RESEARCH

Association of vitamin D receptor genetic polymorphisms with the risk of infertility: a systematic review and meta-analysis

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Abstract

Background The causes of infertility have remained an important challenge. The relationship between VDR gene polymorphisms and infertility has been reported, with controversial findings.

Objective and rationale We aimed to determine this relationship by conducting a systematic review and meta-analysis.

Search methods The study was started with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) declaration and the final draft was registered as a protocol in PROSPERO (ID: CRD42023416535). The international electronic databases including PubMed (Medline), Scopus, Web of Sciences, and Cumulative Index to Nursing and Allied Health Literature (CINHAL) were searched until January 30, 2023, by using appropriate keywords. The quality of the final studies was assessed using the NOS Checklist for case–control studies. The odds ratios (ORs) for each of the genetic models were pooled, and a subgroup analysis based on geographical region and types of infertility was carried out by the MetaGenyo online tool.

Outcomes Case–control studies including 18 and 2 studies about infertility in women and men, respectively, and 4 miscarriage studies were entered into the meta-analysis. The VDR gene TaqI polymorphism was associated with infertility susceptibility in women in the allele contrast [OR = 1.2065, 95% CI (1.0846–1.3421); $P = 0.0005$], Recessive model [OR = 1.3836, 95% CI (1.1197–1.7096); $P = 0.002$], Dominant model [OR = 1.2146, 95% CI (0.0484–1.4072); $P = 0.009$], Homozygote [OR = 1.4596, 95% CI (1.1627–1.8325); $P = 0.001$], and TT vs. Tt [OR = 1.2853, 95% CI (1.0249–1.6117); $P = 0.029$. ApaI and FokI gene polymorphisms were found to be significantly protective SNPs against women and men infertility in the Dominant model [OR = 0.8379, 95% CI (0.7039- 0.9975); $P = 0.046$] and Recessive model [OR = 0.421, 95% CI (0.1821–0.9767); $P = 0.043$], respectively. Sub-group meta-analysis showed a protection association of ApaI in dominant [OR = 0.7738, 95% CI = 0.6249–0.9580; $P = 0.018$] and AA vs. aa [OR = 0.7404, 95 CI% (0.5860–0.9353) $P = 0.011725$] models in PCOS subgroup, however, a negative association with idiopathic infertility was found in AA vs. Aa [OR = 1.7063, 95% CI (1.1039–2.6375); $P = 0.016187$] and Aa vs. aa [OR = 0.6069, 95% CI (0.3761–0.9792); $P = 0.040754$]. TaqI SNP was significantly associated with infertility in the African population and BsmI was associated with the disease mostly in the Asian population.

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Conclusion This meta-analysis showed that the TaqI polymorphism may be linked to women's infertility susceptibility. However, Apal and FokI might be the protective SNPs against infertility in Women and men, respectively.

Keywords Infertility, Miscarriage, Vitamin D receptor, Polymorphism, Meta-Analysis, Systematic review

Introduction

Infertility is a disease of the female or male reproductive system in which pregnancy does not occur after 12 months of regular unprotected sex [1]. This disease is a very common condition that affects between 48.5 and 186 million males and females worldwide, respectively. According to WHO, almost one out of six people of reproductive age experience infertility during their lifetime [2, 3]. Genetic, environmental, and some idiopathic factors are among the effective causes of infertility[4]. Male infertility is usually due to problems in the semen existence, the absence or low levels of sperm, or the abnormal shape and movement of sperm, and infertility in women is also caused by a range of abnormalities of the ovaries, uterus, fallopian tubes, the endocrine system, etc. [5]. Furthermore, Miscarriage is generally defined as the loss of a pregnancy before viability, which is considered the other complication of successful pregnancy [6]. It is estimated that 23 million miscarriages occur worldwide each year [7]. The short-term national economic cost of miscarriage in the UK was estimated at 471 million pounds annually in 2005 [8]. Physical consequences of miscarriage include bleeding or infection and psychological consequences such as increased risk of anxiety, depression, post-traumatic stress disorder, and suicide [9]. Its determinants include fetal genetic and chromosomal abnormalities, genital anatomy, endometrial pathology, hereditary thrombophilia, antiphospholipid syndrome, etc. Most of these factors are difficult to correct, but there are also controllable ones whose negative effects can be completely reduced before conception. These include nutritional deficiencies, including vitamin D (Vit D) deficiency [10, 11].

Vit D is a hormone that has a fundamental role in endocrine function, regulation of cell proliferation, and other metabolic pathways, such as pathways involved in the immune response [12]. Recent studies show the relationship between vitamin D deficiency and adverse pregnancy outcomes, including miscarriage [13–15]. Vit D is locally metabolized in the male reproductive system and the expression of Vitamin D receptor (VDR) has been shown in human testes and in ejaculated human sperms [16]. Studies have proven that Men who receive more diet and supplements produce sperm with less DNA damage [17]. Maternal Vit D deficiency is associated with many gynecological and obstetric diseases such as polycystic ovary syndrome, endometriosis, ovarian cancer, as well

as gestational diabetes, which are all associated with reduced successful pregnancy. Preeclampsia and preterm labor are related, which can affect fertility [4, 18, 19]. Polycystic ovary syndrome (PCOS) is the most common endocrine metabolic disorder that affects 5 to 10% of women of reproductive age and is one of the common causes of ovulatory infertility [20]. The VDR gene is considered an important candidate gene for PCOS [21].

Since new research studies indicated the significance of vitamin D in the endocrine system and its relation not only with bone mineral density but also with certain cancers, autoimmune diseases, diabetes mellitus, depression, allergy, cardiovascular disease, pregnancy complications, infertility, and even frailty, vitamin D deficiency has just been identified as endemic to a variety of health consequences [22, 23]. The results of various studies taken together have shown that a variety of environmental and genetic factors influence vitamin D status variations. Studying the genetic basis of vitamin D metabolism, however, has brought to light the significance of multiple genes, including CG, DHCR1, CYP2R1, CYP24A1, and VDR [24]. By interacting with the vitamin D receptor (VDR), a member of the superfamily of steroid/thyroid hormone receptors, 1,25(OH)2D3, the active form of vitamin D, affects the transcriptional activation and repression of several target genes [25]. The VDR gene has many single-nucleotide polymorphisms (SNPs), which have been linked to a variety of physiological and pathological characteristics including different pregnancy complications in numerous populations [26–28]. VDR gene polymorphisms most likely have an impact on the expression and function of VDR [29].VDRs are found in the endometrium, placenta, decidual cells, ovarian granulosa cells, fallopian tube epithelium, pituitary gland, and hypothalamus. [30] Expression of the VDR in the placenta and decidua, which probably has an active role in the local autocrine and paracrine response, suggests that the local synthesis of Vit D potentially modulates placental function and fetal growth. Therefore, VDR gene function could be influenced by several factors such as genetic polymorphism that might related to susceptibility to fertility problems [31, 32]. The most intensively studied VDR polymorphisms are FokI (rs2228570), TaqI (rs731236), BsmI (rs1544410), and ApaI (rs7975232) variants. The association of these polymorphisms with different types of infertility complications including PCOS, endometriosis, miscarriage, etc. has been investigated

in single studies, with conflicting results. Considering the above-mentioned observations, our meta-analysis study aimed to more powerfully and comprehensively assess the association between four VDR polymorphisms (rs2228570, rs1544410, rs7975232, rs731236) and infertility and miscarriage in different populations and geographical regions by conducting a systematic review.

Methods

This systematic review and meta-analysis were conducted based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (Fig. 1) [33]. The PROSPERO registration number and the published protocol were CRD42023416535.

Search strategy and screening process

For this meta-analysis, we accessed several international databases, including PubMed (Medline), Web of Science, and Scopus. These databases were searched for literature published up to January 2023, using specific search terms and their synonyms: "Infertility," "miscarriage," "VDR" or "vitamin D receptor," and "Polymorphism." Furthermore, we conducted a manual search within these databases, carefully examining the references of relevant studies, and also looked through grey literature to identify any additional related studies that might not have been captured through the initial database search.

To ensure thoroughness and accuracy, the screening process was carried out independently by two authors (AM, MA). In cases where there were disagreements, they were resolved through discussion and consensus with a third author (YM). This rigorous approach helped maintain the integrity of the study selection process and ensured that all relevant studies were included for analysis.

Eligibility criteria

Eligible studies were limited to those [1] case–control studies whose main purpose was to determine the association between VDR gene polymorphisms ApaI, BsmI, TaqI, and FokI and the risk of infertility and miscarriage, (2) studies that have reported the frequencies of genotypes or alleles by comparing at least two groups, a group including Infertility or miscarriage against healthy groups, (3) and, studies report odds ratio (ORs) and 95% confidence interval (CIs). Exclusion criteria included (1) all other types of studies including cohorts, cross-sectional, case reports, case series, letters to the editor, reports, clinical trial studies, and review studies, (2) Case–control studies without reporting inclusion criteria, (3) Repetitive and non-English language studies.

Data extraction

The process of data extraction involved utilizing a structured form designed to gather essential information from
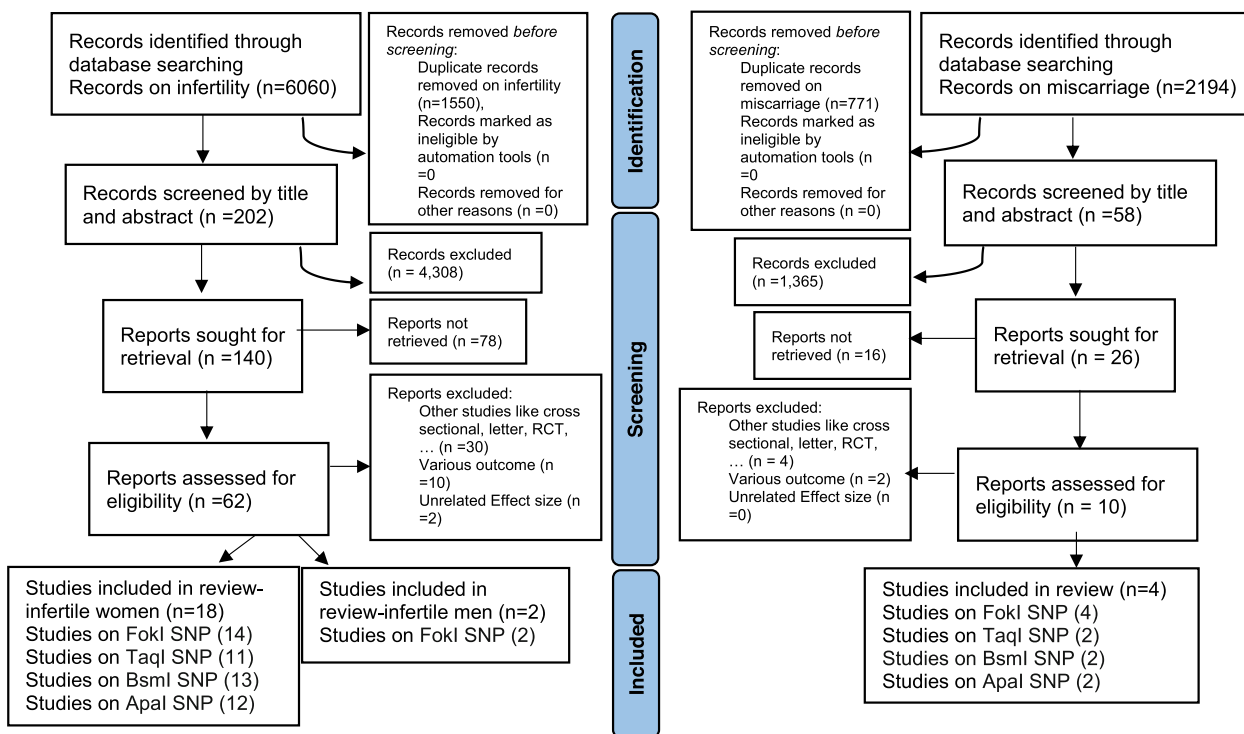

Fig. 1 Flow diagram of study selection process

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each included study. This information encompassed various key aspects, such as the author's name, study location, publication date, ethnicity of the participants, mean age of the study population, sample size, genotyping methods employed, as well as the number of cases and controls pertaining to VDR gene polymorphisms.

