Salud, Ciencia y Tecnología. 2025; 5:1072
doi: 10.56294/saludcyt20251072

ORIGINAL

The role of vitamin d receptor gene polymorphisms in obesity: a systematic review and meta-analysis

El papel de los polimorfismos genéticos del receptor de vitamina d en la obesidad: una revisión sistemática y un metanálisis

Tri Hartini Yuliawati[1,2*], Dewi Ratna Sari[1,2*], Citrawati Dyah Kencono Wungu[2,3], Zakiyatul Faizah[2,4], Berliana Hamidah[2,4], Bella Amanda[2,4], Lucky Prasetiowati[1,2], Rimbun[1,2], Kusuma Eko Purwantari[1,2], Ninik Darsini[2,4], Faisal Yusuf Ashari[2,4], Wan Rohani Wan Taib[5], Zilfalil Bin Alwi[6]

[1]Department of Anatomy, Histology and Pharmacology, Faculty of Medicine, Universitas Airlangga. Surabaya, Indonesia.
[2]Unit of Human Genetics, Faculty of Medicine, Universitas Airlangga. Surabaya, Indonesia.
[3]Department of Physiology and Medical Biochemistry, Faculty of Medicine, Universitas Airlangga. Surabaya, Indonesia.
[4]Department of Medical Biology, Faculty of Medicine, Universitas Airlangga. Surabaya, Indonesia.
[5]School of Biomedicine, Faculty of Health Sciences, Universiti Sultan Zainal Abidin. Terengganu, Malaysia.
[6]Human Genome Centre, School of Medical Sciences, Universiti Sains Malaysia. Kelantan, Malaysia.

***Note:** Both the first and second authors (Tri Hartini Yuliawati and Dewi Ratna Sari) contributed equally in the present investigation.

Cite as: Yuliawati TH, Ratna Sari D, Kencono Wungu CD, Faizah Z, Hamidah B, Amanda B, et al. The role of vitamin d receptor gene polymorphisms in obesity: a systematic review and meta-analysis. Salud, Ciencia y Tecnología. 2025; 5:1072. https://doi.org/10.56294/saludcyt20251072

Submitted: 29-03-2024 **Revised:** 12-07-2024 **Accepted:** 13-11-2024 **Published:** 01-01-2025

Editor: Dr. William Castillo-González

Corresponding Author: Citrawati Dyah Kencono Wungu

ABSTRACT

Introduction: obesity has become a major global issue since it can increase the risk of fatal disease. Genetic variation in the vitamin D receptor (VDR) gene is a potential candidate for obesity, though findings are inconclusive.
Objectives: this meta-analysis aims to determine the association between VDR polymorphisms and obesity risk.
Method: all relevant studies from 1990 to January 2024 were screened using PubMed, Web of Science, Science Direct, and Scopus. This meta-analysis included studies meeting PROSPERO-registered eligibility criteria. Pooled odds ratios (OR) with 95 % confidence intervals (CI) for six VDR gene polymorphisms (BsmI, FokI, TaqI, ApaI, and Cdx2) were generated using RevMan 5.4.
Results: this meta-analysis included 23 studies with 5715 obese/overweight and 4887 non-obese individuals from China, Malaysia, Egypt, Turkey, India, Iran, UAE, Saudi Arabia, Czech Republic, Greece, USA, Denmark, Hungary, and Belgium. The findings show an association between VDR ApaI polymorphism and reduced obesity risk in homozygous models [aa vs. AA: OR=0,76, CI=0,60-0,97; P=0,03]. The TaqI variant is linked to increased obesity risk in Europeans under allelic [t vs. T: OR=1,33, CI=1,11-1,60; P=0,002], homozygous [tt vs. TT: OR=1,68, CI=1,13-2,50; P=0,010], dominant [tt vs. TT+Tt: OR=1,47, CI=1,07-2,03; P=0,02], and recessive [Tt+tt vs. TT: OR=1,43, CI=1,08-1,89; P=0,01] models.
Conclusions: this meta-analysis suggests the aa genotype of VDR ApaI polymorphism may protect against obesity across populations. In Europeans, the t allele of VDR TaqI polymorphism is identified as an obesity risk factor.

Keywords: Genetics; Meta-Analysis; Obesity; Polymorphism; Vitamin D Receptor.

RESUMEN

Introducción: la obesidad se ha convertido en un problema mundial importante, ya que puede aumentar el riesgo de enfermedades mortales. La variación genética en el gen del receptor de vitamina D (VDR) es un candidato potencial para la obesidad, aunque los hallazgos no son concluyentes.
Objetivos: este metanálisis tiene como objetivo determinar la asociación entre los polimorfismos del VDR y el riesgo de obesidad.
Método: todos los estudios relevantes desde 1990 hasta enero de 2024 se examinaron mediante PubMed, Web of Science, Science Direct y Scopus. Este metanálisis incluyó estudios que cumplían los criterios de elegibilidad registrados en PROSPERO. Se generaron razones de probabilidades (OR) agrupadas con intervalos de confianza (IC) del 95 % para seis polimorfismos del gen VDR (BsmI, FokI, TaqI, ApaI y Cdx2) utilizando RevMan 5.4.
Resultados: este metanálisis incluyó 23 estudios con 5715 individuos obesos/con sobrepeso y 4887 no obesos de China, Malasia, Egipto, Turquía, India, Irán, Emiratos Árabes Unidos, Arabia Saudita, República Checa, Grecia, Estados Unidos, Dinamarca, Hungría y Bélgica. Los hallazgos muestran una asociación entre el polimorfismo VDR ApaI y un menor riesgo de obesidad en modelos homocigotos [aa vs. AA: OR=0,76, IC=0,60-0,97; P=0,03]. La variante TaqI está vinculada a un mayor riesgo de obesidad en europeos bajo alelo [t vs. T: OR=1,33, IC=1,11-1,60; P=0,002], homocigoto [tt vs. TT: OR=1,68, IC=1,13-2,50; P=0,010], dominante [tt vs. TT+Tt: OR=1,47, IC=1,07-2,03; P=0,02] y modelos recesivos [Tt+tt vs. TT: OR=1,43, IC=1,08-1,89; P=0,01].
Conclusiones: este metanálisis sugiere que el genotipo aa del polimorfismo ApaI del VDR puede proteger contra la obesidad en distintas poblaciones. En los europeos, el alelo t del polimorfismo TaqI del VDR se identifica como un factor de riesgo de obesidad.

Palabras clave: Genética; Metanálisis; Obesidad; Polimorfismo; Receptor de Vitamina D.

INTRODUCTION

Obesity is a condition characterized by an increase in body weight due to the accumulation of fat in the body. Obesity occurs when food intake and energy expenditure are out of balance. Multiple variables, including genetic, environmental, and psychological ones, contribute to the development of obesity.[1] According to data from the Centers for Disease Control and Prevention (CDC) for 2020-2022, obesity prevalence among adults in all states and territories in the United States was more than 20 %. By ethnicity, the prevalence of obesity among non-Hispanic American Indian or Alaska Native people is at least 35 % in 33 of the 47 states. Additionally, there were differences in the prevalence of obesity among young adults depending on their age group, with 20,5 % between the ages of 18 and 24 and 39,9 % between the ages of 45 and 54. However, there is no apparent difference in this prevalence between men and women.[2] In Indonesia, the percentage of obese individuals over the age of 18 rose from 14,8 % in 2013 to 21,8 % in 2018.[3] Respectively, obesity may raise the risk of several diseases, including type 2 diabetes mellitus (DM), cardiovascular disease, cerebrovascular disease, and numerous forms of cancer.[4] Therefore, the increasing prevalence of obesity and its accompanying complications create a socio-economic and psychological burden for families, communities, and countries.[5]

Chromosome abnormalities, single gene disorders, polygenic obesity, and obesity syndromes connected to other phenotypic abnormalities can all cause obesity.[6] Data from genome-wide association studies state that nine gene loci are known to cause monogenic obesity, and 58 loci are involved in polygenic forms of obesity.[7] Few cases of obesity are brought on by chromosomal abnormalities or mutations, such as the 2-3 % reported in cases of mutations in the pro-opiomelanocortin (POMC), leptin receptor (LEPR), leptin protein (LEP), and melanocortin 4 receptor (MC4R) genes.[8,9] Single nucleotide polymorphisms in genes, including the LEP, LEPR, insulin receptor (INSR), and other genes have been linked to an increased risk of obesity in some populations,[10,11] with the polymorphism in the VDR gene being the most recent detected to be associated with obesity.[12,13]

Calcium homeostasis and bone mineralization are the two most well-known biological functions of vitamin D.[14] However, VDR is also important for many other cellular activities, and it has been discovered in almost all cell types. Therefore, the epidemic of vitamin D deficiency may have a significant role in some obesity-related issues, including obesity and metabolic syndrome. Due to the widespread presence of VDRs in numerous body tissues, gene polymorphisms in these receptors may regulate the biological function of vitamin D as well as predispose to obesity.[15] The VDR genes contain numerous polymorphisms that can alter the activity level of VDR. Only five of the 470 known Single nucleotide polymorphisms (SNP) at the VDR locus—Cdx2 (rs11568820), FokI (rs2228570), TaqI (rs731236), BsmI (rs1544410), and ApaI (rs7975232)—have received extensive research attention because of their impacts on a variety of physiological and pathological phenotypes.[16,17,18] They are

situated in different sites of chromosome 12q. Cdx2 is located in the exon 1 promoter region.[19] FokI is found in exon 2, near the 5' untranslated region within the VDR DNA-binding domain. TaqI is established in exon 9, while BsmI and ApaI are placed on intron 8. They are found near the 3' untranslated region.[20]

Numerous genetic association studies between the prevalence of obesity and the VDR gene polymorphism have produced contradictory or ambiguous results.[21,22,23] Several studies have examined the association between these polymorphisms and the likelihood of becoming obese using this conceptual framework. However, more studies in various populations are required to understand the effect of these SNPs on the propensity to become obese. As a result of the foregoing, this meta-analysis was conducted to examine the association between the risk of obesity and specific polymorphisms in the VDR gene, specifically BsmI (rs1544410), TaqI (rs731236), ApaI (rs7975232), FokI (rs2228570), and Cdx2 (rs11568820).

METHOD

Search strategy

All related references were retrieved from PubMed, Web of Science, Science Direct, and Scopus from 1990 until January 2024. The search strategy involved a combination of the following keywords i.e Obesity (OR Obes* OR Pediatric obes* OR Adult obes* OR Central obes* OR Abdominal obes* OR Adiposity OR BMI OR Overweight) AND Receptors, calcitriol (OR Cholecalciferol OR Calcitriol receptor* OR Vitamin D receptor* OR Cholecalciferol receptor* OR Vitamin D) AND Polymorphism, genetic OR Polymorphism, single nucleotide OR Genetic variation OR Genetic polymorphism* OR Single nucleotide polymorphism* OR Genetic variation* OR Polymorphism* OR Mutation OR Variant* OR *BsmI* OR *ApaI* OR *FokI* OR *TaqI* OR *Cdx2*. The identification of any additional eligible studies was also manually screened through website searching to retrieve potential articles. Ten reviewers performed data searching independently, and any discrepancies were settled by discussion and consensus among them.

Protocol and Guidance

This search method adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. The protocol for this meta-analysis has been registered in PROSPERO (registration number CRD42021271339). Ethical approval and patient consent were not required because all results and analyses were obtained from previously published studies.

Selection criteria

All published articles were selected based on the following inclusion criteria: 1. Case-control or cross-sectional studies; 2. Evaluating the association between VDR polymorphisms and obesity; 3. Overweight and obesity were defined according to the respective criteria of included studies. Body Mass Index (BMI) $\geq$ 23 kg/m^2, or $\geq$ 25 kg/m^2, or $\geq$ 25 kg/m^2 to < 30 kg/m^2 was categorized as overweight and $\geq$ 28 kg/m^2 or $\geq$ 30 kg/m^2 was classified into obese for adults and not pregnant. While, for children or adolescents, overweight and obesity were defined as $\geq 85^{th}$ to $<95^{th}$ and $\geq 95^{th}$ percentile of BMI, respectively; 4. Genotype frequencies were provided for calculating the odds ratio (OR) with 95 % confidence interval (CI); 5. The distribution of VDR polymorphism met the criteria for the Hardy-Weinberg Equilibrium (HWE); 6. Full-text was available; and 7. English articles.

The duplicated articles, non-human studies, abstracts, case reports/series, reviews, meta-analysis, editorial articles, and studies with incomplete data were excluded from this meta-analysis.

Data extraction

A standardized form was used to obtain the full description of study characteristics, i.e., first author, publication year, country, study design, sample size, obesity criteria, gender, age, genotype identification method, source of control, HWE test, and polymorphism loci. The genotypes of 5 VDR gene polymorphisms (BsmI, FokI, TaqI, ApaI, and Cdx2) were defined by B, F, T, A, and G, respectively if the restriction sites for corresponding enzymes were absent. Otherwise, b,f,t,a,g were used. The label of BsmI [G (or C) / A (or T)] corresponds to BsmI (b/B), FokI [A (or T) / G (or C)] corresponds to FokI (f/F), TaqI [G (or T) / A (or C)] corresponds to TaqI (t/T), ApaI [G (or C) / A (or T)] corresponds to ApaI (a/A), and for Cdx2, there is two allelic group based on presence of A or G nucleotide.

Quality assessment

Three independent reviewers applied the Newcastle-Ottawa Scale (NOS) to evaluate the quality of the included studies. The three aspects used as indicators were: selection, comparability, and exposure/outcome. The study with > 6 stars was considered to have high quality.

Statistical analysis

The data were analyzed via Review Manager 5.4 (Cochrane Collaboration, UK). The associations between

obesity risk and VDR polymorphisms were determined by computing the crude Odds Ratio (OR) and 95 % CI. We evaluated six genetic models (allelic, homozygous, heterozygous, dominant, additive, and recessive models). Events were defined as the polymorphism genotypes for each analysis model. Test for overall effect used the pooled OR and was considered significant if $p < 0,05$. The subgroup analysis was also carried out based on ethnicity (Asian and European). Heterogeneity among studies was quantified statistically using Chi^2 and the I^2. A random-effects (heterogeneous, $p<0,10$ and $I^2>50$ %) or fixed-effects (homogeneous, $p>0,10$ and $I^2<50$ %) model was used to estimate the pooled effects. Funnel plot asymmetry was applied to determine publication bias. Sensitivity analysis was done to evaluate whether any individual study had a substantial impact on the results by eliminating each study at a time.

RESULTS

Characteristics of eligible studies

Initially, 18706 studies were collected through database searching engine and 11382 studies were removed after checking for duplicates and marked as ineligible by automation tools. Further screening of the title and abstract was conducted and 6913 were eliminated due to insufficient data, unqualified articles, irrelevant study design, topics, and population. The rest of the articles were assessed for eligibility by checking the full text and 386 articles were eliminated due to irrelevant SNPs, diseases, or conditions; insufficient genotyping data or frequencies; irrelevant study design and HWE test result. After combining the results from database and website searching, we found 23 articles to be finally included. The PRISMA flow chart for the detailed study selection is shown in figure 1.

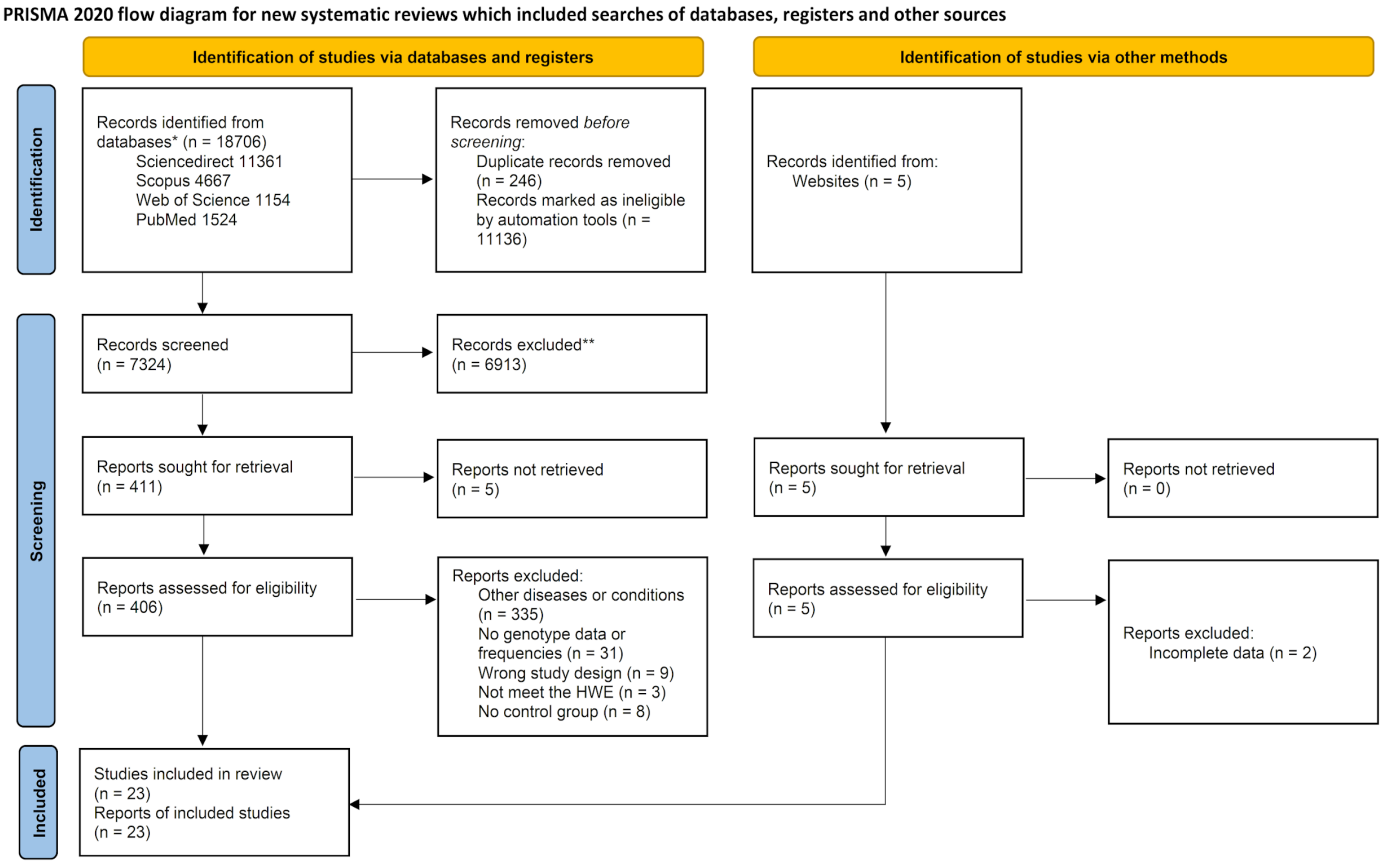


Figure 1. The PRISMA flow chart for the detailed study selection

This meta-analysis incorporated a total of 23 case-control and cross-sectional studies, encompassing 5715 obese/overweight and 4887 non-obese individuals who adhered to predefined inclusion and exclusion criteria (table 1). The association of VDR BsmI polymorphism with obesity risk was assessed by ten studies,[17,22,24,25,26,27,28,29,30,31] the VDR ApaI polymorphism by ten studies,[17,18,22,27,32,33,34,35,36,37] VDR FokI polymorphism by twelve studies,[17,18,24,27,29,32,35,38,39,40,41,42] VDR TaqI polymorphism by ten studies[15,17,18,27,32,33,34,36,38,39] and VDR Cdx2 polymorphism by two studies.[17,18] The characteristics of all included articles are listed in table 1. Most of the included studies had high quality based on NOS criteria (table 1).

Table 1. Study characteristics of each article included in our meta-analysis

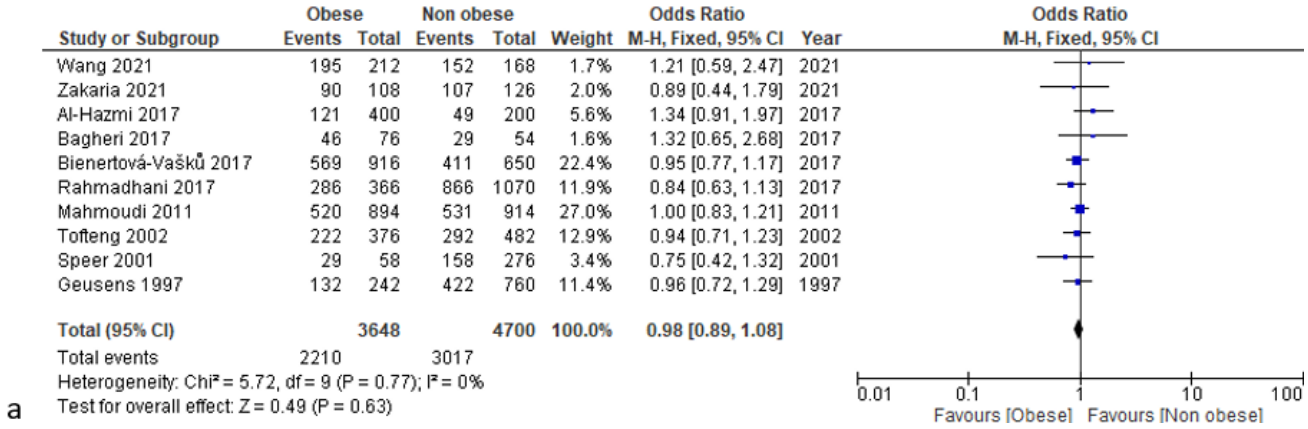
No	First author	Year	Study design	Country	Population	Sample size	Case (n=5715)	Control (n=4887)	Gender	Genotype method	Genetic polymorphisms	NOS
1.	Gariballa, et al.[38]	2023	Cross sectional	United Arab Emirates	Adult	266	201	65	Male & Female	PCR-TaqMan Genotyping Assay	FokI, TaqI	10
2.	Bagci, et al.[32]	2023	Cross sectional	Turkey	Adults	139	68	71	Male & Female	PCR-RFLP	FokI, TaqI, ApaI	7
3.	Wang, et al.[17]	2021	Case control	China	Children	191	106	85	Male & Female	PCR sequencing	BsmI, FokI, TaqI, ApaI, Cdx2	7
4.	Zakaria, et al.[24]	2021	Case control	Malaysia	Adults	117	54	63	Male & Female	PCR-RFLP	BsmI, FokI	6
5.	Hassan, et al.[33]	2021	Cross sectional	Egypt	Adults	97	66	31	Female	PCR-RFLP	TaqI, ApaI	7
6.	Bhatt et al.[39]	2021	Cross sectional	India	Adults	300	230	70	Male & Female	PCR-TaqMan Genotyping Assay	FokI, TaqI	10
7.	Rashidi et al.[34]	2021	Case control	Iran	Adults	167	87	80	Male & Female	PCR-RFLP	TaqI, ApaI	6
8.	Xie, et al.[40]	2021	Cross sectional	China	Childrens	452	225	227	Male & Female	PCR-RFLP	FokI	10
9.	Hussain, et al.[41]	2018	Case control	United Arab Emirates	Adults	340	97	243	Female	PCR-RFLP	FokI	6
10.	Rahmadhani, et al.[25]	2017	Cross sectional	Malaysia	Children	718	183	535	Male & Female	Sequenom MassARRAY	BsmI	7
11.	Al-Hazmi, et al.[22]	2017	Case control	Saudi Arabia	Adults	300	200	100	Male	PCR-RFLP	BsmI, ApaI	8
12.	Bagheri, et al.[26]	2017	Case control	Iran	Adults	65	38	27	Female	PCR sequencing	BsmI	9
13.	Bienertová-Vašků, et al.[27]	2017	Cross sectional	Czech Republic	Adults	882	511	371	Male & Female	PCR-RFLP	BsmI, FokI, TaqI, ApaI	7
14.	Fan, et al.[35]	2015	Case control	China	Adults	529	245	284	Male & Female	PCR-RFLP	FokI, ApaI	9
15.	Zhou, et al.[18]	2015	Cross sectional	China	Adults	181	99	82	Male	PCR-RFLP	FokI, TaqI, ApaI, Cdx2	8
16.	El-Shal, et al.[36]	2013	Case control	Egypt	Adults	300	235	65	Female	PCR-RFLP	TaqI, ApaI	7
17.	Vasilopoulos, et al.[15]	2013	Case control	Greece	Adults	184	82	102	Male & Female	PCR -RFLP	TaqI	6
18.	Mahmoudi, et al.[28]	2011	Case control	Iran	Adults	904	447	457	Male & Female	PCR-RFLP	BsmI	7
19.	Mahmoudi, et al.[37]	2010	Case control	Iran	Adults	160	68	92	Male & Female	PCR-RFLP	ApaI	7
20.	Slattery, et al.[42]	2004	Case control	United States	Adults	3213	2135	1078	Male & Female	PCR-RFLP	FokI	6
21.	Tofteng, et al.[29]	2002	Cross sectional	Denmark	Adults	429	188	241	Female	PCR-RFLP	BsmI, FokI	6
22.	Speer, et al.[30]	2001	Case control	Hungary	Adults	167	29	138	Male & Female	PCR-RFLP	BsmI	7
23.	Geusens, et al.[31]	1997	Cross sectional	Belgium	Elderly	501	121	380	Female	PCR-RFLP	BsmI	10

Nota: PCR-RFLP – polymerase chain reaction-restriction fragment length polymorphism; NOS – Newcastle-Ottawa Scale.

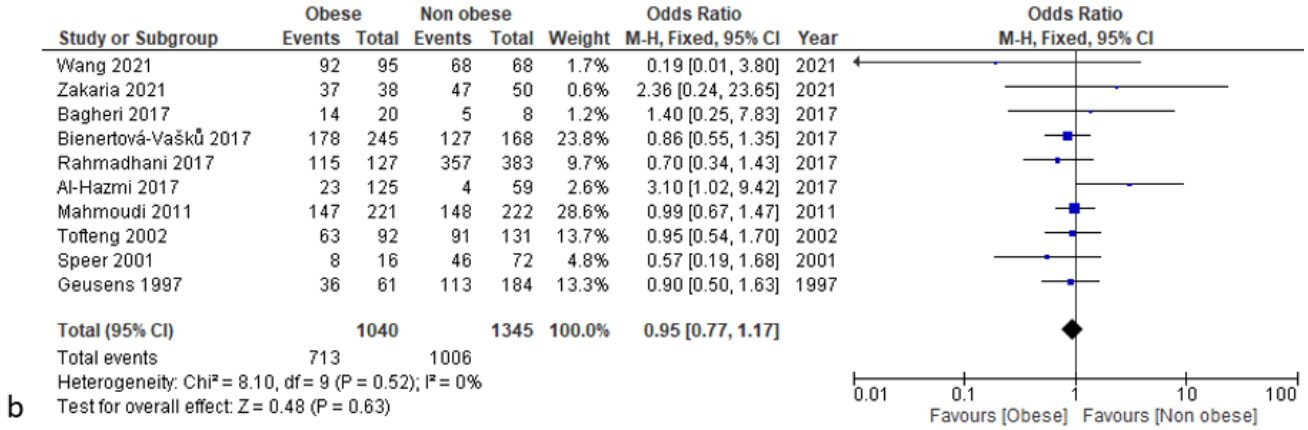
https://doi.org/10.56294/saludcyt20251072

The analyses of the association between VDR polymorphism and obesity risk in all genetic models and subgroup analyses are displayed in table 2 and 3.

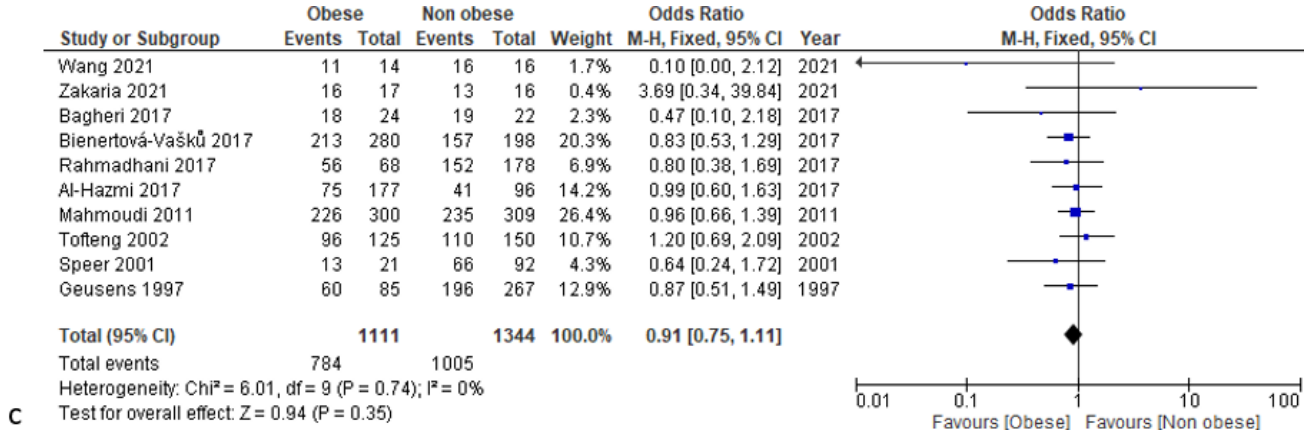
Association between VDR BsmI polymorphism and risk of obesity



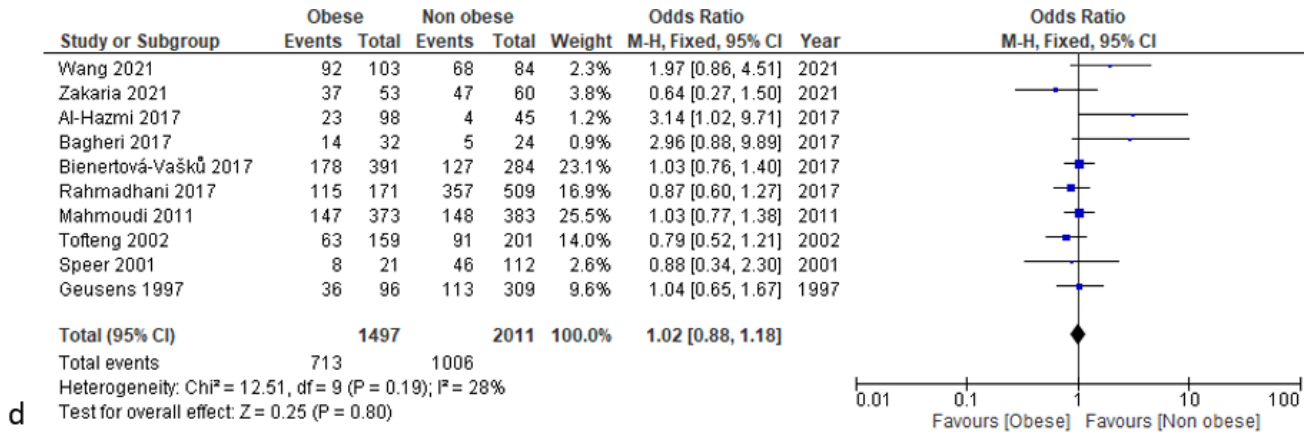
a



b



c



d

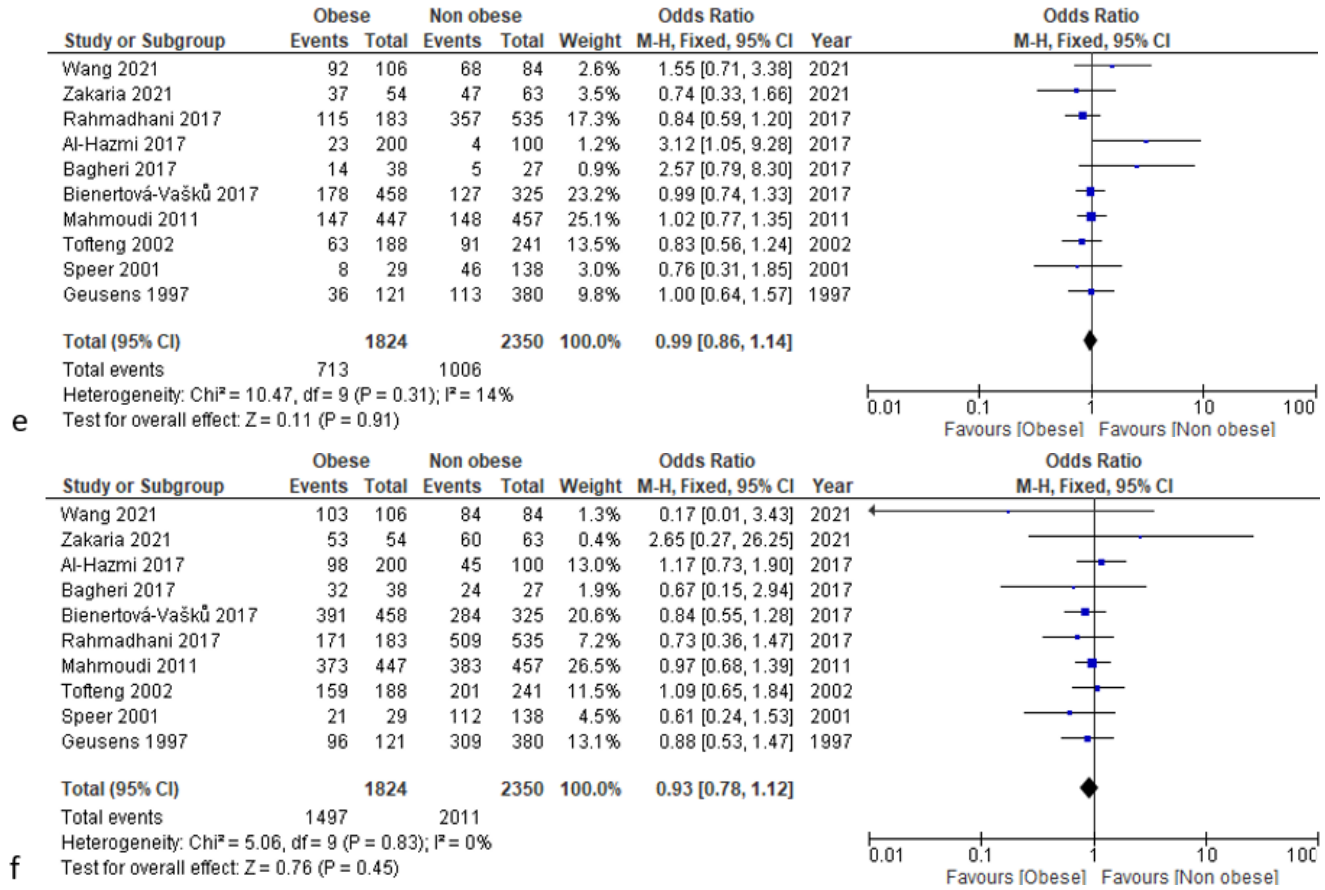
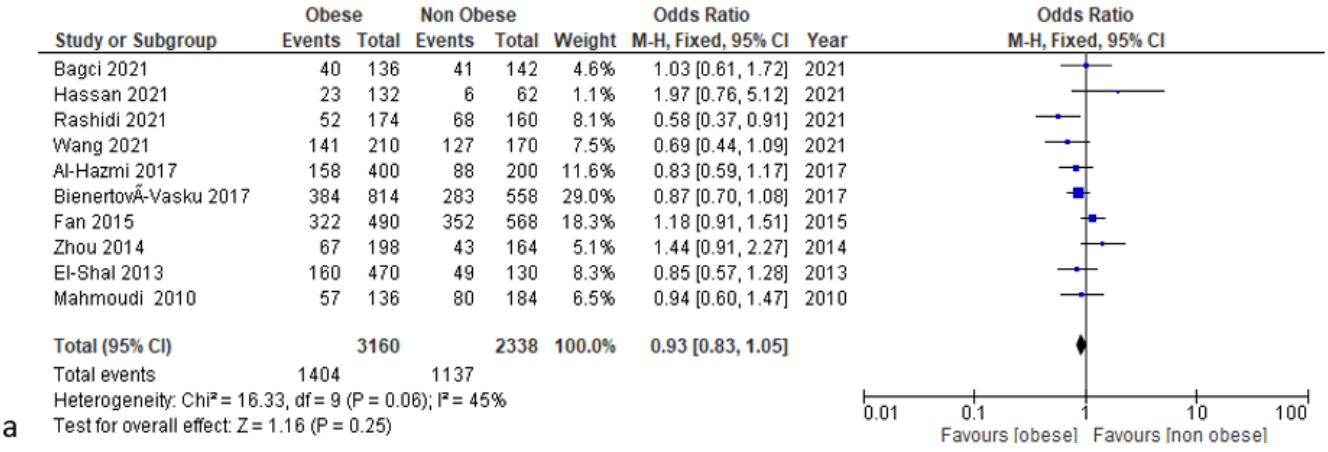


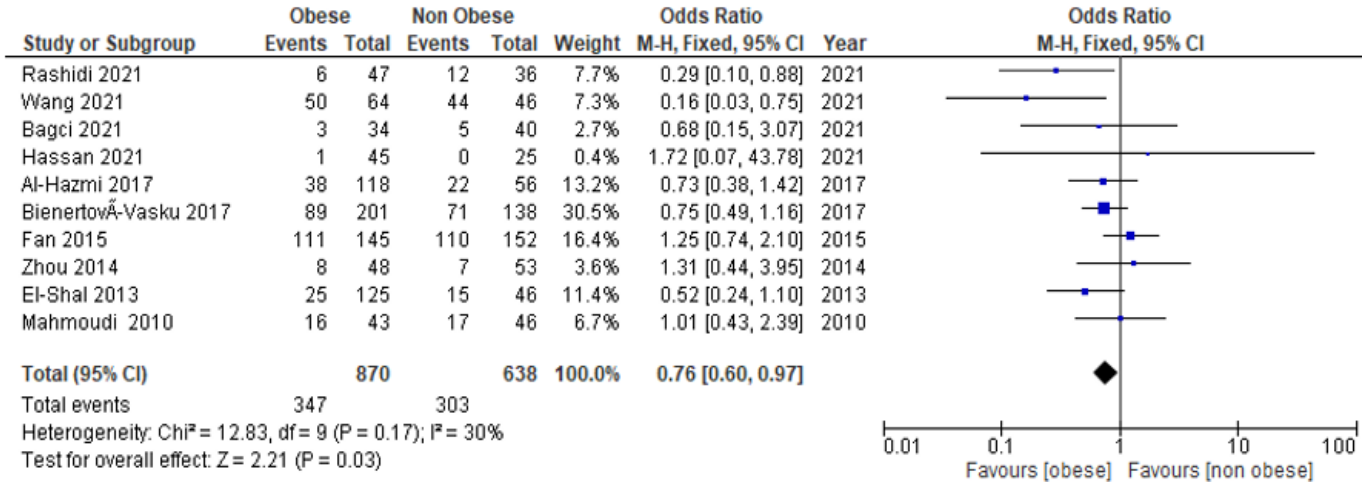
Figure 2. Forest plot of the association between VDR gene BsmI polymorphism and obesity risk in all population under: (a) b vs. B model; (b) bb vs. BB model; (c) Bb vs. BB model; (d) bb vs. Bb model; (e) bb vs. BB+Bb model; (f) Bb+bb vs. BB model

Analysis of the association between BsmI polymorphism and risk of obesity involved ten studies with 1877 cases and 2397 controls. The heterogeneity test and association between BsmI SNP and propensity to obesity is exhibited in table 2. Our meta-analysis found no significant association between VDR BsmI polymorphism and obesity risk in all genetic models and subgroup analyses (table 2 and 3, figure 2).

