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Programa de Pós-Graduação de Pós-Graduação em Nutrição e Saúde

Luiz Julio Rocha de Oliveira

A INFLUÊNCIA DA ETNIA E DOS POLIMORFISMOS GENÉTICOS NA APNEIA OBSTRUTIVA DO SONO: UMA REVISÃO SISTEMÁTICA E META-ANÁLISE

Belo Horizonte

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Dissertação apresentada ao Programa de Pós-Graduação em Nutrição e Saúde da Escola de Enfermagem da Universidade Federal de Minas Gerais, como requisito parcial à obtenção do título de Mestre em Nutrição e Saúde.

Orientadora: Prof.ª Dr.ª Luciana Bastos-Rodrigues
Coorientador: Prof.ª Dr.ª Nathália Sernizon Guimarães

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ATA DE NÚMERO 117 (CENTO E DEZESSETE) DA SESSÃO DE ARGUIÇÃO E DEFESA DA DISSERTAÇÃO APRESENTADA PELO CANDIDATO LUIZ JULIO ROCHA DE OLIVEIRA PARA OBTENÇÃO DO TÍTULO DE MESTRE EM NUTRIÇÃO E SAÚDE.

Aos 14 (quatorze) dias do mês de janeiro de dois mil e vinte e cinco, às 09:00 horas, realizou-se por meio de videoconferência, a sessão pública para apresentação e defesa da dissertação "A INFLUÊNCIA DA ETNIA E DOS POLIMORFISMOS GENÉTICOS NA APNEIA OBSTRUTIVA DO SONO: UMA REVISÃO SISTEMÁTICA E META-ANÁLISE", do aluno ***Luiz Julio Rocha de Oliveira***, candidato ao título de "Mestre em Nutrição e Saúde", linha de pesquisa "Nutrição Clínica e Experimental". A Comissão Examinadora foi constituída pelas professoras doutoras Luciana Bastos Rodrigues, Nathália Sernizon Guimarães, Melania Dirce Oliveira Marques e Raquel Liboredo Perini, sob a presidência da primeira. Abrindo a sessão, a Senhora Presidente da Comissão, após dar conhecimento aos presentes do teor das Normas Regulamentares do Trabalho Final, passou a palavra ao candidato para apresentação de seu trabalho. Seguiu-se a arguição pelos examinadores com a respectiva defesa do candidato. Logo após, a Comissão se reuniu sem a presença do candidato, para julgamento e expedição do seguinte resultado final:

(X) APROVADO;

( ) APROVADO COM AS MODIFICAÇÕES CONTIDAS NA FOLHA EM ANEXO;

( ) REPROVADO.

O resultado final foi comunicado publicamente ao candidato pela Senhora Presidente da Comissão. Nada mais havendo a tratar, eu, Luciana Bastos Rodrigues, Presidente da Comissão Examinadora, lavrei a presente Ata, que depois de lida e aprovada será assinada por mim e pelos demais membros da Comissão Examinadora.

Belo Horizonte, 14 de janeiro de 2025.

Profa. Dra. Luciana Bastos Rodrigues
Orientadora (UFMG)

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Resumo

A apneia obstrutiva do sono (AOS) é uma condição prevalente caracterizada por episódios recorrentes de obstrução das vias aéreas superiores durante o sono. Este estudo teve como objetivo investigar a influência de polimorfismos genéticos e etnia na ocorrência e gravidade da AOS por meio de uma revisão sistemática e meta-análise. Esta pesquisa foi realizada com base no Guideline da Cochrane Library e redigida de acordo com a lista de verificação PRISMA. O protocolo foi previamente registrado na plataforma PROSPERO, sob o código #CRD42024548801. A busca pela informação foi realizada nas bases eletrônicas de dados MEDLINE (by PubMed), Embase, Web of Science, LILACS, WPRIM e CENRAL (by Cochrane Library) até o mês de junho de 2024. Considerou-se como critério de elegibilidade os estudos observacionais que avaliaram os efeitos de polimorfismos genéticos e etnia na ocorrência da AOS. Como critério de exclusão foram desconsiderados os estudos que envolveram crianças ou adolescentes, que não separaram dados por etnia ou raça, que não abordaram a base genética da OSA e aqueles que não relataram ORs. A análise de cinco estudos envolvendo 3.606 indivíduos revelou uma associação moderada entre polimorfismos genéticos e AOS (OR 1,25; IC 95%: 0,85–1,86), com heterogeneidade significativa (I^2 = 76%). Subgrupos étnicos apresentaram variações notáveis, sendo que indivíduos brasileiros de ascendência europeia apresentaram maior risco (OR 2,80; IC 95%: 1,11–7,08), enquanto indivíduos de ascendência africana mostraram efeito protetor (OR 0,26; IC 95%: 0,09–0,74). Estes achados destacam a importância de abordagens personalizadas no manejo clínico da AOS, considerando diferenças genéticas e étnicas.

Palavras-chave: Apneia obstrutiva do sono; Polimorfismos genéticos; Etnia; Meta-análise; Fator de Risco.

Abstract

Obstructive sleep apnea (OSA) is a prevalent condition characterized by recurrent episodes of upper airway obstruction during sleep. This study aimed to investigate the influence of genetic polymorphisms and ethnicity on the occurrence and severity of OSA through a systematic review and meta-analysis. The research was conducted based on the Cochrane Library Guideline and written according to the PRISMA checklist. The protocol was previously registered on the PROSPERO platform under the code #CRD42024548801. Information was retrieved from the electronic databases MEDLINE (via PubMed), Embase, Web of Science, LILACS, WPRIM, and CENTRAL (via Cochrane Library) up to June 2024. The eligibility criteria included observational studies evaluating the effects of genetic polymorphisms and ethnicity on the occurrence of OSA. Exclusion criteria ruled out studies involving children or adolescents, studies that did not separate data by ethnicity or race, those that did not address the genetic basis of OSA, and studies that did not report ORs. The analysis of five studies involving 3,606 individuals revealed a moderate association between genetic polymorphisms and OSA (OR 1.25; 95% CI: 0.85–1.86), with significant heterogeneity (I^2 = 76%). Ethnic subgroups showed notable variations, with Brazilian individuals of European ancestry presenting a higher risk (OR 2.80; 95% CI: 1.11–7.08), while individuals of African ancestry exhibited a protective effect (OR 0.26; 95% CI: 0.09–0.74). These findings underscore the importance of personalized approaches in the clinical management of OSA, considering genetic and ethnic differences.

Keywords: Obstructive sleep apnea; Genetic polymorphisms; Ethnicity; Meta-analysis; Risk factor.

Lista de Ilustrações

Lista de Tabelas

Lista de Abreviaturas

AOS: Apneia Obstrutiva do Sono

AHI: Índice de Apneia-Hipopneia

BMI: Índice de Massa Corporal

OR: Odds Ratio (Razão de Chances)

CI: Intervalo de Confiança

LEPR: Receptor de Leptina

5-HTT: Transportador de Serotonina

CRP: Proteína C-Reativa

IL-6: Interleucina-6

TNF-α: Fator de Necrose Tumoral Alfa

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RE: Efeito Aleatório (*Random Effect*)

PECO: População, Exposição, Comparação e Desfecho

SUMÁRIO

Considerações iniciais

A apneia obstrutiva do sono (AOS) é uma condição respiratória comum caracterizada por obstruções parciais ou totais das vias aéreas superiores durante o sono devido à fragmentação do sono e hipoxemia intermitente. Essa condição pode levar a vários problemas de saúde como hipertensão, diabetes tipo 2 e aumento do risco de doenças cardiovasculares. Estudos recentes indicam que fatores genéticos e características étnicas têm influência significativa na predisposição e gravidade da AOS, o que ressalta a importância de abordagens personalizadas no tratamento dessa condição. [22]

Embora a obesidade seja reconhecida como um fator de risco importante para a AOS, há cada vez mais evidências de que outros fatores como as estruturas ósseas do rosto e respostas neuromusculares também desempenham um papel significativo nessa condição complexa. Além disso, estudos genéticos identificaram associações entre variações em genes específicos com potencial influência na suscetibilidade à AOS demonstrando a natureza multifatorial dessa condição complexa. [11,23]

Estudos populacionais têm explorado a conexão entre a ancestralidade genética e a AOS, no que tange à com a incidência e gravidade desta, haja vista à variação nos padrões de distribuição de gordura e características craniofaciais entre diferentes grupos étnicos que têm sido relacionadas às disparidades na prevalência e intensidade da doença. Essas descobertas ressaltam a importância de investigar as interações entre genética e fatores ambientais para compreender melhor a apneia obstrutiva do sono. [24]

Desta forma, o presente estudo busca investigar de maneira sistemática e abrangente as influências genéticas e étnicas na gravidade da AOS, baseando-se em metodologias rigorosas de revisão sistemática e meta-análise para extrair as evidências científicas disponíveis sobre o tema. A abordagem proposta almeja não apenas contribuir para o entendimento da fisiopatologia da AOS, mas também fornecer subsídios para estratégias mais eficazes de prevenção e tratamento, alinhadas às características individuais dos pacientes. [25]

Title

The Influence of Ethnicity and Genetic Polymorphisms at Obstructive Sleep Apnea: A Systematic Review and Meta-Analysis

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Abstract

Purpose: The relationship of the influence of ethnicity and molecular markers on obstructive sleep apnea syndrome (OSAS) remains unclear. Therefore, we sought to identify the effect of ethnicity and polymorphism on the occurrence and degree of severity of obstructive sleep apnea (OSA) among adults.