Risk of *Bias*

The Newcastle–Ottawa Quality Assessment Scale (NOS) checklist was used with the purpose of methodological quality and risk evaluation of non-randomized studies in Meta-Analysis. The NOS consists of eight items divided into three categories: Selection of cases and controls, comparability of them, and Ascertainment of exposure. Items can be awarded a maximum of one star for each one within the two first categories and a maximum of two stars for Comparability. The scoring ranged from zero to nine. A score of 6 and above indicates the high quality of the study[34].

Statistical analysis

The control genotype distribution was assessed by the Hardy–Weinberg equilibrium (HWE) ($p < 0.05$ was considered meaningful). Calculation of ORs and 95% confidence intervals (CIs) in seven different genetic models was used to estimate its effect on a forest plot and the strength of the relationship between VDR polymorphisms and the risk of infertility and miscarriage. genetic models of polymorphisms are discussed in the following: TaqI —allele contrast (t vs. T), recessive model (tt vs. Tt + TT), dominant model (tt + Tt vs. TT), over dominant (Tt vs. TT + tt), tt vs. TT model, TT vs. Tt model, Tt vs. tt model; FokI — allele contrast (f vs. F), recessive model (ff vs. Ff + FF), dominant model (ff + Ff vs. FF), over-dominant model (Ff vs. FF + ff), ff vs. FF model, FF vs. Ff model, Ff vs. ff model; ApaI —allele contrast (a vs. A), recessive model (aa vs. Aa + AA), dominant model (aa + Aa vs. AA), over dominant model (Aa vs. AA + aa), aa vs. AA model, AA vs. Aa model, Aa vs. aa model; BsmI —allele contrast (b vs. B), recessive model (bb vs. Bb + BB), dominant model (bb + Bb vs. BB), over dominant model (Bb vs. BB + bb), bb vs. BB model, BB vs. Bb model, Bb vs. bb model. Also, heterogeneity between studies was assessed by Q Cochrane tests and I^2. To test Publication biases, funnel plots and Egger's test ($p < 0.05$) were used. All statistical analyses were done using MetaGenyo; a web tool to conduct a meta-analysis of genetic association studies [35]. The forest plot and funnel plot pertaining to all examined polymorphisms are depicted in (Figs. 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 and 16).

Results

Description of Studies

Out of a total of 6060 and 2194 relevant citations on infertility and miscarriage, respectively, 5930 references remained after eliminating duplicates. Following title and abstract screening, and full-text review, 24 studies meeting the search criteria were identified, comprising 3424 cases and 3697 controls (refer to Tables 1, 2 and 3). Notably, the total cases and controls were categorized based on the methodology of the studies rather than individual SNP analysis. Among these studies, 18 investigated the association of VDR genetic polymorphisms with female infertility, 2 with male infertility, and 4 with miscarriage. Tables 4, 5, and 6 summarizes the characteristics and genotype frequencies of the included studies.

Association between VDR Genetic Polymorphisms and Infertility in Women
FokI (rs2228570) SNP

Fourteen studies involving 5,210 participants reported on the association between FokI SNP and female infertility. While a protective association was observed in the FF vs. Ff model (OR = 0.87, 95% CI = 0.76–1.00, $P = 0.05$), no significant association was found in other genetic models.

BsmI (rs1544410) SNP

Thirteen studies examined the association between BsmI SNP and infertility, with no significant correlation found in any of the genetic models assessed.

TaqI (rs731236) SNP

Eleven studies focused on TaqI SNP, reporting a positive association in some genetic models, including Allele contrast and Recessive model, but not in others.

ApaI (rs7975232) SNP

Twelve case–control studies evaluated the ApaI SNP, showing a protective association in the Dominant model and Aa vs. aa model, but no significant association in other genetic models.

Association between VDR Genetic Polymorphisms and Infertility in Men
FokI (rs2228570) SNP

Two studies involving 404 participants investigated the association between FokI SNP and male infertility, revealing a protective association in the Recessive model.

Fig. 2 Forest plot of different genetic models in infertile women in FokI (rs2228570) SNP A; Allele contrast (F vs. f), B; Recessive model, C; Dominant model, D; Over dominant model, E; Homozygote model, F; FF vs. Ff model, G; Ff vs. ff model

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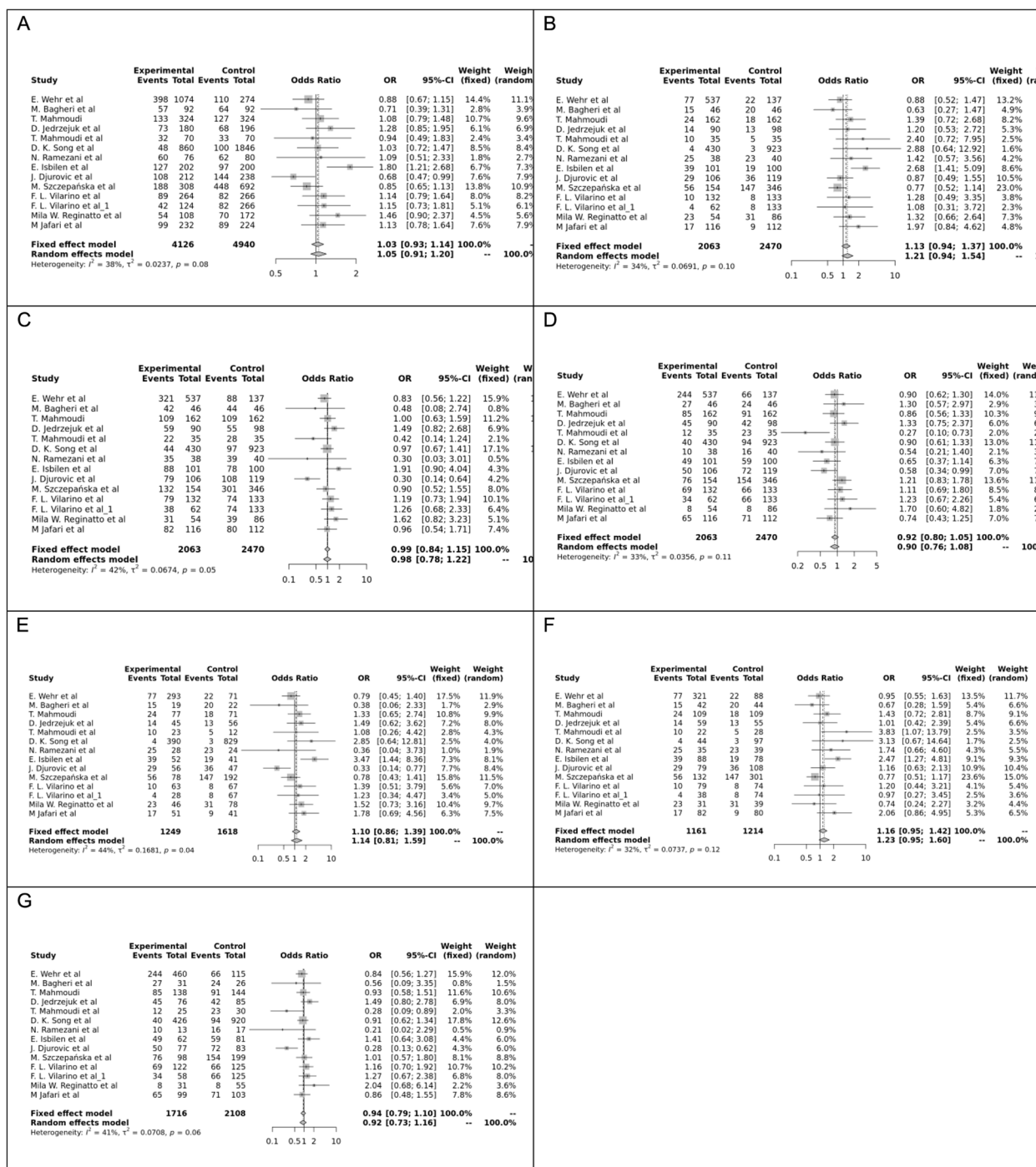
Fig. 3 Forest plot of different genetic models in infertile women in BsmI (rs1544410) SNP A; Allele contrast (B vs. b), B; Recessive model, C; Dominant model, D; Over dominant model, E; Homozygote model, F; BB vs. Bb model, G; Bb vs. bb model

Association between VDR Genetic Polymorphisms and Miscarriage

Four studies examined the association between VDR genetic polymorphisms and miscarriage, evaluating TaqI, ApaI, FokI, and BsmI SNPs. Characteristics of these studies are summarized in Tables 7,8 and 9.

Heterogeneity, Publication *Bias*, and Sensitivity Analysis

Heterogeneity was observed in certain genetic models, particularly in the TaqI SNP. Egger's tests revealed no publication bias. The results of sensitivity analysis are presented in relevant charts.

A — Allele contrast (T vs. t)

Study	Exp. Events	Exp. Total	Ctrl Events	Ctrl Total	OR	95%-CI	Weight (fixed)	Weight (random)
E. Wehr et al	382	1072	111	274	0.81	[0.62; 1.07]	15.4%	10.3%
M. Bagheri et al	30	76	23	76	1.50	[0.77; 2.94]	2.5%	5.3%
A. S. El-Shal et al	146	300	101	300	1.87	[1.34; 2.60]	10.4%	9.4%
T. Mahmoudi	111	324	104	324	1.13	[0.79; 1.53]	10.6%	9.5%
D. Jedrzejuk et al	61	180	61	196	1.13	[0.74; 1.75]	6.1%	8.0%
T. Mahmoudi et al	26	70	24	70	1.13	[0.57; 2.26]	2.4%	5.1%
E. Isbilen et al	77	202	31	198	3.32	[2.06; 5.35]	5.0%	7.4%
J. Djurovic et al	88	228	94	256	1.08	[0.75; 1.57]	8.4%	8.9%
S. Dasgupta et al	186	502	179	504	1.07	[0.83; 1.38]	17.2%	10.5%
F. L. Vilarino et al	92	264	95	266	0.96	[0.67; 1.37]	8.9%	9.1%
F. L. Vilarino et al_1	54	124	95	266	1.39	[0.90; 2.14]	6.0%	8.0%
M Jafari et al	82	232	61	228	1.50	[1.01; 2.23]	7.2%	8.5%
Fixed effect model		3574		2958	1.21	[1.08; 1.34]	100.0%	--
Random effects model					1.28	[1.04; 1.57]	--	100.0%

Heterogeneity: $I^2 = 70\%$, $\tau^2 = 0.0866$, $p < 0.01$

B — Recessive model

Study	Exp. Events	Exp. Total	Ctrl Events	Ctrl Total	OR	95%-CI	Weight (fixed)	Weight (random)
E. Wehr et al	72	536	23	137	0.77	[0.46; 1.28]	17.1%	14.2%
M. Bagheri et al	8	38	2	38	4.80	[0.95; 24.34]	1.7%	2.4%
A. S. El-Shal et al	36	150	20	150	2.05	[1.12; 3.75]	12.4%	11.8%
T. Mahmoudi	20	162	14	162	1.49	[0.72; 3.06]	8.6%	9.3%
D. Jedrzejuk et al	8	90	12	98	0.70	[0.27; 1.80]	5.0%	6.2%
T. Mahmoudi et al	6	35	4	35	1.60	[0.41; 6.26]	2.4%	3.3%
E. Isbilen et al	20	101	8	99	2.81	[1.17; 6.72]	5.9%	7.0%
J. Djurovic et al	21	114	20	128	1.22	[0.62; 2.39]	9.9%	10.2%
S. Dasgupta et al	47	251	37	252	1.34	[0.84; 2.15]	20.1%	15.5%
F. L. Vilarino et al	15	132	12	133	1.29	[0.58; 2.88]	7.0%	8.0%
F. L. Vilarino et al_1	12	62	12	133	2.42	[1.02; 5.75]	6.0%	7.1%
M Jafari et al	9	116	6	114	1.51	[0.52; 4.40]	3.9%	5.1%
Fixed effect model		1787		1479	1.38	[1.12; 1.71]	100.0%	--
Random effects model					1.43	[1.10; 1.86]	--	100.0%

