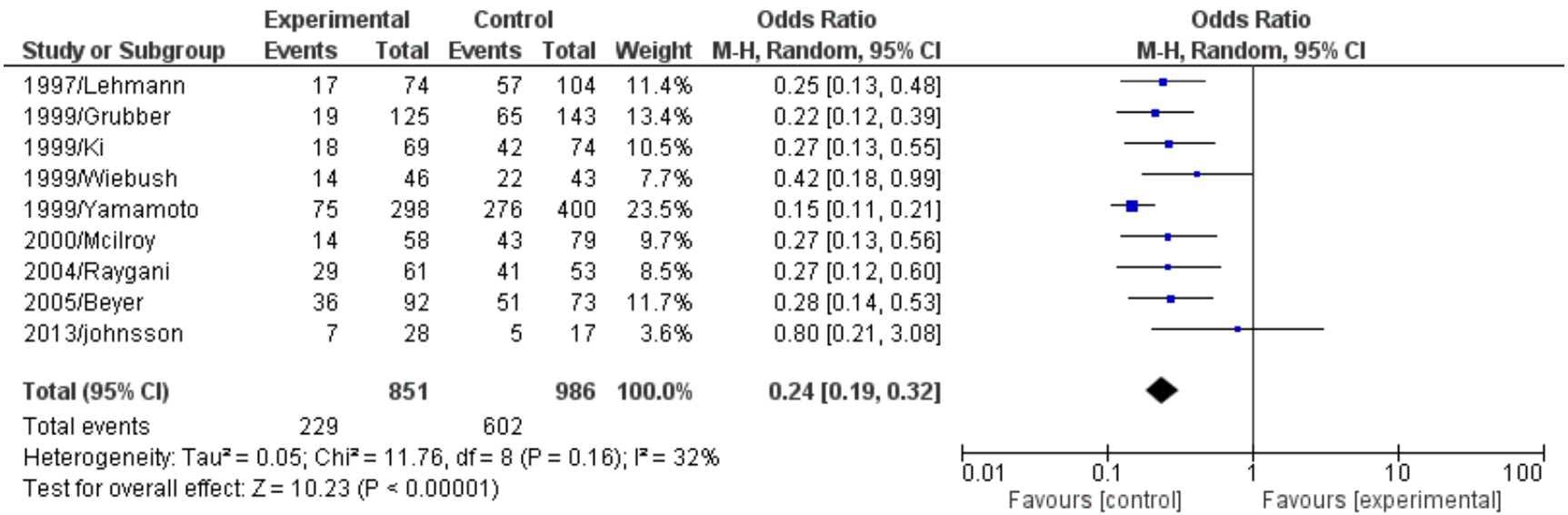
APOE4(+), carrier of allele E4 of apolipoprotein E; *BCHE-K* (-), non-carrier of variant K of butyrylcholinesterase.

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.



