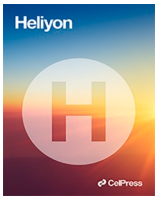
Heliyon 10 (2024) e27213

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Meta-analysis investigating the impact of the LEPR rs1137101 (A>G) polymorphism on obesity risk in Asian and Caucasian ethnicities

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ARTICLE INFO

Keywords:
Obesity
Genetic predisposition
LEPR polymorphism
Meta-analysis

ABSTRACT

Obesity is a chronic condition which is identified by the buildup of excess body fat caused by a combination of various factors, including genetic predisposition and lifestyle choices. rs1137101 (A > G) polymorphism in the CHR1 domain of LEPR protein linked to different diseases including obesity. Nevertheless, the connection between this polymorphism and the likelihood of developing obesity has not been determined definitively. Therefore, a meta-analysis was conducted to assess the relationship between rs1137101 and the risk of obesity. The meta-analysis included all studies meeting pre-defined criteria, found through searching databases up until February 2023. A combined odds ratio with a 95% confidence interval was estimated as overall and in continent subgroups for homozygous, heterozygous, recessive, dominant and allelic models using the fixed or the random-effects model. The meta-analysis identified 39 eligible studies with cases and controls (6099 cases/6711 controls) in 38 articles under different ethnic backgrounds. The results indicated a significant relationship between rs1137101 and the likelihood of developing obesity in each of the genetic models [the homozygous model (GG vs. AA: 95% Confidence Interval = 1.12–1.73, Odds Ratio = 1.39, P value = 0.003); the heterozygous model (AG vs. AA: 95% Confidence Interval = 1.07–1.42, Odds Ratio = 1.23, P value = 0.005); the dominant model (AG/GG vs AA: 95% Confidence Interval = 1.10–1.49, Odds Ratio = 1.28, P value = 0.001); the recessive model (GG vs AA/AG: 95% Confidence Interval = 1.02–1.45, Odds Ratio = 1.21, P value = 0.03); and the allelic model (G vs A; 95% Confidence Interval = 1.07–1.33, Odds Ratio = 1.19, P value = 0.002)] tested. Additionally, with an FDR <0.05, all genotypic models demonstrated statistical significance. The association remained significant among subgroups of Asian and Caucasian populations, although analysis in some genetic models did not show a significant association. Begg's and Egger's tests did not show publication biases. In sensitivity analysis, one particular study was found to have an impact on the Recessive model's significance, but other

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https://doi.org/10.1016/j.heliyon.2024.e27213
Received 3 July 2023; Received in revised form 12 December 2023; Accepted 26 February 2024
Available online 4 March 2024

models remained unaffected. The current meta-analysis found significant indications supporting the association between rs1137101 and obesity. To avail a deeper understanding of this association, future research should include large-scale studies conducted in diverse ethnic populations.

1. Introduction

The term obesity is characterized as an abnormal and excessive accumulation of body fat. This condition not only poses a risk to leading a healthy lifestyle but is also increasingly prevalent worldwide [1,2]. World Health Organization (WHO) recommended a Body Mass Index (BMI) of 30 or more are classified as obese in adulthood, while in children underneath 5 years, a weight-for-height ratio more than 3 and a BMI-for-age ratio greater than 2 in 5- to 19-year-old children are considered signs of obesity. According to data from 2016, approximately 1.9 billion (13%) adults were classified as obese in the world in which women were found (13%) more obese than men (11%) [2–4]. Research suggests that childhood and teenage obesity is linked with obesity in adulthood that is associated with a range of health disorders specially cancer, type 2 diabetes, and cardiovascular problems [5–7]. Lauby-Secretan et al. suggested that there was enough data to link overweight, and obesity with different types of thirteen cancers [8]. Obesity or overweight condition is a complex metabolic disorder and involves the complicated interaction of numerous elements, including genetic, ecological, dietary, personal habits, affecting the progression of adiposity as well as obesity [9]. On the basis of genetic as well as phenotypic traits, there are three different obesity types. Among them, monogenic obesity is mostly caused due to mutations in different genes which include proopiomelanocortin (POMC) genes, leptin (LEP) genes, melanocortin-4 receptor (MC4R) genes, and leptin receptor (LEPR) genes. These mutations affect the melanocortin/leptin pathway, which controls appetite [10].

Leptin (LEP) is an anti-obesity non-glycosylated hormone encoded by the LEP gene belonging to the family of type 1 cytokine receptors [11,12]. Leptin controls body mass by modulating food consumption and energy utilization [13]. Leptin performs its function by interacting with a particular receptor known as the leptin receptor (LEPR). Leptin receptors are single transmembrane proteins of the type 1 cytokine receptors family usually located in the hypothalamus and brain and widely present in the liver, gonads, kidneys, and adipose tissue [14]. Different studies reported several mutations in the LEPR gene [15–17] that alter the function of leptin by decreasing the binding affinity between leptin and leptin receptor [18,19]. The LEPR gene with 24 exons at 1p31.3 has a mutation (NC_000001.11:g.65592830A > G) called rs1137101 in exon 6 in the CRH1 domain. This alteration involves the replacement of glutamine with arginine at position 223 (Gln223Arg) within the LEPR protein [15,17,20]. CRH1 is indispensable for leptin and the leptin receptor's CHR2 domain to interact with strong affinity [20] where rs1137101 polymorphism in the CHR1 domain linked to different diseases including obesity as reported in previous studies [21–24]. Major A allele and Minor G allele frequencies for rs1137101 found from the 1000 Genome project is 54% and 46% respectively which differ across various ethnic populations [20].

Over the past ten years, advancements in Single nucleotide polymorphism (SNP) genotyping methods along with genome-wide association studies (GWAS) makes it easier to mark out obesity risk associated with multiple loci or SNPs [25]. Several GWAS conducted on different ethnic populations elucidated the link between LEPR rs1137101 polymorphism with obesity risk, increasing plasma leptin level, body weight, and body composition variability [14,21,26–28], whereas some other studies did not find any association with obesity [29–33]. According to the findings of these research, association of Q223R polymorphism with the risk of obesity is contested as well as equivocal. Therefore, to shed more light on the potential link of Gln223Arg polymorphism of LEPR and obesity, this study undertook an extensive analysis of data from 39 GWAS. The study included a diverse population of individuals from Asian, Caucasian, and African ethnic groups, with a total of 6099 cases and 6711 controls.

2. Materials and methods

2.1. Data acquisition

To find studies examining how the polymorphism (rs1137101) in the LEPR gene relates to obesity susceptibility, an extensive search of articles in several online electronic databases, namely PubMed Central, Science Direct and Google Scholar were employed upon. The search covered articles published from the inception of these databases up to February 2023 and pertinent articles were filtered for further analysis. The study utilized a systematic search strategy that incorporated the polymorphism-related terms (encompassing the MeSH term "Polymorphism, Single Nucleotide") in combination with obesity-related terms (encompassing the MeSH term "obesity"). A set of precise keywords, including "leptin receptor gene" OR "LEPR" AND ″Q223R" OR "rs1137101" OR ″668A > G″ OR ″668A/G″ AND "obesity" OR "Adiposity" OR "Adipose tissue" OR "Body composition" OR "Over-Weight" OR "Weight" OR "Body Mass Index" OR "BMI" were used. Reference lists from the retrieved articles were also checked to find out if there were further papers that hadn't been identified through the aforementioned search approach. In the event of multiple publications on the same subjects, the study providing the most comprehensive analysis were selected.

2.2. Data eligibility criteria

A number of eligibility criteria were considered to find studies that fit the criteria for the research question. This study investigated the link between the LEPR gene polymorphism (rs1137101) and a susceptibility to obesity, the inclusion and exclusion criteria were considered to ensure that only studies with high-quality data and relevant information were included.

The following were the inclusion criteria taken into consideration in this meta-analysis: 1) The study ought to be a unique case-control study focused on humans, either from same population or different populations, 2) Publication of the study in peer-reviewed journals is necessary, 3) The investigation of the correlation between the LEPR gene polymorphism (rs1137101) and obesity requires separate, independent genome-wide association studies as well as genetic association studies, 4) The study should process relevant allelic and genotypic frequency details of both case and control groups, enabling the calculation of p-value and OR along with 95% confidence interval, and 5) The study should include information regarding the genotyping procedure and technique along with the ethnic background of the participants being studied.

In contrast, the criteria for exclusion were used to exclude studies that did not meet the above inclusion criteria. The criteria for exclusion were considered in this meta-analysis were: 1) The study should not be a review article, editorial, case report, or commentary, 2) Studies with no healthy control group, 3) Studies which include inaccessible data were not extracted, 4) Studies without genotypic models and ethnic stipulations, and 5) Studies investigating the association of SNP rs1137101 of LEPR gene with disorders other than obesity.

2.3. Data extraction and quality appraisal

The following information was taken from each of the publications that was chosen: first author name, publication year, country, ethnicity of the subjects (Asian vs. Caucasian), genotyping techniques, the number of cases and controls, the genotype and frequency of alleles, deviation from the control genotype distribution, and body mass index (BMI). In instances where the publications did not specify the conduct of a Hardy-Weinberg equilibrium (HWE) test, the genotype data were utilized to perform the test. Any discrepancies in the collection of data and quality assessment procedures were clarified by consulting a third reviewer.

2.4. Statistical analysis

The assessment of the association between LEPR gene polymorphism (rs1137101) and obesity was conducted by calculating odds ratios (ORs) and their corresponding 95% confidence intervals (CIs). Five different genetic models (allele, dominant, recessive, heterozygous and homozygous) were utilized to determine the total ORs, with each model producing its own separate estimate. The combined ORs for LEPR rs1137101 (A > G) were calculated by using homozygous model (GG vs. AA), heterozygous model (AG vs. AA),

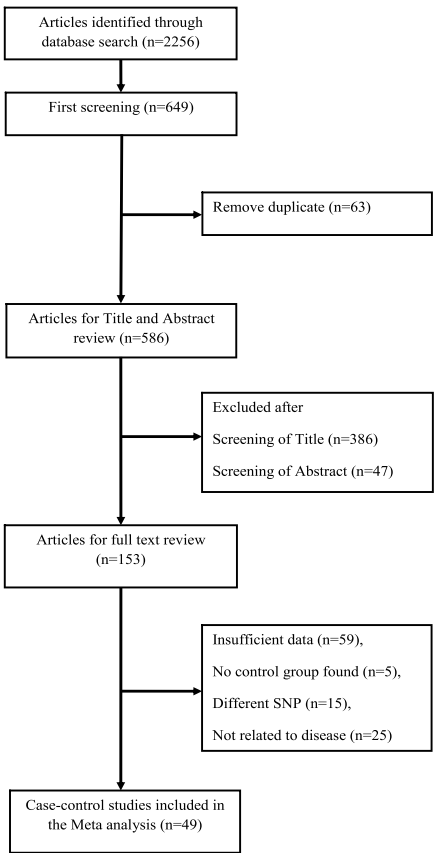


Fig. 1. A flow diagram depicting the study selection process and the literature search.

