Association between alzheimer's disease and apoe gene genotypic polymorphisms: systematic review and meta-analysis

Associação entre doença de alzheimer e polimorfismos genotipicos do gene apoe: revisão sistemática e metanálise

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ABSTRACT
Introduction- Alzheimer's disease (AD) is classified as neurodegenerative, progressive and irreversible and is clinically characterized by a progressive decline in neurological functions. Objective- To evaluate the association among the genotypic variations of the APOE gene with Alzheimer's Disease. Methods- This is a systematic review and meta-analysis, and, according to the inclusion criteria, 59 articles were selected from the PubMed, Latin American and Caribbean Literature in Health Sciences (LILACS) and Scientific databases Electronic Library Online (SciELO) and of this total, 22 contributed data for systematic review and meta-analysis. Statistical tests were performed with the aid of the STATA® 16.0 software, considering the significance limit equal to 5% (p-value = 0.05). Thus, the DerSimonian-Laird and Mantel Haenszel tests were applied according to heterogeneity, for the evaluation of Odds Ratios (OR). Results- The results showed an association of predisposition to the development of AD, considering the genotypes Ɛ3Ɛ4 and Ɛ4Ɛ4, respectively OR = 2.63 (95% CI = 2.18-318) and OR = 5.37 (95% CI = 3.57- 8.08), on the other hand, the genotypes Ɛ2Ɛ3 and Ɛ3Ɛ3, showed

association as a protective factor against AD, respectively OR = 0.49 (95% CI = 0.42-0.57) and OR = 0.53 (95% CI = 0.42-0.68). Conclusion- The present meta-analysis showed a strong association of risk to AD when the genotype Ɛ4Ɛ4 and genotype Ɛ3Ɛ4 were evaluated, on the other hand, there was an association of protection to AD for Ɛ2Ɛ3 and Ɛ3Ɛ3. The other genotypes showed no association.

Keywords: Alzheimer's Disease, Polymorphism, Apoe Gene, Genotype.

RESUMO

Introdução- A doença de Alzheimer (DA) é classificada como neurodegenerativa, progressiva e irreversível e caracterizada clinicamente por declínio progressivo das funções neurológicas. Objetivo- Avaliar a associação entre as variações genotípicas do gene APOE com a Doença de Alzheimer. Métodos- Trata-se de uma revisão sistemática e meta-análise, e, de acordo com os critérios de inclusão, foram selecionados 59 artigos nas bases de dados PubMed, Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS) e Scientific Eletronic Library Online (SciELO) e deste total, 22 contribuíram com dados para revisão sistemática e meta-análise. Os testes estatísticos foram realizados com auxílio do software STATA® 16.0, considerado o limite de significância igual a 5% (p-valor=0,05). Desta forma foram aplicados os testes DerSimonian-Laird e Mantel Haenszel de acordo com a heterogeneidade, para avaliação das Odds Ratios (OR). Resultados- Os resultados apontaram associação de predisposição ao desenvolvimento de DA, considerando os genótipos Ɛ3Ɛ4 e Ɛ4Ɛ4, respectivamente OR= 2,63 (IC95%= 2,18-318) e OR= 5,37 (IC95%= 3,57-8,08), por outro lado, os genótipos Ɛ2Ɛ3 e Ɛ3Ɛ3, apresentaram associação como fator protetivo à DA, respectivamente OR= 0,49 (IC95%= 0,42-0,57) e OR= 0,53 (IC95%= 0,42-0,68). Conclusão- A presente meta-análise apontou forte associação de risco a DA quando avaliado o genótipo Ɛ4Ɛ4 e o genótipo Ɛ3Ɛ4, por outro lado houve associação de proteção a DA para Ɛ2Ɛ3 e Ɛ3Ɛ3. Os demais genótipos não apontaram associação.

Palavras-Chave: Doença de Alzheimer, Polimorfismo, Gene Apoe, Genótipo.

1 INTRODUCTION

Alzheimer's disease (AD) was first described and diagnosed by Alois Alzheimer, in 1907[1]. It is classified as a neurodegenerative, progressive and irreversible disease, clinically characterized by a progressive decline in neurological functions, such as memory loss, dementia, and loss of motor control, communication difficulties and emotional instability[2]. In its development there is formation of extracellular amyloid plaques, resulting from accumulations of beta-amyloid-42 proteins (βA-42) and neurofibrillary tangles, formed by agglomeration of Tau-phosphorylated protein (p-Tau), resulting in intracellular instability, culminating in important neuronal losses, oxidative stress, synaptic decrease and inflammation[3]. Patients with AD assessed post-mortem, also present with atrophied brain anatomy in the temporal, frontal and parietal regions, due to neuronal losses[4].

The causes of AD are considered diverse, having intrinsic and extrinsic influences, triggered by genetic and environmental factors, as well as lifestyle[5]. The World Health Organization (WHO) predicts that by 2050, there will be more than 150 million people with dementia worldwide, with AD being responsible for approximately 80% of cases. In the last ranking published in 2016 by the WHO, AD and other dementias were responsible for around two million deaths, ranking fifth in the ranking of the 10 main global causes of death[6].

After the dementia, condition due to AD is installed; all available treatments are only for palliative purposes, aiming only to offer better quality and longer survival time to patients. The late diagnosis brings several aggravating factors for the carrier of the disease; therefore, the early diagnosis is highly desired. Once diagnosed early, patients will have a greater chance of delaying symptoms due to the rapid onset of treatment[7].