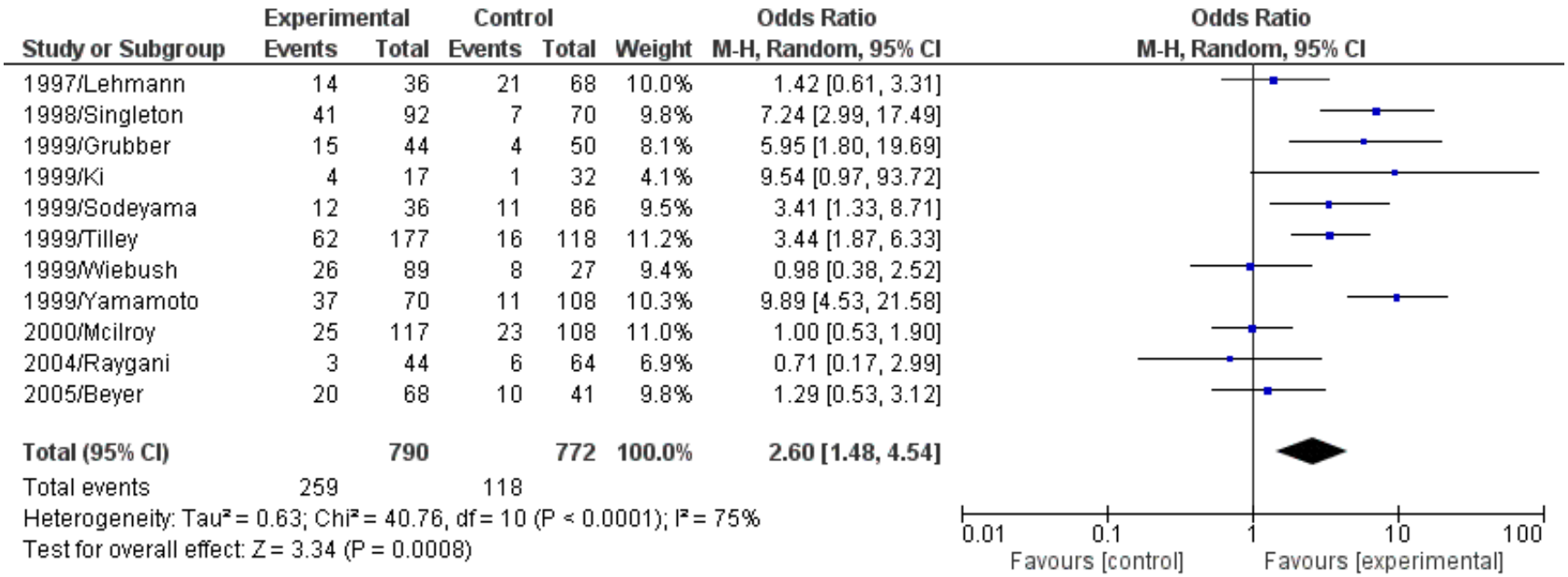
APOE4(-), non-carrier of allele E4 of apolipoprotein E; *BCHE-K* (+), carrier of variant K of butyrylcholinesterase.

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.



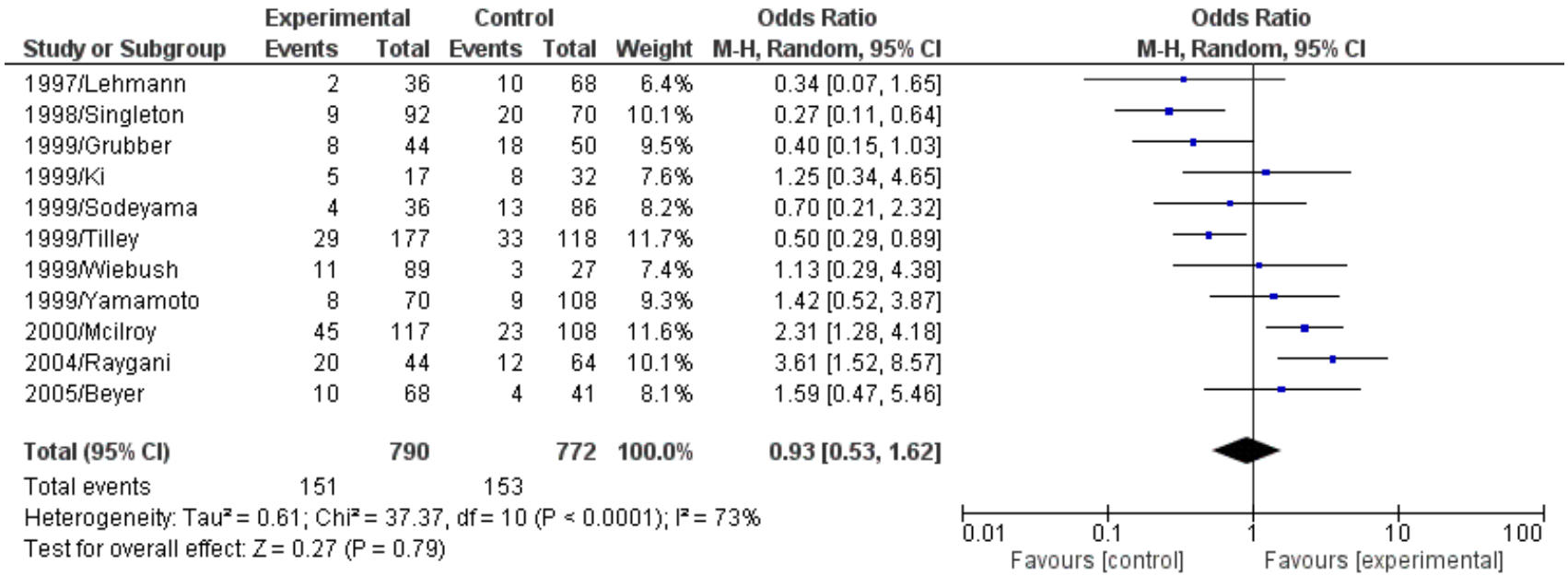
APOE4(-), non-carrier of allele E4 of apolipoprotein E; *BCHE-K* (-), non-carrier of variant K of butyrylcholinesterase.