Methods: We searched MEDLINE (by PubMed), Embase, Web of Science, LILACS, WPRIM and CENTRAL (by Cochrane Library) up to June, 2024. Additionally, references of selected studies were evaluated. We included observational studies that evaluated the effects of genetic polymorphisms and ethnicity at occurrence of OSAS. A random-effects meta-analysis model was used to calculate odds ratios (OR). Subgroup analyses were performed using ethnicity, sex and OSAS diagnosis.

Results: Five studies including 3,606 individuals were selected. The pooled analysis showed overall odds ratio (OR) of 1.25 [95% CI: 0.85-1.86] for the association between genetic polymorphisms and OSA. Significant heterogeneity was observed across studies ($I^2 = 76\%$, $p < 0.01$). Subgroup analysis showed significant differences by ethnicity, with Brazilians of European descent showing higher risk (OR 2.80 [95% CI: 1.11-7.08]) and those with West African ethnicity showing protection (OR 0.26 [95% CI: 0.09-0.74]).

Conclusions: This systematic review and meta-analysis underscores the noteworthy influence of genetic variants and ethnicity on OSA occurrence and severity. Certain populations showed differential genetic susceptibility, implying the need for personalized approaches in clinical management.

Keywords: Meta-analysis, Obstructive sleep apnea syndrome, Ethnicity, Risk, Polymorphisms

Introduction

Obstructive sleep apnea syndrome (OSAS) is a sleep problem where there are repeated episodes of blocked airflow, in the airway during sleep resulting in intermittent low oxygen levels and disrupted sleep cycles.[1] This condition not only causes daytime tiredness and impacts overall well-being but also links to metabolic syndrome and serious heart related issues, like high blood pressure, heart disease, stroke and heart failure.[2] The worldwide occurrence of obstructive sleep apnea (OSA) is believed to surpass 1 billion individuals, with a growing acknowledgment of its variability among populations based on factors, like age, sex, and ethnicity.[3]

Current studies have revealed a considerable difference in OSA frequency across populations.[4] For example, Mongolia population shows a OSA occurrence of 93% and in the other side Slovakia (non-Roma subjects) presents a 12% occurrence.[4] The overall OSA global occurrence report in the referred study is approximately 54%.[4]

As it represents a global public health problem, with high occurrence and enormous negative consequences, OSAS should receive more attention. Consequently, improving our understanding of the pathogenesis of OSAS is essential for the development of effective and safe therapies.[3]

Recent advancements in genomics have offered perspectives into the components that play a role in OSA.[5] This implies that molecular indicators like nucleotide polymorphisms (SNPs)

might impact both the likelihood and seriousness of the condition.[6] Exploration of these variations, such as variations in genes linked to metabolic activities and inflammatory responses well as biological clock functions, has revealed potential molecular pathways connecting OSA with heart related outcomes.[7] For example, the researchers have demonstrated that variations in genes like Interleukin-6 (IL-6), TNF-α, PTGER3, LPAR1, C-reactive protein (CRP), GDNF and the serotonin transporter are connected to a vulnerability to OSA.[8-11]

One crucial aspect of these discoveries is how one's ethnicity can influence susceptibility to genetic risks.[12] Studies on different ethnic groups such as Chinese Han, Hispanics and African Americans have revealed different levels of some genetic signs for OSA in different populations.[12-13] It's so important to consider these dissimilarities because they could affect OSA's occurrence, degree of severity, and treatment outcomes.[14] Although there are an increasing number of publications concerning this issue, there is still a lack of understanding about the link between genetic polymorphisms in target genes, ethnicity and comorbidities with OSA.

The aim of this systematic review and meta-analysis is to assess the effect of ethnicity and molecular markers on the occurrence of OSA among adult individuals. The findings will clarify the genetic contributions to OSA and may suggest the need for targeted interventions based on genetic ethnicity.

The review objective is to evaluate how ethnicity and genetic polymorphisms can affect the occurrence and degree of severity of obstructive sleep apnea among people from different ethnic backgrounds.

Methods

Study Design and Registration

This systematic review and meta-analysis was realized based to Cochrane Handbook and writing according to PRISMA checklist. The protocol was registered in PROSPERO platform, under code #CRD42024548801.

PECO

To frame the central question of this review, we used the PECO acronym where P (Population) refers to adult individuals with OSA. The review included individuals across different age groups and ethnicities who had been clinically diagnosed with OSA, to keep the population adult to focus on genetic influences on this condition.

E (Exposure) includes genetic characteristics, specifically looking at different genetic polymorphisms that may predispose to OSA. Unlike intervention-based studies, this review looks at the genetic markers, how certain inherited traits affect the likelihood and degree of severity of OSA, not the external treatments or prevention.

C (Comparison) is looking at differences between ethnic groups. The review wants to know how genetic predispositions to OSA differ between populations, to highlight the disparities in prevalence and degree of severity based on ethnic and genetic background. This is important to see if there are significant variations that can be attributed to genetic lineage and ethnicity.

O (Outcome) is the occurrence and degree of severity of obstructive sleep apnea, measured by incidence rates and degree of severity of the condition as measured by clinical indices such as Apnea-Hypopnea Index (AHI). The main goal is to see how genetic polymorphisms affect the likelihood and degree of severity of OSA across different ethnic groups.

This review combines observational and cohort studies that looked at the association between genetic polymorphisms, ethnicity and obstructive sleep apnea. Using the PECO framework, we want to get the overall picture of the genetic factors that contribute to OSA differences between ethnic groups.

Outcome Measures

Our primary outcomes were, using the AHI and other indices included, the occurrence as well as seriousness of OSA. Genetic polymorphisms influence on OSA occurrence was estimated using ORs. The secondary outcomes consisted of how certain genetic polymorphisms appeared among various ethnic populations.

Search Strategy

We conducted a broad literature review in MEDLINE (by PubMed), EMBASE, Web of Science, LILACS, WPRIM and Cochrane Library electronic databases for studies published in English, Spanish or Portuguese languages. The search included several keywords related to OSA and genetic polymorphisms: “Obstructive Sleep Apnea” and its variations, “Genetic Polymorphisms”, “Single Nucleotide Polymorphism” and terms related to ethnicity and ancestry.

The descriptors used were from recognized controlled vocabularies such as MeSH, Health Sciences Descriptors and Emtree. The search strategies for each database are in Appendix A.

Eligibility criteria

The inclusion criteria for this review and meta-analysis were designed to match the main aim of exploring the effect of ethnicity and genetic markers on OSA. Studies were included if they met the following: Adults 18 years and above with diagnosed OSA were the population of interest. We only included studies that looked at genetic inheritance and OSA, with a focus on occurrence and degree of severity of the condition. Included studies had to provide comparisons across different ethnic groups or among individuals with different genetic profiles so we could look at genetic susceptibility to OSA. The primary outcome was the reporting of ORs for genetic polymorphisms associated with OSA, with AHI as the main outcome measure for severity of the condition.

Study design: We included observational studies such as cohort, case-control and cross-sectional studies that looked at genetic variations and ethnicity in OSA. This broad inclusion criterion was to capture all genetic predispositions across different populations.

Exclusion Criteria: To focus on adult population, we excluded studies that involved children or adolescents. We also excluded articles that did not separate data by ethnicity or race as this did not allow us to look at genetic and ethnicity variations that affect OSA degree of severity. We also excluded studies that did not address the genetic basis of OSA and those that did not report ORs which is necessary for the meta-analytical synthesis of the genetic associations.

Data Extraction

Data extraction was done using standard template by two reviewers independently. When there were any differences in opinion, a third party was called upon for arbitration. Extracted information comprised study details such as author(s), publication year, population characteristics, genes investigated, ethnic background, sample size as well as odds ratios and their respective confidence intervals relating genetic features to OSA degree of severity.

Risk of Bias Assessment

We used the Newcastle-Ottawa Scale for observational studies to determine how good these studies were. The researchers looked at whether there was a bias in the way subjects were selected, if the groups were similar enough and whether or not the evaluation of the results was done properly. In case of any inconsistencies, they were resolved through agreement while any other remaining ones were settled by a third reviewer.

