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

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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 (Bsml, Fokl, Taql, Apal, 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 Apal polymorphism and reduced obesity risk in homozygous models [aa vs. AA: OR=0,76, CI=0,60-0,97; P=0,03]. The Taql 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 Apal 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.

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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 Apal 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 Taql 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 Apal del VDR puede proteger contra la obesidad en distintas poblaciones. En los europeos, el alelo t del polimorfismo Taql 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⁾ Fokl is found in exon 2, near the 5' untranslated region within the VDR DNA-binding domain. Taql is established in exon 9, while Bsml and Apal 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 Bsml (rs1544410), Taql (rs731236), Apal (rs7975232), Fokl (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 *Bsml* OR *Apal* OR *Fokl* OR *Taql* 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 crosssectional 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/ m², or \geq 25 kg/m², or \geq 25 kg/m² to < 30 kg/m² was categorized as overweight and \geq 28 kg/m² or \geq 30 kg/ m² was classified into obese for adults and not pregnant. While, for children or adolescents, overweight and obesity were defined as \geq 85th to <95th and \geq 95th 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 (Bsml, Fokl, Taql, Apal, 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 Bsml [G (or C) / A (or T)] corresponds to Bsml (b/B), Fokl [A (or T) / G (or C)] corresponds to Fokl (f/F), Taql [G (or T) / A (or C)] corresponds to Taql (t/T), Apal [G (or C) / A (or T)] corresponds to Apal (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 Chi² and the I². A random-effects (heterogeneous, p<0,10 and I²>50 %) or fixed-effects (homogeneous, p>0,10 and I²<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 Bsml polymorphism with obesity risk was assessed by ten studies, ^(17,22,24,25,26,27,28,29,30,31) the VDRApal polymorphism byten studies, ^(17,18,22,27,32,33,34,35,36,37) VDRFokl polymorphism by twelve studies, ^(17,18,24,27,29,32,35,38,39,40,41,42) VDR Taql 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 Sample Case													
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	Fokl, Taql	10		
2.	Bagci, et al. ⁽³²⁾	2023	Cross sectional	Turkey	Adults	139	68	71	Male & Female	PCR-RFLP	Fokl, Taql, Apal	7		
3.	Wang, et al. ⁽¹⁷⁾	2021	Case control	China	Children	191	106	85	Male & Female	PCR sequencing	Bsml, Fokl, Taql, Apal, Cdx2	7		
4.	Zakaria, et al. ⁽²⁴⁾	2021	Case control	Malaysia	Adults	117	54	63	Male & Female	PCR-RFLP	Bsml, Fokl	6		
5.	Hassan, et al. ⁽³³⁾	2021	Cross sectional	Egypt	Adults	97	66	31	Female	PCR-RFLP	Taql, Apal	7		
6.	Bhatt et al. ⁽³⁹⁾	2021	Cross sectional	India	Adults	300	230	70	Male & Female	PCR-TaqMan Genotyping Assay	Fokl, Taql	10		
7.	Rashidi et al. ⁽³⁴⁾	2021	Case control	Iran	Adults	167	87	80	Male & Female	PCR-RFLP	Taql, Apal	6		
8.	Xie, et al. ⁽⁴⁰⁾	2021	Cross sectional	China	Childrens	452	225	227	Male & Female	PCR-RFLP	Fokl	10		
9.	Hussain, et al. ⁽⁴¹⁾	2018	Case control	United Arab Emirates	Adults	340	97	243	Female	PCR-RFLP	Fokl	6		
10.	Rahmadhani, et al. ⁽²⁵⁾	2017	Cross sectional	Malaysia	Children	718	183	535	Male & Female	Sequenom MassARRAY	Bsml	7		
11.	Al-Hazmi, et al. ⁽²²⁾	2017	Case control	Saudi Arabia	Adults	300	200	100	Male	PCR-RFLP	Bsml, Apal	8		
12.	Bagheri, et al. ⁽²⁶⁾	2017	Case control	Iran	Adults	65	38	27	Female	PCR sequencing	Bsml	9		
13.	Bienertová-Vašků, et al. ⁽²⁷⁾	2017	Cross sectional	Czech Republic	Adults	882	511	371	Male & Female	PCR-RFLP	Bsml, Fokl, Taql, Apal	7		
14.	Fan, et al. ⁽³⁵⁾	2015	Case control	China	Adults	529	245	284	Male & Female	PCR-RFLP	Fokl, Apal	9		
15.	Zhou, et al. ⁽¹⁸⁾	2015	Cross sectional	China	Adults	181	99	82	Male	PCR-RFLP	Fokl, Taql, Apal, Cdx2	8		
16.	El-Shal, et al. ⁽³⁶⁾	2013	Case control	Egypt	Adults	300	235	65	Female	PCR-RFLP	Taql, Apal	7		
17.	Vasilopoulos, et al. ⁽¹⁵⁾	2013	Case control	Greece	Adults	184	82	102	Male & Female	PCR -RFLP	Taql	6		
18.	Mahmoudi, et al. ⁽²⁸⁾	2011	Case control	Iran	Adults	904	447	457	Male & Female	PCR-RFLP	Bsml	7		
19.	Mahmoudi, et al. ⁽³⁷⁾	2010	Case control	Iran	Adults	160	68	92	Male & Female	PCR-RFLP	Apal	7		
20.	Slattery, et al. ⁽⁴²⁾	2004	Case control	United States	Adults	3213	2135	1078	Male & Female	PCR-RFLP	Fokl	6		
21.	Tofteng, et al. ⁽²⁹⁾	2002	Cross sectional	Denmark	Adults	429	188	241	Female	PCR-RFLP	Bsml, Fokl	6		
22.	Speer, et al. ⁽³⁰⁾	2001	Case control	Hungary	Adults	167	29	138	Male & Female	PCR-RFLP	Bsml	7		
23.	Geusens, et al. ⁽³¹⁾	1997	Cross sectional	Belgium	Elderly	501	121	380	Female	PCR-RFLP	Bsml	10		
Nota	PCR-RELP - polymerase	chain I	reaction-restriction	on fragment length poly	morphism: N(DS - Newca	stle-Ottawa	Scale						

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 Bsml polymorphism and risk of obesity