Table 1
Information on the Genotype and Features of the Studies Chosen for the rs1137101 Meta-Analysis.

Author name	Publication year	Ethnicity	Country	Genotyping technique	No. of Cases	No. of Controls	AA Case	AG Case	GG Case	AA Control	AG Control	GG Control	HWE
Endo [50]	2000	Asian	Japan	PCR-RFLP	90	463	2	25	63	13	109	341	0.24
Yiannakouris [21]	2001	Caucasian	Turkey	PCR-RFLP	29	89	13	10	6	39	46	4	0.04
Mattevi [51]	2002	Caucasian	Brazil	PCR-RFLP	183	152	52	97	34	59	80	13	0.05
Guízar-Mendoza [52]	2005	Caucasian	Mexico	PCR-RFLP	55	48	24	29	2	18	25	5	0.49
Portole's [53]	2006	Caucasian	Spain	PCR	293	570	135	132	26	244	249	77	0.29
Duarte [27]	2007	Caucasian	Brazil	PCR-RFLP	200	150	53	120	27	56	71	23	0.95
Mergen [54]	2007	Caucasian	Turkey	PCR	262	138	92	141	29	65	61	12	0.66
Pyrżak [55]	2008	Caucasian	Poland	PCR-RFLP	101	41	21	56	24	13	22	6	0.49
Mizuta [56]	2008	Asian	Japan	Taqman PCR	913	908	684	201	28	664	229	15	0.35
Ali [14]	2009	Caucasian	Tunisia	PCR-RFLP	391	302	133	198	60	113	140	49	0.61
Liew [57]	2009	Asian	Malaysia	PCR-RFLP	50	112	22	19	9	51	43	18	0.09
Constantin [58]	2010	Caucasian	Romania	PCR-RFLP	108	94	29	59	20	33	52	9	0.08
Boumaiza [59]	2012	Caucasian	Tunisia	PCR-RFLP	160	169	58	67	35	78	65	26	0.05
Angel-Chávez [60]	2012	Caucasian	Mexico	PCR-RFLP	76	52	20	35	21	17	22	13	0.28
Shahid [61]	2012	Asian	Pakistan	PCR-RFLP	237	131	105	98	34	57	56	18	0.58
Linjawi [62]	2012	Asian	Saudi-Arabia	PCR-RFLP	74	106	34	30	10	49	48	9	0.56
Komsu-Ornek [48]	2012	Caucasian	Turkey	PCR-RFLP	92	99	25	30	37	24	31	44	0.0006
Oliveira [63]	2013	Caucasian	Brazil	PCR-RFLP	148	178	62	61	25	84	78	16	0.73
Şahın [33]	2013	Caucasian	Turkey	PCR-RFLP	127	105	50	56	21	50	46	9	0.73
Jonathan [64]	2013	Caucasian	Mexico	PCR-RFLP	117	43	27	61	29	6	27	10	0.08
Fan [45]	2014	Asian	Malaysia	PCR-RFLP	190	218	14	59	117	14	58	146	0.02
Janković [65]	2014	Caucasian	Croatia	PCR-RFLP	30	30	12	13	5	8	19	3	0.097
Reyes [66]	2015	Caucasian	Mexico	PCR-RFLP	100	100	33	46	21	30	50	20	0.92
Chavarria-Avila [67]	2015	Caucasian	Mexico	PCR-RFLP	82	154	15	50	17	52	65	37	0.067
Shabana [43]	2015	Asian	Pakistan	PCR	250	225	138	65	47	161	43	21	<0.00001
Mărginean [68]	2016	Caucasian	Romania	PCR-RFLP	121	143	20	74	27	54	63	26	0.32
Gajewska [69]	2016	Caucasian	Poland	PCR-RFLP	101	67	27	53	21	14	35	18	0.69
Abdalla [70]	2016	Asian	Egypt	PCR-RFLP	44	44	14	20	10	33	10	1	0.82
Yevleva [49]	2016	Caucasian	Russia	PCR-RFLP	65	58	25	28	12	21	24	13	0.23
S.V. Zyablitsev [71]	2016	Caucasian	Russia	TaqMan Assay	52	51	19	29	4	10	31	10	0.12
Zayani [72]	2017	Caucasian	Tunisia	PCR-RFLP	400	721	216	157	27	369	278	74	0.05
Farzam [46]	2017	Asian	Iran	PCR-RFLP	60	60	52	5	3	28	31	1	0.02
Ievleva [73]	2016	Caucasian	Russia	PCR-RFLP	68	46	22	33	13	12	15	19	0.02
Olza [74]	2017	Caucasian	Spain	Illumina GoldenGate Assay	285	234	85	135	65	76	117	41	0.73
Becer [44]	2017	Caucasian	Turkey	PCR-RFLP	115	85	40	48	27	38	25	22	0.0003
Almeida [42]	2018	Caucasian	Portugal	Real-Time PCR	171	385	52	86	33	115	165	105	0.005
Eldosouky [75]	2018	Asian	Saudi-Arabia	Real-Time PCR	168	126	42	72	54	66	48	12	0.45
Sansom (1) [76]	2018	Caucasian	Mixed	TaqMan, OpenArray	40	85	6	30	4	35	33	17	0.08
Sansom (2) [76]	2018	African	Mixed	Taqman, OpenArray	7	19	3	4	0	8	10	1	0.34
Daghestani [28]	2019	Asian	Saudi-Arabia	PCR	62	62	39	10	13	42	15	5	0.05
Ali [77]	2019	Caucasian	Egypt	PCR	110	122	49	42	19	78	36	8	0.18
Kumari [78]	2019	Asian	India	PCR-RFLP	120	109	42	56	22	67	34	8	0.22
Illangasekera [79]	2020	Asian	Sri Lanka	Real-Time PCR, TaqMan assays	264	266	53	141	70	54	131	81	0.94
Diéguez-Campa [80]	2020	Caucasian	Mexico	PCR	56	103	20	29	7	33	50	20	0.89
Garavito [81]	2020	Caucasian	Colombia	PCR	111	155	38	49	24	50	70	35	0.27
Chavez [82]	2020	Caucasian	Mexico	PCR	56	103	20	29	7	33	50	20	0.89
Halvatsiotis [47]	2021	Caucasian	Greece	PCR-RFLP	32	108	0	8	24	70	20	18	<0.00001
Bilge [83]	2021	Caucasian	Turkey	PCR	146	150	68	54	24	55	77	18	0.25
Yarim [84]	2022	Caucasian	Turkey	Real-Time PCR	150	150	99	49	2	122	25	3	0.22

dominant model (AG + GG vs. AA), recessive model (GG vs. AA + AG), and allelic (G vs. A) genetic models. Each study's HWE was determined by applying the Chi-square test to compare the observed and anticipated genotype frequencies of the control group, where $P < 0.05$ was regarded as a substantial inconsistency. We developed a linear diagram to show the comparison between Asian and Caucasian for average HWE. A random effects model was utilized to account for any potential heterogeneity (I^2>50%) between studies [34], and when such heterogeneity was not determined to be substantial ($I^2 \leq 50\%$), a fixed effects model was used to conduct the analysis [35]. Sensitivity analysis was carried out with the leave-one-out method to check the consistency and dependability of the findings [36]. To evaluate any possible publication bias among studies funnel plot was generated for each genetic model. Symmetry and asymmetry in funnel plots were evaluated according to Peters JL et al. (2008) [37]. Begg's [38] and Egger's [39] tests were also applied to assess any possibility of publication bias along with the funnel plot. $P < 0.05$ for Begg's and Egger's tests was considered to have bias amongst the studies. Stata version 14.1 statistical software (StataCorp. College Station, TX, USA) and Review Manager (Version: 5.4.1) with a two-sided P-value were used to conduct the statistical analyses. Unless otherwise stated, the P-value threshold for statistical significance was set at 0.05.

Multiple testing correction was executed using the False Discovery Rate (FDR) Benjamini-Hochberg method [40]. The False Discovery Rate (FDR) correction was applied using Python code adapted from the 'statsmodels' library (version 0.13.5) [41]. Our considered FDR threshold was <0.05 for statistical significance.