Several published studies aimed to identify risk factors that could contribute to the development of AD, and among the related factors, there is apolipoprotein E (ApoE), a plasma lipoprotein with 299 amino acids and a molecular mass equal to 34 kDa[8]. Apolipoprotein E is one of the most important plasma proteins, acting as a cholesterol transporter between cells and tissues. It is expressed in several tissues, the main sources being the liver and brain organs. In the nervous system it is produced mainly in astrocytes, microglia and neurons, it functions as a lipid transporter, providing nutrients for cell proliferation and regeneration, in addition to acting in the remyelination of damaged neuronal membranes[3].

The gene responsible for the synthesis of apolipoprotein E, is also called APOE, it is a polymorphic gene located on chromosome 19 (19q13.2) it has 3 allelic variants being epsilon 2 (Ɛ2), epsilon 3 (Ɛ3) and epsilon 4 (Ɛ4), which encode the ApoE2, ApoE3 and ApoE4 isoforms, differ from each other due to the Cysteine and Arginine content in the positions of codons 112 and 158 located in exon 4, which form the synthesized apolipoproteins[9]. From the allelic variants, six different genotypes originate, being Ɛ2Ɛ2, Ɛ2Ɛ3, Ɛ2Ɛ4, Ɛ3Ɛ3, Ɛ3Ɛ4 and Ɛ4Ɛ4. The ApoEƐ3 variant form has 112 Cysteine and 158 Arginine residues, ApoEƐ4 has only Arginine residues in both positions, and ApoEƐ2 has only Cysteinein both residues[10]. Several studies that evaluated the allelic profile of the population show that the Ɛ3 allele is the most frequent comprising about 70 to 80% of the population, while the Ɛ4 and Ɛ2 alleles correspond to about 10 to 15% and 5 to 10% of the population, respectively[11–14].

Research shows that these polymorphic expressions may be involved in an AD triggering process. However, there are no sure statements about which genotypes are most likely to develop their carrier[15–17]. The objective of the present research was to evaluate the association between the genotypic variations of the APOE gene and the predisposition to Alzheimer's Disease.

2 METHODOLOGY

2.1 LITERATURE SEARCH

This research consisted of a systematic review and meta-analysis. Articles published between 2016 and 2019 were considered for the descriptive aspect. For systematic review and meta-analysis, all research was considered in accordance with the pre-established criteria, restricted to studies published in English and Portuguese. Searches for articles were carried out in the PubMed database on the website of the National Center for Biotechnology Information (NCBI), in the database of the Scientific Electronic Library Online (SciELO) and in the databases of the Virtual Health Library (VHL), considering Latin American and Caribbean Literature in Health Sciences (LILACS). The retrieval strategy for the articles consisted of searching for the following Medical Subject Heading (MeSH) terms: “Alzheimer Disease”, “apolipoprotein e” and “polimorphysm APOE gene” and the terms in the Health Sciences Descriptors “Alzheimer's Disease”, “Apolipoprotein E” and “APOE gene polymorphism”. In LILACS, 51 references were found, in SciELO 6 and PubMed 2453. Replications and publications that were not related to the topic were excluded, resulting in 37 references used in the descriptive aspect and 22 references considered for meta-analysis (Figure 1)

The data collected were country in which the research was published, first author, year, diagnostic criterion, molecular method used in genotyping, age of participants, total number of cases and controls and genotypic frequency of APOE gene polymorphisms. All data collection, as well as systematic review and meta-analysis, were carried out according to the instructions and recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA)[18].

2.2 DATA EXTRACTION

Two reviewers carried out the evaluation of the articles and there were no disagreements regarding the interpretations. The data tabulated in the qualitative analysis were characterized as dichotomous. In this way, data were collected regarding

comparisons between individuals in the case group (individuals with AD) and the control group (healthy individuals), then considering two possibilities: presence or absence of the polymorphic variants of the APOE gene, through their respective genotypes.

Throughout the data collection, exclusion criteria were considered works published in conference proceedings, monographs, master's dissertations and doctoral theses and research with superficial, outdated or incomplete information on the subject. The selected articles, underwent an initial evaluation by reading the abstract, subsequent to this, all were read in full. Thus, 22 articles were included in the systematic review and meta-analysis, according to the eligibility criteria, as represented in Figure 1.