Statistical Analysis

R version 4.2.2 software were used in carrying out the meta-analysis. A random-effects model was employed to cater for any dissimilarities that may exist between the studies. The I^2 statistic was employed to determine the extent of heterogeneity while the Q-test was applied to determine whether there was any difference seen among the groups being compared. Analysis of subgroups was also planned so as to investigate how different ethnicity and genetic polymorphisms could affect OSA occurrence. The investigators carried out meta-regression analysis with an intention of determining whether factors such as ethnicity, sex, AHI, reduction of respiratory airflow by 30% with a 4% decrease in oxygen saturation and geographic region have any moderating effect.

Subgroup and Sensitivity Analyses

The subgroup analyses in this review were mainly focused on ethnicities, including Chinese Han, Hispanic/Latino, African American and European. By looking at each group separately we could see if there were differences in the genetic associations with OSA and degree of severity of OSA across different ethnicities. This allowed us to get a more detailed understanding of how genetic predisposition to OSA might vary across different ethnicities, the complex interplay between genetics and ethnicity.

In addition to ethnicity, subgroup analyses also looked at sex as a variable. Given the known differences in OSA occurrence and manifestation between men and women, we wanted to see if genetic factors had different associations based on sex.

Subgroup analyses were done based on the diagnostic criteria used in the included studies. These studies used different cut-offs to define OSA degree of severity, such as mild, moderate or severe based on AHI. Some studies defined OSA degree of severity as AHI > 5 events per hour with symptoms or AHI $\geq$ 15 events per hour regardless of symptoms. By categorizing the results based on these diagnostic definitions, the analysis aimed to see if the genetic associations were consistent across different definitions of OSA degree of severity and if genetic effects were more pronounced at specific degree of severity levels.

Sensitivity analyses were also done to check the results. These analyses involved excluding studies that were deemed to have high risk of bias based on the Newcastle-Ottawa Scale.

Despite this thorough assessment, no studies were excluded based on high bias risk which further supports the results.

Results

Study Selection

In June 2024, a comprehensive database search conducted using predefined search criteria across PubMed, EMBASE, Web of Science, LILACS, WPRIM, and Cochrane Library identified a total of 727 records. After removing 96 duplicates, 677 studies remained for title and abstract screening. Based on the pre-established inclusion and exclusion criteria, two independent reviewers assessed these studies. The conflicts between reviewers were resolved by a third reviewer when necessary. As a result of the initial screening phase, 663 studies were excluded due to the exclusion criteria- Appendix B, leaving 14 articles for eligibility assessment. Ultimately, five studies met the full eligibility criteria and were included in the systematic review and meta-analysis. A detailed PRISMA flowchart of the study selection process can be found in **Fig. 1**.

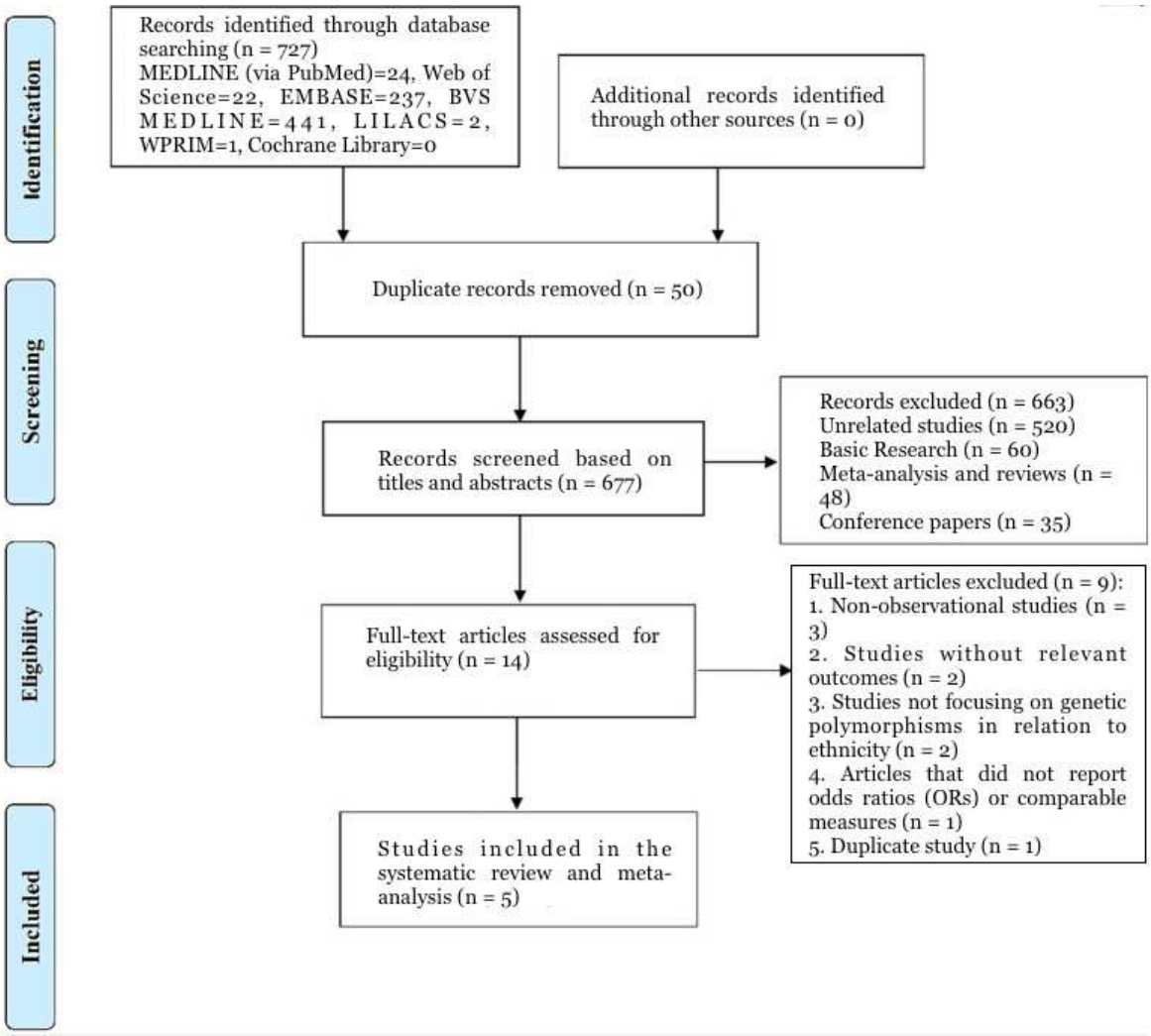

Fig. 1. Flow diagram of the systematic review and meta-analysis study selection process. The systematic search across PubMed, EMBASE, Web of Science, LILACS, WPRIM, and Cochrane Library initially identified 727 records. After removing 96 duplicates, 677 studies

remained for title and abstract screening. Application of inclusion/exclusion criteria led to 14 articles for full-text review. Finally, 5 studies met all eligibility criteria and were included in the systematic review and meta-analysis. The diagram details each step of the screening process, including reasons for exclusion, following PRISMA guidelines for transparent reporting of systematic reviews.

A total of 3,606 people from a variety of ethnic backgrounds, including Chinese Han (25.3%), African Americans (27.4%), European Americans (19.2%), and populations of mixed ethnicity from Brazil (28%) that included European, West African, and Native American ancestry, are included in five studies. These investigations assessed various sets of genetic markers connected to the occurrence of OSA, offering a thorough analysis of genetic variants linked to the condition. The leptin receptor (LEPR), serotonin transporter (5-HTT), GDNF, IL-6, and other inflammatory indicators including TNF-α and CRP were among the genes that were searched for in the study. The main outcome measure used in all the research to indicate the occurrence and degree of severity of OSA was the AHI. The main statistical method for evaluating the connection between genetic variations and OSA outcomes was thought to be the ORs. A detailed review of the sample sizes, demographics, and genes analyzed is given in **Table 1**.

Table 1. Characteristics of studies investigating the association between genetic polymorphisms and OSA across different ethnic populations.