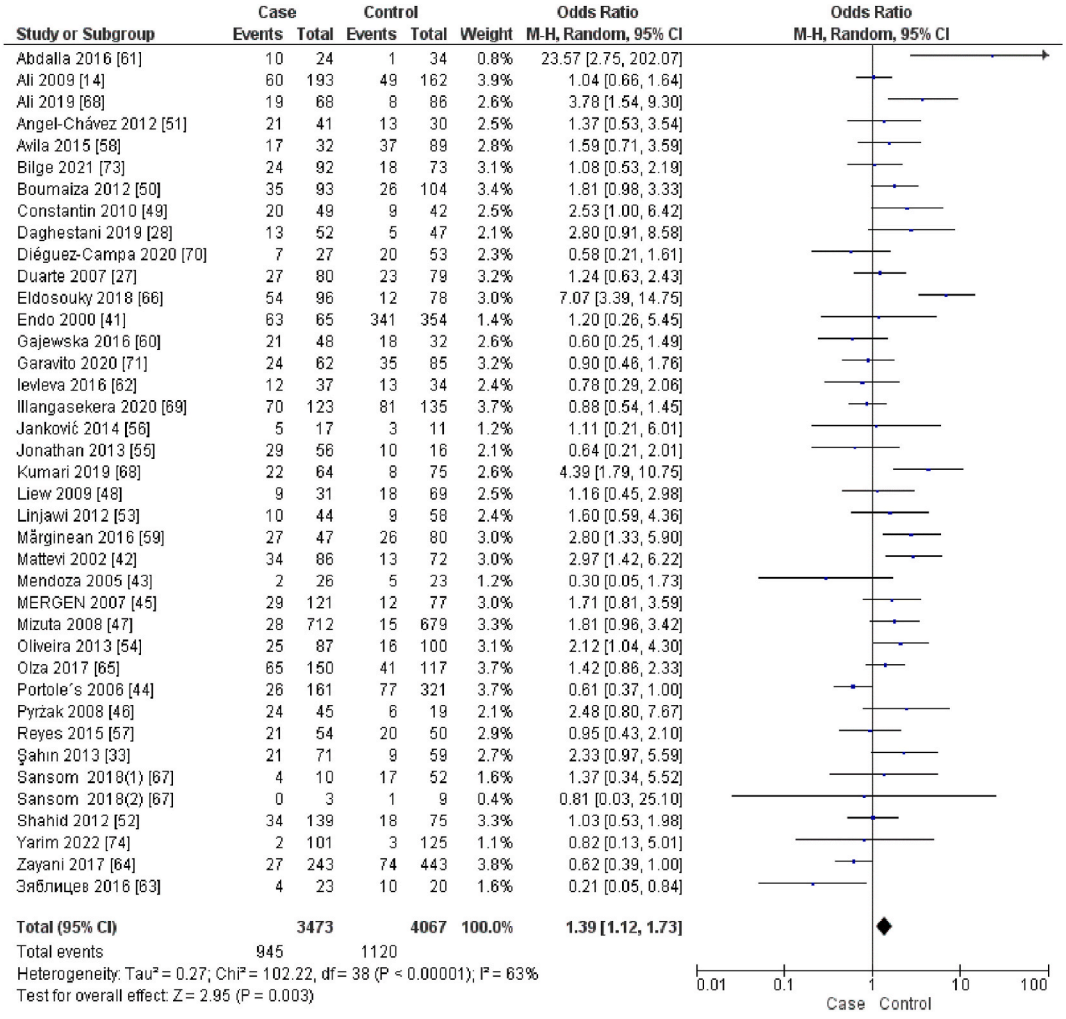


Fig. 2. The Forest plot of the Homozygous model (GG vs. AA) depicting the association between rs1137101 polymorphism and susceptibility to obesity.

3. Results

3.1. Data acquisition and selection

At the onset of the investigation, an extensive exploration was conducted in the four renowned databases, namely, Science Direct, PubMed Central and Google Scholar, leading to the extraction of 2256 studies. Specifically, Google Scholar contributed 1700 studies, PubMed Central contributed 401 studies, and Science Direct contributed 155 studies. Initially, 649 articles were sorted out from a pool of 2256 articles by removing 1607 articles due to obvious irrelevance. Afterward, 63 duplicated studies were excluded, 6 articles were excluded because of being written on a different language instead of English language followed by the elimination of 433 studies based on their abstracts and titles. After reviewing the full documents of the 147 studies that remained, 53 studies were excluded from the analysis as they did not contain enough appropriate meta-analysis data, 15 were not included due to varying SNPs, and 5 were excluded because they did not have a control group and 25 studies were excluded due to the irrelevance to the diseases of interest. Additional unique studies were not found from the screening of reference lists of the retrieved articles. Therefore, the study includes 49 articles altogether which satisfy the standards outlined in the methodology. Out of those, we found nine studies from the LEPR polymorphism group [21,42–48] that were found to be inconsistent with HWE value. Hence, we only used 38 publications that consisted of 6099 case studies and 6711 controls for the meta-analysis. Fig. 1 depicts the sorting process.

3.2. Included study characteristics

The following Table 1 and Table S1 provides a brief review of the characteristics of the retrieved studies. A linear diagram showing

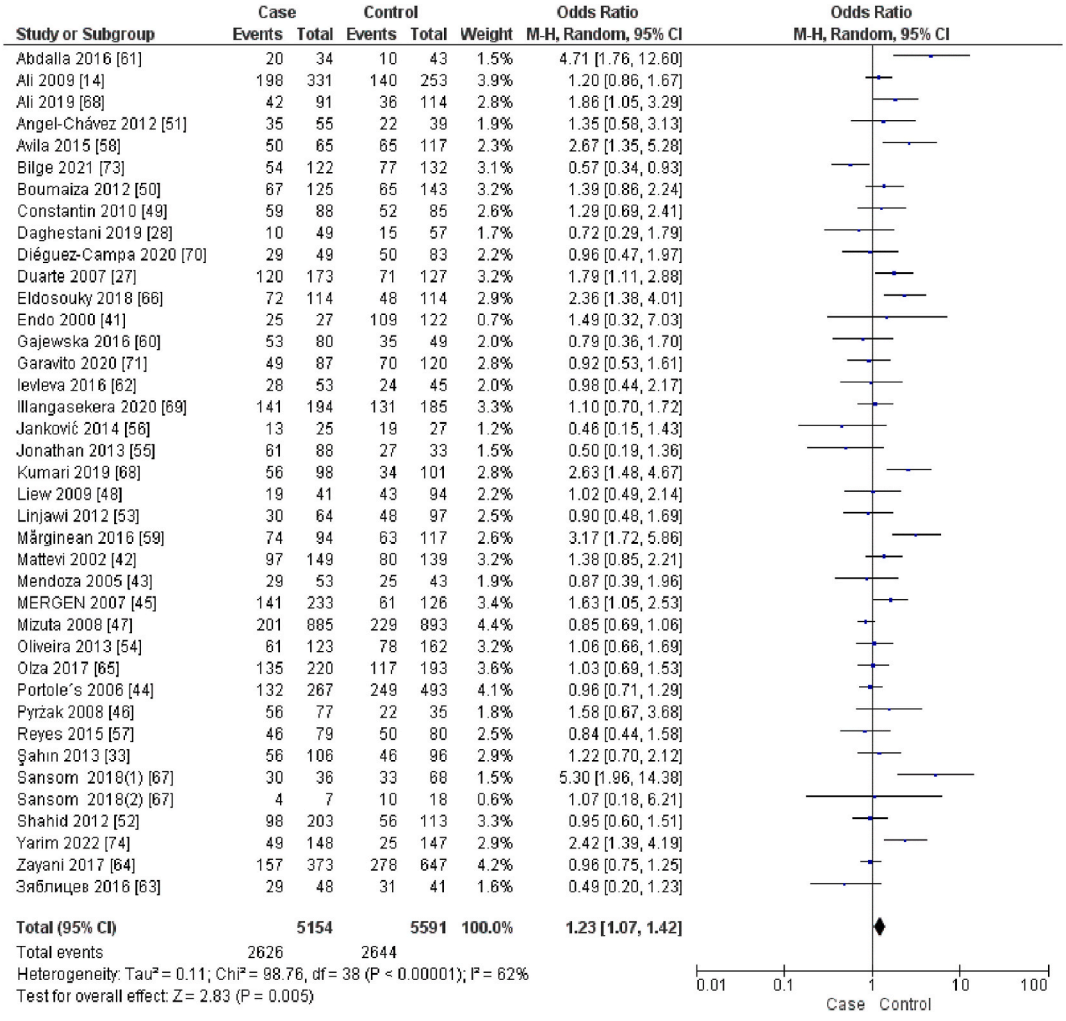


Fig. 3. The Forest plot of the Heterozygous model (AG vs. AA) depicting the association between rs1137101 polymorphism and susceptibility to obesity.

the average HWE value for case data within both Asian and Caucasian populations is displayed in Fig. S1. The controls in each study had a genotype distribution that was consistent with the Hardy-Weinberg Equilibrium (HWE), except nine studies from the LEPR polymorphism group [21,42–49]. Consequently, 39 case-control studies were employed to conduct the meta-analysis (published in 38 articles) that examined 6099 individuals diagnosed with obesity and 6711 healthy individuals defined as control groups. The studies included participants from Caucasian and Asian ethnicities, with 28 studies comprising Caucasian populations, 10 with Asian populations, and 1 with African population. All eligible research had information on the genotypes or alleles. The studies were analyzed using five genetic models, as shown in Figs. 2–6, generating ORs and 95% CIs, and pooled estimates.

3.3. Association of LEPR gene polymorphism (rs1137101) with obesity risk

A meta-analysis was conducted to look into the relationship between LEPR gene polymorphisms and obesity at loci of rs1137101 (A > G) under homozygous, dominant, heterozygous, allelic and recessive genetic models. Based on the analysis we conducted, it appears that there is a significant correlation between the rs1137101 polymorphism and the likelihood of developing obesity in all of the genetic models tested. Due to the higher level of variability observed among the studies, we used the random effect model in nearly all of the five models. In the homozygous model (GG vs. AA), the OR was 1.39 (95% CI = 1.12–1.73, P = 0.003). The heterozygous model (AG vs. AA) showed an Odds Ratio of 1.23 (95% Confidence Interval = 1.07–1.42, P value = 0.005). The dominant model (AG/GG vs. AA) with an Odds Ratio of 1.28 (95% Confidence Interval = 1.10–1.49, P value = 0.001). The recessive model (GG vs. AA/AG) showed an Odds Ratio of 1.21 (95% Confidence Interval = 1.02–1.45, P = 0.03). Lastly, in the allelic model (G vs. A), the Odds Ratio was 1.19 (95% Confidence Interval = 1.07–1.33, P value = 0.002). These findings imply a significant relationship between the LEPR rs1137101 polymorphism and obesity susceptibility in the general population. Furthermore, it is worth noting that all genotypic models exhibited a statistically significant correlation between LEPR polymorphism and obesity, with a false discovery rate (FDR) of