		Obes	e	Non ob	ese		Odds Ratio			Odds Ratio
	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year		M-H, Fixed, 95% Cl
	Wang 2021	195	212	152	168	1.7%	1.21 [0.59, 2.47]	2021		_ _
	Zakaria 2021	90	108	107	126	2.0%	0.89 [0.44, 1.79]	2021		
	Al-Hazmi 2017	121	400	49	200	5.6%	1.34 [0.91, 1.97]	2017		
	Bagneri 2017 Bioportové Vočků 2017	45	75	29	54	1.6%	1.32 [0.65, 2.68]	2017		
	Dierieriuva-vasku 2017 Dobrodboni 2017	208	266	066	1070	22.4%	0.95[0.77, 1.17]	2017		_1
	Mahmoudi 2017	520	894	531	914	27.0%	1 00 0 83 1 21	2017		+
	Tofteng 2002	222	376	292	482	12.9%	0.94 [0.71, 1.23]	2002		-
	Speer 2001	29	58	158	276	3.4%	0.75 [0.42, 1.32]	2001		
	Geusens 1997	132	242	422	760	11.4%	0.96 [0.72, 1.29]	1997		-+
	Total (DEN) CIV		2040		4700	400.0%	0.00.00.4.001			
	Total (95% CI)	224.0	3648	2047	4700	100.0%	0.98 [0.89, 1.08]			1
	Hotorogonaity: Chiž = 5.71	2210 2 df = 0 /5	- 0.77	3017 201 – ≊⊢ ∩06					—	
Э	Test for overall effect: 7 =	0.49 (P =	0.63)	7,1 - 0 %	,				0.01	0.1 1 10 100
a		0.40 () -	0.007							Favours [Obese] Favours [Non obese]
		Obes	е	Non ob	ese		Odds Ratio			Odds Ratio
	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year		M-H, Fixed, 95% Cl
-	Wang 2021	92	95	68	68	1.7%	0.19 [0.01, 3.80]	2021	4	
	Zakaria 2021	37	38	47	50	0.6%	2.36 [0.24, 23.65]	2021		
	Bagheri 2017	14	20	5	8	1.2%	1.40 [0.25, 7.83]	2017		
	Bienertová-Vašků 2017	178	245	127	168	23.8%	0.86 [0.55, 1.35]	2017		
	Rahmadhani 2017	115	127	357	383	9.7%	0.70 [0.34, 1.43]	2017		
	Al-Hazmi 2017	23	125	4	59	2.6%	3.10 [1.02, 9.42]	2017		
	Mahmoudi 2011	147	221	148	222	28.6%	0.99 [0.67, 1.47]	2011		
	Fotteng 2002 Speer 2001	63	92	91	131	13.7%	0.95 [0.54, 1.70]	2002		
	Geusens 1997	36	61	113	184	4.070	0.57 [0.19, 1.08]	1997		
	000000101007	50	0.	115	104	10.070	0.00 [0.00, 1.00]	1331		
	Total (95% CI)		1040		1345	100.0%	0.95 [0.77, 1.17]			•
	Total events	713		1006						
I.,	Heterogeneity: Chi ² = 8.10), df = 9 (P	' = 0.52	?); I* = 0%					0.01	0.1 1 10 100
D	Test for overall effect. $\angle =$	0.48 (P =	0.63)							Favours [Obese] Favours [Non obese]
		Ohes	0	Non ob	000		Odde Ratio			Odds Patio
	Study or Subaroup	Obes Events	e Total	Non ob Events	ese Total	Weight	Odds Ratio M-H. Fixed, 95% Cl	Year		Odds Ratio M-H. Fixed, 95% Cl
	Study or Subgroup	Obes Events	e Total 14	Non ob Events	ese Total 16	Weight	Odds Ratio M-H, Fixed, 95% CI	Year 2021	-	Odds Ratio M-H, Fixed, 95% Cl
-	Study or Subgroup Wang 2021 Zakaria 2021	Obes Events 11 16	e Total 14 17	Non ob Events 16 13	ese Total 16 16	Weight 1.7% 0.4%	Odds Ratio M-H, Fixed, 95% CI 0.10 [0.00, 2.12] 3.69 [0.34, 39.84]	Year 2021 2021		Odds Ratio M-H, Fixed, 95% Cl
	Study or Subgroup Wang 2021 Zakaria 2021 Bagheri 2017	Obes Events 11 16 18	ie Total 14 17 24	Non ob Events 16 13 19	ese Total 16 16 22	Weight 1.7% 0.4% 2.3%	Odds Ratio M-H, Fixed, 95% CI 0.10 [0.00, 2.12] 3.69 [0.34, 39.84] 0.47 [0.10, 2.18]	Year 2021 2021 2021 2017		Odds Ratio M-H, Fixed, 95% Cl
-	Study or Subgroup Wang 2021 Zakaria 2021 Bagheri 2017 Bienertová-Vašků 2017	Obes Events 11 16 18 213	ie Total 14 17 24 280	Non ob Events 16 13 19 157	ese Total 16 16 22 198	Weight 1.7% 0.4% 2.3% 20.3%	Odds Ratio M-H, Fixed, 95% Cl 0.10 (0.00, 2.12) 3.69 (0.34, 39.84) 0.47 (0.10, 2.18) 0.83 (0.53, 1.29)	Year 2021 2021 2017 2017	•	Odds Ratio M-H, Fixed, 95% Cl
-	Study or Subgroup Wang 2021 Zakaria 2021 Bagheri 2017 Bienertová-Vašků 2017 Rahmadhani 2017	Obes Events 11 16 18 213 56	e Total 14 17 24 280 68	Non ob Events 16 13 19 157 152	ese Total 16 16 22 198 178	Weight 1.7% 0.4% 2.3% 20.3% 6.9%	Odds Ratio M-H, Fixed, 95% Cl 0.10 (0.00, 2.12) 3.69 (0.34, 39.84) 0.47 (0.10, 2.18) 0.83 (0.53, 1.29) 0.80 (0.38, 1.69)	Year 2021 2021 2017 2017 2017	•	Odds Ratio M-H, Fixed, 95% Cl
-	Study or Subgroup Wang 2021 Zakaria 2021 Bagheri 2017 Bienertová-Vašků 2017 Rahmadhani 2017 Al-Hazmi 2017	Obes Events 11 16 18 213 56 75	e Total 14 17 24 280 68 177	Non ob Events 16 13 19 157 152 41	ese Total 16 16 22 198 178 96	Weight 1.7% 0.4% 2.3% 20.3% 6.9% 14.2%	Odds Ratio M-H, Fixed, 95% Cl 0.10 (0.00, 2.12) 3.69 (0.34, 39.84) 0.47 (0.10, 2.18) 0.83 (0.53, 1.29) 0.80 (0.38, 1.69) 0.99 (0.60, 1.63)	Year 2021 2021 2017 2017 2017 2017	•	Odds Ratio M-H, Fixed, 95% Cl
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-	Study or Subgroup Wang 2021 Zakaria 2021 Bagheri 2017 Bienertová-Vašků 2017 Rahmadhani 2017 Al-Hazmi 2017 Mahmoudi 2011 Tofteng 2002 Speer 2001 Geusens 1997 Total (95% CI)	Obes Events 11 16 18 213 56 75 226 96 13 60	e <u>Total</u> 14 17 24 280 68 177 300 125 21 85 1111	Non ob Events 16 13 19 157 152 41 235 110 66 196	ese <u>Total</u> 16 12 198 178 96 309 150 92 267 1344	Weight 1.7% 0.4% 2.3% 20.3% 6.9% 14.2% 26.4% 10.7% 4.3% 12.9% 100.0%	Odds Ratio M-H, Fixed, 95% Cl 0.10 (0.00, 2.12) 3.69 (0.34, 39.84) 0.47 (0.10, 2.18) 0.83 (0.53, 1.29) 0.80 (0.38, 1.69) 0.99 (0.60, 1.63) 0.99 (0.66, 1.39) 1.20 (0.69, 2.09) 0.64 (0.24, 1.72) 0.87 (0.51, 1.49) 0.91 [0.75, 1.11]	Year 2021 2021 2017 2017 2017 2017 2017 2011 2002 2001 1997	4	Odds Ratio M-H, Fixed, 95% Cl
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-	Study or Subgroup Wang 2021 Zakaria 2021 Bagheri 2017 Bienertová-Vašků 2017 Rahmadhani 2017 Al-Hazmi 2017 Mahmoudi 2011 Tofteng 2002 Speer 2001 Geusens 1997 Total (95% CI) Total events Heterogeneity: Chi ² = 6.0°	Obes Events 11 16 18 213 56 75 226 96 13 60 784 1, df = 9 (F	ee Total 14 17 24 280 68 177 300 125 21 85 1111 2 = 0.74	Non ob Events 16 13 19 157 152 41 235 110 66 196 1005); I² = 0%	ese Total 16 22 198 178 96 309 150 92 267 1344	Weight 1.7% 0.4% 2.3% 20.3% 6.9% 14.2% 26.4% 10.7% 4.3% 12.9% 100.0%	Odds Ratio M-H, Fixed, 95% Cl 0.10 (0.00, 2.12) 3.69 (0.34, 39.84) 0.47 (0.10, 2.18) 0.83 (0.53, 1.29) 0.80 (0.38, 1.69) 0.99 (0.60, 1.63) 0.99 (0.66, 1.39) 1.20 (0.69, 2.09) 0.64 (0.24, 1.72) 0.87 (0.51, 1.49) 0.91 [0.75, 1.11]	Year 2021 2021 2017 2017 2017 2017 2011 2002 2001 1997	← − − − − − − − − − − − − − − − − − − −	Odds Ratio M-H, Fixed, 95% Cl
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с	Study or Subgroup Wang 2021 Zakaria 2021 Bagheri 2017 Bienertová-Vašků 2017 Rahmadhani 2017 Al-Hazmi 2017 Mahmoudi 2011 Tofteng 2002 Speer 2001 Geusens 1997 Total (95% CI) Total events Heterogeneity: Chi² = 6.0° Test for overall effect: Z = Study or Subgroup Wang 2021 Zakaria 2021 Al-Hazmi 2017 Bagheri 2017 Bienertová-Vašků 2017 Rahmadhani 2017 Namadhani 2017 Speer 2001 Ocuracei 2002 Speer 2001 Ocuracei 1007	Obess Events 111 16 18 213 56 75 226 96 13 60 784 1, df = 9 (F 0.94 (P = Obess Events 92 37 23 14 178 115 147 63 8 2 2 2 3 2 2 3 2 2 3 2 2 3 2 3 2 3 2 3 2 3 2 3 3 2 3 3 2 3 3 3 3 2 3 3 3 3 3 3 3 3 3 4 3 5 5 5 5 5 5 5 5 5 5 5 5 5	Total 14 17 24 280 68 177 300 125 21 85 1111 2 103 53 98 322 391 171 373 159 21 21	Non ob Events 16 13 19 157 152 41 235 110 66 196 1005 1); I ² = 0% Non ob Events 68 47 4 5 127 357 148 91 46 127 128 100 1005	ese Total 16 16 22 198 178 96 309 150 92 267 1344 84 60 45 24 284 509 383 201 112 202	Weight 1.7% 0.4% 2.3% 20.3% 6.9% 14.2% 26.4% 10.7% 4.3% 12.9% 100.0% Weight 2.3% 3.8% 1.2% 0.9% 2.3.1% 16.9% 25.5% 14.0% 26.5% 14.0% 26.5% 14.0% 26.5% 14.0% 26.5% 14.0% 26.5% 14.0% 26.5% 14.0% 26.5% 14.0% 26.5% 14.0% 26.5% 14.0% 26.5% 14.0% 26.5% 14.0% 26.5%	Odds Ratio M-H, Fixed, 95% Cl 0.10 (0.00, 2.12) 3.69 (0.34, 39.84) 0.47 (0.10, 2.18) 0.83 (0.53, 1.29) 0.80 (0.38, 1.69) 0.99 (0.60, 1.63) 0.99 (0.66, 1.39) 1.20 (0.69, 2.09) 0.64 (0.24, 1.72) 0.87 (0.51, 1.49) 0.91 [0.75, 1.11] 0.91 [0.75, 1.11] 0.94 (0.27, 1.50) 3.14 (1.02, 9.71) 2.96 (0.88, 9.89) 1.03 (0.76, 1.40) 0.87 (0.60, 1.27) 1.03 (0.77, 1.38) 0.79 (0.52, 1.21) 0.88 (0.34, 2.30) 4.04 (0.27, 1.50) 3.14 (1.02, 9.71) 3.98 (0.34, 2.30) 0.79 (0.52, 1.21) 0.88 (0.34, 2.30) 4.04 (0.27, 1.50) 3.14 (1.02, 9.71) 3.14 (1.02, 9.71)	Year 2021 2017 2017 2017 2017 2017 2011 2002 2001 1997 Year 2021 2021 2021 2017 2017 2017 2017 2017	•	Odds Ratio M-H, Fixed, 95% CI
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с	Study or Subgroup Wang 2021 Zakaria 2021 Bagheri 2017 Bienertová-Vašků 2017 Rahmadhani 2017 Al-Hazmi 2017 Mahmoudi 2011 Tofteng 2002 Speer 2001 Geusens 1997 Total (95% CI) Total events Heterogeneity: Chi² = 6.0° Test for overall effect: Z = Study or Subgroup Wang 2021 Zakaria 2021 AL-Hazmi 2017 Bagheri 2017 Bienertová-Vašků 2017 Rahmadhani 2017 Bagheri 2017 Bienertová-Vašků 2017 Rahmadhani 2017 Geusens 1997 Totle (95% CI)	Obess Events 11 16 18 213 56 75 226 96 13 60 784 1, df = 9 (F 0.94 (P = Obess Events 92 37 23 14 178 115 147 63 8 36	Total 14 17 24 280 68 177 3000 125 121 85 1111 P = 0.74 0.35) re Total 103 53 98 32 391 171 373 159 21 96 1497	Non ob Events 16 13 19 157 152 41 235 110 66 196 1005	ese Total 16 16 22 198 178 96 309 150 92 267 1344 0 9 50 9 267 1344 84 60 45 24 284 509 383 201 112 309 2011	Weight 1.7% 0.4% 2.3% 20.3% 6.9% 14.2% 26.4% 10.7% 4.3% 12.9% 100.0% Weight 2.3% 3.8% 2.5% 14.0% 2.5% 14.0% 2.5% 14.0% 2.6% 9.6% 100.0%	Odds Ratio M-H, Fixed, 95% Cl 0.10 (0.00, 2.12) 3.69 (0.34, 39.84) 0.47 (0.10, 2.18) 0.83 (0.53, 1.29) 0.80 (0.38, 1.69) 0.99 (0.60, 1.63) 0.96 (0.66, 1.39) 1.20 (0.69, 2.09) 0.64 (0.24, 1.72) 0.87 (0.51, 1.49) 0.91 [0.75, 1.11] 0.91 [0.75, 1.11] 0.91 [0.75, 1.11] 0.91 [0.75, 1.11] 1.97 (0.86, 4.51) 0.64 (0.27, 1.50) 3.14 (1.02, 9.71) 2.96 (0.88, 9.89) 1.03 (0.76, 1.40) 0.87 (0.60, 1.27) 1.03 (0.77, 1.38) 0.79 (0.52, 1.21) 0.88 (0.34, 2.30) 1.04 (0.65, 1.67] 1.02 [0.88, 1.18]	Year 2021 2017 2017 2017 2017 2017 2001 1997 Year 2021 2021 2021 2021 2021 2017 2017 2017	¢	Odds Ratio M-H, Fixed, 95% CI
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c .	Study or SubgroupWang 2021Zakaria 2021Bagheri 2017Bienertová-Vašků 2017Rahmadhani 2017Al-Hazmi 2017Mahmoudi 2011Tofteng 2002Speer 2001Geusens 1997Total (95% CI)Total eventsHeterogeneity: Chi² = 6.0°Test for overall effect: Z =Study or SubgroupWang 2021Zakaria 2021Al-Hazmi 2017Bagheri 2017Bienertová-Vašků 2017Rahmadhani 2017Mahmoudi 2011Tofteng 2002Speer 2001Geusens 1997Total (95% CI)Total eventsHeterogeneity: Chi² = 12.3Test for overall effect: Z =	Obess Events 111 16 18 213 56 75 226 96 13 60 784 1, df = 9 (F 0.94 (P = Obess Events 92 37 23 14 178 115 147 63 8 36 713 51, df = 9 0.25 (P =	ret Total 14 17 24 280 68 177 3000 125 111 P = 0.74 0.35) re Total 103 53 98 32 391 171 373 159 21 96 1497 (P = 0.1 0.80)	Non ob Events 16 13 19 157 152 41 235 110 66 196 1005	ese Total 16 16 22 198 178 96 309 150 92 267 1344 0 50 45 24 284 509 383 201 112 309 2011	Weight 1.7% 0.4% 2.3% 20.3% 6.9% 14.2% 26.4% 10.7% 4.3% 12.9% 100.0% Weight 2.3% 3.8% 1.2% 0.9% 23.1% 16.9% 25.5% 14.0% 2.6% 9.6% 100.0%	Odds Ratio M-H, Fixed, 95% Cl 0.10 (0.00, 2.12) 3.69 (0.34, 39.84) 0.47 (0.10, 2.18) 0.83 (0.53, 1.29) 0.80 (0.38, 1.69) 0.99 (0.60, 1.63) 0.96 (0.66, 1.39) 1.20 (0.69, 2.09) 0.64 (0.24, 1.72) 0.87 (0.51, 1.49) 0.91 [0.75, 1.11] 0.91 [0.75, 1.11] 0.91 [0.75, 1.11] 0.92 (0.88, 4.51) 0.64 (0.27, 1.50) 3.14 (1.02, 9.71) 2.96 (0.88, 9.89) 1.03 (0.76, 1.40) 0.87 (0.60, 1.27) 1.03 (0.77, 1.38) 0.79 (0.52, 1.21) 0.88 (0.34, 2.30) 1.04 (0.65, 1.67] 1.02 [0.88, 1.18]	Year 2021 2017 2017 2017 2017 2011 2001 1997 Year 2021 2021 2021 2021 2017 2017 2017 2017	0.01	Odds Ratio M-H, Fixed, 95% CI

