A meta-analysis study: Vitamin D receptor genetic polymorphism in *Respiratory tuberculosis*

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Abstract

Our study performed meta-analysis of all available literature on numerous features of relation concerning vitamin D genetic polymorphisms and pulmonary tuberculosis. PubMed and Springer databases were hunted and out of 365 articles, 40 studies were chosen for the present review to examine the relation of PTB with vitamin D receptors (VDR). A total of 18637 patients and 25515 controls, with 35 investigations on VDR FokI polymorphism, 33 on VDR TaqI polymorphism, 25 on VDR BsmI polymorphism and 22 on VDR ApaI polymorphism were included. To understand the connection of polymorphisms with Tuberculosis (TB) hazard, the odds ratios (ORs) and the conforming 95% confidence intervals (CIs) were estimated rendering to the occurrences of genotypes. P values of 0.05 were considered statistically relevant. Funnel maps were used to evaluate publication bias.

Several published articles observed the relation of FokI, ApaI, BsmI and TaqI genepolymorphism of VDR with pulmonary tuberculosis (PTB). Their outcomes were unpredictable; hence we did a meta-analysis to find the precise relativeness of the four. Our findings complement many studies being conducted on various communities across the world to better understand the significance of VDR polymorphism in PTB. FokI, TaqI and ApaIshowed risk and TaqI showed no risk of PTB development in the population. Depleted amounts of vitamin D were seen in TB patients. Our analysis exposed the relation between vitamin D receptor gene polymorphism and TB. This meta-analysis shows that VDR Fok*I polymorphism pays to the hazard of pulmonary TB.*

Keywords: VDR polymorphism, Vitamin D receptor, Pulmonary tuberculosis.

Introduction

At present, Tuberculosis (TB) ranks among the primary causes of illness and death on a global scale. World Health Organization (WHO) report of 2023 showed 7.5 million TB in 2022, India being the highest burden country. In 2022, India alone reported for 29% of such deaths[56].

An up-to-date meta-analysis was performed to originate a farther dependable valuation of the relation among *Fok*I polymorphisms and TB hazard[8]. Susceptibility to tuberculosis was triggered by a variation in genetic and environmental factor.

The prevalence of Vitamin D insufficiency affects people of all age groups, with an estimated global count of approximately one billion individuals experiencing low levels of Vitamin D[4,31]. This deficiency is observed in both developed and developing nations and it is recognized as a contributing factor to weakened immune systems[32]. Studies said that the vitamin D route is participating in the immune system, specifically in immune cells like macrophages, which enhance the manufacturing of antimicrobial peptides, thereby regulating the inflammatory response[10]. One such defense molecule, known as cathelicidin antimicrobial peptide, operates immunity (innate and adaptive), influencing infections through Toll-like receptors. Cathelicidin expression contributes to restraining the growth of *Mycobacterium tuberculosis (M. tb)*, a bacterium accountable for tuberculosis[12,23].

Cathelicidins are a group of proteins characterized by a cationic anti-microbial peptide (CAMP)domain located at their C-terminus. Activation of these proteins occurs through a cut at the N-N-terminal cathelin part of the propeptide and is deposited in the granules of neutrophils, further releasing at sites of microbial infection. Several white blood cells (WBC) are also expressed in this peptide[2,51]. Studies have demonstrated that the introduction of cathelicidin from external sources or the increased expression of cathelicidin within macrophages considerably diminishes the persistence of *M. tb* bacteria privileged the cells when compared to control cells[50].

Recent studies conclude its non-traditional function in regulating the immune system, which has become increasingly significant due to the high frequency of vitamin D3 deficiency among adults[9,11]. Macrophages, a type of immune cell, are known as vitamin D3 receptors (VDR)that secrete an enzyme called Cyp27B1 (1α-hydroxylase). This enzyme plays a crucial role in converting 25-hydroxyvitamin D3 into its biological form, 1α,25-dihydroxyvitamin D3[25].

Humans have 4 common VDR gene SNPs: FokI T/C(rs2228570), BsmI G/A (rs1544410), TaqI T/C (rs731236) and ApaI G/T (rs7975232). The locations of VDR BsmI and ApaI are on 8 intron and TaqI on 9 exon and these are occupied in amending the strength of the VDR mRNA[16,52]. At the time of translation, the FokI gene changes its structure (T/C) in exon 2 in the 5′ coding section of the gene resulting in a fresh start codon (ATG to ACG) which

leads to a briefer VDR protein of 424 amino acids instead of 427 amino acids[53]. Numerous studies said that VDR gene polymorphism and its effects on resistance against TB are different in the population and the effect is still unknown. In this study, we combined all data related to meta-analysis to show the susceptibility or resistance in PTB infection of four prevalent VDR gene polymorphisms like ApaI, BsmI, FokI and TaqI.

Material and Methods

Data collection: Rigorous literature searches on multiple databases, including PubMed and Springer link SCIhub and Google Scholar up to December 2022 were done. Keywords to conduct our literature search were Vitamin D receptors (VDR) and *M. tuberculosis* and susceptibility or resistance, ApaI, BsmI, FokI and TaqI polymorphism.

Table 1
Detail of studies comprised in the FOKI rs 2228570 meta-analysis.

First Author	Year	Country	Ethnicity	Total Cases	Total Control
Selvaraj	2003	India	South Asian	80	120
Bornman	2004	UK	Asian	416	718
Roth	2004	Peru	South American	200	201
Selvaraj	2004	India	South Asian	46	64
W.Liu	2004	China	East Asian	120	240
Lombard	2006	South Africa	African	95	117
Babb	2007	South Africa	African	249	352
Olesen	2007	Gambia	African	320	344
Søborg	2007	Tanzania	African	435	416
Wilbur	2007	USA	African	91	290
Selvaraj	2008	India	South Asian	51	60
Alagarasu	2009	India	South Asian	105	144
Merza	2009	Iran	South Asian	117	60
Selvaraj	2009	India	South Asian	65	60
Vidyarani	2009	India	South Asian	40	49
Banoei	2010	Iran	South Asian	60	62
Marashian	2010	Iran	South Asian	164	50
Kang	2011	Korea	East Asian	103	105
Sharma	2011	India	South Asian	238	924
Singh	2011	India	South Asian	101	225
Rathored	2012	India	South Asian	338	205
Joshi	2013	India	South Asian	110	115
Sinaga	2014	Indonesia	South Asian	76	76
Ferna´ndez-Mestre	2015	Venezuela	African	93	102
Linlin Wu	2015	China	East Asian	151	453
Salimi	2015	Iran	South Asian	120	131
Acen	2016	Uganda	African	41	41
Jafari	2016	Iran	South Asian	96	122
Lee	2016	Taiwan	East Asian	198	170
Medapati	2017	India	South Asian	89	83
Devi	2018	India	South Asian	169	227
Zhang	2018	China	East Asian	128	59
Beatriz Silva-Ramírez	2019	Mexican	African	257	457
Panda	2019	India	South Asian	150	150
Maria Eduarda de Albuquerque Borborema	2020	Brazil	African	138	191

Table 2
Detail of reports comprised in the TAQI rs 731236 meta-analysis.

First Author	Year	Country	Ethnicity	Total Cases	Total Control
Delgado	2002	USA	African	358	106
Bornman	2004	UK	Asian	416	718
Fitness	2004	UK	Asian	397	672
Roth	2004	Peru	South American	200	201
Selvaraj	2004	India	South Asian	46	64
W.Liu	2004	China	East Asian	120	240
Lombard	2006	South Africa	African	95	117
Babb	2007	South Africa	African	249	352
Olesen	2007	Gambia	African	320	344
Søborg	2007	Tanzania	African	435	416
Wilbur	2007	USA	African	91	290
Selvaraj	2008	India	South Asian	51	60
Alagarasu	2009	India	South Asian	105	144
Selvaraj	2009	India	South Asian	65	60
Vidyarani	2009	India	South Asian	40	49
Banoei	2010	Iran	South Asian	60	62
Marashian	2010	Iran	South Asian	164	50
Kang	2011	Korea	East Asian	103	105
Sharma	2011	India	South Asian	238	924
Singh	2011	India	South Asian	101	225
Rathored	2012	India	South Asian	338	205
Ferna´ndez-Mestre	2015	Venezuela	African	93	102
Linlin Wu	2015	China	East Asian	151	453
Salimi	2015	Iran	South Asian	120	131
Harishankar	2016	India	South Asian	90	89
Jafari	2016	Iran	South Asian	96	122
Lee	2016	Taiwan	East Asian	198	170
Panwar	2016	India	South Asian	106	106
Rizvi	2016	India	South Asian	130	130
Medapati	2017	India	South Asian	89	83
Devi	2018	India	South Asian	169	227
Zhang	2018	China	East Asian	128	59
Beatriz Silva-Ramírez	2019	Mexican	African	257	457

Criteria for Inclusion and exclusion: Criteria for searching articles were: (1) The studies focused on ApaI, BsmI, FokI and TaqI VDR polymorphism with PTB, (2) The studies followed an independent case-control design, either based on hospital or population, (3) Comprehensive data of both frequencies genotypic and allelic, (4) Studies need comprehensive statistical indices, providing adequate data to measure odds ratios (OR) with confidence intervals (CI) of 95%, (5) Occurrence of genotype in cases and controls had to be within Hardy-Weinberg equilibrium (HWE), (6) Articles were considered in only English language.

Several reasons led to the exclusion of certain studies: (1) Studies from which data could not be extracted from the published results, were excluded, (2) Studies with inappropriate outcomes were not included (3) To avoid redundancy, duplicate studies were excluded, (4) Only case studies were not considered for this analysis; (5) Studies lacking all three genotype frequencies were excluded.

Data extraction: In our study, we independently examined all the appropriate articles, examining the essential criteria of every paper and extracting data using uniform data-abstraction forms. The information extracted for the literature encompassed the name of the first author, publication year,ethnicity, total cases and control. In case of any disagreements, they were determined through discussion. The description of the data involved in this meta-analysis investigating the relation of PTB with SNPs of VDR polymorphisms FokI, BsmI, ApaI and TaqI, as well as the genotype dispersal from each study, are presented in tables 5 to 8.

Table 3
Detail of analyses comprised in the BSMI rs 1544410 meta-analysis.

First Author	Year	Country	Ethnicity	Total Cases	Total Control
Selvaraj	2003	India	South Asian	80	120
Bornman	2004	UK	Asian	416	718
Fitness	2004	UK	Asian	397	672
Selvaraj	2004	India	South Asian	46	64
Lombard	2006	South Africa	African	95	117
Olesen	2007	Gambia	African	320	344
Selvaraj	2008	India	South Asian	51	60
Alagarasu	2009	India	South Asian	105	144
Merza	2009	Iran	South Asian	117	60
Selvaraj	2009	India	South Asian	65	60
Vidyarani	2009	India	South Asian	40	49
Banoei	2010	Iran	South Asian	60	62
Marashian	2010	Iran	South Asian	164	50
Kang	2011	Korea	East Asian	103	105
Sharma	2011	India	South Asian	238	924
Singh	2011	India	South Asian	101	225
Rathored	2012	India	South Asian	338	205
Joshi	2013	India	South Asian	110	115
Sinaga	2014	Indonesia	South Asian	76	76
Salimi	2015	Iran	South Asian	120	131
Jafari	2016	Iran	South Asian	96	122
Lee	2016	Taiwan	East Asian	198	170
Devi	2018	India	South Asian	169	227
Zhang	2018	China	East Asian	128	59
Beatriz Silva-Ramírez	2019	Mexican	African	257	457

Table 4
Detail of readings comprised in the APAI rs 7975232 meta-analysis.