Study	Country	Population Size (n)	Age (Mean/ Range)	Male (%)	Genes Analyzed	OSA Measurement	Covariates	Study Design
Emma K. Larkin et al., 2010	USA	African Americans: 259	51.1 ± 13.0 years	58%	IL6 (polymorphisms: IL6–1111, IL6–1510, IL6–2892, IL6–3572, IL6–6021, IL6–7592)	AHI ≥ 15 or current treatment with CPAP; AHI < 5 for controls	Age, Sex, BMI	Case-control
C. Guindalini et al., 2010	Brazil	Adults from São Paulo (admixed ancestry including European, West African, and Native American): 1,010	Mean 42.4 years	44.30 %	31 ancestry-informative markers (AIMs)	Polysomnography (AHI >5 events/h with symptoms or ≥15 events/h regardless of symptoms)	Sex, age, BMI, socioeconomic status	Cross-sectional

Juan Li et al., 2019	China	Chinese Han: 322	55.3 ± 10.8	85.80 %	LEPR	Polysomnography, AHI ≥ 5 events/h	Age, sex, BMI, triglycerides, TC, LDL-C, HDL-C, FBG, smoking status, alcohol use	Case-control
Weihua Yue et al., 2008	China	Chinese Han: 592 (254 OSAS patients, 338 controls)	45.2 (OSAS), 43.2 (controls)	86.6% (OSAS), 86.1% (controls)	Serotonin transporter (5-HTT) gene polymorphisms (5-HTTLPR and STin2.VNTR)	Polysomnography with AHI > 5 events/h	Excluded subjects with psychiatric disorders, serotonergic medication, and conditions affecting serotonin levels	Case-control
Emma K. Larkin et al., 2010	USA	European Americans and African American: 694 European Americans, 729 African Americans	European Americans: Mean 38.8 (Range 3-81); African Americans: Mean 36.4 (Range 3-82)	European Americans: 47%; African Americans: 42%	CRP, GDNF, HTR2A	AHI ≥15	Age, age-squared, sex, body mass index (BMI), racial admixture	Cross-sectional

Abbreviations: BMI, body mass index; AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea.

Meta-analysis

The pooled ORs for the relationship between genetic polymorphisms and the occurrence of OSA were estimated using a random-effects model, reflecting the heterogeneity among the studies ($I^2 = 76\%$, $p < 0.01$). A possible moderate link between specific genetic variants and the occurrence of OSA was indicated by the overall pooled OR of 1.25 [95% CI: 0.85–1.86], although the large confidence intervals raise doubts about the strength of this relationship without statistical difference.

Subgroup analyses including several ethnic groups showed a notable variation in genetic correlations. Brazilians with European ethnicity, for example, showed a significantly higher OR of 2.80 [95% CI: 1.11–7.08], as shown in the forest plots - **Fig. 2**, indicating a stronger genetic propensity to OSA degree of severity in this group. Brazilians with West African ethnicity, on the other hand, had a significantly reduced OR of 0.26 [95% CI: 0.09–0.74],

suggesting that this community may be genetically protected against severe OSA. The intricacy of genetic factors to OSA across a range of groups is highlighted by this ethnic variation.

Analysis of Asian populations revealed that Chinese Han subjects with the LEPR rs3790435 CC genotype demonstrated significant protection against OSA compared to carriers of other genotypes. In one key study by Li et al., which included 322 Chinese Han individuals, subjects with the CC genotype had a markedly lower risk of developing OSA compared to those with TT/TC genotypes (OR 0.462, 95% CI: 0.250-0.854, p=0.014). Among obese subjects specifically, those with the CC genotype maintained this protective effect (OR 0.191, 95% CI: 0.041-0.878, p=0.033), suggesting the variant's protective influence persists even in the presence of this major risk factor.[15]

The analysis of serotonergic pathway genes revealed significant associations with OSA risk. Variants in the HTR2A gene, particularly the rs9526240 polymorphism, demonstrated a strong association with increased OSA susceptibility in African Americans (OR 2.1; 95% CI: 1.5–2.9) . Similarly, polymorphisms in the serotonin transporter gene (5-HTT), including 5-HTTLPR and STin2.VNTR, were associated with OSA in Chinese Han populations. Notably, the 10-repeat allele of STin2.VNTR showed a significant association with OSA in males (OR 1.94; 95% CI: 1.26–3.00). These findings highlight the role of serotonergic mechanisms in upper airway control and the potential for genetic variants in these pathways to influence OSA susceptibility across diverse populations.[6][7]

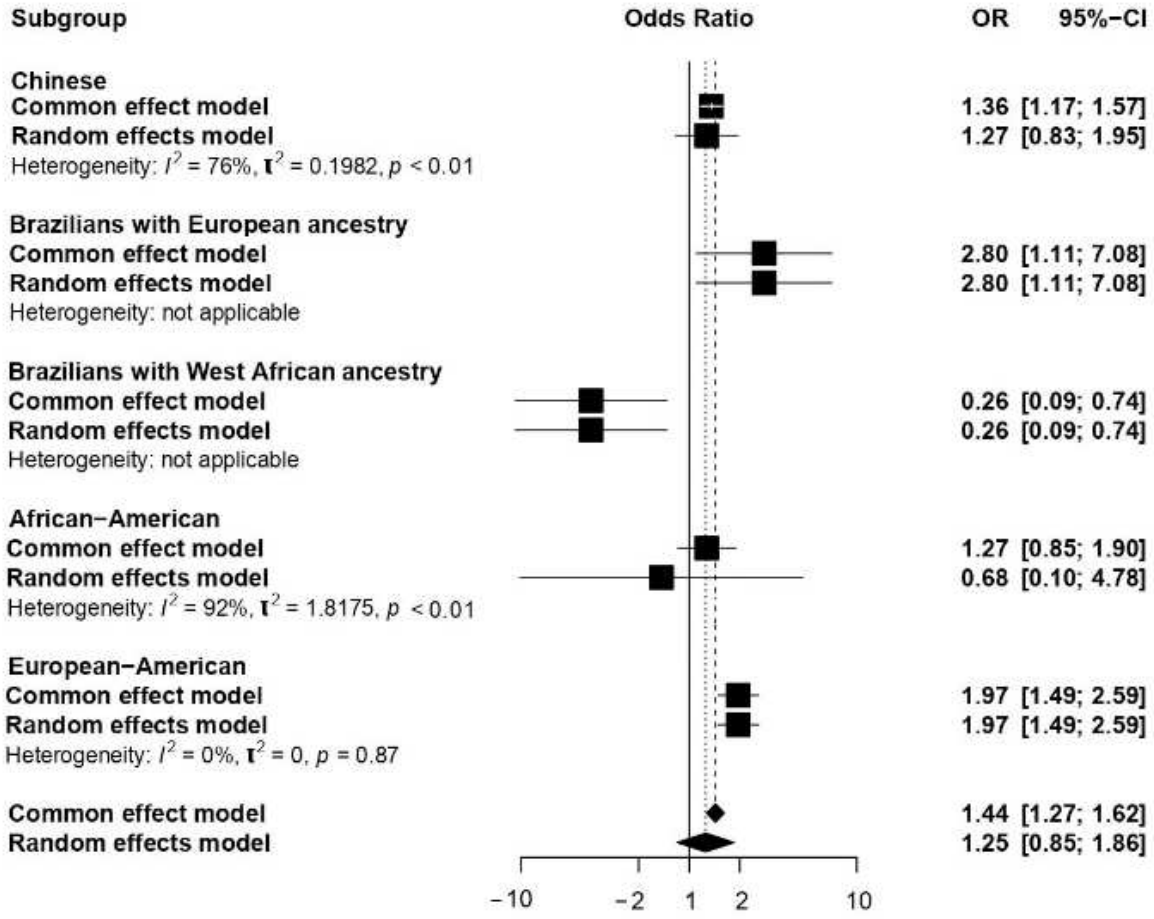

Fig. 2 Forest plot showing pooled estimates and subgroup analyses of genetic associations with OSA across different ethnic groups. The plot displays odds ratios with 95% confidence intervals for Chinese, Brazilians with European ancestry, Brazilians with West African ancestry, African-American and European-American populations. Common and random effects models are shown for each subgroup, with heterogeneity assessments where applicable. Values greater than 1 indicate increased OSA risk, while values less than 1 indicate protective effects. OR: Odds Ratio; CI: Confidence Interval.

Subgroup and Sensitivity Analyses

Another subgroup analyses were executed to understand the differences in OSA occurrence based on sex, ethnicity, and clinical OSA characteristics. **Fig. 3** shows the relationship between genetic polymorphisms and OSA was strong in male participants (OR: 1.59 [95% CI: 1.21–2.08]), compared to studies including both sexes (OR: 1.16 [95% CI: 0.70–1.90]).

Also, airflow cessation duration and apnea-hypopnea events per hour were analyzed in a clinical subgroups base. For example, the OR for apnea-hypopnea with desaturation of 3% per hour of sleep was 1.92 [95% CI: 1.50–2.47] (**Fig. 4)**. Additionally, sensitivity analyses were performed to assess the robustness of the results by excluding studies with a higher risk of bias, as determined by the Newcastle-Ottawa Scale. The findings remained consistent, confirming the validity of the meta-analysis.