2.3 ANALYZE OF THE DATA

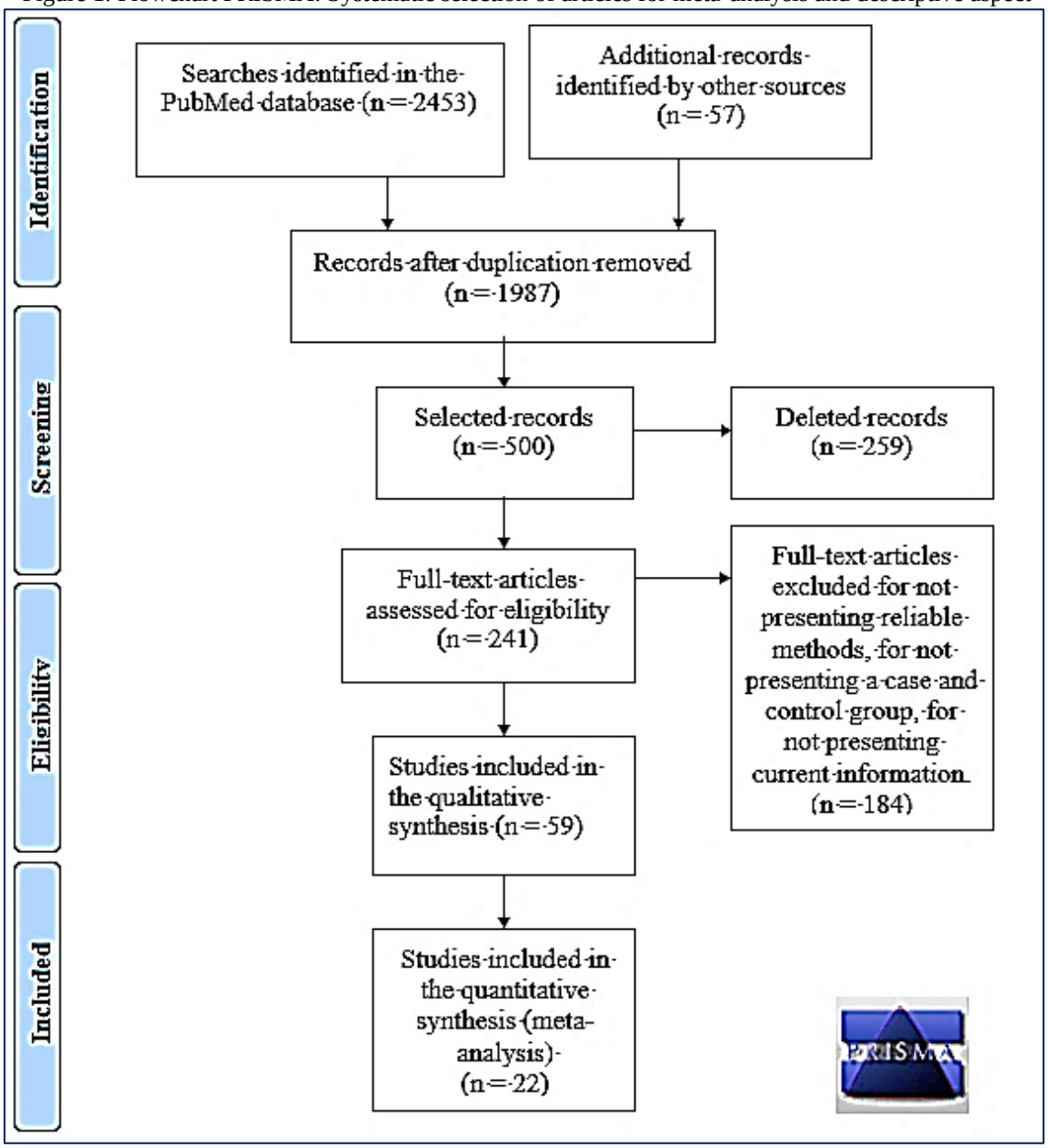
The articles used in this meta-analysis evaluated the genotypes Ɛ2Ɛ2, Ɛ2Ɛ3, Ɛ2Ɛ4, Ɛ3Ɛ3, Ɛ3Ɛ4 and Ɛ4Ɛ4 of the APOE gene, comparing the group of patients with AD with the control group, with age ranging from 50 to 100 years, without discrimination by ethnicity and gender. These data were necessary to analyze how these polymorphic variants can influence the predisposition to AD. Data were extracted from 22 articles for statistical tests. The methods of evaluation of the gene polymorphism in the selected researches were Conventional PCR, PCR-RFLP and ARMS-PCR. After data extraction and combination, 10,587 individuals were evaluated for the APOE gene genotypes. Of these, 37.3% were included in the case group, diagnosed with AD, and 62.7% of the individuals were part of the control group. In both groups, all six possible genotypes were evaluated. The data were grouped in each article, according to the values of the frequencies of the genotypes, in the case and control groups. Thus, Odds Ratios (OR) were calculated for each study, considering a confidence interval equal to 95%, consequently an alpha equal to 0.05 or 5% for the significance of the results (Table 1).

2.4 STATISTICAL ANALYSIS

According to the significance of the heterogeneity of the Higgins and Thompson (I^2) test, the DerSimonian-Laird and Mantel-Haenszel tests were applied. The DerSimonian-Laird and Mantel-Haenszel tests aim to compare the proportions of events between groups[19]. When the I^2 test showed ≥50%, the DerSimonian-Laird randomized effect test was applied. Otherwise, when the result was <50%, a Mantel-Haenszel fixed effect test was applied. Thus, the hypothesis evaluated was: “the presence of the genotype “x” of the APOE gene, is associated with AD. When there was no difference between

groups, the null hypothesis was considered. To determine the risk of bias, the Begg test was performed. Statistical analyzes and graphic designs were performed with the aid of the STATA 16.0 software.

Figure 1. Flowchart PRISMA: Systematic selection of articles for meta-analysis and descriptive aspect



3 RESULTS

The risk of bias assessment for the data for each genotype resulted in: Ɛ2Ɛ2: p = 1.00; Ɛ2Ɛ3: p = 1.04; Ɛ2Ɛ4: p = 0.66; Ɛ3Ɛ3: p = 1.28; Ɛ3Ɛ4: p = 0.07; Ɛ4Ɛ4: p = 1.11. The results showed a risk of bias without statistical significance. The dispersion of the individual results of each survey considered for meta-analysis can be observed in the Funnel Plot graph (Figure 2).