First Author	Year	Country	Ethnicity	Total Cases	Total Control
Selvaraj	2003	India	South Asian	80	120
Bornman	2004	UK	Asian	416	718
Fitness	2004	UK	Asian	397	672
Selvaraj	2004	India	South Asian	46	64
Lombard	2006	South Africa	African	95	117
Babb	2007	South Africa	African	249	352
Olesen	2007	Gambia	African	320	344
Søborg	2007	Tanzania	African	435	416
Selvaraj	2008	India	South Asian	51	60
Alagarasu	2009	India	South Asian	105	144
Selvaraj	2009	India	South Asian	65	60
Vidyarani	2009	India	South Asian	40	49
Marashian	2010	Iran	South Asian	164	50
Sharma	2011	India	South Asian	238	924
Ferna´ndez-Mestre	2015	Venezuela	African	93	102
Jafari	2016	Iran	South Asian	96	122
Lee	2016	Taiwan	East Aian	198	170
Panwar	2016	India	South Asian	106	106
Rizvi	2016	India	South Asian	130	130
Devi	2018	India	South Asian	169	227
Zhang	2018	China	East Aian	128	59
Beatriz Silva-Ramírez	2019	Mexican	African	257	457

Table 5
Genotype distribution of VDR FOKI polymorphism

First Author	Year	Country	Genotype Cases			Genotype Control		
			FF	Ff	ff	FF	Ff	Ff
Selvaraj[42]	2003	India	43	29	8	78	36	6
Bornman[7]	2004	UK	258	138	20	444	242	32
Roth[39]	2004	Peru	119	60	21	109	78	14
Selvaraj[43]	2004	India	28	15	3	38	23	3
W.Liu[26]	2004	China	29	63	28	85	120	35
Lombard[27]	2006	South Africa	62	30	3	90	24	3
Babb[5]	2007	South Africa	132	104	13	203	129	20
Olesen[34]	2007	Gambia	198	106	16	207	118	19
Søborg[49]	2007	Tanzania	19	128	288	21	128	267
Wilbur[55]	2007	USA	64	26	1	165	120	5
Selvaraj[44]	2008	India	31	16	4	27	33	0
Alagarasu[3]	2009	India	65	31	9	81	59	4
Merza[30]	2009	Iran	67	46	4	35	25	0
Selvaraj[41]	2009	India	33	29	3	33	26	1
Vidyarani[54]	2009	India	23	14	3	20	29	0
Banoei[6]	2010	Iran	30	21	9	29	27	6
Marashian[28]	2010	Iran	97	57	10	15	30	5
Kang[22]	2011	Korea	30	58	15	41	43	21
Sharma[45]	2011	India	113	95	30	585	311	28
Singh[48]	2011	India	55	40	6	96	110	19
Rathored[37]	2012	India	175	115	48	118	80	7
Joshi[21]	2013	India	51	46	13	63	41	11
Sinaga[47]	2014	Indonesia	27	42	7	30	34	12
Ferna´ndez-Mestre[17]	2015	Venezuela	34	47	12	26	60	16
Linlin Wu[57]	2015	China	57	70	24	226	181	46
Salimi[40]	2015	Iran	65	44	11	93	31	7
Acen[1]	2016	Uganda	36	3	2	38	1	2
Jafari[20]	2016	Iran	41	50	5	55	61	6
Lee[24]	2016	Taiwan	44	104	50	51	87	32
Medapati[29]	2017	India	5	76	8	12	61	10
Devi[15]	2018	India	59	106	4	119	90	18
Zhang[58]	2018	China	14	61	53	21	25	13
Beatriz Silva-Ramírez[46]	2019	Mexican	62	119	76	159	218	80
Panda[35]	2019	India	55	58	37	86	51	13
de Albuquerque Borborema[13]	2020	Brazil	88	45	5	110	59	22

Table 6
Genotype distribution of VDR TAQI polymorphism

First Author	Year	Country	Genotype Cases			Genotype Control		
			TT	Tt	tt	TT	Tt	Tt
Delgado[14]	2002	USA	325	30	3	96	10	0
Bornman[7]	2004	UK	258	138	20	444	242	32
Fitness[18]	2004	UK	261	118	18	384	241	47
Roth[39]	2004	Peru	119	60	21	109	78	14
Selvaraj[43]	2004	India	28	15	3	38	23	3
W.Liu[26]	2004	China	29	63	28	85	120	35
Lombard[27]	2006	South Africa	62	30	3	90	24	3
Babb[5]	2007	South Africa	132	104	13	203	129	20
Olesen[34]	2007	Gambia	198	106	16	207	118	19

Søborg[49]	2007	Tanzania	19	128	288	21	128	267
Wilbur[55]	2007	USA	64	26	1	165	120	5
Selvaraj[44]	2008	India	31	16	4	27	33	0
Alagarasu[3]	2009	India	65	31	9	81	59	4
Selvaraj[41]	2009	India	33	29	3	33	26	1
Vidyarani[57]	2009	India	23	14	3	20	29	0
Banoei[6]	2010	Iran	30	21	9	29	27	6
Marashian[28]	2010	Iran	97	57	10	15	30	5
Kang[22]	2011	Korea	30	58	15	41	43	21
Sharma[45]	2011	India	113	95	30	585	311	28
Singh[48]	2011	India	55	40	6	96	110	19
Rathored[37]	2012	India	175	115	48	118	80	7
Ferna´ndez-Mestre[17]	2015	Venezuela	34	47	12	26	60	16
Linlin Wu[57]	2015	China	57	70	24	226	181	46
Salimi[40]	2015	Iran	65	44	11	93	31	7
Harishankar[19]	2016	India	36	39	15	42	39	8
Jafari[20]	2016	Iran	41	50	5	55	61	6
Lee[24]	2016	Taiwan	44	104	50	51	87	32
Panwar[36]	2016	India	66	28	12	90	14	2
Rizvi[38]	2016	India	92	27	11	104	22	4
Medapati[29]	2017	India	5	76	8	12	61	10
Devi[15]	2018	India	59	106	4	119	90	18
Zhang[58]	2018	China	14	61	53	21	25	13
Beatriz Silva-Ramírez[46]	2019	Mexican	62	119	76	159	218	80

Table 7
Genotype distribution of VDR BSMI polymorph

First Author	Year	Country	Genotype Cases			Genotype Control		
			BB	Bb	bb	BB	Bb	Bb
Selvaraj[42]	2003	India	43	29	8	78	36	6
Bornman[7]	2004	UK	258	138	20	444	242	32
Fitness[18]	2004	UK	261	118	18	384	241	47
Selvaraj[43]	2004	India	28	15	3	38	23	3
Lombard[27]	2006	South Africa	62	30	3	90	24	3
Olesen[34]	2007	Gambia	198	106	16	207	118	19
Selvaraj[44]	2008	India	31	16	4	27	33	0
Alagarasu[3]	2009	India	65	31	9	81	59	4
Merza[30]	2009	Iran	67	46	4	35	25	0
Selvaraj[41]	2009	India	33	29	3	33	26	1
Vidyarani[54]	2009	India	23	14	3	20	29	0
Banoei[6]	2010	Iran	30	21	9	29	27	6
Marashian[28]	2010	Iran	97	57	10	15	30	5
Kang[22]	2011	Korea	30	58	15	41	43	21
Sharma[45]	2011	India	113	95	30	585	311	28
Singh[48]	2011	India	55	40	6	96	110	19
Rathored[37]	2012	India	175	115	48	118	80	7
Joshi[21]	2013	India	51	46	13	63	41	11
Sinaga[47]	2014	Indonesia	27	42	7	30	34	12
Salimi[40]	2015	Iran	65	44	11	93	31	7
Jafari[20]	2016	Iran	41	50	5	55	61	6
Lee[24]	2016	Taiwan	44	104	50	51	87	32
Devi[15]	2018	India	59	106	4	119	90	18
Zhang[58]	2018	China	14	61	53	21	25	13
Beatriz Silva-Ramírez[46]	2019	Mexican	62	119	76	159	218	80

Table 8
Genotype distribution of VDR APAI polymorphism

First Author	Year	Country	Genotype Cases			Genotype Control		
			AA	Aa	aa	AA	Aa	Aa
Selvaraj[42]	2003	India	43	29	8	78	36	6
Bornman[7]	2004	UK	258	138	20	444	242	32
Fitness[18]	2004	UK	261	118	18	384	241	47
Selvaraj[43]	2004	India	28	15	3	38	23	3
Lombard[27]	2006	South Africa	62	30	3	90	24	3
Babb[5]	2007	South Africa	132	104	13	203	129	20
Olesen[34]	2007	Gambia	198	106	16	207	118	19
Søborg[49]	2007	Tanzania	19	128	288	21	128	267
Selvaraj[44]	2008	India	31	16	4	27	33	0
Alagarasu[3]	2009	India	65	31	9	81	59	4
Selvaraj[41]	2009	India	33	29	3	33	26	1
Vidyarani[54]	2009	India	23	14	3	20	29	0
Marashian[28]	2010	Iran	97	57	10	15	30	5
Sharma[45]	2011	India	113	95	30	585	311	28
Ferna´ndez-Mestre[17]	2015	Venezuela	34	47	12	26	60	16
Jafari[20]	2016	Iran	41	50	5	55	61	6
Lee[24]	2016	Taiwan	44	104	50	51	87	32
Panwar[36]	2016	India	66	28	12	90	14	2
Rizvi[38]	2016	India	92	27	11	104	22	4
Devi[15]	2018	India	59	106	4	119	90	18
Zhang[58]	2018	China	14	61	53	21	25	13
Beatriz Silva-Ramírez[46]	2019	Mexican	62	119	76	159	218	80

Statistical scrutiny: STATA, type 13.0 (STATA Corp., College Station, TX, USA) was applied for the data scrutiny. The relationship of BsmI, ApaI, FokI and TaqI polymorphisms in the jeopardy of PTB was evaluated by calculating pooled ORs and their consequent 95% CIs. A random-effect form was employed when heterogeneity exceeded 50%, as measured by the I^2 method, while a fixed-effect form was taken into consideration when heterogeneity was below 50%. To check for publication bias, a funnel map was visually inspected. A P-value less than 0.05 was considered statistically significant[33].

Various genetic forms were applied for the analysis. For the FokI polymorphism, the allelic form compared F vs. f, the dominant form compared FF+Ff vs. ff and the recessive form compared ff vs. fF+FF. For the TaqI polymorphism, the allelic form compared T vs. b, the dominant form compared TT+Tt vs. tt and the recessive form compared tt vs. tT+TT. For the BsmI polymorphism, the allelic form compared B vs. b, the dominant form compared BB+Bb vs. bb and the recessive form compared bb vs. bB+BB.

Lastly, for the ApaI polymorphism, the allelic form compared A vs. a, the dominant form compared AA+Aa vs. aa and the recessiveform compared aa vs. aA+AA. To measure the relation between each polymorphism and the hazard of PTB, these genetic representations were used.

Results

Relation of the FOKI VDR polymorphism with PTB: To understand the relation of the FOKI polymorphism with PTB, 35 eligible studies were included. Fixed-effects forms were used. In our analysis, we found a significant association in all the forms including the allele form: f vs F (OR = 0.17; 95% CI = -0.37, 0.04; P = 0.00)(Fig. 2), dominant form: FF+Ff vs. ff (OR = -0.16, 95% CI = -0.33,0.00; P 0.00) (Fig. 3), recessive form: ff vs FF+Ff (OR = -0.26, 95% CI = -0.53,0.01; P = 0.00) (Fig. 4) and co- dominant form: FF vs ff(OR = -0.42, 95%CI = -0.69,-0.14;, P = 0.00) (Fig. 5).

Relation of the TAQI VDR polymorphism with PTB: To understand the relation of the TAQI polymorphism with PTB, 33 eligible studies were included. Fixed-effects forms were used. Our analysis depicts the significant associations in all the forms including the allele form: T vs t (OR = -0.03; 95% CI = -0.23, 0.17; P = 0.01)(Fig. 6), dominant form: TT+Tt vs. tt (OR = -0.11, 95% CI = -0.25,0.04; P = 0.00) (Fig. 7), recessive form: tt vs TT+Tt (OR = -0.29, 95% CI = -0.54,-0.04; P = 0.00) (Fig. 8) and co-dominant form: TT vs tt (OR = -0.34, 95%CI = -0.64,-0.05; P = 0.00) (Fig. 9).