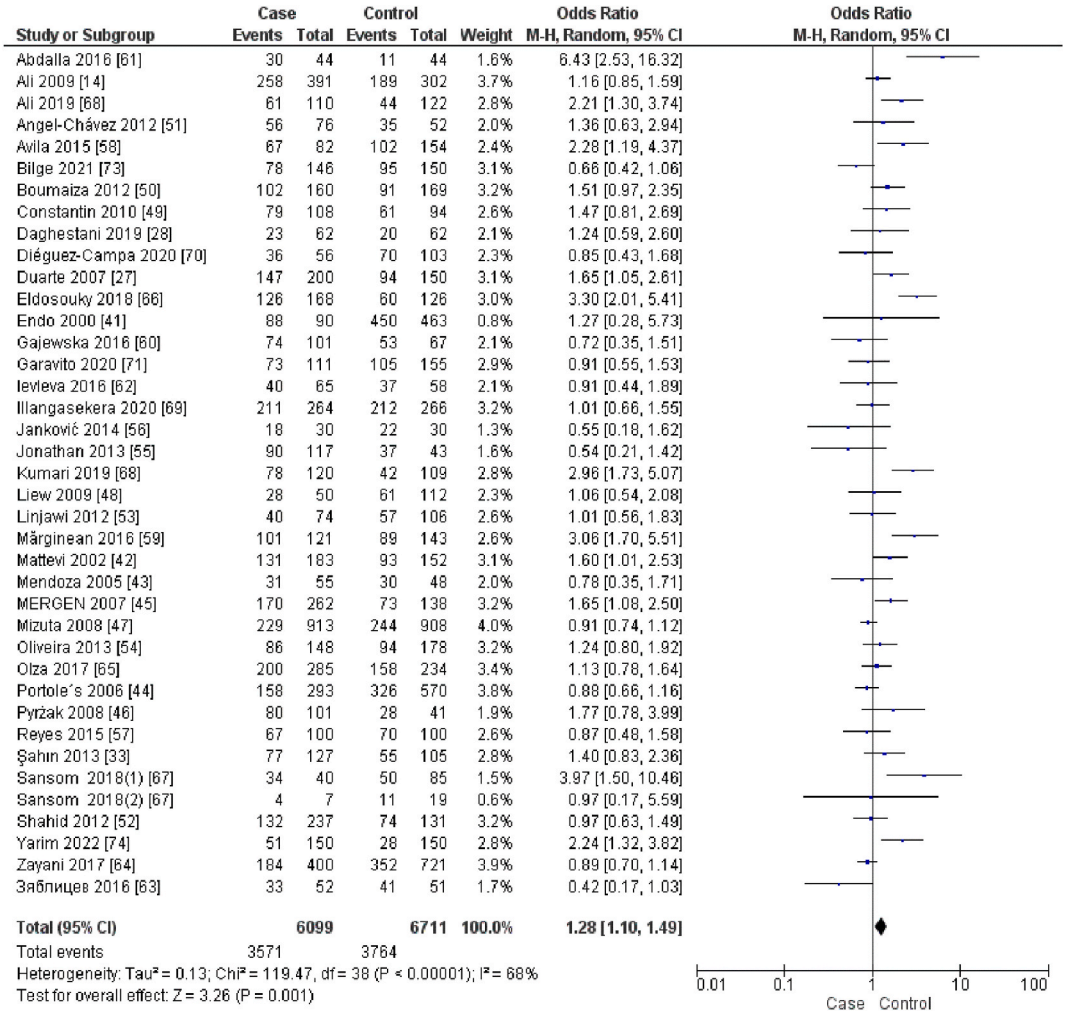


Fig. 4. The Forest plot of the Dominant model (AG + GG vs. AA) depicting the relationship between rs1137101 polymorphism and obesity.

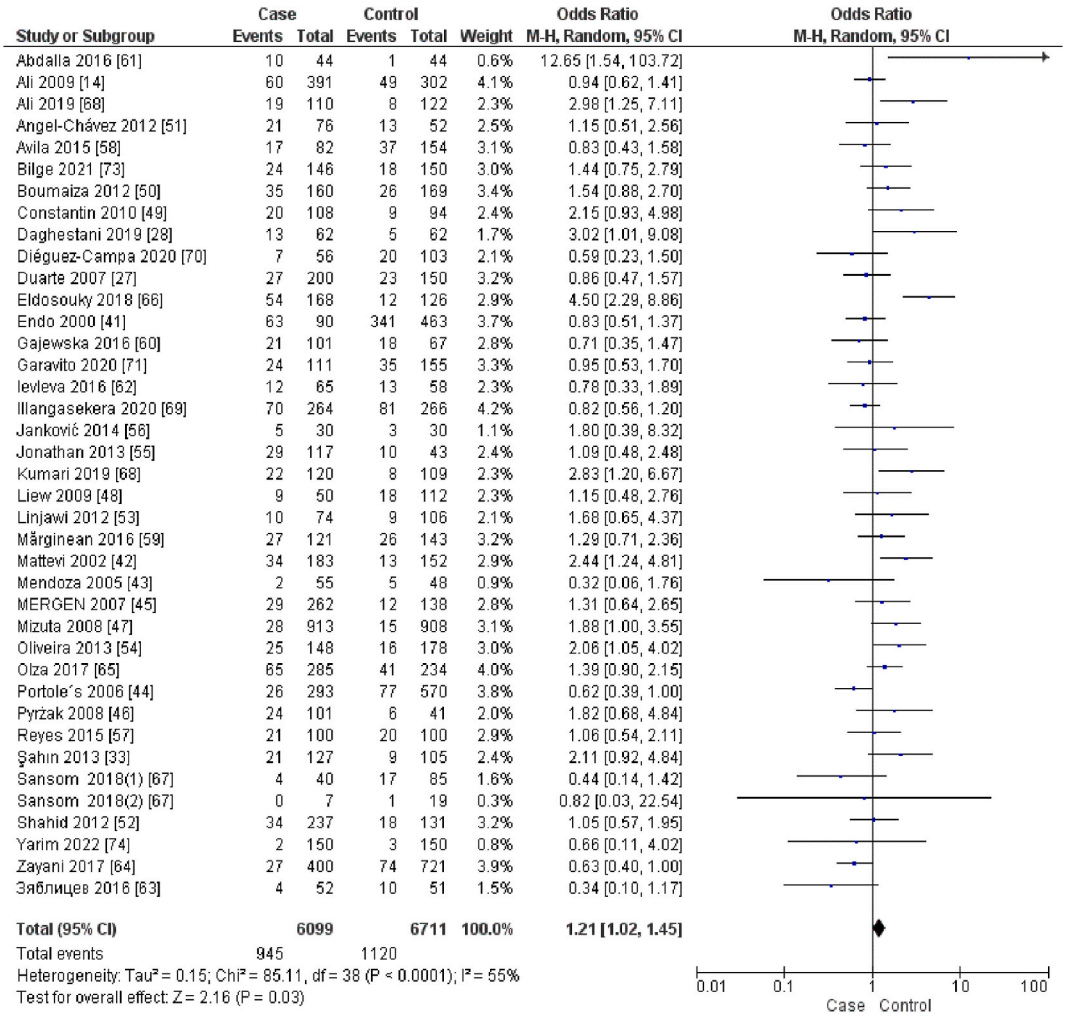


Fig. 5. The Forest plot of Recessive model (GG vs. AA + AG) depicting the association between rs1137101 polymorphism and susceptibility to obesity.

less than 0.05.

The ethnicity-based subgroup analysis found that both the Caucasian and the Asian populations exhibited a significant relationship between LEPR rs1137101 polymorphism and obesity susceptibility, even though some genetic models did not show any significant association (with the P value > 0.05) (Table 2 and Figs. 2–6). The genetic models for Asians, the homozygous model (GG vs. AA: P value = 0.007, Odds Ratio = 2.12, 95% Confidence Interval = 1.23–3.64), heterozygous model (AG vs. AA: P value = 0.11, Odds Ratio = 1.31, 95% Confidence Interval = 0.94–1.84), dominant model (AG/GG vs AA: P value = 0.03, Odds Ratio = 1.52, 95% Confidence Interval = 1.03–2.22), recessive model (GG vs AA/AG: P value = 0.02, Odds Ratio = 1.70, 95% Confidence Interval = 1.09–2.64), and allelic model (G vs A; P value = 0.02, Odds Ratio = 1.43, 95% Confidence Interval = 1.06–1.94) showed significant association (with P < 0.05), except for the heterozygous model (with P > 0.05). Additionally, for the Asian population, only the heterozygous model was not statistically significant after correcting the P-value by FDR (FDR >0.05). On the other hand, Caucasian subgroup analysis showed that the homozygous model (GG vs. AA: Odds Ratio = 1.23, 95% Confidence Interval = 0.98–1.54, P value = 0.08), heterozygous model (AG vs. AA: Odds Ratio = 1.21, 95% Confidence Interval = 1.03–1.43, P value = 0.02), dominant model (AG/GG vs AA: Odds Ratio = 1.23, 95% Confidence Interval = 1.04–1.44, P value = 0.01), recessive model (GG vs AA/AG: Odds Ratio = 1.10, 95% Confidence Interval = 0.92–1.32, P value = 0.31), and allelic model (G vs A; Odds Ratio = 1.13, 95% Confidence Interval = 1.02–1.26, P value = 0.02) showed a strong association (with P < 0.05), except the homozygous and recessive models (with P > 0.05). After correcting the P-value based on FDR, both homozygous and recessive models for the Caucasian population still remained statistically insignificant. It can be concluded that while some genetic models (where P > 0.05) showed an insignificant correlation between the LEPR rs1137101 polymorphism and the susceptibility of obesity, other genetic models (Table 2 and Figs. 2–6) showed a significant correlation.