In the case group, the following data were obtained: Ɛ2Ɛ2 genotype identified in 14 individuals (0.4%), Ɛ2Ɛ3 genotype in 237 individuals (6%), Ɛ2Ɛ4 genotype in 112 individuals (2.9%), Ɛ3Ɛ3 genotype in 1800 individuals (45.6%), Ɛ3Ɛ4 genotype in 1426 (36.1%) and Ɛ4Ɛ4 genotype in 358 individuals (9%). The control group was subjected to the same subdivision by genotypes, with 52 individuals (0.8%) presenting the Ɛ2Ɛ2 genotype, 798 individuals (12%) presenting the Ɛ2Ɛ3 genotype, 403 individuals (6.1%) presenting the Ɛ2Ɛ4 genotype, 3816 individuals (57.5%) had Ɛ3Ɛ3 genotype, 1436 individuals (21.6%) had Ɛ3Ɛ4 genotype and 135 individuals (2%) had Ɛ4Ɛ4 genotype of that gene. The relative and absolute frequencies of the ApoE genotypes of individuals in the case and control groups, considering the 22 surveys, described in table 1.

Figure 2. Funnel Plot: Dispersion of the results of the research considered for meta-analysis.

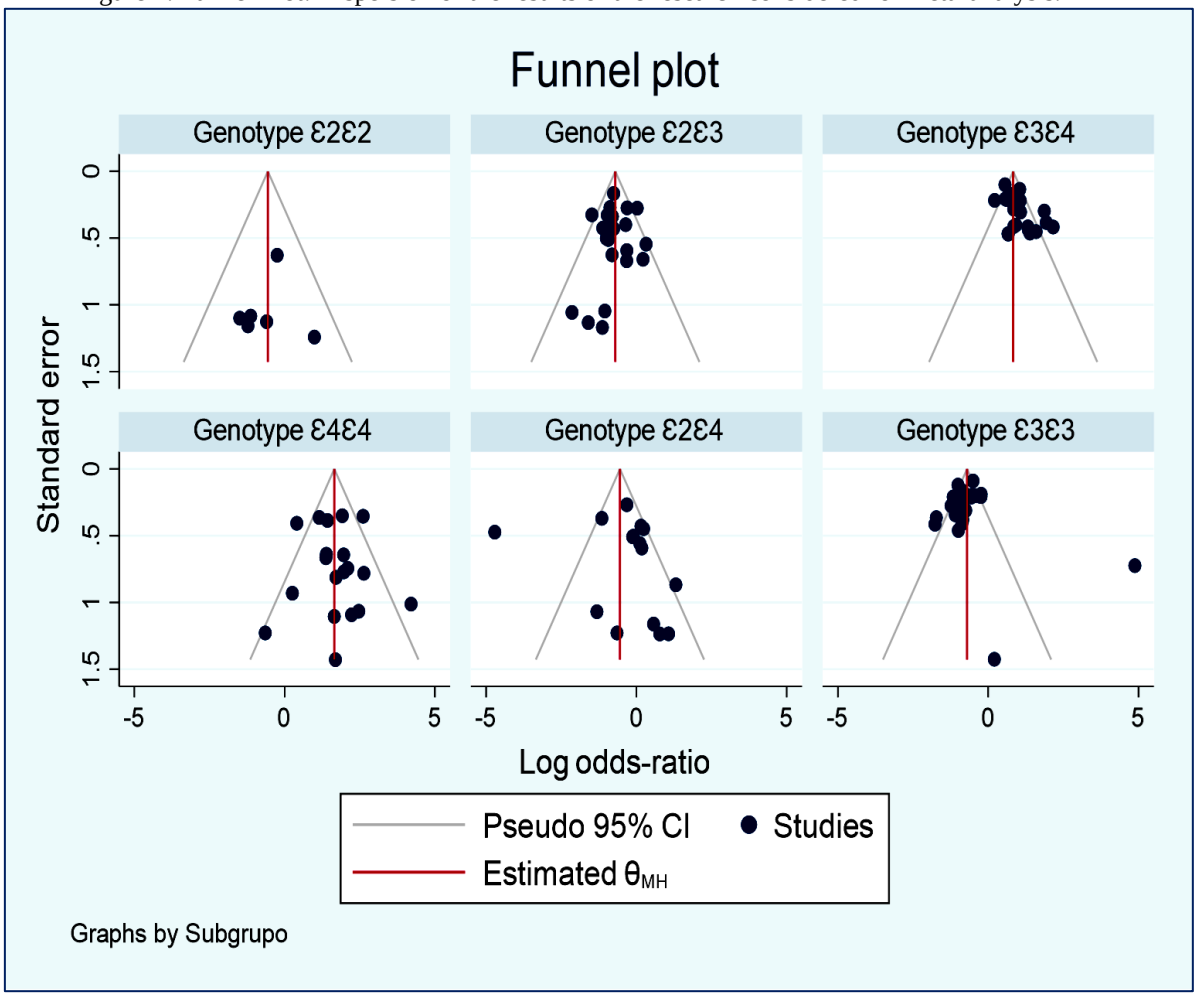
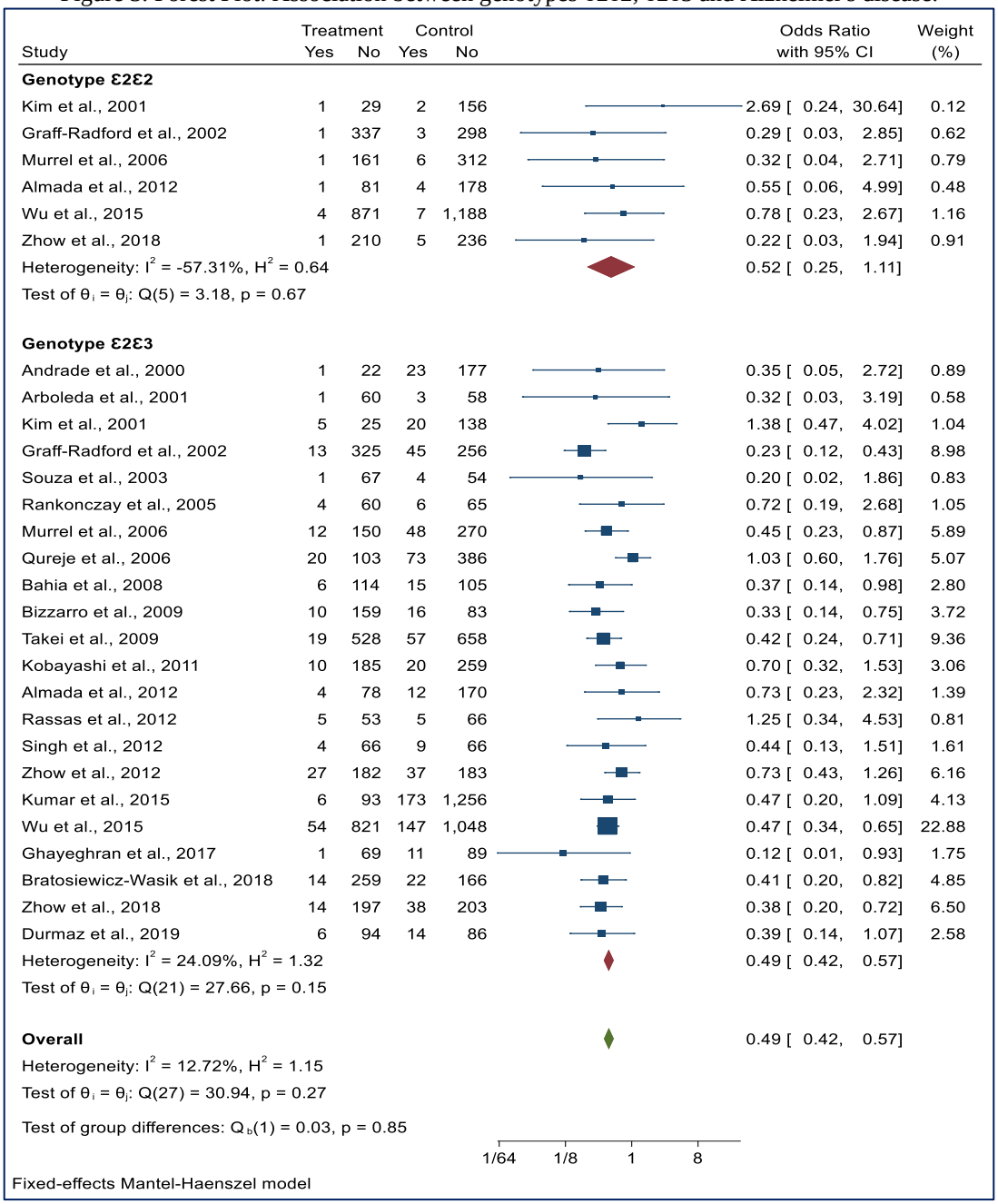