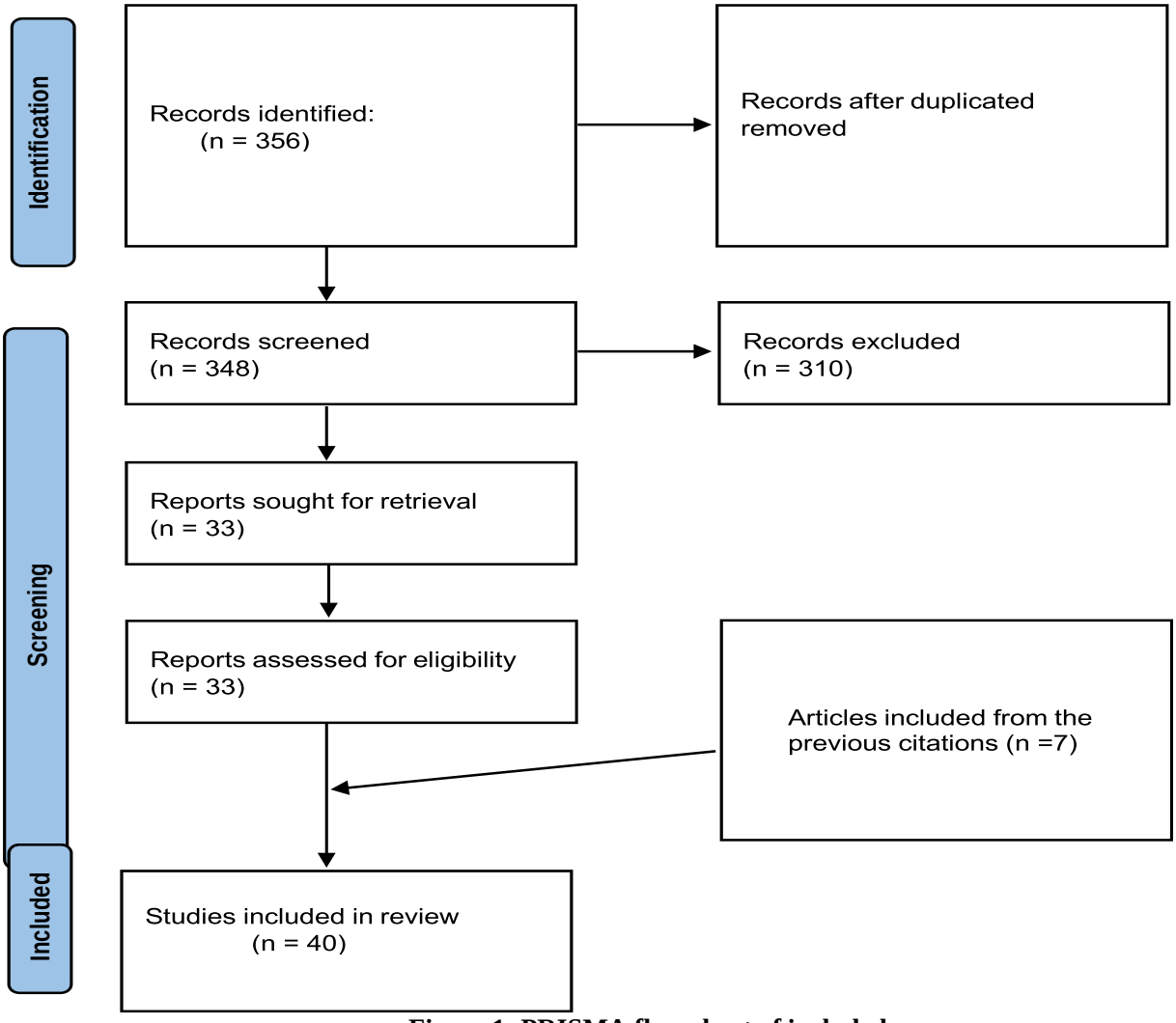


Figure 1: PRISMA flow chart of included

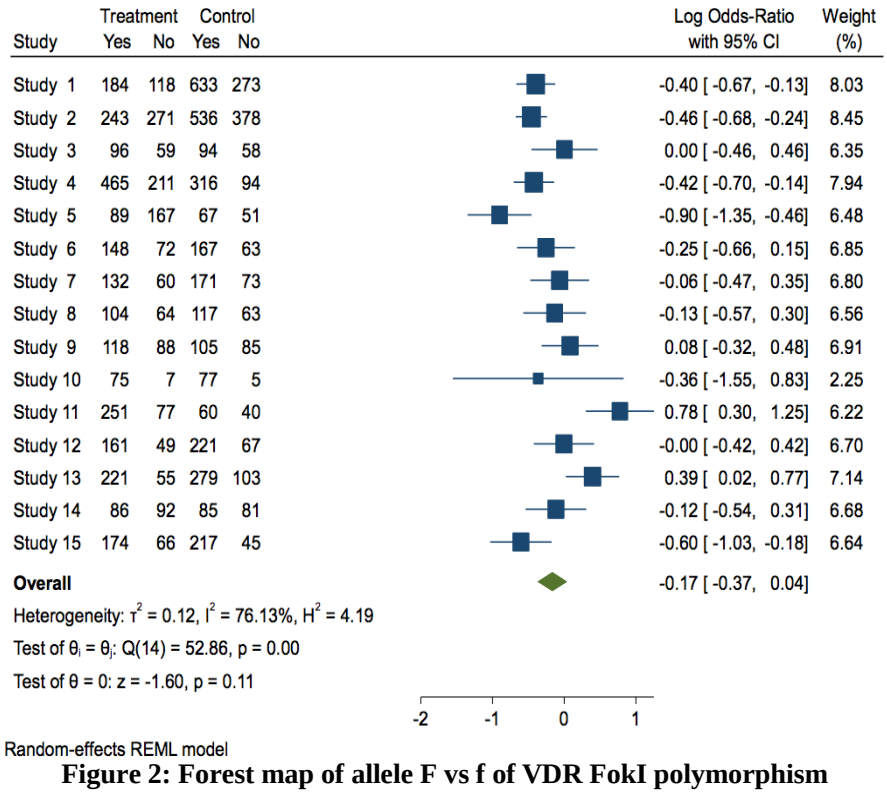


Figure 2: Forest map of allele F vs f of VDR FokI polymorphism

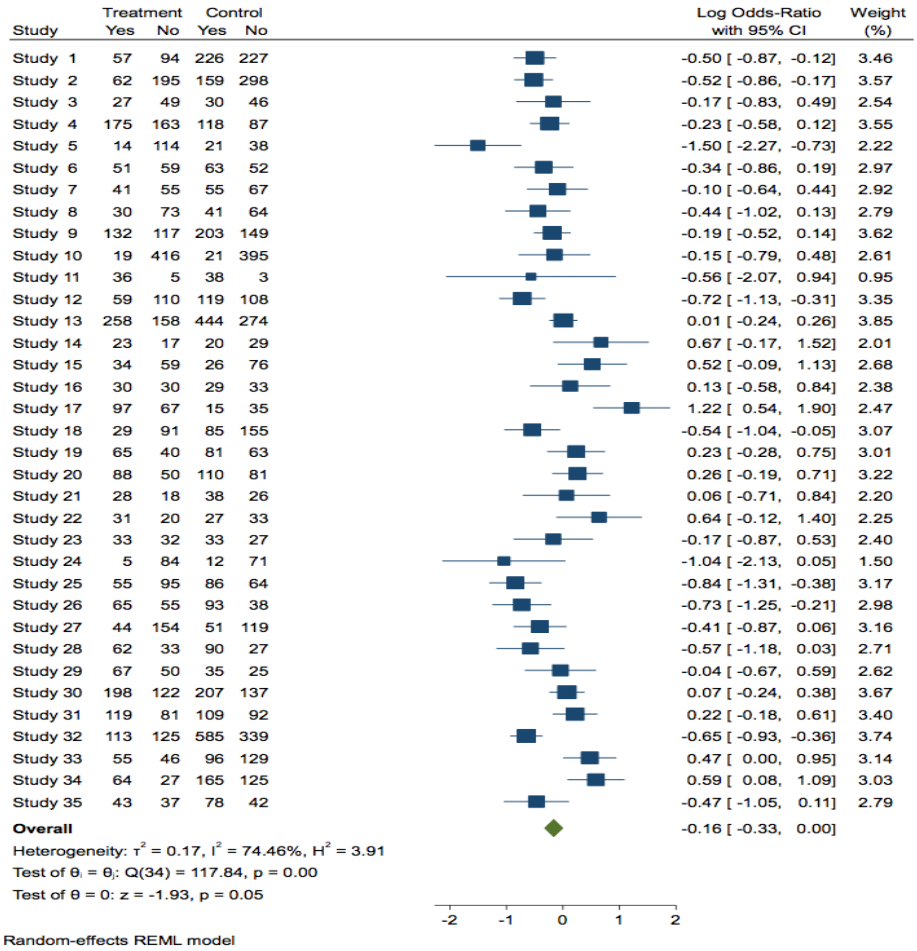


Figure 3: Forest map of dominant genetic form of FF+Ff vs. ff of VDR FokI polymorphism

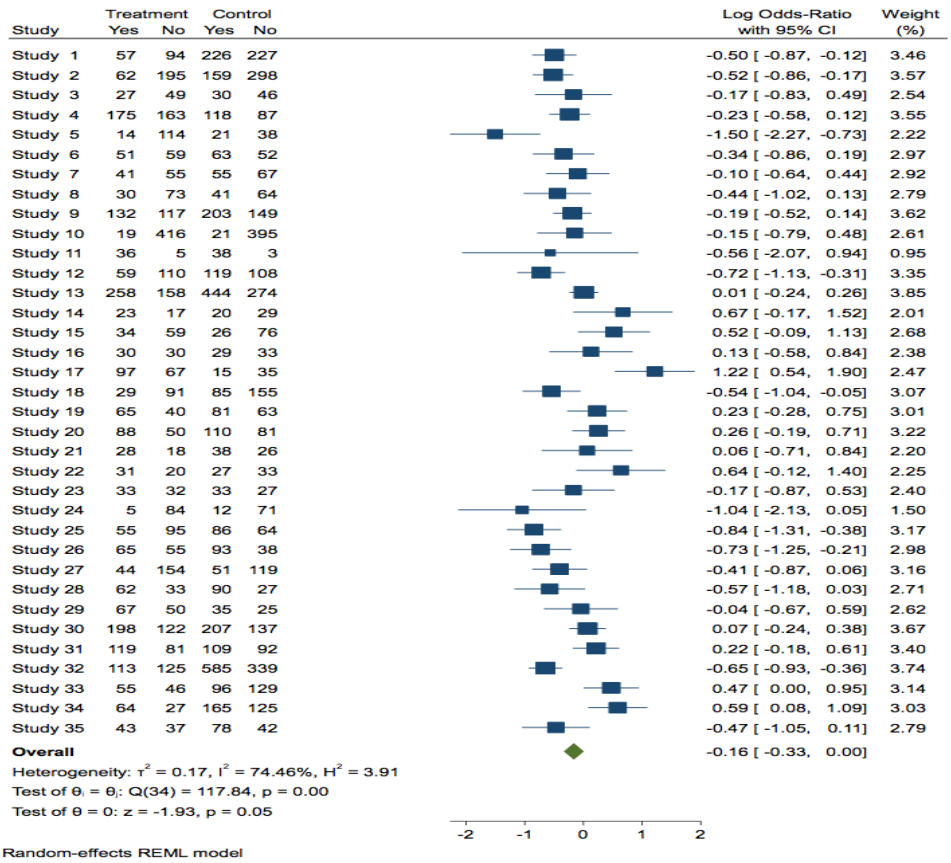


Figure 4: Forest map of recessive genetic form of ff vs. FF+Ff of VDR FokI polymorphism