Heterogeneity: $I^2 = 29\%$, $\tau^2 = 0.0580$, $p = 0.17$

C — Dominant model

Study	Exp. Events	Exp. Total	Ctrl Events	Ctrl Total	OR	95%-CI	Weight (fixed)	Weight (random)
E. Wehr et al	310	536	88	137	0.76	[0.52; 1.13]	14.3%	10.1%
M. Bagheri et al	22	38	21	38	1.11	[0.45; 2.76]	2.6%	5.4%
A. S. El-Shal et al	110	150	81	150	2.34	[1.44; 3.80]	9.3%	9.1%
T. Mahmoudi	91	162	90	162	1.03	[0.66; 1.59]	11.3%	9.6%
D. Jedrzejuk et al	53	90	49	98	1.43	[0.80; 2.55]	6.5%	8.2%
T. Mahmoudi et al	20	35	20	35	1.00	[0.39; 2.58]	2.4%	5.1%
E. Isbilen et al	57	101	23	99	4.28	[2.33; 7.88]	5.8%	7.8%
J. Djurovic et al	67	114	74	128	1.04	[0.62; 1.74]	8.3%	8.8%
S. Dasgupta et al	139	251	142	252	0.96	[0.68; 1.37]	17.5%	10.5%
F. L. Vilarino et al	77	132	83	133	0.84	[0.52; 1.38]	8.9%	9.0%
F. L. Vilarino et al_1	42	62	83	133	1.27	[0.67; 2.39]	5.3%	7.6%
M Jafari et al	73	116	55	114	1.82	[1.08; 3.08]	7.8%	8.7%
Fixed effect model		1787		1479	1.21	[1.05; 1.41]	100.0%	--
Random effects model					1.29	[0.98; 1.71]	--	100.0%

Heterogeneity: $I^2 = 70\%$, $\tau^2 = 0.1603$, $p < 0.01$

D — Over dominant model

Study	Exp. Events	Exp. Total	Ctrl Events	Ctrl Total	OR	95%-CI	Weight (fixed)	Weight (random)
E. Wehr et al	238	536	65	137	0.88	[0.61; 1.29]	15.1%	11.1%
M. Bagheri et al	14	38	19	38	0.58	[0.23; 1.46]	2.5%	4.5%
A. S. El-Shal et al	74	150	61	150	1.42	[0.90; 2.24]	10.2%	9.7%
T. Mahmoudi	71	162	76	162	0.88	[0.57; 1.37]	11.2%	10.1%
D. Jedrzejuk et al	45	90	37	98	1.65	[0.92; 2.95]	6.3%	7.9%
T. Mahmoudi et al	14	35	16	35	0.79	[0.31; 2.04]	2.4%	4.3%
E. Isbilen et al	37	101	15	99	3.24	[1.64; 6.41]	4.6%	6.6%
J. Djurovic et al	46	114	54	128	0.93	[0.56; 1.55]	8.1%	8.8%
S. Dasgupta et al	92	251	105	252	0.81	[0.57; 1.16]	16.6%	11.4%
F. L. Vilarino et al	62	132	71	133	0.77	[0.48; 1.25]	9.2%	9.3%
F. L. Vilarino et al_1	30	62	71	133	0.82	[0.45; 1.50]	5.9%	7.6%
M Jafari et al	64	116	49	114	1.63	[0.97; 2.75]	7.9%	8.7%
Fixed effect model		1787		1479	1.03	[0.89; 1.20]	100.0%	--
Random effects model					1.07	[0.85; 1.34]	--	100.0%

Heterogeneity: $I^2 = 56\%$, $\tau^2 = 0.0865$, $p < 0.01$

E — Homozygote model

Study	Exp. Events	Exp. Total	Ctrl Events	Ctrl Total	OR	95%-CI	Weight (fixed)	Weight (random)
E. Wehr et al	72	298	23	72	0.68	[0.39; 1.19]	16.4%	12.0%
M. Bagheri et al	8	24	2	19	4.25	[0.78; 23.11]	1.8%	3.4%
A. S. El-Shal et al	36	76	20	89	3.10	[1.59; 6.08]	11.5%	10.6%
D. Jedrzejuk et al	20	91	14	86	1.45	[0.68; 3.09]	9.0%	9.5%
T. Mahmoudi et al	8	45	12	61	0.88	[0.33; 2.38]	5.3%	7.2%
T. Mahmoudi et al	6	21	4	19	1.50	[0.35; 6.42]	2.4%	4.3%
E. Isbilen et al	20	64	8	84	4.32	[2.33; 7.88]	6.4%	8.0%
J. Djurovic et al	21	68	20	74	1.21	[0.58; 2.49]	9.8%	9.9%
S. Dasgupta et al	47	159	37	147	1.25	[0.75; 2.07]	20.3%	12.8%
F. L. Vilarino et al	15	70	12	62	1.14	[0.49; 2.66]	7.2%	8.5%
F. L. Vilarino et al_1	12	32	12	62	2.50	[0.96; 6.49]	5.7%	7.5%
M Jafari et al	9	52	6	65	2.06	[0.68; 6.22]	4.2%	6.3%
Fixed effect model		1000		840	1.46	[1.16; 1.83]	100.0%	--
Random effects model					1.58	[1.12; 2.23]	--	100.0%

Heterogeneity: $I^2 = 51\%$, $\tau^2 = 0.1778$, $p = 0.02$

F — TT vs Tt model

Study	Exp. Events	Exp. Total	Ctrl Events	Ctrl Total	OR	95%-CI	Weight (fixed)	Weight (random)
E. Wehr et al	72	310	23	88	0.85	[0.50; 1.47]	17.3%	17.3%
M. Bagheri et al	8	22	2	21	5.43	[1.00; 29.61]	1.8%	1.8%
A. S. El-Shal et al	36	110	20	81	1.48	[0.78; 2.82]	12.4%	12.4%
T. Mahmoudi	20	91	14	90	1.53	[0.72; 3.26]	9.0%	9.0%
D. Jedrzejuk et al	8	53	12	49	0.55	[0.20; 1.48]	5.2%	5.2%
T. Mahmoudi et al	6	20	4	20	1.71	[0.40; 7.34]	2.4%	2.4%
E. Isbilen et al	20	57	8	23	1.01	[0.37; 2.80]	5.0%	5.0%
J. Djurovic et al	21	67	20	74	1.23	[0.60; 2.55]	9.7%	9.7%
S. Dasgupta et al	47	139	37	142	1.45	[0.87; 2.42]	19.4%	19.4%
F. L. Vilarino et al	15	77	12	83	1.43	[0.62; 3.29]	7.4%	7.4%
F. L. Vilarino et al_1	12	42	12	83	2.37	[0.96; 5.86]	6.2%	6.2%
M Jafari et al	9	73	6	55	1.15	[0.38; 3.44]	4.3%	4.3%
Fixed effect model		1061		809	1.29	[1.02; 1.61]	100.0%	--
Random effects model					1.29	[1.02; 1.61]	--	100.0%

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.48$

G — Tt vs tt model

Study	Exp. Events	Exp. Total	Ctrl Events	Ctrl Total	OR	95%-CI	Weight (fixed)	Weight (random)
E. Wehr et al	238	464	65	114	0.79	[0.53; 1.20]	14.5%	10.4%
M. Bagheri et al	14	30	19	36	0.78	[0.30; 2.07]	2.6%	5.1%
A. S. El-Shal et al	74	114	61	130	2.09	[1.25; 3.51]	9.3%	9.2%
T. Mahmoudi	71	142	76	148	0.95	[0.60; 1.50]	11.6%	9.9%
D. Jedrzejuk et al	45	82	37	86	1.61	[0.88; 2.96]	6.6%	8.2%
T. Mahmoudi et al	14	29	16	31	0.88	[0.32; 2.41]	2.4%	4.8%
E. Isbilen et al	37	81	15	91	4.26	[2.10; 8.63]	5.0%	7.2%
J. Djurovic et al	46	93	54	108	0.98	[0.56; 1.70]	8.0%	8.8%
S. Dasgupta et al	92	204	105	215	0.86	[0.59; 1.26]	16.7%	10.8%
F. L. Vilarino et al	62	117	71	121	0.79	[0.48; 1.33]	9.4%	9.3%
F. L. Vilarino et al_1	30	50	71	121	1.06	[0.54; 2.07]	5.5%	7.5%
M Jafari et al	64	107	49	108	1.79	[1.04; 3.08]	8.4%	8.9%
Fixed effect model		1513		1309	1.13	[0.97; 1.33]	100.0%	--
Random effects model					1.20	[0.91; 1.58]	--	100.0%

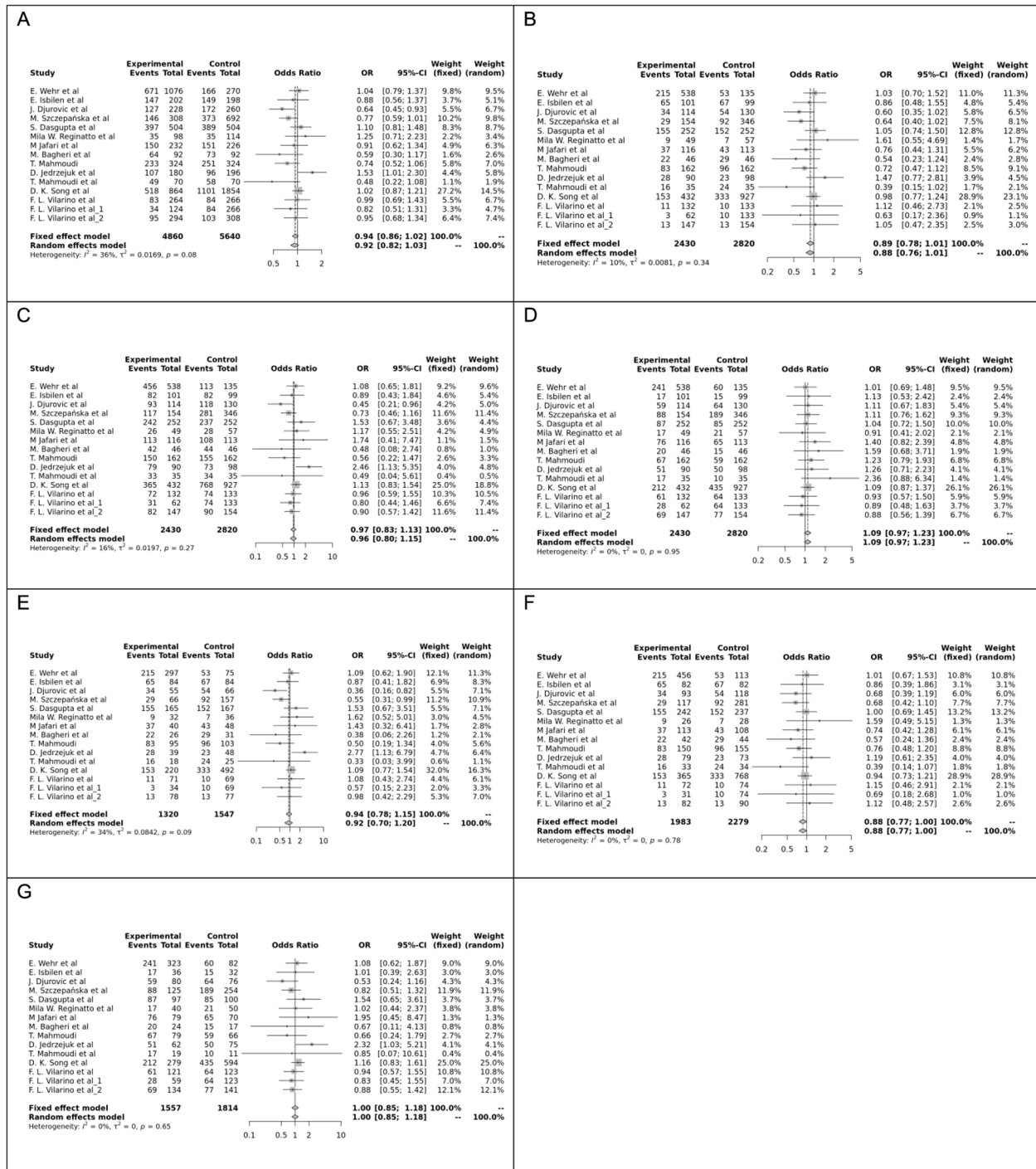Heterogeneity: $I^2 = 65\%$, $\tau^2 = 0.1461$, $p < 0.01$