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	Obes	e	Non ob	ese		Odds Ratio			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year		M-H, Fixed, 95% CI
Wang 2021	92	106	68	84	2.6%	1.55 [0.71, 3.38]	2021		
Zakaria 2021	37	54	47	63	3.5%	0.74 [0.33, 1.66]	2021		
Rahmadhani 2017	115	183	357	535	17.3%	0.84 [0.59, 1.20]	2017		
Al-Hazmi 2017	23	200	4	100	1.2%	3.12 [1.05, 9.28]	2017		
Bagheri 2017	14	38	5	27	0.9%	2.57 [0.79, 8.30]	2017		+
Bienertová-Vašků 2017	178	458	127	325	23.2%	0.99 [0.74, 1.33]	2017		+
Mahmoudi 2011	147	447	148	457	25.1%	1.02 [0.77, 1.35]	2011		+
Tofteng 2002	63	188	91	241	13.5%	0.83 [0.56, 1.24]	2002		
Speer 2001	8	29	46	138	3.0%	0.76 [0.31, 1.85]	2001		
Geusens 1997	36	121	113	380	9.8%	1.00 [0.64, 1.57]	1997		-
Total (95% CI)		1824		2350	100.0%	0.99 [0.86, 1.14]			•
Total events	713		1006						
Heterogeneity: Chi ² = 10.4	47. df = 9 i	(P = 0.3)	$(1): \vec{r} = 1$	4%				L	<u></u>
Test for overall effect: Z =	0.11 (P =	0.91)						0.01	0.1 1 10 100
									Favours (Obeset Favours (Non obeset
	Obes	e	Non ob	ese		Odds Ratio			Odds Ratio
Study or Subgroup	Obes Events	e Total	Non ob Events	ese Total	Weight	Odds Ratio M-H, Fixed, 95% Cl	Year		Odds Ratio M-H, Fixed, 95% Cl
Study or Subgroup Wang 2021	Obes Events 103	e Total 106	Non ob Events 84	ese Total 84	Weight 1.3%	Odds Ratio M-H, Fixed, 95% Cl 0.17 [0.01, 3.43]	Year 2021	←	Odds Ratio M-H, Fixed, 95% Cl
Study or Subgroup Wang 2021 Zakaria 2021	Obes Events 103 53	e Total 106 54	Non ob Events 84 60	ese Total 84 63	Weight 1.3% 0.4%	Odds Ratio M-H, Fixed, 95% Cl 0.17 [0.01, 3.43] 2.65 [0.27, 26.25]	Year 2021 2021	4	Odds Ratio M-H, Fixed, 95% Cl
Study or Subgroup Wang 2021 Zakaria 2021 Al-Hazmi 2017	Obes Events 103 53 98	e Total 106 54 200	Non ob Events 84 60 45	ese Total 84 63 100	Weight 1.3% 0.4% 13.0%	Odds Ratio M-H, Fixed, 95% Cl 0.17 [0.01, 3.43] 2.65 [0.27, 26.25] 1.17 [0.73, 1.90]	Year 2021 2021 2021 2017		Odds Ratio M-H, Fixed, 95% Cl
Study or Subgroup Wang 2021 Zakaria 2021 Al-Hazmi 2017 Bagheri 2017	Obes Events 103 53 98 32	e Total 106 54 200 38	Non ob Events 84 60 45 24	ese Total 84 63 100 27	Weight 1.3% 0.4% 13.0% 1.9%	Odds Ratio M-H, Fixed, 95% CI 0.17 [0.01, 3.43] 2.65 [0.27, 26.25] 1.17 [0.73, 1.90] 0.67 [0.15, 2.94]	Year 2021 2021 2017 2017		Odds Ratio M-H, Fixed, 95% Cl
Study or Subgroup Wang 2021 Zakaria 2021 Al-Hazmi 2017 Bagheri 2017 Bienertová-Vašků 2017	Obes <u>Events</u> 103 53 98 32 391	e Total 106 54 200 38 458	Non ob Events 84 60 45 24 284	ese Total 84 63 100 27 325	Weight 1.3% 0.4% 13.0% 1.9% 20.6%	Odds Ratio M-H, Fixed, 95% CI 0.17 [0.01, 3.43] 2.65 [0.27, 26.25] 1.17 [0.73, 1.90] 0.67 [0.15, 2.94] 0.84 [0.55, 1.28]	Year 2021 2021 2017 2017 2017		Odds Ratio M-H, Fixed, 95% Cl
Study or Subgroup Wang 2021 Zakaria 2021 Al-Hazmi 2017 Bagheri 2017 Bienertová-Vašků 2017 Rahmadhani 2017	Obes Events 103 53 98 32 391 171	e Total 106 54 200 38 458 183	Non ob Events 84 60 45 24 284 509	ese <u>Total</u> 84 63 100 27 325 535	Weight 1.3% 0.4% 13.0% 1.9% 20.6% 7.2%	Odds Ratio M-H, Fixed, 95% CI 0.17 [0.01, 3.43] 2.65 [0.27, 26.25] 1.17 [0.73, 1.90] 0.67 [0.15, 2.94] 0.84 [0.55, 1.28] 0.73 [0.36, 1.47]	Year 2021 2021 2017 2017 2017 2017	•	Odds Ratio M-H, Fixed, 95% Cl
Study or Subgroup Wang 2021 Zakaria 2021 Al-Hazmi 2017 Bagheri 2017 Bienertová-Vašků 2017 Rahmadhani 2017 Mahmoudi 2011	Obes Events 103 53 98 32 391 171 373	e Total 106 54 200 38 458 183 447	Non ob Events 84 60 45 24 284 509 383	ese Total 84 63 100 27 325 535 457	Weight 1.3% 0.4% 13.0% 1.9% 20.6% 7.2% 26.5%	Odds Ratio M-H, Fixed, 95% CI 0.17 [0.01, 3.43] 2.65 [0.27, 26.25] 1.17 [0.73, 1.90] 0.67 [0.15, 2.94] 0.84 [0.55, 1.28] 0.73 [0.36, 1.47] 0.97 [0.68, 1.39]	Year 2021 2021 2017 2017 2017 2017 2017 2011	4	Odds Ratio M-H, Fixed, 95% Cl
Study or Subgroup Wang 2021 Zakaria 2021 Al-Hazmi 2017 Bagheri 2017 Bienertová-Vašků 2017 Rahmadhani 2017 Mahmoudi 2011 Tofteng 2002	Obes <u>Events</u> 103 53 98 32 391 171 373 159	e Total 106 54 200 38 458 183 447 188	Non ob Events 84 60 45 24 284 509 383 201	ese Total 84 63 100 27 325 535 535 457 241	Weight 1.3% 0.4% 13.0% 1.9% 20.6% 7.2% 26.5% 11.5%	Odds Ratio M-H, Fixed, 95% CI 0.17 [0.01, 3.43] 2.65 [0.27, 26.25] 1.17 [0.73, 1.90] 0.67 [0.15, 2.94] 0.84 [0.55, 1.28] 0.73 [0.36, 1.47] 0.97 [0.68, 1.39] 1.09 [0.65, 1.84]	Year 2021 2021 2017 2017 2017 2017 2017 2011 2002	4	Odds Ratio M-H, Fixed, 95% Cl
Study or Subgroup Wang 2021 Zakaria 2021 Al-Hazmi 2017 Bagheri 2017 Bienertová-Vašků 2017 Rahmadhani 2017 Mahmoudi 2011 Tofteng 2002 Speer 2001	Obes Events 103 53 98 32 391 171 373 159 21	e Total 106 54 200 38 458 183 447 188 29	Non ob Events 84 60 45 24 284 509 383 201 112	ese Total 84 63 100 27 325 535 457 241 138	Weight 1.3% 0.4% 13.0% 20.6% 7.2% 26.5% 11.5% 4.5%	Odds Ratio M-H, Fixed, 95% CI 0.17 [0.01, 3.43] 2.65 [0.27, 26.25] 1.17 [0.73, 1.90] 0.67 [0.15, 2.94] 0.84 [0.55, 1.28] 0.73 [0.36, 1.47] 0.97 [0.68, 1.39] 1.09 [0.65, 1.84] 0.61 [0.24, 1.53]	Year 2021 2021 2017 2017 2017 2017 2017 2011 2002 2001	4	Odds Ratio M-H, Fixed, 95% Cl
Study or Subgroup Wang 2021 Zakaria 2021 Al-Hazmi 2017 Bagheri 2017 Bienertová-Vašků 2017 Rahmadhani 2017 Mahmoudi 2011 Tofteng 2002 Speer 2001 Geusens 1997	Obes Events 103 53 98 32 391 171 373 159 21 96	re Total 106 54 200 38 458 183 447 188 29 121	Non ob Events 84 60 45 24 284 509 383 201 112 309	ese Total 84 63 100 27 325 535 535 457 241 138 380	Weight 1.3% 0.4% 13.0% 1.9% 20.6% 7.2% 26.5% 11.5% 4.5% 13.1%	Odds Ratio M-H, Fixed, 95% CI 0.17 [0.01, 3.43] 2.65 [0.27, 26.25] 1.17 [0.73, 1.90] 0.67 [0.15, 2.94] 0.84 [0.55, 1.28] 0.73 [0.36, 1.47] 0.97 [0.68, 1.39] 1.09 [0.65, 1.84] 0.61 [0.24, 1.53] 0.88 [0.53, 1.47]	Year 2021 2021 2017 2017 2017 2017 2017 2011 2002 2001 1997	<u>ـــــ</u>	Odds Ratio M-H, Fixed, 95% Cl
Study or Subgroup Wang 2021 Zakaria 2021 AI-Hazmi 2017 Bagheri 2017 Bienertová-Vašků 2017 Rahmadhani 2017 Mahmoudi 2011 Tofteng 2002 Speer 2001 Geusens 1997 Total (95% CI)	Obes Events 103 53 98 32 391 171 373 159 21 96	e Total 106 54 200 38 458 183 447 188 29 121 1824	Non ob <u>Events</u> 84 60 45 24 284 509 383 201 112 309	ese Total 84 63 100 27 325 535 457 241 138 380 2350	Weight 1.3% 0.4% 13.0% 1.9% 20.6% 7.2% 26.5% 11.5% 4.5% 13.1% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.17 [0.01, 3.43] 2.65 [0.27, 26.25] 1.17 [0.73, 1.90] 0.67 [0.15, 2.94] 0.84 [0.55, 1.28] 0.73 [0.36, 1.47] 0.97 [0.68, 1.39] 1.09 [0.65, 1.84] 0.61 [0.24, 1.53] 0.88 [0.53, 1.47] 0.93 [0.78, 1.12]	Year 2021 2021 2017 2017 2017 2017 2011 2002 2001 1997	4	Odds Ratio M-H, Fixed, 95% CI
Study or Subgroup Wang 2021 Zakaria 2021 AI-Hazmi 2017 Bagheri 2017 Bienertová-Vašků 2017 Rahmadhani 2017 Mahmoudi 2011 Tofteng 2002 Speer 2001 Geusens 1997 Total (95% CI) Total events	Obes <u>Events</u> 103 53 98 32 391 171 373 159 21 96 1497	re Total 106 54 200 38 458 183 447 188 29 121 1824	Non ob Events 84 60 45 24 284 509 383 201 112 309 2011	ese Total 84 63 100 27 325 535 457 241 138 380 2350	Weight 1.3% 0.4% 13.0% 1.9% 20.6% 7.2% 26.5% 11.5% 4.5% 13.1% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.17 [0.01, 3.43] 2.65 [0.27, 26.25] 1.17 [0.73, 1.90] 0.67 [0.15, 2.94] 0.84 [0.55, 1.28] 0.73 [0.36, 1.47] 0.97 [0.68, 1.39] 1.09 [0.65, 1.84] 0.61 [0.24, 1.53] 0.88 [0.53, 1.47] 0.93 [0.78, 1.12]	Year 2021 2021 2017 2017 2017 2017 2011 2002 2001 1997	4	Odds Ratio M-H, Fixed, 95% CI
Study or Subgroup Wang 2021 Zakaria 2021 Al-Hazmi 2017 Bagheri 2017 Bienertová-Vašků 2017 Rahmadhani 2017 Mahmoudi 2011 Tofteng 2002 Speer 2001 Geusens 1997 Total (95% CI) Total events Heterogeneity: Chi ² = 5.06	Obes <u>Events</u> 103 53 98 32 391 171 373 159 21 96 1497 5, df = 9 (F	e <u>Total</u> 106 54 200 38 458 183 447 188 29 121 1824 P = 0.83	Non ob Events 84 60 45 24 284 509 383 201 112 309 2011); I ² = 0%	ese <u>Total</u> 84 63 100 27 325 535 457 241 138 380 2350	Weight 1.3% 0.4% 13.0% 1.9% 20.6% 7.2% 26.5% 11.5% 4.5% 13.1% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.17 [0.01, 3.43] 2.65 [0.27, 26.25] 1.17 [0.73, 1.90] 0.67 [0.15, 2.94] 0.84 [0.55, 1.28] 0.73 [0.36, 1.47] 0.97 [0.68, 1.39] 1.09 [0.65, 1.84] 0.61 [0.24, 1.53] 0.88 [0.53, 1.47] 0.93 [0.78, 1.12]	Year 2021 2021 2017 2017 2017 2017 2011 2002 2001 1997	↓	Odds Ratio M-H, Fixed, 95% CI