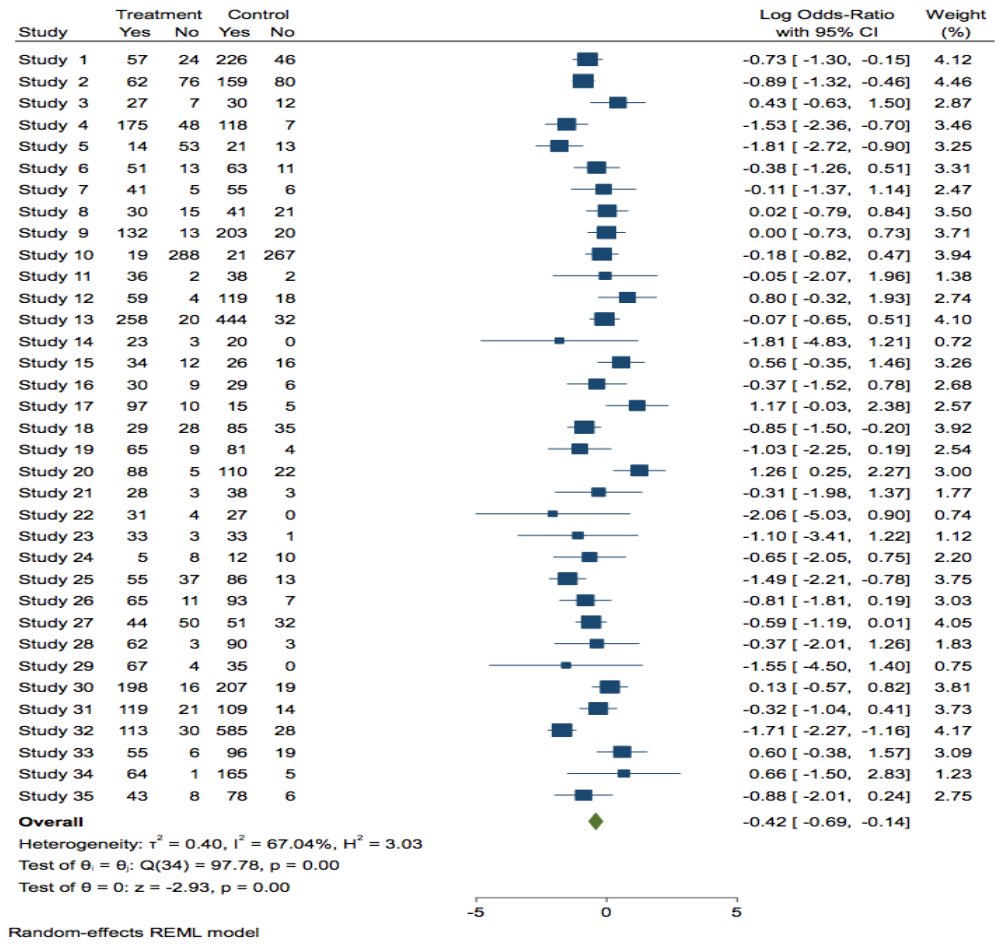


Figure 5: Forest map of co-dominant genetic form of FF vs ff of VDR FokI polymorphism