Fig. 4 Forest plot of different genetic models in infertile women in TaqI (rs731236) SNP A; Allele contrast (T vs. t), B; Recessive model, C; Dominant model, D; Over dominant model, E; Homozygote model, F; TT vs. Tt model, G; Tt vs. tt model
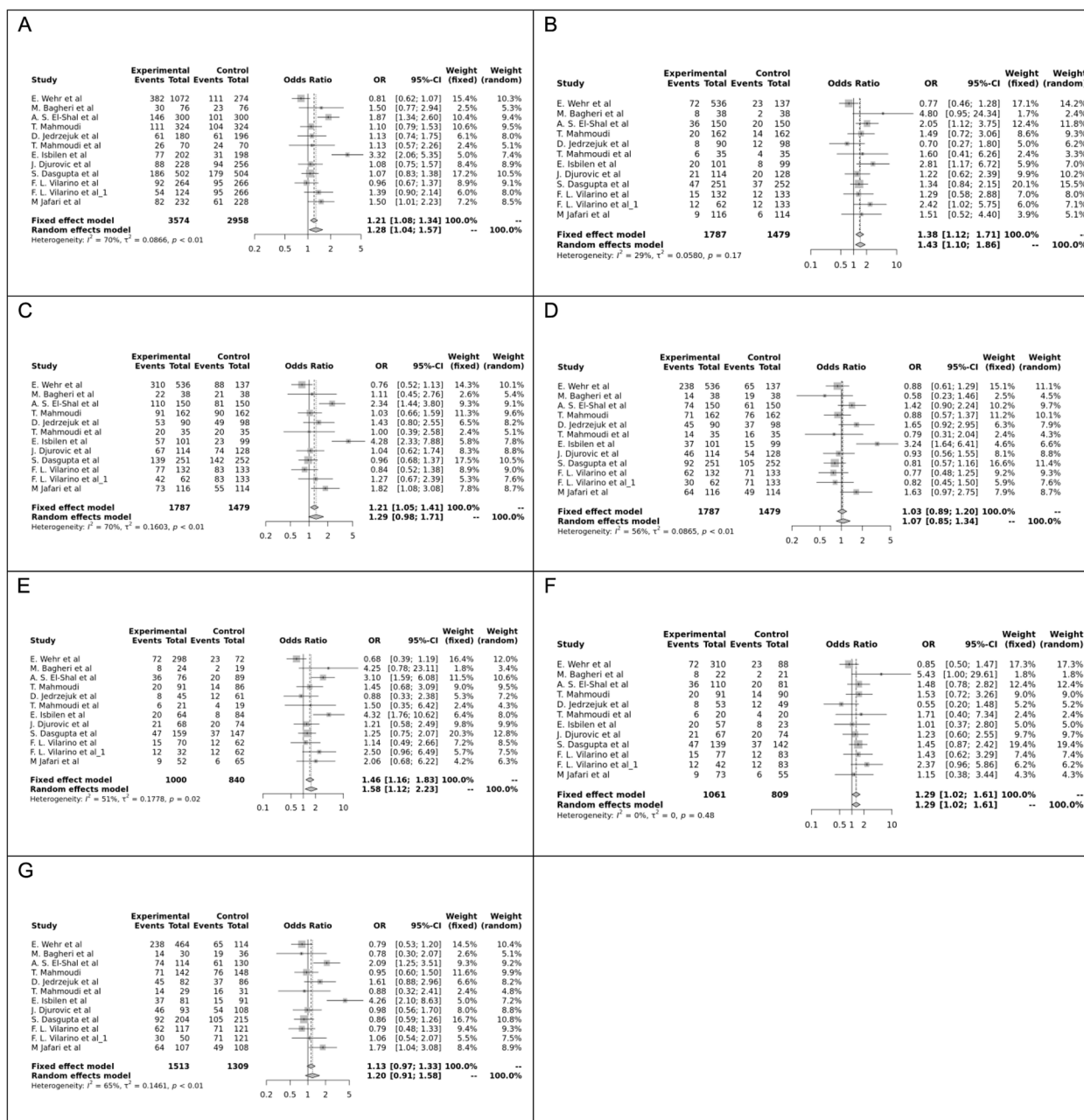
Discussion