Figure 2. Forest plot of the association between VDR gene Bsml 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 Apal polymorphism and risk of obesity

The association between VDR Apal 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 Apal 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 Apal polymorphism and the risk of obesity (table 3, annexes).

	Obes	e	Non Ob	ese		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	M-H, Fixed, 95% CI
Bagci 2021	40	136	41	142	4.6%	1.03 [0.61, 1.72]	2021	
Hassan 2021	23	132	6	62	1.1%	1.97 [0.76, 5.12]	2021	
Rashidi 2021	52	174	68	160	8.1%	0.58 [0.37, 0.91]	2021	
Wang 2021	141	210	127	170	7.5%	0.69 [0.44, 1.09]	2021	
Al-Hazmi 2017	158	400	88	200	11.6%	0.83 [0.59, 1.17]	2017	
BienertovÃ-Vasku 2017	384	814	283	558	29.0%	0.87 [0.70, 1.08]	2017	-
Fan 2015	322	490	352	568	18.3%	1.18 [0.91, 1.51]	2015	+
Zhou 2014	67	198	43	164	5.1%	1.44 [0.91, 2.27]	2014	+
El-Shal 2013	160	470	49	130	8.3%	0.85 [0.57, 1.28]	2013	
Mahmoudi 2010	57	136	80	184	6.5%	0.94 [0.60, 1.47]	2010	-
Total (95% CI)		3160		2338	100.0%	0.93 [0.83, 1.05]		•
Total events	1404		1137					
Heterogeneity: Chi ² = 16.33, df = 9 (P = 0.06); I ² = 45%								
Test for overall effect: Z =	1.16 (P =	0.25)						Eavours [obese] Eavours [non obese]





347

303



Total events

10

100

0.1

0.01

f

g

а

Bagci 2021

Hassan 2021

Al-Hazmi 2017

BienertovÄ-Vasku 2017

	Obe	se	Non Ob	ese	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	87	12	80	5.1%	0.42 [0.15, 1.18]	2021			
Wang 2021	50	105	44	85	11.2%	0.85 [0.48, 1.50]	2021			
Bagci 2021	3	68	5	71	2.1%	0.61 [0.14, 2.65]	2021			
Hassan 2021	1	66	0	31	0.3%	1.44 [0.06, 36.42]	2021			
Al-Hazmi 2017	38	200	22	100	10.5%	0.83 [0.46, 1.50]	2017	·		
BienertovÃ-Vasku 2017	89	407	71	279	29.0%	0.82 [0.57, 1.17]	2017	·		
Fan 2015	111	245	110	284	24.6%	1.31 [0.93, 1.85]	2015	; + -		
Zhou 2014	8	99	7	82	3.1%	0.94 [0.33, 2.72]	2014	· · · · · · · · · · · · · · · · · · ·		
El-Shal 2013	25	235	15	65	9.3%	0.40 [0.19, 0.81]	2013	·		
Mahmoudi 2010	16	68	17	92	4.9%	1.36 [0.63, 2.93]	2010	·		
Total (95% CI)		1580		1169	100.0%	0.91 [0.76, 1.10]		•		
Total events	347		303							
Heterogeneity: Chi ² = 13.	53, df = 9	(P = 0.1)	14); I ² = 3	3%						
Test for overall effect: Z =	0.96 (P =	0.34)								
	Obese	1	Non Obes	e		Odds Ratio		Odds Ratio		
Study or Subgroup	Events T	fotal E	vents T	otal V	/eight N	I-H, Random, 95% CI	Year	M-H, Random, 95% CI		
Rashidi 2021	46	87	56	80 1	0.0%	0.48 [0.25, 0.91]	2021			
Wang 2021	91	105	83	85	3.1%	0.16 [0.03, 0.71]	2021			

Fan 2015 1.08 [0.66, 1.76] 2015 211 245 242 284 12.5% Zhou 2014 59 99 36 82 10.7% 1.88 [1.04, 3.41] 2014 El-Shal 2013 135 235 34 65 11.4% 1.23 [0.71, 2.14] 2013 Mahmoudi 2010 0.70 [0.36, 1.35] 2010 41 68 63 92 9.7% Total (95% CI) 1580 1169 100.0% 0.93 [0.70, 1.25] Total events 1057 834 Heterogeneity: Tau² = 0.12; Chi² = 20.70, df = 9 (P = 0.01); l² = 57% 0.01 0.1 10 100 Test for overall effect: Z = 0.46 (P = 0.64) Favours [Obese] Favours [Non obese]

1.16 [0.60, 2.26] 2021

2.08 [0.75, 5.82] 2021

0.77 [0.47, 1.28] 2017

0.83 [0.59, 1.18] 2017

Figure 3. Forest plot of the association between VDR gene Apal 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 Fokl polymorphism and risk of obesity

37

22

120

295

68

66

200

407

36

6

66

212

71

31

100

279

9.6%

5.7%

12.3%

15.0%

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).

	Obes	e	Non Obese		Odds Ratio			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	M-H, Fixed, 95% Cl
Gariballa 2023	128	402	45	130	3.5%	0.88 [0.58, 1.34]	2023	
Bagci 2021	21	68	24	71	1.2%	0.88 [0.43, 1.78]	2021	
Bhatt 2021	133	460	32	140	2.7%	1.37 [0.88, 2.14]	2021	<u>+</u>
Wang 2021	102	210	65	150	3.0%	1.24 [0.81, 1.88]	2021	
Xie 2021	96	224	101	226	4.4%	0.93 [0.64, 1.35]	2021	
Zakaria 2021	45	108	56	126	2.3%	0.89 [0.53, 1.50]	2021	
Bienertová-Vašků 2017	378	920	299	650	15.8%	0.82 [0.67, 1.00]	2017	-
Fan 2015	178	490	191	568	8.6%	1.13 [0.87, 1.45]	2015	+-
Zhou 2015	50	99	36	82	1.5%	1.30 [0.72, 2.35]	2015	
Slattery 2004	1565	4270	788	2156	50.7%	1.00 [0.90, 1.12]	2004	•
Tofteng 2002	129	358	147	452	6.3%	1.17 [0.87, 1.57]	2002	+
Total (95% CI)		7609		4751	100.0%	1.01 [0.93, 1.09]		4
Total events	2825		1784					
Heterogeneity: Chi ² = 10.2	.42); I ² = 3	2%						
Test for overall effect: Z =					0.0	Favours [Obese] Eavours [Non obese]		
								Favours iobeser Favours involi obeser



 Total events
 2470
 1699

 Heterogeneity: Chi^z = 12.22, df = 11 (P = 0.35); l^z = 10%
 P
 Test for overall effect: Z = 0.28 (P = 0.78)

109

179

4098

125

226

2809 100.0%

5.8%

1.26 [0.84, 1.87] 2002

0.99 [0.89, 1.09]



Tofteng 2002

Total (95% CI)

f

а

b

	Obes	se	Non Ob	ese	Odds Ratio			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	M-H, Fixed, 95% Cl
Gariballa 2023	22	201	7	65	2.6%	1.02 [0.41, 2.51]	2023	3
Wang 2021	25	105	13	75	3.2%	1.49 [0.71, 3.15]	2021	
Xie 2021	46	225	39	227	8.7%	1.24 [0.77, 1.99]	2021	
Zakaria 2021	10	54	10	63	2.1%	1.20 [0.46, 3.16]	2021	
Bagci 2021	7	68	6	71	1.5%	1.24 [0.40, 3.91]	2021	
Bhatt 2021	21	230	4	70	1.6%	1.66 [0.55, 5.00]	2021	
Bienertová-Vašků 2017	75	460	73	325	20.1%	0.67 [0.47, 0.96]	2017	
Fan 2015	34	245	40	284	8.9%	0.98 [0.60, 1.61]	2015	; –
Zhou 2015	28	99	14	82	3.1%	1.92 [0.93, 3.95]	2015	; +
Slattery 2004	281	2135	134	1078	43.4%	1.07 [0.86, 1.33]	2004	↓
Tofteng 2002	20	179	22	226	4.8%	1.17 [0.61, 2.21]	2002	2
Total (95% CI)		4001		2566	100.0%	1.05 [0.91, 1.22]		•
Total events	569		362					
Heterogeneity: Chi ² = 10.90, df = 10 (P = 0.37); l ² = 8%								
Test for overall effect: Z = 0.70 (P = 0.48)								U.UT U.T 1 10 100 Favours [Obese] Favours [Non obese]

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 Taql polymorphism and risk of obesity

Ten studies with 1685 cases and 1022 controls were included to determine the association between *Taql* 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 *Taql* polymorphism and the risk of obesity in all genetic models (figure 5). Furthermore, subgroup analysis was performed based on ethnicity. *Taql* 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.