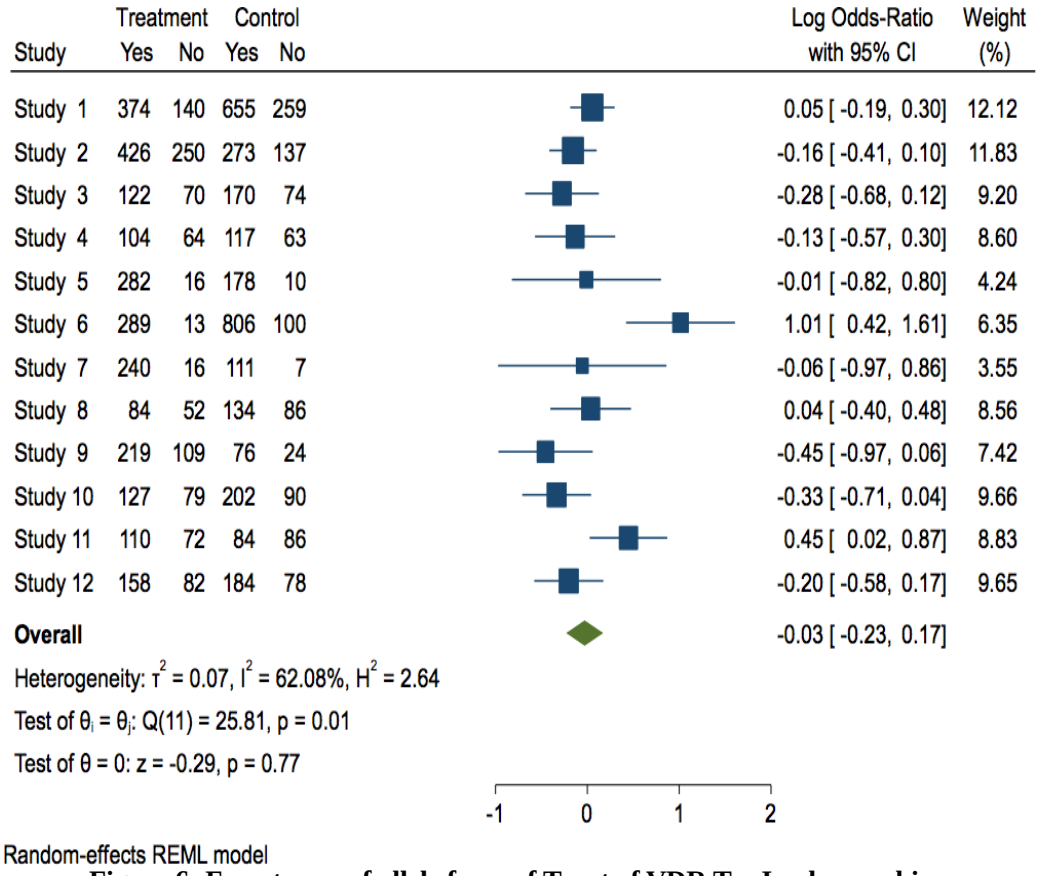


Figure 6: Forest map of allele form of T vs t of VDR TaqI polymorphism

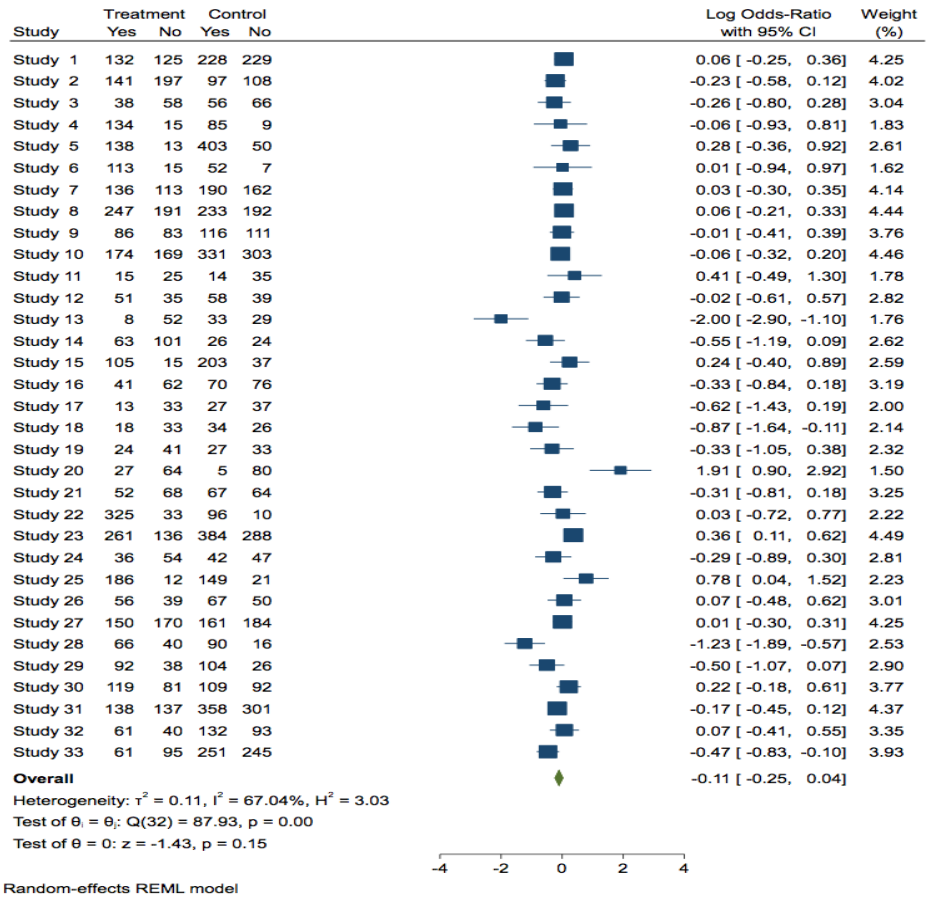


Figure 7: Forest map of dominant form of TT+Tt vs tt of VDR TaqI polymorphism

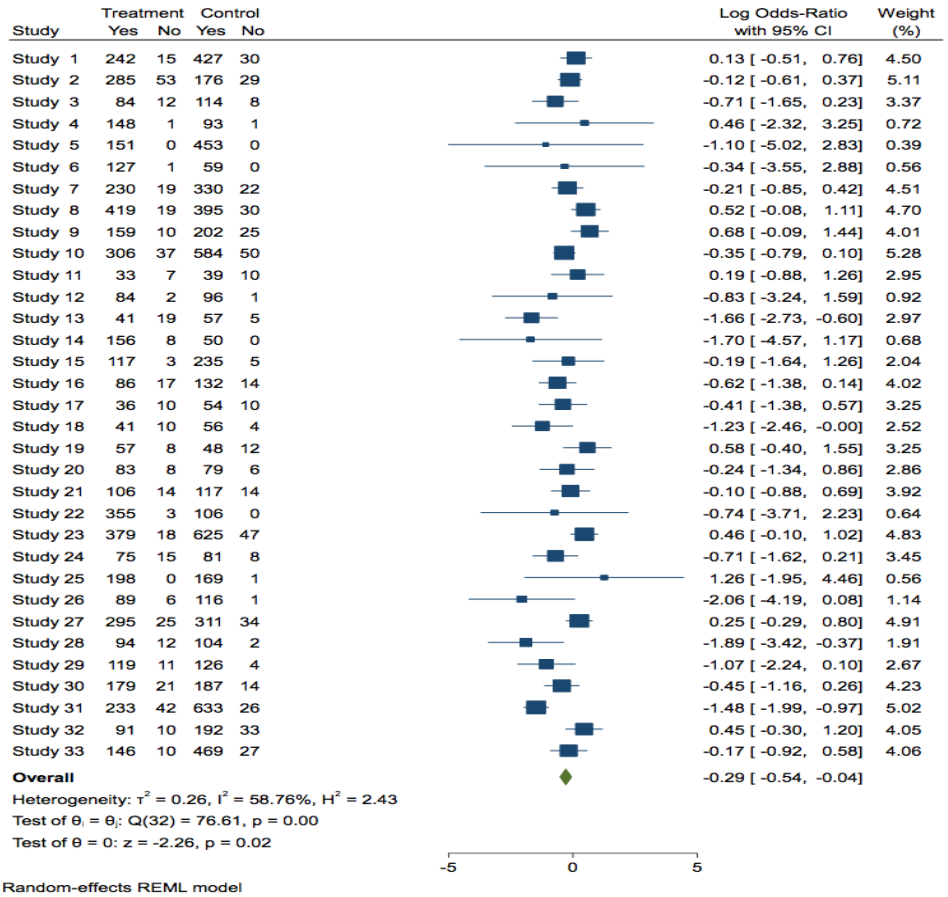


Figure 8: Forest map of recessive form of tt vs. TT+Tt of VDR TaqI polymorphism

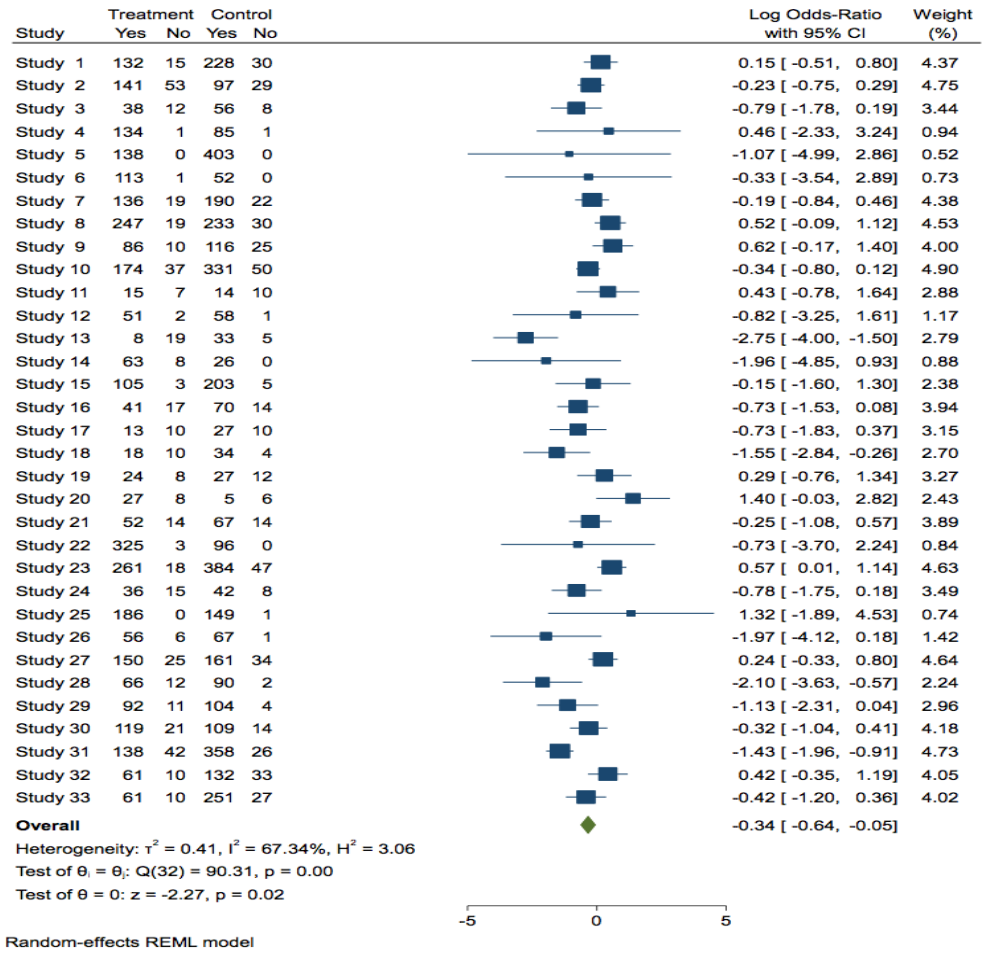


Figure 9: Forest map of co-dominant form of TT vs tt of VDR TaqI polymorphism

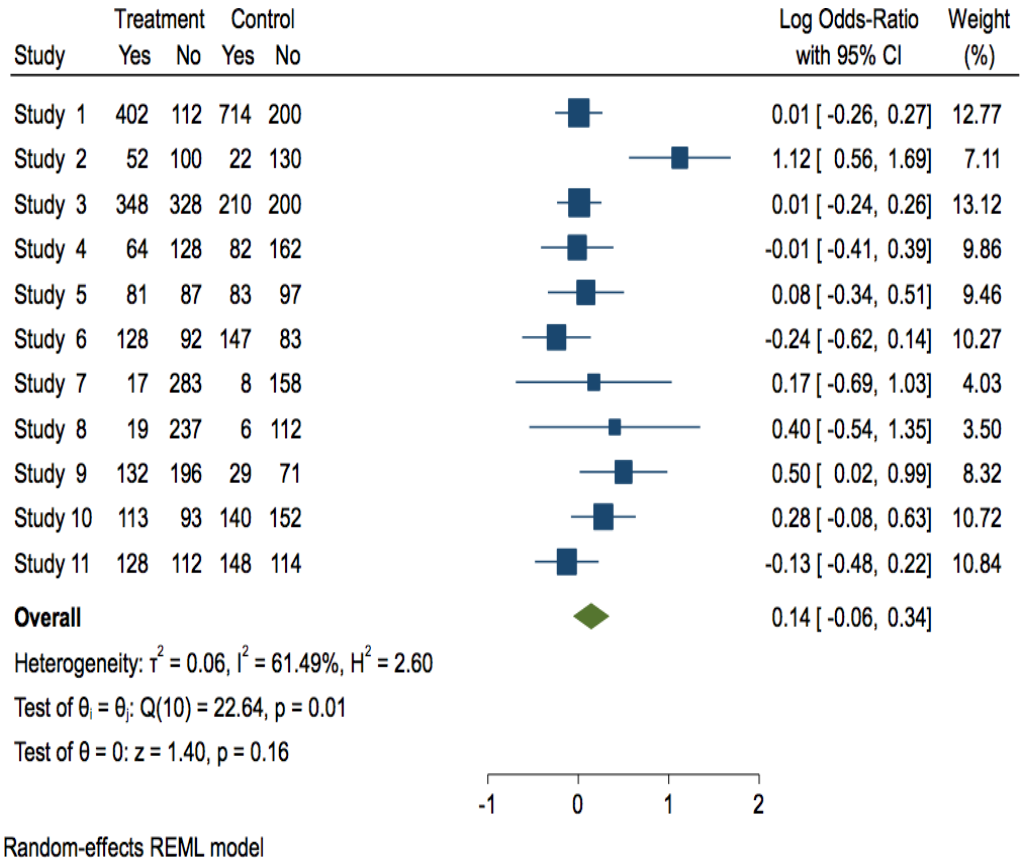


Figure 10: Forest map of allele form of B vs b of VDR BsmI polymorphism

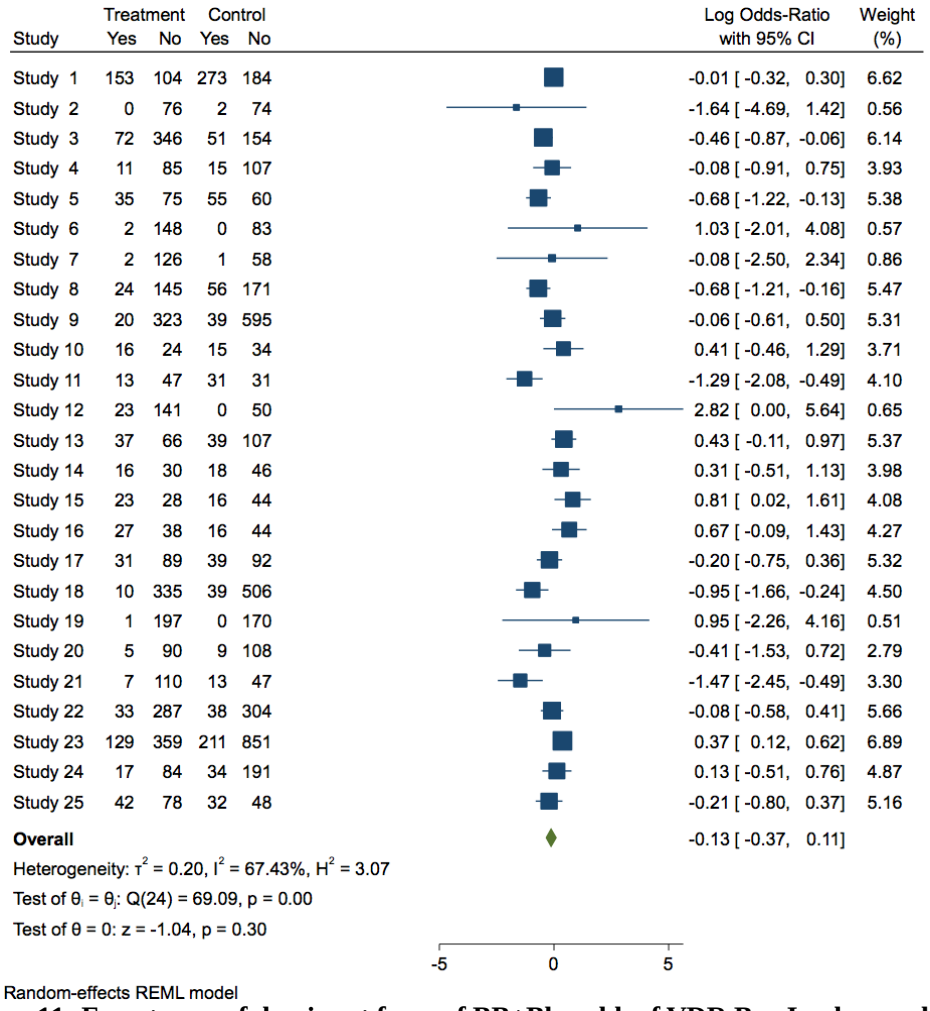


Figure 11: Forest map of dominant form of BB+Bb vs bb of VDR BsmI polymorphism

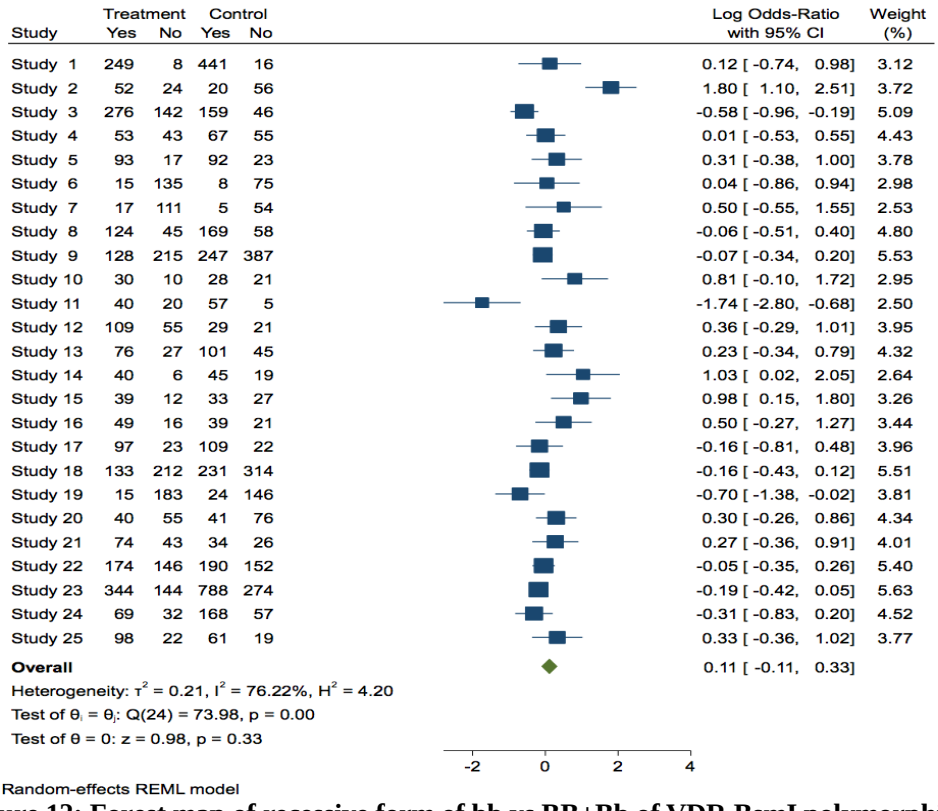


Figure 12: Forest map of recessive form of bb vs BB+Bb of VDR BsmI polymorphism

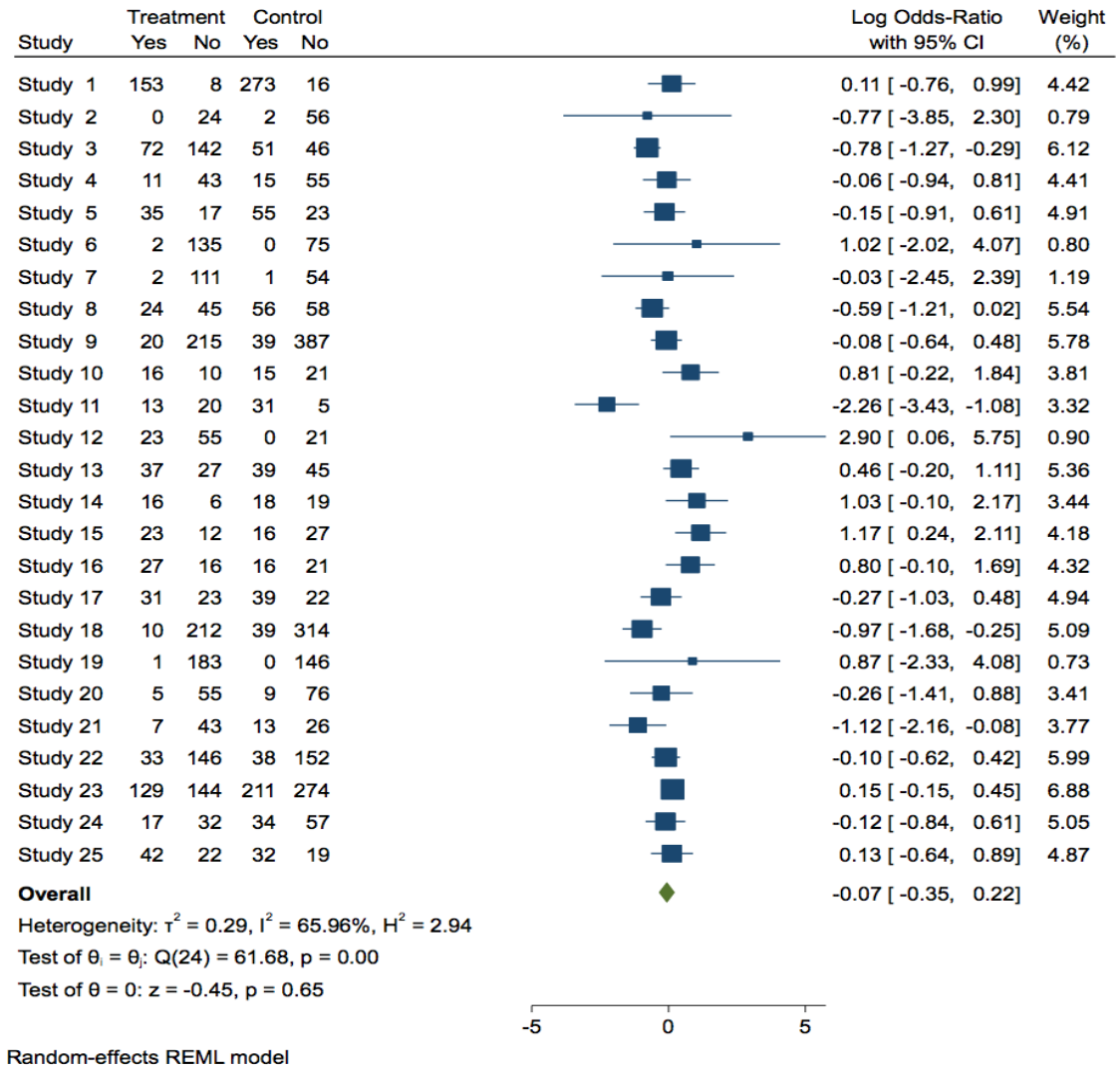


Figure 13: Forest map of co-dominant form of BB vs bb of VDR BsmI polymorphism

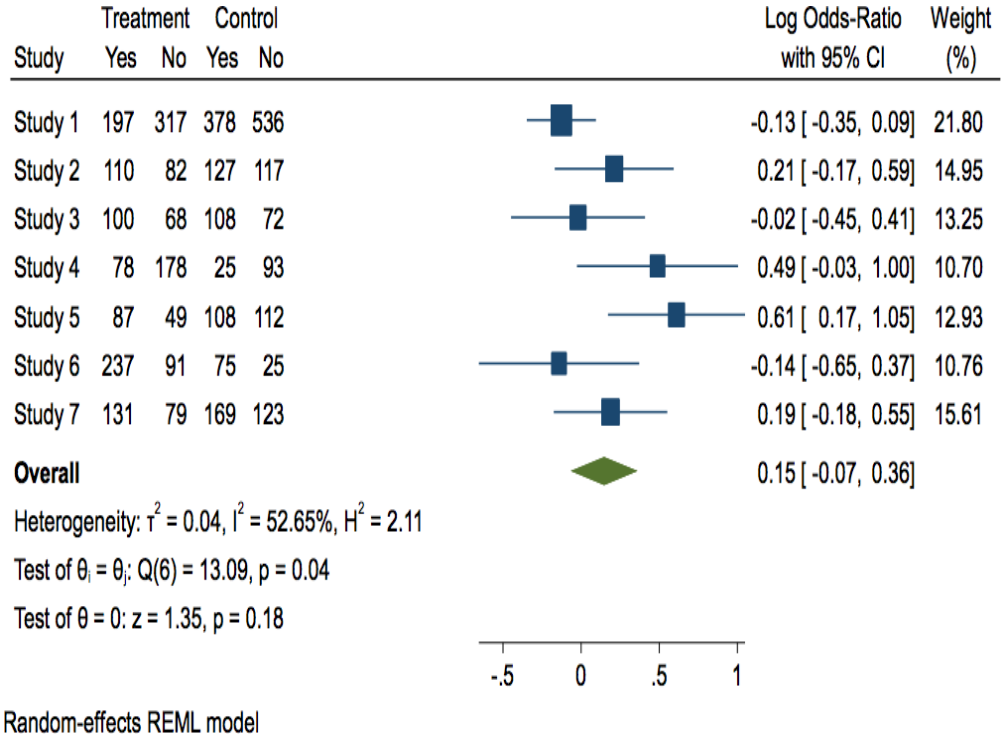


Figure 14: Forest map of allele form A vs a of VDR ApaI polymorphism

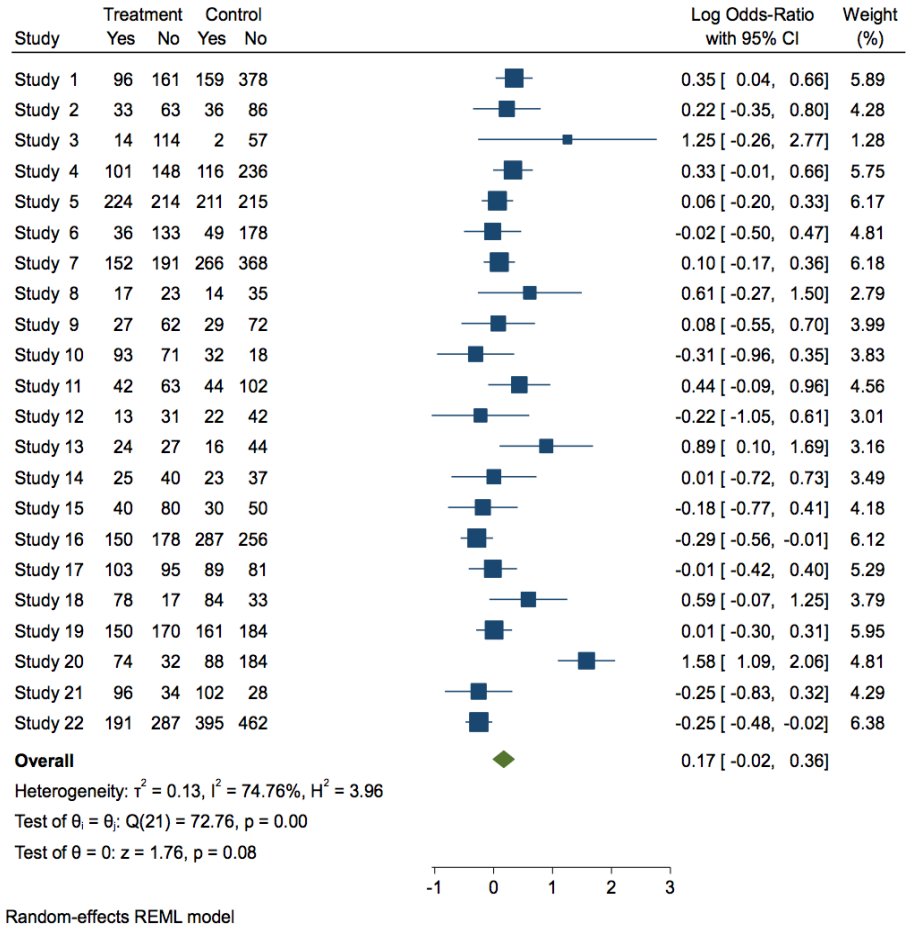


Figure 15: Forest map of dominant form AA + Aa vs aa of VDR ApaI polymorphism

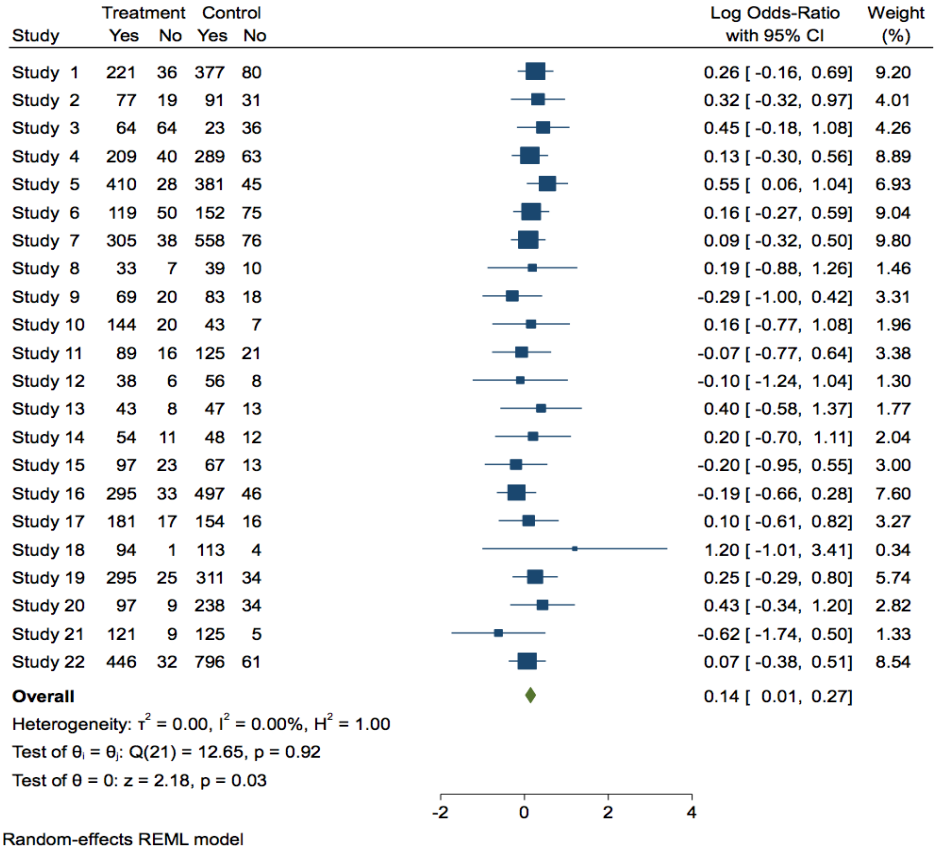