Table 1. Relative and absolute frequency of the genotypes that characterize polymorphism in the APOE gene.

Author	Years	Country	With Alzheimer's Disease (Treatment)							Without Alzheimer's Disease (Control)						
			Ɛ2Ɛ2	Ɛ2Ɛ3	Ɛ2Ɛ4	Ɛ3Ɛ3	Ɛ3Ɛ4	Ɛ4Ɛ4	Total	Ɛ2Ɛ2	Ɛ2Ɛ3	Ɛ2Ɛ4	Ɛ3Ɛ3	Ɛ3Ɛ4	Ɛ4Ɛ4	Total
			f(%)	f(%)	f(%)	f(%)	f(%)	f(%)		f(%)	f(%)	f(%)	f(%)	f(%)	f(%)	
Andrade et al.[20]	2000	**Brazil**	0	4.3	8.7	34.8	34.8	17.4	**23**	0.5	11.5	2.5	59	21.5	5	**200**
Arboleda et al.[21]	2001	**Colombia**	--	1.6	3.3	41	37.7	16.4	**61**	--	5	0	80.3	13.1	1.6	**61**
Kim et al.[22]	2001	**South Korea**	3.3	16.7	13.3	36.7	26.7	3.3	**30**	1.3	12.7	11.4	58.2	15.8	0.6	**158**
Graff-Radford et al.[23]	2002	**USA**	0.3	3.8	3.8	30.8	42.3	19	**338**	1	15	3.3	51.1	26.2	3.4	**301**
Souza et al.[24]	2003	**Brazil**	0	1.5	0	53	41	4.5	**68**	0	7	1.7	72.4	15.5	3.4	**58**
Rankonczay et al. [25]	2005	**Hungary**	0	6.2	0	50	36	7.8	**64**	1.4	8.4	1.4	70.5	18.3	0	**71**
Murrel et al.[26]	2006	**USA**	0.6	7.5	3.7	37.6	37.6	13	**162**	1.9	15.1	4.1	51.2	24.2	3.5	**318**
Qureje et al.[27]	2006	**Nigeria**	0	16.2	4	39	33.5	7.3	**123**	0.9	15.9	4.6	44.9	28.7	5	**459**
Bahia et al.[28]	2008	**Brazil**	0	5	1.6	44	38.4	11	**120**	3.3	12.5	0	65	17.5	1.7	**120**
Bizzarro et al.[29]	2009	**Italy**	0	6	1.7	45	40.8	6.5	**169**	0	16.1	1	73.8	9.1	0	**99**
Takei et al.[30]	2009	**Japan**	0	3.5	1	51	35.9	8.6	**547**	0.5	8	1	74	16.4	0.1	**715**