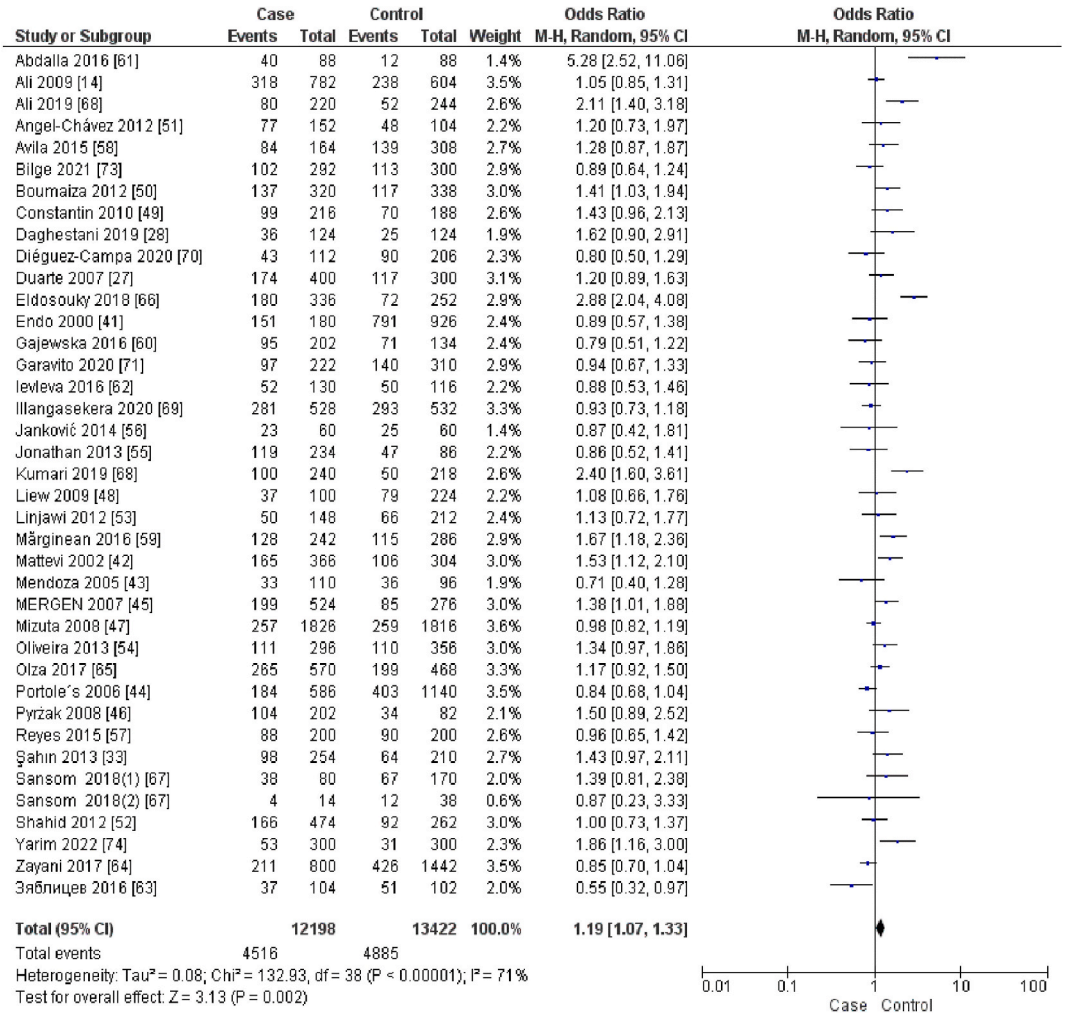


Fig. 6. The Forest plot of Allelic model (G vs. A) depicting the relationship between rs1137101 polymorphism and obesity.

3.4. Quantifying publication bias

We employed Egger's and Begg Mazumdar's tests to determine the likelihood of publication bias for each genetic model. The symmetry of the funnel plot displayed in Fig. 7 suggests that no publication bias is present. Begg's and Egger's approaches were employed in formal testing to investigate if any observable publication bias is present. The findings of the tests for all models, indicated that the P-values were all above the threshold values ($P > 0.05$) (Table 2). This means that studies with weaker effects or smaller sample sizes are not excluded from publication. Consequently, the overall results are not biased towards any particular direction.

3.5. Sensitivity analysis

A sensitivity analysis was imperative in evaluating the robustness and reliability of the meta-analysis. The sensitivity analysis utilized in this study was the leave-one-out method. (Fig. 8). The analysis depicted that removing any of the studies did not significantly alter the results for the homozygous model (GG vs. AA), heterozygous model (AG vs. AA), dominant model (AG + GG vs. AA), and allelic model (G vs. A), which all remained statistically significant. However, the study done by Eldosouky et al. holds significant influence inside the recessive model (GG vs AG + AA). Significantly, the statistical significance of this model showed a decrease when the data from Eldosouky et al. was excluded. Despite this, it is noteworthy that none of the studies altered the direction or magnitude of the association, and the pooled OR remained delicately poised on the brink of statistical significance. This observation underscores the stability and reliability of our meta-analysis across all four genetic models (homozygous, heterozygous, dominant, and allelic). Nonetheless, a minor degree of instability is apparent within the recessive model.

Table 2
A Pooled examination of the association between rs1137101 and obesity under homozygous, heterozygous, dominant, recessive, and allelic genetic models.

Genetic model	Association test				Heterogeneity test		
	Odds ratio (OR)	95% Confidence Interval (CI)	P value	False Discovery Rate (FDR)	Model	P value	I^2(%)
Homozygous							
Overall	1.39	1.12–1.73	0.003	0.015	Random	<0.00001	63%
Asian	2.12	1.23–3.64	0.007	0.021	Random	<0.0001	75%
Caucasian	1.23	0.98–1.54	0.08	0.092	Random	0.0002	55%
Heterozygous							
Overall	1.23	1.07–1.42	0.005	0.019	Random	<0.00001	62%
Asian	1.31	0.94–1.84	0.11	0.118	Random	0.0002	72%
Caucasian	1.21	1.03–1.43	0.02	0.03	Random	<0.0001	59%
Dominant							
Overall	1.28	1.10–1.49	0.001	0.015	Random	<0.00001	68%
Asian	1.52	1.03–2.22	0.03	0.038	Random	<0.00001	81%
Caucasian	1.23	1.04–1.44	0.01	0.025	Random	<0.00001	62%
Recessive							
Overall	1.21	1.02–1.45	0.03	0.038	Random	<0.0001	55%
Asian	1.70	1.09–2.64	0.02	0.03	Random	<0.0001	73%
Caucasian	1.10	0.92–1.32	0.31	0.31	Fixed	0.007	44%
Allelic							
Overall	1.19	1.07–1.33	0.002	0.015	Random	<0.00001	71%
Asian	1.43	1.06–1.94	0.02	0.03	Random	<0.00001	86%
Caucasian	1.13	1.02–1.26	0.02	0.03	Random	<0.0001	60%

4. Discussion

Obesity has evolved into a prevalent and pressing global health issue, posing medical risks that can lead to several ailments, including cardiovascular disease, elevated blood pressure, diabetes, and some specific cancers [84]. The link between changes in the LEPR and LEP genes and obesity in individuals is still a topic of ongoing debate. Among these genes, the LEP rs7799039 variant has been extensively studied. Several studies have suggested a connection between the G allele of LEP rs7799039 and elevated anthropometric measures, as well as an increased risk of obesity [1,2]. One of the most prevalent polymorphisms is the rs1137101 variation in the LEPR gene, which is related to an impaired ability of LEPR signaling and, consequently, with higher body weight and a high leptin level. However, limited research has demonstrated the association between LEPR SNPs and obesity as well as leptin levels [3,4]. According to the Global Obesity Atlas report that is published in 2022 by the International Obesity Federation is estimated that by 2030, the number of obese individuals worldwide will outstretch one billion, with one in five women and one in seven men being affected [85]. In 2017, the global fatalities attributed to obesity-related causes surpassed four million individuals, according to the global burden of illness estimates [4]. Considering this information and certain observations, a meta-analysis was undertaken to explore the potential association between the LEPR rs1137101 (A > G) polymorphism and the probability of developing obesity.

Studies found that LEPR 1137101 polymorphism is responsible for increasing body weight because this polymorphism damaged the capacity of LEPR signaling [14]. LEPR is a recpetor molecule of leptin involved in signaling and both molecules play an important role in hunger response [85] through leptin-melanocortin pathway which is a crucial pathway for controlling appetite [86–88]. Mutation occurring in those genes leads to development of severe obesity [86,88] and severe early onset obesity [87,89]. The Q223R (dbSNP: rs1137101) polymorphism arises from a non-conservative A-to-G replacement at codon 223 in exon 6, resulting in a change from glutamine to arginine at the corresponding amino acid level. This particular variation has notable functional importance, as it interferes with the ability of leptin to bind, hence impairing the effectiveness of leptin signaling [90].

Through a transformational process, the replacement of an amino acid results in the conversion of a previously neutral entity into a counterpart with a positive charge. The process of this mutation has a substantial effect on the effectiveness of both signaling and receptor function. The significance of this phenomenon is particularly noteworthy among individuals who possess the homozygous G allele. The increased presence of leptin has been closely associated with an elevated vulnerability to breast cancer in women who carry this genetic alteration, revealing a significant interaction between this genetic modification and a noteworthy health hazard [23]. Numerous studies conducted on various populations have constantly reproduced the association between Q223R single nucleotide polymorphisms (SNPs) and indicators of obesity. It is worth noting that the existence of the variation G allele increases the vulnerability to obesity, thereby emphasizing its significance as a distinguishable risk factor [21,27]. Moreover, it is important to highlight those significant findings have shed light on the impact of differences in the functioning of the leptin receptor gene on the prevalence of obesity and Body Mass Index (BMI) [90].