	Obes	se	Non ob	ese		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
Gariballa 2023	177	402	57	130	12.6%	1.01 [0.68, 1.50]	2023	
Bagci 2021	92	136	85	142	10.4%	1.40 [0.86, 2.29]	2021	+
Bhatt 2021	90	460	13	140	8.1%	2.38 [1.28, 4.40]	2021	_
Hassan 2021	23	132	14	62	6.3%	0.72 [0.34, 1.53]	2021	
Rashidi 2021	58	174	61	160	11.4%	0.81 [0.52, 1.27]	2021	
Wang 2021	196	212	159	170	5.8%	0.85 [0.38, 1.88]	2021	
Bienertová-Väsků 2017	315	804	184	550	17.3%	1.28 [1.02, 1.61]	2017	-
Zhou 2014	7	198	8	164	3.8%	0.71 [0.25, 2.01]	2015	
El-Shal 2013	268	470	85	130	12.4%	0.70 [0.47, 1.05]	2013	
Vasilopoulos 2013	109	164	117	204	11.9%	1.47 [0.96, 2.26]	2013	
Total (95% CI)		3152		1852	100.0%	1.09 [0.87, 1.36]		•
Total events	1335		783					-
Heterogeneity: Tau ² = 0.08	6; Chi² = 1	19.36, d	if = 9 (P =	0.02);	²= 54%			
Test for overall effect: Z =	0.74 (P =	0.46)						Favours [Obese] Favours [Non obese]

	Obes	se	Non ob	ese		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Fixed, 95% CI
Gariballa 2023	40	104	12	32	14.0%	1.04 [0.46, 2.36]	2023	_ _
Bhatt 2021	9	158	3	63	5.0%	1.21 [0.32, 4.62]	2021	
Rashidi 2021	8	45	8	35	9.2%	0.73 [0.24, 2.19]	2021	
Wang 2021	92	94	74	74	2.7%	0.25 [0.01, 5.25]	2021	
Bagci 2021	32	40	30	46	6.9%	2.13 [0.80, 5.71]	2021	+
Bienertová-Väsků 2017	62	211	33	157	33.2%	1.56 [0.96, 2.54]	2017	⊢ ∎
El-Shal 2013	78	123	31	42	21.0%	0.62 [0.28, 1.34]	2013	
Vasilopoulos 2013	37	47	29	43	8.0%	1.79 [0.69, 4.60]	2013	+
Total (95% CI)		822		492	100.0%	1.22 [0.91, 1.64]		•
Total events	358		220					
Heterogeneity: Chi ² = 7.88	6, df = 7 (F	P = 0.34	4); I ² = 119	%				
Test for overall effect: Z =	1.31 (P =	0.19)						Eavours [Obese] Eavours [Non obese]



Figure 5. Forest plot of the association between VDR gene Taql 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.

SNPsAuguified studiesTest of association (P)ModelTest of heterogenee (P-value)Test of heterogenee (P-value)ItBsmlb vs. B100,98 [0,89 - 1,08]0,63F0,770Bb vs. BB100,95 [0,77 - 1,17]0,63F0,740Bb vs. BB100,91 [0,75 - 1,11]0,35F0,740bb vs. Bb100,91 [0,75 - 1,11]0,35F0,19128bb vs. Bb100,99 [0,86 - 1,14]0,91F0,3114Bb+bb vs. BB100,93 [0,78 - 1,12]0,45F0,830Apala vs. A100,93 [0,78 - 1,12]0,45F0,06645a vs. AA100,93 [0,70 - 1,34]0,83R0,00661a vs. AA100,96 [0,70 - 1,34]0,83R0,00661a vs. AA100,91 [0,76 - 1,10]0,45F0,11433Aa vs. AA100,91 [0,76 - 1,10]0,45F0,14433Aa+aa vs. AA100,91 [0,76 - 1,10]0,45F0,14433Aa+aa vs. AA100,91 [0,76 - 1,10]0,45F0,14434Fi fi vs. FF111,02 [0,87 - 1,20]0,46F0,2619ff vs. FF111,02 [0,87 - 1,20]0,45F0,3311ff vs. FF+FF111,05 [0,91 - 1,22]0,46F0,3411 <tr< th=""></tr<>
SNPs Comparisons Guillined studies OR [95 % C] p Model heterogeneity Bsml b vs. B 10 0,98 [0,89 - 1,08] 0,63 F 0,77 0 Bsml b 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 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 Apal a vs. A 10 0,93 [0,78 - 1,12] 0,45 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 [0,70 - 1,25] 0,64 R 0,14 33 Aa+aa vs. AA 10 0,91 [0,76 - 1,10] 0,34
OR [95 % C] p p-value I² (%) Bsml 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 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 Apal a vs. A 10 0,93 [0,78 - 1,12] 0,45 F 0,83 0 Apal a vs. A 10 0,76 [0,60 - 0,97] 0,03* F 0,17 30 Aa vs. AA 10 0,96 [0,77 - 1,34] 0,83 R 0,006 61 aa vs. AA 10 0,91 [0,76 - 1,10] 0,34 F 0,14 33 <
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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												
	Ethnicity												
SNPs	Comparisons		Asian		European								
		Ν	OR (95 % CI)	Р	Ν	OR (95 % CI)	Р						
Bsml	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
Apal	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
Fokl	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
Taql	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 Apal (rs7975232) and Taql (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 Bsml, Fokl and Cdx2 polymorphisms. However, this study presented that the Apal 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 Apal 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 Apal 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 (Apal) 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 Apal 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 F2 α , respectively.⁽⁵²⁾ Vitamin D alleviates oxidative stress and suppresses the nuclear factor-kappa β (NF-k β) 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 Apal 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 Apal 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 Taql 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 TagI 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 Tagl 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 Tagl 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 *Apal* gene polymorphism as a protective effect on obesity in all the studied populations and t allele of VDR *Taql* 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 *Apal* genotype for the studied populations and *Taql* genotype for European population.

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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 Bsml polymorphism

	Obes	bese Non obese		Odds Ratio			Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	M-H, Fixed, 95% Cl
Wang 2021	195	212	152	168	3.4%	1.21 [0.59, 2.47]	2021	-
Zakaria 2021	90	108	107	126	4.1%	0.89 [0.44, 1.79]	2021	- _
Al-Hazmi 2017	121	400	49	200	11.2%	1.34 [0.91, 1.97]	2017	+
Bagheri 2017	46	76	29	54	3.3%	1.32 [0.65, 2.68]	2017	_ +-
Rahmadhani 2017	286	366	866	1070	23.8%	0.84 [0.63, 1.13]	2017	
Mahmoudi 2011	520	894	531	914	54.2%	1.00 [0.83, 1.21]	2011	+
Total (95% CI)		2056		2532	100.0%	1.01 [0.88, 1.16]		4
Total events	1258		1734					
Heterogeneity: Chi ² =	4.45, df=	5 (P =	0.49); l ^z =	:0%				
Test for overall effect:	Z = 0.21 ((P = 0.8	33)					Favours [Obese] Favours [Non obese]

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

	Obes	se	Non ob	ese		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	M-H, Fixed, 95% Cl
Bienertová-Vašků 2017	569	916	411	650	44.7%	0.95 [0.77, 1.17]	2017	+
Tofteng 2002	222	376	292	482	25.8%	0.94 [0.71, 1.23]	2002	-
Speer 2001	29	58	158	276	6.7%	0.75 [0.42, 1.32]	2001	
Geusens 1997	132	242	422	760	22.8%	0.96 [0.72, 1.29]	1997	-
Total (95% CI)		1592		2168	100.0%	0.94 [0.82, 1.08]		•
Total events	952		1283					
Heterogeneity: Chi ² = 0.67	', df = 3 (F	P = 0.88	3); I² = 0%)				
Test for overall effect: Z = I	0.91 (P =	0.36)					0.0	Favours (Obese) Favours (Non obese)

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

	Obes	e	Non ob	ese		Odds Ratio			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year		M-H, Fixed, 95% CI
Wang 2021	92	95	68	68	3.8%	0.19 [0.01, 3.80]	2021	←	
Zakaria 2021	37	38	47	50	1.4%	2.36 [0.24, 23.65]	2021		
Al-Hazmi 2017	23	125	4	59	5.8%	3.10 [1.02, 9.42]	2017		
Bagheri 2017	14	20	5	8	2.8%	1.40 [0.25, 7.83]	2017		
Rahmadhani 2017	115	127	357	383	21.9%	0.70 [0.34, 1.43]	2017		
Mahmoudi 2011	147	221	148	222	64.4%	0.99 [0.67, 1.47]	2011		
Total (95% CI)		626		790	100.0%	1.05 [0.77, 1.44]			◆
Total events	428		629						
Heterogeneity: Chi ² =	6.80, df=	5 (P =	0.24); l² =	: 26%				L 0.01	
Test for overall effect:	Z = 0.31 ((P = 0.7	'6)		0.01	Favours [Obese] Favours [Non obese]			

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

	Obes	e	Non ob	ese		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	M-H, Fixed, 95% CI
Bienertová-Vašků 2017	178	245	127	168	42.8%	0.86 [0.55, 1.35]	2017	· _ _ _
Tofteng 2002	63	92	91	131	24.6%	0.95 [0.54, 1.70]	2002	2
Speer 2001	8	16	46	72	8.7%	0.57 [0.19, 1.68]	2001	
Geusens 1997	36	61	113	184	23.9%	0.90 [0.50, 1.63]	1997	·
Total (95% CI)		414		555	100.0%	0.87 [0.65, 1.16]		•
Total events	285		377					
Heterogeneity: Chi ² = 0.72	, df = 3 (F	² = 0.87	"); I ² = 0%					
Test for overall effect: Z = 0	0.95 (P =	0.34)						Favours [Obese] Favours [Non obese]

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

	Obes	e	Non obese		Odds Ratio			Odds Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year		M-H, Fixed, 95% Cl		
Wang 2021	11	14	16	16	3.2%	0.10 [0.00, 2.12]	2021	•			
Zakaria 2021	16	17	13	16	0.7%	3.69 [0.34, 39.84]	2021				
Al-Hazmi 2017	75	177	41	96	27.4%	0.99 [0.60, 1.63]	2017		-+-		
Bagheri 2017	18	24	19	22	4.4%	0.47 [0.10, 2.18]	2017				
Rahmadhani 2017	56	68	152	178	13.2%	0.80 [0.38, 1.69]	2017				
Mahmoudi 2011	226	300	235	309	51.0%	0.96 [0.66, 1.39]	2011				
Total (95% CI)		600		637	100.0%	0.92 [0.70, 1.20]			•		
Total events	402		476								
Heterogeneity: Chi ² =	4.34, df =	5 (P =	0.50); l² =	:0%						H	
Test for overall effect: $Z = 0.64$ (P = 0.52)									Favours [Obese] Favours [Non obese]	U	



	Obes	se	Non ob	ese		Odds Ratio			Odds	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year		M-H, Fixe	d, 95% Cl		
Bienertová-Vašků 2017	213	280	157	198	42.2%	0.83 [0.53, 1.29]	2017			-		
Tofteng 2002	96	125	110	150	22.2%	1.20 [0.69, 2.09]	2002		_	-		
Speer 2001	13	21	66	92	9.0%	0.64 [0.24, 1.72]	2001			<u> </u>		
Geusens 1997	60	85	196	267	26.7%	0.87 [0.51, 1.49]	1997			<u> </u>		
Total (95% CI)		511		707	100.0%	0.91 [0.69, 1.20]			•			
Total events	382		529									
Heterogeneity: Chi ² = 1.67	', df = 3 (F	P = 0.64	l); l² = 0%)					0.1		+	100
Test for overall effect: Z = (0.69 (P =	0.49)						0.01	Favours [Obese]	Favours [N	on obes	;e]

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

	Obese Non obese		ese	Odds Ratio			Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	M-H, Fixed, 95% Cl
Wang 2021	92	106	68	84	5.1%	1.55 [0.71, 3.38]	2021	
Zakaria 2021	37	54	47	63	6.9%	0.74 [0.33, 1.66]	2021	
Al-Hazmi 2017	23	200	4	100	2.4%	3.12 [1.05, 9.28]	2017	
Bagheri 2017	14	38	5	27	1.9%	2.57 [0.79, 8.30]	2017	
Rahmadhani 2017	115	183	357	535	34.2%	0.84 [0.59, 1.20]	2017	
Mahmoudi 2011	147	447	148	457	49.6%	1.02 [0.77, 1.35]	2011	+
Total (95% CI)		1028		1266	100.0%	1.05 [0.86, 1.27]		♦
Total events	428		629					
Heterogeneity: Chi ² =	9.25, df =	5 (P =	0.10); l² =	= 46%			H	1 01 1 10 100
Test for overall effect:	Z=0.47 ((P = 0.8	i4)				0.0	Favours [Obese] Favours [Non obese]