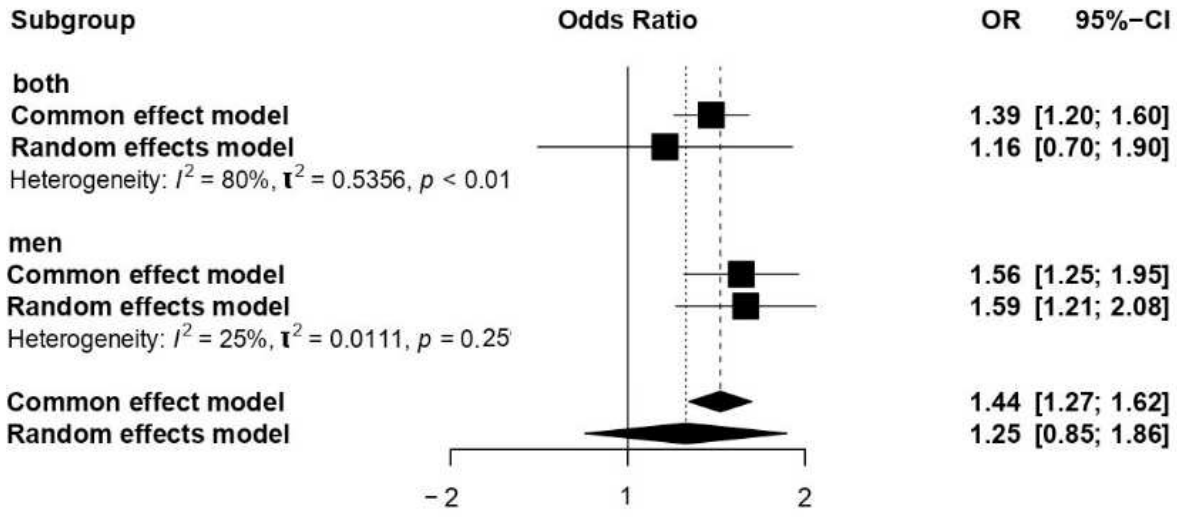

Fig. 3 Forest plot of meta-analysis evaluating genetic associations with OSA stratified by sex showing subgroup analysis for both sexes and men separately, with common and random effects models. Results display odds ratios and 95% confidence intervals with heterogeneity assessments. RE: random effect; OR: Odds Ratio; CI: Confidence Interval

The results indicate that the genetic associations with OSA vary based on the definitions used for apnea-hypopnea events. **Fig. 5** presents a subgroup analysis comparing two criteria. For airflow cessation of ≥10 seconds, the random-effects model showed an OR of 1.05 [95% CI: 0.62–1.78], with significant heterogeneity (I^2 = 80%, $p < 0.01$). Conversely, for apnea-hypopnea events requiring a desaturation of 3% per hour of sleep, the random-effects model

revealed a stronger genetic association, with an OR of 1.92 [95% CI: 1.50–2.47] and no evidence of heterogeneity (I^2 = 0%, p = 0.82). The overall pooled OR for these criteria was 1.25 [95% CI: 0.85–1.86]. These findings emphasize the importance of phenotype definitions in genetic studies of OSA and their influence on the strength of observed genetic associations.

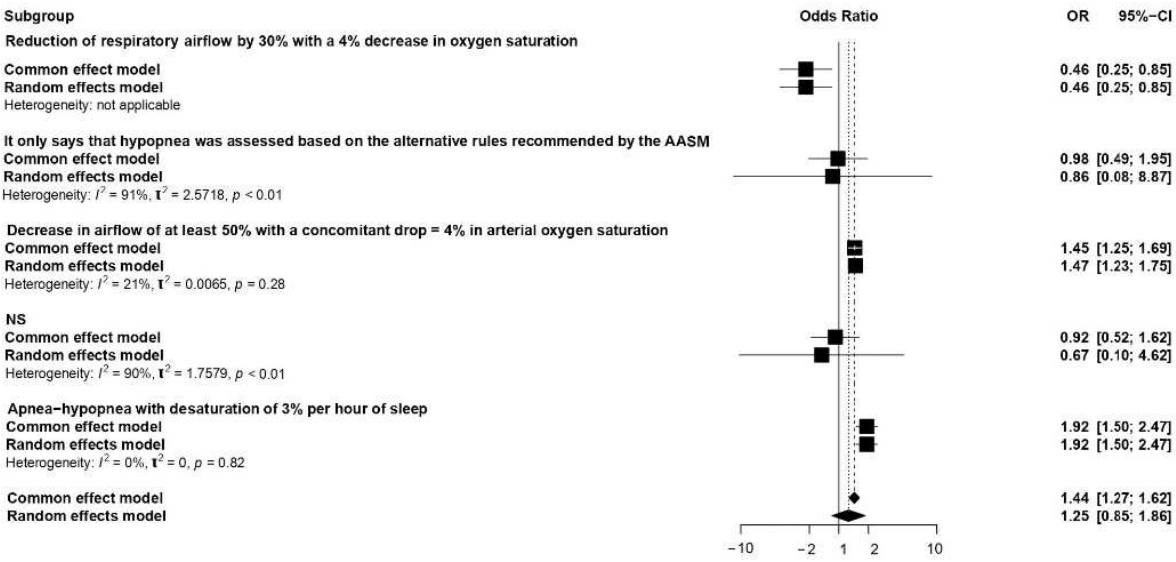

Fig. 4 Forest plot of genetic associations with OSA by diagnostic criteria, comparing airflow cessation and apnea-hypopnea events. Analysis shows pooled estimates using random effects models with odds ratios and 95% confidence intervals. RE: random effect; OR: Odds Ratio; CI: Confidence Interval.

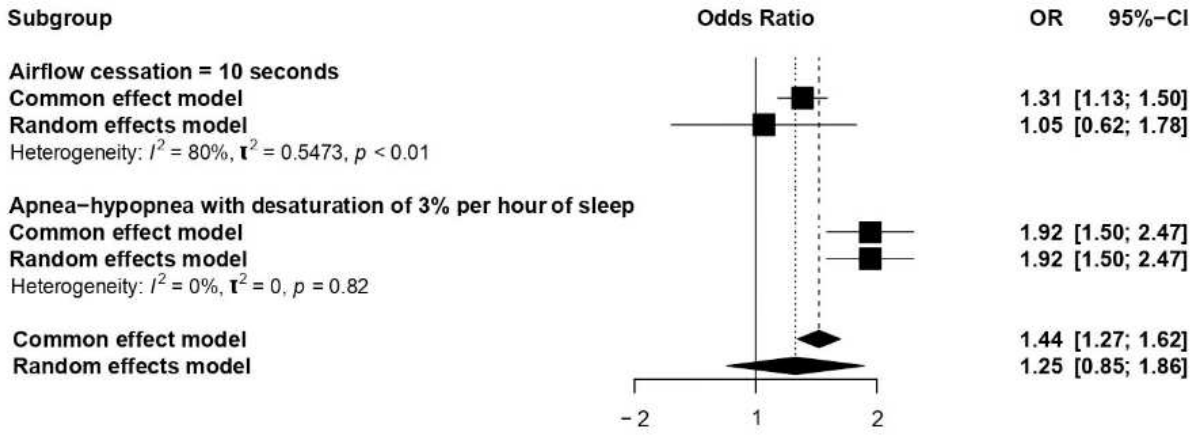

Fig. 5 Pooled estimates of studies evaluating genetic associations with OSA by definition of apnea-hypopnea event, comparing different diagnostic thresholds with common and random effects models. RE: random effect; OR: Odds Ratio; CI: Confidence Interval.

The subgroup analysis based on varying diagnostic criteria revealed distinct genetic associations with OSA. Studies employing a diagnostic threshold of AHI > 5 events/hour reported a pooled OR of 1.27 [95% CI: 0.83–1.95], with notable heterogeneity (I^2 = 76%, p <

0.01). In studies using more stringent criteria, such as AHI ≥ 15 events/hour, the genetic association with OSA was stronger, yielding an OR of 1.37 [95% CI: 0.70–2.69] and moderate heterogeneity (I^2 = 75%, p < 0.01). Conversely, when the diagnostic criteria included both AHI ≥ 5 with symptoms or AHI ≥ 15 regardless of symptoms, the pooled OR dropped to 0.86 [95% CI: 0.08–8.87], showing the weakest association and the highest heterogeneity (I^2 = 91%, p < 0.01). These findings, summarized in **Fig. 6**, also highlight the critical influence of phenotype definitions on the strength and consistency of genetic associations in OSA research.