Kobayashi et al.[31]	2011	**Japan**	0	5.1	2.6	48.8	36.4	7.1	**195**	0	7.2	74.5	0.7	16.5	1.1	**279**
Almada et al.[32]	2012	**Brazil**	1.2	4.9	1.2	36.6	42.6	13.4	**82**	2.2	6.6	4.3	61.6	24.2	1.1	**182**
Rassas et al.[33]	2012	**Tunisia**	0	8.6	41.4	1.7	34.5	13.8	**58**	1.4	7	69	1.4	18.3	2.9	**71**
Singh et al. [34]	2012	**India**	0	5.7	2.9	32.9	57.1	1.4	**70**	0	12	1.4	73.3	13.3	0	**75**
Zhow et al.[35]	2012	**China**	0	12.9	0.5	57.9	28.2	0.5	**209**	0	16.8	0.9	68.2	13.2	0.9	**220**
Kumar et al.[36]	2015	**Norway**	0	6.1	NR	41.4	42.4	10.1	**99**	0.7	12.1	NR	55.4	28.4	3.4	**1429**
Wu et al.[37]	2015	**China**	0.5	6.2	2.5	48.4	33	9.4	**875**	0.6	12	3	61.7	22	0.7	**1195**
Ghayeghran et al.[38]	2017	**Iran**	1.4	1.4	2.9	55.7	30	8.6	**70**	0	11	1	79	8	1	**100**
Bratosiewicz-Wasik et al.[39]	2018	**Polonia**	1.1	5.1	0	49.8	36	8.05	**273**	0	11.7	3.2	76	8	1.1	**188**
Zhow et al.[40]	2018	**China**	0.5	6.6	5.2	46	37	4.7	**211**	2	15.8	4.2	51.9	24.9	1.2	**241**
Durmaz et al.[5]	2019	**Turkey**	1	6	1	60	27	5	**100**	0	14	0	76	9	1	**100**
Total			**0.4**	**6**	**2.9**	**45.6**	**36.1**	**9**	**3947**	**0.8**	**12**	**6.1**	**57.5**	**21.6**	**2**	**6640**

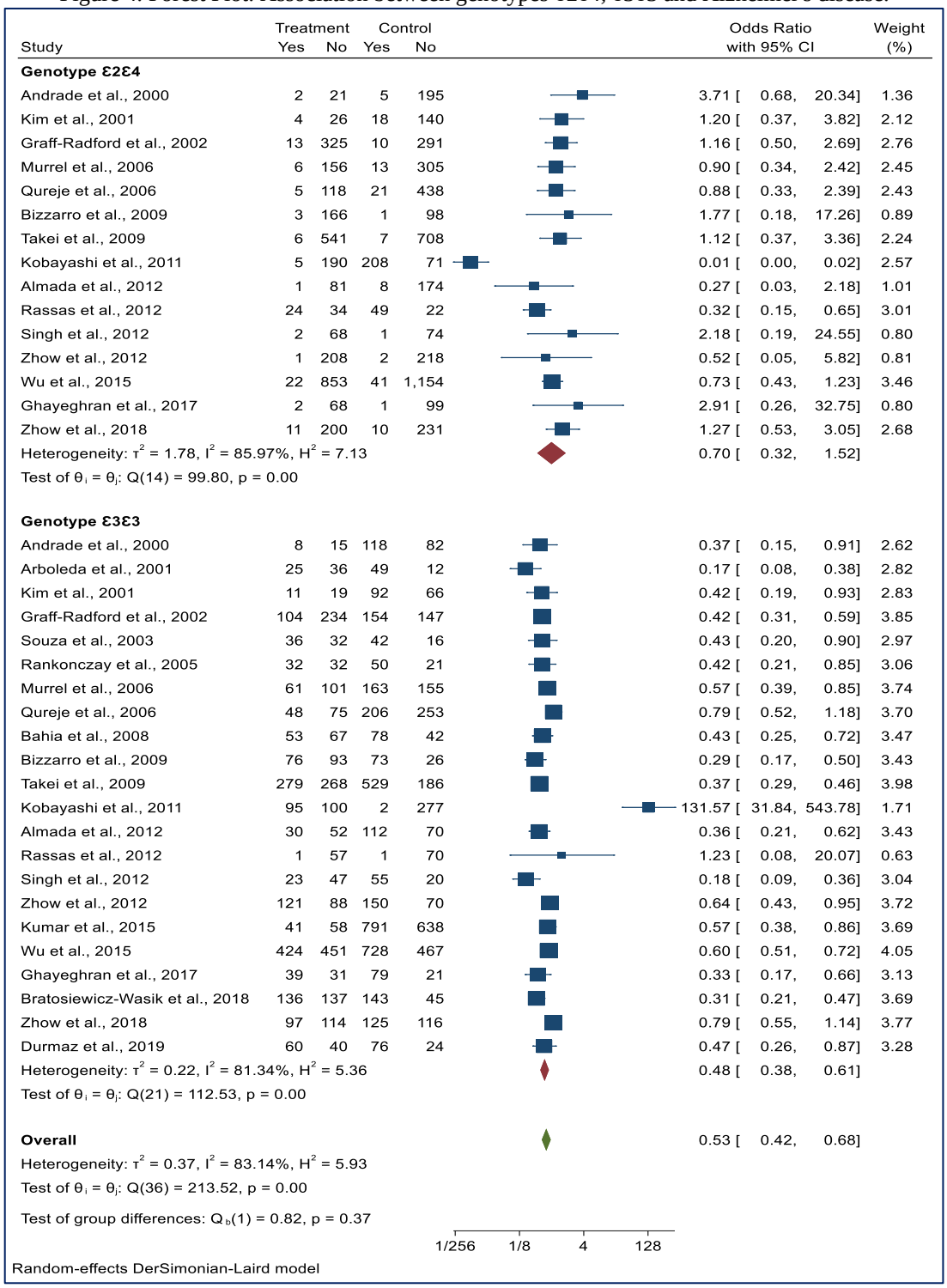
There was no association between the Ɛ2Ɛ2 genotype with AD, however, the Ɛ2Ɛ3 genotype showed a higher frequency in the group without AD, with OR = 0.49 (95% CI = 0.42-0.57; I² = 24.09%. The result confirms a protective association between genotype Ɛ2Ɛ3 and AD (Figure 3).