This meta-analysis suggests that vitamin D receptor gene variations may play a role in infertility risk and outcome. The TaqI polymorphism may increase the susceptibility to infertility in women, possibly by affecting the implantation and placentation processes. The ApaI and FokI polymorphisms may have protective effects against infertility in women and men, respectively, possibly by modulating the immune system and the hormonal balance. These findings may have implications for the diagnosis, prevention, and treatment of infertility, as well as for the understanding of the molecular mechanisms of reproductive health. In the development of pregnancy problems, genetic variables have grown increasingly relevant. Previous research has linked VDR gene variations to infertility in women and men due to PCOS, endometriosis, preeclampsia, idiopathic infertility, and other causes [36, 37]. Serum 25-hydroxyvitamin D [25 (OH) D] has been found to inhibit VDR-mediated pathogenesis by modulating target gene expression [38]. The VDR
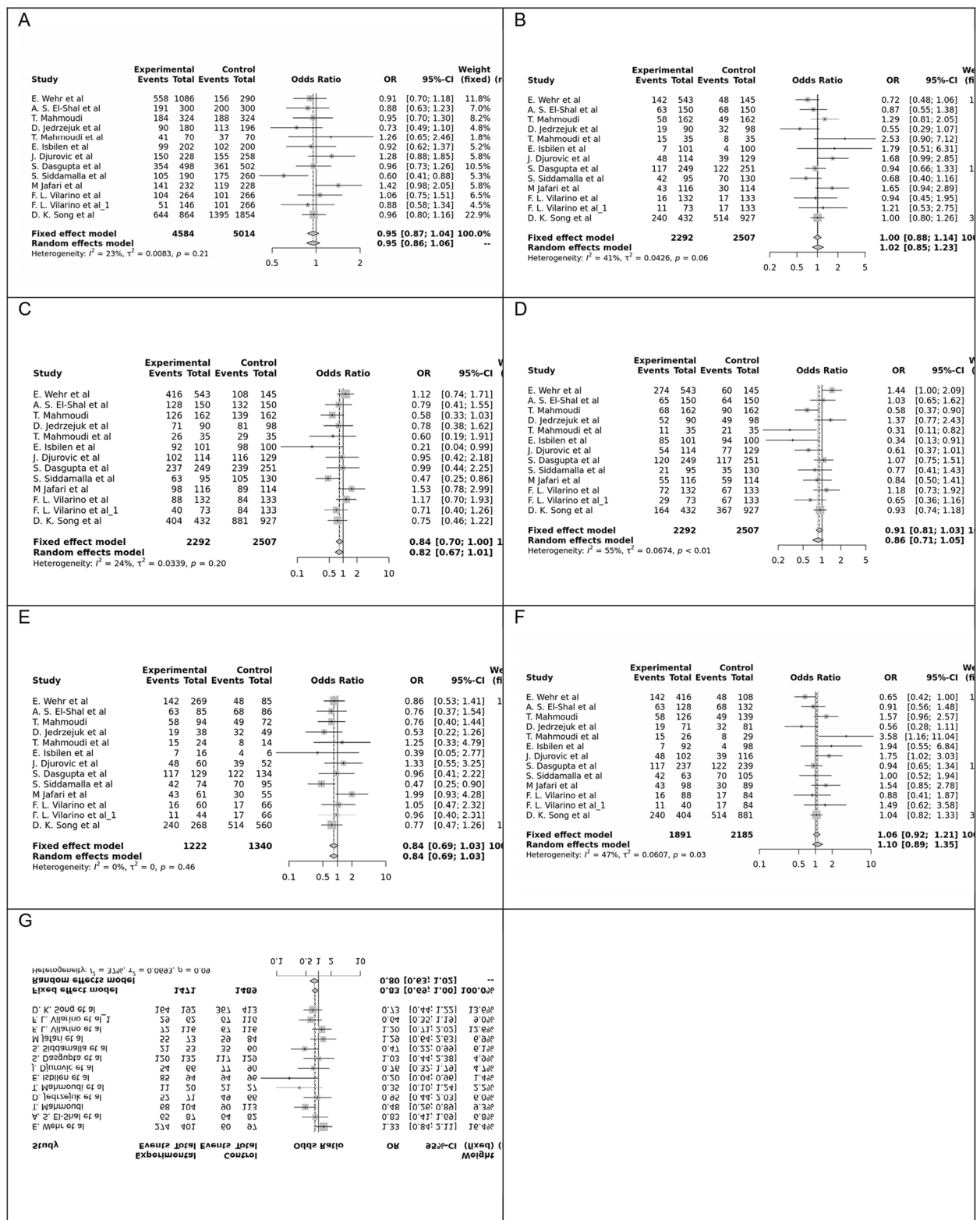
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Fig. 5 Forest plot of different genetic models in infertile women in Apal (rs7975232) SNP A; Allele contrast (A vs. a), B; Recessive model, C; Dominant model, D; Over dominant model, E; Homozygote model, F; AA vs. Aa model, G; Aa vs. aa model
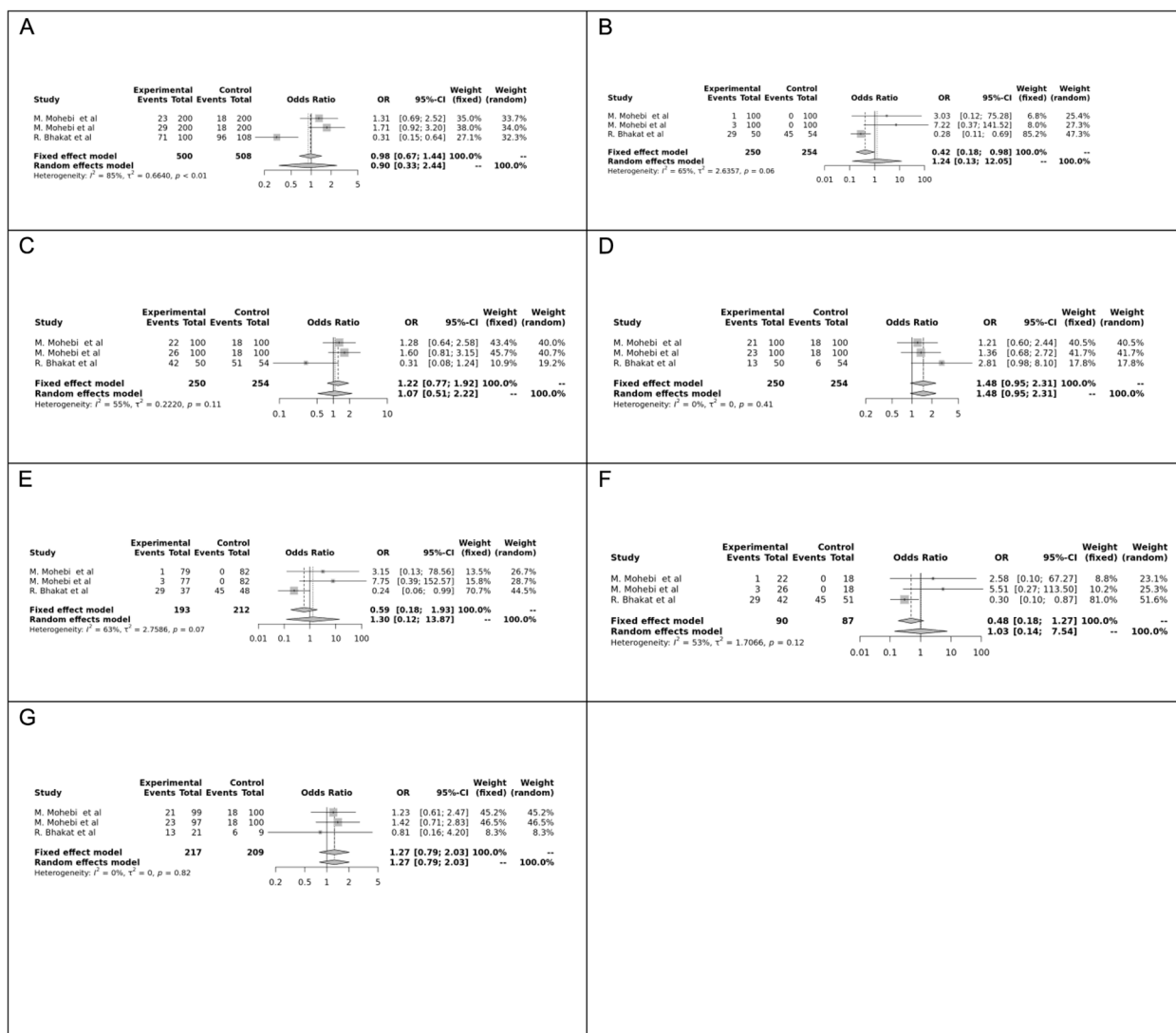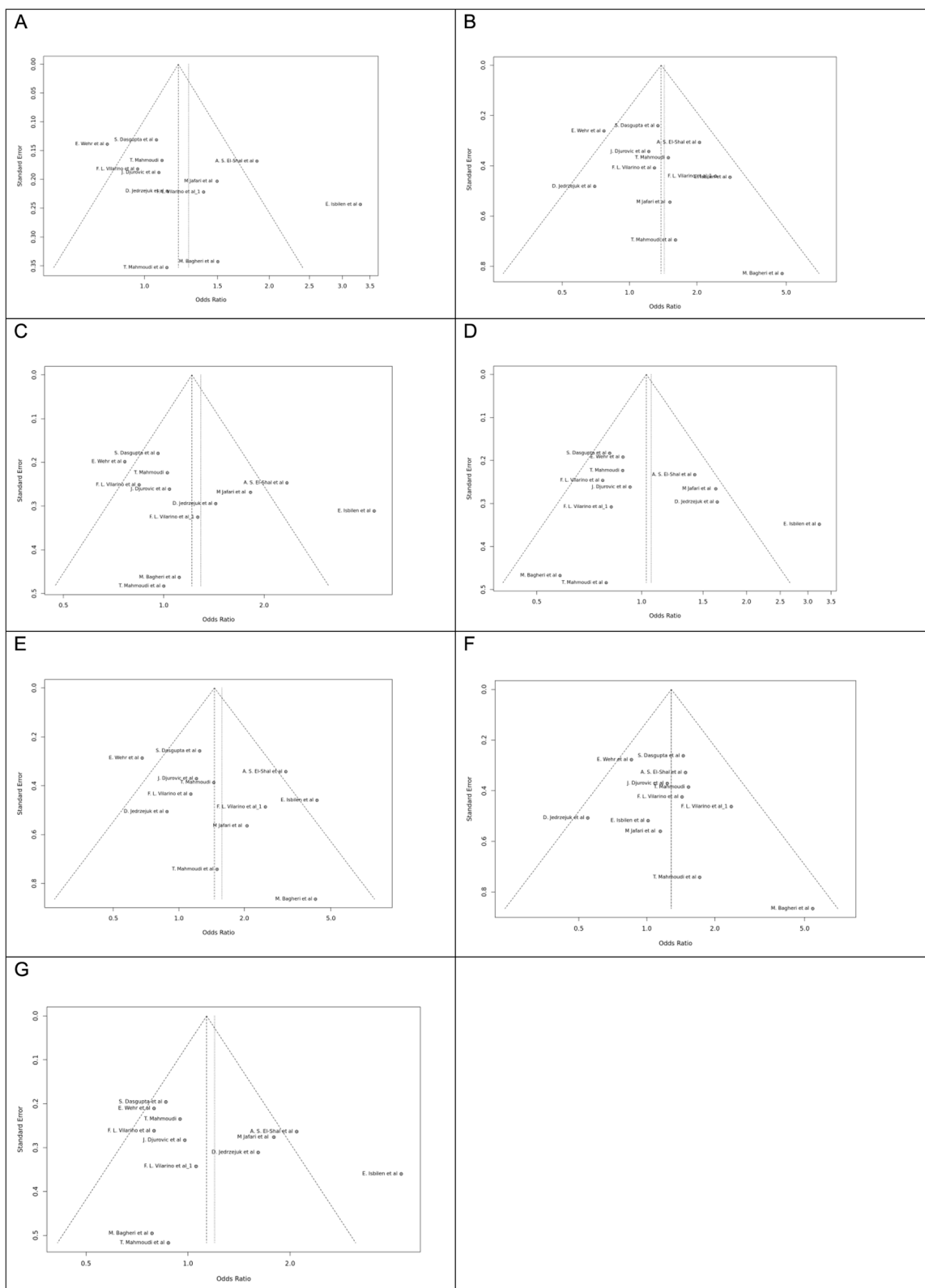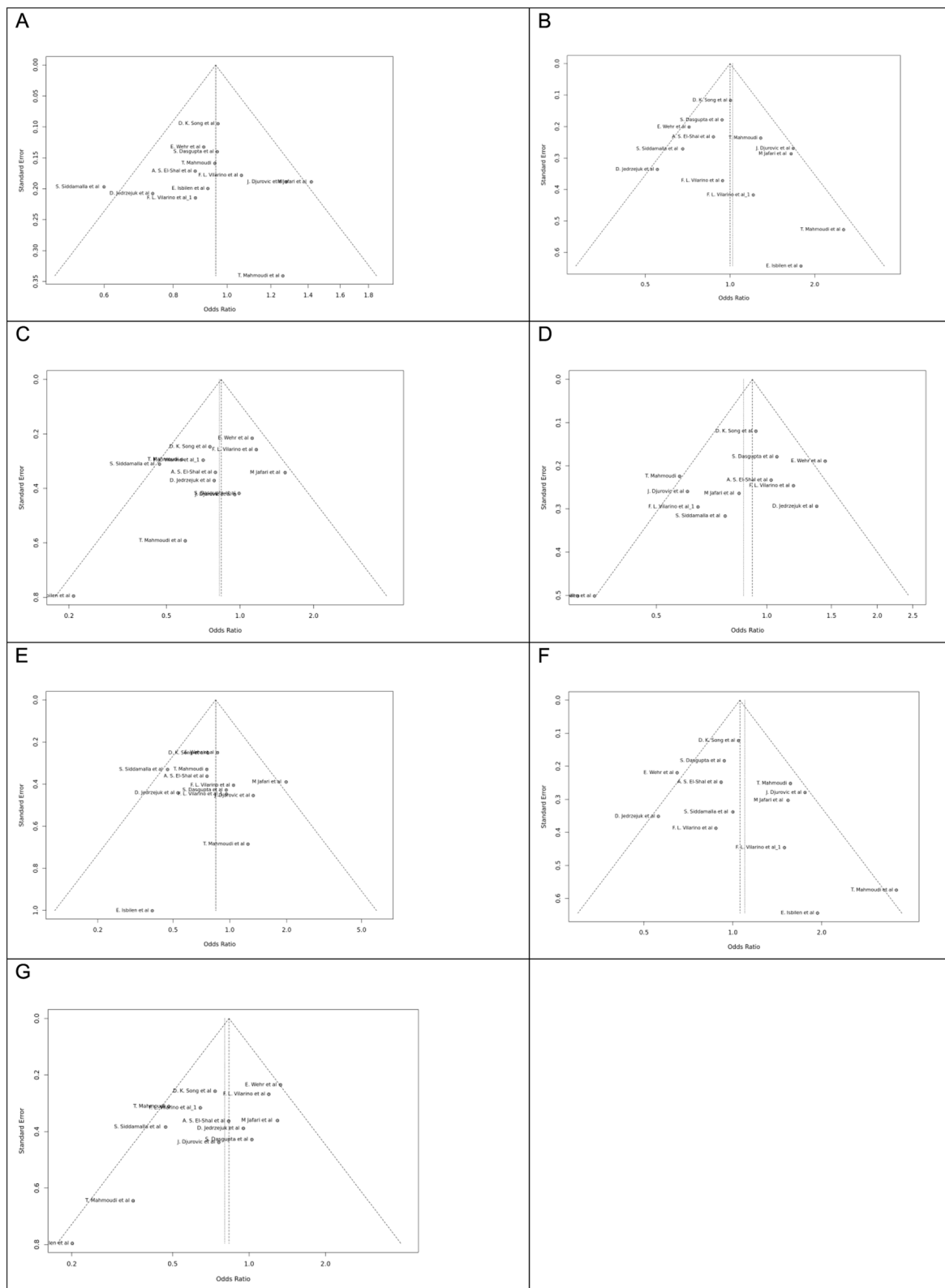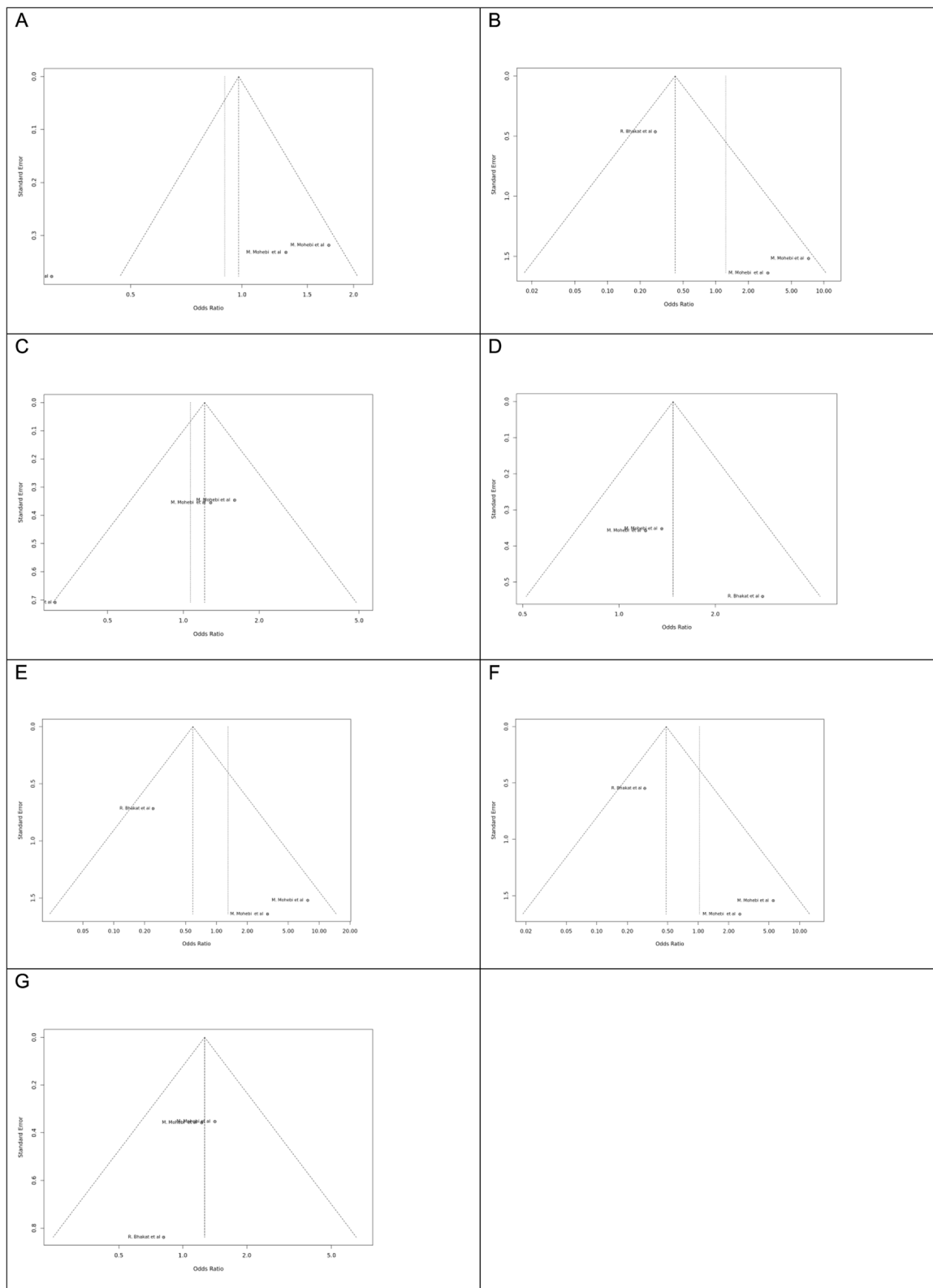
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Fig. 6 Forest plot of different genetic models in infertile men in FokI (rs2228570) SNP A; Allele contrast (F vs. f), B; Recessive model, C; Dominant model, D; Over dominant model, E; Homozygote model, F; FF vs. Ff model, G; Ff vs. ff model
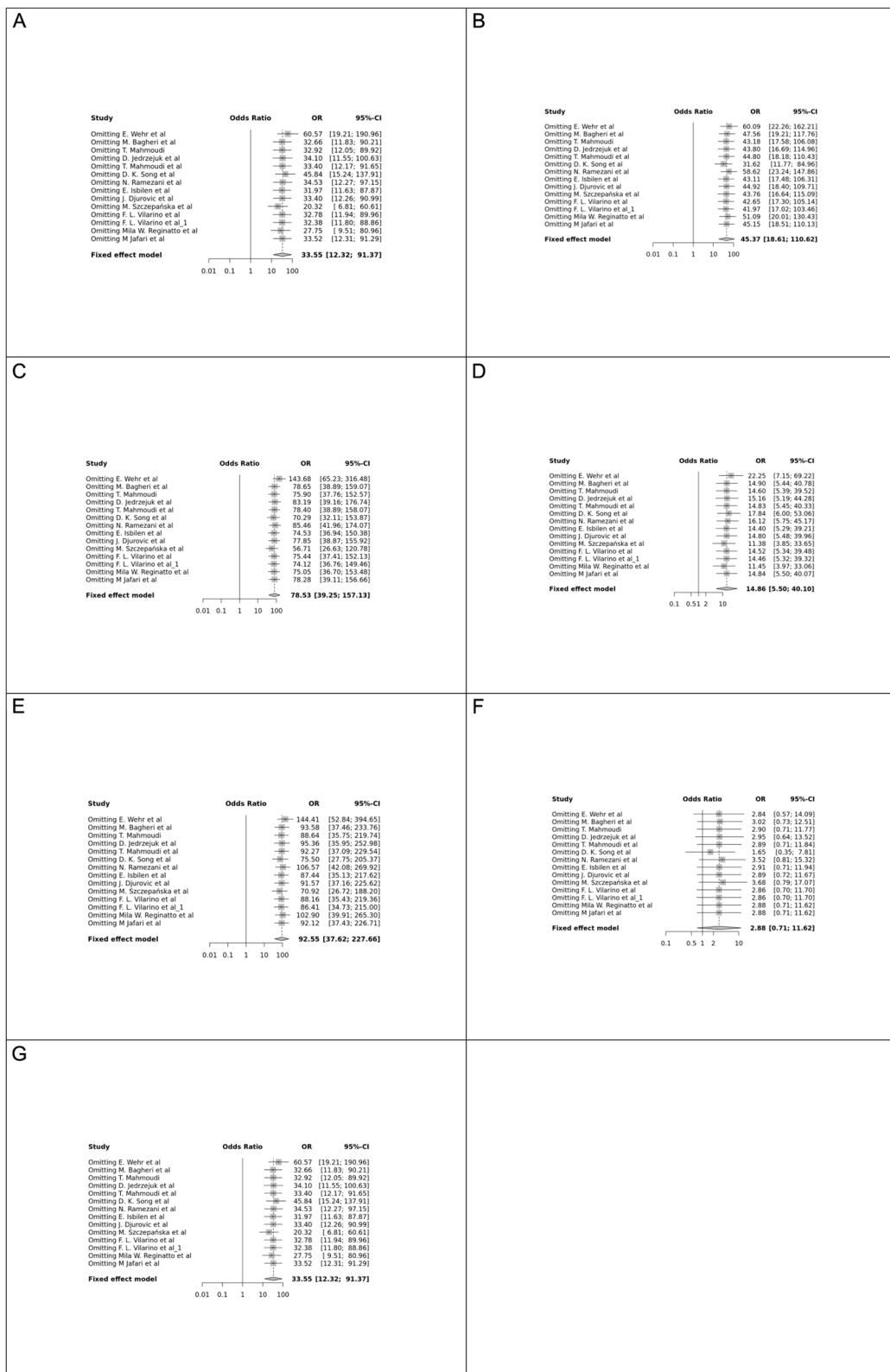
gene is a potential gene for infertility because it controls several genes that participate in diverse molecular and cellular processes [39]. Recurrent miscarriages (RM), which occur at a rate of 1 to 3% of female reproductive age, are another major medical, social, and psychological complication associated with pregnancy. Although numerous pathways for the development of RM have already been discovered, the underlying causes of around 50% of patients remain unexplained [13, 14]. Nevertheless, the multifaceted etiology of this problem, including immune system irregularities and vitamin D inadequacy, has been recognized for some time. As a result, it seems that altered metabolism of the VD/VDR complex via immune response modulation might be significant in the pathogenesis of both spontaneous abortion and RM [40]. Furthermore, VDR is a receptor with a pleiotropic action on human cells. remarkably, the presence of polymorphic variations in the VDR gene may affect VDR activity [41]. Regarding the evaluation of the connection between VDR gene polymorphisms and infertility/recurrent miscarriage in numerous single studies in different populations, the findings are contradictory. Given the volume of data accumulated and the ambiguous role of VDR in the etiology of infertility/recurrent miscarriage in general, we decided to conduct a comprehensive meta-analysis of any published research on the association between the most studied VDR polymorphisms and any infertility/recurrent miscarriage.
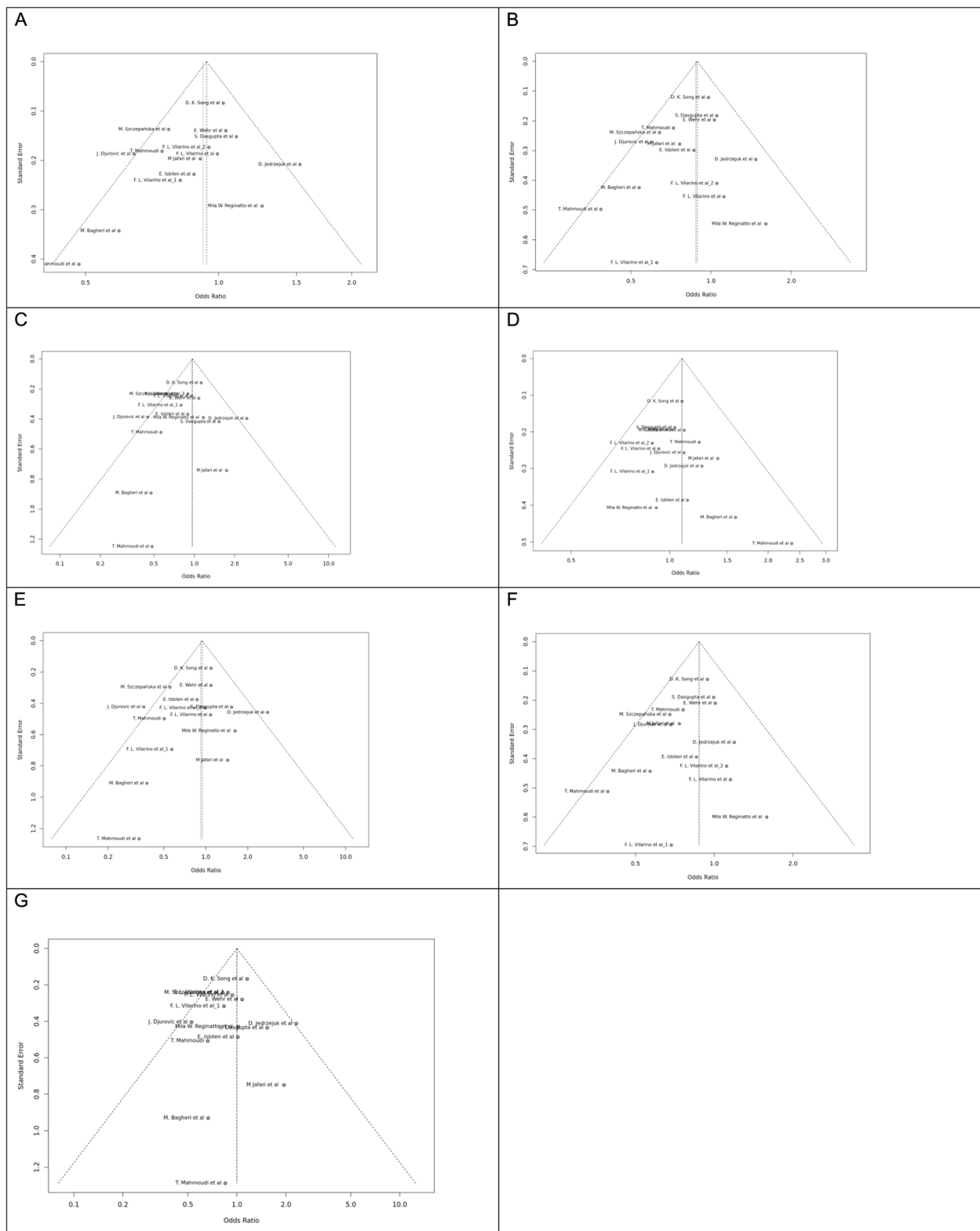
Fig. 7 Funnel plot of different genetic models in infertile women in FokI (rs2228570) SNP A; Allele contrast (F vs. f), B; Recessive model, C; Dominant model, D; Over dominant model, E; Homozygote model, F; FF vs. Ff model, G; Ff vs. ff model
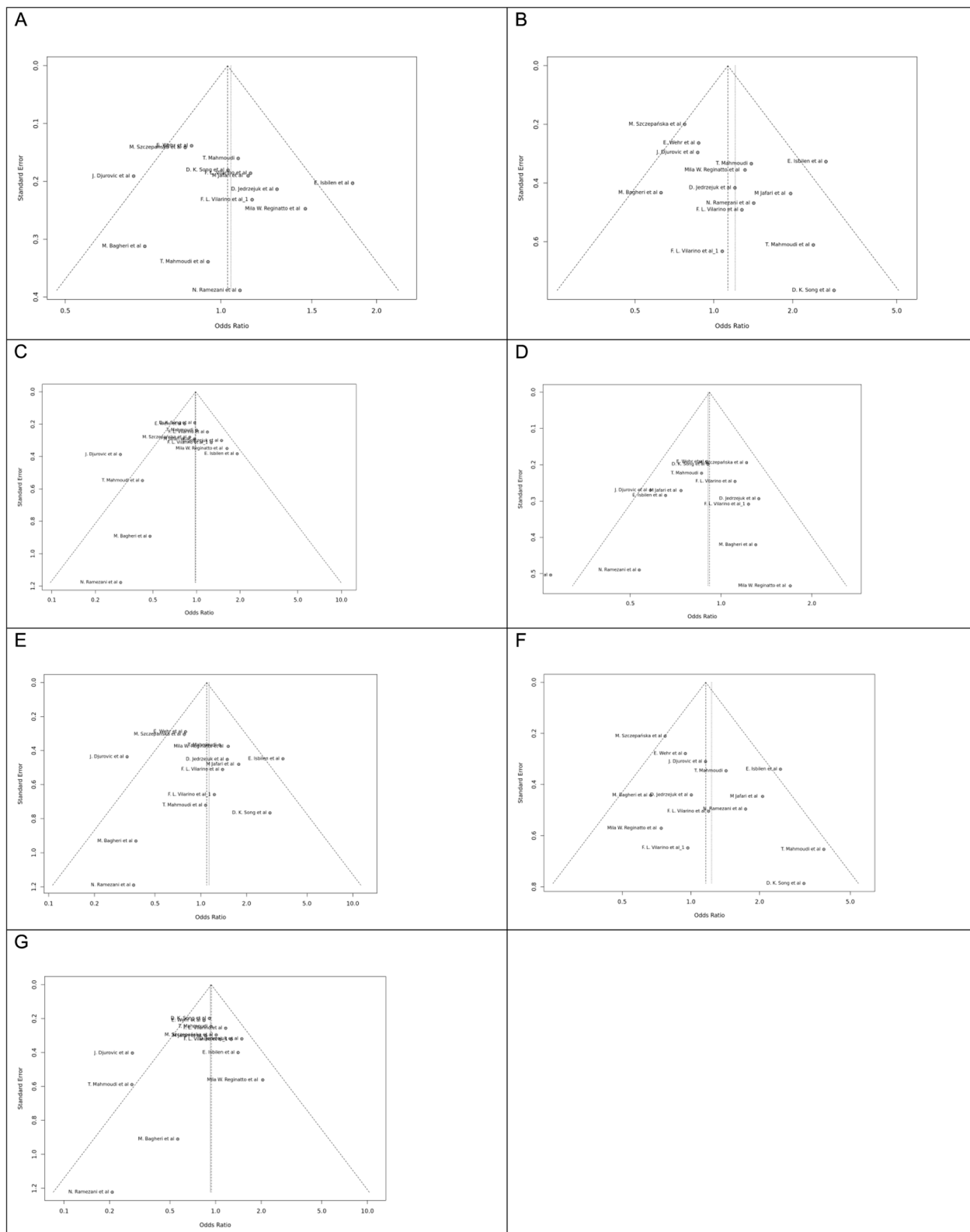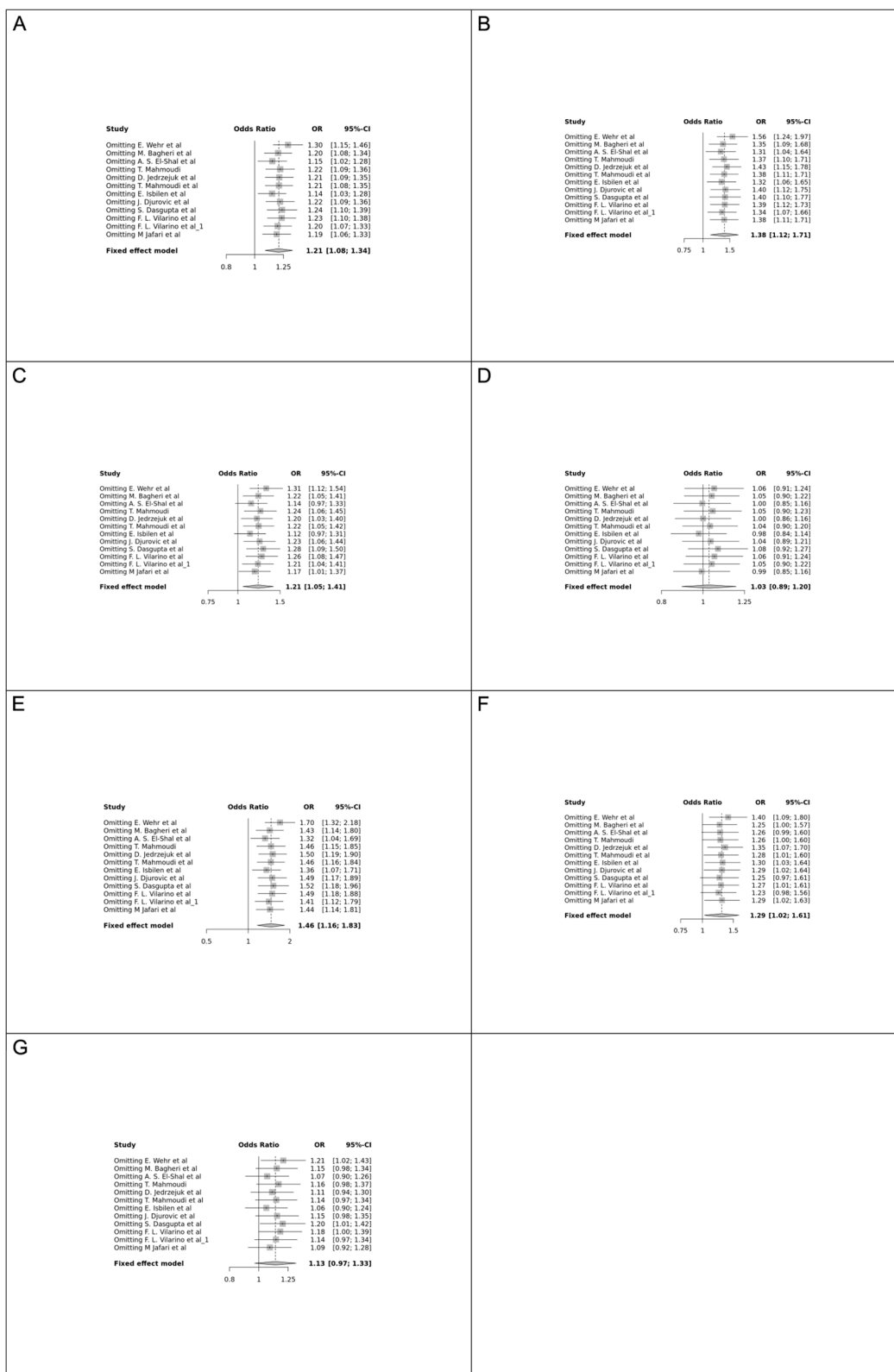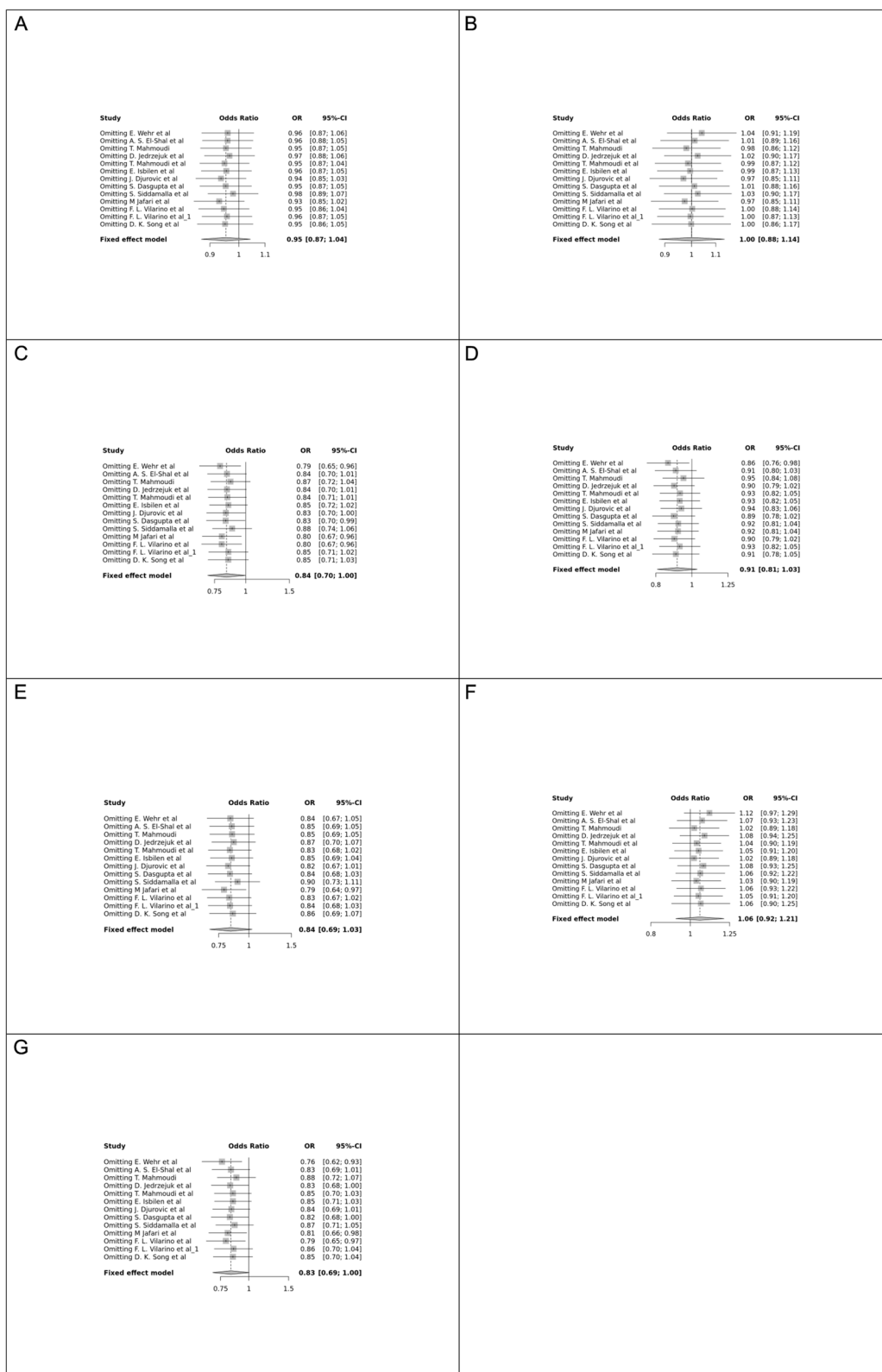
Fig. 8 Funnel plot of different genetic models in infertile women in BsmI (rs1544410) SNP A; Allele contrast (B vs. b), B; Recessive model, C; Dominant model, D; Over dominant model, E; Homozygote model, F; BB vs. Bb model, G; Bb vs. bb model