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



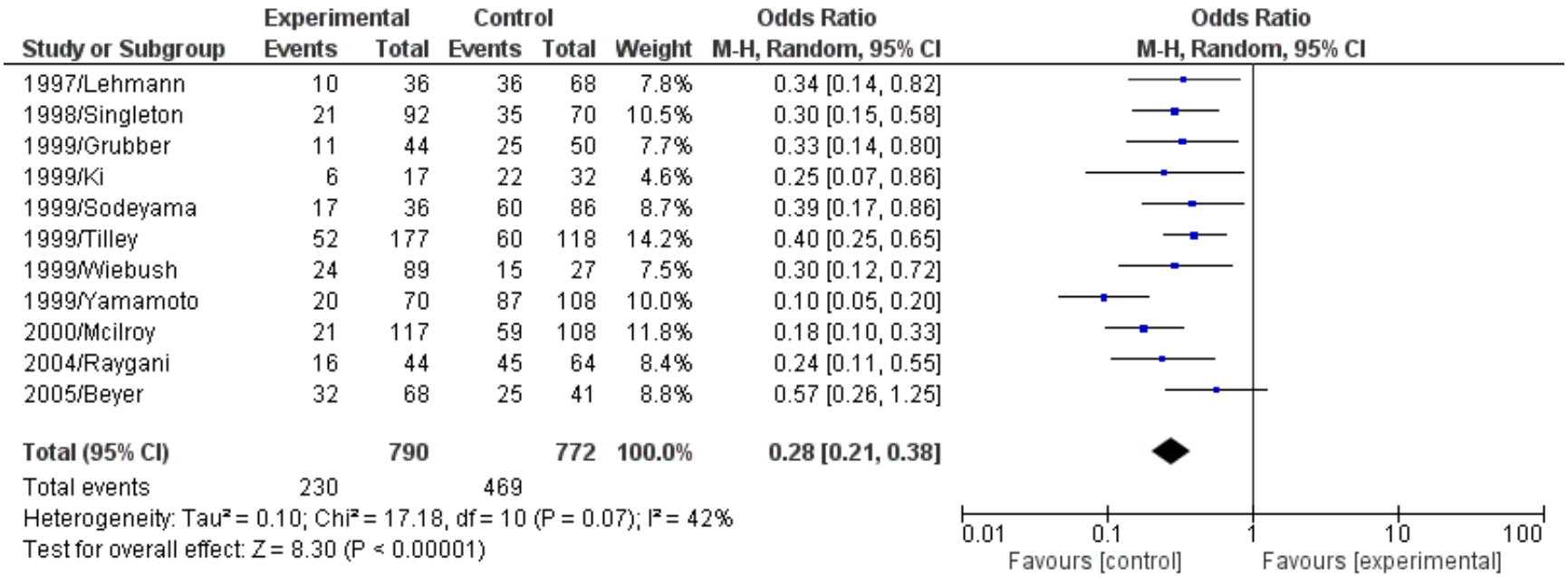
APOE4(+), carrier of allele E4 of apolipoprotein E; *BCHE-K* (-), non-carrier of variant K of butyrylcholinesterase.