Figure 3. Forest Plot: Association between genotypes Ɛ2Ɛ2, Ɛ2Ɛ3 and Alzheimer's disease.



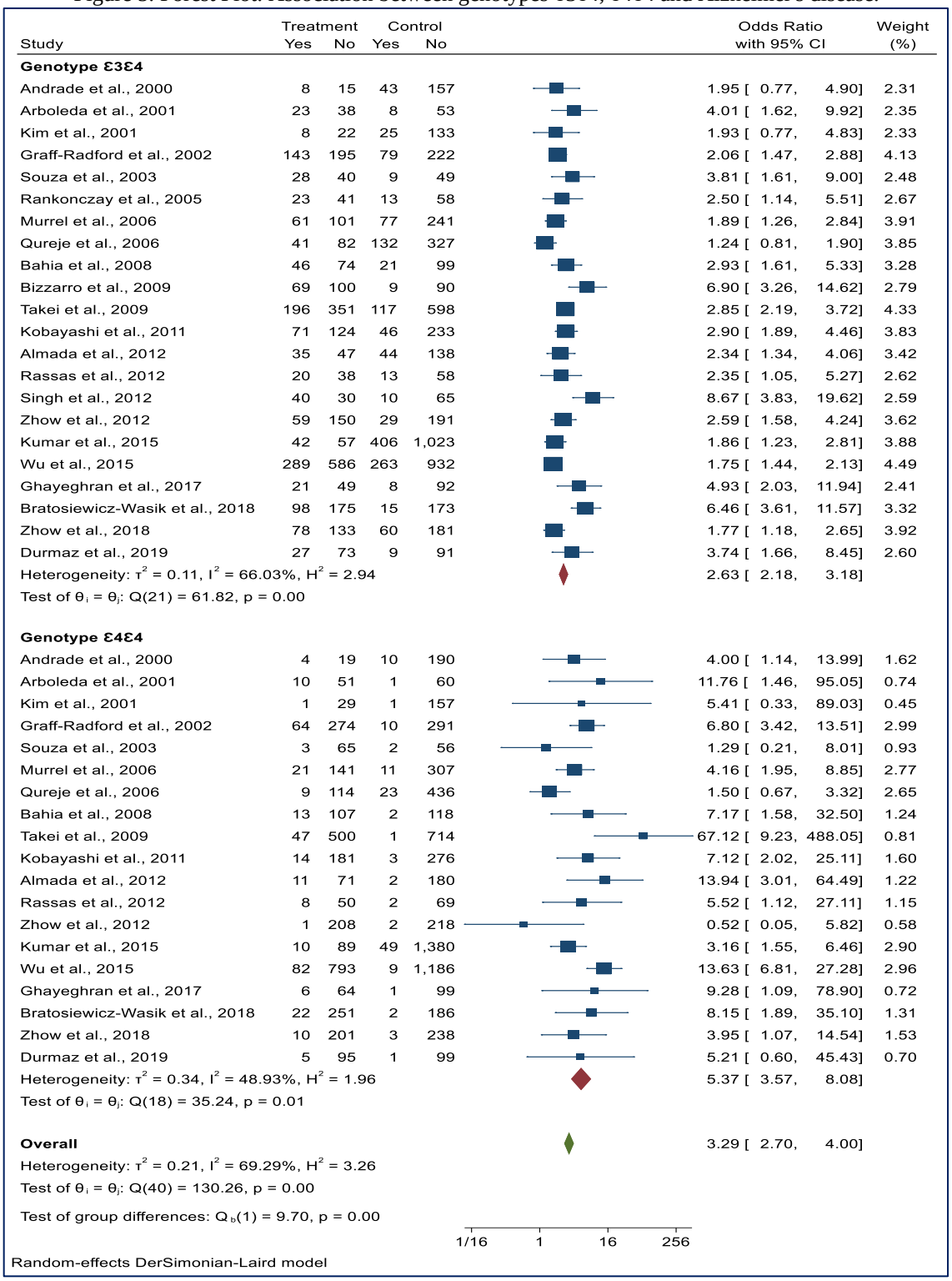
The presence of the Ɛ2Ɛ4 genotype did not indicate an association with AD, on the other hand, the Ɛ3Ɛ3 genotype showed a higher frequency in the group without AD, with OR = 0.48 (95% CI = 0.38-0.61; I² = 81, 34%), qualifying the presence as a genetic factor of protection against AD (Figure 4).