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

	Obes	se	Non ob	ese	Odds Ratio			Odds Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	M-H, Fixed, 95% Cl			
Bienertová-Vašků 2017	178	458	127	325	46.9%	0.99 [0.74, 1.33]	2017	+			
Tofteng 2002	63	188	91	241	27.4%	0.83 [0.56, 1.24]	2002				
Speer 2001	8	29	46	138	6.0%	0.76 [0.31, 1.85]	2001				
Geusens 1997	36	121	113	380	19.8%	1.00 [0.64, 1.57]	1997	+			
Total (95% CI)		796		1084	100.0%	0.94 [0.76, 1.15]		•			
Total events	285		377								
Heterogeneity: Chi ² = 0.78	, df = 3 (F	P = 0.85	5); I² = 0%)							
Test for overall effect: Z = (D.65 (P =	0.52)						Favours [Obese] Favours [Non obese]			

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

	Obes	se	Non obese			Odds Ratio		Odds Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year		M-H, Fixed, 95%	6 CI	
Wang 2021	103	106	84	84	2.6%	0.17 [0.01, 3.43]	2021	4	•	_	
Zakaria 2021	53	54	60	63	0.9%	2.65 [0.27, 26.25]	2021				
Al-Hazmi 2017	98	200	45	100	25.7%	1.17 [0.73, 1.90]	2017				
Bagheri 2017	32	38	24	27	3.7%	0.67 [0.15, 2.94]	2017	-	•	-	
Rahmadhani 2017	171	183	509	535	14.3%	0.73 [0.36, 1.47]	2017				
Mahmoudi 2011	373	447	383	457	52.8%	0.97 [0.68, 1.39]	2011		-		
Total (95% CI)		1028		1266	100.0%	0.97 [0.75, 1.26]			•		
Total events	830		1105								
Heterogeneity: Chi ² =	3.49, df=	5 (P =	0.62); l² =	:0%						10	100
Test for overall effect: Z = 0.21 (P = 0.83)								Favour	s [Obese] Favo	urs (Non obes	3e]

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

	Obes	e	Non ob	ese		Odds Ratio			Odds	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year		M-H, Fixe	d, 95% Cl		
Bienertová-Vašků 2017	391	458	284	325	41.4%	0.84 [0.55, 1.28]	2017			-		
Tofteng 2002	159	188	201	241	23.2%	1.09 [0.65, 1.84]	2002		-	-		
Speer 2001	21	29	112	138	9.1%	0.61 [0.24, 1.53]	2001			_		
Geusens 1997	96	121	309	380	26.3%	0.88 [0.53, 1.47]	1997			_		
Total (95% CI)		796		1084	100.0%	0.89 [0.68, 1.16]			•	,		
Total events	667		906									
Heterogeneity: Chi ² = 1.31	, df = 3 (F	^o = 0.73	3); i² = 0%)					4		10	100
Test for overall effect: Z = 0	0.88 (P =	0.38)						Fav	ours [Obese]	Favours [1	Von obe	ese]

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 Apal polymorphism

	Obes	se	Non Obese			Odds Ratio		Odds Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year		M-H, Rando	om, 95% Cl		
Rashidi 2021	52	174	68	160	14.9%	0.58 [0.37, 0.91]	2021					
Wang 2021	141	210	127	170	14.9%	0.69 [0.44, 1.09]	2021			-		
Al-Hazmi 2017	158	400	88	200	18.5%	0.83 [0.59, 1.17]	2017		-	-		
Fan 2015	322	490	352	568	21.9%	1.18 [0.91, 1.51]	2015		-	-		
Zhou 2014	67	198	43	164	14.8%	1.44 [0.91, 2.27]	2014		-	-		
Mahmoudi 2010	57	136	80	184	15.0%	0.94 [0.60, 1.47]	2010			-		
Total (95% CI)		1608		1446	100.0%	0.91 [0.71, 1.18]			•			
Total events	797		758									
Heterogeneity: Tau ² =	0.06; Chi	i ² = 13.1	14, df = 5	(P = 0.0	02); P = 60	2%			01		+	100
Test for overall effect:	Z = 0.70 ((P = 0.4	8)					0.01	Favours [obese]	Favours [no	n obes	e]

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

	Obes	se	Non Ob	ese		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Bagci 2021	40	136	41	142	13.8%	1.03 [0.61, 1.72]	· · · · · · · · · · · · · · · · · · ·
BienertovÁ-Vasku 2017	384	814	283	558	86.2%	0.87 [0.70, 1.08]	
Total (95% CI)		950		700	100.0%	0.89 [0.73, 1.09]	
Total events	424		324				
Heterogeneity: Chi ² = 0.34	4, df = 1 (F	P = 0.58	6); I ² = 0%				
Test for overall effect: Z =	1.15 (P =	0.25)					Favours [obese] Favours [non obese]

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

	Obes	e	Non Ob	ese		Odds Ratio			Odds	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year		M-H, Rand	om, 95% Cl		
Rashidi 2021	6	47	12	36	13.6%	0.29 [0.10, 0.88]	2021					
Wang 2021	50	64	44	46	8.8%	0.16 [0.03, 0.75]	2021					
Al-Hazmi 2017	38	118	22	56	21.7%	0.73 [0.38, 1.42]	2017			-		
Fan 2015	111	145	110	152	24.7%	1.25 [0.74, 2.10]	2015		-	-		
Zhou 2014	8	48	7	53	13.6%	1.31 [0.44, 3.95]	2014			•		
Mahmoudi 2010	16	43	17	46	17.6%	1.01 [0.43, 2.39]	2010					
Total (95% CI)		465		389	100.0%	0.74 [0.43, 1.26]			•	•		
Total events	229		212									
Heterogeneity: Tau ² =	0.23; Chi	i ^z = 11.1	13, df = 5	(P = 0.0	05); I² = 56	5%			01			100
Test for overall effect:	Z = 1.10 ((P = 0.2	!7)					0.01	Favours [obese]	Favours (non	obese]

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

01	Obes	e	Non Ob	ese		Odds Ratio		Odds Ratio	
Study or Subgroup	Events	lotal	Events	lotal	weight	M-H, FIXEd, 95% CI		M-H, Fixed, 95% Cl	
Bagci 2021	3	34	5	40	8.2%	0.68 [0.15, 3.07]			
BienertovÄ-Vasku 2017	89	201	71	138	91.8%	0.75 [0.49, 1.16]			
Total (95% CI)		235		178	100.0%	0.74 [0.49, 1.13]		•	
Total events	92		76						
Heterogeneity: Chi ² = 0.02	, df = 1 (F	P = 0.90)); I² = 0%						10 100
Test for overall effect: Z = 1	1.39 (P =	0.17)					0.01	Favours [obese] Favours [i	non obese]

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

	Obes	se	Non Ob	ese		Odds Ratio			Odds	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year		M-H, Rand	om, 95% Cl		
Rashidi 2021	40	81	44	68	17.7%	0.53 [0.27, 1.03]	2021					
Wang 2021	41	55	39	41	7.2%	0.15 [0.03, 0.70]	2021	-				
Al-Hazmi 2017	82	162	44	78	19.8%	0.79 [0.46, 1.36]	2017			-		
Fan 2015	100	134	132	174	20.2%	0.94 [0.56, 1.58]	2015			—		
Zhou 2014	51	91	29	75	18.4%	2.02 [1.09, 3.77]	2014					
Mahmoudi 2010	25	52	46	75	16.8%	0.58 [0.29, 1.19]	2010			-		
Total (95% CI)		575		511	100.0%	0.76 [0.47, 1.25]			•	-		
Total events	339		334									
Heterogeneity: Tau ² =	0.24; Chi	i ^z = 15.4	49, df = 5	(P = 0.0	008); I ² = 6	38%			0.1			100
Test for overall effect:	Z = 1.08 ((P = 0.2	28)					0.01	Favours [Obese]	Favours [Nor	u 1 obesej]

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

	Obes	se	Non Ob	ese		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		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: Chi ² = 0.77	7, df = 1 (F	P = 0.38	3); I² = 0%				0.01	0.1 1 10 100
Test for overall effect: $Z =$	0.34 (P =	0.74)						Favours [Obese] Favours [Non obese]

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

	Obes	e	Non Ob	ese		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	M-H, Fixed, 95% Cl
Rashidi 2021	6	46	12	56	8.3%	0.55 [0.19, 1.60]	2021	
Wang 2021	50	91	44	83	18.2%	1.08 [0.60, 1.96]	2021	_ -
Al-Hazmi 2017	38	120	22	66	17.0%	0.93 [0.49, 1.76]	2017	
Fan 2015	111	211	110	242	42.7%	1.33 [0.92, 1.93]	2015	+∎-
Zhou 2014	8	59	7	36	6.6%	0.65 [0.21, 1.98]	2014	
Mahmoudi 2010	16	41	17	63	7.2%	1.73 [0.75, 4.01]	2010	+
Total (95% CI)		568		546	100.0%	1.14 [0.88, 1.46]		+
Total events	229		212					
Heterogeneity: Chi ² =	4.83, df=	5 (P =	0.44); l²=	:0%				
Test for overall effect:	Z = 0.99 ((P = 0.3	32)					Favours [Non obese] Favours [obese]

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

	Obes	se	Non Ob	ese		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Bagci 2021	3	37	5	36	7.5%	0.55 [0.12, 2.48]	
BienertovÄ-Vasku 2017	89	295	71	212	92.5%	0.86 [0.59, 1.25]	
Total (95% CI)		332		248	100.0%	0.83 [0.58, 1.20]	•
Total events	92		76				
Heterogeneity: Chi ² = 0.32	2, df = 1 (F	P = 0.57	?); I² = 0%	1			
Test for overall effect: Z = I	0.97 (P =	0.33)					Favours [Non obese] Favours [obese]

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

	Obes	e	Non Ob	ese		Odds Ratio			Odds	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year		M-H, Fixe	d, 95% Cl		
Rashidi 2021	6	87	12	80	8.6%	0.42 [0.15, 1.18]	2021			-		
Wang 2021	50	105	44	85	18.9%	0.85 [0.48, 1.50]	2021			—		
Al-Hazmi 2017	38	200	22	100	17.6%	0.83 [0.46, 1.50]	2017			_		
Fan 2015	111	245	110	284	41.4%	1.31 [0.93, 1.85]	2015		-	-		
Zhou 2014	8	99	7	82	5.2%	0.94 [0.33, 2.72]	2014					
Mahmoudi 2010	16	68	17	92	8.2%	1.36 [0.63, 2.93]	2010			•		
Total (95% CI)		804		723	100.0%	1.05 [0.83, 1.32]			•			
Total events	229		212									
Heterogeneity: Chi ² =	6.21, df=	5 (P =	0.29); l² =	:19%						10		100
Test for overall effect:	Z = 0.37 ((P = 0.7	'1)					0.01	Favours [Obese]	Favours [Non	obese]	100

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

	Obes	se	Non Ob	ese		Odds Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed, 95% Cl	
Bagci 2021	3	68	5	71	6.6%	0.61 [0.14, 2.65]			
BienertovÃ-Vasku 2017	89	407	71	279	93.4%	0.82 [0.57, 1.17]			
Total (95% CI)		475		350	100.0%	0.81 [0.57, 1.14]		•	
Total events	92		76						
Heterogeneity: Chi ² = 0.15	i, df = 1 (F	P = 0.70)); I² = 0%					01 1	10 100
Test for overall effect: Z = 1	1.22 (P =	0.22)					0.01	Favours [Obese] Favours [N	on obese]

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

	Obes	se	Non Ob	ese		Odds Ratio			Odds	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year		M-H, Rand	om, 95% Cl		
Rashidi 2021	46	87	56	80	17.5%	0.48 [0.25, 0.91]	2021					
Wang 2021	91	105	83	85	7.1%	0.16 [0.03, 0.71]	2021					
Al-Hazmi 2017	120	200	66	100	19.9%	0.77 [0.47, 1.28]	2017			-		
Fan 2015	211	245	242	284	20.1%	1.08 [0.66, 1.76]	2015		_			
Zhou 2014	59	99	36	82	18.3%	1.88 [1.04, 3.41]	2014					
Mahmoudi 2010	41	68	63	92	17.2%	0.70 [0.36, 1.35]	2010			_		
Total (95% CI)		804		723	100.0%	0.79 [0.49, 1.26]			-	•		
Total events	568		546									
Heterogeneity: Tau ² =	0.23; Chi	i ² = 16.3	22, df = 5	(P = 0.0	006); I ² = 6	69%			01			100
Test for overall effect:	Z=1.00 ((P = 0.3	32)					0.01	Favours [Obese]	Favours [Nor) Nobese]]