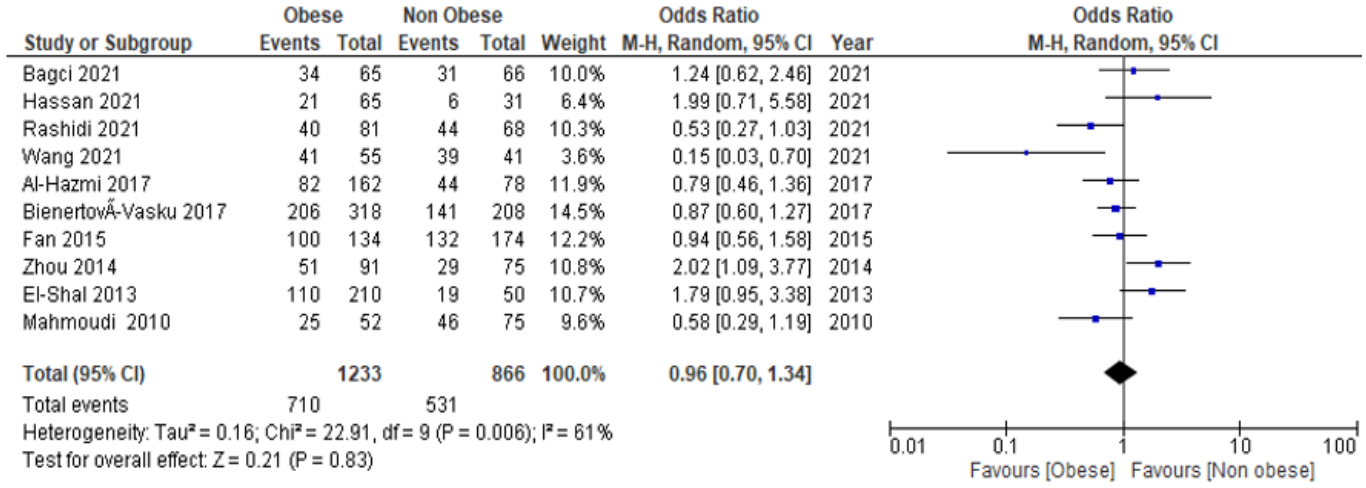
Association between the VDR ApaI polymorphism and risk of obesity

The association between VDR ApaI polymorphism and risk of obesity was analyzed from ten studies, with 1685 cases and 1261 controls included (table 1). The results of heterogeneity and association tests can be seen in table 2. There was a significant association [p = 0,03] in homozygous model analysis (aa vs. AA) with OR 0,76 [95 % CI 0,60 - 0,97], which implies the aa genotype of ApaI may confer a protective effect on obesity in overall populations (figure 3). Furthermore, in subgroup analysis based on Asian or European populations, no significant correlation was found between VDR ApaI polymorphism and the risk of obesity (table 3, annexes).

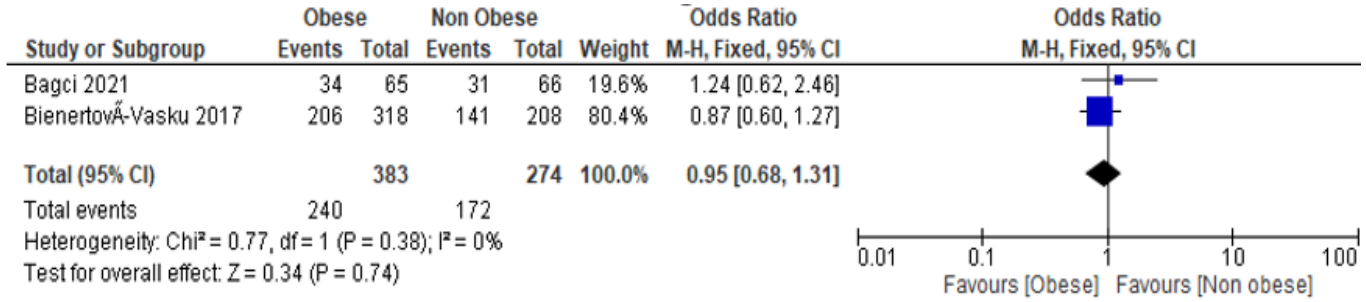



Obese
Non Obese
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI Year
M-H, Fixed, 95% CI
Rashidi 2021 6 47 12 36 7.7% 0.29 [0.10, 0.88] 2021
Wang 2021 50 64 44 46 7.3% 0.16 [0.03, 0.75] 2021
Bagci 2021 3 34 5 40 2.7% 0.68 [0.15, 3.07] 2021
Hassan 2021 1 45 0 25 0.4% 1.72 [0.07, 43.78] 2021
Al-Hazmi 2017 38 118 22 56 13.2% 0.73 [0.38, 1.42] 2017
BienertovÃ-Vasku 2017 89 201 71 138 30.5% 0.75 [0.49, 1.16] 2017
Fan 2015 111 145 110 152 16.4% 1.25 [0.74, 2.10] 2015
Zhou 2014 8 48 7 53 3.6% 1.31 [0.44, 3.95] 2014
El-Shal 2013 25 125 15 46 11.4% 0.52 [0.24, 1.10] 2013
Mahmoudi 2010 16 43 17 46 6.7% 1.01 [0.43, 2.39] 2010
Total (95% CI) 870 638 100.0% 0.76 [0.60, 0.97]
Total events 347 303
Heterogeneity: Chi² = 12.83, df = 9 (P = 0.17); I² = 30%
Test for overall effect: Z = 2.21 (P = 0.03)
0.01 0.1 1 10 100
Favours [obese] Favours [non obese]

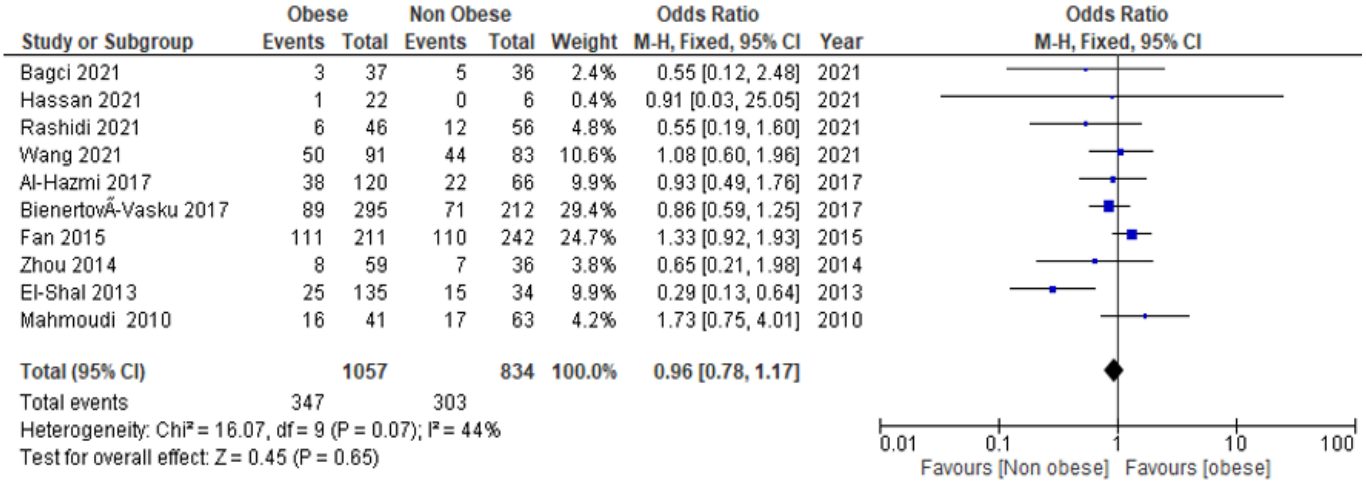
b


Obese
Non Obese
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Year
M-H, Random, 95% CI
Bagci 2021 34 65 31 66 10.0% 1.24 [0.62, 2.46] 2021
Hassan 2021 21 65 6 31 6.4% 1.99 [0.71, 5.58] 2021
Rashidi 2021 40 81 44 68 10.3% 0.53 [0.27, 1.03] 2021
Wang 2021 41 55 39 41 3.6% 0.15 [0.03, 0.70] 2021
Al-Hazmi 2017 82 162 44 78 11.9% 0.79 [0.46, 1.36] 2017
BienertovÃ-Vasku 2017 206 318 141 208 14.5% 0.87 [0.60, 1.27] 2017
Fan 2015 100 134 132 174 12.2% 0.94 [0.56, 1.58] 2015
Zhou 2014 51 91 29 75 10.8% 2.02 [1.09, 3.77] 2014
El-Shal 2013 110 210 19 50 10.7% 1.79 [0.95, 3.38] 2013
Mahmoudi 2010 25 52 46 75 9.6% 0.58 [0.29, 1.19] 2010
Total (95% CI) 1233 866 100.0% 0.96 [0.70, 1.34]
Total events 710 531
Heterogeneity: Tau² = 0.16; Chi² = 22.91, df = 9 (P = 0.006); I² = 61%
Test for overall effect: Z = 0.21 (P = 0.83)
0.01 0.1 1 10 100
Favours [Obese] Favours [Non obese]

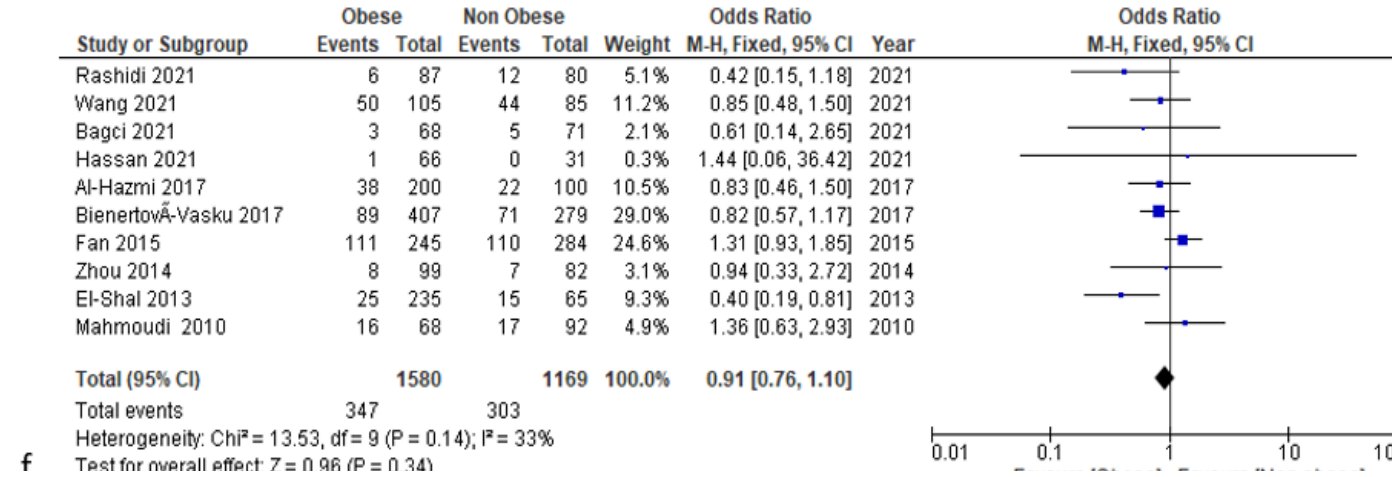
c


Obese
Non Obese
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Bagci 2021 34 65 31 66 19.6% 1.24 [0.62, 2.46]
BienertovÃ-Vasku 2017 206 318 141 208 80.4% 0.87 [0.60, 1.27]
Total (95% CI) 383 274 100.0% 0.95 [0.68, 1.31]
Total events 240 172
Heterogeneity: Chi² = 0.77, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 0.34 (P = 0.74)
0.01 0.1 1 10 100
Favours [Obese] Favours [Non obese]

d


Obese
Non Obese
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI Year
M-H, Fixed, 95% CI
Bagci 2021 3 37 5 36 2.4% 0.55 [0.12, 2.48] 2021
Hassan 2021 1 22 0 6 0.4% 0.91 [0.03, 25.05] 2021
Rashidi 2021 6 46 12 56 4.8% 0.55 [0.19, 1.60] 2021
Wang 2021 50 91 44 83 10.6% 1.08 [0.60, 1.96] 2021
Al-Hazmi 2017 38 120 22 66 9.9% 0.93 [0.49, 1.76] 2017
BienertovÃ-Vasku 2017 89 295 71 212 29.4% 0.86 [0.59, 1.25] 2017
Fan 2015 111 211 110 242 24.7% 1.33 [0.92, 1.93] 2015
Zhou 2014 8 59 7 36 3.8% 0.65 [0.21, 1.98] 2014
El-Shal 2013 25 135 15 34 9.9% 0.29 [0.13, 0.64] 2013
Mahmoudi 2010 16 41 17 63 4.2% 1.73 [0.75, 4.01] 2010
Total (95% CI) 1057 834 100.0% 0.96 [0.78, 1.17]
Total events 347 303
Heterogeneity: Chi² = 16.07, df = 9 (P = 0.07); I² = 44%
Test for overall effect: Z = 0.45 (P = 0.65)
0.01 0.1 1 10 100
Favours [Non obese] Favours [obese]

e



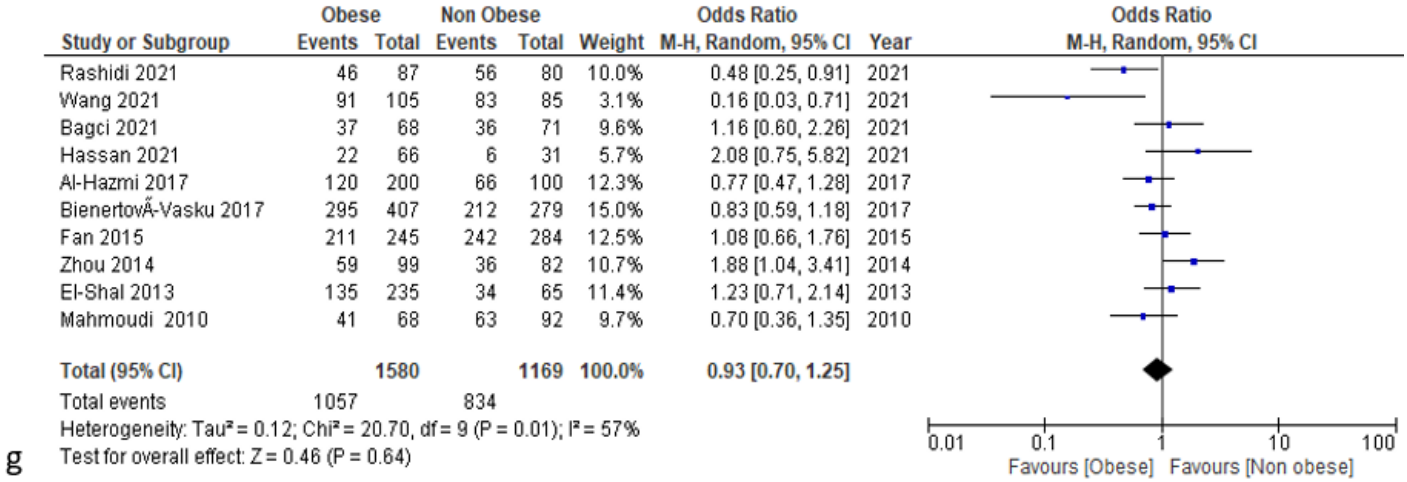
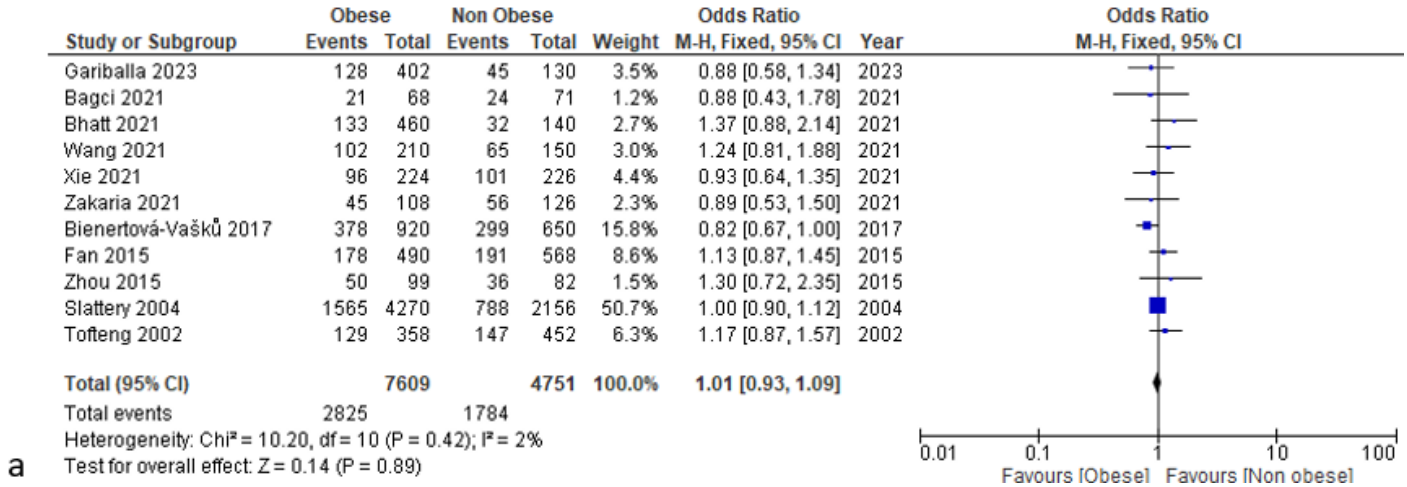
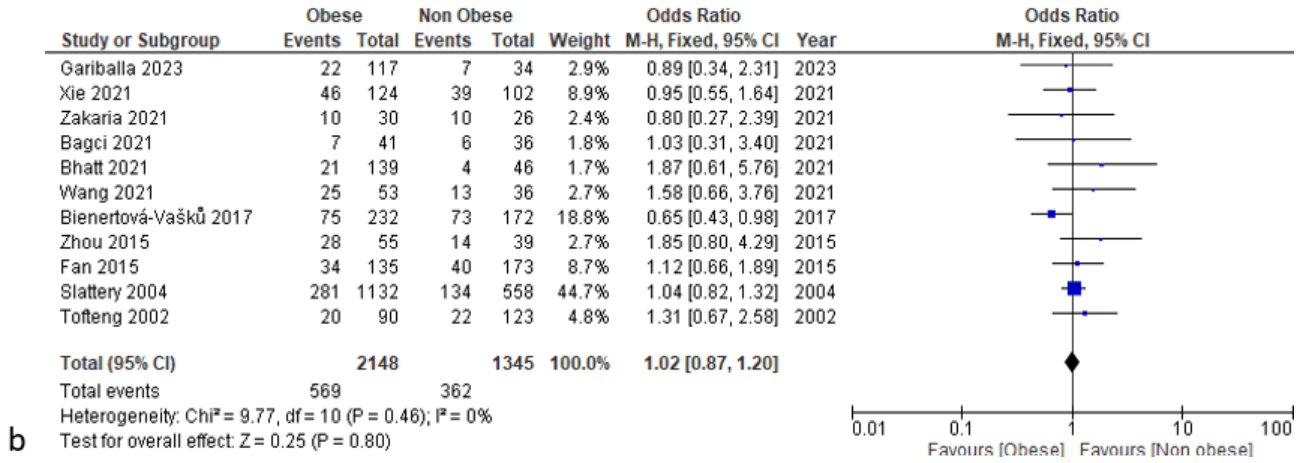


Figure 3. Forest plot of the association between VDR gene ApaI polymorphism and obesity risk in all population under: (a) a vs. A model; (b) aa vs. AA model; (c) Aa vs. AA model; (d) Aa vs. AA model; (e) aa vs. Aa model; (f) aa vs. AA+Aa model; (g) Aa+aa vs. AA model

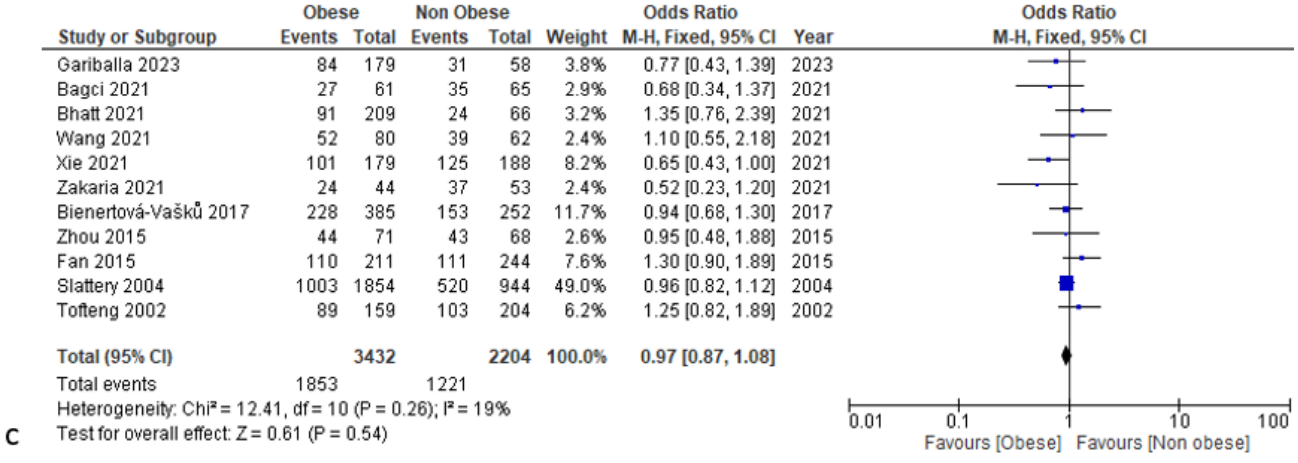
Association between the VDR FokI polymorphism and risk of obesity

Twelve studies were included to analyze the association between the VDR *FokI* polymorphism and risk of obesity with 4159 cases and 2880 controls. As FF and Ff+ff genotypes were the only data available in the paper, Hussain's study from 2018 was only included in one subgroup analysis (FF vs. Ff+ff). The heterogeneity and association test can be seen in table 2 and figure 4. Further analysis of subgroups showed no correlation between VDR *FokI* polymorphism and risk of obesity (table 3, annexes).

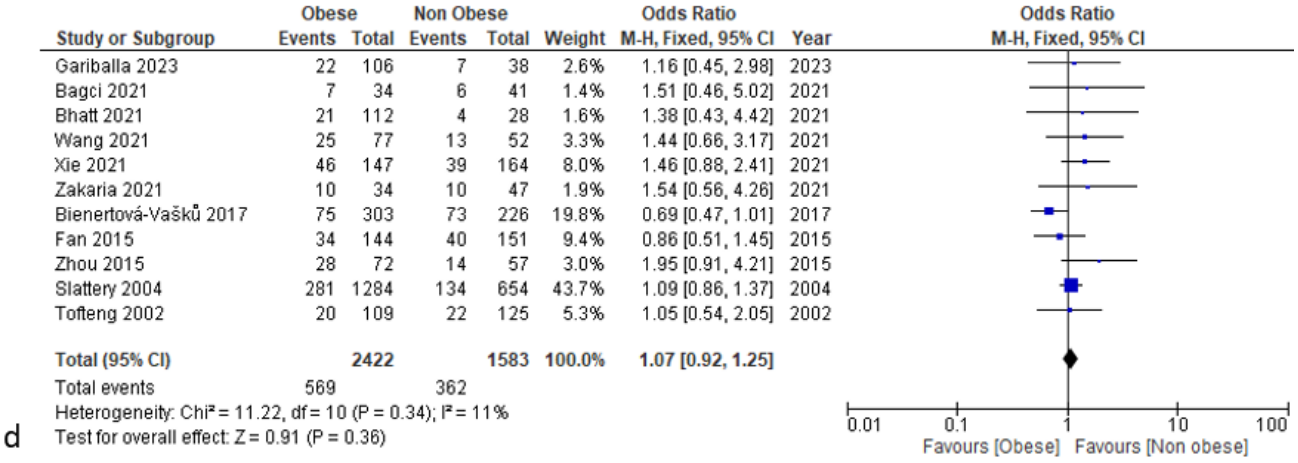




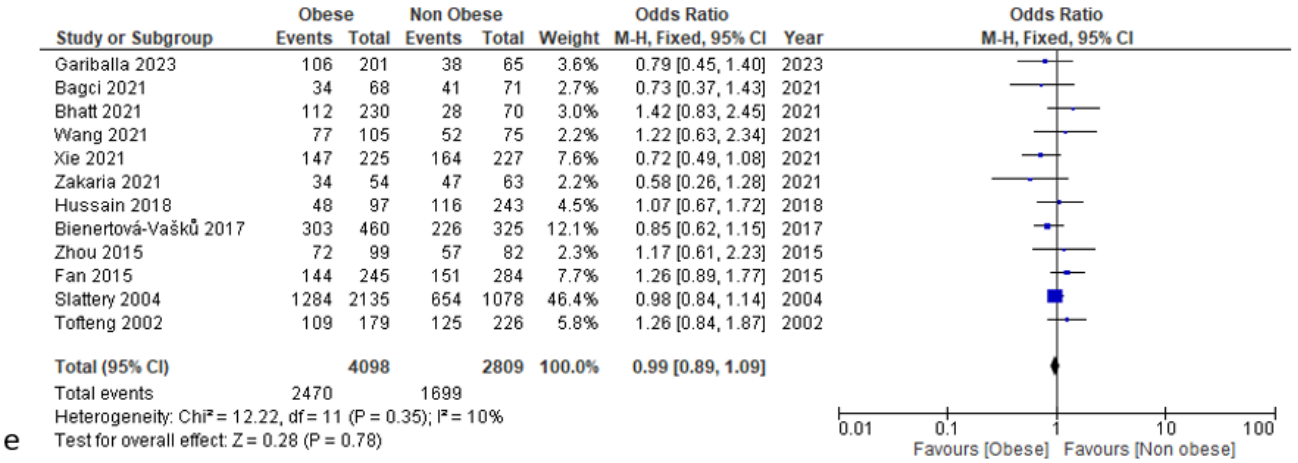
b



c

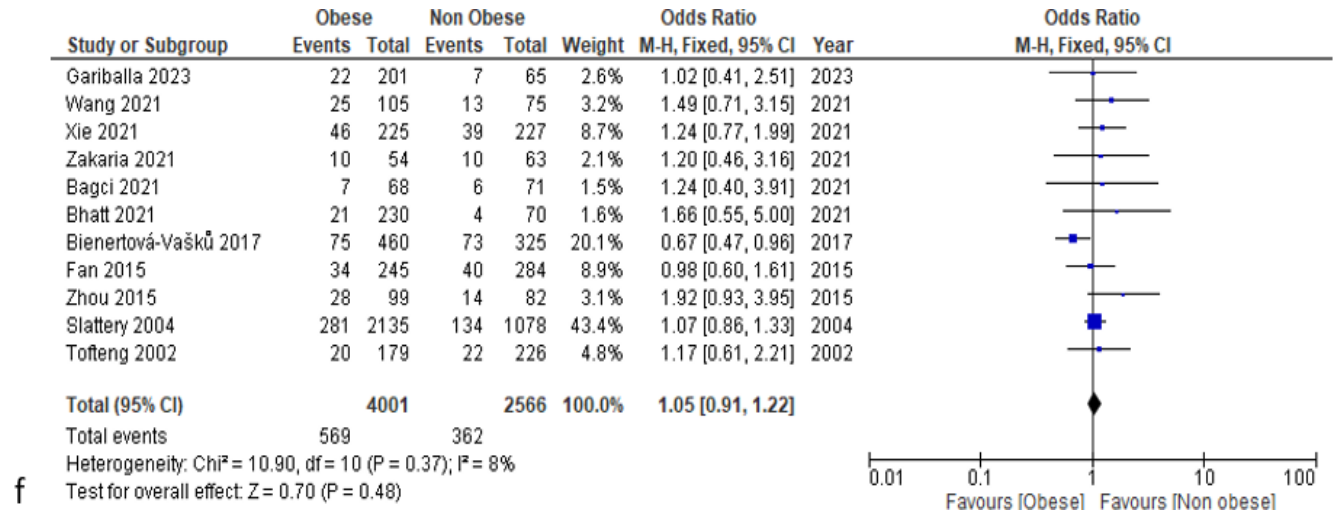


d



e

https://doi.org/10.56294/saludcyt20251072

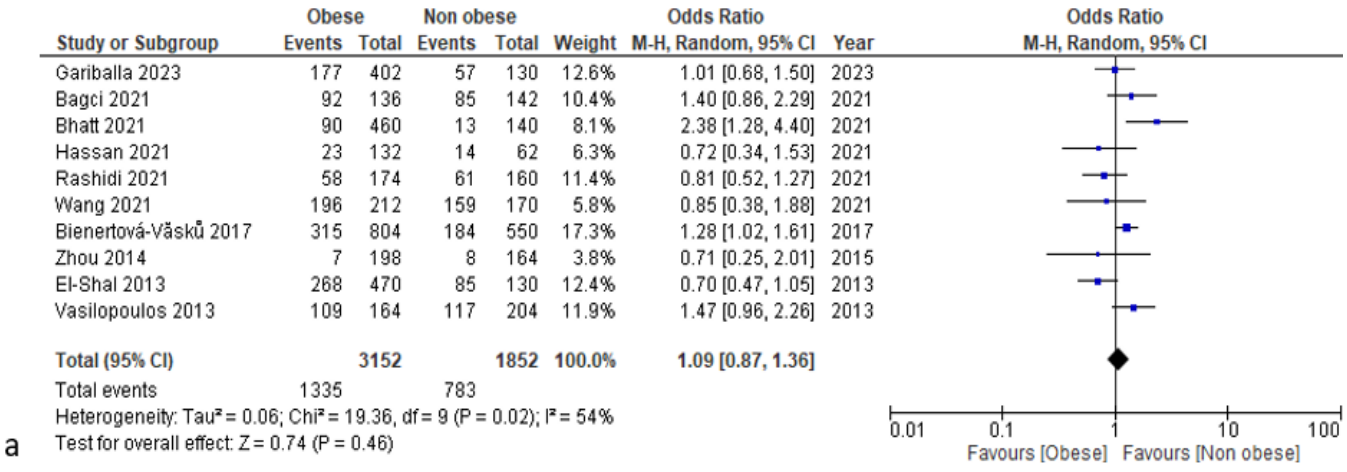


f

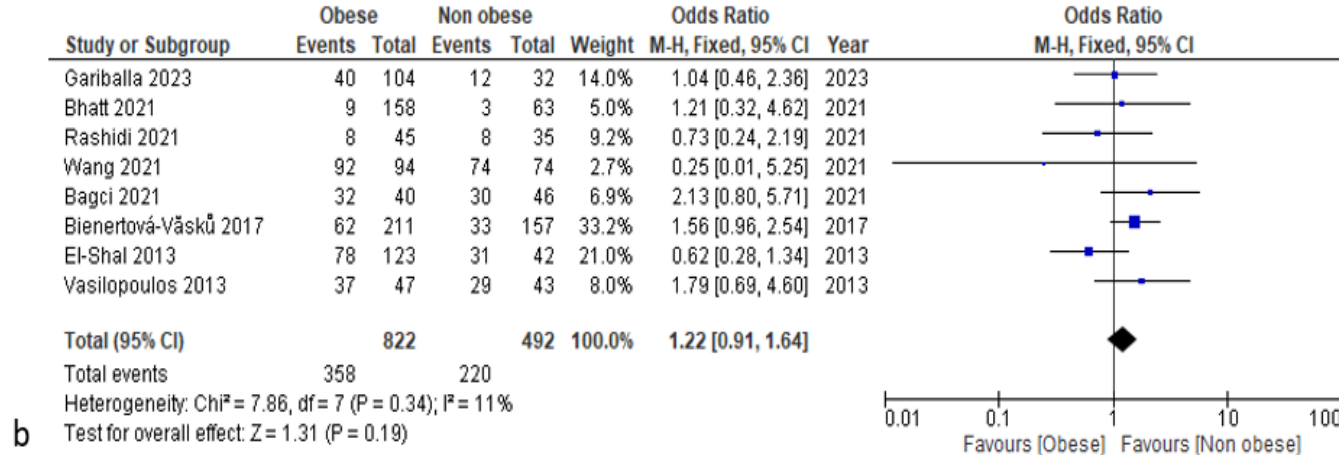
Figure 4. Forest plot of the association between VDR gene *FokI* polymorphism and obesity risk in all population under: (a) f vs. F model; (b) ff vs. FF model; (c) Ff vs. FF model; (d) ff vs. Ff model; (e) ff vs. FF+Ff model; (f) Ff+ff vs FF model