Figure 16: Forest map of recessive form aa vs AA + Aa of VDR ApaI polymorphism

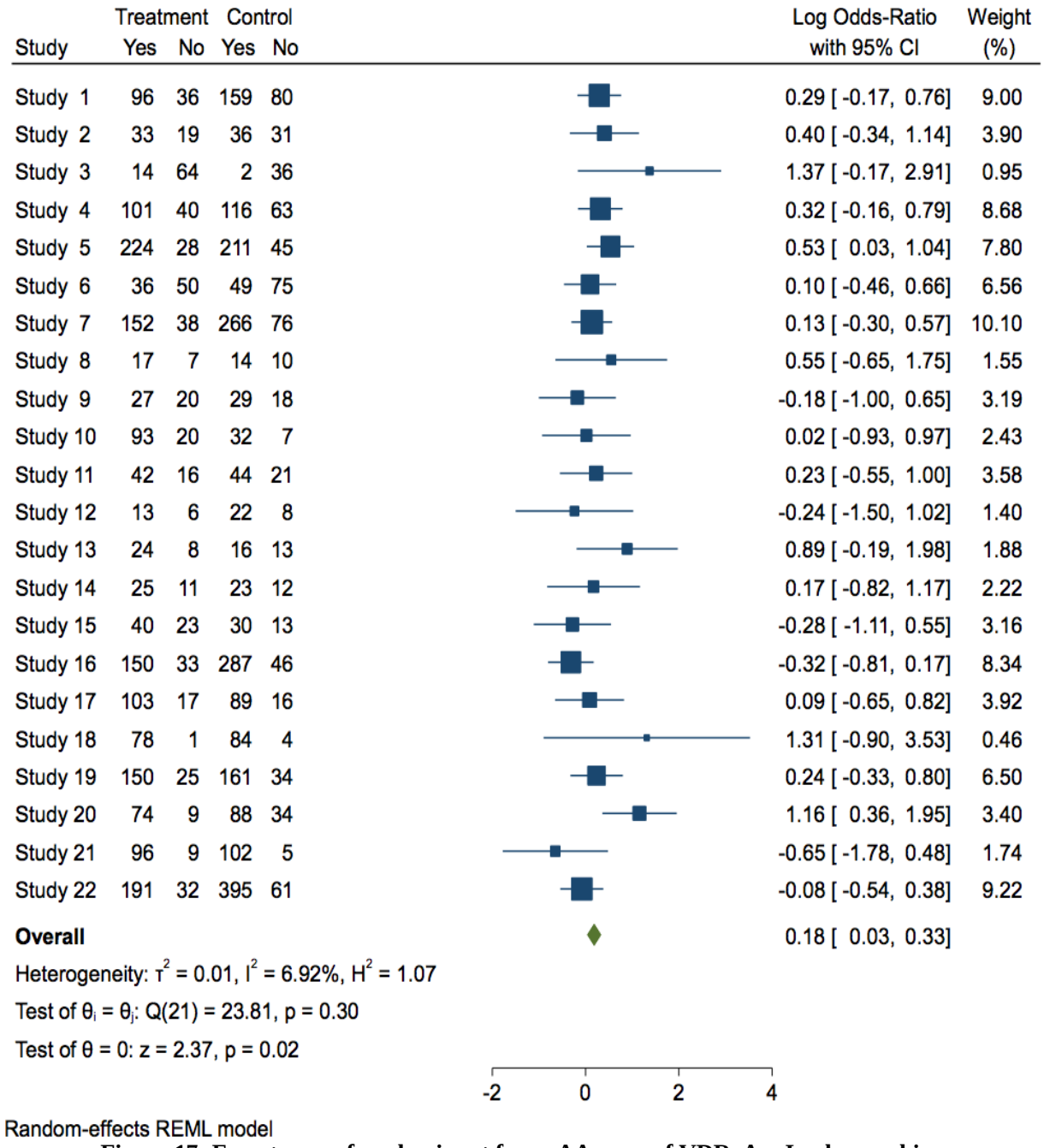
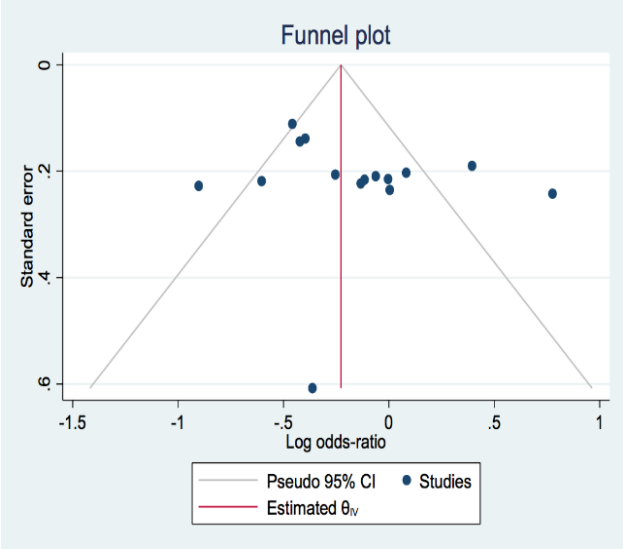


Figure 17: Forest map of co-dominant form AA vs aa of VDR ApaI polymorphism

Relation of the BSMI VDR polymorphism with PTB: To understand the association of the BSMI polymorphism with PTB, 25 eligible studies were included. Fixed-effects forms were used. Our analysis observed significant associations in all the forms including the allele form: B vs b (OR = 0.14; 95% CI = -0.06, 0.34; P = 0.01) (Fig. 10), dominant form: BB+Bb vs. bb (OR = -0.13, 95% CI = -0.37,0.11; P = 0.00) (Fig. 11), recessive form: tt vs TT+Tt (OR = 0.11, 95% CI = -0.11,0.33; P = 0.00) (Fig. 12) and co-dominant form: TT vs tt (OR = -0.07, 95%CI = -0.35,0.22; P = 0.00) (Fig. 13).

Association of the APAI VDR polymorphism with PTB: To understand the association of the APAI polymorphism with PTB, 22 eligible studies were included. Fixed-effects forms were used. Our analysis shows that only one form had significant associations in all the forms including the allele form: A vs an (OR = 0.15; 95% CI = -0.07, 0.36; P = 0.04) (Fig. 14), dominant form: AA+Aa vs aa (OR = 0.17, 