The study includes different populations to observe the diversity of the cause and symptoms of obesity. In the study, we mainly focus on the Asian and Caucasian populations where Asian ethnicity includes people from Egypt, Saudi-Arabia, Japan, Sri Lanka, Northern India, Malaysia, and Pakistan; on the other hand, Caucasian ethnicity includes Tunisia, Mexico, Turkey, Romania, Brazil, Poland, Colombia, Russia, Croatia, Turkey, Spain, Mixed Americans. The population diversity mainly reflects their different environmental and genetic backgrounds for the development of obesity. The incidence of obesity varied amongst populations, as Polynesia had higher obesity rates than Melanesia, and urban areas showed more obesity due to Western diets and less physical activity due to

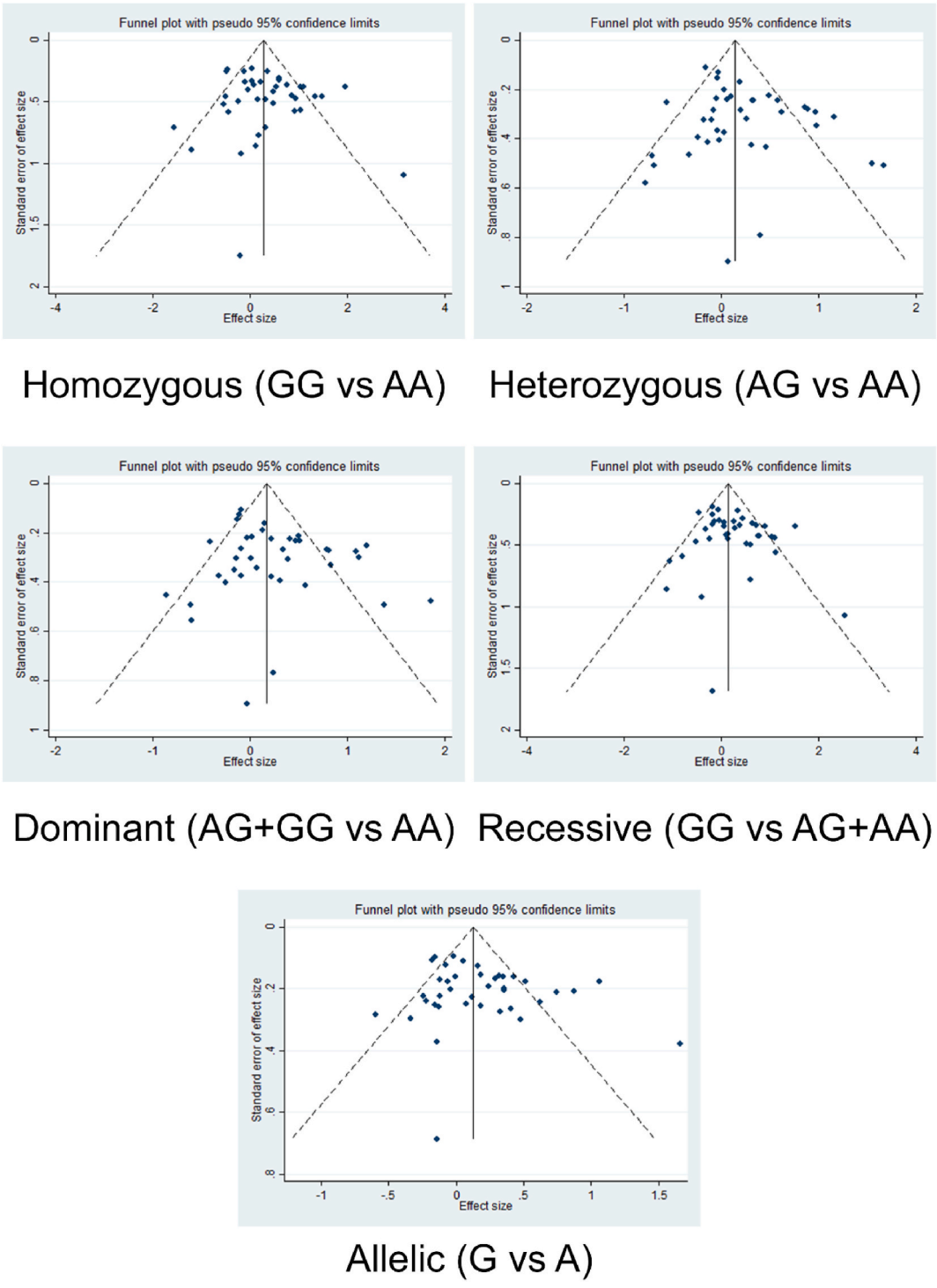
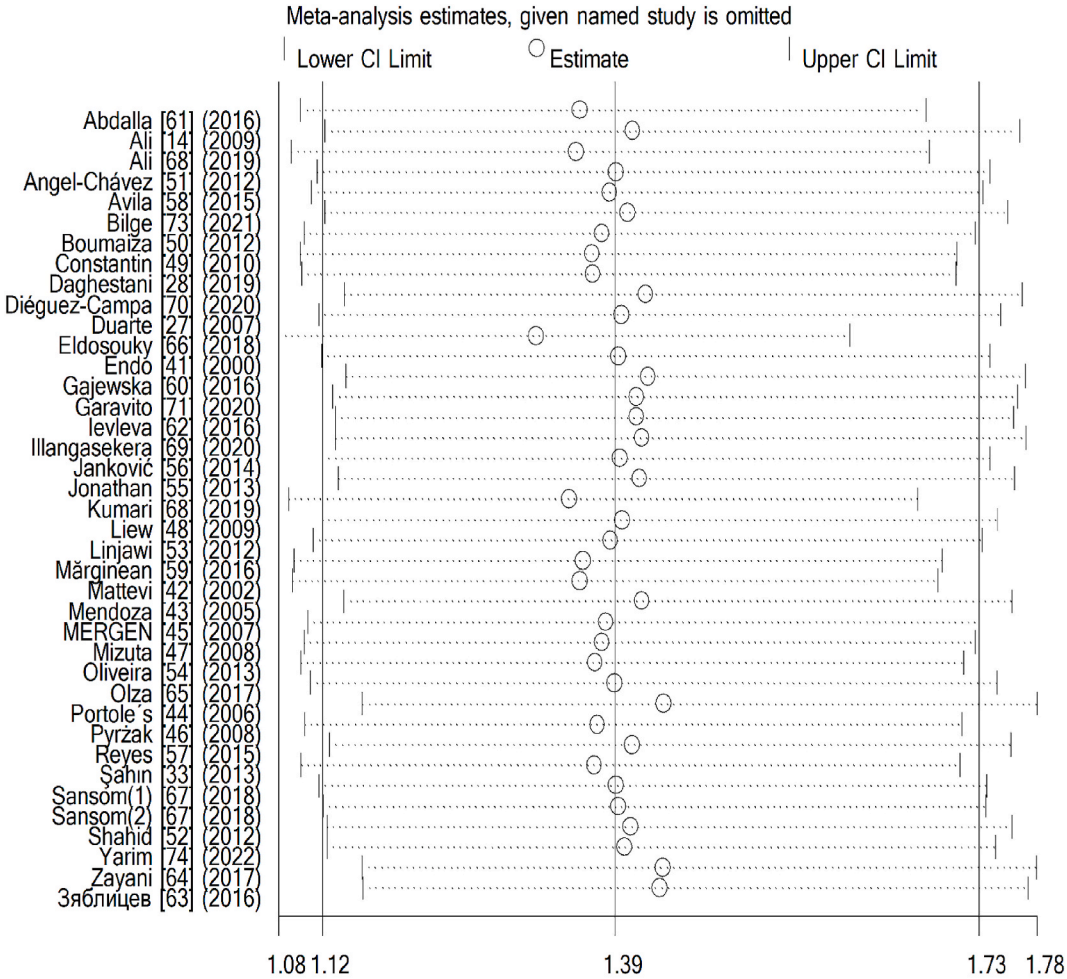


Fig. 7. The Funnel plots for examining the publication bias.

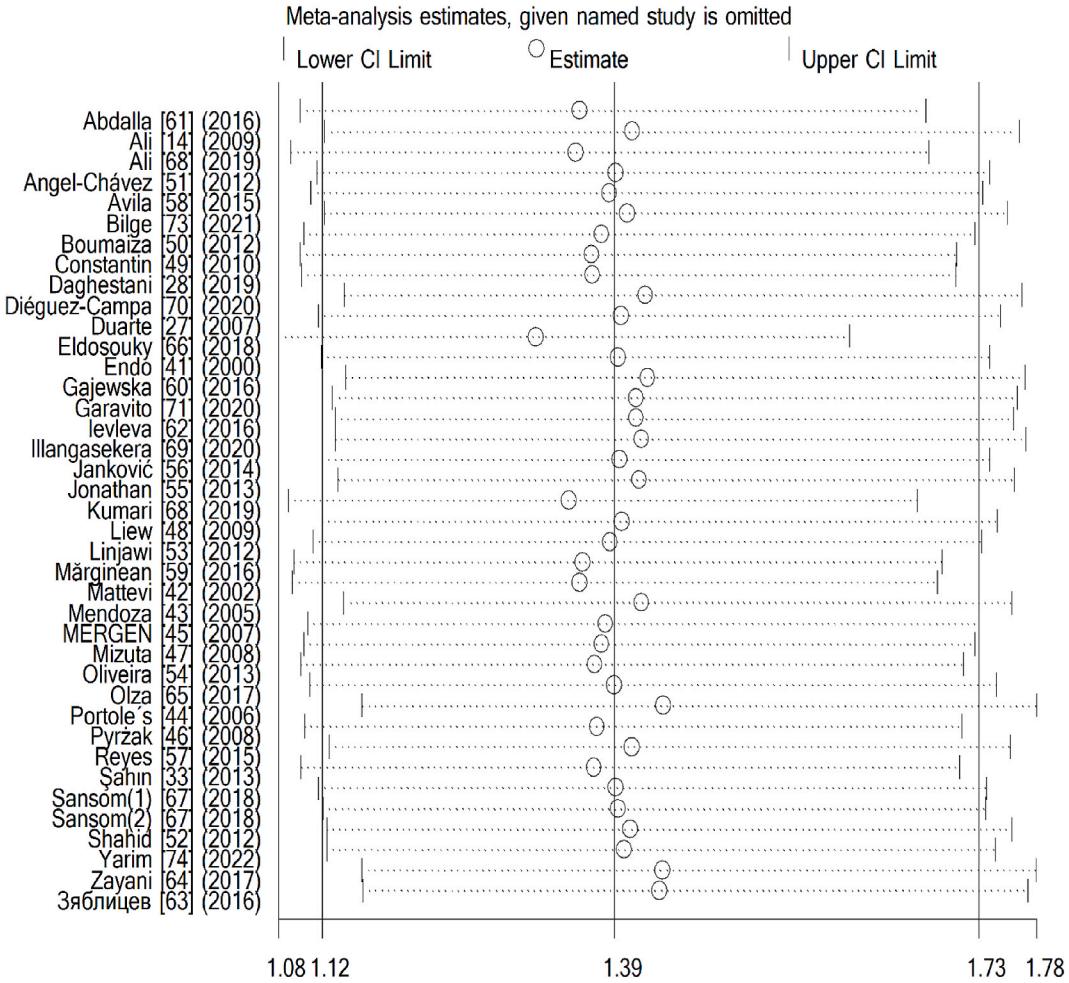
modernization [91]. Another study found that the Q223R leptin receptor polymorphism associated with obesity in Brazilian multi-ethnic subjects is different from previous studies in terms of not only genetic circumstances but also culture, traditions, climate, type of diet, lifestyle, and prevalence of exposure to common environmental risk factors for obesity and related disorders [27]. Rising obesity in developing countries due to urbanization indicates how environment affects weight gain. Less physical activity at work and during leisure, along with lots of high-calorie food, is a big risk for global health [92]. While the majority of built environment variables did



a) The Homozygous model (GG vs. AA)