Association between TaqI polymorphism and risk of obesity

Ten studies with 1685 cases and 1022 controls were included to determine the association between *TaqI* SNP and obesity risk. Due to limited numbers of case for tt genotype in the studies by Hassan et al (2021) and Zhou et al (2014), they could only be used for allele model (t vs T), heterozygote model (Tt vs TT) and recessive model (Tt + tt vs TT) analysis. As shown in table 2, there was no significant association between *TaqI* polymorphism and the risk of obesity in all genetic models (figure 5). Furthermore, subgroup analysis was performed based on ethnicity. *TaqI* polymorphism significantly increased the risk of obesity in European population in allele model (t vs T) [p= 0,002], homozygote (tt vs TT) [p=0,010], dominant (tt vs TT + Tt) [p=0,02] and recessive (Tt + tt vs TT) [p=0,01] as shown in table 3 and annexes.



a



b

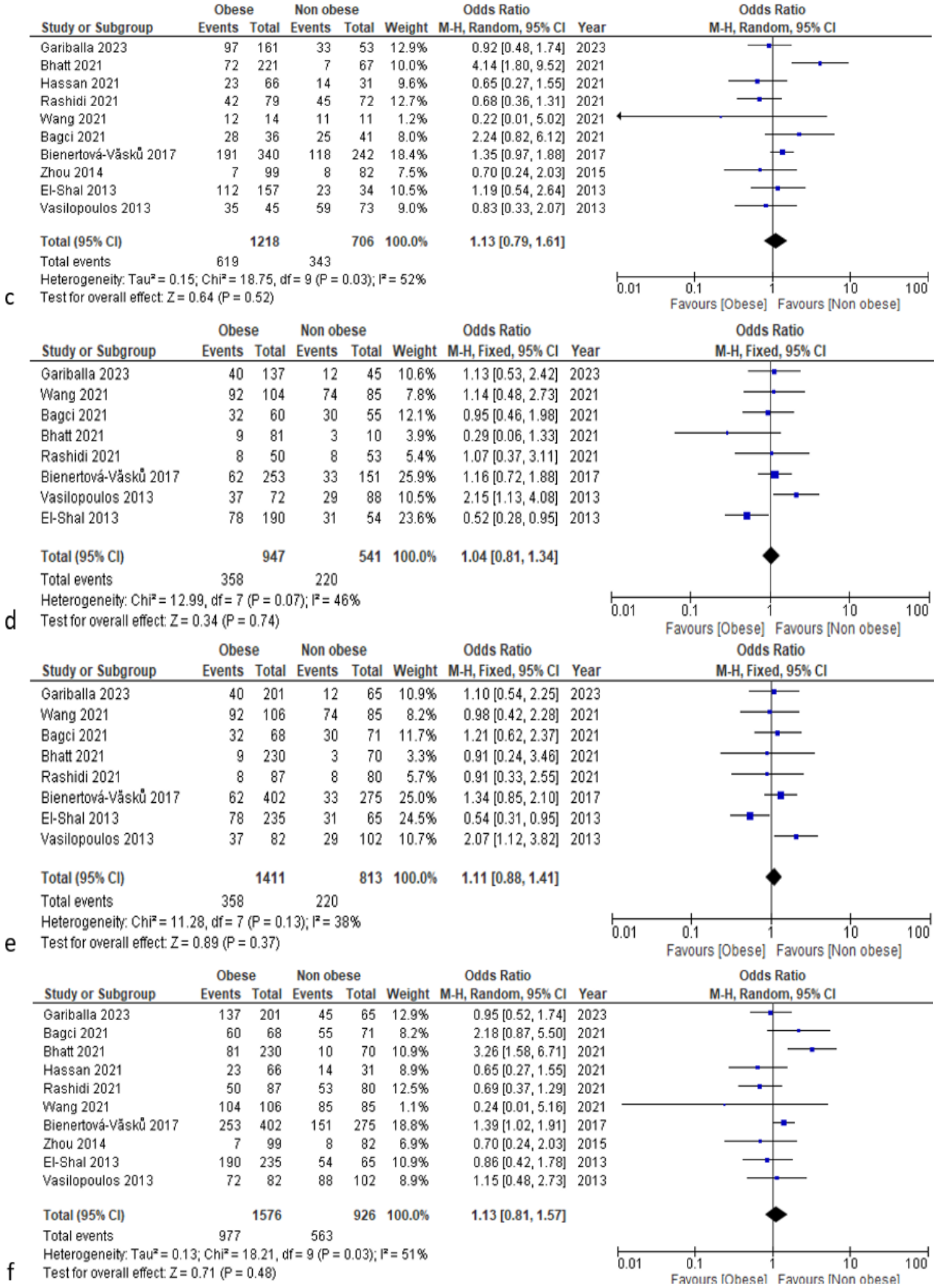


Figure 5. Forest plot of the association between VDR gene TaqI polymorphism and obesity risk in all population under: (a) t vs. T model; (b) tt vs. TT model; (c) Tt vs TT model; (d) tt vs Tt model; (e) tt vs TT + Tt model; (f) Tt + tt vs TT model

Association between the VDR Cdx2 polymorphism and risk of obesity

A total of 205 cases and 167 controls from two different studies were included to determine the association between VDR Cdx2 polymorphism and the risk of obesity. However, there was no association between Cdx2 polymorphism and the risk of obesity in all models (table 2 and annexes). The subgroup analysis could not be performed because of the limited number of studies being included.

Table 2. Overall meta-analysis of polymorphisms in VDR genes

SNPs	Comparisons	Qualified studies	Test of association		Model	Test of heterogeneity	
			OR [95 % CI]	p		p-value	I^2 (%)
BsmI	b vs. B	10	0,98 [0,89 - 1,08]	0,63	F	0,77	0
	bb vs. BB	10	0,95 [0,77 - 1,17]	0,63	F	0,52	0
	Bb vs. BB	10	0,91 [0,75 - 1,11]	0,35	F	0,74	0
	bb vs. Bb	10	1,02 [0,88 - 1,18]	0,80	F	0,19	28
	bb vs. BB+Bb	10	0,99 [0,86 - 1,14]	0,91	F	0,31	14
	Bb+bb vs. BB	10	0,93 [0,78 - 1,12]	0,45	F	0,83	0
ApaI	a vs. A	10	0,93 [0,83 - 1,05]	0,25	F	0,06	45
	aa vs. AA	10	0,76 [0,60 - 0,97]	0,03*	F	0,17	30
	Aa vs. AA	10	0,96 [0,70 - 1,34]	0,83	R	0,006	61
	aa vs. Aa	10	0,96 [0,78 - 1,17]	0,65	F	0,07	44
	aa vs. AA + Aa	10	0,91 [0,76 - 1,10]	0,34	F	0,14	33
	Aa+aa vs. AA	10	0,93 [0,70 - 1,25]	0,64	R	0,01	57
FokI	f vs. F	11	1,01 [0,93 - 1,09]	0,89	F	0,42	2
	ff vs. FF	11	1,02 [0,87 - 1,20]	0,80	F	0,46	0
	Ff vs. FF	11	0,97 [0,87 - 1,08]	0,54	F	0,26	19
	ff vs. Ff	11	1,07 [0,92 - 1,25]	0,36	F	0,34	11
	ff vs. FF+Ff	11	1,05 [0,91 - 1,22]	0,48	F	0,37	8
	Ff+ff vs. FF	12	0,99 [0,89 - 1,09]	0,78	F	0,35	10
TaqI	t vs. T	10	1,09 [0,87 - 1,36]	0,46	R	0,02	54
	tt vs. TT	8	1,22 [0,91 - 1,64]	0,19	F	0,34	11
	Tt vs. TT	10	1,13 [0,79 - 1,61]	0,52	R	0,03	52
	tt vs. Tt	8	1,04 [0,81 - 1,34]	0,74	F	0,07	46
	tt vs. TT+Tt	8	1,11 [0,88 - 1,41]	0,37	F	0,13	38
	Tt+tt vs. TT	10	1,13 [0,81 - 1,57]	0,48	R	0,03	51
Cdx2	A vs. G	2	1,23 [0,92 - 1,65]	0,16	F	0,32	0
	AA vs. GG	2	1,46 [0,82 - 2,59]	0,20	F	0,36	0
	GA vs. GG	2	1,20 [0,76 - 1,90]	0,44	F	0,62	0
	AA vs.GA	2	1,21 [0,70 - 2,12]	0,49	F	0,59	0
	AA vs. GG+GA	2	1,32 [0,79 - 2,20]	0,29	F	0,42	0
	GA+AA vs. GG	2	1,28 [0,84 - 1,97]	0,25	F	0,46	0

Note: OR – odds ratio; CI – confidence interval; R – random-effects; F – fixed-effects.

Table 3. Subgroup analyses of polymorphism in VDR gene based on ethnicity

SNPs	Comparisons	Ethnicity					
		Asian			European		
		N	OR (95 % CI)	p	N	OR (95 % CI)	p
BsmI	b vs. B	6	1,01 [0,88 - 1,16]	0,83	4	0,94 [0,82 - 1,08]	0,36
	bb vs. BB	6	1,05 [0,77 - 1,44]	0,76	4	0,87 [0,65 - 1,16]	0,34
	Bb vs. BB	6	0,92 [0,70 - 1,20]	0,52	4	0,91 [0,69 - 1,20]	0,49
	bb vs. Bb	6	1,08 [0,88 - 1,32]	0,47	4	0,96 [0,77 - 1,19]	0,70

	bb vs. BB+Bb	6	1,05 [0,86 - 1,27]	0,64	4	0,94 [0,76 - 1,15]	0,52
	Bb+bb vs. BB	6	0,97 [0,75 - 1,26]	0,83	4	0,89 [0,68 - 1,16]	0,38
ApaI	a vs. A	6	0,91 [0,71 - 1,18]	0,48	2	0,89 [0,73 - 1,09]	0,25
	aa vs. AA	6	0,74 [0,43 – 1,26]	0,27	2	0,74 [0,49 - 1,13]	0,17
	Aa vs. AA	6	0,76 [0,47 - 1,25]	0,28	2	0,95 [0,68 - 1,31]	0,74
	aa vs. Aa	6	1,14 [0,88 - 1,46]	0,32	2	0,83 [0,58 - 1,20]	0,33
	aa vs. AA + Aa	6	1,05 [0,83 - 1,32]	0,71	2	0,81 [0,57 - 1,14]	0,22
	Aa+aa vs. AA	6	0,79 [0,49 - 1,26]	0,32	2	0,89 [0,66 - 1,22]	0,48
FokI	f vs. F	9	0,98 [0,87 - 1,10]	0,77	2	1,02 [0,92 - 1,13]	0,66
	ff vs. FF	9	0,97 [0,78 - 1,22]	0,80	2	1,07 [0,86 - 1,34]	0,55
	Ff vs. FF	9	0,93 [0,79 - 1,10]	0,42	2	0,99 [0,86 - 1,15]	0,92
	ff vs. Ff	9	1,06 [0,86 - 1,32]	0,57	2	1,08 [0,87 - 1,35]	0,47
	ff vs. FF+Ff	9	1,03 [0,84 - 1,26]	0,77	2	1,08 [0,87 - 1,33]	0,48
	Ff+ff vs. FF	10	0,96 [0,83 - 1,11]	0,58	2	1,01 [0,88 - 1,16]	0,90
TaqI	t vs. T	5	1,06 [0,71 - 1,59]	0,77	3	1,33 [1,11 -1,60]	0,002*
	tt vs. TT	4	0,91 [0,51 - 1,60]	0,73	3	1,68 [1,13 - 2,50]	0,010*
	Tt vs. TT	5	1,06 [0,49 – 2,31]	0,88	3	1,34 [1,00 - 1,80]	0,05
	tt vs. Tt	4	0,84 [0,52 - 1,38]	0,50	3	1,32 [0,94 - 1,86]	0,11
	tt vs. TT+Tt	4	1,00 [0,64 - 1,58]	0,99	3	1,47 [1,07 - 2,03]	0,02*
	Tt+tt vs. TT	5	1,05 [0,52 - 2,11]	0,89	3	1,43 [1,08 - 1,89]	0,01*

Publication bias

Visual inspection of the funnel plot was performed to assess the potential publication bias among studies (annexes). The analysis outcomes showed that there was no obvious publication bias for BsmI and FokI. In SNP TaqI and ApaI funnel plot analyses, some outliers were found. However, after omitting them from the analyses, the pooled results remain unchanged. It was found that the study from Wang et al (2021) was the outlier in heterozygous (Tt vs TT; tt vs Tt) and recessive (Tt + tt vs TT) models of SNP TaqI analysis, and also in heterozygous (Aa vs AA) and recessive (Aa+aa vs AA) models of SNP ApaI analysis. The study from El-Shal et al (2013) was also an outlier in the heterozygous (aa vs Aa) model of SNP ApaI analysis.

Sensitivity analysis

As heterogeneity was found in the statistical analysis, sensitivity analysis was further conducted to evaluate the stability of the overall results by removing each study successively. In this meta-analysis, eliminating each study did not result in significant alterations in the pooled OR, implying that no single study changed the statistical significance of the overall conclusion.

DISCUSSION

Based on twenty-three studies, this updated meta-analysis specifically explores the relationship between genetic variation of the VDR gene and obesity risk in all populations. Vitamin D has essential roles in metabolism. Low vitamin D level is associated with high inflammation, a condition related to obesity. On the contrary, the supplementation of vitamin D can reduce the levels of pro-inflammatory markers and inflammation-related diseases, such as cardiovascular diseases, hypertension, dyslipidemia, type 2 DM, and others.[43] Previous research has also demonstrated that vitamin D insufficiency and enhanced VDR expression within subcutaneous adipose tissue (SAT) are common features of human obesity. Adipose tissue overexpression of human VDR results in increased fat mass (FM), lower glucose tolerance, and higher energy expenditure.[44] Intriguingly, the imbalance in VDR expression is also associated with increased production of pro-inflammatory cytokines through the modulation of inflammasome.[21] Chromosome 12 (12q12-q14) is the specific genomic location of the VDR gene. The ApaI (rs7975232) and TaqI (rs731236) variants are identified near the 3' untranslated region in intron 8 and exon 9, respectively.[45,46] Point mutations commonly occur in this region. The change of untranslated region would influence the transcriptional regulation, mRNA stability or protein translation efficiency which eventually affects the VDR protein levels.[47]

Genetic association studies are a robust method for identifying genes that make individuals more susceptible to prevalent diseases. Nevertheless, the findings of these investigations lack reliable reproducibility. To address the constraints of individual research, it is necessary to employ bigger sample sizes or do a meta-analysis. Meta-analysis could merge findings from multiple-research on a certain subject, thereby enhancing statistical power

and accuracy. Genetic association studies do not adopt a specific model, and thus multiple genetic models need to be examined.[48] Therefore, in this study, six genetic models (allelic, homozygous, heterozygous, dominant, additive, and recessive models) were applied to increase the robustness of the analysis.

According to our findings, there was no association between obesity risk and BsmI, FokI and Cdx2 polymorphisms. However, this study presented that the ApaI variant was statistically associated with lowering the risk of obesity on a homozygous model in overall populations. A prior investigation on 668 Iranian populations was in line with our findings which found the association between VDR gene polymorphisms with the anthropometric and biochemical parameters related to obesity. In this study, individuals who carried a allele had lower serum levels of fasting blood glucose (FBG) and BMI.[34] Wang, et al. (2021) reported that the AA genotype significantly elevated four times the risk of abdominal obesity and plasma glucose levels in Chinese children. The AA genotype of the ApaI SNP was more frequently found in overweight/obese than in the control groups, in which the serum 25-hydroxyvitamin D (25(OH)D) levels were considerably lower in overweight/obese children.[17] A similar study in Lebanese students showed that ApaI was linked with 25(OH)D levels, where the TT genotype had significantly lower levels than those with the GG genotype.[49] Thai adult populations with genotypes TG and TG+TT of rs7975232 were significantly associated with an increased risk of metabolic syndrome compared to GG.[50] In a study of 131 young female students in Saudi Arabia, minor allele A of rs 7975232 (ApaI) might be a protective factor against increased BMI.[51] According to those studies, it can be concluded that the aa genotype provides a protective effect against adiposity and glucose metabolism. The possible reason that might explain this condition is probably the association of genetic variations of VDR with inflammation, oxidative stress, and lipid metabolism.

A cross-sectional study of 155 Caucasian Spanish children who were vitamin D sufficient also discovered that the minor allele A of ApaI plays a role in protecting from inflammatory processes and oxidative stress through the decline of serum tumor necrosis factor-α (TNF-α) and 8-isoprostaglandin F2α, respectively.[52] Vitamin D alleviates oxidative stress and suppresses the nuclear factor-kappa ß (NF-kß) signaling pathway, and eventually restricts the inflammation process.[53,54] Moreover, vitamin D protects against obesity by enhancing adipocyte metabolic activity, inhibiting fat storage and inducing lipolysis via increasing Nicotinamide adenine dinucleotide (NAD) concentration and SIRT1 activity.[55] The location of ApaI SNP has no effect on the structure and amino acid sequence of the VDR protein. Nevertheless, it has potential to modify the stability of the VDR mRNA and/or disrupt VDR transcription. Altered mRNA stability, leading to decreased translation of the VDR protein, will result in diminished vitamin D responses. In this regard, the ApaI polymorphism may act as an intronic enhancer by mediating alternative splicing of the VDR mRNA, and/or it may be important as an enhancer that elevates gene transcription.[52]

On the other hand, current findings demonstrated that the VDR TaqI polymorphism was related to an enhanced risk of obesity under allelic, homozygous, dominant, and recessive models in the European populations. Our findings are supported by a multicenter study on 553 obese European populations that revealed the VDR TaqI G allele in the AG and GG genotypes (dominant model analysis), which has significantly higher means of BMI, waist circumference, and fat mass compared to non-carriers.[44] Previous studies reported the association between vitamin D levels and obesity. Vitamin D deficiency or insufficiency is mostly found in children, adolescents, and adults with overweight or obesity in several European countries.[56,57,58] Vitamin D deficiency is also related to the increased risk of metabolic syndrome, such as central obesity and low HDL, in a cross-sectional study of 697 Caucasian women in Russia.[56] A VDR gene polymorphism study in the obese Greek population reported that the TaqI t allele doubled the risk of vitamin D deficiency, while individuals with Tt genotype had a 3,5-fold greater risk of low 25(OH)D3 levels.[59] Individuals from Northern and Central Greece with the T allele of TaqI contributed to a raised 3 kg/m2 BMI per risk allele, resulting in a twice-higher risk of obesity. Furthermore, homozygotes with the C allele had higher triglyceride and HDL levels than heterozygotes and homozygotes.[15] The study of 882 Central European Caucasian participants of the Czech presented TaqI GG genotype was associated with greater central adiposity compared to the AA genotype.[27] A study by Abouzid et al (2021) observed the subjects in Poland with the TaqI genotype. He found that hypercholesterolemia and lower 25(OH)D3 levels were more frequently observed in the TT genotype than in the CC and TC genotypes.[60] A study in Turkey also found that obese individuals had lower osteocalcin levels than normal individuals.[61] Osteocalcin can improve insulin synthesis and insulin sensitivity in the pancreas as well as peripheral insulin target organs (adipose tissue, muscle tissue and liver), increase adiponectin, and reduce fat mass.[62]

Our findings could explain that VDR plays a crucial role in lipid regulation, presumably through its action in adipocyte calcium metabolism. The lower vitamin D level triggers parathyroid hormone secretion, facilitating calcium influx into adipocytes and accelerating lipogenesis.[63] Vitamin D has a vital role in the modulation of adipokine formation and energy balance through the regulation of leptin synthesis.[64] Low vitamin D levels can also promote adipogenesis by affecting the transcription factors of preadipocyte cells, which enhance leptin levels. This condition reduces lipid oxidation in insulin-sensitive tissue and is related to higher free fatty acid and inflammatory cytokine levels, leading to lipotoxicity and insulin resistance.[65]

Another possible mechanism that could explain the contribution of VDR to obesity was demonstrated by a prior in vivo study on intestinal VDR knockout mice. This study found that activation of intestinal VDR affects energy and

controls lipid metabolism in extra-intestinal tissue, including adipose tissue and the liver, via suppression of the lipase regulator angiopoietin-like 4 (Angptl4). VDR has a substantial impact on the enlargement and inflammation of adipose tissue by upregulating the expression of the triglyceride synthesizing enzyme and the expression of inflammation markers (CC-chemokine ligand 2 and macrophage F4/80), along with a molecular shift toward a pro-inflammatory state in adipose tissue. This similar condition was also observed in the liver, where VDR promotes fat accumulation and inflammation in this organ.[66]

The result of this study is in accordance with a previous meta-analysis by Chen et al (2019) which reported that VDR gene polymorphism was associated with obesity.[67] However, our study is more comprehensive by including more updated twenty-three studies from different countries that can robustly describe the effect of VDR gene polymorphisms on different ethnic groups. Moreover, we also have included the Cdx2 gene in the analysis, which was not included in the previous study. Another systematic review by Faghfouri has also determined the role of VDR polymorphism in obesity.[45] However, the study was inconclusive due to being conducted qualitatively without any meta-analysis. Hereby, this meta-analysis could provide a better understanding regarding the role of each VDR gene polymorphism in obesity. Most of the included study also had low risk of bias. This ensures that the studies included in our meta-analysis are more reliable and less prone to biases.

Nonetheless, this meta-analysis still had several limitations. First, there were only two included studies found for VDR Cdx2 polymorphism. Second, this study did not analyze other risk factors that can affect susceptibility to obesity, such as gender, age, ethnicity, and underlying disease that may contribute to obesity development. Third, this meta-analysis could not generate a per-patient haplotype analysis that can demonstrate the gene-gene and gene-environment interactions to provide a better understanding between VDR gene polymorphisms and obesity.

CONCLUSIONS

In conclusion, this meta-analysis determined the role of aa genotype of VDR *ApaI* gene polymorphism as a protective effect on obesity in all the studied populations and t allele of VDR *TaqI* gene polymorphism as a risk factor related to obesity in the European population. Therefore, it is important to determine VDR genotypes in individuals in order to reduce the extent of complications and mortality trends in the obesity population, in particular for *ApaI* genotype for the studied populations and *TaqI* genotype for European population.

BIBLIOGRAPHIC REFERENCES

1. Chang A, Elleson LH, Epstein JI, Frank KM, Frosch MP, Horvai A, et al. Robbins Basic Pathology. 10th ed. Kumar V, Abbas AK, Aster JC, editores. Canada; 2018.

2. Center for Disease Control and Prevention (CDC). Adult Obesity Prevalence Maps [Internet]. U.S. Dept of Health and Human Services. 2022 [citado el 8 de noviembre de 2023]. Disponible en: https://www.cdc.gov/obesity/php/data-research/adult-obesity-prevalence-maps.html

3. Ministry of Health of the Republic of Indonesia. Laporan Nasional Riskesdas 2018 [Internet]. Jakarta; 2019. Disponible en: https://repository.badankebijakan.kemkes.go.id/id/eprint/3514/1/Laporan Riskesdas 2018 Nasional.pdf

4. Tremmel M, Gerdtham U-G, Nilsson P, Saha S. Economic Burden of Obesity: A Systematic Literature Review. Int J Environ Res Public Health [Internet]. 2017;14(4):435. doi:10.3390/ijerph14040435

5. Abu El Maaty MA, Hassanein SI, Hanafi RS, Gad MZ. Insights on vitamin D's role in cardiovascular disease: Investigating the association of 25-hydroxyvitamin D with the dimethylated arginines. J Nutr Sci Vitaminol (Tokyo). 2013;59(3):172–7. doi:10.3177/jnsv.59.172

6. Choquet H, Meyre D. Genetics of Obesity: What have we Learned? Curr Genomics [Internet]. 2011;12(3):169–79. doi:10.2174/138920211795677895

7. Huvenne H, Dubern B, Clément K, Poitou C. Rare Genetic Forms of Obesity: Clinical Approach and Current Treatments in 2016. Obes Facts. 2016;9(3):158–73. doi:10.1159/000445061

8. Baxter J, Armijo PR, Flores L, Krause C, Samreen S, Tanner T. Updates on Monogenic Obesity in a Multifactorial Disease. Obes Surg. 2019;29(12):4077–83. doi:10.1007/s11695-019-04200-z

9. Hassan NE, El-Masry SA, Zarouk W, El Banna RA, Mosaad RM, Al-Tohamy M, et al. Obesity phenotype in relation to gene polymorphism among samples of Egyptian children and their mothers. Genes Dis [Internet]. 2018;5(2):150–7. doi:10.1016/j.gendis.2017.12.004

10. Kim HJ, Lee SY, Kim CM. Association between gene polymorphisms and obesity and physical fitness in Korean children. Biol Sport. 2018;35(1):21–7. doi:10.5114/biolsport.2018.70748

11. Sharif E, Swaidan N, Shurbaji S, Rizk N. Associations of Vitamin D Receptor Polymorphism rs1544410 with Adiposity Phenotypes. Endocrinol Int J [Internet]. 2016;3(6):165–72. doi:10.15406/emij.2016.03.00069

12. Shen F, Wang Y, Sun H, Zhang D, Yu F, Yu S, et al. Vitamin D receptor gene polymorphisms are associated with triceps skin fold thickness and body fat percentage but not with body mass index or waist circumference in Han Chinese. Lipids Health Dis. 2019;18(1):97. doi:10.1186/s12944-019-1027-2

13. Dawkins RL, Willamson JF, Lester S, Dawkins ST. Mutation versus polymorphism in evolution. Genomics [Internet]. 2013;101(4):211–2. doi:10.1016/j.ygeno.2013.01.002

14. Khammissa RAG, Fourie J, Motswaledi MH, Ballyram R, Lemmer J, Feller L. The Biological Activities of Vitamin D and Its Receptor in Relation to Calcium and Bone Homeostasis, Cancer, Immune and Cardiovascular Systems, Skin Biology, and Oral Health. Biomed Res Int. 2018;2018. doi:10.1155/2018/9276380

15. Vasilopoulos Y, Sarafidou T, Kotsa K, Papadimitriou M, Goutzelas Y, Stamatis C, et al. VDR TaqI is associated with obesity in the Greek population. Gene [Internet]. 2013;512(2):237–9. doi:10.1016/j.gene.2012.10.044

16. Sygitowicz G, Pera Ł, Sitkiewicz D. Vitamin D receptor (VDR) polymorphism and the risk of cardiovascular events. Kardiol Pol. 2014;72(1):64–6. doi:10.5603/KP.2014.0005

17. Wang D, Su K, Ding Z, Zhang Z, Wang C. Association of Vitamin D Receptor Gene Polymorphisms with Metabolic Syndrome in Chinese Children. Int J Gen Med. 2021;14:57–66. doi:10.2147/IJGM.S287205

18. Zhou JC, Zhu YM, Chen Z, Mo JL, Xie FZ, Wen YH, et al. Oral vitamin D supplementation has a lower bioavailability and reduces hypersecretion of parathyroid hormone and insulin resistance in obese Chinese males. Public Health Nutr. 2015;18(12):2211–9. doi:10.1017/S1368980014002845

19. Meyer V, Bornman L. Cdx-2 polymorphism in the vitamin D receptor gene (VDR) marks VDR expression in monocyte/macrophages through VDR promoter methylation. Immunogenetics [Internet]. 2018;70(8):523–32. doi:10.1007/s00251-018-1063-5

20. González Rojo P, Pérez Ramírez C, Gálvez Navas JM, Pineda Lancheros LE, Rojo Tolosa S, Ramírez Tortosa M del C, et al. Vitamin D-Related Single Nucleotide Polymorphisms as Risk Biomarker of Cardiovascular Disease. Int J Mol Sci. 2022;23(15). doi:10.3390/ijms23158686

21. Al-Daghri NM, Guerini FR, Al-Attas OS, Alokail MS, Alkharfy KM, Draz HM, et al. Vitamin D Receptor Gene Polymorphisms Are Associated with Obesity and Inflammosome Activity. Mittal B, editor. PLoS One [Internet]. 2014;9(7):e102141. doi:10.1371/journal.pone.0102141

22. Al-Hazmi AS, Al-Mehmadi MM, Al-Bogami SM, Shami AA, Al-Askary AA, Alomery AM, et al. Vitamin D receptor gene polymorphisms as a risk factor for obesity in Saudi men. Electron physician [Internet]. 2017;9(10):5427–33. doi:10.19082/5427

23. Yu S, Li X, Yu F, Mao Z, Wang Y, Xue Y, et al. New evidence for associations between vitamin D receptor polymorphism and obesity: case-control and family-based studies. J Hum Genet [Internet]. 2020;65(3):281–5. doi:10.1038/s10038-019-0702-5

24. Zakaria WNA, Yunus NM, Yaacob NM, Omar J, Wan Mohamed WMI, Sirajudeen KNS, et al. Association between vitamin d receptor polymorphisms (Bsmi and foki) and glycemic control among patients with type 2 diabetes. Int J Environ Res Public Health. 2021;18(4):1–18. doi:10.3390/ijerph18041595

25. Rahmadhani R, Zaharan NL, Mohamed Z, Moy FM, Jalaludin MY. The associations between VDR BsmI polymorphisms and risk of vitamin D deficiency, obesity and insulin resistance in adolescents residing in a tropical country. Zhu Z, editor. PLoS One [Internet]. 2017;12(6):e0178695. doi:10.1371/journal.pone.0178695

26. Bagheri M, Bahadori F, Gheibi S, Behrooz Lak T, Kuse-Lu Z, Sahebozamani Z, et al. Vitamin D Receptor Gene Haplotype and Late-Onset Obesity in Iranian Azeri Turkish Women. Maedica (Buchar) [Internet]. 2017;12(2):81–

6. Disponible en: http://www.ncbi.nlm.nih.gov/pubmed/29090026%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC5649038

27. Bienertová-Vašku J, Zlámal F, Pohořalá A, Mikeš O, Goldbergová-Pávková M, Novák J, et al. Allelic variants in vitamin D receptor gene are associated with adiposity measures in the central-European population. BMC Med Genet. 2017;18(1):1–9. doi:10.1186/s12881-017-0454-z

28. Mahmoudi T, Karimi K, Mohebbi SR, Fatemi SR, Zali MR. Start codon FokI and intron 8 BsmI variants in the vitamin D receptor gene and susceptibility to colorectal cancer. Mol Biol Rep [Internet]. 2011;38(7):4765–70. doi:10.1007/s11033-010-0613-1

29. Tofteng CL, Jensen JEB, Abrahamsen B, Odum L, Brot C. Two polymorphisms in the vitamin D receptor gene--association with bone mass and 5-year change in bone mass with or without hormone-replacement therapy in postmenopausal women: the Danish Osteoporosis Prevention Study. J bone Miner Res Off J Am Soc Bone Miner Res. 2002;17(8):1535–44. doi:10.1359/jbmr.2002.17.8.1535

30. Speer G, Cseh K, Winkler G, Vargha P, Braun E, Takacs I, et al. Vitamin D and estrogen receptor gene polymorphisms in type 2 diabetes mellitus and in android type obesity. Eur J Endocrinol [Internet]. 2001;144(4):385–9. doi:10.1530/eje.0.1440385

31. Geusens P, Vandevyver C, Vanhoof J, Cassiman JJ, Boonen S, Raus J. Quadriceps and grip strength are related to vitamin D receptor genotype in elderly nonobese women. J bone Miner Res Off J Am Soc Bone Miner Res. 1997;12(12):2082–8. doi:10.1359/jbmr.1997.12.12.2082

32. Bağcı G, Hüzmeli C, Bağcı B, Candan F. Vitamin D Receptor Polymorphisms in Overweight/Obese Chronic Kidney Disease Patients on Dialysis. Turkish J Nephrol [Internet]. 2023;33(2):217–22. doi:10.5152/turkjnephrol.2023.23369

33. Hassan NE, El-Masry SA, Zarouk WA, Eldeen GN, Mosaad RM, Afify MAS, et al. Narrative role of vitamin D receptor with osteoporosis and obesity in a sample of Egyptian females: a pilot study. J Genet Eng Biotechnol [Internet]. 2021;19(1):115. doi:10.1186/s43141-021-00216-0

34. Rashidi F, Ostadsharif M. Association of VDR gene ApaI polymorphism with obesity in Iranian population. Biomédica [Internet]. 2021;41(4):651–9. doi:10.7705/biomedica.5898

35. Fan H-R, Lin L-Q, Ma H, Li Y, Sun C-H. Association between vitamin D receptor gene polymorphism (TaqI) and obesity in Chinese population. J Genet [Internet]. 2015;94(3):473–8. doi:10.1007/s12041-015-0541-x

36. El-Shal AS, Shalaby SM, Aly NM, Rashad NM, Abdelaziz AM. Genetic variation in the vitamin D receptor gene and vitamin D serum levels in Egyptian women with polycystic ovary syndrome. Mol Biol Rep [Internet]. 2013;40(11):6063–73. doi:10.1007/s11033-013-2716-y

37. Mahmoudi T, Mohebbi SR, Pourhoseingholi MA, Fatemi SR, Zali MR. Vitamin D Receptor Gene ApaI Polymorphism Is Associated with Susceptibility to Colorectal Cancer. Dig Dis Sci [Internet]. 2010;55(7):2008–13. doi:10.1007/s10620-009-0989-8

38. Gariballa S, Al-Bluwi GSM, Yasin J. Frequency of Vitamin D Receptor Gene Polymorphisms in a Population with a very High Prevalence of Vitamin D Deficiency, Obesity, Diabetes and Hypertension. Biomedicines. 2023;11(4). doi:10.3390/biomedicines11041202

39. Bhatt SP, Guleria R. Polymorphisms in vitamin D receptor and parathyroid hormone genes in the development and progression of obstructive sleep apnea in Asian Indians. Nutrition [Internet]. 2021;89:111237. doi:10.1016/j.nut.2021.111237

40. Xie H, Min M, Guo S, Xian Y, Yang F, Wang X, et al. Impact of Vitamin D and Vitamin D Receptor on Risk of Cardiovascular Diseases in Children and Adolescents with Obesity in Sichuan, China: A Cross-Sectional Study. Ann Nutr Metab [Internet]. 2021;76(6):396–404. doi:10.1159/000513287

41. Hussain S, Hussain S, AbdRaboh NR. Vitamin D receptor Fok1 polymorphism and its relationship

with premenstrual syndrome. Gene Reports [Internet]. 2018;12:324–8. doi:https://doi.org/10.1016/j.genrep.2018.08.001