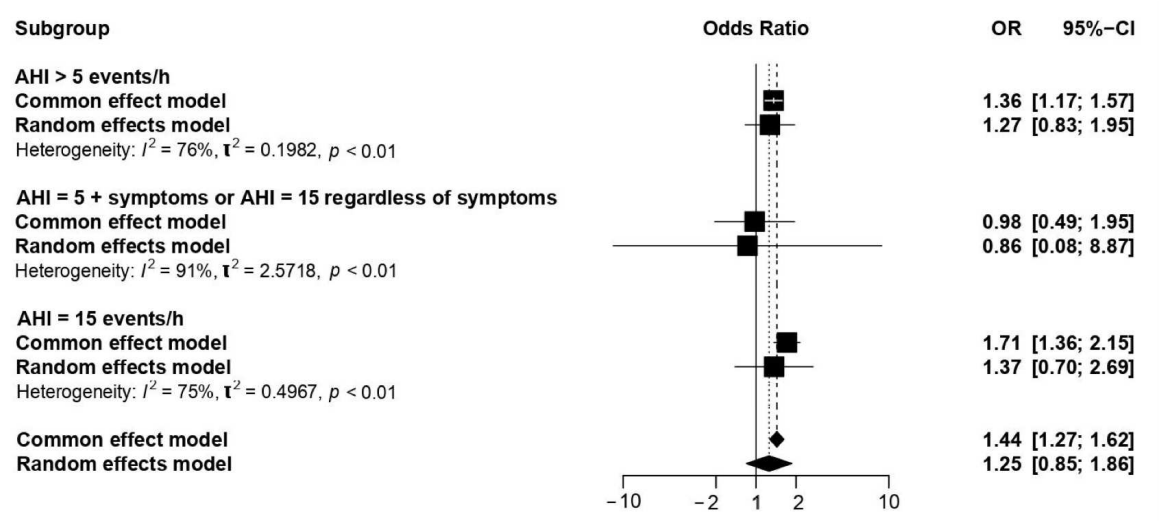

Fig. 6 Forest plot of genetic associations with OSA stratified by diagnostic criteria showing subgroup analysis of AHI thresholds. Results display odds ratios and 95% confidence intervals with heterogeneity assessments. RE: random effect; OR: Odds Ratio; CI: Confidence Interval.

Heterogeneity and Publication Bias

A significant amount of heterogeneity in several subgroup analyses, especially in those that involved distinct ethnic populations (I^2 = 76%, p < 0.01). This implies that underlying ethnic and genetic factors are probably influencing the genetic connections with OSA occurrence.

The findings of this meta-analysis point to a moderately strong correlation, with notable inter-ethnic variability, between the occurrence of OSA and a few genetic variants. These results highlight how crucial it is to take genetic history and heritage into account while managing OSA clinically.

Discussion

This systematic review and meta-analysis provides important insights into the complex relationship between genetic polymorphisms, ethnicity, and OSA risk. Our findings reveal significant ethnic variations in genetic susceptibility to OSA and identify key pathways through which genetic factors may influence disease development.

The meta-analysis identified a modest overall association between genetic variants and OSA (OR 1.25 [95% CI: 0.85-1.86]), but with significant heterogeneity (I^2 = 76%, p < 0.01) that

appears largely attributable to ethnic differences. Notably, we found striking ethnic variations in genetic susceptibility, with Brazilians of European ethnicity showing significantly increased risk (OR 2.80 [95% CI: 1.11-7.08]) while those with West African ethnicity demonstrated protection against OSA (OR 0.26 [95% CI: 0.09-0.74]). These findings align with previous admixture mapping studies in Hispanic/Latino populations that have identified differential genetic effects based on ethnicity background.[12]

The genetic associations with OSA showed a distinct pattern in sex-stratified analyses (**Fig. 3**), with stronger effects observed in males (OR 1.59 [95% CI: 1.21-2.08]) compared to mixed-sex populations (OR 1.16 [95% CI: 0.70-1.90]). This difference supports existing clinical evidence indicating sexual dimorphism in OSA presentation and progression. The findings align with previous large-scale genetic studies, such as the Million Veteran Program, which revealed sex-specific genetic architectures in OSA.[5] However, it is important to note the significant heterogeneity observed in the analyses (I^2 = 80% for mixed-sex populations and 25% for males). This heterogeneity likely reflects variability in population characteristics, study designs, and genetic markers evaluated across studies. Such variability underscores the complexity of genetic contributions to OSA and highlights the necessity for future studies to adopt standardized methodologies and carefully account for population-specific factors. These results emphasize the importance of considering sex as a biological variable in genetic research and suggest that tailored interventions based on sex may optimize OSA management and outcomes.

The analysis of varying diagnostic criteria for OSA, as presented in **Fig. 6**, demonstrates that the genetic association with OSA is most pronounced when applying a threshold of AHI ≥ 15 events/hour (OR 1.71 [95% CI: 1.36–2.15]). This stronger association suggests that genetic factors may exert a greater influence on more severe cases of the condition. Conversely, studies utilizing less stringent diagnostic criteria, such as AHI > 5 events/hour, reported weaker associations (OR 1.27 [95% CI: 0.83–1.95]), while those using combined criteria (AHI ≥ 5 with symptoms or AHI ≥ 15 regardless of symptoms) yielded the weakest association (OR 0.86 [95% CI: 0.08–8.87]) and the highest heterogeneity (I^2 = 91%, $p < 0.01$). These findings highlight the importance of diagnostic standardization and suggest that more severe disease phenotypes may be more strongly influenced by genetic factors. This aligns with evidence from twin studies, which indicate greater heritability for severe forms of OSA compared to mild or moderate cases. The observed heterogeneity across diagnostic thresholds underscores the complexity of genetic contributions to OSA and emphasizes the need for consistency in phenotype definitions to improve the reliability of genetic association studies.[17-18]

Our findings regarding inflammatory pathway genes are particularly noteworthy. The associations with CRP variants in European Americans persisted after BMI adjustment, suggesting inflammation may contribute to OSA pathogenesis independently of obesity. This supports emerging evidence that OSA may be maintained and exacerbated by inflammatory mechanisms beyond simple anatomical considerations.[16, 19]

The protective effect of certain leptin receptor variants in Chinese populations, particularly the LEPR rs3790435 CC genotype, provides new insights into the genetic basis of OSA in Asian populations. This finding may help explain some of the ethnic differences in OSA susceptibility, though larger studies in Asian populations are needed for confirmation.[15]

Serotonergic pathway genes showed consistent associations across populations, with variants in HTR2A and 5-HTT demonstrating effects on OSA risk. The identification of the HTR2A rs9526240 variant as a risk factor specifically in African Americans represents a novel finding that may have therapeutic implications, given the role of serotonergic mechanisms in upper airway control.[6-7]

Our analysis of apnea-hypopnea event subgroups, as depicted in **Fig. 5**, underscores the importance of standardized diagnostic criteria in genetic studies of OSA. The findings revealed a stronger genetic association when using AHI criteria that included a 3% oxygen desaturation requirement (OR 1.92 [95% CI: 1.50-2.47]). This robust association suggests that genetic factors may have a greater impact on phenotypes defined by more stringent clinical thresholds, which likely represent more severe disease presentations. These results align with previous research emphasizing the significance of phenotype definitions in elucidating genetic underpinnings of OSA. Such standardization may also help address the heterogeneity observed in earlier studies, facilitating a clearer understanding of how genetic variations contribute to the pathophysiology of OSA. Future research should prioritize the use of consistent diagnostic criteria to enhance the comparability and reliability of genetic findings in this field. [1,20]

Some limitations should be considered in this study. First, while we identified significant ethnic differences in genetic effects, the number of studies in some populations was small, limiting our ability to draw firm conclusions about population-specific associations. Second, the heterogeneity in OSA definition and degree of severity classification across studies complicated the interpretation of pooled estimates. Additionally, the reliance on self-reported ethnicity in some studies may have led to misclassification of genetic ethnicity. [11,14,21]

These findings have important implications for both research and clinical practice. The strong ethnic variation in genetic effects suggests that genetic risk prediction tools for OSA may need to be ethnicity-specific. The identification of pathway-specific associations (inflammatory, serotonergic, and metabolic) provides potential therapeutic targets that may be more or less relevant in different populations [11, 12, 14]. This aligns with recent studies showing differential genetic effects based on ancestry background in Hispanic/Latino populations [12], and findings from the Million Veteran Program that revealed distinct genetic architectures across ethnic groups [5]. Studies on Chinese Han, Hispanic, and African American populations have demonstrated varying levels of genetic markers for OSA, suggesting the need for ancestry-informed therapeutic approaches [12, 13]. The implications for treatment are particularly relevant given the emerging evidence from admixture mapping studies that highlight how genetic predisposition to OSA and treatment responses can vary significantly across different ancestral backgrounds [12].