95% CI = - 0.02,0.36; P = 0.00) (Fig. 15), recessive form: aa vs AA+Aa (OR = 0.14, 95% CI = 0.01,0.27; P = 0.92) (Fig. 16) and co-dominant form: AA vs aa (OR = 0.18, 95%CI = 0.03,0.33; P = 0.30) (Fig. 17).

Publication bias: Each study was eliminated from the sensitivity scrutiny one at a time to examine the robustness of the obtained results. The meta-analysis results were statistically significant since all the associated pooled ORs in all of the dispersed subgroup investigation remained relatively steady. The symmetrical distribution revealed that there was no publication bias.



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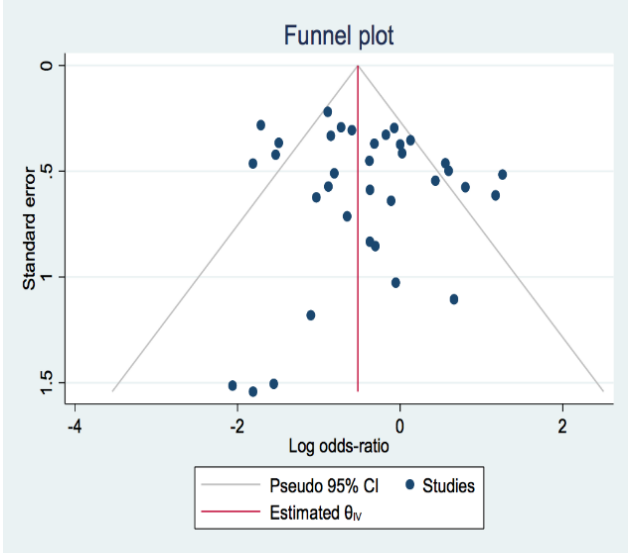

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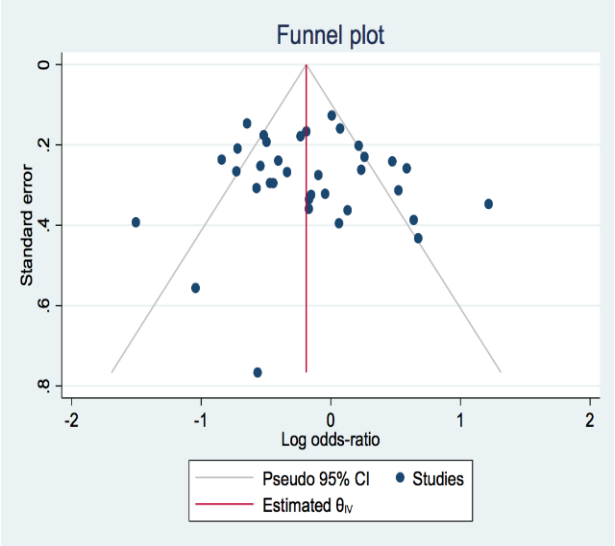

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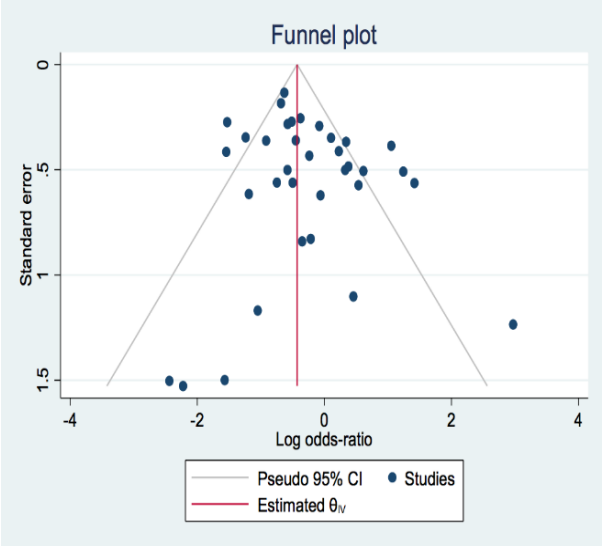
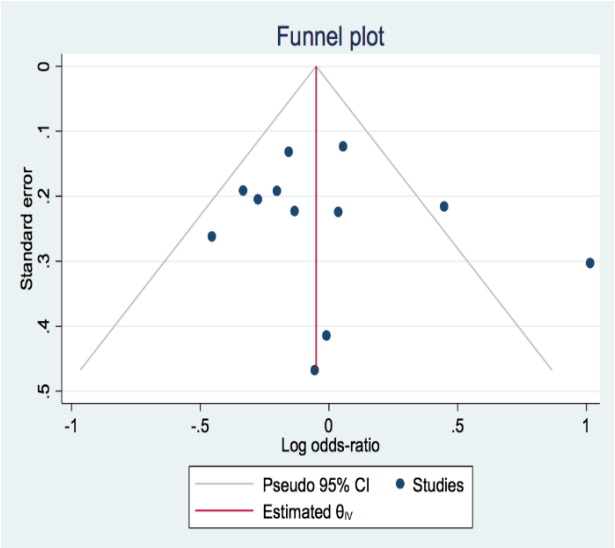


(d)

Fig. 18: Funnel map of VDR FokI polymorphism; A) allele form; B) co-dominant form; C) dominant form; D) recessive form



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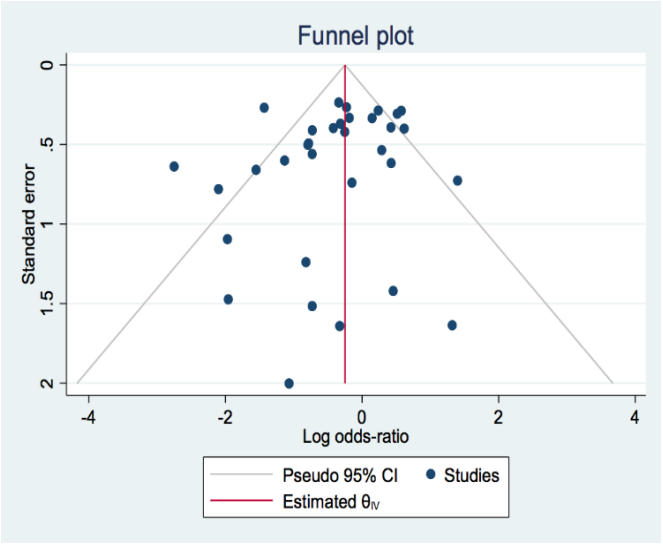

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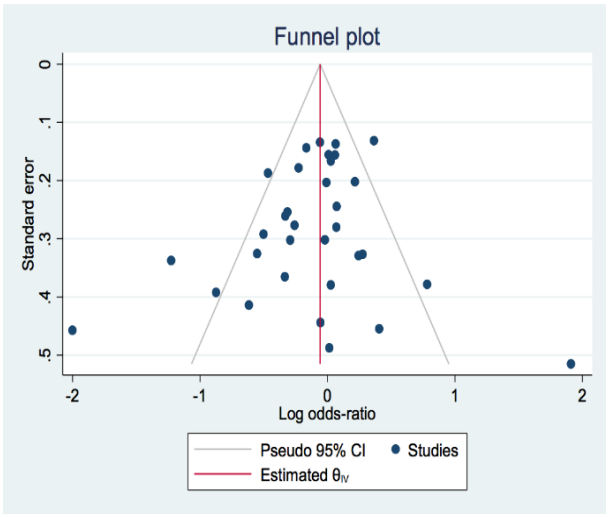