Fig. 8. Sensitivity analysis graphic for the examination of the relationship between rs1137101 polymorphism and obesity. a) Homozygous model (GG vs. AA); b) Heterozygous model (AG vs. AA); c) Dominant model (AG + GG vs. AA); d) Recessive model (GG vs. AA + AG); e) Allelic model (G vs. A).

not clearly correlate with weight-related outcomes, others, such as proximity to fast food restaurants, urbanization, mixed land use, and urban sprawl, consistently indicated a correlation [91]. According to recent studies, second generation migrants in the US are typically more overweight than their parents who were immigrants. Particular racial or ethnic groups are more likely to gain weight in situations that encourage obesity. This suggests that in addition to significant environmental influences, genetic factors also affect an individual's susceptibility to obesity [92]. Beside those environmental factors the genetic determinants of obesity have been studied to identify the genes that are altered as a result of the hereditary components of obesity. It is generally known that when there is a receptor or post-receptor malfunction in hormone activity, hormone levels are raised. Leptin binding abnormalities or other post-receptor problems may cause the hormone to be secreted in excess amounts, dramatically boosting its level and ultimately causing obesity [28]. Additionally, Tartaglia, L.A. et al. presented a potential mechanism and clarified that leptin resistance, rather than insufficient levels of leptin itself, is more likely to be the cause of the majority of obesity [15]. A study found a significant correlation between leptin and insulin resistance in the obese population, suggesting that Gln223Arg in LEPR may have an impact on insulin resistance in the obese Saudi women population [28]. Another study revealed that one of the most frequent causes of juvenile-onset obesity is mutations in the long isoform of the leptin receptor's coding area [29]. In our study, we have mainly focused on the genetic influence and tried to explore the association of LEPR polymorphism with obesity between people from different countries. From our selected studies, people from different countries were included. In those studies, healthy subjects as control and obese subjects as case



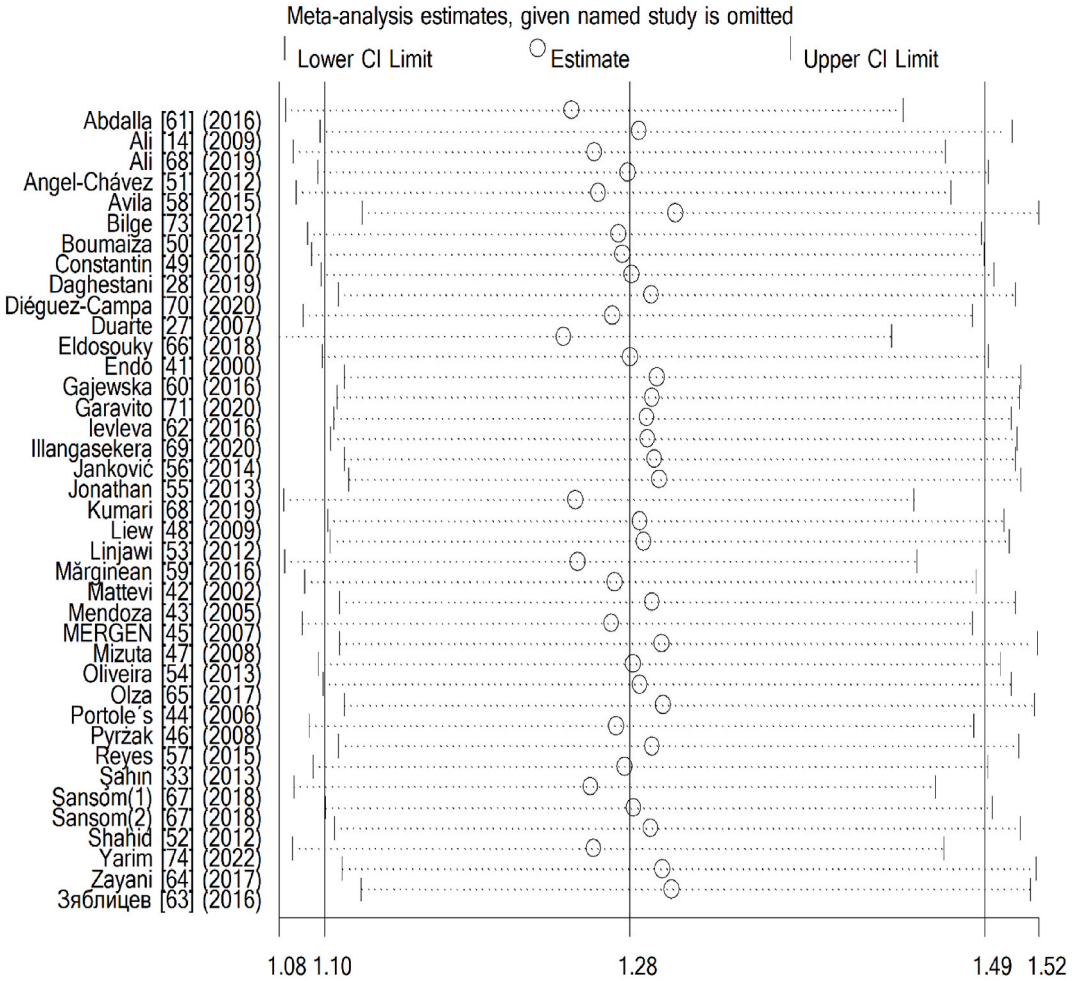
b) The Heterozygous model (AG vs. AA)

Fig. 8. (*continued*).

were categorized based on BMI given in (Table S1).

In this study we encompassed the evaluation of data from 39 case-control studies, which were documented in 38 published articles, included a total of 6099 individuals who had been diagnosed with obesity alongside a control group of 6711 healthy individuals. In order to minimize the risk of biased results from inadequate studies, we implemented stringent criteria for the inclusion and the exclusion process. These criteria were designed to ensure that only high-quality studies were incorporated in this meta-analysis. We excluded data from the study conducted by Yiannakouris et al. 2001, Almeida et al. 2018, Shabana et al. 2015, Becer et al. 2017, Fan et al. 2014, Farzam et al. 2017, Halvatsiotis et al. 2021, Komsu-Ornek et al. 2012, Yevleva et al. 2016 [21,42–49] from the pooled analysis due to deviation from the Hardy-Weinberg Equilibrium (HWE) among the individuals comprising the control group. This deviation indicates genotyping errors mediated by different factors and including those studies arise biased result [93,94]. The outcomes of the meta-analysis unequivocally reveal a significant correlation between LEPR polymorphism and predisposition to obesity across all the examined genetic models ($P < 0.05$), demonstrating that the rs1137101 polymorphism located in LEPR is a risk factor for obesity.

To present the results in a quantitative manner, forest plots were generated using either a random-effects model or a fixed-effects model. We selected one of these models based on the heterogeneity level across the studies as measured by the I^2 statistic [34,35,95]. The I^2 value for the recessive model of the Caucasian group has found a moderate level (44%) heterogeneity due to the clinical outcome and intervention effect of each study of the Caucasian group having very much similar results to other models and groups [86]. Thus, we used fixed effect model for this group. Beside that due to significant heterogeneity found in different models of this study; a

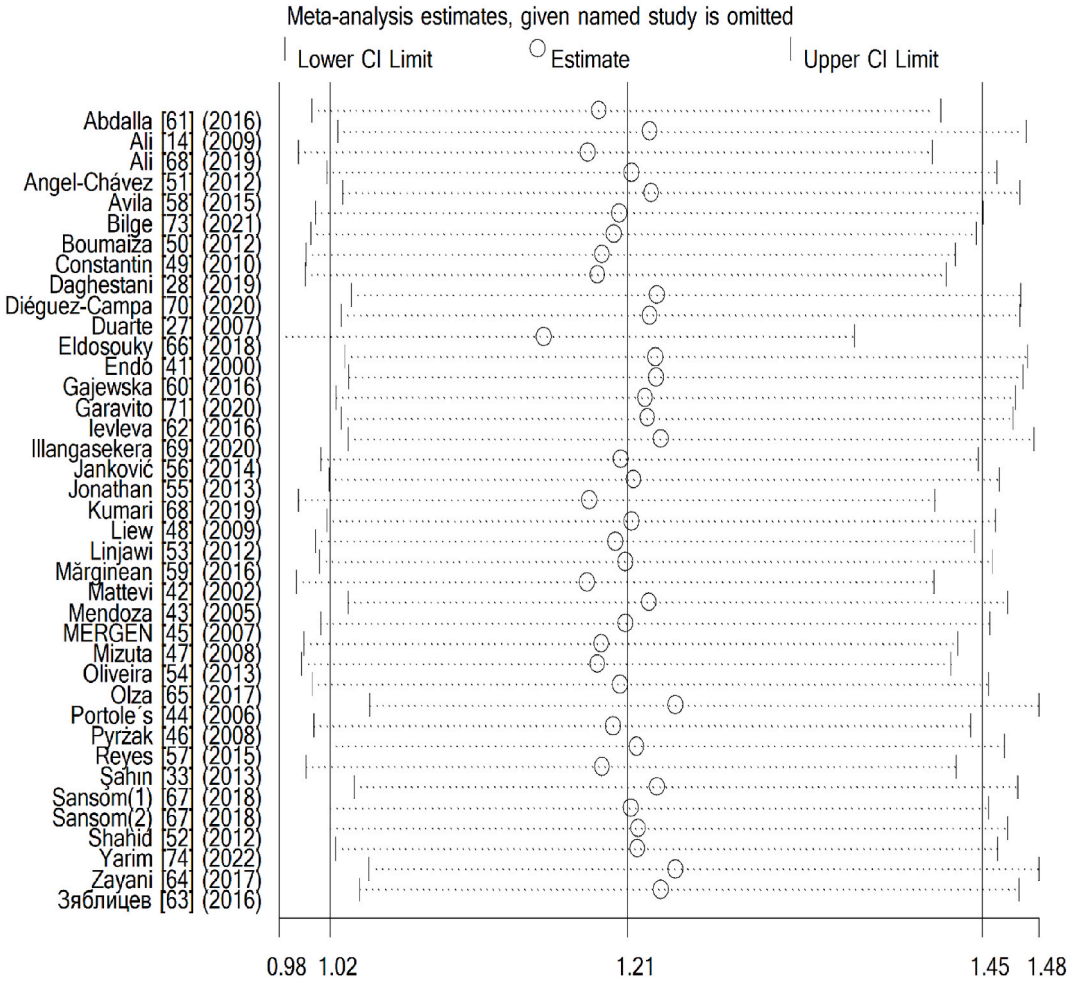


c) The Dominant model (AG+GG vs. AA)