Study or Subgroup	Obes Events	se Total	Non Ob Events	ese Total	Weight	Odds Ratio M-H, Fixed, 95% CI		Odds Ratio M-H, Fixed, 95% Cl	
Bagci 2021	37	68	36	71	18.8%	1.16 [0.60, 2.26]			
BienertovÄ-Vasku 2017	295	407	212	279	81.2%	0.83 [0.59, 1.18]		-	
Total (95% CI)		475		350	100.0%	0.89 [0.66, 1.22]		•	
Total events	332		248						
Heterogeneity: Chi ² = 0.75	, df = 1 (F	P = 0.39	3); I² = 0%						100
Test for overall effect: Z = 0	0.71 (P =	0.48)					0.01	Favours [Obese] Favours [Non obese]



3. Vitamin D Receptor gene Fokl polymorphism

	Obes	se	Non Ob	ese		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	r M-H, Fixed, 95% Cl
Gariballa 2023	128	402	45	130	8.2%	0.88 [0.58, 1.34]	2023	3 -+
Zakaria 2021	45	108	56	126	5.4%	0.89 [0.53, 1.50]	2021	_ - -
Bagci 2021	21	68	24	71	2.9%	0.88 [0.43, 1.78]	2021	· · · · · · · · · · · · · · · · · · ·
Bhatt 2021	133	460	32	140	6.2%	1.37 [0.88, 2.14]	2021	↓ +
Wang 2021	102	210	65	150	6.9%	1.24 [0.81, 1.88]	2021	↓ →
Xie 2021	96	224	101	226	10.2%	0.93 [0.64, 1.35]	2021	− ∎ <mark>−</mark>
Bienertová-Vašků 2017	378	920	299	650	36.7%	0.82 [0.67, 1.00]	2017	· -
Fan 2015	178	490	191	568	20.0%	1.13 [0.87, 1.45]	2015	5 🗕 🗕
Zhou 2015	50	99	36	82	3.5%	1.30 [0.72, 2.35]	2015	5 +
Total (95% CI)		2981		2143	100.0%	0.98 [0.87, 1.10]		•
Total events	1131		849					
Heterogeneity: Chi ² = 9.01	, df = 8 (F	P = 0.34	l); l² = 119	λ				
Test for overall effect: Z = (0.30 (P =	0.77)						U.UI U.I I IU IUU Eavours [Obese] Eavours [Non obese]
restion overall effect. Z = (0.30 (F -	0.77)						Favours [Obese] Favours [Non obese]

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

	Obes	se	Non Ob	ese		Odds Ratio		Odds R	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed	, 95% CI	
Slattery 2004	1565	4270	788	2156	88.9%	1.00 [0.90, 1.12]				
Tofteng 2002	129	358	147	452	11.1%	1.17 [0.87, 1.57]		+	-	
Total (95% CI)		4628		2608	100.0%	1.02 [0.92, 1.13]		•		
Total events	1694		935							
Heterogeneity: Chi ² =	0.91, df=	1 (P =	0.34); I ^z =	:0%						400
Test for overall effect:	Z=0.44	(P = 0.6	i6)				0.01	Favours [Obese]	Favours (Non	obese]

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

	Obes	se	Non Ob	ese		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	M-H, Fixed, 95% Cl
Gariballa 2023	22	117	7	34	5.8%	0.89 [0.34, 2.31]	2023	
Wang 2021	25	53	13	36	5.4%	1.58 [0.66, 3.76]	2021	_ +•
Xie 2021	46	124	39	102	17.7%	0.95 [0.55, 1.64]	2021	
Zakaria 2021	10	30	10	26	4.7%	0.80 [0.27, 2.39]	2021	
Bagci 2021	7	41	6	36	3.5%	1.03 [0.31, 3.40]	2021	
Bhatt 2021	21	139	4	46	3.3%	1.87 [0.61, 5.76]	2021	
Bienertová-Vašků 2017	75	232	73	172	37.2%	0.65 [0.43, 0.98]	2017	
Fan 2015	34	135	40	173	17.2%	1.12 [0.66, 1.89]	2015	
Zhou 2015	28	55	14	39	5.3%	1.85 [0.80, 4.29]	2015	+
Total (95% CI)		926		664	100.0%	0.97 [0.78, 1.22]		
Total events	268		206					
Heterogeneity: Chi ² = 8.98), df = 8 (F	P = 0.34	4); I² = 119	Хо				
Test for overall effect: Z =	0.25 (P =	0.80)						U.UT U.T T TU TUU Eavours [Obese] Eavours [Non obese]

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 *Fokl* polymorphism and obesity risk under ff vs. FF model in European

	Obese Non Obese		ese	Odds Ratio			Odds Ratio					
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year		M-H, Fixe	d, 95% CI		
Gariballa 2023	84	179	31	58	8.6%	0.77 [0.43, 1.39]	2023			_		
Bagci 2021	27	61	35	65	6.5%	0.68 [0.34, 1.37]	2021			-		
Bhatt 2021	91	209	24	66	7.1%	1.35 [0.76, 2.39]	2021		-			
Wang 2021	52	80	39	62	5.3%	1.10 [0.55, 2.18]	2021			<u> </u>		
Xie 2021	101	179	125	188	18.4%	0.65 [0.43, 1.00]	2021					
Zakaria 2021	24	44	37	53	5.3%	0.52 [0.23, 1.20]	2021			-		
Bienertová-Vašků 2017	228	385	153	252	26.1%	0.94 [0.68, 1.30]	2017			-		
Fan 2015	110	211	111	244	17.0%	1.30 [0.90, 1.89]	2015		+	-		
Zhou 2015	44	71	43	68	5.8%	0.95 [0.48, 1.88]	2015					
Total (95% CI)		1419		1056	100.0%	0.93 [0.79, 1.10]			•			
Total events	761		598									
Heterogeneity: Chi ² = 10.8	0, df = 8 i	(P = 0.2	21); I ² = 26	5%				H 01				400
Test for overall effect: Z = (0.81 (P =	0.42)						0.01 E	U.I 1 avours [Obese]	Favours [Non	ohesel	100
									avours [obese]	r avours [rvorr	opeacl	

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

	Obese	Non Ob	ese		Odds Ratio		Odds Ratio
Study or Subgroup	Events To	otal Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed, 95% Cl
Slattery 2004	1003 18	854 520	944	88.8%	0.96 [0.82, 1.12]		
Tofteng 2002	89 1	159 103	204	11.2%	1.25 [0.82, 1.89]		
Total (95% CI)	20	013	1148	100.0%	0.99 [0.86, 1.15]		•
Total events	1092	623					
Heterogeneity: Chi ² =	1.31, df = 1 ((P = 0.25); l ² =	= 24%				
Test for overall effect:	Z = 0.09 (P =	= 0.92)			0.01	Favours [Obese] Favours [Non obese]	

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

	Obes	se	Non Ob	ese		Odds Ratio			Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year		M-H, Fixe	d, 95% CI	
Gariballa 2023	22	106	7	38	5.0%	1.16 [0.45, 2.98]	2023				
Bagci 2021	7	34	6	41	2.7%	1.51 [0.46, 5.02]	2021				
Bhatt 2021	21	112	4	28	3.2%	1.38 [0.43, 4.42]	2021			•	
Wang 2021	25	- 77	13	52	6.5%	1.44 [0.66, 3.17]	2021			•	
Xie 2021	46	147	39	164	15.7%	1.46 [0.88, 2.41]	2021		+	•	
Zakaria 2021	10	34	10	47	3.7%	1.54 [0.56, 4.26]	2021				
Bienertová-Vašků 2017	75	303	73	226	38.9%	0.69 [0.47, 1.01]	2017				
Zhou 2015	28	72	14	57	5.9%	1.95 [0.91, 4.21]	2015		+		
Fan 2015	34	144	40	151	18.4%	0.86 [0.51, 1.45]	2015			_	
Total (95% CI)		1029		804	100.0%	1.06 [0.86, 1.32]			•	•	
Total events	268		206								
Heterogeneity: Chi ² = 11.1	9, df = 8	(P = 0.1	9); I 2 = 29	3%							100
Test for overall effect: Z =	0.57 (P =	0.57)						0.01	Favours [Obese]	Favours [Non ob	esel

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

	Obes	e	Non Ob	ese		Odds Ratio		Odds Ra	tio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed,	95% CI	
Slattery 2004	281	1284	134	654	89.2%	1.09 [0.86, 1.37]				
Tofteng 2002	20	109	22	125	10.8%	1.05 [0.54, 2.05]		-+-	_	
Total (95% CI)		1393		779	100.0%	1.08 [0.87, 1.35]		•		
Total events	301		156							
Heterogeneity: Chi ² =	0.01, df=	1 (P =	0.93); I ² =	0%					10	100
Test for overall effect:	Z = 0.72 ((P = 0.4	7)	0.01	Favours [Obese] Fa	avours [Non ob	esel			

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

	Obes	se	Non Ob	ese		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	M-H, Fixed, 95% Cl
Gariballa 2023	22	201	7	65	5.1%	1.02 [0.41, 2.51]	2023)
Bagci 2021	7	68	6	71	2.9%	1.24 [0.40, 3.91]	2021	
Bhatt 2021	21	230	4	70	3.0%	1.66 [0.55, 5.00]	2021	
Wang 2021	25	105	13	75	6.3%	1.49 [0.71, 3.15]	2021	
Xie 2021	46	225	39	227	16.7%	1.24 [0.77, 1.99]	2021	
Zakaria 2021	10	54	10	63	4.1%	1.20 [0.46, 3.16]	2021	
Bienertová-Vašků 2017	75	460	73	325	38.8%	0.67 [0.47, 0.96]	2017	·
Fan 2015	34	245	40	284	17.3%	0.98 [0.60, 1.61]	2015	;
Zhou 2015	28	99	14	82	5.9%	1.92 [0.93, 3.95]	2015	; •
Total (95% CI)		1687		1262	100.0%	1.03 [0.84, 1.26]		•
Total events	268		206					
Heterogeneity: Chi ² = 10.7	2, df = 8 i	(P = 0.2	22); I² = 26	5%				
Test for overall effect: Z = I	0.30 (P =	0.77)						Eavours [Obese] Favours [Non obese]

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

	Obes	se	Non Ob	ese		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed, 95% CI
Slattery 2004	281	2135	134	1078	90.0%	1.07 [0.86, 1.33]		
Tofteng 2002	20	179	22	226	10.0%	1.17 [0.61, 2.21]		
Total (95% CI)		2314		1304	100.0%	1.08 [0.87, 1.33]		•
Total events	301		156					
Heterogeneity: Chi ² =	0.07, df=	: 1 (P =	0.80); I ² =	:0%				
Test for overall effect:	Z = 0.70 ((P = 0.4	8)				0.01	Eavours [Obese] Eavours [Non obese]