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



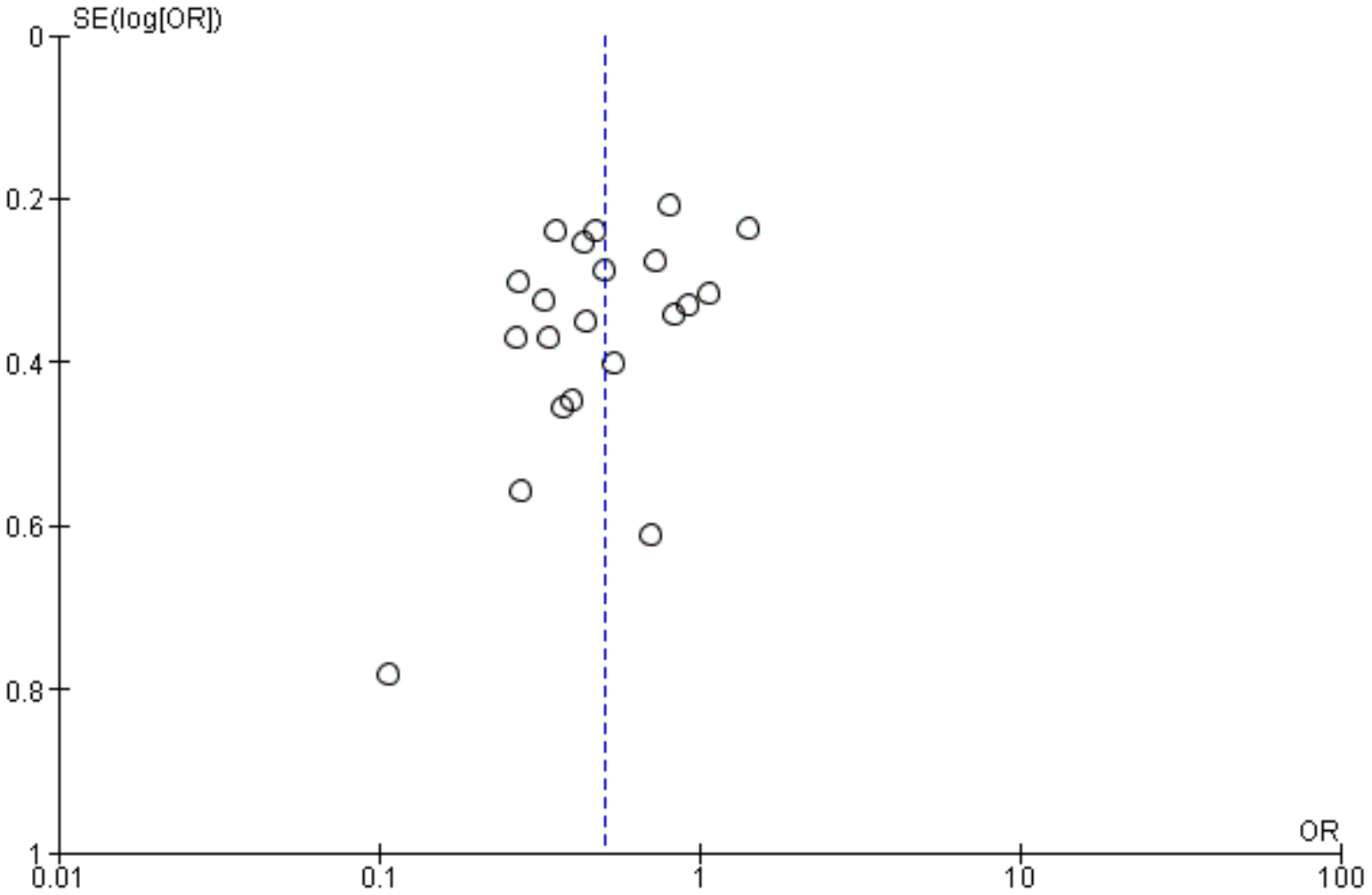
APOE4(-), non-carrier of allele E4 of apolipoprotein E; *BCHE-K* (+), carrier of variant K of butyrylcholinesterase.