Fig. 9 Funnel plot of different genetic models in infertile women in TaqI (rs731236) SNP A; Allele contrast (T vs. t), B; Recessive model, C; Dominant model, D; Over dominant model, E; Homozygote model, F; TT vs. Tt model, G; Tt vs. tt model
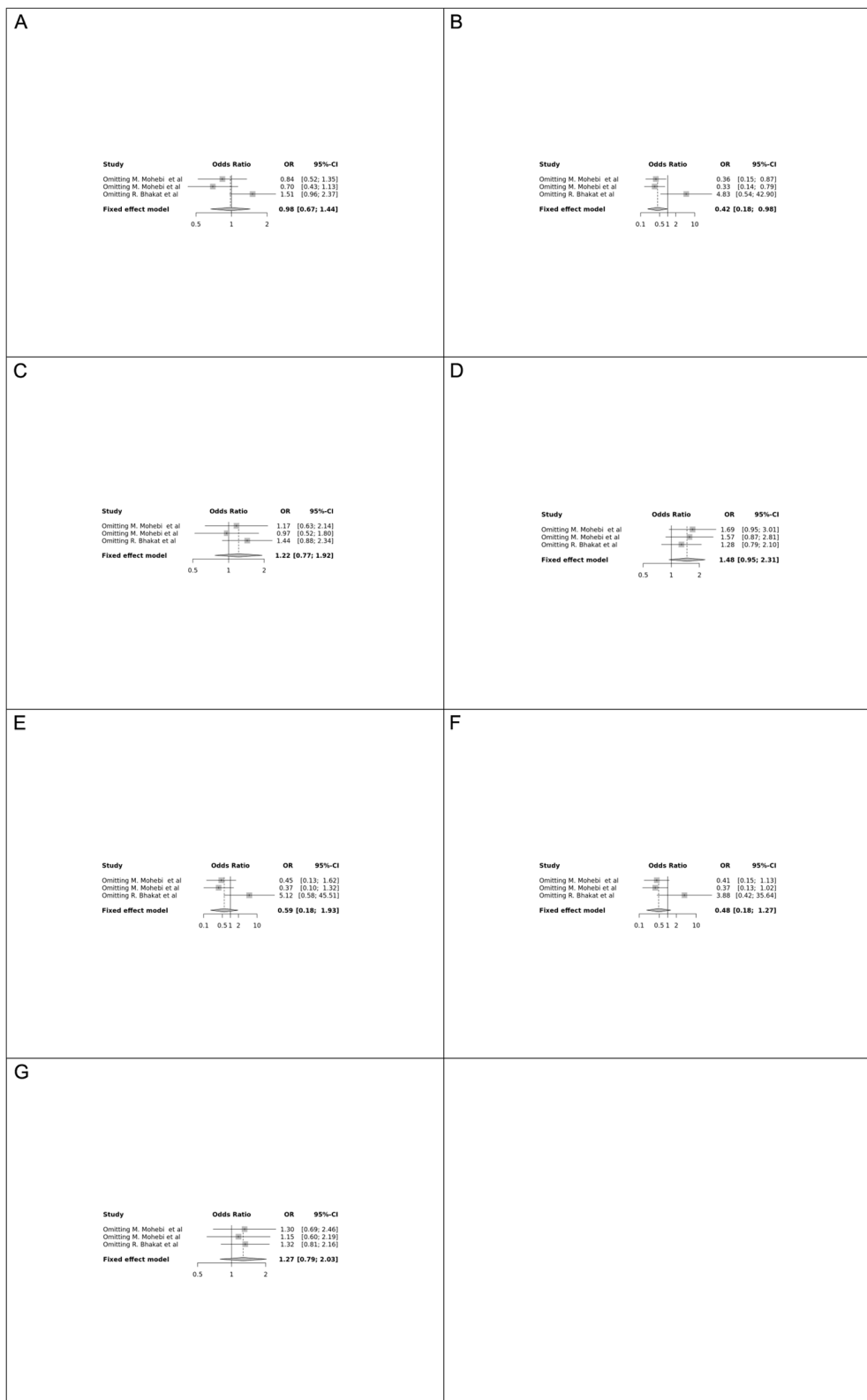
Fig. 10 Funnel plot of different genetic models in infertile women in Apal (rs7975232) SNP A; Allele contrast (A vs. a), B; Recessive model, C; Dominant model, D; Over dominant model, E; Homozygote model, F; AA vs. Aa model, G; Aa vs. aa model