Fig. 8. (*continued*).

subsequent step was taken to perform a subgroup analysis, stratifying the data based on participants' ethnicity. Given the limited availability of data, a subgroup analysis for the African subgroup was not performed. In every genetic model, except for the heterozygous model ($P > 0.05$) for Asian populations, a robust and statistically significant ($P < 0.05$) association between the LEPR rs1137101 variant and obesity was observed. Upon conducting a subgroup analysis for the Caucasian population, Homozygous, and Recessive models were not found to show any significant association ($P > 0.05$) of rs1137101 with obesity, whereas the other three models showed a signification correlation ($P < 0.05$). To mitigate the concern of multiple comparisons, we additionally conducted a False Discovery Rate (FDR) analysis. The P values associated with FDR (False Discovery Rate) analysis indicate that all of the genotypic models had statistical significance. Within the Asian population, a significant correlation was observed between LEPR polymorphism and obesity, as indicated by four genotypic models: homozygous, dominant, recessive, and allelic (FDR <0.05). However, the heterozygous model did not yield statistically significant results (FDR >0.05). Additionally, within the Caucasian population, it was shown that only the homozygous and recessive models did not exhibit a statistically significant association (FDR >0.05).

Examination of the funnel plot, to visualize, along with Begg's and Egger's tests, revealed a symmetrical distribution of data points, suggesting the absence of publication bias in this meta-analysis. To assess the impact of every individual study on the combined odds ratios (ORs), we performed a sensitivity analysis. The robustness of all four genotypic models, namely Homozygous, Heterozygous, Dominant, and Allelic models, has been confirmed by the conducted sensitivity analysis (shown in Fig. 8a, b, 8c. 8e). However, one study conducted by Eldosouky et al. [75] affected the result of the recessive model. According to the sensitivity analysis where we have performed the leave-one-out method, after removing the study by Eldosouky et al., 2018, the lower CI for the recessive model turned to

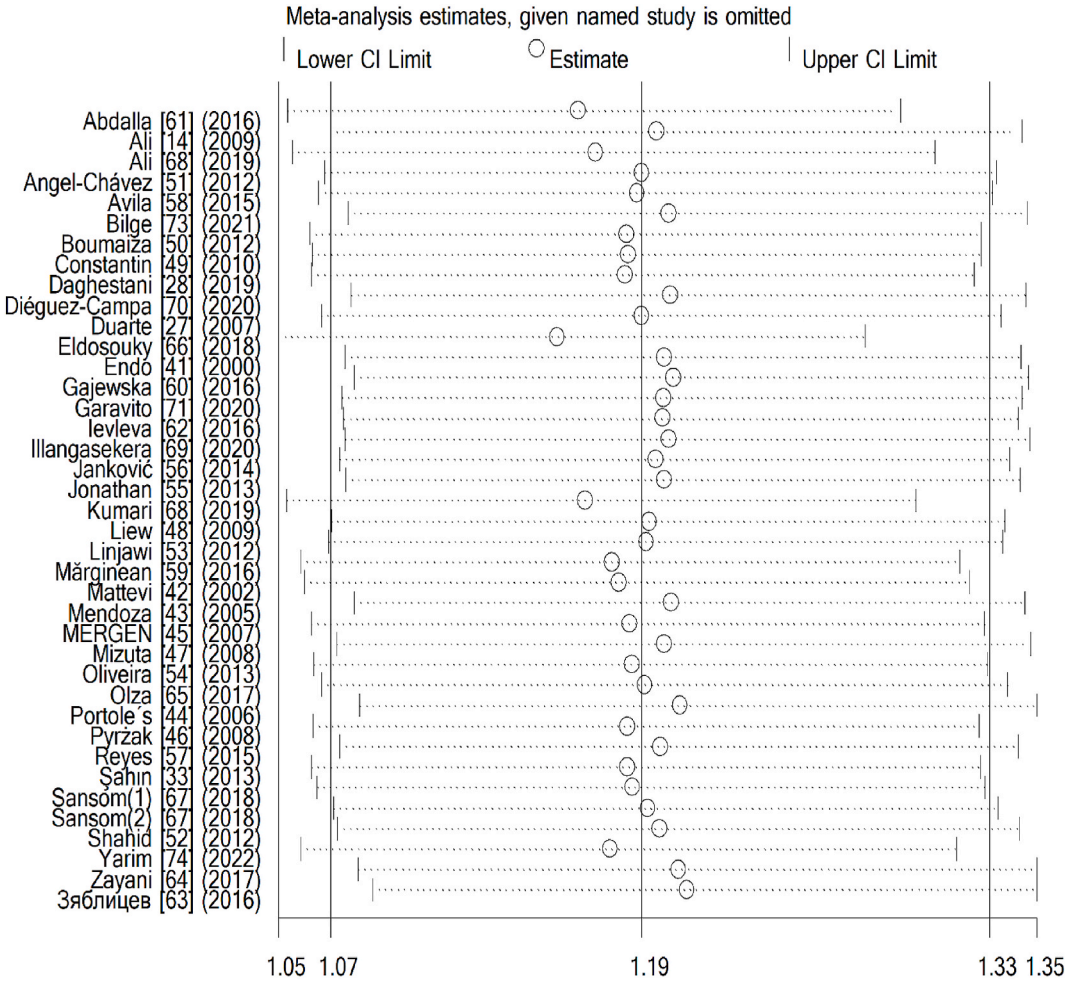


d) The Recessive model (GG vs. AG+AA)

Fig. 8. (*continued*).

0.98 from 1.02. This implies that the study by Eldosouky et al. (2018) plays a significant influential role within this genotypic model, consequently introducing a degree of influence that has rendered the recessive model somewhat less stable. Similar result was found from a different meta-analysis study conducted by SC Tan et al. (2020) [96] where they found some of their included studies influence the result of different models. The comprehensive analysis provided compelling evidence supporting the reliability and robustness of the meta-analysis findings.

However, meta-analysis has some limitations. We have included 39 different GWAS studies that can provide a sufficient amount of information about LEPR rs1137101 polymorphism. But some included studies such as Constantin 2010, Angel-Chávez 2012, Linjawi 2012, Jonathan 2013, Janković, 2013, Gajewska 2016, Abdalla 2016, Ievleva 2016, S.V. Zyablitsev 2016, Farzam 2017, Becer 2017, Sansom 2018, Daghestani 2019, Diéguez-Campa 2020, Chavez 2020 contained low number of samples compared to other study [28,44,46,49,58,60,62,64,65,69–71,74,76,80,82]. The relatively large sample-sized studies provide more statistical power with a better understanding of the linkage between obesity and LEPR rs1137101 polymorphism among these populations was the first limitation of this study. Another limitation of this analysis was the scarcity of African and other population studies. During the literature search, only one study was found that focused on African populations, preventing from conducting a subgroup analysis for this ethnicity. Beside those, this study was limited to show interaction of gene to gene and gene to environment due to limited information were provided by the included studies. Moreover; it is imperative to adjust more potential confounders by increasing the sample size by including more subjects to enhance the robustness of the results. Despite these limitations, the findings of this study serve as a significant contribution to the existing work, providing valuable insights onto the association between the LEPR polymorphism (rs1137101) and the risk of obesity.



e) The Allelic model (G vs. A)

Fig. 8. (*continued*).

5. Conclusion

This study's goal was to carry out a comprehensive meta-analysis on Asian, Caucasian, and African ethnic populations to explore the relationship of LEPR rs1137101 (A > G) polymorphism and the likelihood of developing obesity. We have obtained conclusive evidence through our investigation that there is a correlation between rs1137101 and the probability of developing obesity. Moving forward, it will be important to expand upon these findings by exploring this genetic polymorphism and their relationship to obesity in diverse populations. Future studies should also look into how this genetic variation interacts with environmental factors to cause obesity as well as potential therapeutic approaches based on this genetic link. Overall, this study highlights the need for continued research efforts in the field of genetics and obesity, as a greater understanding of these complex relationships may ultimately lead to more effective prevention and treatment strategies for this global health challenge.

Data availability statement

Data associated with this study has not been deposited into any publicly available repository. Data will be made available on request.

CRediT authorship contribution statement

Dilara Akhter Supti: Writing – original draft, Visualization, Software, Formal analysis, Data curation. **Farzana Akter:** Writing – original draft, Project administration. **Md Imranur Rahman:** Writing – original draft, Formal analysis, Data curation. **Md Adnan Munim:** Formal analysis, Data curation. **Mahafujul Islam Quadery Tonmoy:** Writing – original draft, Validation. **Rabia Jahan Tarin:** Visualization, Validation, Software, Resources. **Sumaiya Afroz:** Visualization, Validation, Software, Formal analysis. **Hasan Al Reza:** Visualization, Formal analysis, Data curation. **Roksana Yeasmin:** Writing – review & editing, Validation, Supervision. **Mohammad Rahanur Alam:** Writing – review & editing, Supervision, Project administration, Conceptualization. **Md Shahadat Hossain:** Writing – review & editing, Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e27213.

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