42. Slattery ML, Murtaugh M, Caan B, Ma KN, Wolff R, Samowitz W. Associations between BMI, energy intake, energy expenditure, VDR genotype and colon and rectal cancers (United States). Cancer Causes Control [Internet]. 2004;15(9):863–72. doi:10.1007/s10552-004-1048-6

43. Vranić L, Mikolašević I, Milić S. Vitamin D Deficiency: Consequence or Cause of Obesity? Medicina (B Aires) [Internet]. 2019;55(9):541. doi:10.3390/medicina55090541

44. Pramono A, Jocken JWE, Adriaens ME, Hjorth MF, Astrup A, Saris WHM, et al. The association between vitamin D receptor polymorphisms and tissue-specific insulin resistance in human obesity. Int J Obes [Internet]. 2021;45(4):818–27. doi:10.1038/s41366-021-00744-2

45. Faghfouri AH, Faghfuri E, Maleki V, Payahoo L, Balmoral A, Khaje Bishak Y. A comprehensive insight into the potential roles of VDR gene polymorphism in obesity: a systematic review. Arch Physiol Biochem [Internet]. 2020;128(6):1645–57. doi:10.1080/13813455.2020.1788097

46. Castillo-Avila RG, González-Castro TB, Tovilla-Zárate CA, Juárez-Rojop IE, López-Narváez ML, Rodríguez-Pérez JM, et al. The role of TaqI, ApaI and BsmI polymorphisms of VDR gene in lumbar spine pathologies: systematic review and meta-analysis. Eur Spine J [Internet]. 2021;30(7):2049–59. doi:10.1007/s00586-021-06872-7

47. Valdivielso JM, Fernandez E. Vitamin D receptor polymorphisms and diseases. Clin Chim Acta. 2006;371(1–2):1–12. doi:10.1016/j.cca.2006.02.016

48. Lee YH. Meta-analysis of genetic association studies. Ann Lab Med [Internet]. 2015;35(3):283–7. doi:10.3343/alm.2015.35.3.283

49. Hajj A, Chedid R, Chouery E, Megarbané A, Gannagé-Yared MH. Relationship between Vitamin D receptor gene polymorphisms, cardiovascular risk factors and adiponectin in a healthy young population. Pharmacogenomics. 2016;17(15):1675–86. doi:10.2217/pgs-2016-0045

50. Karuwanarint P, Phonrat B, Tungtrongchitr A, Suriyaprom K, Chuengsamarn S, Tungtronchitr R. Genetic variations of vitamin D receptor gene in metabolic syndrome and related diseases in the Thai population. Asia Pac J Clin Nutr [Internet]. 2018;27(4):935–44. doi:10.6133/apjcn.122017.04

51. Al Asoom LI, Al Afandi DT, Al Abdulhadi AS, Rafique N, Chathoth S, Al Sunni AA. Protective association of single nucleotide polymorphisms RS1861868-FTO and RS7975232-VDR and obesity in Saudi females. Int J Gen Med. 2020;13:235–41. doi:10.2147/IJGM.S251466

52. Ferrer-Suay S, Alonso-Iglesias E, Tortajada-Girbés M, Carrasco-Luna J, Codoñer-Franch P. Vitamin D receptor gene ApaI and FokI polymorphisms and its association with inflammation and oxidative stress in vitamin D sufficient Caucasian Spanish children. Transl Pediatr [Internet]. 2021;10(1):103–11. doi:10.21037/tp-20-198

53. Ionica M, Aburel OM, Vaduva A, Petrus A, Ratţiu S, Olariu S, et al. Vitamin D alleviates oxidative stress in adipose tissue and mesenteric vessels from obese patients with subclinical inflammation. Can J Physiol Pharmacol. 2020;98(2):85–92. doi:10.1139/cjpp-2019-0340

54. Ağar M, Güngör K, Güngör ND, Kavrut M, Madenli AA. Vitamin D supplementation inhibits NF-kß signaling pathway in lean and obese women with PCOS. Eur Rev Med Pharmacol Sci. 2022;26(11):3973–7. doi:10.26355/eurrev_202206_28967

55. Chang E, Kim Y. Vitamin D decreases adipocyte lipid storage and increases NAD-SIRT1 pathway in 3T3-L1 adipocytes. Nutrition [Internet]. 2016;32(6):702–8. doi:10.1016/j.nut.2015.12.032

56. Karonova T, Grineva E, Belyaeva O, Bystrova A, Jude EB, Andreeva A, et al. Relationship Between Vitamin D Status and Vitamin D Receptor Gene Polymorphisms With Markers of Metabolic Syndrome Among Adults. Front Endocrinol (Lausanne) [Internet]. 2018;9(AUG):1–7. doi:10.3389/fendo.2018.00448

57. Zakharova I, Klimov L, Kuryaninova V, Nikitina I, Malyavskaya S, Dolbnya S, et al. Vitamin D Insufficiency in

Overweight and Obese Children and Adolescents. Front Endocrinol (Lausanne) [Internet]. 2019;10. doi:10.3389/fendo.2019.00103

58. Smirnova D V., Rehm CD, Fritz RD, Kutepova IS, Soshina MS, Berezhnaya YA. Vitamin D status of the Russian adult population from 2013 to 2018. Sci Rep [Internet]. 2022;12(1):16604. doi:10.1038/s41598-022-21221-4

59. Divanoglou N, Komninou D, Stea EA, Argiriou A, Papatzikas G, Tsakalof A, et al. Association of Vitamin D Receptor Gene Polymorphisms with Serum Vitamin D Levels in a Greek Rural Population (Velestino Study). Lifestyle Genomics. 2021;14(3):81–90. doi:10.1159/000514338

60. Abouzid M, Kruszyna M, Burchardt P, Kruszyna Ł, Główka FK, Karaźniewicz-łada M. Vitamin d receptor gene polymorphism and vitamin d status in population of patients with cardiovascular disease—a preliminary study. Nutrients. 2021;13(9). doi:10.3390/nu13093117

61. Yaylali YT, Fidan-Yaylali G, Dedeoglu O, Senol H. Osteocalcin and epicardial adipose tissue in obesity: new hints for epicardial adipose tissue–bone crosstalk. Scand Cardiovasc J [Internet]. 2019;53(6):296–8. doi:10.1080/14017431.2019.1659397

62. Bonnet N. Bone-Derived Factors: A New Gateway to Regulate Glycemia. Calcif Tissue Int. 2017;100(2):174–83. doi:10.1007/s00223-016-0210-y

63. Akter R, Afrose A, Sharmin S, Rezwan R, Rahman MR, Neelotpol S. A comprehensive look into the association of vitamin D levels and vitamin D receptor gene polymorphism with obesity in children. Biomed Pharmacother. 2022;153:113285. doi:10.1016/j.biopha.2022.113285

64. Szymczak-Pajor I, Śliwińska A. Analysis of Association between Vitamin D Deficiency and Insulin Resistance. Nutrients [Internet]. 2019;11(4):794. doi:10.3390/nu11040794

65. Juliaty A, Putri SH, Ganda IJ. Leptin Level in Obese Children with Vitamin D Deficiency. Open Access Maced J Med Sci. 2022;10(B):1102–6. doi:10.3889/oamjms.2022.8276

66. Jahn D, Dorbath D, Schilling AK, Gildein L, Meier C, Vuille-dit-Bille RN, et al. Intestinal vitamin D receptor modulates lipid metabolism, adipose tissue inflammation and liver steatosis in obese mice. Biochim Biophys Acta - Mol Basis Dis [Internet]. 2019;1865(6):1567–78. doi:10.1016/j.bbadis.2019.03.007

67. Chen X, Wang W, Wang Y, Han X, Gao L. Vitamin D Receptor Polymorphisms Associated with Susceptibility to Obesity: A Meta-Analysis. Med Sci Monit [Internet]. 2019;25:8297–305. doi:10.12659/MSM.915678

FINANCING

No financing.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORSHIP CONTRIBUTION

Conceptualization: Tri Hartini Yuliawati, Dewi Ratna Sari.

Investigation: Tri Hartini Yuliawati, Dewi Ratna Sari, Citrawati Dyah Kencono Wungu, Zakiyatul Faizah, Berliana Hamidah, Bella Amanda, Lucky Prasetiowati, Rimbun, Kusuma Eko Purwantari, Ninik Darsini, Faisal Yusuf Ashari, Wan Rohani Wan Taib, Zilfalil Bin Alwi.

Methodology: Tri Hartini Yuliawati, Dewi Ratna Sari, Citrawati Dyah Kencono Wungu, Zakiyatul Faizah, Berliana Hamidah, Bella Amanda, Lucky Prasetiowati, Rimbun, Kusuma Eko Purwantari, Ninik Darsini, Faisal Yusuf Ashari, Wan Rohani Wan Taib, Zilfalil Bin Alwi.

Writing - original draft: Dewi Ratna Sari, Citrawati Dyah Kencono Wungu, Tri Hartini Yuliawati, Zakiyatul Faizah, Berliana Hamidah, Bella Amanda, Lucky Prasetiowati, Rimbun, Kusuma Eko Purwantari, Ninik Darsini, Faisal Yusuf Ashari, Wan Rohani Wan Taib, Zilfalil Bin Alwi.

Writing - review and editing: Dewi Ratna Sari, Citrawati Dyah Kencono Wungu, Tri Hartini Yuliawati, Zakiyatul Faizah, Berliana Hamidah, Bella Amanda, Lucky Prasetiowati, Rimbun, Kusuma Eko Purwantari, Ninik Darsini, Faisal Yusuf Ashari, Wan Rohani Wan Taib, Zilfalil Bin Alwi.

ANNEXES

Supplementary information

Abbreviations

R: Random-effects
F: Fixed-effects
BMI: Body Mass Index
CDC: Centers for Disease Control and Prevention
CI: Confidence Interval
DM: Diabetes Mellitus
FBG: Fasting Blood Glucose
FM: Fat Mass
HDL: High-Density Lipoprotein
HWE: Hardy-Weinberg Equilibrium
INSR: Insulin Receptor
LEP: Leptin Protein
LEPR: Leptin Receptor
MC4R: Melanocortin 4 Receptor
NAD: Nicotinamide Adenine Dinucleotide
NOS: Newcastle-Ottawa Scale
25(OH)D: 25-hydroxyvitamin D
OR: Odds Ratio
PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism
PCR: Polymerase Chain Reaction
POMC: Pro-Opiomelanocortin
RLFP: Restriction Fragment Length Polymorphism
PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis
SAT: Subcutaneous Adipose Tissue
SIRT: Sirtuin
SNP: Single nucleotide polymorphisms
TNF-α: Tumor Necrosis Factor-α
VDR: Vitamin D receptor

1. Vitamin D Receptor gene BsmI polymorphism

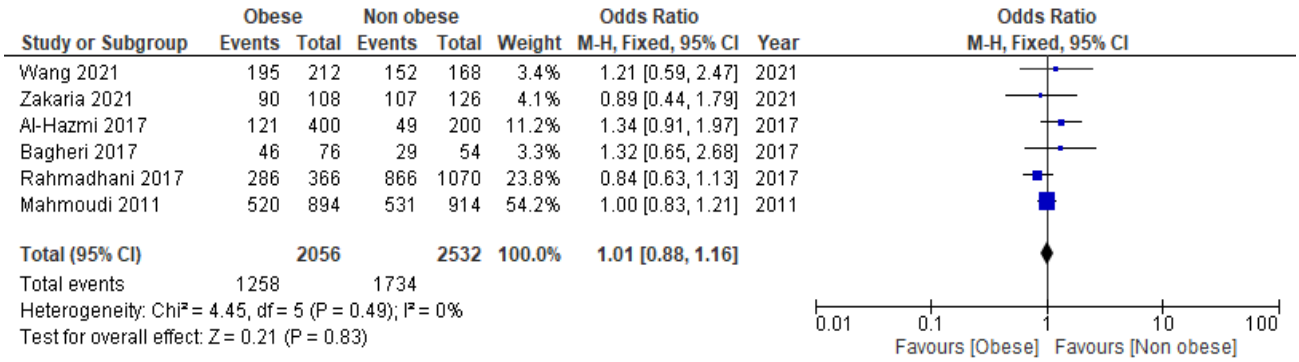


Figure 1.1. Forest plot of the association between VDR *BsmI* polymorphism and obesity risk under b vs. B model in Asian

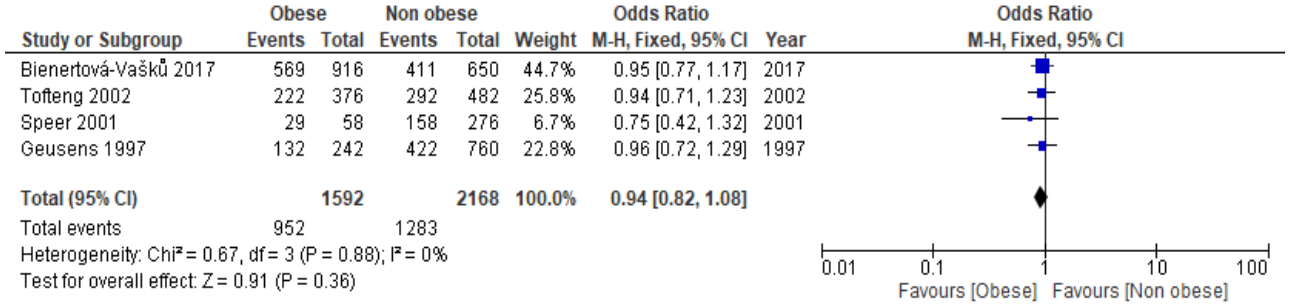


Figure 1.2. Forest plot of the association between VDR *BsmI* polymorphism and obesity risk under b vs. B model in European

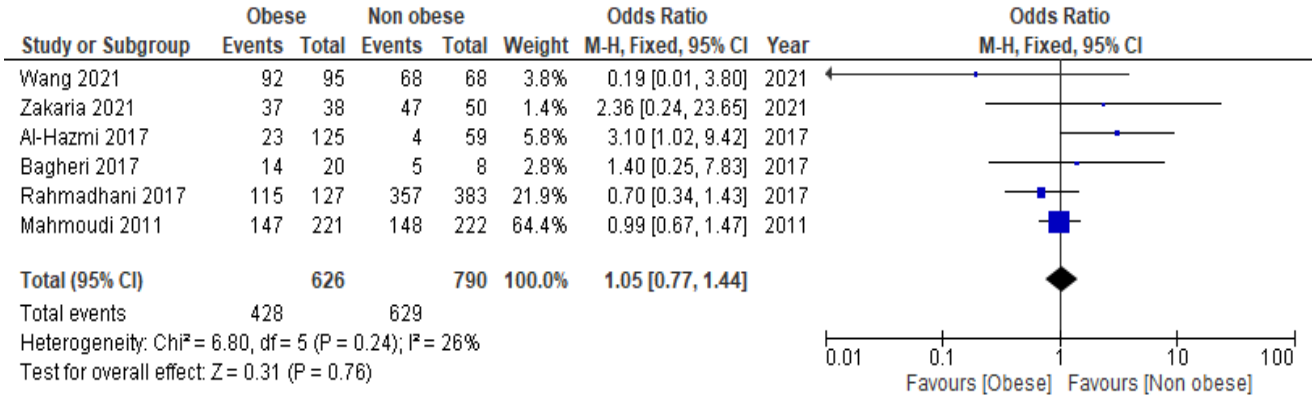


Figure 1.3. Forest plot of the association between VDR *BsmI* polymorphism and obesity risk under bb vs. BB model in Asian

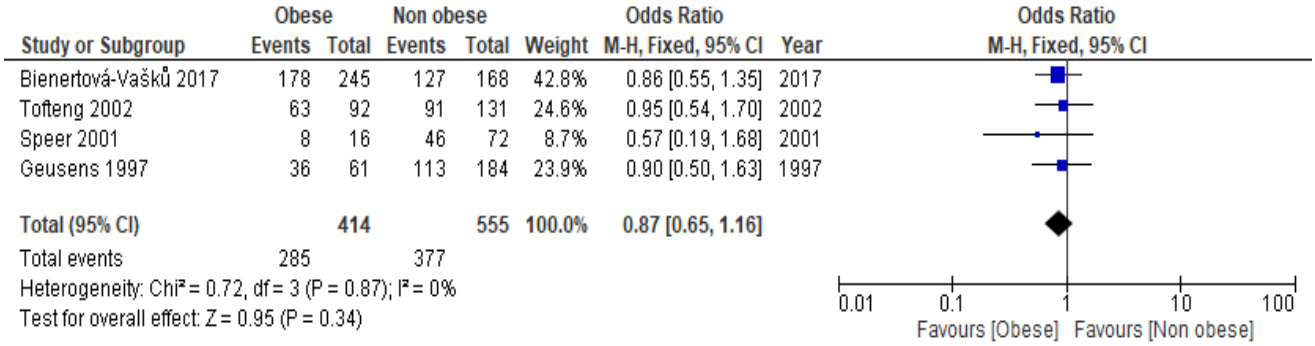


Figure 1.4. Forest plot of the association between VDR *BsmI* polymorphism and obesity risk under bb vs. BB model in European

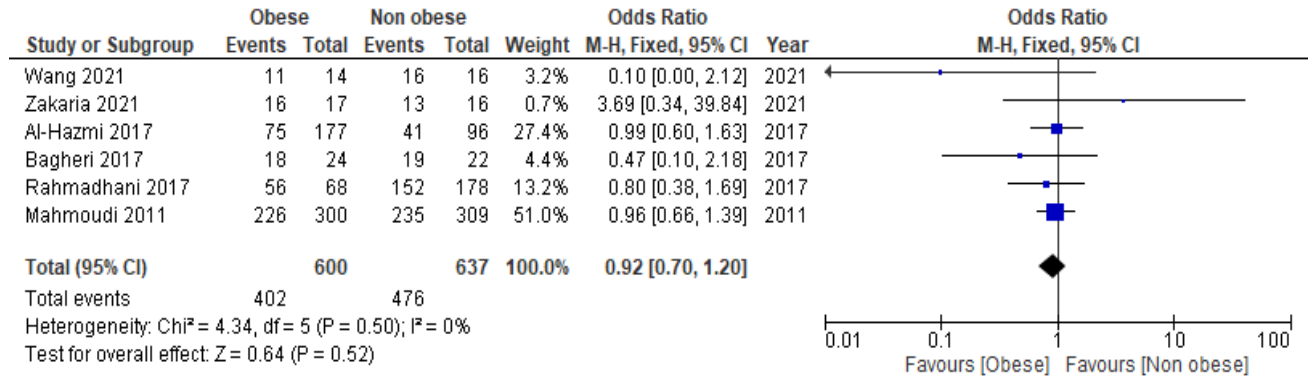


Figure 1.5. Forest plot of the association between VDR *BsmI* polymorphism and obesity risk under Bb vs. BB model in Asian

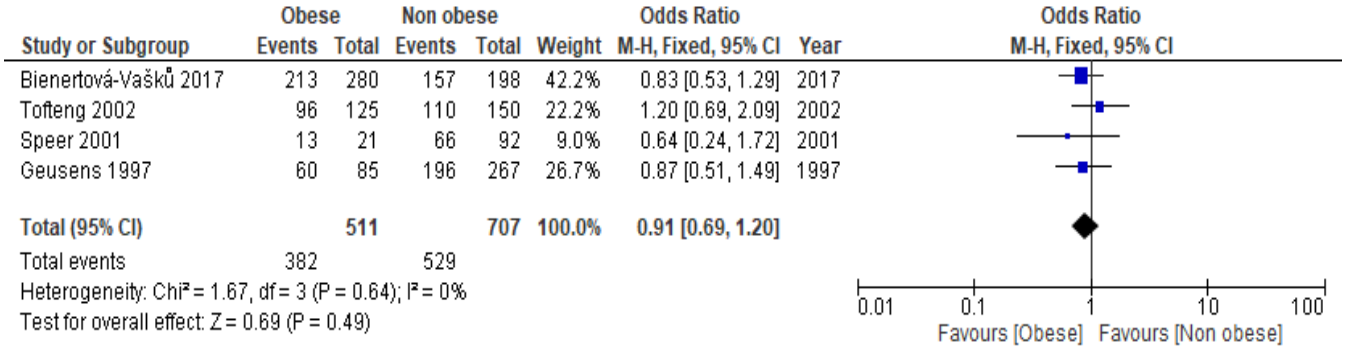


Figure 1.6. Forest plot of the association between VDR *BsmI* polymorphism and obesity risk under Bb vs. BB model in European

https://doi.org/10.56294/saludcyt20251072

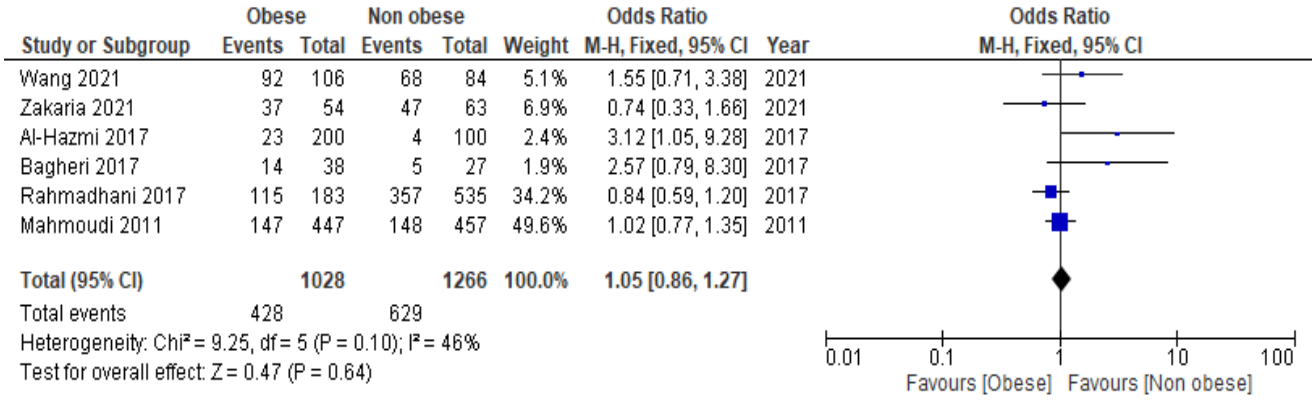


Figure 1.7. Forest plot of the association between VDR *BsmI* polymorphism and obesity risk under bb vs. BB+Bb model in Asian

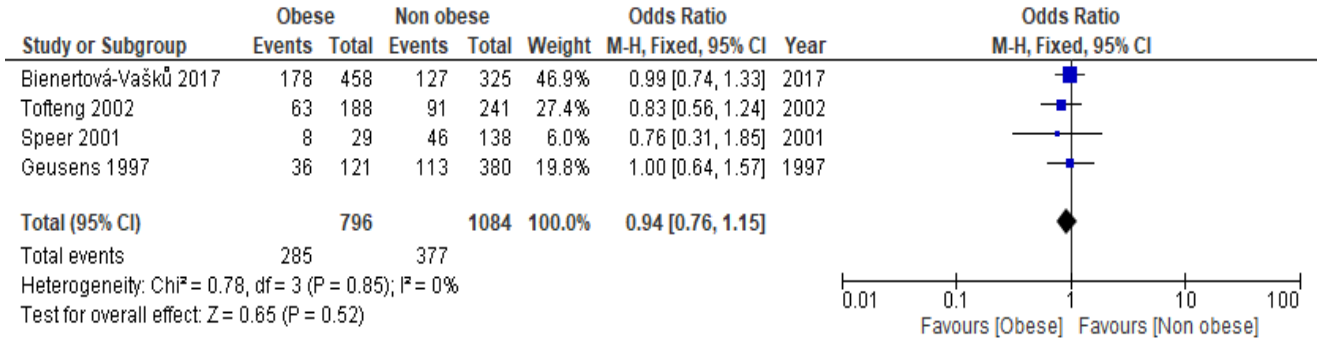


Figure 1.8. Forest plot of the association between VDR *BsmI* polymorphism and obesity risk under bb vs. BB+Bb model in European

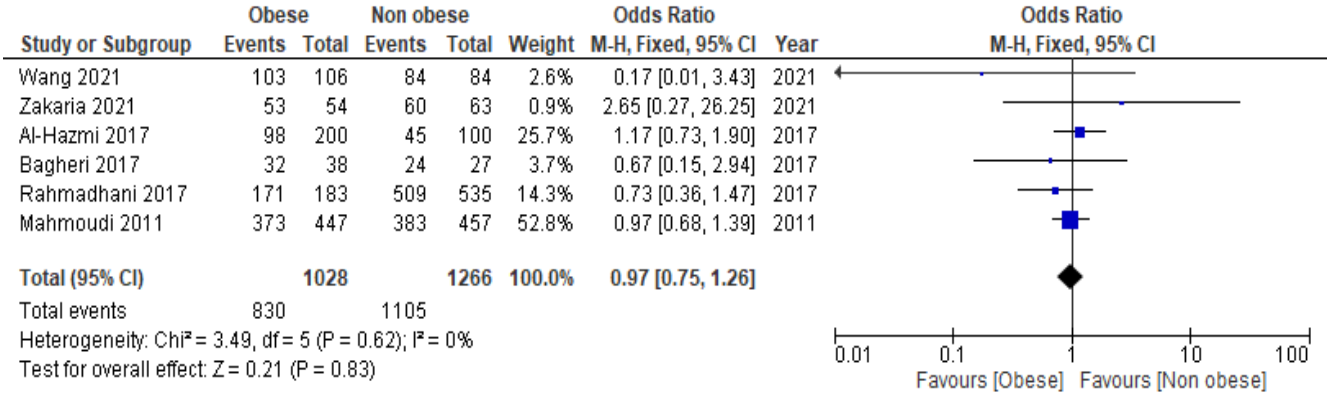


Figure 1.9. Forest plot of the association between VDR *BsmI* polymorphism and obesity risk under Bb+bb vs. BB model in Asian

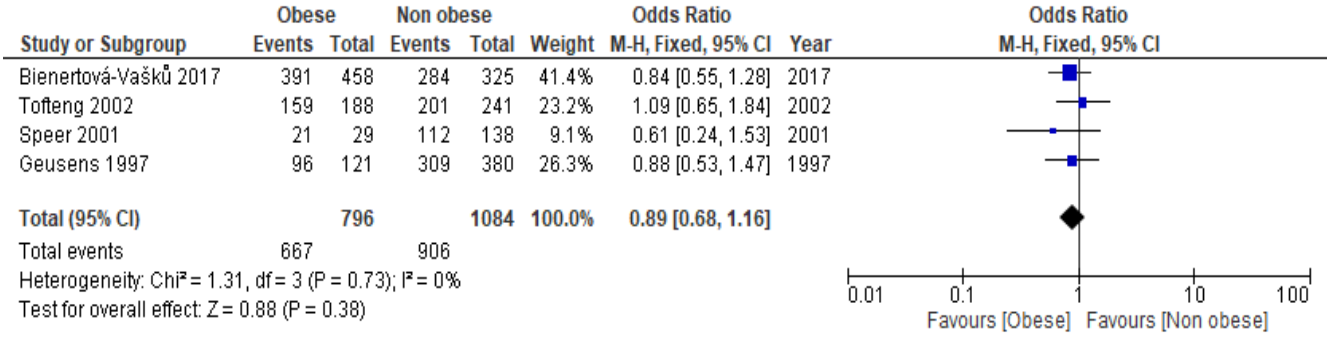


Figure 1.10. Forest plot of the association between VDR *BsmI* polymorphism and obesity risk under Bb+bb vs. BB model in European

2. Vitamin D Receptor gene ApaI polymorphism

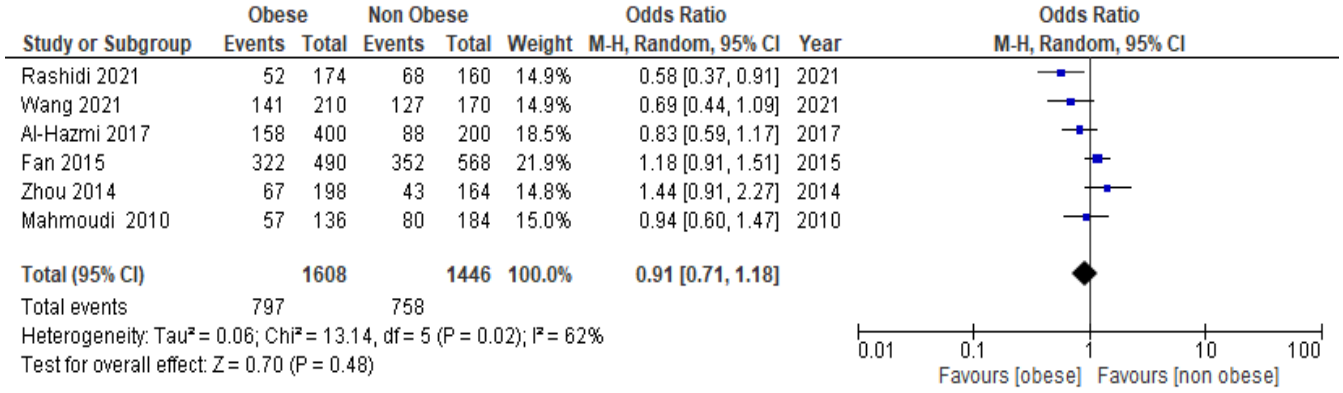


Figure 2.1. Forest plot of the association between VDR *ApaI* polymorphism and obesity risk under a vs. A model in Asian

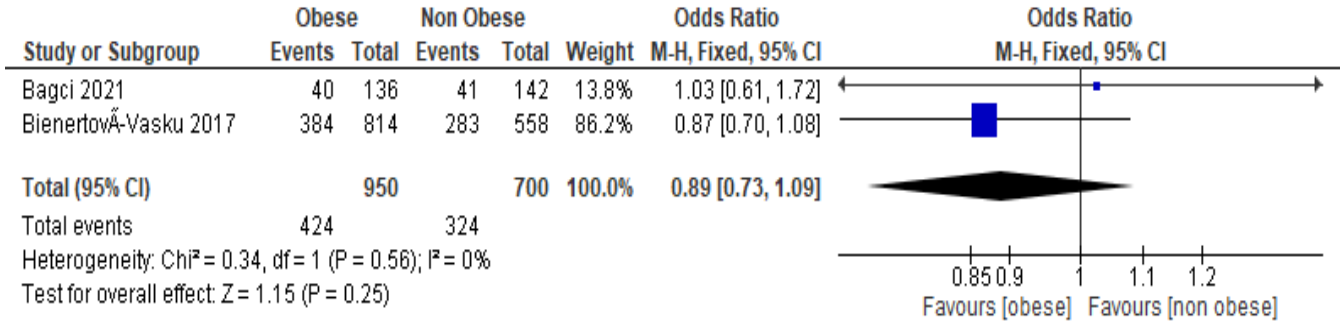


Figure 2.2. Forest plot of the association between VDR *ApaI* polymorphism and obesity risk under a vs. A model in European

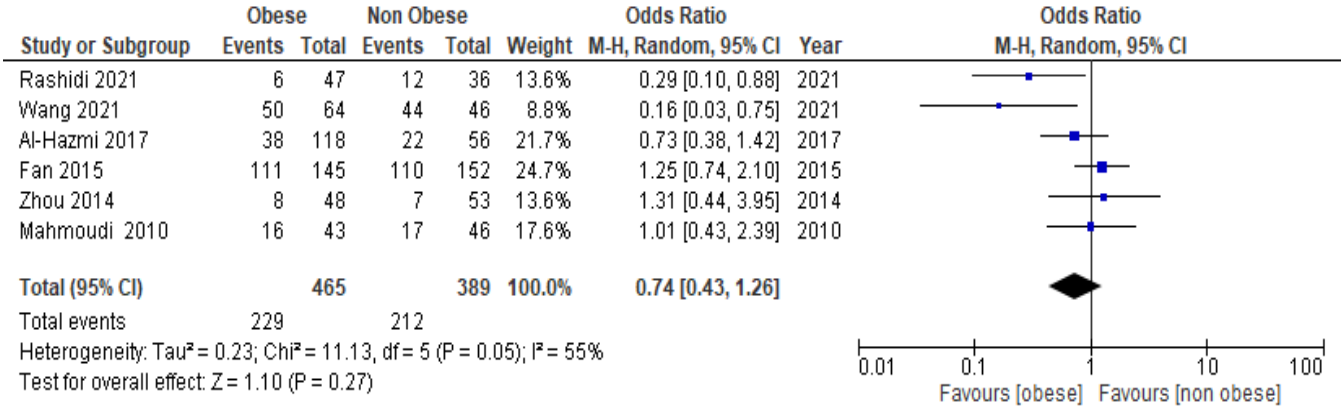


Figure 2.3. Forest plot of the association between VDR *ApaI* polymorphism and obesity risk under aa vs. AA model in Asian

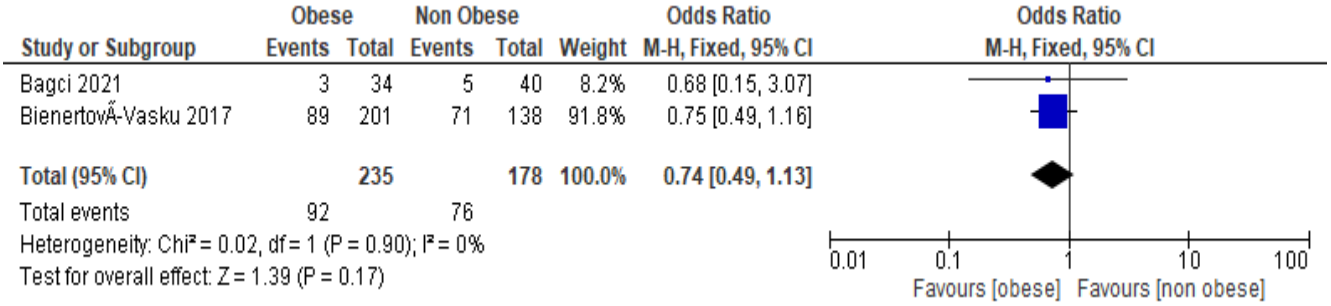


Figure 2.4. Forest plot of the association between VDR *ApaI* polymorphism and obesity risk under aa vs. AA model in European

https://doi.org/10.56294/saludcyt20251072

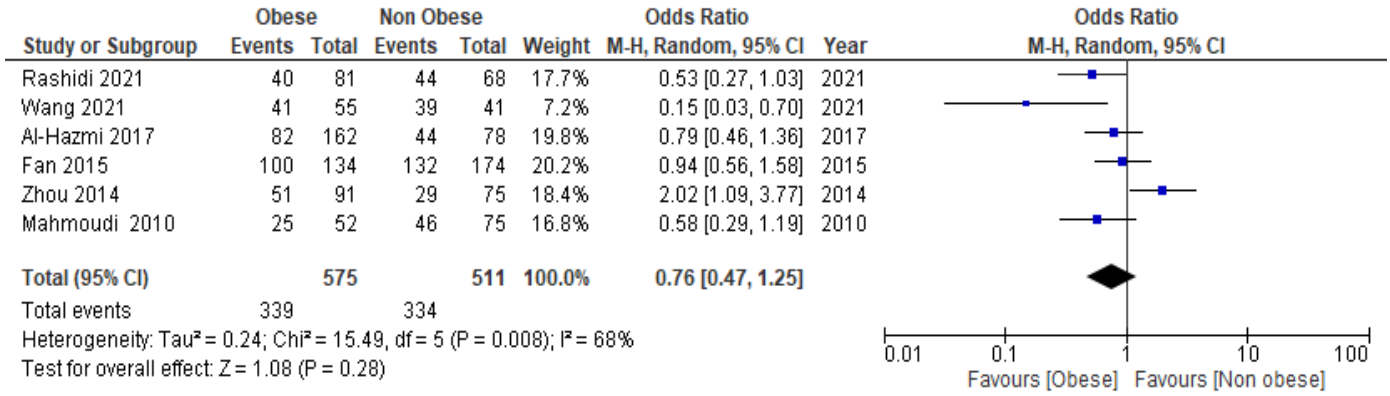


Figure 2.5. Forest plot of the association between VDR *ApaI* polymorphism and obesity risk under Aa vs. AA model in Asian