Figure 4. Forest Plot: Association between genotypes Ɛ2Ɛ4, Ɛ3Ɛ3 and Alzheimer's disease.



The genotypes Ɛ3Ɛ4 and Ɛ4Ɛ4 are more frequent in the group with AD, respectively OR = 2.63 (95% CI = 2.18-3.18; I^2 = 66%) and OR = 5.37 (95% CI = 3.57- 8.08; I^2 = 48.8%). The results confirm and qualify the Ɛ3Ɛ4 and Ɛ4Ɛ4 genotypes as genetic risk factors for the development of Alzheimer's disease (Figure 5).

Figure 5. Forest Plot: Association between genotypes Ɛ3Ɛ4, Ɛ4Ɛ4 and Alzheimer's disease.



4 DISCUSSÃO

AD is associated with lifestyle, environmental and genetic factors. The polymorphism of the APOE gene is one of the genetic factors related to the development of AD[41, 42].

The APOE gene has three polymorphic allelic variants, APOEƐ2, APOEƐ3 and APOEƐ4 and, therefore, can have six genotypes, three homozygous Ɛ2Ɛ2, Ɛ3Ɛ3 and Ɛ4Ɛ4, and three heterozygous, Ɛ2Ɛ3, Ɛ2Ɛ4 and Ɛ3Ɛ4. These alleles are derived from 2 single nucleotide polymorphisms (SNPs) in residues 7412 and 429358[43–45]. According to Lahiri et al.[46], the role developed by ApoE in the body is associated with metabolism and lipid transport, coordinating the mobilization and redistribution of cholesterol from myelin and neuronal membranes. In addition, it is involved in synaptic repair in response to tissue injury, maintenance of neuronal structure and cholinergic function[47]. Several studies have evaluated the relationship of the APOE gene polymorphisms and the main proteins involved in the pathophysiological triggering of the disease. Research results show a relationship between the Ɛ4 allele and the cascade of inflammation and neurodegeneration, while the Ɛ2 and Ɛ3 alleles play a protective role. However, they have not clearly explained how these point polymorphisms of APOE interfere in the production and action of these proteins in neurophysiopathology[48–53].

We observed an association of risk between AD and the genotypic profiles Ɛ3Ɛ4 and ot4Ɛ4, of the APOE gene, since the genotypic frequencies found in the analyzed groups were statistically significant. While the genotypes Ɛ2Ɛ3 and Ɛ3Ɛ3 were statistically related to a condition of genetic protection against AD. The Ɛ2Ɛ2 Ɛ2Ɛ4 genotypes were not associated with the disease. Our study demonstrated that the Ɛ4Ɛ4 genotype increases the risk of developing AD up to 5 times. Several studies have highlighted the increased risk of AD associated with the presence of the genotype Ɛ4Ɛ4[5,8,29,30,46].

Concurrent to these and to our study, Garcia et al.[54], demonstrated insignificance between the Ɛ4 allele and the AD, a cohort study was conducted, in which it evaluated 52 elderly individuals from the population of Fernando de Noronha, 87% presented cognitive deficit of according to the diagnostic protocols of the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), and only 10% were genotyped with the Ɛ4 allele. However, the research was carried out with small sampling, which can interfere with the significance of the event. A meta-analysis conducted by Ward et al.[55] confirms the reasoning for the need for sample heterogeneity, they assessed the prevalence of APOEƐ4 status and the Ɛ4Ɛ4 genotype in 27,109 patients diagnosed with AD in 33 countries. They obtained a combined global estimate for the prevalence of carriers of the Ɛ4 allele of 48.7% and a prevalence of 9.6% of carriers for the homozygous Ɛ4Ɛ4. In addition, they observed heterogeneity in the stratified analysis of the regions, and noted that northern Europe had a higher prevalence of the Ɛ4 allele

and the Ɛ4Ɛ4 genotype, respectively 63.3% and 14.1%. The results found by Ward et al.[55] are congruent with our results.

Regarding the genotypic frequencies of the APOE gene, Zhou et al.[40] and Demarchi et al.[56] presented results very similar to those found in this meta-analysis. When evaluated together, they demonstrated that the Ɛ4 allele plays a role as a risk factor, while the Ɛ2 allele has a protective factor weight, agreeing with our results on its association with the genetic protection condition.

Early diagnosis of AD is highly desirable because most patients are diagnosed at an advanced stage, with significant neuronal losses. The diagnosis for AD is made by clinical exam and complementary exams, this fact hinders its previous diagnosis, as patients already present the clinical manifestations when they seek assistance[7,42,57]

Barros et al.[44], highlighted that the confirmation and discoveries of the genetic factors that influence the development of AD, contribute to the detection of individuals most likely to develop the disease. Thus, the associations found in our study are significant for early diagnosis, since the establishment of these with AD, makes it possible to use them in genotyping exams, as a prediction and follow-up tool for AD[58,59].

5 CONCLUSION

The data from this meta-analysis demonstrate that individuals with AD have presence of the genotypes Ɛ3Ɛ4 and Ɛ4Ɛ4 proportionally higher, when compared to individuals without AD, qualifying them as genetic factors of predisposition to the disease. On the other hand, the genotypes Ɛ3Ɛ3 and Ɛ2Ɛ3 were proportionally superior in the group without AD, qualifying them as protective genetic factors. The another genotypes were not associated with AD.

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