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



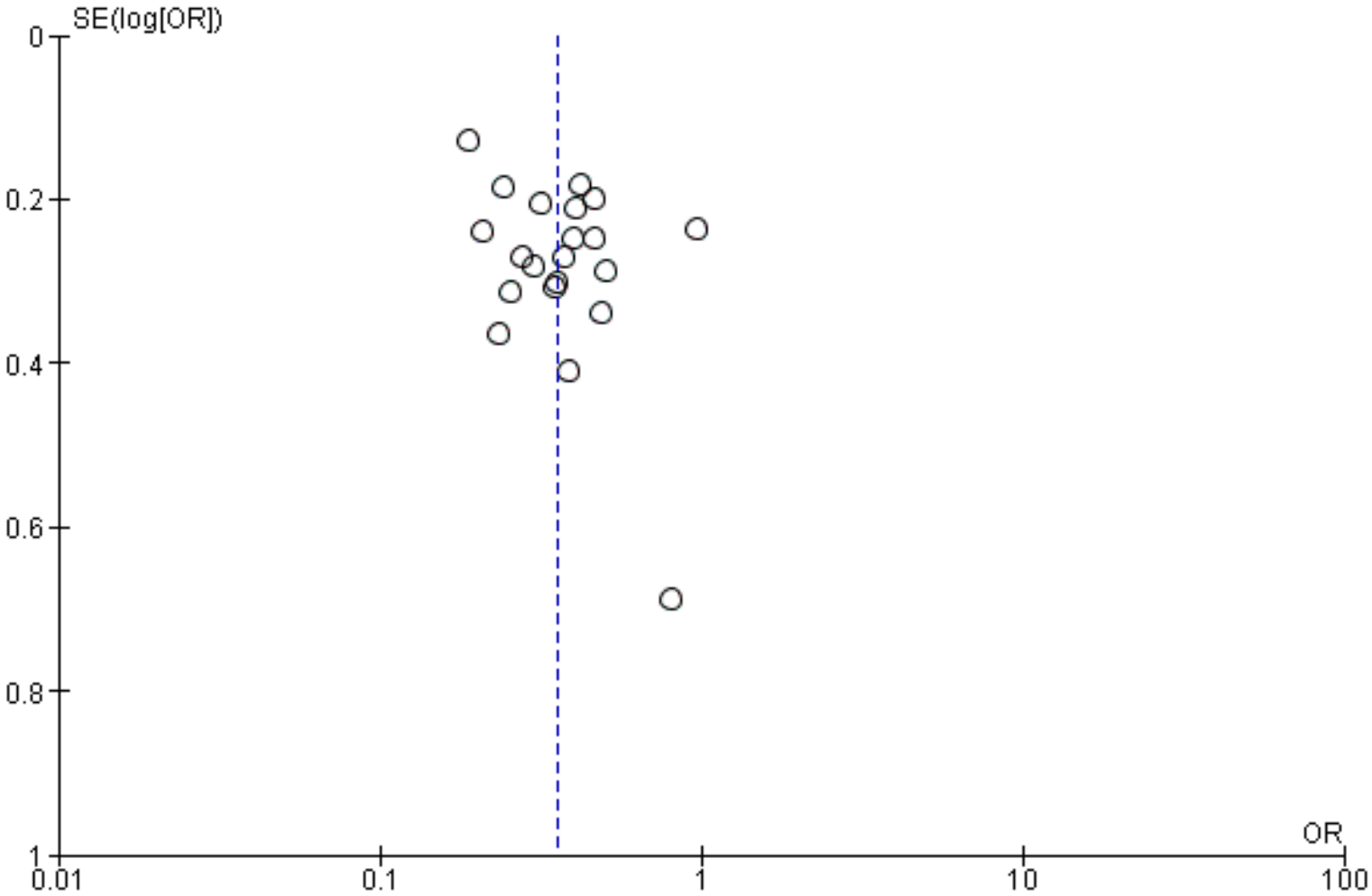
APOE4(-), non-carrier of allele E4 of apolipoprotein E; *BCHE-K* (-), non-carrier of variant K of butyrylcholinesterase.