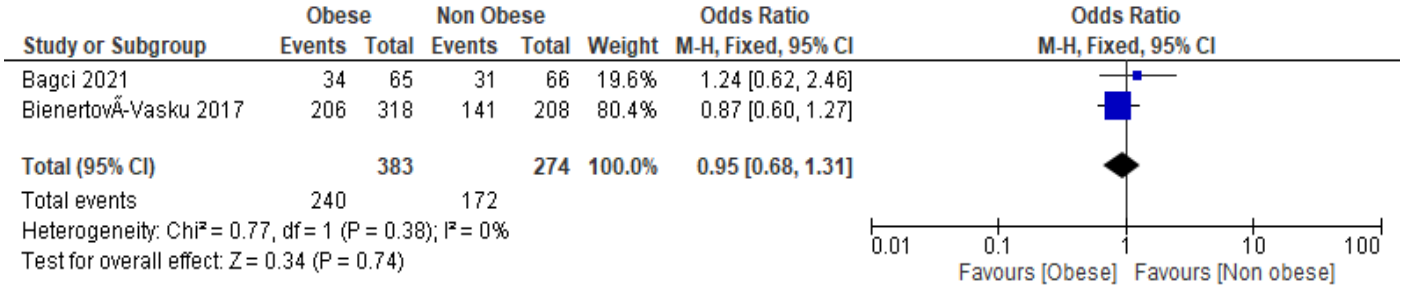


Figure 2.6. Forest plot of the association between VDR *ApaI* polymorphism and obesity risk under Aa vs. AA model in European

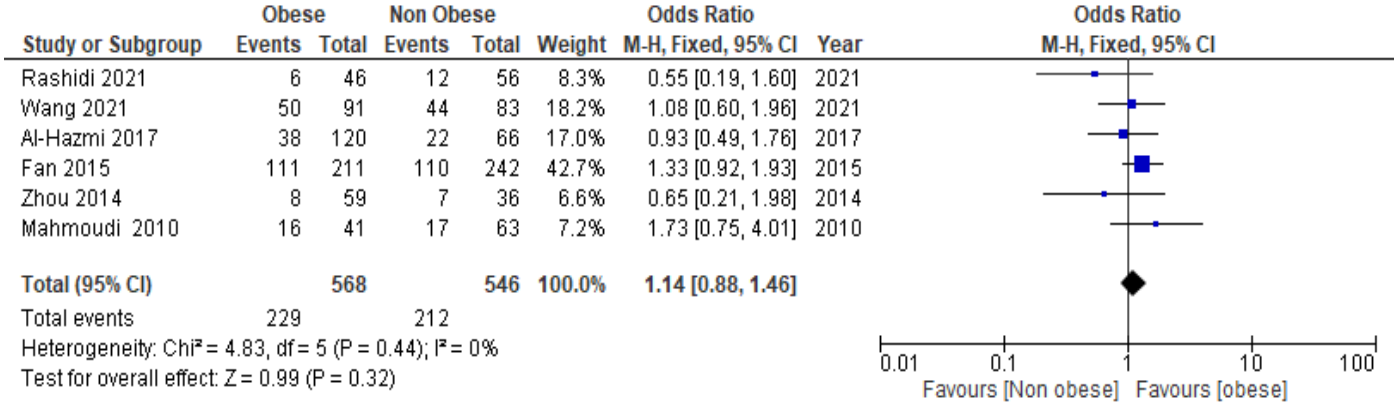


Figure 2.7. Forest plot of the association between VDR *ApaI* polymorphism and obesity risk under aa vs. Aa model in Asian

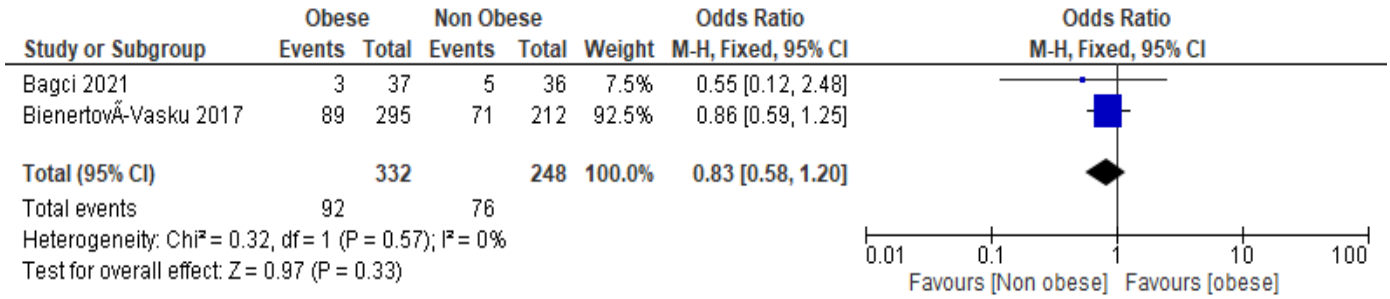


Figure 2.8. Forest plot of the association between VDR *ApaI* polymorphism and obesity risk under aa vs. Aa model in European

https://doi.org/10.56294/saludcyt20251072

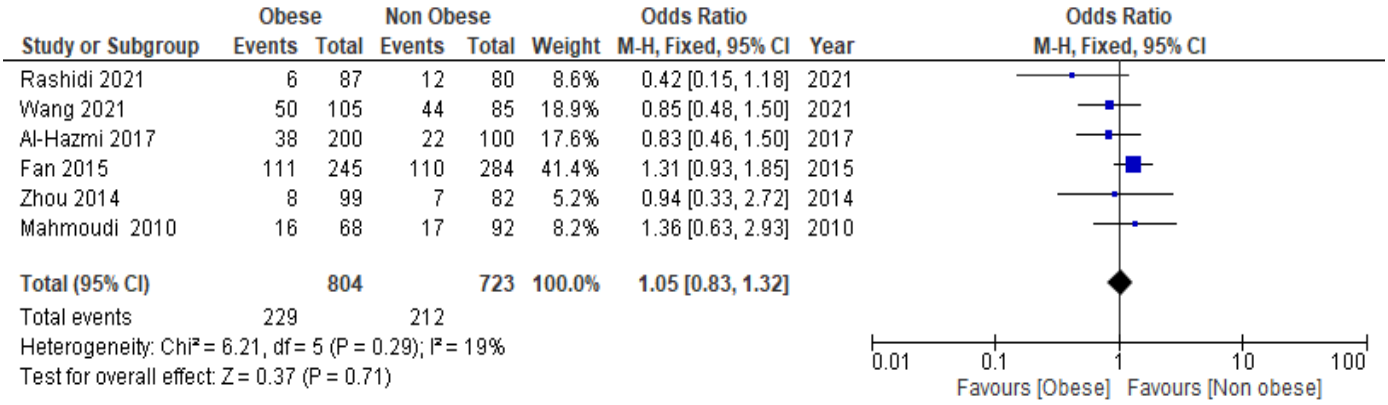


Figure 2.9. Forest plot of the association between VDR *ApaI* polymorphism and obesity risk under aa vs. AA+Aa model in Asian

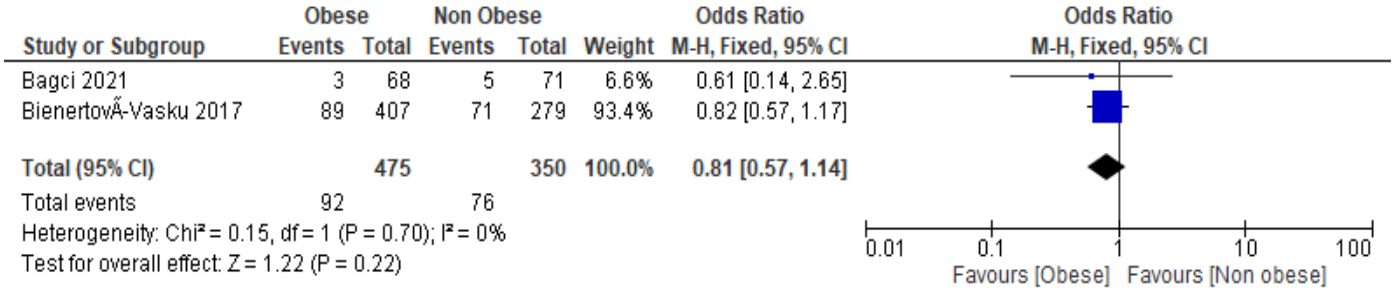


Figure 2.10. Forest plot of the association between VDR *ApaI* polymorphism and obesity risk under aa vs. AA+Aa model in European

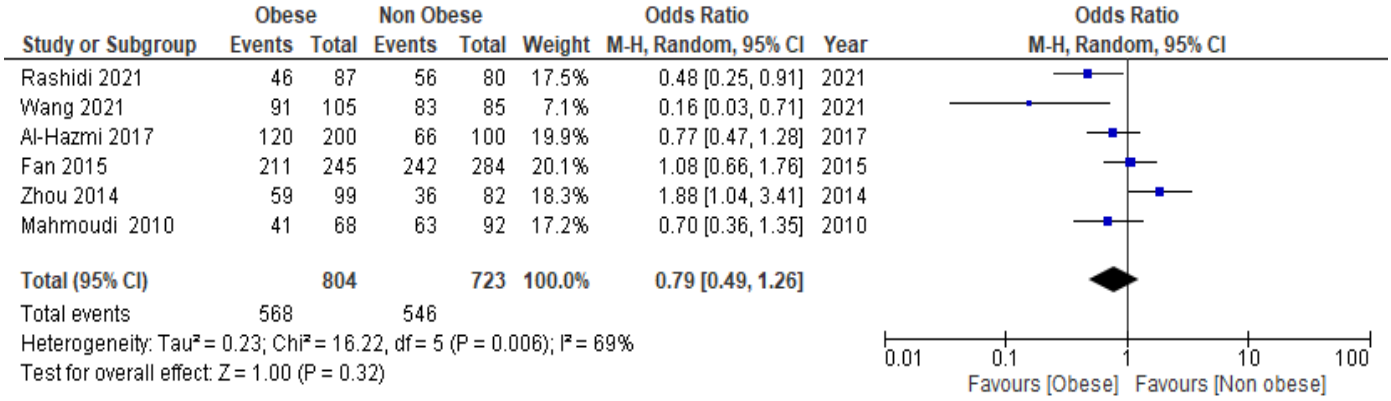


Figure 2.11. Forest plot of the association between VDR *ApaI* polymorphism and obesity risk under Aa+aa vs. AA model in Asian

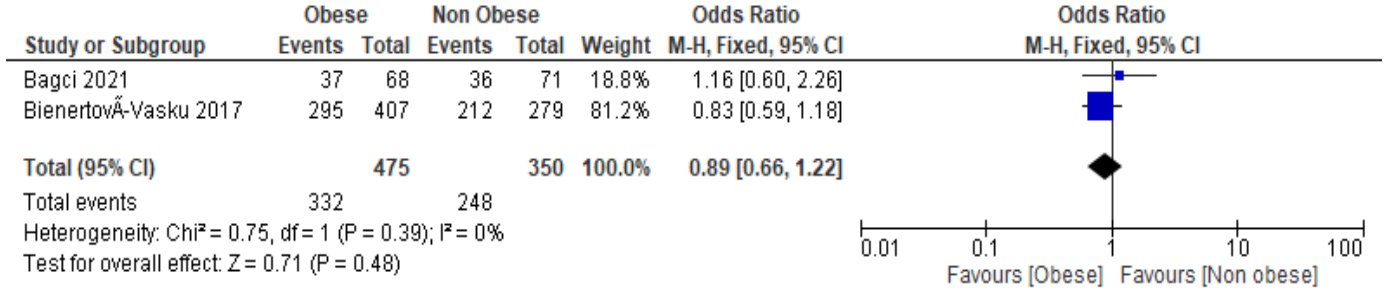


Figure 2.12. Forest plot of the association between VDR *ApaI* polymorphism and obesity risk under Aa+aa vs. AA model in European

https://doi.org/10.56294/saludcyt20251072

3. Vitamin D Receptor gene FokI polymorphism

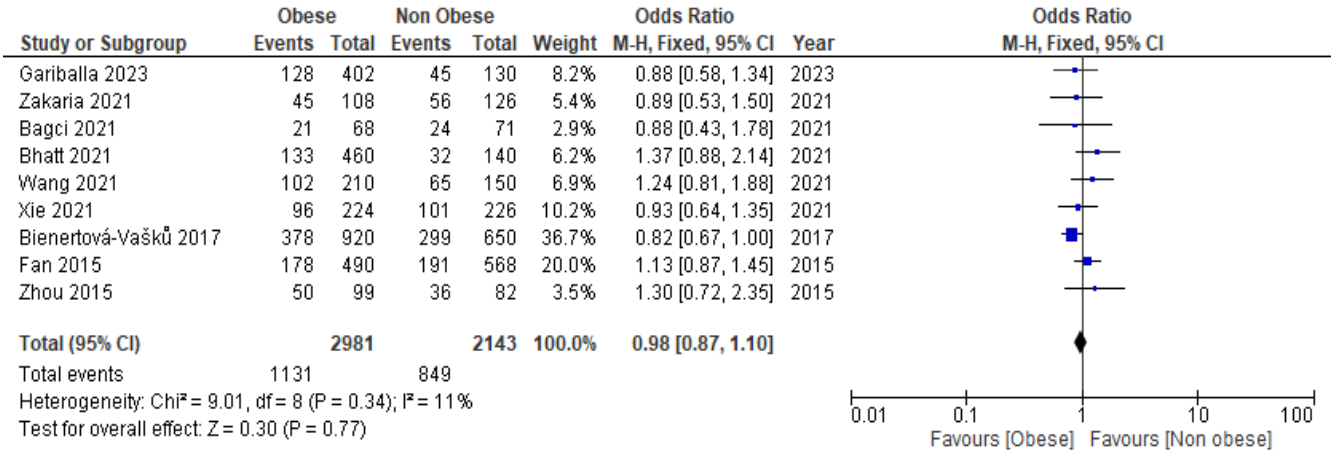


Figure 3.1. Forest plot of the association between VDR gene *FokI* polymorphism and obesity risk under f vs. F model in Asian

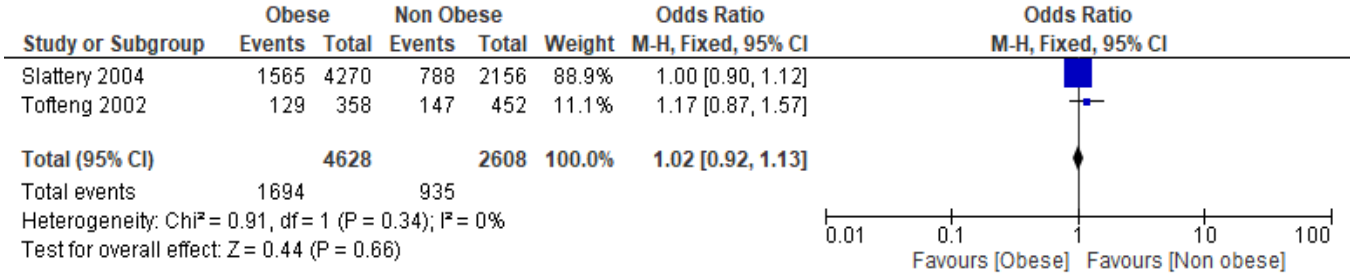


Figure 3.2. Forest plot of the association between VDR gene *FokI* polymorphism and obesity risk under f vs. F model in European

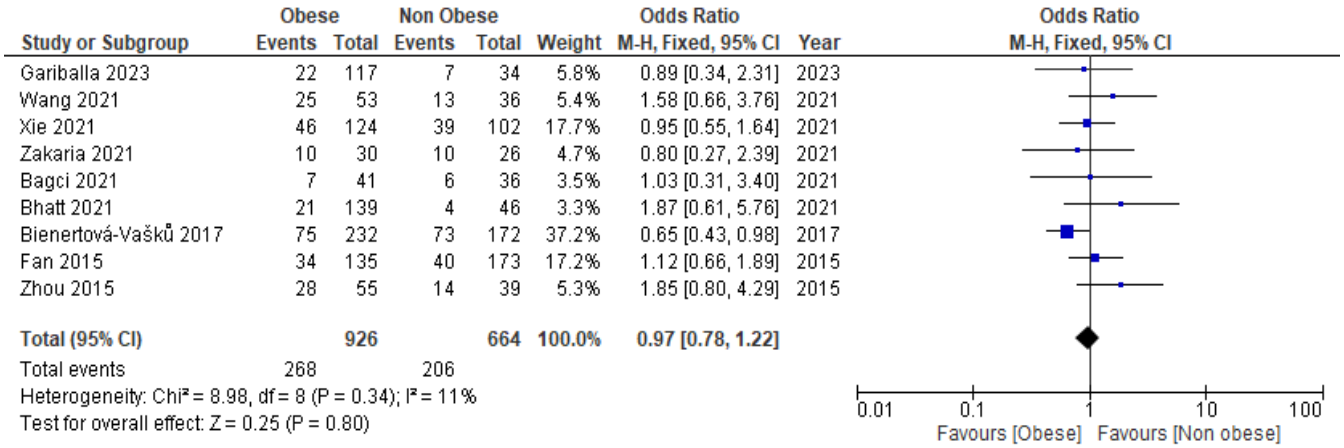


Figure 3.3. Forest plot of the association between VDR gene *FokI* polymorphism and obesity risk under ff vs. FF model in Asian

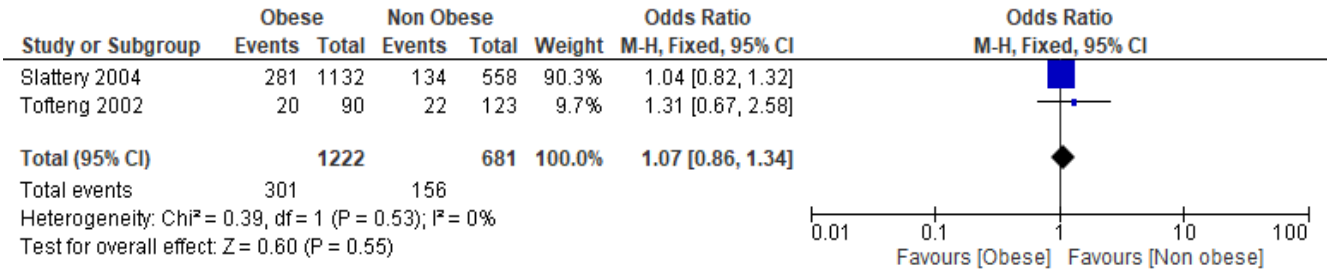


Figure 3.4. Forest plot of the association between VDR gene *FokI* polymorphism and obesity risk under ff vs. FF model in European

https://doi.org/10.56294/saludcyt20251072

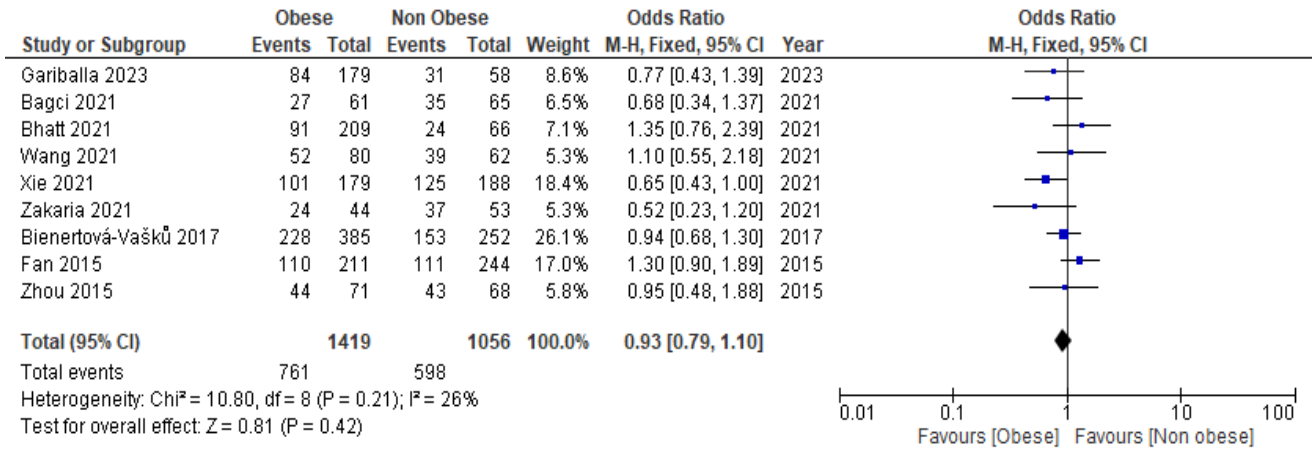


Figure 3.5. Forest plot of the association between VDR gene *FokI* polymorphism and obesity risk under Ff vs. FF model in Asian

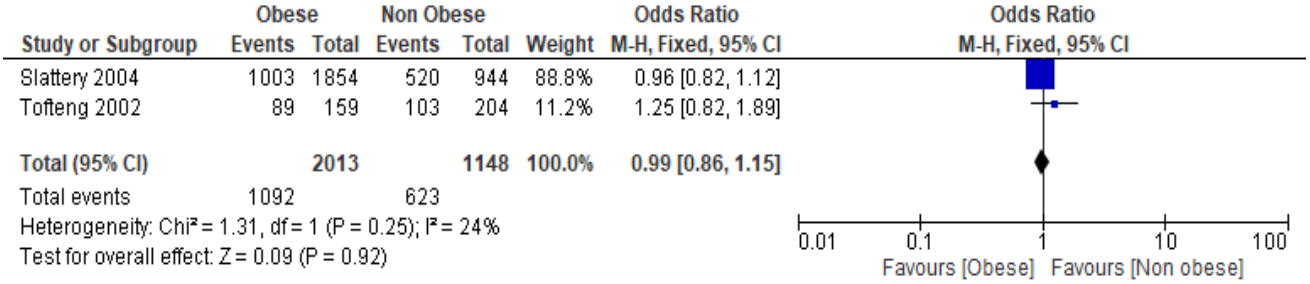


Figure 3.6. Forest plot of the association between VDR gene *FokI* polymorphism and obesity risk under Ff vs. FF model in European

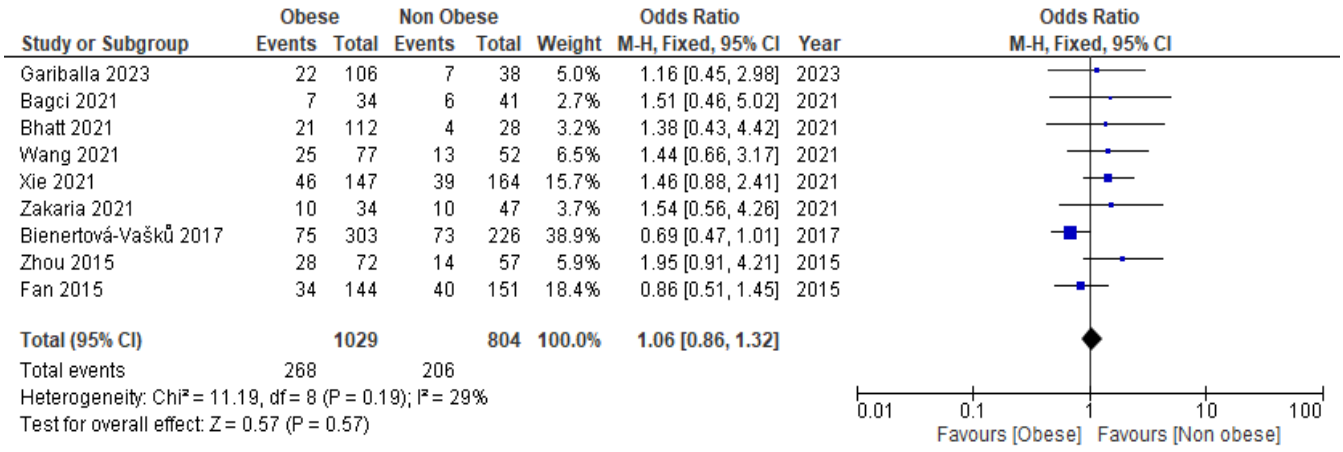


Figure 3.7. Forest plot of the association between VDR gene *FokI* polymorphism and obesity risk under ff vs. Ff model in Asian

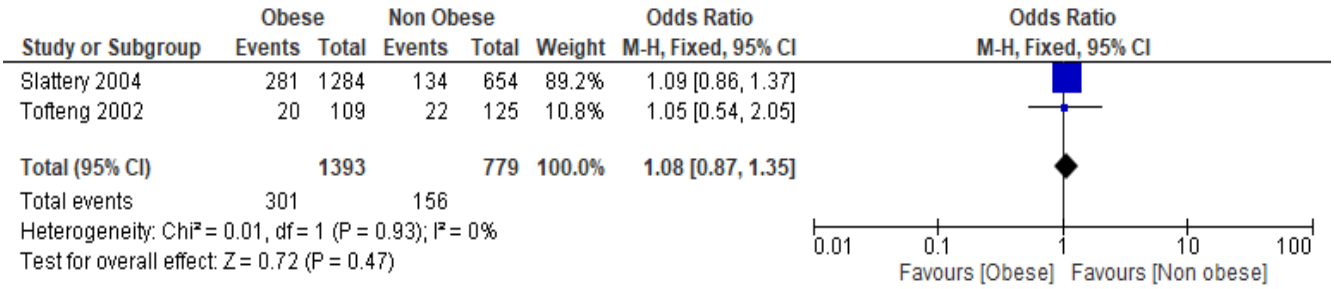


Figure 3.8. Forest plot of the association between VDR gene *FokI* polymorphism and obesity risk under ff vs. Ff model in European

https://doi.org/10.56294/saludcyt20251072

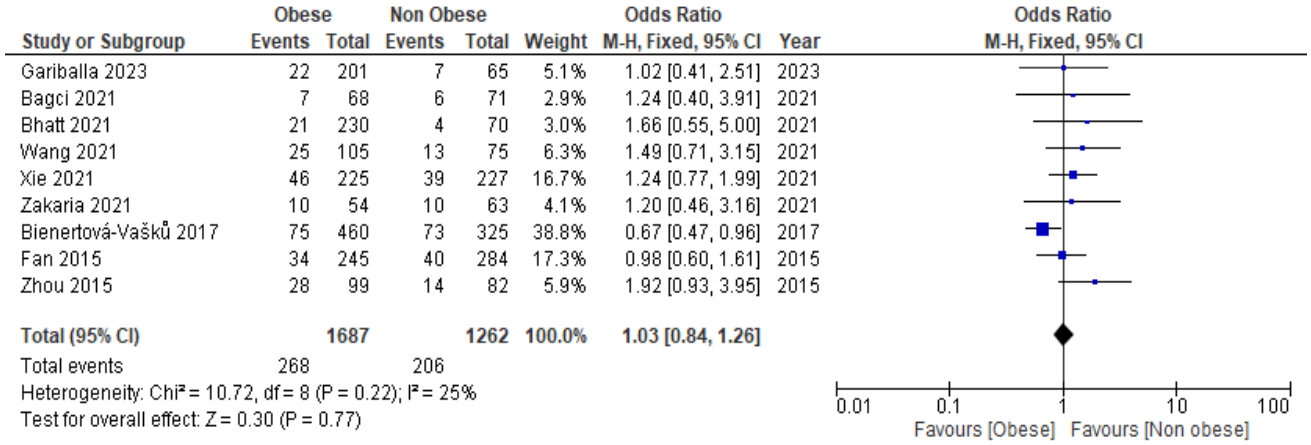


Figure 3.9. Forest plot of the association between VDR gene *FokI* polymorphism and obesity risk under ff vs. FF+Ff model in Asian

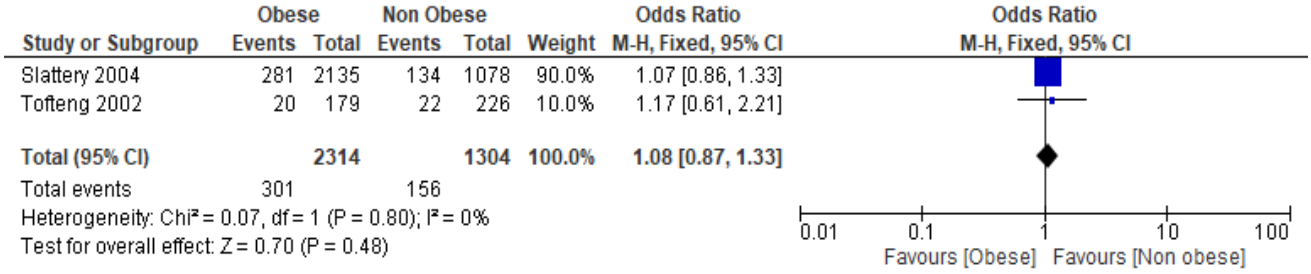


Figure 3.10. Forest plot of the association between VDR gene *FokI* polymorphism and obesity risk under ff vs. FF+Ff model in European

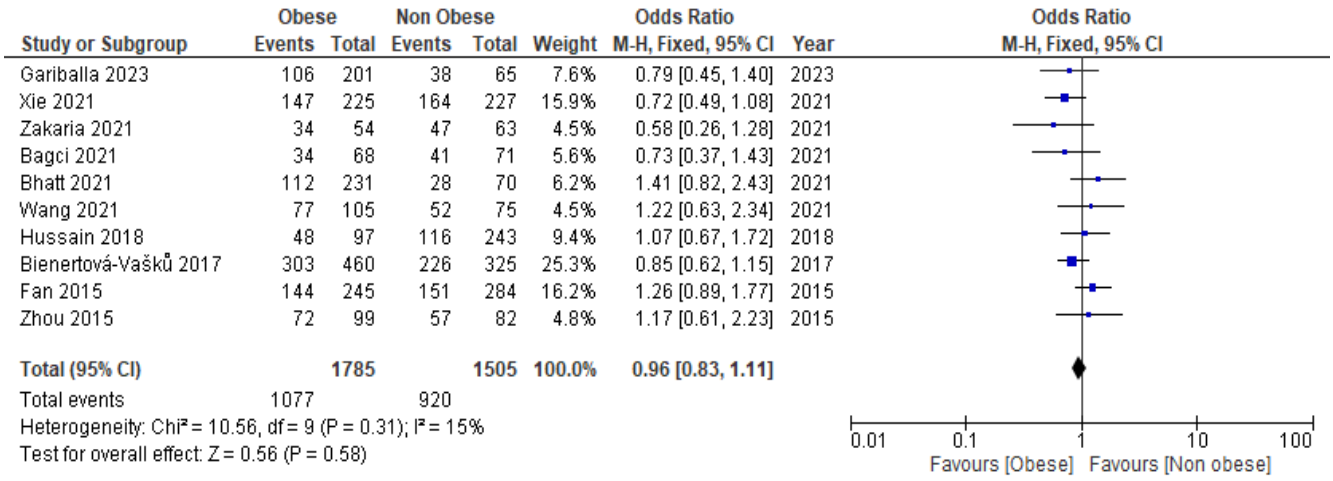


Figure 3.11. Forest plot of the association between VDR gene *FokI* polymorphism and obesity risk under Ff+ff vs FF model in Asian

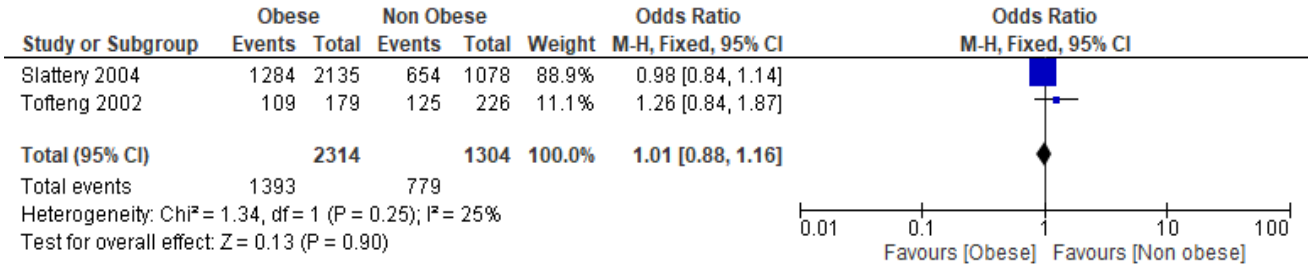


Figure 3.12. Forest plot of the association between VDR gene *FokI* polymorphism and obesity risk under Ff+ff vs FF model in European

https://doi.org/10.56294/saludcyt20251072

4. Vitamin D Receptor gene TaqI polymorphism

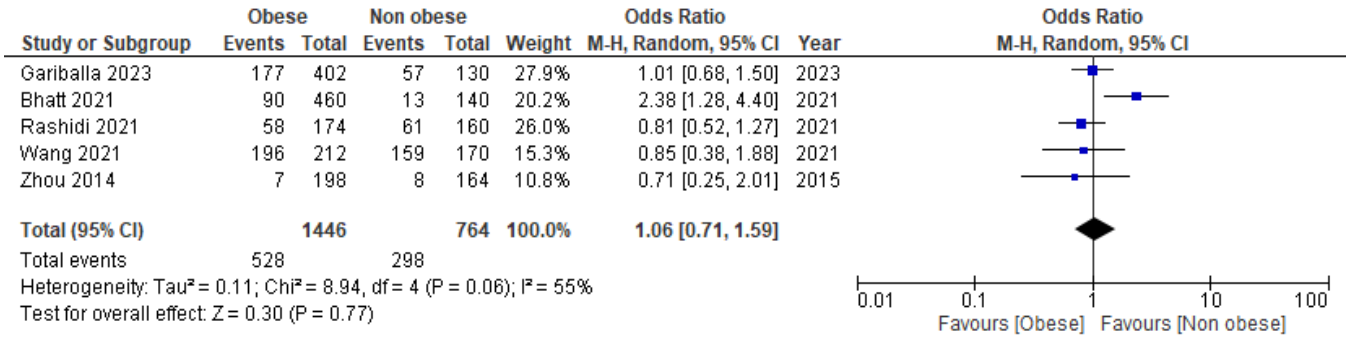


Figure 4.1. Forest plot of the association between VDR gene *TaqI* polymorphism and obesity risk under t vs. T model in Asian

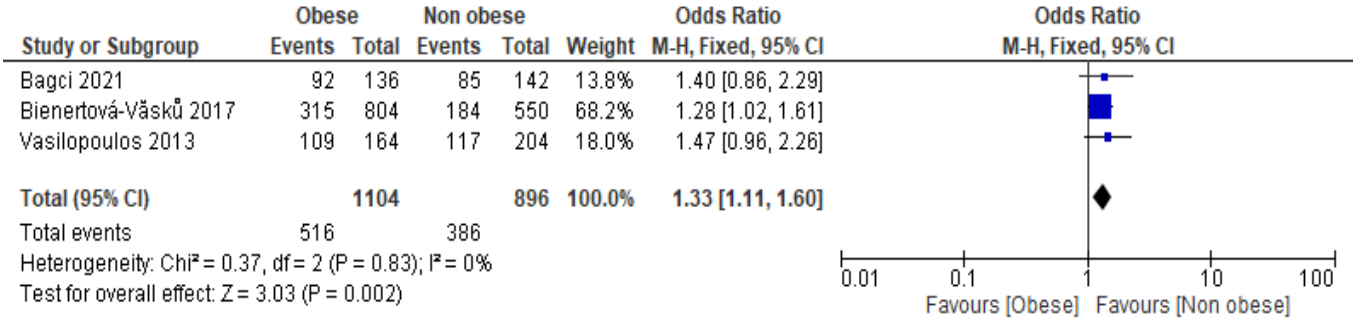


Figure 4.2. Forest plot of the association between VDR gene *TaqI* polymorphism and obesity risk under t vs. T model in European