Fig. 11 Funnel plot of different genetic models in infertile men in FokI (rs2228570) SNP A; Allele contrast (F vs. f), B; Recessive model, C; Dominant model, D; Over dominant model, E; Homozygote model, F; FF vs. Ff model, G; Ff vs. ff model
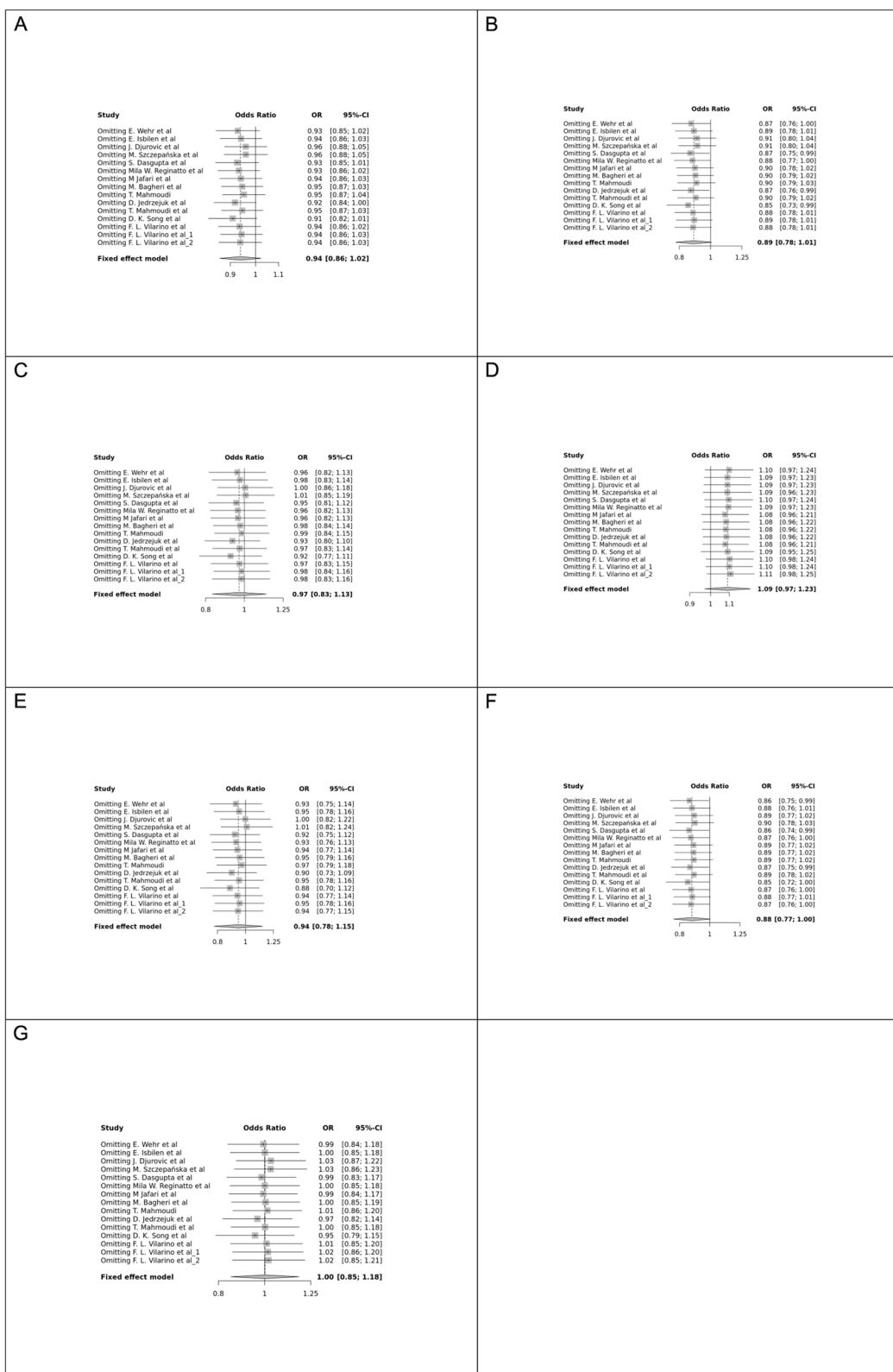
Fig. 12 Sensitivity plot of different genetic models in infertile women in FokI (rs2228570) SNP A; Allele contrast (F vs. f), B; Recessive model, C; Dominant model, D; Over dominant model, E; Homozygote model, F; FF vs. Ff model, G; Ff vs. ff model