Future research should focus on large-scale genetic studies in non-European populations, given the significant ethnic differences observed. Additionally, standardization of OSA phenotype definitions and degree of severity criteria would facilitate more robust genetic association studies. The role of gene-environment interactions, particularly with factors like obesity and craniofacial structure, also warrants further investigation. [2,10,12]

The significant heterogeneity observed in our analyses (I^2 ranging from 75-92% across different subgroups) underscores the complex nature of OSA genetics and suggests that larger, more ethnically diverse cohorts will be needed to fully understand the genetic architecture of

this disorder. The stronger genetic associations observed with standardized diagnostic criteria also highlight the importance of careful phenotype definition in future genetic studies of OSA. [2,10,12]

Conclusion

This systematic review and meta-analysis demonstrate the important impact that genetic variants play in the occurrence and degree of severity of obstructive sleep apnea. Understanding these genetic predispositions requires an awareness of the role played by ethnicity, with certain ethnic groups exhibiting a higher hereditary risk for severe OSA and others perhaps possessing protective genetic characteristics. These results highlight the need for more study in a variety of ethnic groups to improve our understanding of the genetic contributions to this prevalent and significant sleep disease, and they have significant implications for the future of personalized health care in the therapy of OSA.

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Appendix A - Search Strategy

Databases to be Searched

- PubMed
- EMBASE
- Web of Science
- LILACS
- WPRIM
- Cochrane Library

Search Terms and Strategy

1. PubMed Search Strategy:

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#1 "Sleep Apnea Syndromes"[Mesh] OR "Apnea Syndrome, Sleep" OR "Apnea Syndromes, Sleep" OR "Sleep Apnea Syndrome" OR "Apnea, Sleep" OR "Apneas, Sleep" OR "Sleep Apnea" OR "Sleep Apneas" OR "Sleep Hypopnea" OR "Hypopnea, Sleep" OR "Hypopneas, Sleep" OR "Sleep Hypopneas" OR "Hypersomnia with Periodic Respiration" OR "Sleep Apnea, Mixed Central and Obstructive" OR "Mixed Central and Obstructive Sleep Apnea" OR "Sleep Apnea, Mixed" OR "Mixed Sleep Apnea" OR "Mixed Sleep Apneas" OR "Sleep Apneas, Mixed" OR "Sleep-Disordered Breathing" OR "Breathing, Sleep-Disordered" OR "Sleep Disordered Breathing" OR "Sleep Apnea, Obstructive"[Mesh] OR "Apneas, Obstructive Sleep" OR "Obstructive Sleep Apneas" OR "Sleep Apneas, Obstructive" OR "Apnea, Obstructive Sleep" OR "Sleep Apnea Hypopnea Syndrome" OR "Obstructive Sleep Apnea Syndrome" OR "Obstructive Sleep Apnea" OR "Syndrome, Obstructive Sleep Apnea" OR "Syndrome, Sleep Apnea, Obstructive" OR "Sleep Apnea Syndrome, Obstructive" OR "OSAHS" OR "Upper Airway Resistance Sleep Apnea Syndrome" OR "Syndrome, Upper Airway Resistance, Sleep Apnea"

#2 "Racial Groups"[Mesh] OR "Group, Racial" OR "Groups, Racial" OR "Racial Group" OR "Race" OR "Races" OR "Racial Stocks" OR "Racial Stock" OR "Stock, Racial" OR "Stocks, Racial" OR "Continental Population Groups" OR "Continental Population Group" OR "Group, Continental Population" OR "Groups, Continental Population" OR "Population Group, Continental" OR "Population Groups, Continental" OR "Pedigree"[Mesh] OR "Ethnicity"[Mesh] OR "Nationality" OR "Nationalities" OR "Ethnic Groups" OR "Ethnic Group"

#3  "Genetics"[Mesh] OR "Polymorphism, Genetic"[Mesh] OR "Polymorphisms, Genetic" OR "Gene Polymorphism" OR "Gene Polymorphisms" OR "Polymorphism, Gene" OR "Polymorphisms, Gene" OR "Polymorphism (Genetics) " OR "Polymorphisms (Genetics) " OR "Genetic Polymorphisms" OR "Genetic Polymorphism"

#1 AND #2 AND #3

("Sleep Apnea Syndromes"[MeSH Terms] OR "apnea syndrome sleep"[All Fields] OR ("Sleep Apnea Syndromes"[MeSH Terms] OR ("sleep"[All Fields] AND "apnea"[All Fields]
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AND "syndromes"[All Fields]) OR "Sleep Apnea Syndromes"[All Fields] OR ("apnea"[All Fields] AND "syndromes"[All Fields] AND "sleep"[All Fields])) OR "Sleep Apnea Syndrome"[All Fields] OR "apnea sleep"[All Fields] OR "apneas sleep"[All Fields] OR "Sleep Apnea"[All Fields] OR "Sleep Apneas"[All Fields] OR "Sleep Hypopnea"[All Fields] OR "hypopnea sleep"[All Fields] OR "hypopneas sleep"[All Fields] OR "Sleep Hypopneas"[All Fields] OR "Hypersomnia with Periodic Respiration"[All Fields] OR ("Sleep Apnea Syndromes"[MeSH Terms] OR ("sleep"[All Fields] AND "apnea"[All Fields] AND "syndromes"[All Fields]) OR "Sleep Apnea Syndromes"[All Fields] OR ("sleep"[All Fields] AND "apnea"[All Fields] AND "mixed"[All Fields] AND "central"[All Fields] AND "obstructive"[All Fields])) OR "Mixed Central and Obstructive Sleep Apnea"[All Fields] OR "sleep apnea mixed"[All Fields] OR "Mixed Sleep Apnea"[All Fields] OR "Mixed Sleep Apneas"[All Fields] OR ("Sleep Apnea Syndromes"[MeSH Terms] OR ("sleep"[All Fields] AND "apnea"[All Fields] AND "syndromes"[All Fields]) OR "Sleep Apnea Syndromes"[All Fields] OR ("sleep"[All Fields] AND "apneas"[All Fields] AND "mixed"[All Fields])) OR "sleep disordered breathing"[All Fields] OR "breathing sleep disordered"[All Fields] OR "sleep disordered breathing"[All Fields] OR "sleep apnea, obstructive"[MeSH Terms] OR "apneas obstructive sleep"[All Fields] OR "Obstructive Sleep Apneas"[All Fields] OR "sleep apneas obstructive"[All Fields] OR "apnea obstructive sleep"[All Fields] OR "Sleep Apnea Hypopnea Syndrome"[All Fields] OR "Obstructive Sleep Apnea Syndrome"[All Fields] OR "Obstructive Sleep Apnea"[All Fields] OR "syndrome obstructive sleep apnea"[All Fields] OR "syndrome sleep apnea obstructive"[All Fields] OR "sleep apnea syndrome obstructive"[All Fields] OR "OSAHS"[All Fields] OR "Upper Airway Resistance Sleep Apnea Syndrome"[All Fields] OR ("sleep apnea, obstructive"[MeSH Terms] OR ("sleep"[All Fields] AND "apnea"[All Fields] AND "obstructive"[All Fields]) OR "Obstructive Sleep Apnea"[All Fields] OR ("syndrome"[All Fields] AND "upper"[All Fields] AND "airway"[All Fields] AND "resistance"[All Fields] AND "sleep"[All Fields] AND "apnea"[All Fields]))) AND ("Racial Groups"[MeSH Terms] OR "group racial"[All Fields] OR "groups racial"[All Fields] OR "Racial Group"[All Fields] OR "Race"[All Fields] OR "Races"[All Fields] OR "Racial Stocks"[All Fields] OR "Racial Stock"[All Fields] OR ("Racial Groups"[MeSH Terms] OR ("racial"[All Fields] AND "groups"[All Fields]) OR "Racial Groups"[All Fields] OR ("stock"[All Fields] AND "racial"[All Fields])) OR ("Racial Groups"[MeSH Terms] OR ("racial"[All Fields] AND "groups"[All Fields]) OR "Racial Groups"[All Fields] OR ("stocks"[All Fields] AND "racial"[All Fields])) OR "Continental Population Groups"[All Fields] OR "Continental Population Group"[All Fields] OR ("Racial Groups"[MeSH Terms] OR ("racial"[All Fields] AND "groups"[All Fields]) OR "Racial Groups"[All Fields] OR ("group"[All Fields] AND "continental"[All Fields] AND "population"[All Fields])) OR ("Racial Groups"[MeSH Terms] OR ("racial"[All Fields] AND "groups"[All Fields]) OR "Racial Groups"[All Fields] OR ("groups"[All Fields] AND "continental"[All Fields] AND "population"[All Fields])) OR ("Racial Groups"[MeSH Terms] OR ("racial"[All Fields] AND "groups"[All Fields]) OR "Racial Groups"[All Fields] OR ("population"[All Fields] AND "group"[All Fields] AND "continental"[All Fields])) OR ("Racial Groups"[MeSH Terms] OR ("racial"[All Fields] AND "groups"[All Fields]) OR "Racial Groups"[All Fields] OR ("population"[All Fields] AND "groups"[All Fields] AND "continental"[All Fields])) OR "Pedigree"[MeSH Terms] OR "Ethnicity"[MeSH Terms] OR "Nationality"[All Fields] OR "Nationalities"[All Fields] OR "Ethnic Groups"[All Fields] OR "Ethnic Group"[All Fields]) AND ("Genetics"[MeSH Terms] OR "polymorphism, genetic"[MeSH Terms] OR