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



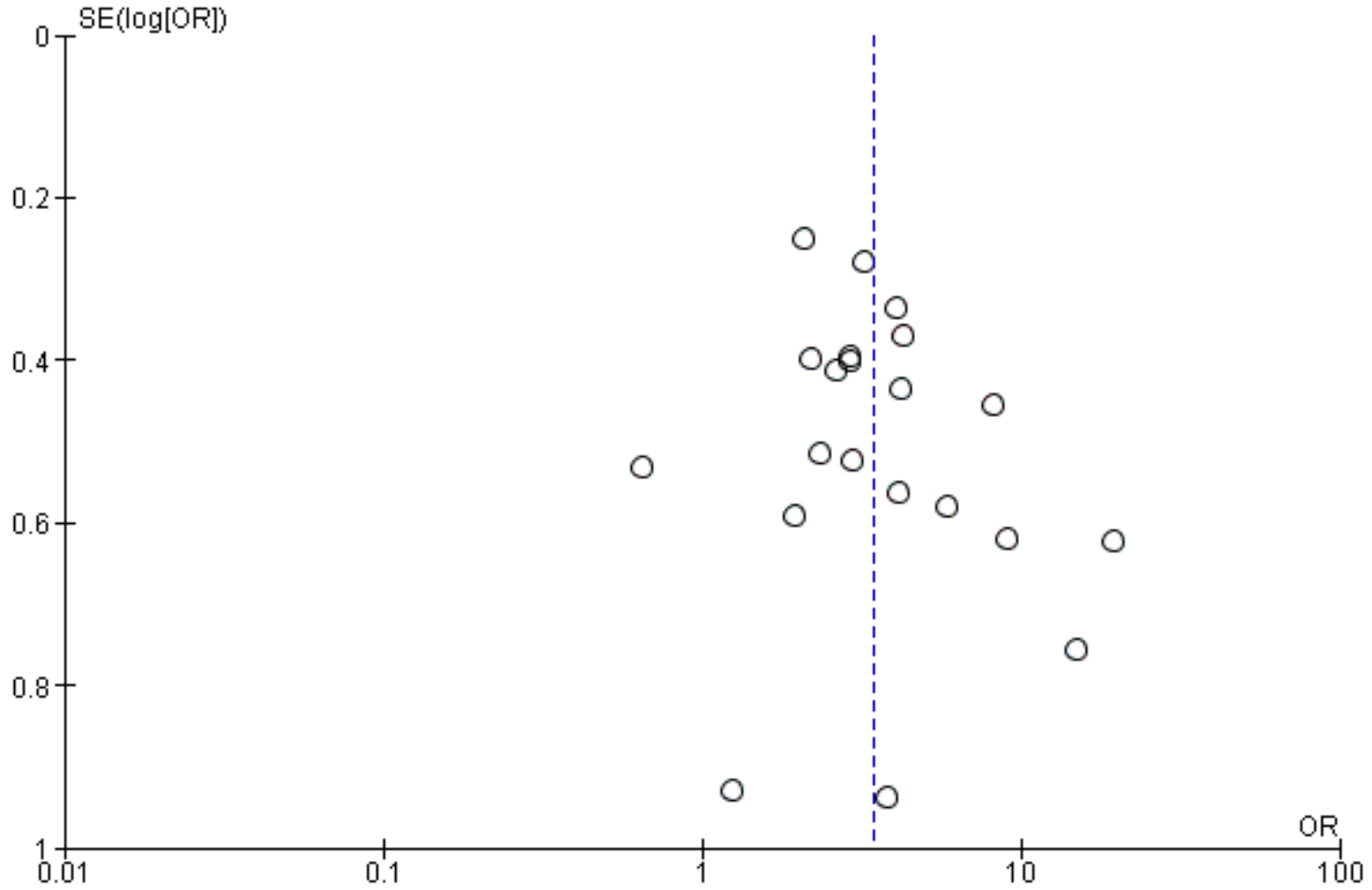
APOE4(-), non-carrier of allele E4 of apolipoprotein E; *BCHE-K* (+), carrier of variant K of butyrylcholinesterase.