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

	Obes	e	Non Ob	ese		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	r M-H, Fixed, 95% Cl
Gariballa 2023	106	201	38	65	7.6%	0.79 [0.45, 1.40]	2023	3
Xie 2021	147	225	164	227	15.9%	0.72 [0.49, 1.08]	2021	I —■-
Zakaria 2021	34	54	47	63	4.5%	0.58 [0.26, 1.28]	2021	I <u>→+</u>
Bagci 2021	34	68	41	71	5.6%	0.73 [0.37, 1.43]	2021	I —•+
Bhatt 2021	112	231	28	70	6.2%	1.41 [0.82, 2.43]	2021	I +
Wang 2021	77	105	52	75	4.5%	1.22 [0.63, 2.34]	2021	I
Hussain 2018	48	97	116	243	9.4%	1.07 [0.67, 1.72]	2018	3 +
Bienertová-Vašků 2017	303	460	226	325	25.3%	0.85 [0.62, 1.15]	2017	7
Fan 2015	144	245	151	284	16.2%	1.26 [0.89, 1.77]	2015	5 +-
Zhou 2015	72	99	57	82	4.8%	1.17 [0.61, 2.23]	2015	5
Total (95% CI)		1785		1505	100.0%	0.96 [0.83, 1.11]		•
Total events	1077		920					
Heterogeneity: Chi ² = 10.5	i6, df = 9 ((P = 0.3)	81); I ² = 16	5%				
Test for overall effect: Z = I	0.56 (P =	0.58)						Eavours [Obese] Eavours [Non obese]

Figure 3.11. Forest plot of the association between VDR gene Fokl 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

Obese Non obese Odds Ratio Odds Ratio M-H, Random, 95% Cl Study or Subgroup Events Total Weight M-H, Random, 95% CI Year Events Total Gariballa 2023 402 57 1.01 [0.68, 1.50] 2023 177 130 27.9% Bhatt 2021 460 2.38 [1.28, 4.40] 90 13 140 20.2% 2021 Rashidi 2021 58 174 61 160 26.0% 0.81 [0.52, 1.27] 2021 Wang 2021 196 212 159 170 15.3% 0.85 [0.38, 1.88] 2021 Zhou 2014 7 198 8 164 10.8% 0.71 [0.25, 2.01] 2015 Total (95% CI) 764 100.0% 1.06 [0.71, 1.59] 1446 Total events 528 298 Heterogeneity: Tau² = 0.11; Chi² = 8.94, df = 4 (P = 0.06); l² = 55% 0.01 100 0.1 10 Test for overall effect: Z = 0.30 (P = 0.77) Favours [Obese] Favours [Non obese]

4. Vitamin D Receptor gene Taql polymorphism

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

	Obes	se	Non ob	ese		Odds Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed, 95% CI	
Bagci 2021	92	136	85	142	13.8%	1.40 [0.86, 2.29]		+	
Bienertová-Väsků 2017	315	804	184	550	68.2%	1.28 [1.02, 1.61]			
Vasilopoulos 2013	109	164	117	204	18.0%	1.47 [0.96, 2.26]			
Total (95% CI)		1104		896	100.0%	1.33 [1.11, 1.60]		•	
Total events	516		386						
Heterogeneity: Chi ² = 0.37	7, df = 2 (F	P = 0.83	3); I ² = 0%						100
Test for overall effect: Z =	3.03 (P =	0.002)					0.01	Favours [Obese] Favours [Non (obese]

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

	Obes	Obese Non obese		ese		Odds Ratio	Odds Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	M-H, Fixed, 95% CI		
Gariballa 2023	40	104	12	32	45.3%	1.04 [0.46, 2.36]	2023	+		
Bhatt 2021	9	158	3	63	16.2%	1.21 [0.32, 4.62]	2021			
Rashidi 2021	8	45	8	35	29.7%	0.73 [0.24, 2.19]	2021			
Wang 2021	92	94	74	74	8.8%	0.25 [0.01, 5.25]	2021			
Total (95% CI)		401		204	100.0%	0.91 [0.51, 1.60]		•		
Total events	149		97							
Heterogeneity: Chi ² =	1.13, df=	3 (P =	0.77); l² =	:0%						
Test for overall effect:	Z=0.34	(P = 0.7	'3)					Favours [Obese] Favours [Non obese]		



	Obes	se	Non ob	ese		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed, 95% Cl
Bagci 2021	32	40	30	46	14.4%	2.13 [0.80, 5.71]		+
Bienertová-Väsků 2017	62	211	33	157	69.0%	1.56 [0.96, 2.54]		+
Vasilopoulos 2013	37	47	29	43	16.6%	1.79 [0.69, 4.60]		+•
Total (95% CI)		298		246	100.0%	1.68 [1.13, 2.50]		◆
Total events	131		92					
Heterogeneity: Chi ² = 0.33), df = 2 (F	P = 0.85	5); I ^z = 0%					
Test for overall effect: Z = 3	2.58 (P =	0.010)					0.01	Favours [Obese] Favours [Non obese]

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



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



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



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

	Obes	se .	Non ob	ese		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Bagci 2021	32	60	30	55	25.0%	0.95 [0.46, 1.98]	
Bienertová-Väsků 2017	62	253	33	151	53.3%	1.16 [0.72, 1.88]	-#-
Vasilopoulos 2013	37	72	29	88	21.7%	2.15 [1.13, 4.08]	
Total (95% CI)		385		294	100.0%	1.32 [0.94, 1.86]	◆
Total events	131		92				
Heterogeneity: Chi ² = 3.28	6, df = 2 (F	° = 0.20	0); I ^z = 39 ^o	%			
Test for overall effect: Z =	1.62 (P =	0.11)					Favours [Obese] Favours [Non obese]

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

	Obes	e	Non ob	ese		Odds Ratio			Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year		M-H, Fixed, 95% Cl	
Gariballa 2023	40	201	12	65	38.9%	1.10 [0.54, 2.25]	2023			
Bhatt 2021	9	230	3	70	11.8%	0.91 [0.24, 3.46]	2021			
Rashidi 2021	8	87	8	80	20.3%	0.91 [0.33, 2.55]	2021			
Wang 2021	92	106	74	85	29.0%	0.98 [0.42, 2.28]	2021		+	
Total (95% CI)		624		300	100.0%	1.00 [0.64, 1.58]			+	
Total events	149		97							
Heterogeneity: Chi ² =	0.12, df=	3 (P =	0.99); l² =	:0%						4
Test for overall effect:	Z = 0.01 ((P = 0.9	99)					0.01	Favours (Obese) Favours (Non obese)	,

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



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

	Obes	e	Non ob	ese		Odds Ratio		Odds Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl			
Gariballa 2023	137	201	45	65	26.4%	0.95 [0.52, 1.74]	2023	_			
Bhatt 2021	81	230	10	70	24.4%	3.26 [1.58, 6.71]	2021				
Rashidi 2021	50	87	53	80	26.0%	0.69 [0.37, 1.29]	2021				
Wang 2021	104	106	85	85	4.5%	0.24 [0.01, 5.16]	2021				
Zhou 2014	7	99	8	82	18.7%	0.70 [0.24, 2.03]	2015				
Total (95% CI)		723		382	100.0%	1.05 [0.52, 2.11]		+			
Total events	379		201								
Heterogeneity: Tau ² =	: 0.38; Chi	r =12.1	77, df = 4	(P = 0.1)	01); I^z = 6!	9%					
Test for overall effect:	Z = 0.14 ((P = 0.8	9)					Favours [Obese] Favours [Non obese]			

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

	Obes	se	Non ob	ese		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Bagci 2021	60	68	55	71	7.7%	2.18 [0.87, 5.50]	
Bienertová-Väsků 2017	253	402	151	275	80.7%	1.39 [1.02, 1.91]	
Vasilopoulos 2013	72	82	88	102	11.6%	1.15 [0.48, 2.73]	
Total (95% CI)		552		448	100.0%	1.43 [1.08, 1.89]	◆
Total events	385		294				
Heterogeneity: Chi ² = 1.08	8, df = 2 (F	P = 0.58	3); I ² = 0%				
Test for overall effect: Z = 3	2.49 (P =	0.01)					Favours [Obese] Favours [Non obese]

Figure 4.12. Forest plot of the association between VDR gene *Taql* 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

	Obes	e	Non ob	ese		Odds Ratio		Odds	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixe	d, 95% Cl		
Wang 2021	97	212	75	170	56.1%	1.07 [0.71, 1.60]		-	-		
Zhou 2014	86	198	57	164	43.9%	1.44 [0.94, 2.21]			┝╋╌		
Total (95% CI)		410		334	100.0%	1.23 [0.92, 1.65]			•		
Total events	183		132								
Heterogeneity: Chi ² =	0.99, df = 7 = 1 207	1 (P =	0.32); i² =	0.01	0.1	1 1	 	100			
restion overall effect.	2-1.581	,г — 0.1	0)					Favours [Obese]	Favours [No	n obese	3]

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

5.2 Analysis of AA vs GG model

	Obes	e	Non ob	ese		Odds Ratio		Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed, 95% Cl		
Wang 2021	24	57	18	46	59.3%	1.13 [0.51, 2.50]		#		
Zhou 2014	22	57	12	49	40.7%	1.94 [0.84, 4.50]		+		
Total (95% CI)		114		95	100.0%	1.46 [0.82, 2.59]		•		
Total events	46		30							
Heterogeneity: Chi ² =	0.83, df = 7 = 4, 20 4	1 (P =	0.36); i² =	:0%			⊢ 0.01 0.1	1	 	100
Test for overall effect.	Z = 1.29 (P = 0.2	:0)				Favou	urs [Obese] Favours	[Non obesi	e]

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

	Obes	se	Non ob	ese		Odds Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed, 95% Cl	
Wang 2021	49	82	39	67	52.4%	1.07 [0.55, 2.05]			
Zhou 2014	42	77	33	70	47.6%	1.35 [0.70, 2.58]			
Total (95% CI)		159		137	100.0%	1.20 [0.76, 1.90]		*	
Total events	91		72						
Heterogeneity: Chi ² =	0.24, df=	1 (P =	0.62); i² =	:0%					400
Test for overall effect:	Z = 0.77 ((P = 0.4)	4)				0.01	U.I I IU Foueuro (Obasa) - Foueuro (Nan abas	100
			r					Favours [Obese] Favours [Non obes	ej

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

	Obes	se 🛛	Non ob	ese		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% Cl
Wang 2021	24	73	18	57	59.5%	1.06 [0.51, 2.23]		
Zhou 2014	22	64	12	45	40.5%	1.44 [0.62, 3.33]		- + •
Total (95% CI)		137		102	100.0%	1.21 [0.70, 2.12]		•
Total events	46		30					
Heterogeneity: Chi ² =	0.29, df=	1 (P =	0.59); l² =					
Test for overall effect:	Z = 0.69 ((P = 0.4)	9)				0.01	Equatra (Obaca) Equatra (Nan obaca)

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

	Obes	se	Non ob	ese		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	I M-H, Fixed, 95% CI
Wang 2021	24	106	18	85	60.2%	1.09 [0.55, 2.17]	ŋ — ₽ —
Zhou 2014	22	99	12	82	39.8%	1.67 [0.77, 3.62]] +=
Total (95% CI)		205		167	100.0%	1.32 [0.79, 2.20]	1 +
Total events	46		30				
Heterogeneity: Chi ² =	0.64, df = 7 = 1.06 (1 (P = (P = 0.2	0.42); l² = /9)	:0%			0.01 0.1 1 10 100
restion overall clicct.	2 - 1.00 ((i = 0.2	,				Favours [Obese] Favours [Non obese]

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

5.6 Analysis of GA + AA vs GG model

	Obes	e	Non ob	ese		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed, 95% Cl
Wang 2021	73	106	57	85	53.1%	1.09 [0.59, 2.00]		
Zhou 2014	64	99	45	82	46.9%	1.50 [0.83, 2.74]		+
Total (95% CI)		205		167	100.0%	1.28 [0.84, 1.97]		•
Total events	137		102					
Heterogeneity: Chi ² =	0.55, df = 7 = 1 14 (1 (P = (P = 0.2	0.46); I² = '5)	L	0.1 1 10 100			
restion over all effect.	2-1.14	, = 0.2	,					Favours [Obese] Favours [Non obese]

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



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



Figure 6.4. Funnel plot of the association between VDR Bsml 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



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



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



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



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



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







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



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 *Fokl* polymorphism and obesity risk under ff vs. FF+Ff model in overall







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



Figure 6.20. Funnel plot of the association between VDR gene *Taq1* polymorphism and obesity risk under tt vs. TT model in overall



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



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



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