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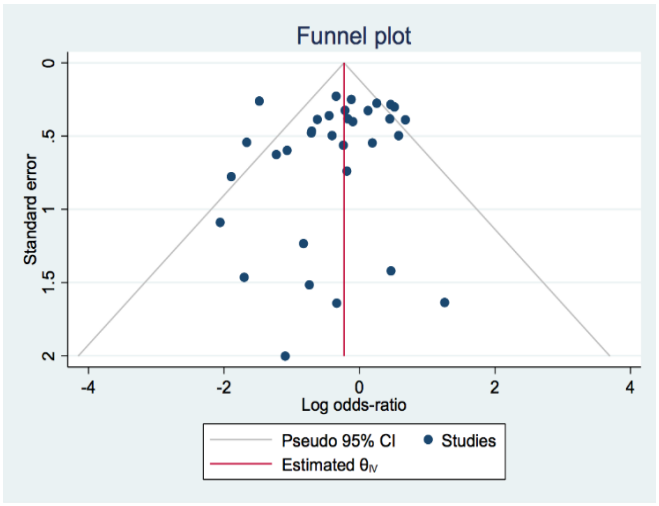
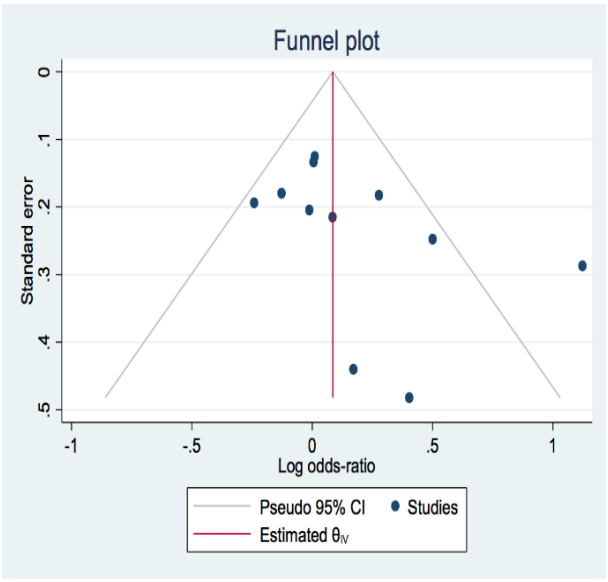


(d)

Fig. 19: Funnel map of VDR TaqI polymorphism; A) allele form; B) co-dominant form; C) dominant form; D) recessive form



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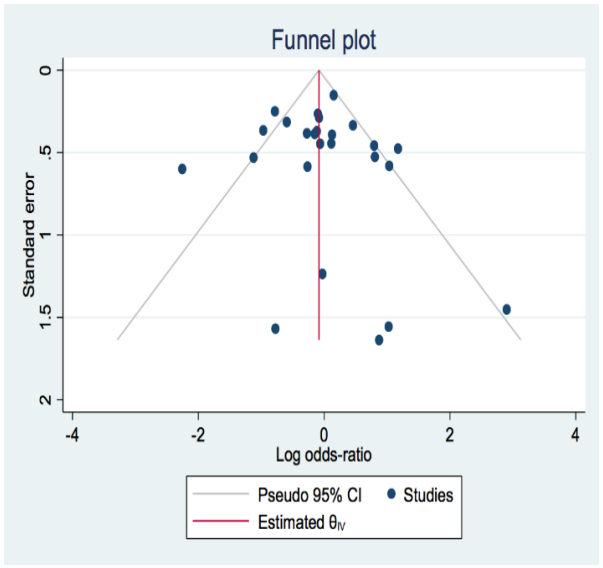

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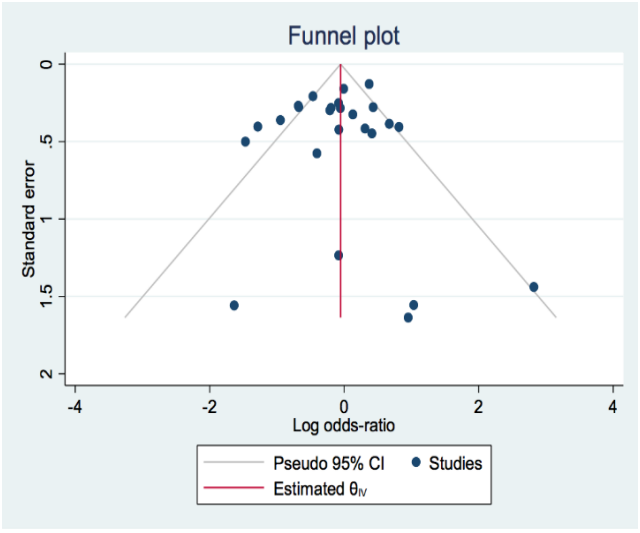

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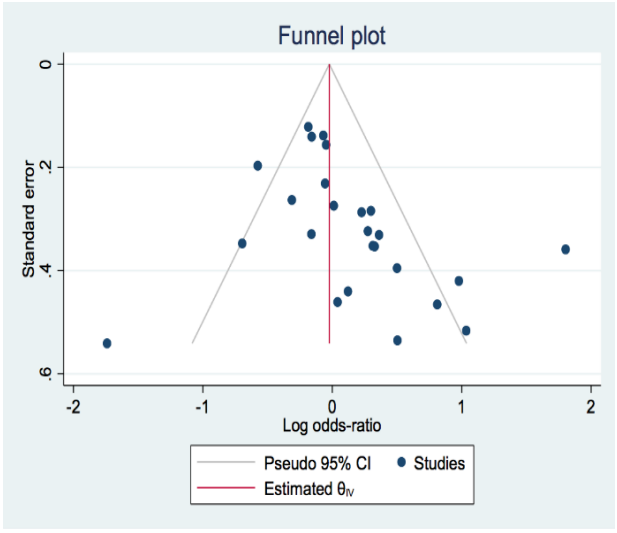

(d)

Fig. 20: Funnel map of *VDR* BsmI polymorphism; A) allele form; B) co-dominant form; C) dominant form; D) recessive form

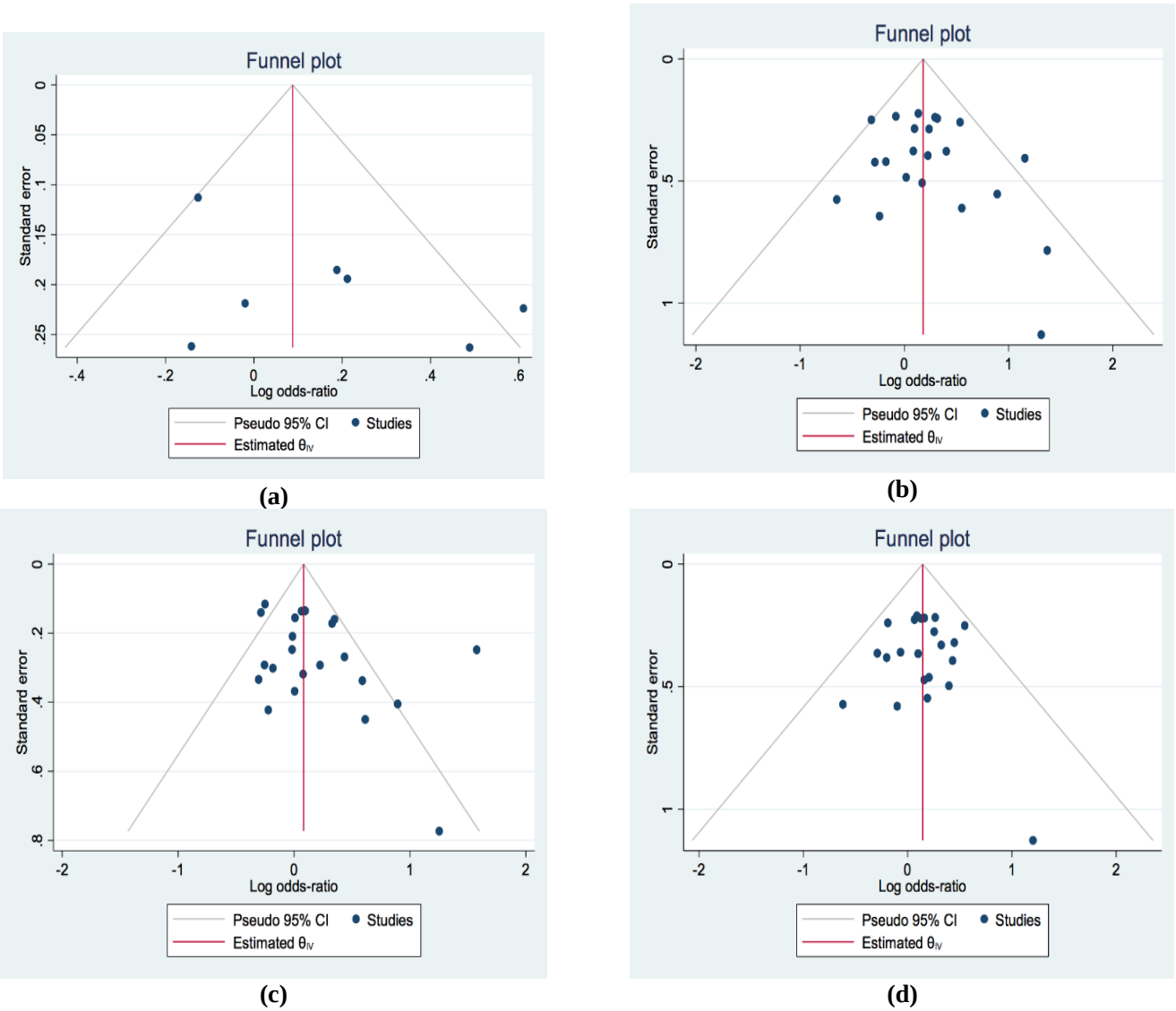

Fig. 21: Funnel map of *VDR* ApaI polymorphism; A) allele form; B) co-dominant form; C) dominant form; D) recessive form

Discussion

Literature displayed that lower vitamin D levels are more common in TB patients than in healthy controls. The VDR gene plays a vital role in immunological pathways by activating responses that combat germs within macrophage cells. Consequently, variations in VDR (polymorphisms) may lead to altered immunological responses. Although many SNPs exist in the VDR gene, only four main variants (FokI, BsmI, TaqI and ApaI) were selected for analysis in the included studies. This meta-analysis with 40 published data specifies that VDR FokI polymorphism contributes to the hazard of TB. Recent meta-analyses conclude that the FF genotype of the FokI polymorphism showed a high hazard of TB in Asian populations but not in Caucasian or African peoples. Limited studies have focused on Latin American populations.

Some studies in Peruvian patients indicated a connection between certain VDR genotypes and the time required for sputum culture conversion, but not with active TB. The meta-analysis was conducted to discover the genetic links amongst the most frequentlystudied VDR gene variations (FokI, TaqI, BsmI and ApaI) and their association with susceptibility to PTB. According to our analysis, TaqI polymorphism does not show any association with PTB. However, the FokI, BsmI and ApaI polymorphisms were found to be significantly correlated with PTB susceptibility. This association was further supported by various forms of analysis, indicating an amplified hazard of PTB with these alleles. In the East Asian people, FokI shows high-risk PTB, due to genetic heterogeneity and differences in clinical characteristics among various populations.

Despite these significant findings, the study had certain limitations, mainly due to the limited availability of data that prevented more extensive research of the VDR polymorphisms' connection with clinical topographies of PTB. Nonetheless, the meta-analysis suggests that the VDR FokI, BsmI and ApaI polymorphisms could serve as genetic biomarkers for certain forms of tuberculosis, highlighting

their potential role in disease susceptibility. However, additional large-scale studies encompassing diverse ethnic populations are required to fully comprehend the roles of VDR polymorphisms in PTB susceptibility. Moreover, future research should explore the involvement of other VDR variants in tuberculosis development.

Conclusion

Our meta-analysis recommended that VDR *Fok*I, BsmI and ApaII gene polymorphism is linked with greater susceptibility to tuberculosis while TaqI was found with no susceptibility to PTB.

Acknowledgement

Dr. Shripad A Patil, Dr. Ekta Sinha and Mr. Shobhit Gupta are acknowledged for their vital contribution to the data collection and analysis.

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