"polymorphisms genetic"[All Fields] OR "Gene Polymorphism"[All Fields] OR "Gene Polymorphisms"[All Fields] OR "polymorphism gene"[All Fields] OR "polymorphisms gene"[All Fields] OR "polymorphism genetics"[All Fields] OR "polymorphisms genetics"[All Fields] OR "Genetic Polymorphisms"[All Fields] OR "Genetic Polymorphism"[All Fields])

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24 studies

**2. Embase Search Strategy:**

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#3 AND #7 AND #10
237
#10
#8 OR #9
2,715,851
#9
'genetic polymorphism'/exp OR 'genetic polymorphism'/syn
507,073
#8
'genetics'/exp OR 'genetics'/syn
2,415,973
#7
#4 OR #5 OR #6
753,714
#6
'ethnicity'/exp OR 'ethnicity'/syn
202,307
#5
'race'/exp OR 'race'/syn
297,766
#4
'ancestry group'/exp OR 'ancestry group'/syn
465,910
#3
#1 OR #2
116,888
#2
'sleep apnea, obstructive'/exp OR 'sleep apnea, obstructive'/syn
67,628
#1
'sleep apnea syndromes'/exp OR 'sleep apnea syndromes'/syn
116,445
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3. Web of Science Search Strategy:

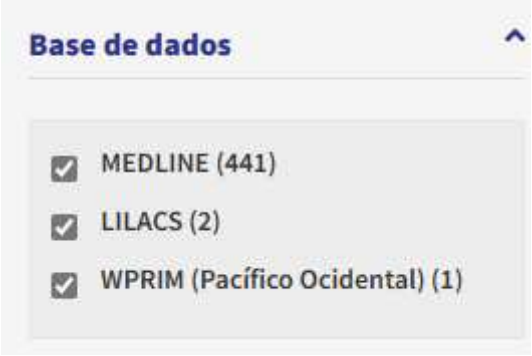
```
(Sleep Apnea Syndromes) OR (Sleep Apnea, Obstructive)  AND (Racial Groups) OR (Pedigree) OR (Ethnicity)  AND (Genetics) OR (Polymorphism, Genetic)
```

22 studies

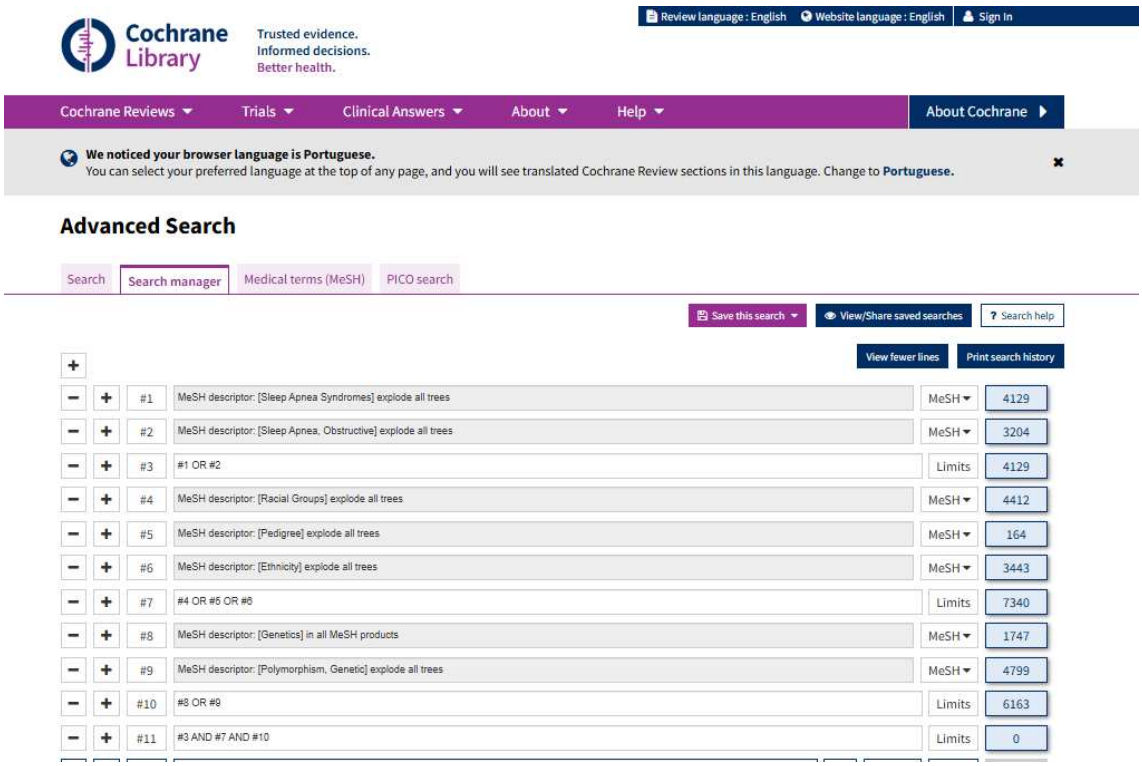
3. BVS Search Strategy:

```
**#1 "Síndromes da Apneia do Sono" OR "Sleep Apnea Syndromes" OR "Síndromes de la Apnea del Sueño"** OR **"Apneia Obstrutiva do Sono" OR "Sleep Apnea, Obstructive" OR  "Apnea Obstructiva del Sueño"**

**"Grupos Raciais" OR "Racial Groups" OR "Grupos Raciales" OR  "Linhagem" OR "Pedigree" OR "Linaje" OR "Etnicidade" OR "Ethnicity" OR  "Etnicidad"**

**"Genética" OR "Genetics" OR" Polimorfismo Genético" OR "Polymorphism, Genetic"**

("Síndromes da Apneia do Sono" OR "Sleep Apnea Syndromes" OR  "Síndromes de la Apnea del Sueño" OR "Apneia Obstrutiva do Sono" OR "Sleep Apnea, Obstructive" OR  "Apnea Obstructiva del Sueño") AND ("Grupos Raciais" OR "Racial Groups" OR "Grupos Raciales" OR  "Linhagem" OR  "Pedigree" OR "Linaje" OR "Etnicidade" OR "Ethnicity" OR "Etnicidad") AND ("Genética" OR  "Genetics" or" Polimorfismo Genético" OR "Polymorphism, Genetic")
```

444 studies



5. Cochrane Search Strategy:



Search Restrictions

- Language: English, Spanish, Portuguese

Appendix B - Exclusion Reasons

In the present systematic review and meta-analysis, the exclusion reasons used during the studies screening process were based on the inclusion and exclusion criteria established:

Exclusion Reasons:

1. **Participants:**
    - Studies involving **children or adolescents** (under 18 years old). The review focused exclusively on adults with a confirmed diagnosis of Obstructive Sleep Apnea (OSA).
    - Studies with **participants without a confirmed diagnosis of OSA**. Studies that did not confirm the clinical condition of OSA were excluded.
2. **Interventions:**
    - Interventions not **related to the treatment of OSA** were excluded. This includes treatments targeting other health conditions without a direct relation to OSA.
    - Studies evaluating interventions that were inappropriate or not recognized for OSA treatment were excluded.
3. **Comparators:**
    - Studies that **did not use standard treatment**, placebo, or another active intervention as a comparator.
    - Studies that did not present adequate or clearly defined comparators were also excluded.
4. **Study Designs:**
    - **Narrative reviews**, systematic reviews, and meta-analyses that had already been published were excluded, as the goal was to conduct an original analysis of primary data.
    - **Case reports and case series**. Studies that reported only case studies without a control group or comparative analysis were excluded.
    - **Non-observational studies** (randomized clinical trials and observational studies were considered suitable, but editorials, letters to the editor, and literature reviews without primary data analysis were excluded).
5. **Other Factors:**
    - Studies that **did not segregate data by ethnicity** or did not provide genomic information, which hindered the analysis of the impact of ethnicity and molecular markers.
    - Studies in which the primary outcomes were not directly related to the degree of severity or occurrence of OSA in specific populations according to genetic variations.

These reasons were applied to ensure that the articles included in the systematic review strictly met the eligibility criteria and aligned with the review's objectives of evaluating the influence of ethnicity and molecular markers on the degree of severity of OSA.