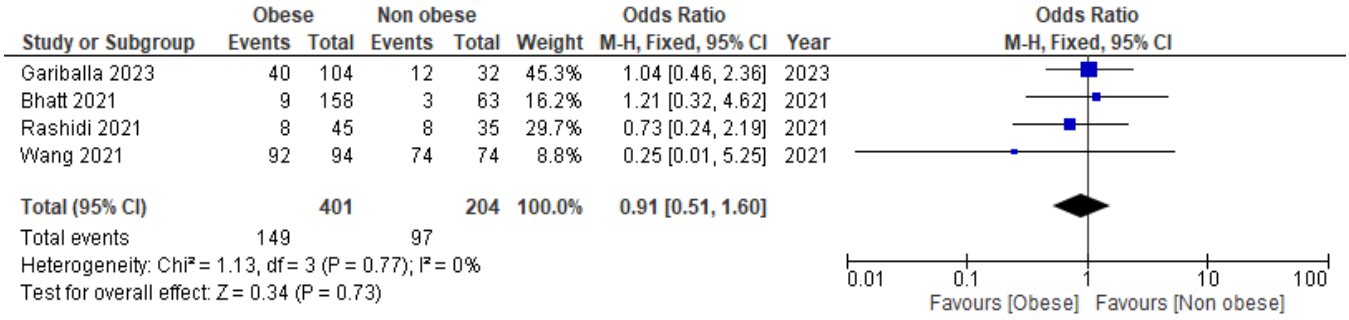


Figure 4.3. Forest plot of the association between VDR gene *TaqI* polymorphism and obesity risk under tt vs. TT model in Asian

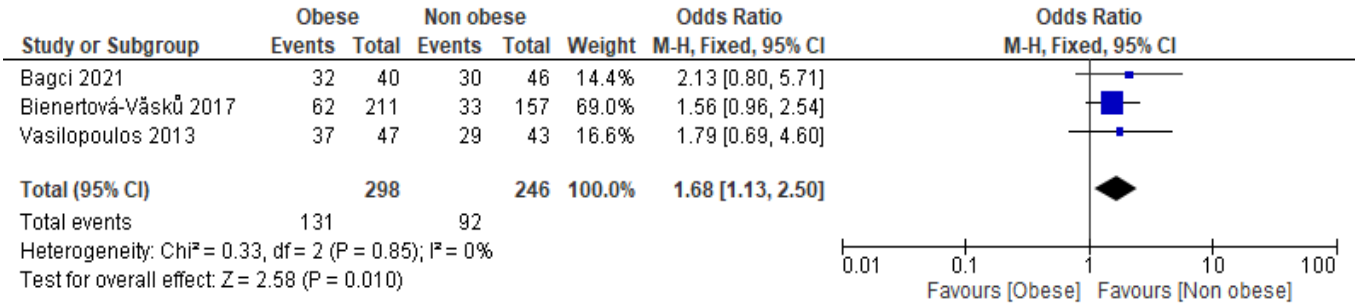


Figure 4.4. Forest plot of the association between VDR gene *TaqI* polymorphism and obesity risk under tt vs. TT model in European

https://doi.org/10.56294/saludcyt20251072

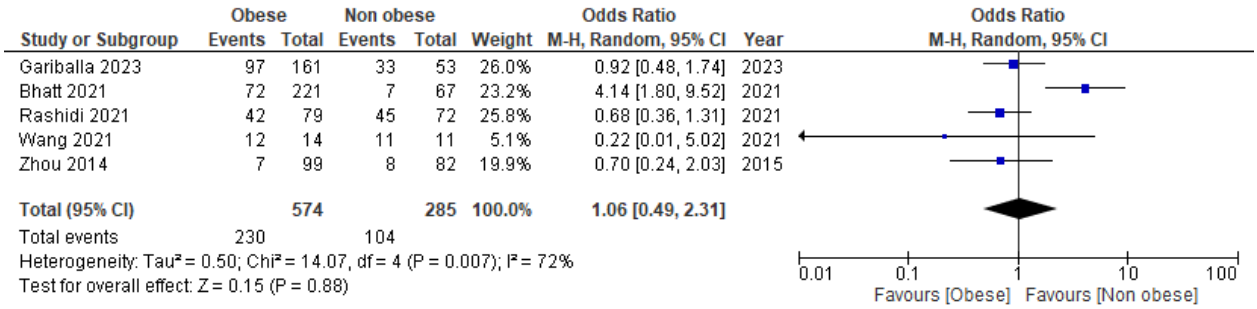


Figure 4.5. Forest plot of the association between VDR gene *TaqI* polymorphism and obesity risk under Tt vs TT model in Asian

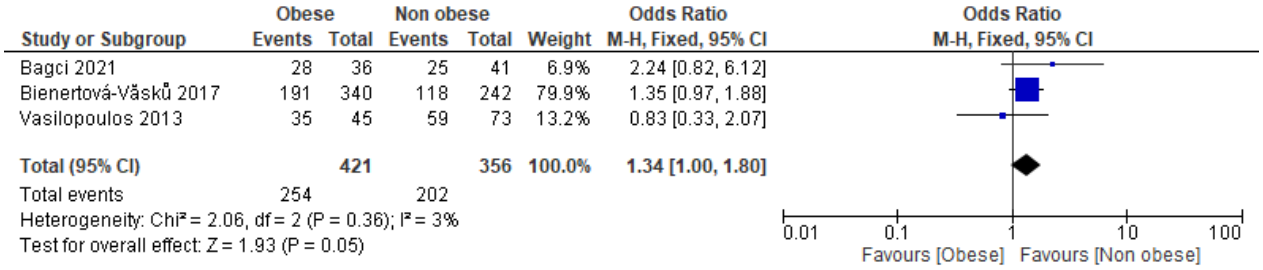


Figure 4.6. Forest plot of the association between VDR gene *TaqI* polymorphism and obesity risk under Tt vs TT model in European

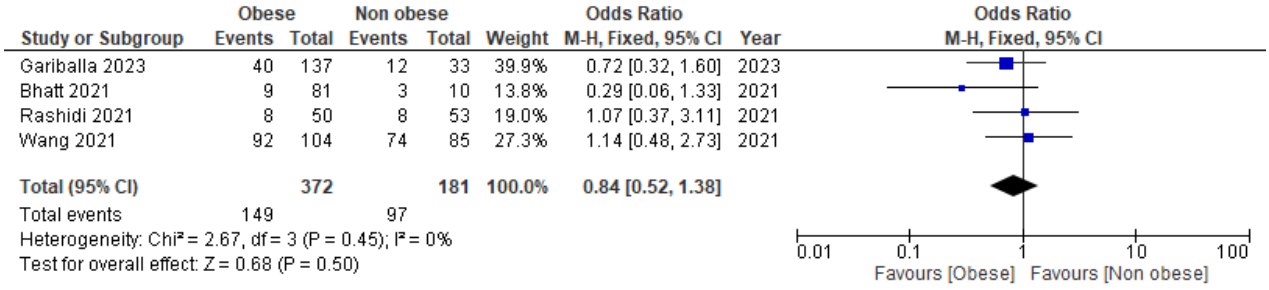


Figure 4.7. Forest plot of the association between VDR gene *TaqI* polymorphism and obesity risk under tt vs Tt model in Asian

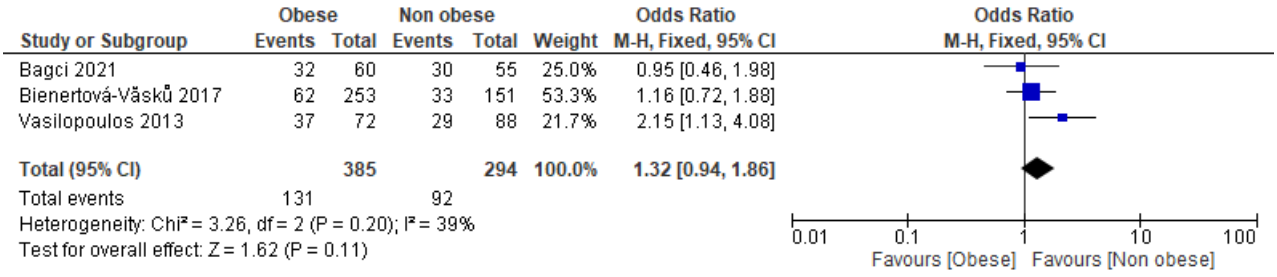


Figure 4.8. Forest plot of the association between VDR gene *TaqI* polymorphism and obesity risk under tt vs Tt model in European

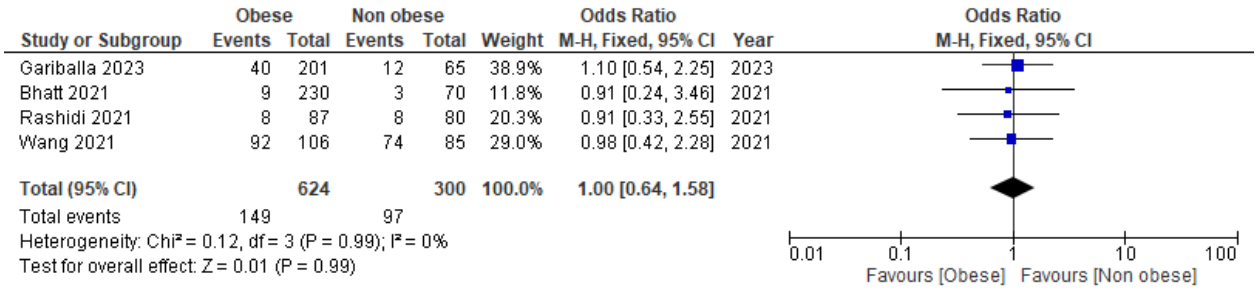


Figure 4.9. Forest plot of the association between VDR gene *TaqI* polymorphism and obesity risk under tt vs TT + Tt model in Asian

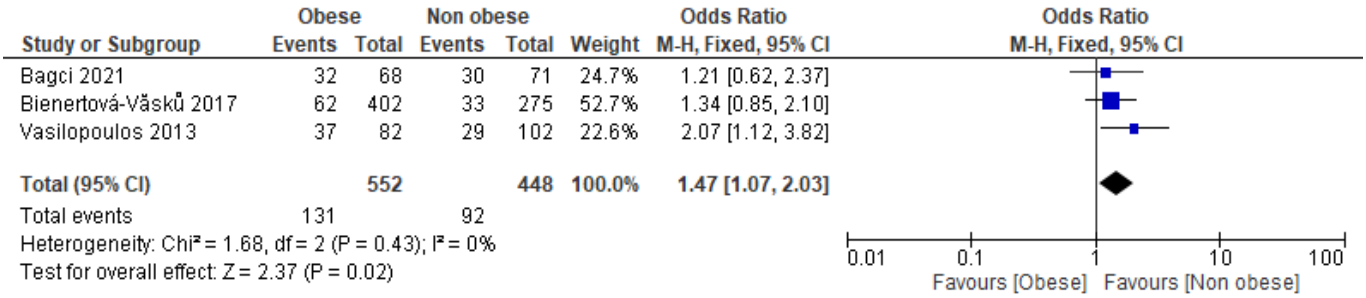


Figure 4.10. Forest plot of the association between VDR gene *TaqI* polymorphism and obesity risk under tt vs TT + Tt model in European

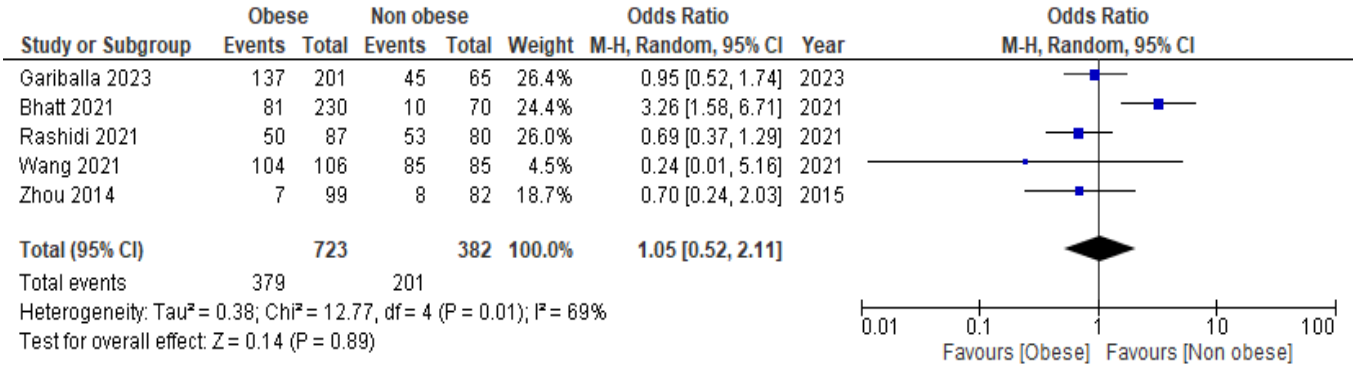


Figure 4.11. Forest plot of the association between VDR gene *TaqI* polymorphism and obesity risk under Tt + tt vs TT model in Asian

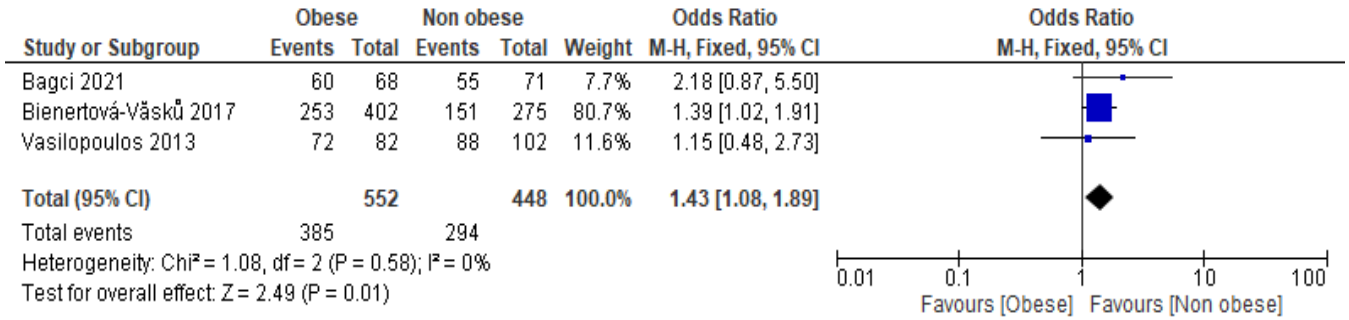


Figure 4.12. Forest plot of the association between VDR gene *TaqI* polymorphism and obesity risk under Tt + tt vs TT model in European

5. Vitamin D Receptor gene Cdx2 polymorphism

5.1 Analysis of A vs G model

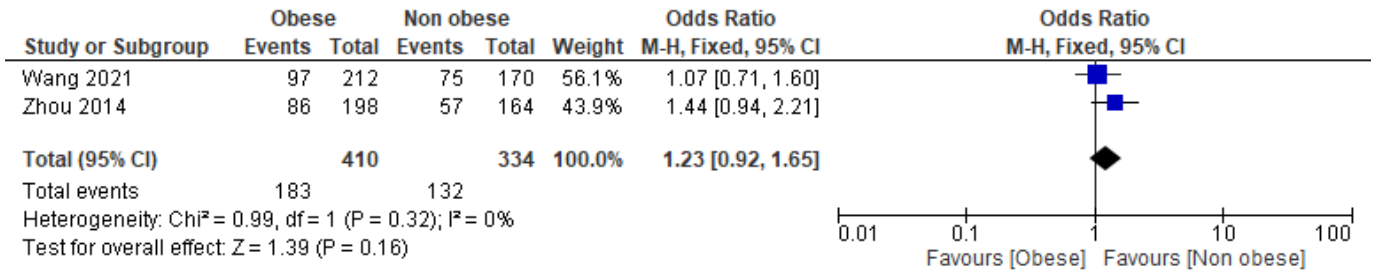


Figure 5.1. Forest plot of the association between VDR gene *Cdx2* polymorphism and obesity risk under A vs G model

https://doi.org/10.56294/saludcyt20251072

5.2 Analysis of AA vs GG model

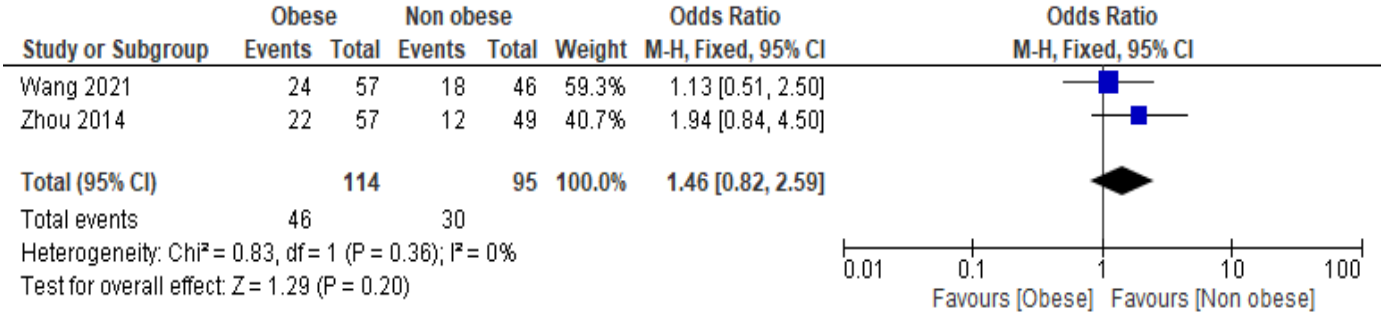


Figure 5.2. Forest plot of the association between VDR gene *Cdx2* polymorphism and obesity risk under AA vs GG model

5.3 Analysis of GA vs GG model

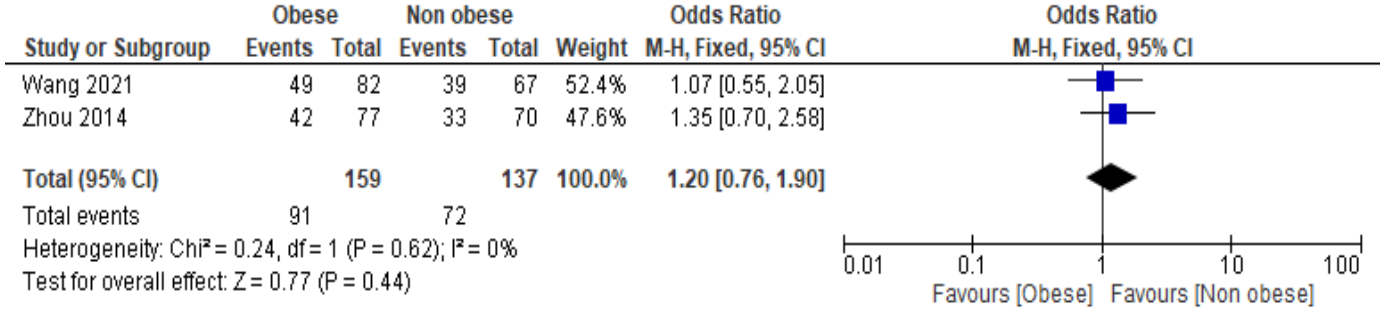


Figure 5.3. Forest plot of the association between VDR gene *Cdx2* polymorphism and obesity risk under GA vs GG model

5.4 Analysis of AA vs GA model

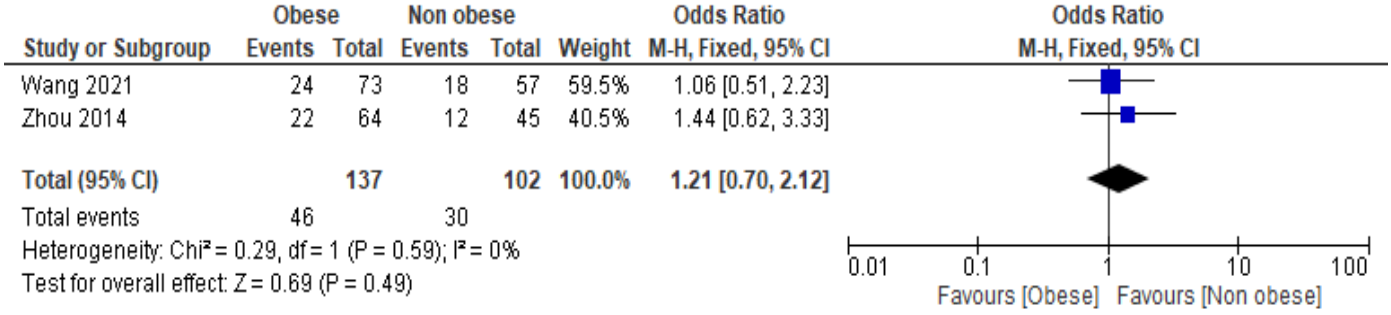


Figure 5.4. Forest plot of the association between VDR gene *Cdx2* polymorphism and obesity risk under AA vs GA model

5.5 Analysis of AA vs GG + GA model

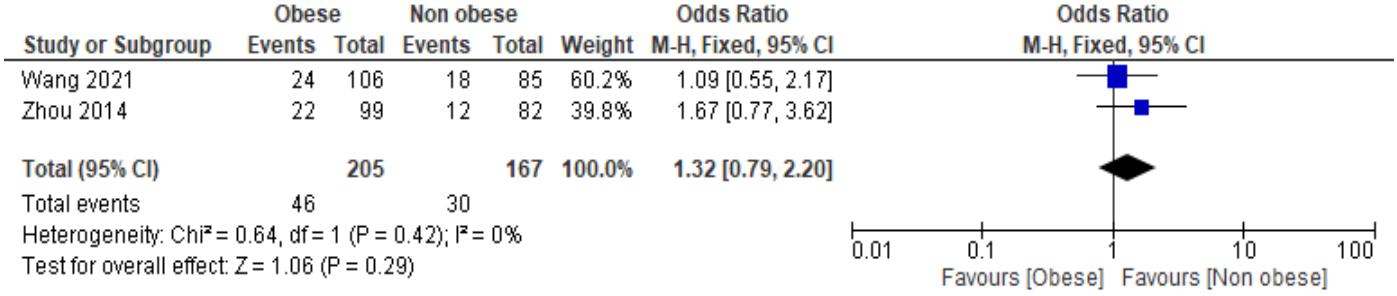


Figure 5.5. Forest plot of the association between VDR gene *Cdx2* polymorphism and obesity risk under AA vs GG + GA model

https://doi.org/10.56294/saludcyt20251072

5.6 Analysis of GA + AA vs GG model

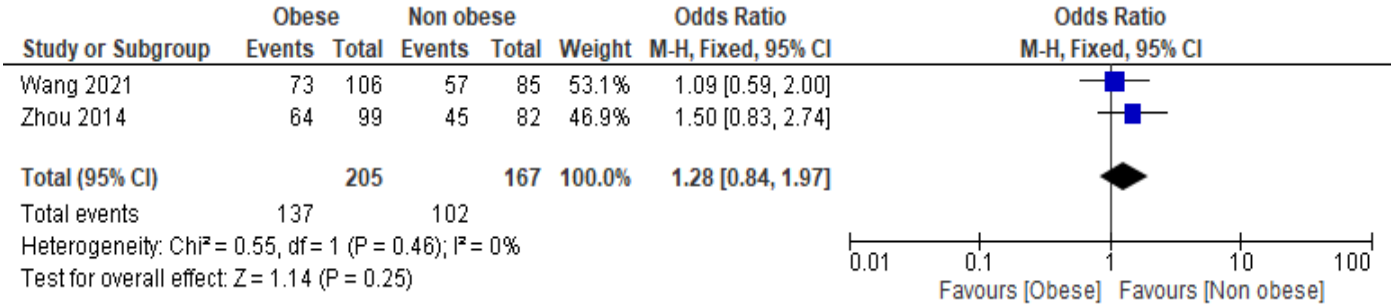


Figure 5.6. Forest plot of the association between VDR gene *Cdx2* polymorphism and obesity risk under GA + AA vs GG model

6. Funnel plots

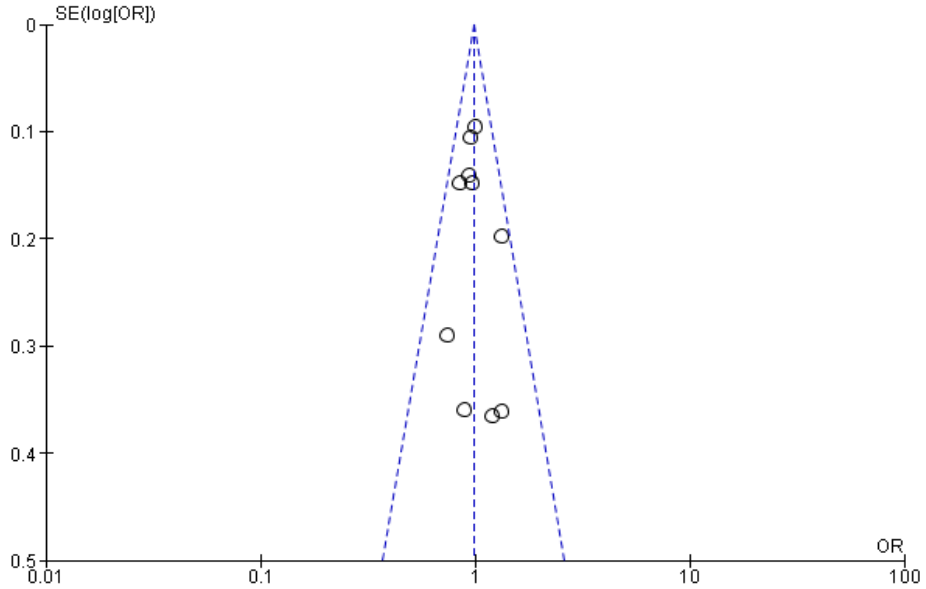


Figure 6.1. Funnel plot of the association between VDR gene *BsmI* polymorphism and obesity risk under b vs. B model in overall

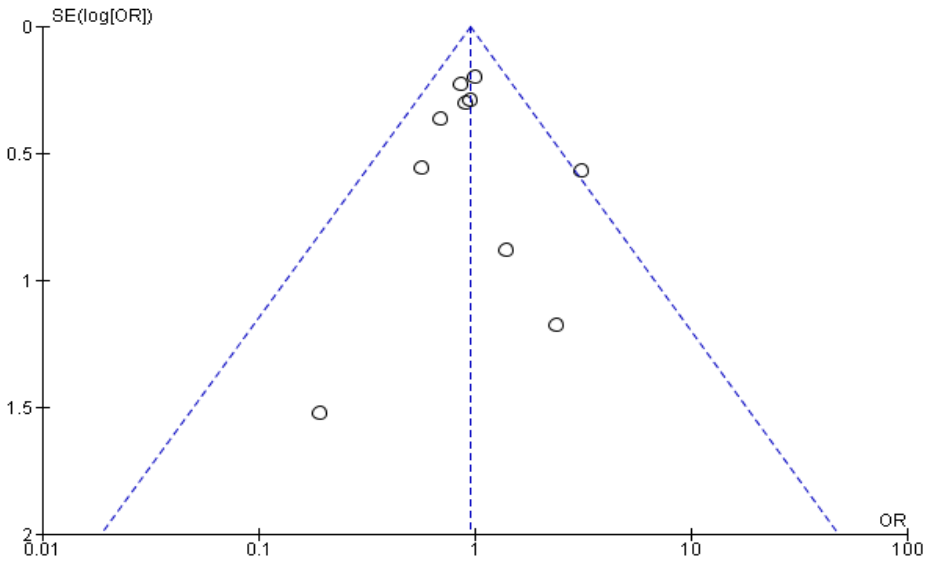


Figure 6.2. Funnel plot of the association between VDR *BsmI* polymorphism and obesity risk under bb vs. BB model in overall

https://doi.org/10.56294/saludcyt20251072

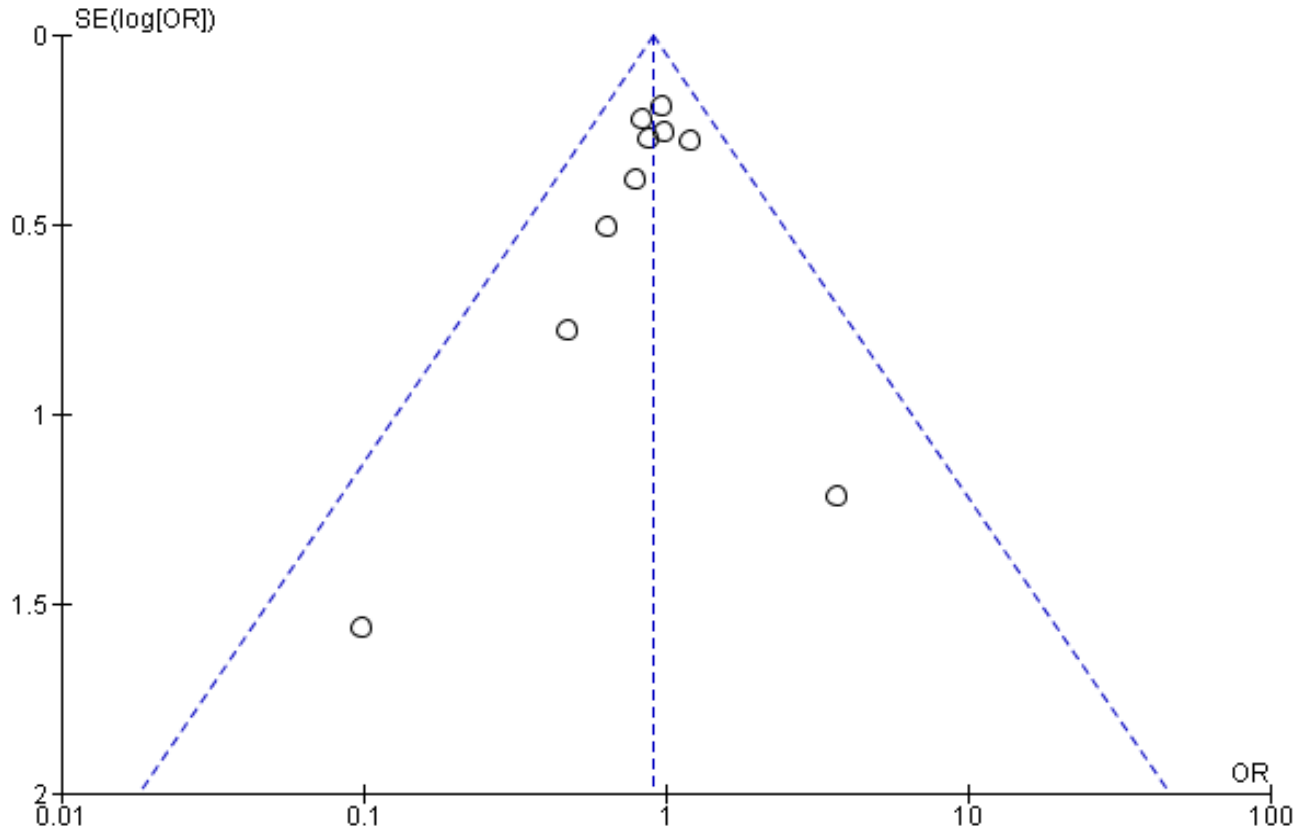


Figure 6.3. Funnel plot of the association between VDR *BsmI* polymorphism and obesity risk under Bb vs. BB model in overall

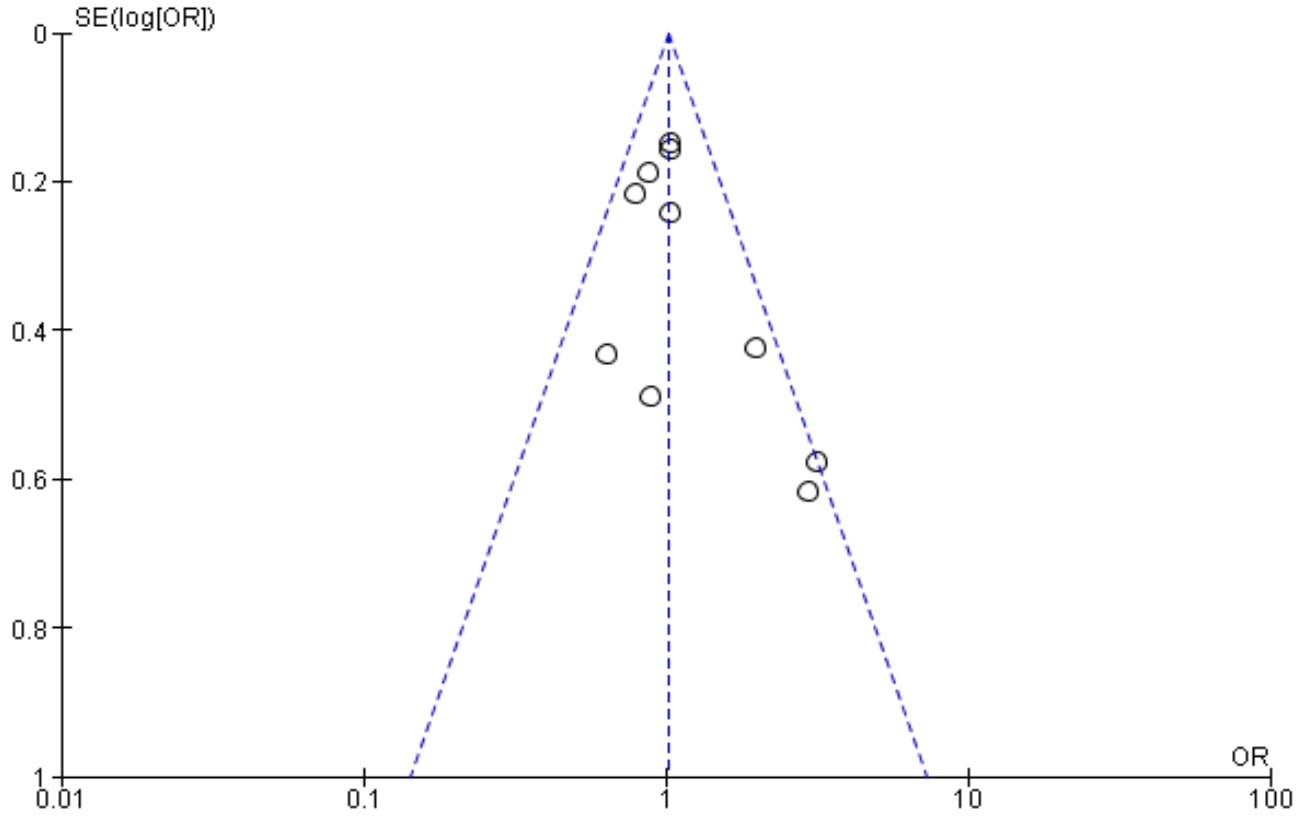


Figure 6.4. Funnel plot of the association between VDR *BsmI* polymorphism and obesity risk under bb vs. Bb model in overall