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



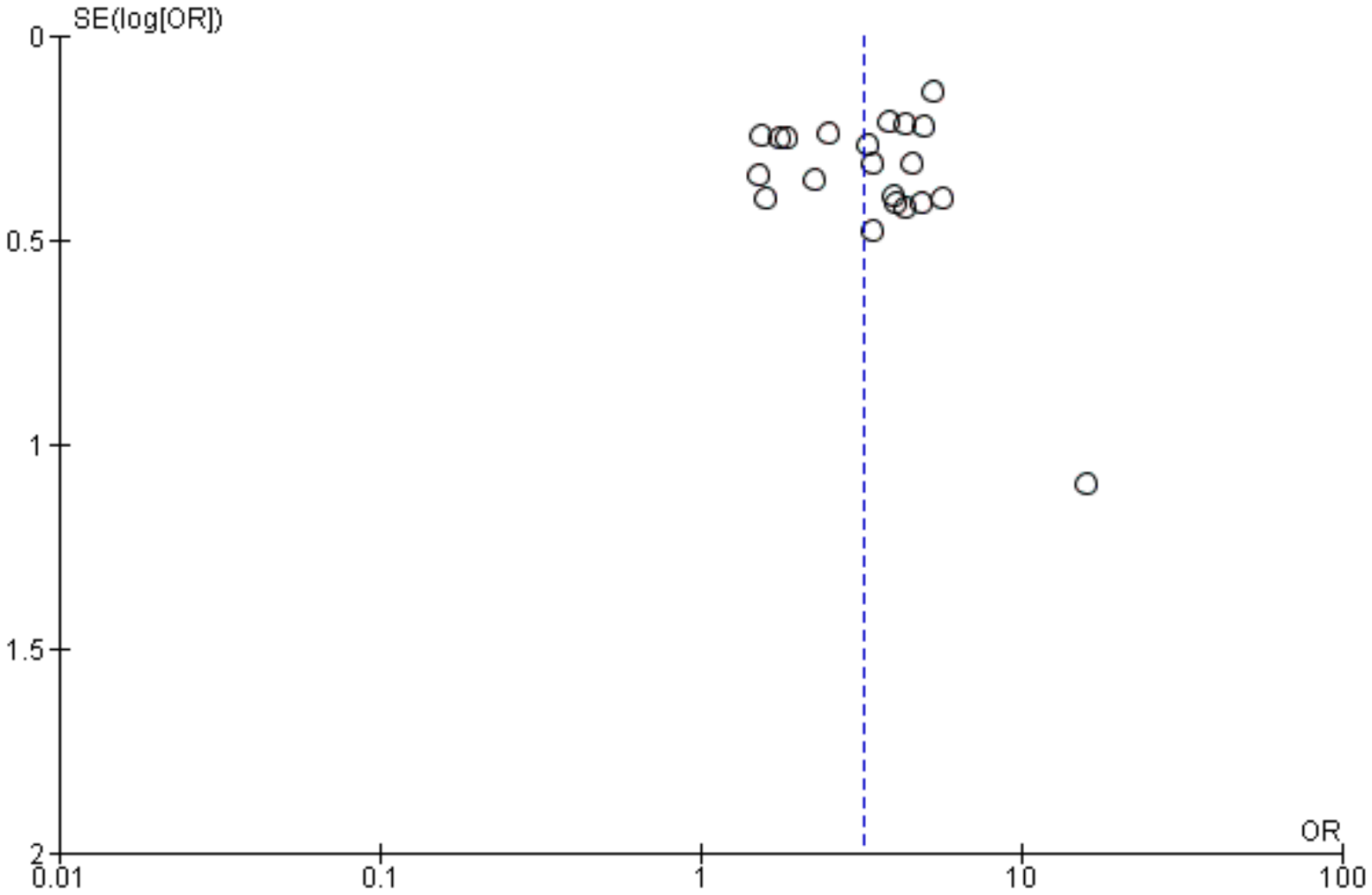
APOE4(-), non-carrier of allele E4 of apolipoprotein E; *BCHE-K* (-), non-carrier of variant K of butyrylcholinesterase.

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