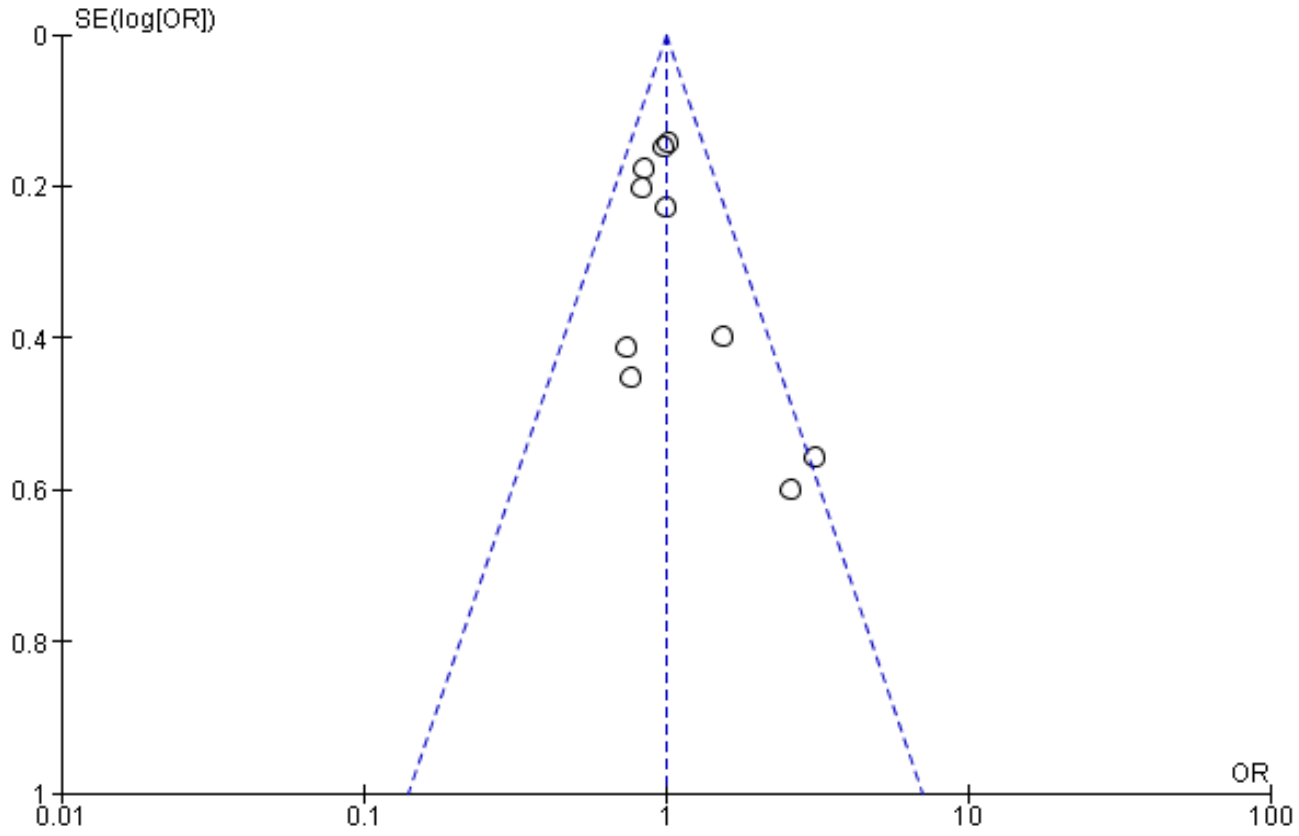


Figure 6.5. Funnel plot of the association between VDR *BsmI* polymorphism and obesity risk under bb vs. BB+Bb model in overall

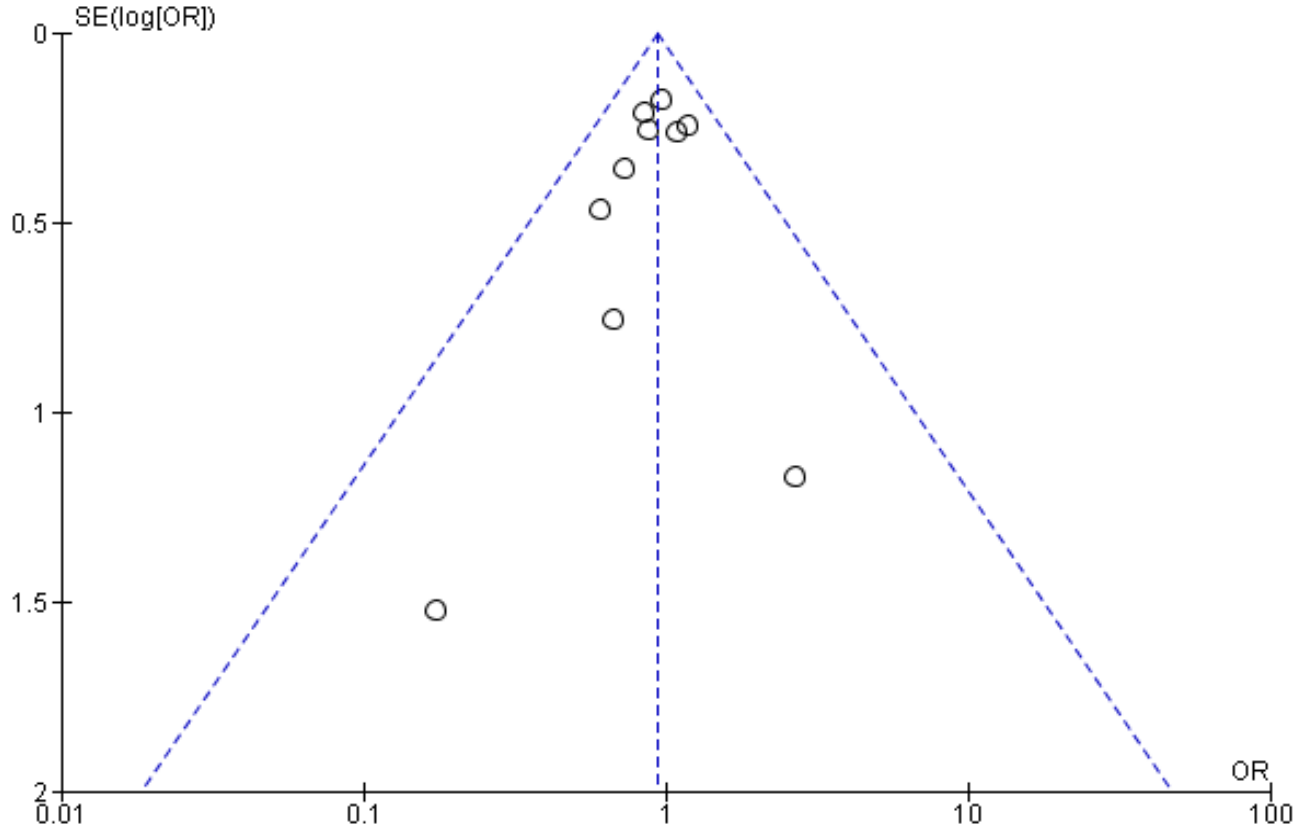


Figure 6.6. Funnel plot of the association between VDR *BsmI* polymorphism and obesity risk under Bb+bb vs. BB model in overall

https://doi.org/10.56294/saludcyt20251072

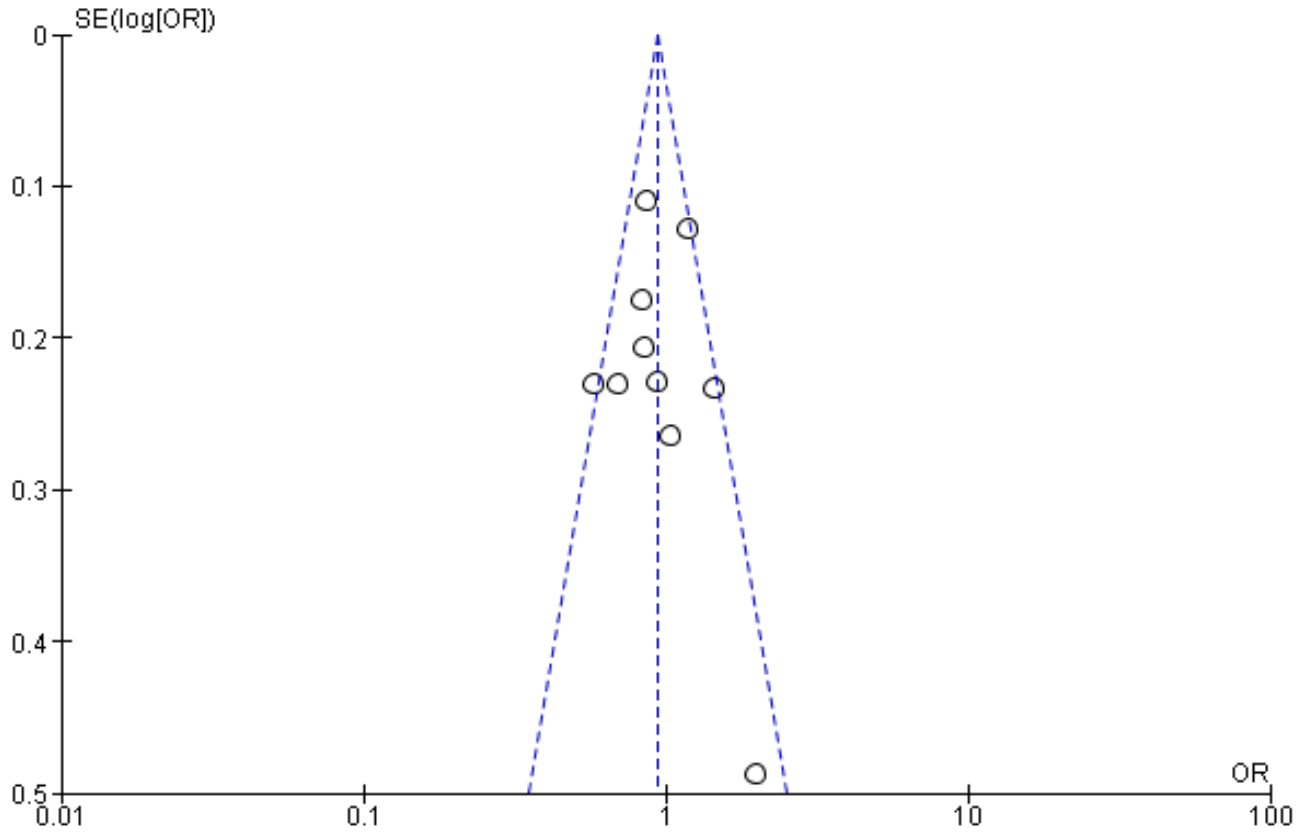


Figure 6.7. Funnel plot of the association between VDR *ApaI* polymorphism and obesity risk under a vs. A model in overall

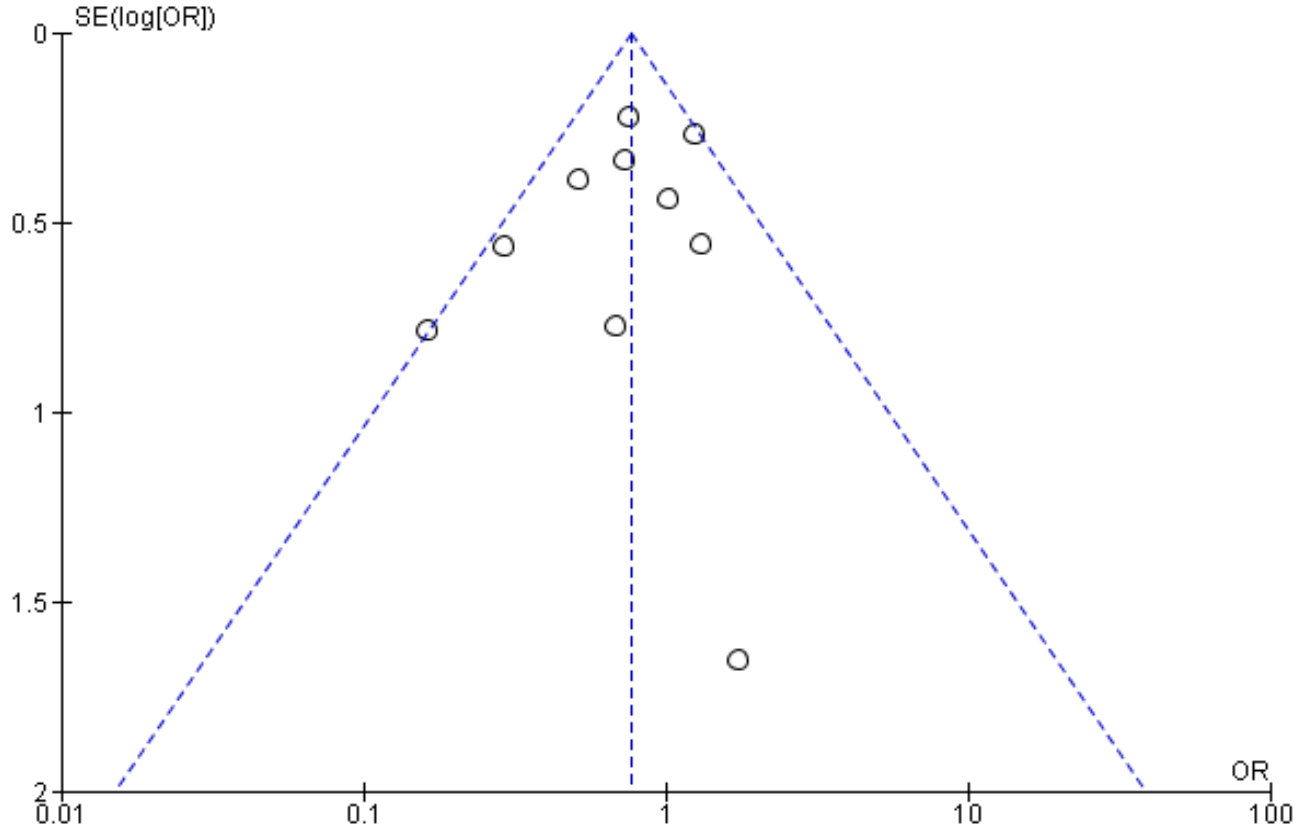


Figure 6.8. Funnel plot of the association between VDR *ApaI* polymorphism and obesity risk under aa vs. AA model in overall

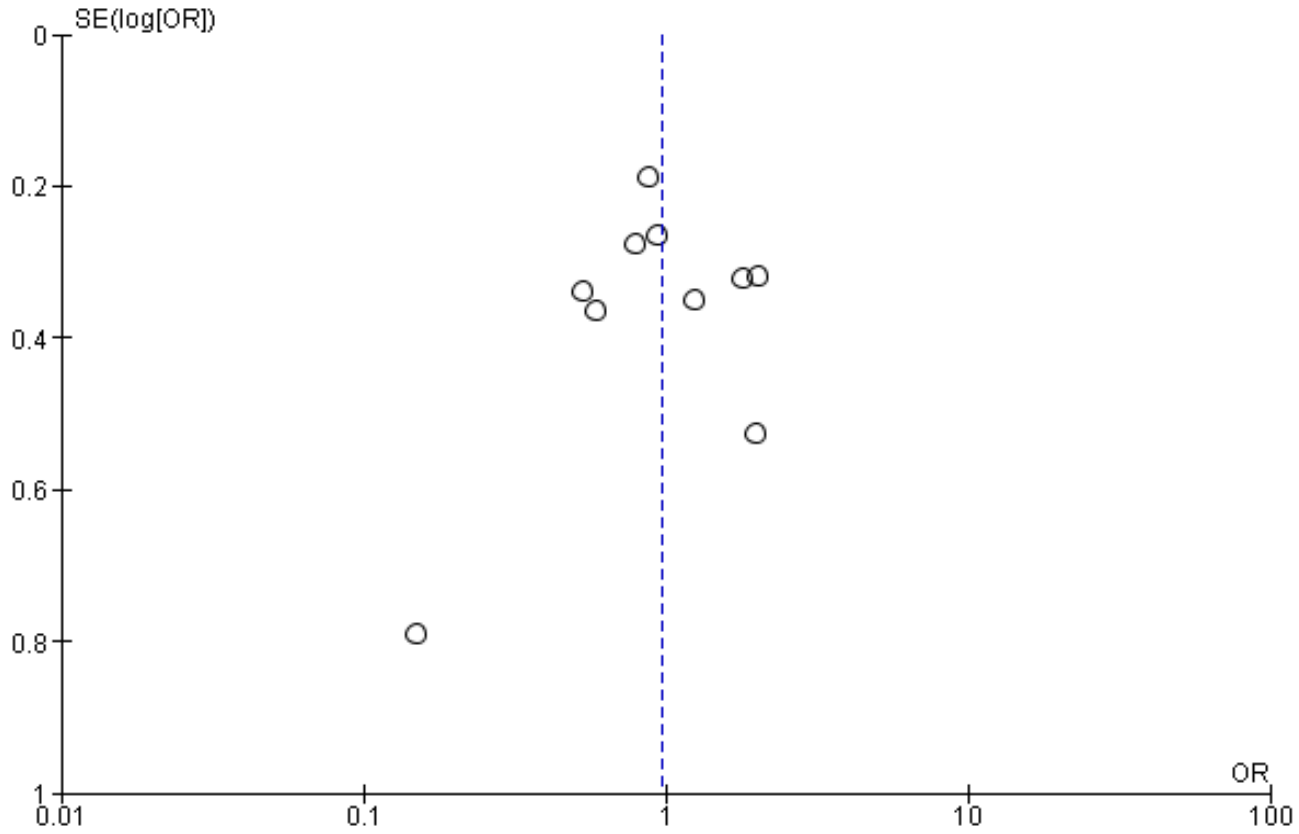


Figure 6.9. Funnel plot of the association between VDR *ApaI* polymorphism and obesity risk under Aa vs. AA model in overall

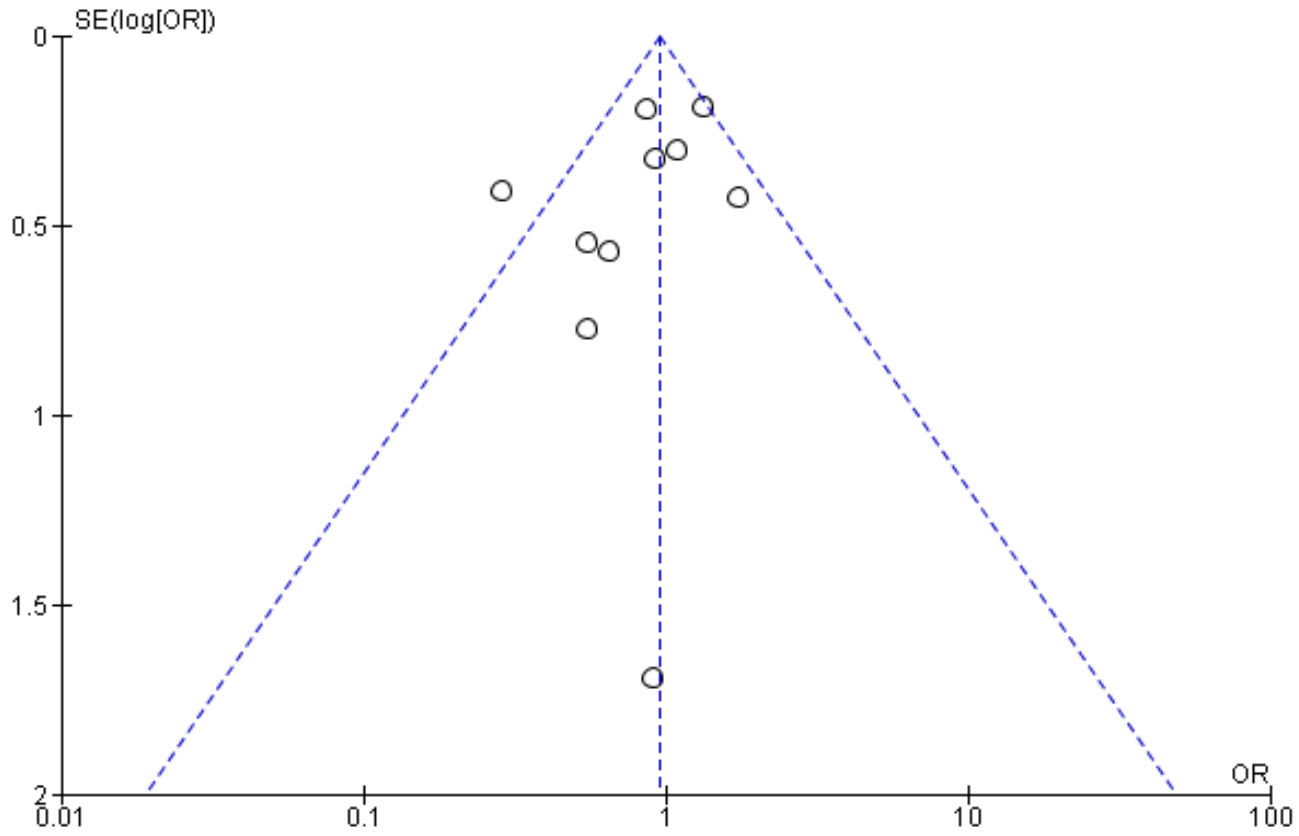


Figure 6.10. Funnel plot of the association between VDR *ApaI* polymorphism and obesity risk under aa vs. Aa model in overall

https://doi.org/10.56294/saludcyt20251072

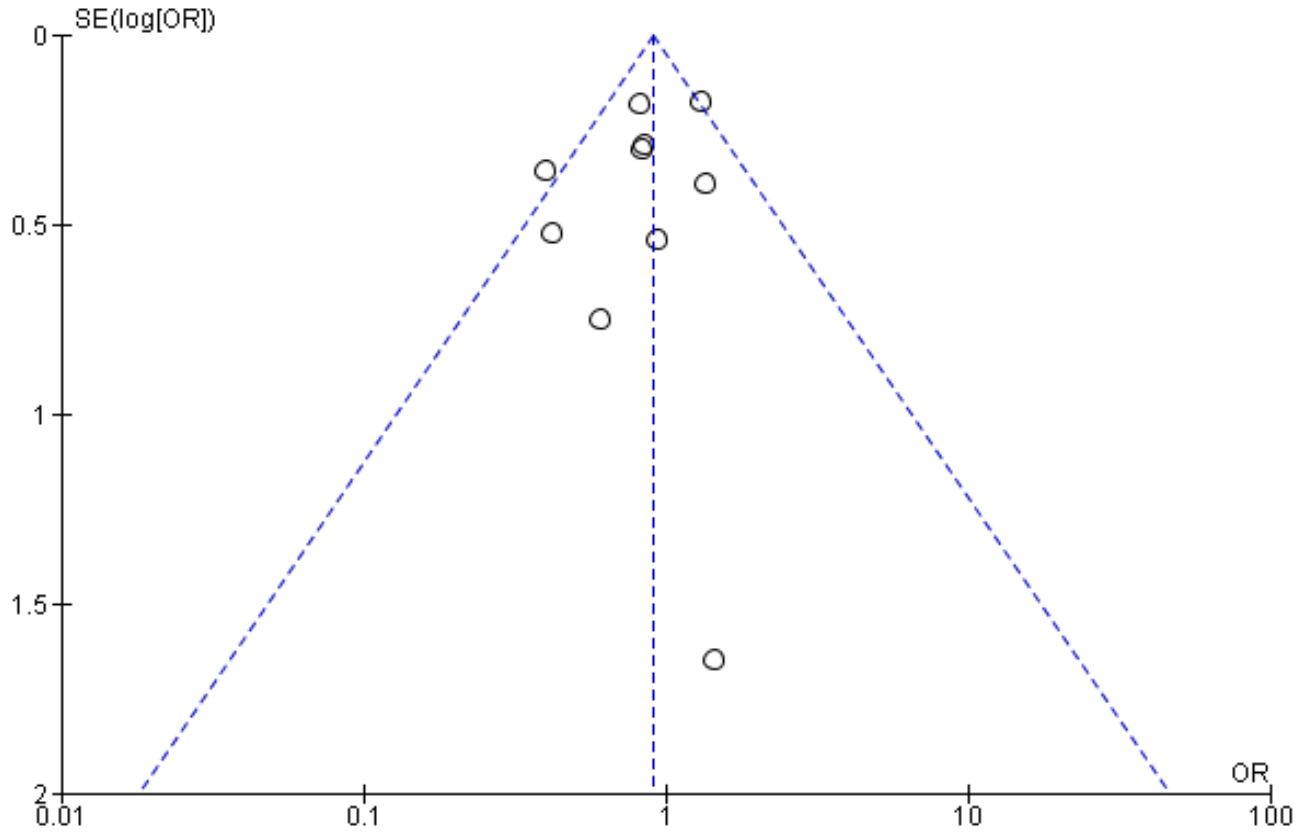


Figure 6.11. Funnel plot of the association between VDR *ApaI* polymorphism and obesity risk under aa vs. AA+Aa model in overall

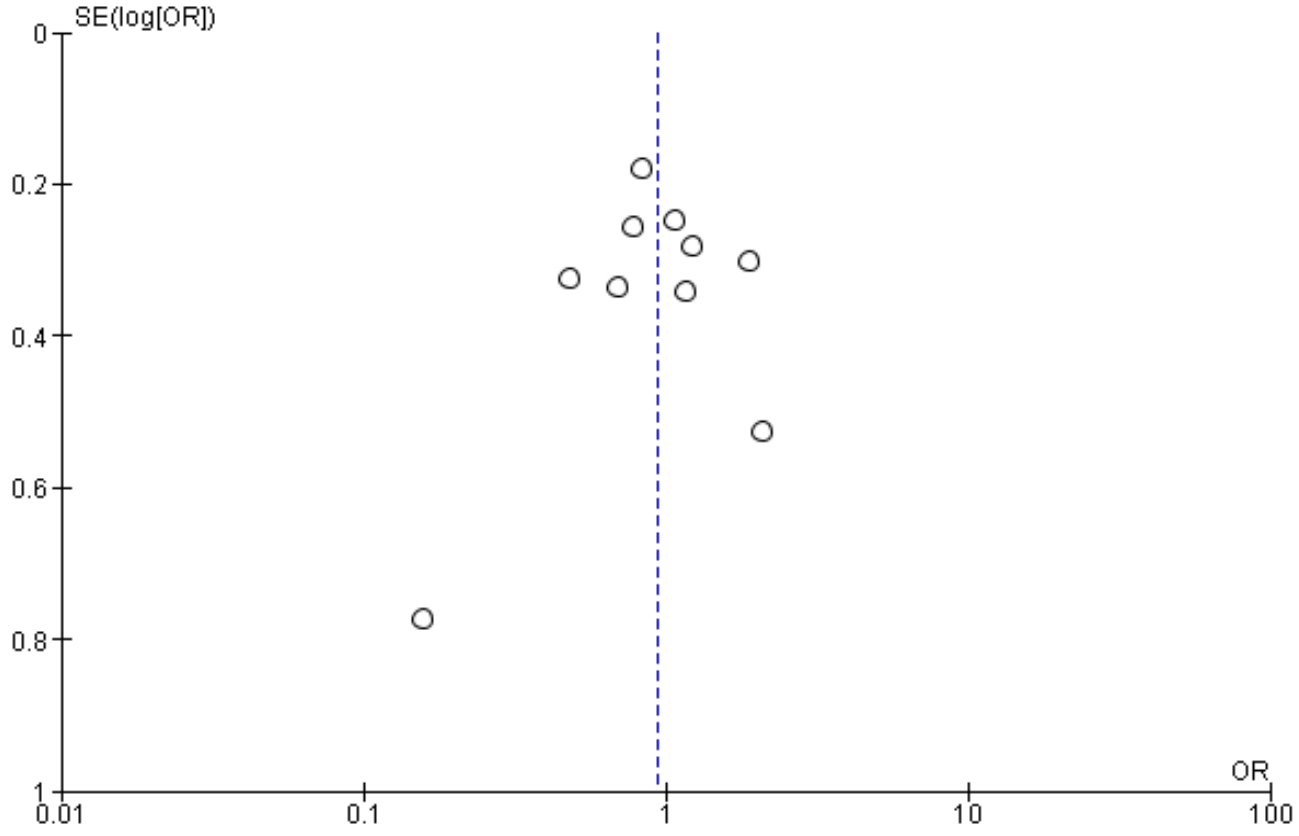


Figure 6.12. Funnel plot of the association between VDR *ApaI* polymorphism and obesity risk under Aa+aa vs. AA model in overall

https://doi.org/10.56294/saludcyt20251072

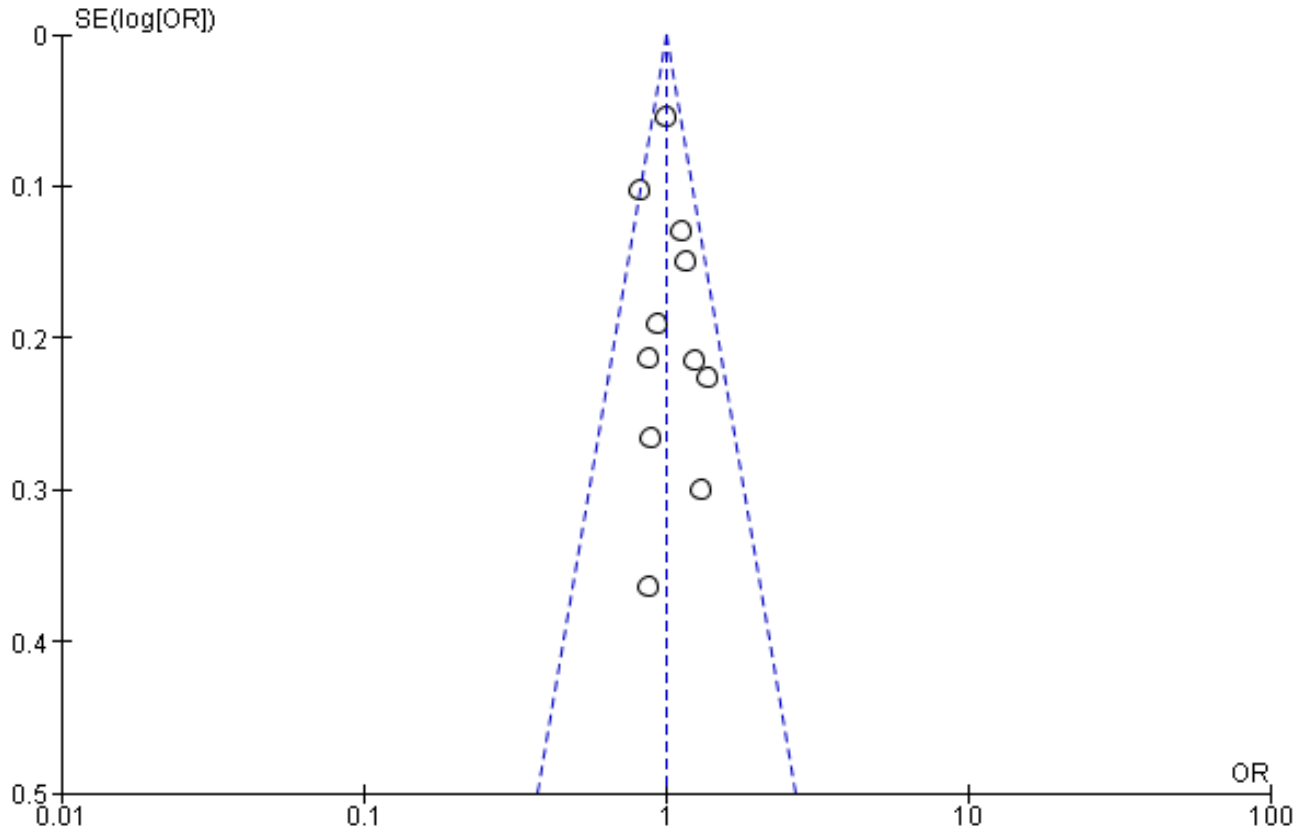


Figure 6.13. Funnel plot of the association between VDR gene *FokI* polymorphism and obesity risk under f vs. F model in overall

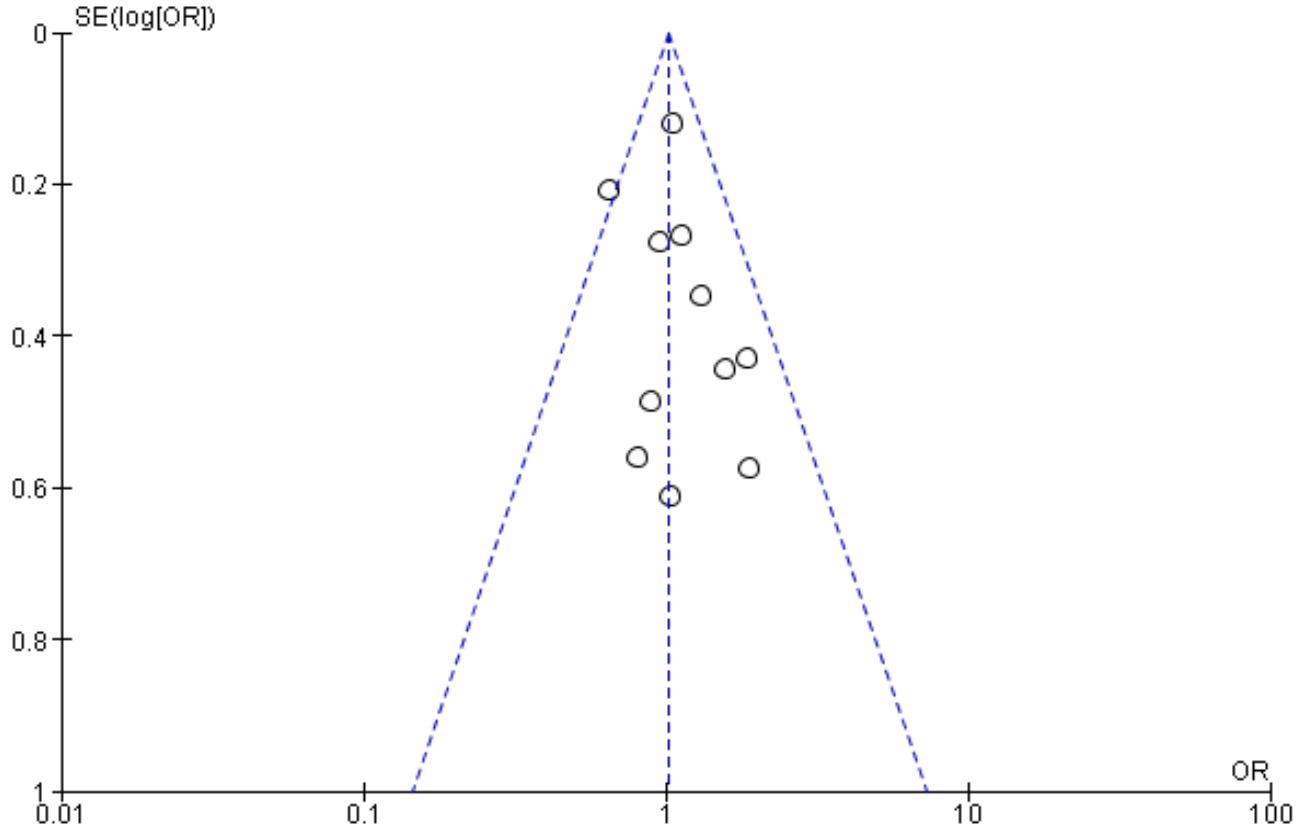


Figure 6.14. Funnel plot of the association between VDR gene *FokI* polymorphism and obesity risk under ff vs. FF model in overall

https://doi.org/10.56294/saludcyt20251072

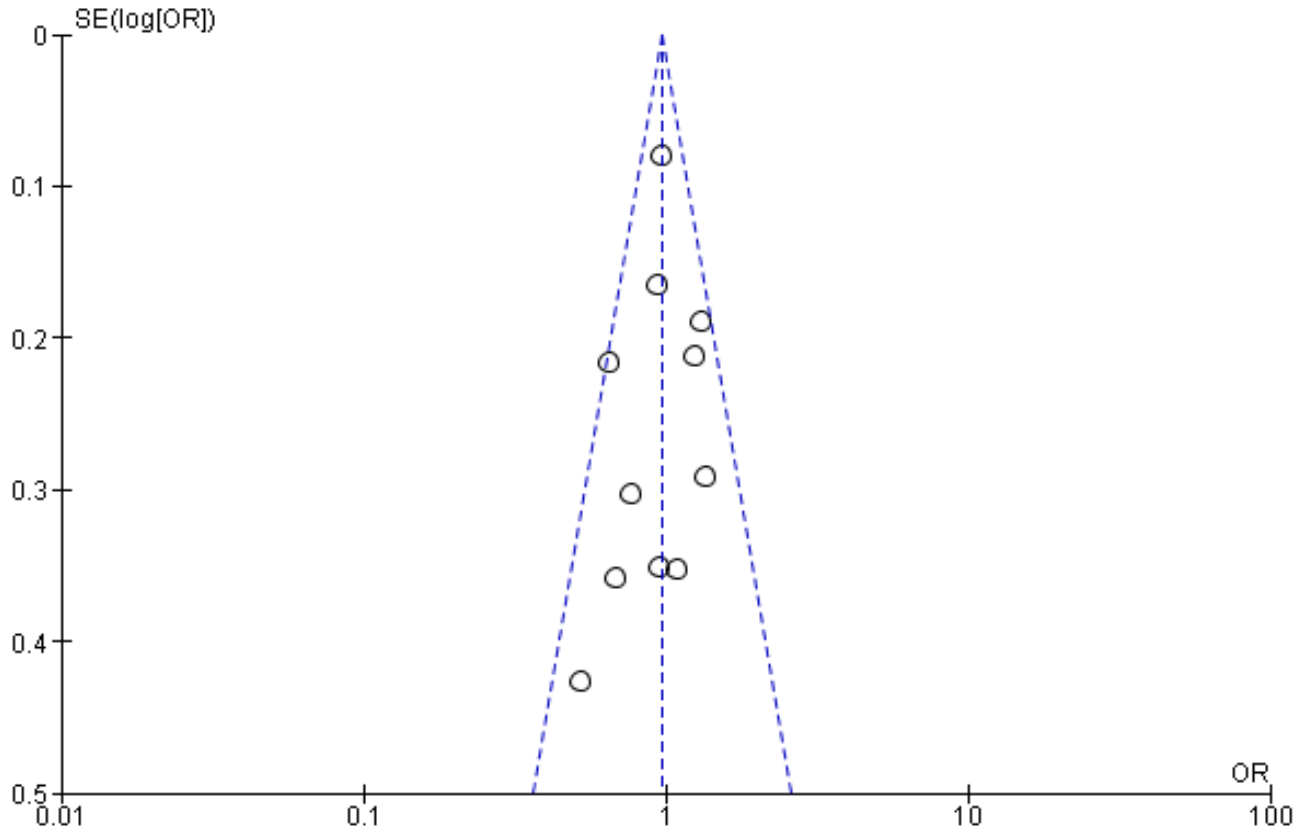


Figure 6.15. Funnel plot of the association between VDR gene *FokI* polymorphism and obesity risk under Ff vs. FF model in overall

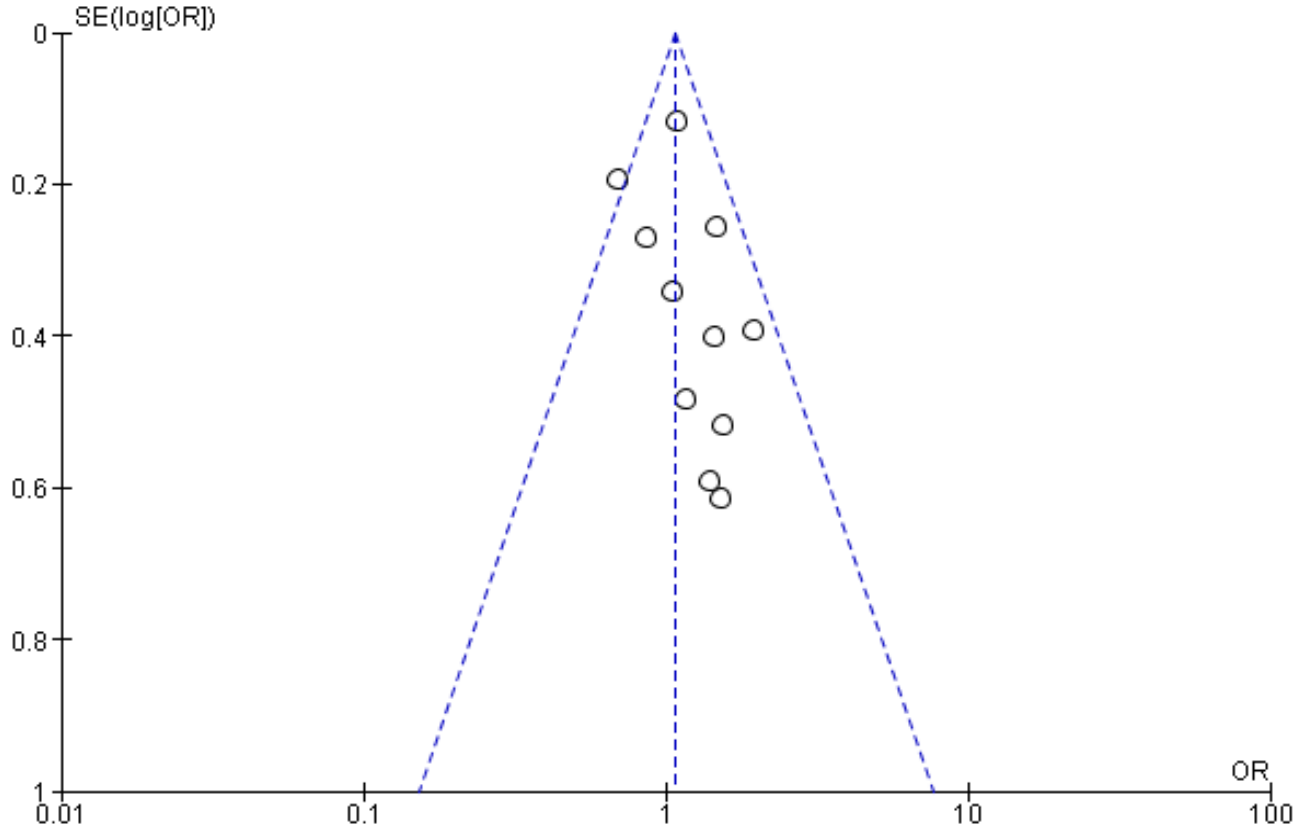


Figure 6.16. Funnel plot of the association between VDR gene *FokI* polymorphism and obesity risk under ff vs. Ff model in overall

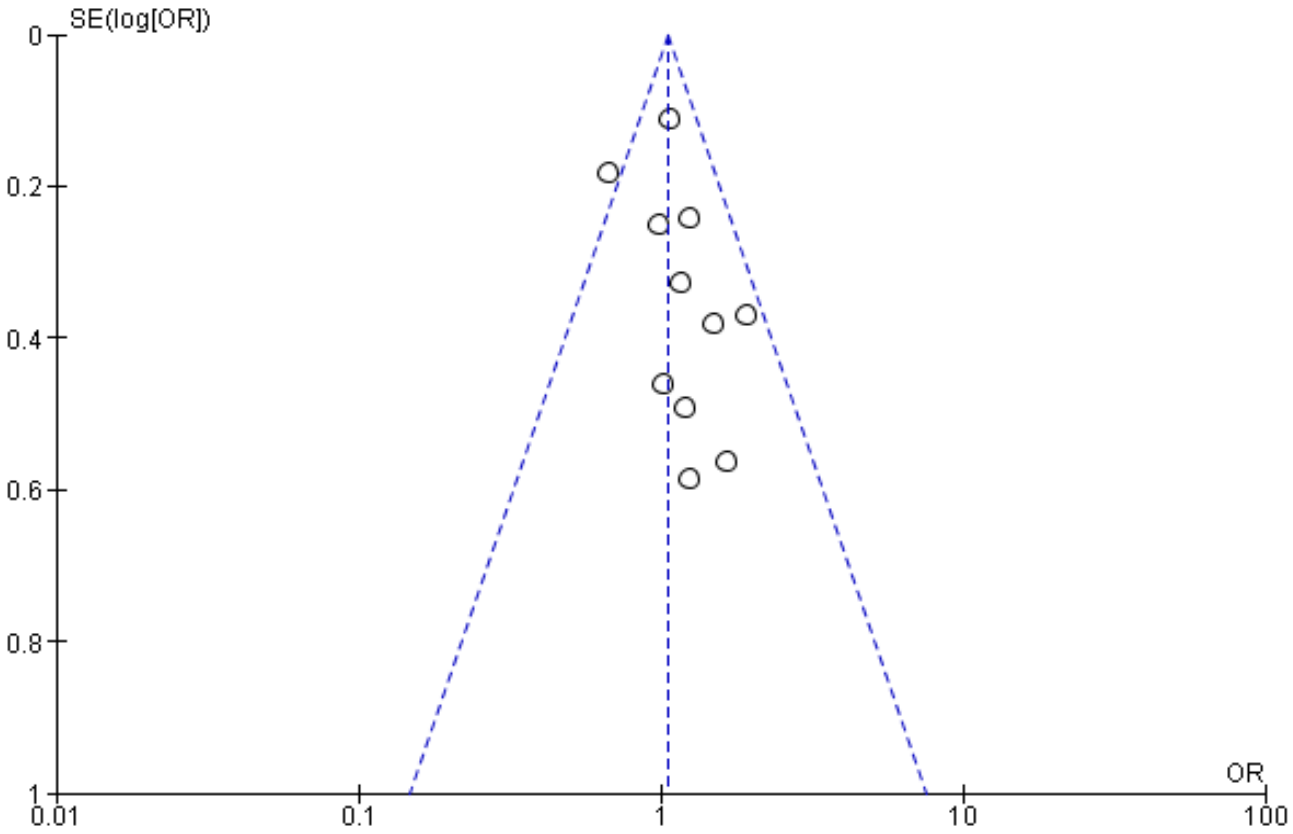


Figure 6.17. Funnel plot of the association between VDR gene *FokI* polymorphism and obesity risk under ff vs. FF+Ff model in overall

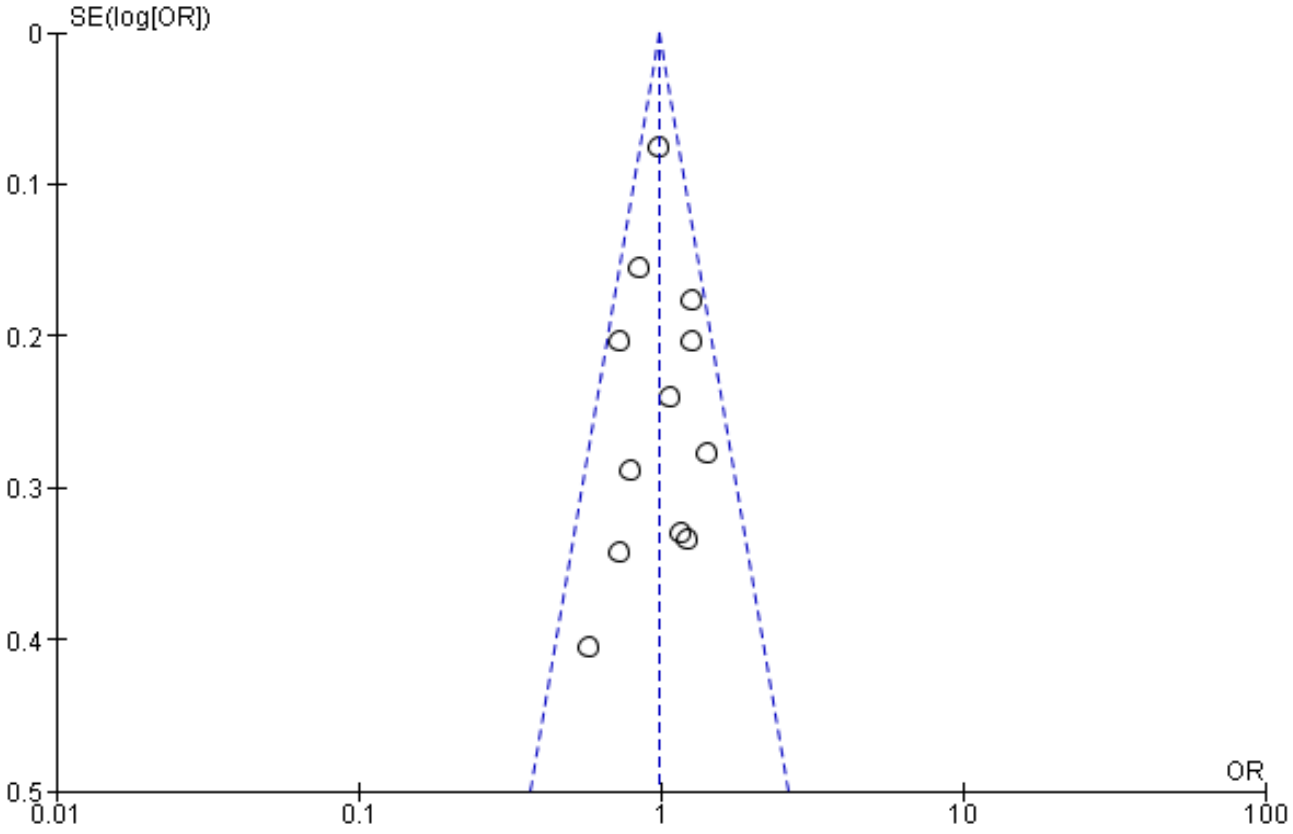


Figure 6.18. Funnel plot of the association between VDR gene *FokI* polymorphism and obesity risk under Ff+ff vs FF model in overall

https://doi.org/10.56294/saludcyt20251072

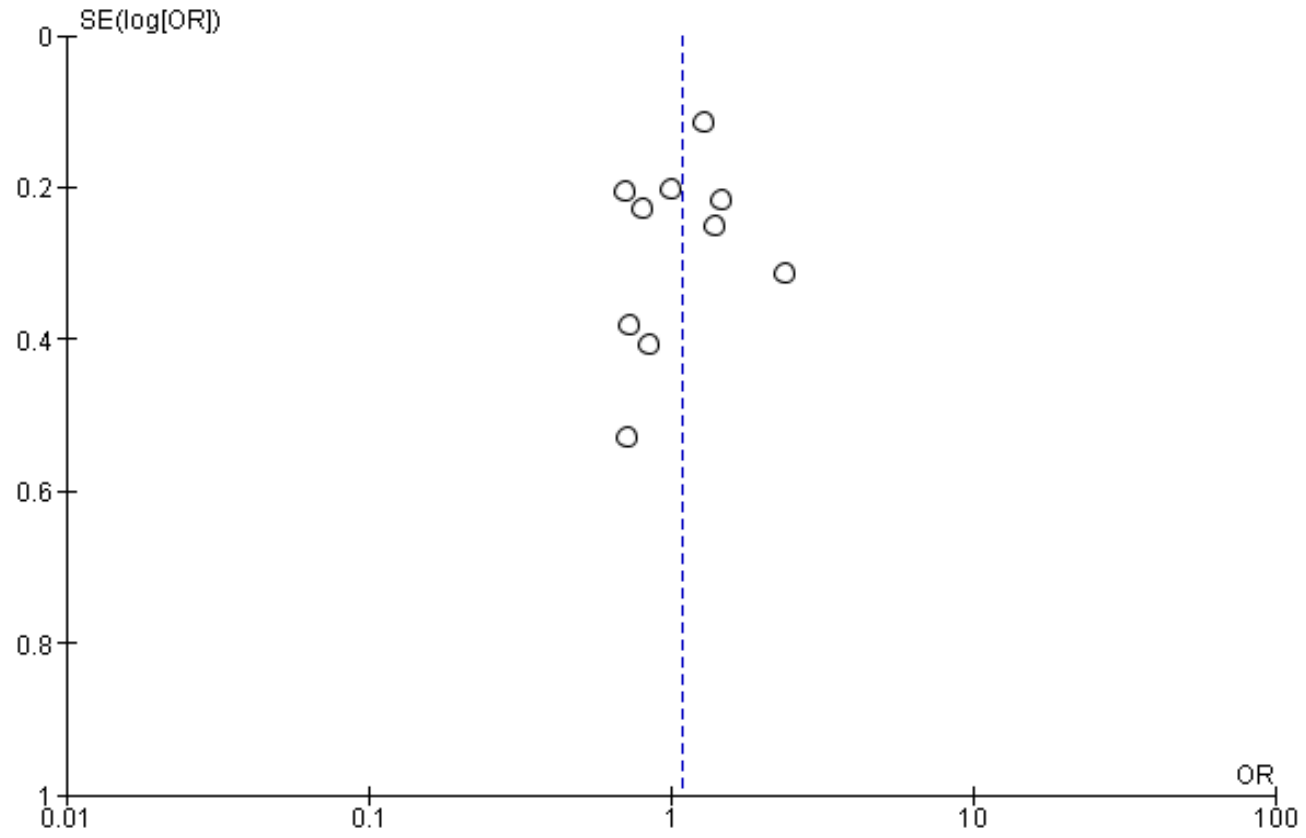


Figure 6.19. Funnel plot of the association between VDR gene *TaqI* polymorphism and obesity risk under t vs. T model in overall

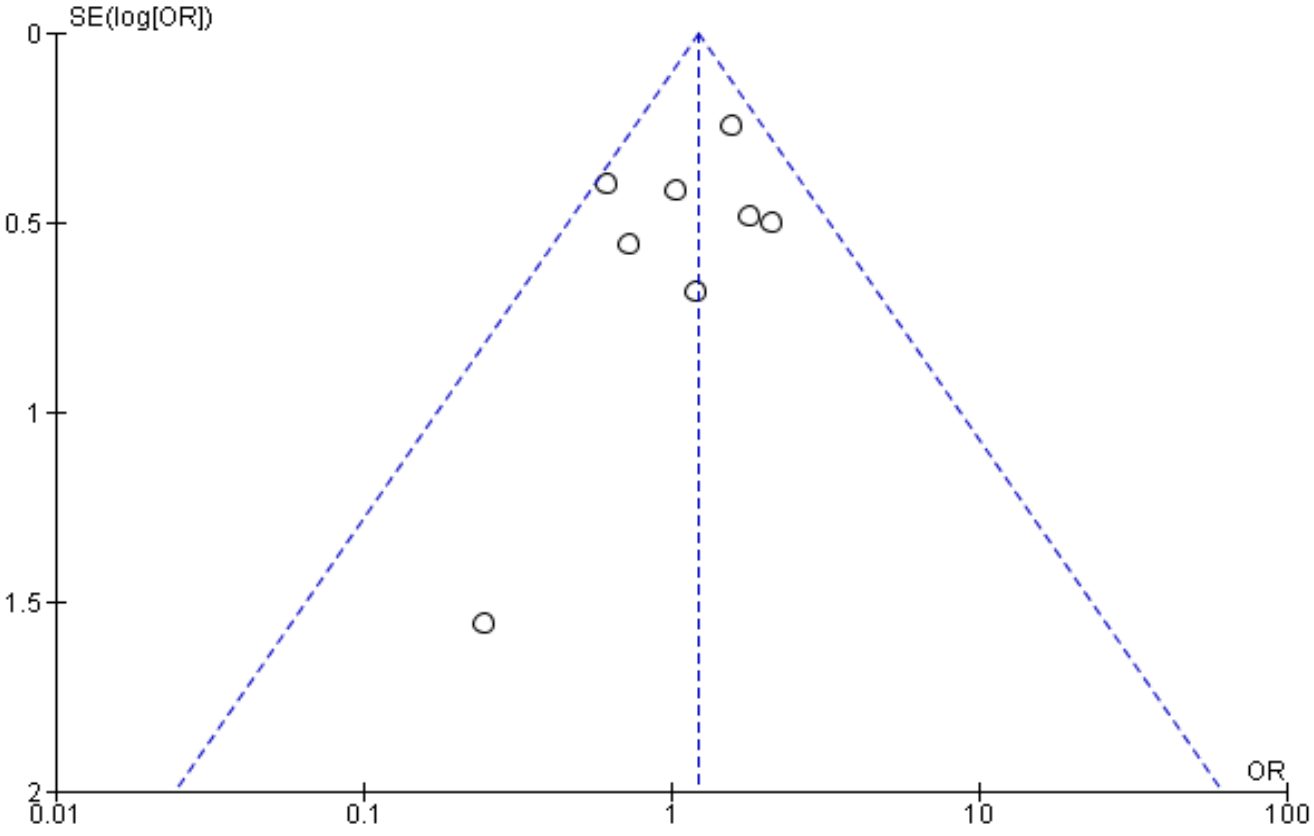


Figure 6.20. Funnel plot of the association between VDR gene *TaqI* polymorphism and obesity risk under tt vs. TT model in overall

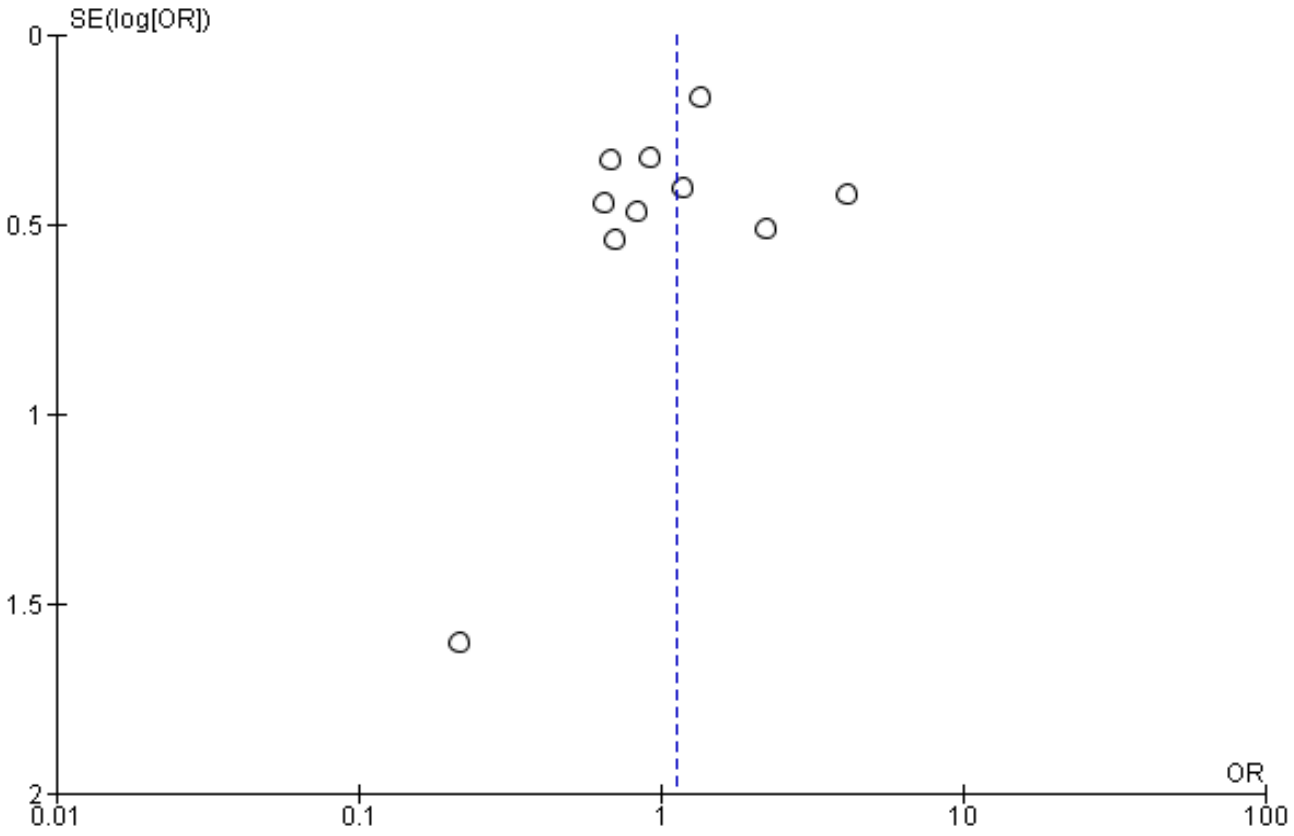


Figure 6.21. Funnel plot of the association between VDR gene *TaqI* polymorphism and obesity risk under Tt vs TT model in overall

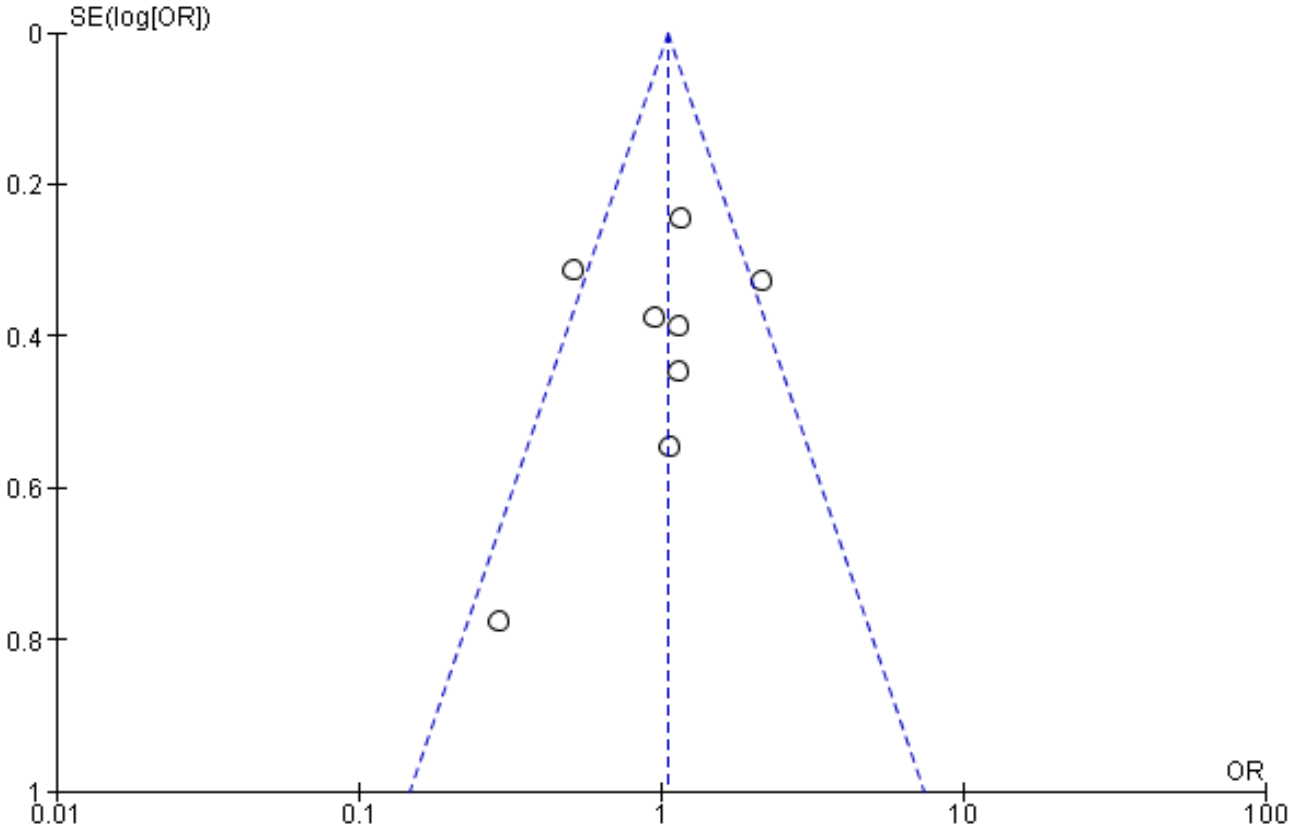


Figure 6.22. Funnel plot of the association between VDR gene *TaqI* polymorphism and obesity risk under tt vs Tt model in overall

https://doi.org/10.56294/saludcyt20251072

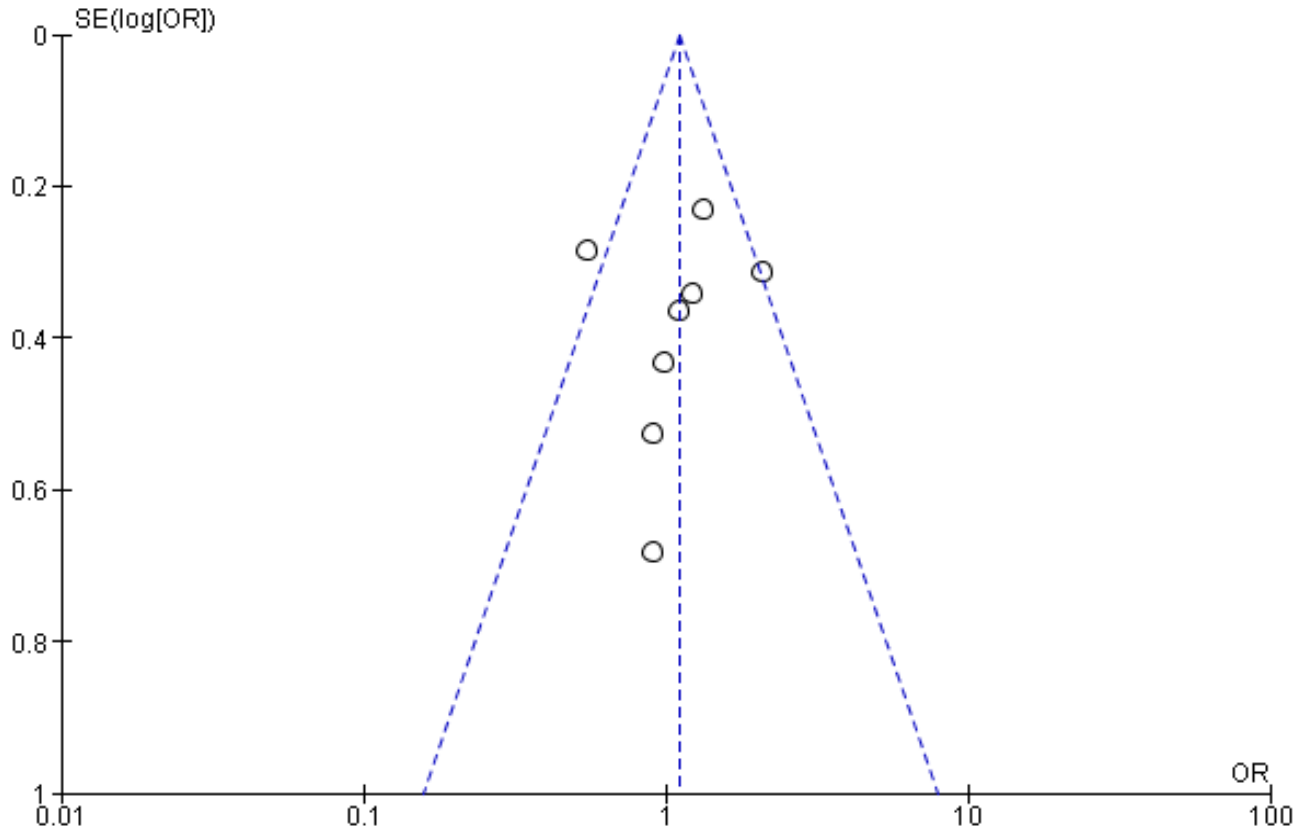


Figure 6.23. Funnel plot of the association between VDR gene *TaqI* polymorphism and obesity risk under tt vs TT + Tt model in overall

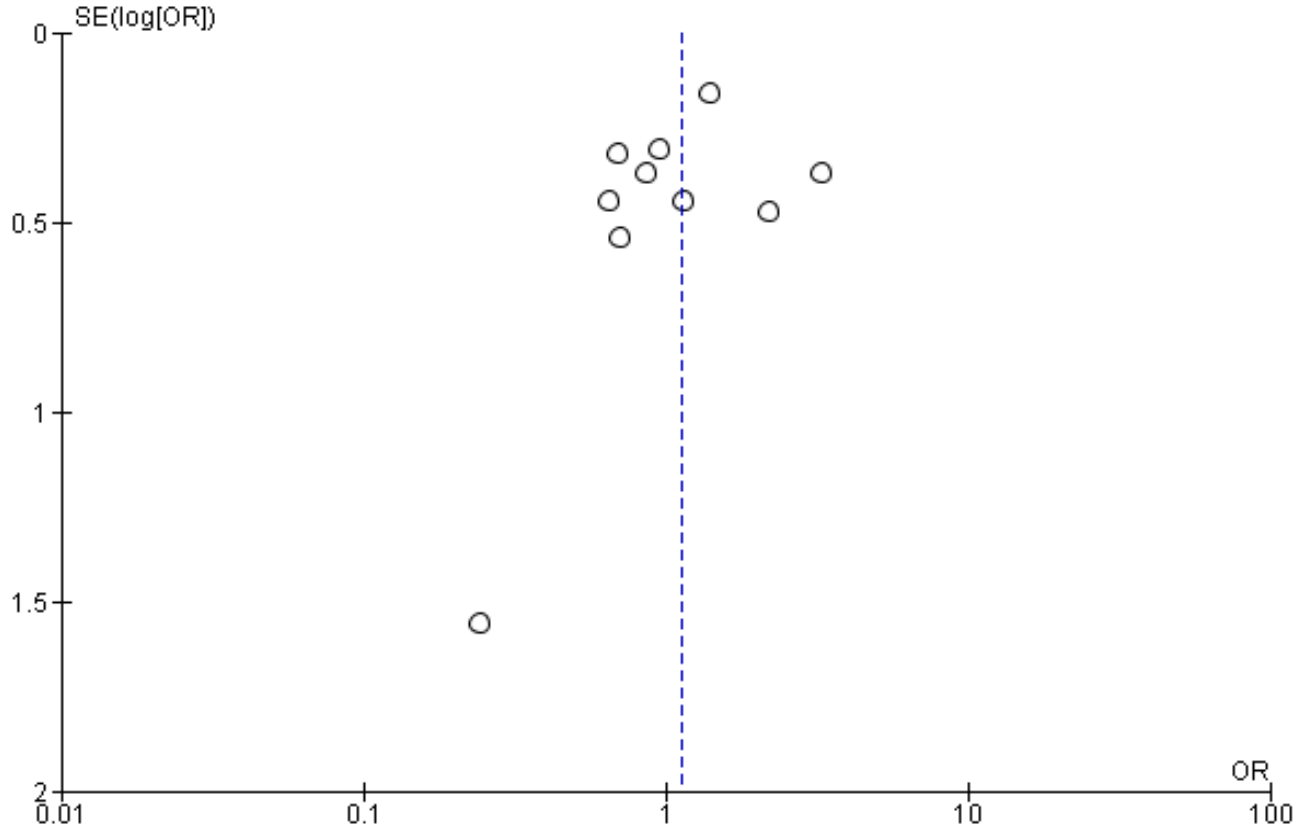


Figure 6.24. Funnel plot of the association between VDR gene *TaqI* polymorphism and obesity risk under Tt + tt vs TT model in overall

https://doi.org/10.56294/saludcyt20251072