Fig. 13 Sensitivity plot of different genetic models in infertile women in BsmI (rs1544410) SNP A; Allele contrast (B vs. b), B; Recessive model, C; Dominant model, D; Over dominant model, E; Homozygote model, F; BB vs. Bb model, G; Bb vs. bb model

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Fig. 14 Sensitivity plot of different genetic models in infertile women in TaqI (rs731236) SNP A; Allele contrast (T vs. t), B; Recessive model, C; Dominant model, D; Over dominant model, E; Homozygote model, F; TT vs. Tt model, G; Tt vs. tt model

Fig. 15 Sensitivity plot of different genetic models in infertile women in Apal (rs7975232) SNP A; Allele contrast (A vs. a), B; Recessive model, C; Dominant model, D; Over dominant model, E; Homozygote model, F; AA vs. Aa model, G; Aa vs. aa model

Fig. 16 Sensitivity plot of different genetic models in infertile men in FokI (rs2228570) SNP A; Allele contrast (F vs. f), B; Recessive model, C; Dominant model, D; Over dominant model, E; Homozygote model, F; FF vs. Ff model, G; Ff vs. ff model

Table 1 Characteristics of studies included in the meta-analysis (infertile women)

Study author	Year	Country	Continent	Ethnicity	Disease	Case/control in each SNP	Age case/control (Mean)	Genotyping Method	NOS score
FokI (rs2228570)									
E. Wehr et al	2011	Austria	Europe		PCOS	538/135	23–31/ 26–36	NucleoSpin Blood method	8
E. Isbilen et al	2020	Turkey	Asia		Idiopathic infertility	101/99	27.45 ± 5.75/ 29.91 ± 4.98	PCR–RFLP	7
J. Djurovic et al	2018	Sebria	Europe		Idiopathic infertility	114/130		PCR–RFLP	6
M. Szczepańska et al	2015	Poland	Europe	Caucasian	Endometriosis-associated infertility	154/346	20–42/ 19–39	PCR–RFLP	8
S. Dasgupta et al	2015	India	Asia		PCOS	252/252		PCR–RFLP	9
Mila W. Reginatto et al	2018	Brazil	America		Idiopathic infertility	49/57	35 ± 0.5/ 44 ± 0.9	TaqMan qPCR and Sanger sequencing	8
M Jafari et al	2021	Iran	Asia		Endometriosis-associated infertility	116/113	32 ± 12/ 31 ± 14	ARMS-PCR and PCR–RFLP	9
M. Bagheri et al	2012	Iran	Asia		PCOS	46/46	26.58 ± 3.33/ 28.24 ± 5.25	PCR–RFLP	8
T. Mahmoudi et al	2009	Iran	Asia		PCOS	162/162	28.92 ± 0.41/ 29.91 ± 0.58	PCR	9
D. Jedrzejuk et al	2015	Poland	Europe	Caucasian	PCOS	90/98		PCR and mini-sequencing	9
T. Mahmoudi et al	2015	Iran	Asia		PCOS	35/35	19–42/ 19–44	PCR–RFLP	8
D. K. Song et al	2019	Korea	Asia		PCOS	432/927	24 ± 5/ 27 ± 5		8
F. L. Vilarino et al	2011	Brazil	America		Endometriosis-associated infertility	132/133	35.1 ± 3.9/ 39.7 ± 3.2	PCR–RFLP	7
F. L. Vilarino et al	2011	Brazil	America		Idiopathic infertility	62/133	35.7 ± 5.0/ 39.7 ± 3.2	PCR–RFLP	7
F. L. Vilarino et al	2011	Brazil	America		Endometriosis-associated infertility	147/154		PCR–RFLP	6
TaqI (rs731236)									
E. Wehr et al	2011	Austria	Europe		PCOS	536/137	23–31/ 26–36	NucleoSpin Blood method	8
M. Bagheri et al	2013	Iran	Asia		PCOS	38/38	26.03 ± 4.98/ 27.18 ± 4.95	PCR–RFLP	8
A. S. El-Shal et al	2013	Egypt	Africa	Caucasian	PCOS	150/150	29.8 ± 5.6/ 29.3 ± 6.2	PCR–RFLP	9
T. Mahmoudi et al	2009	Iran	Asia		PCOS	162/162	28.92 ± 0.41/ 29.91 ± 0.58	PCR	9
D. Jedrzejuk et al	2015	Poland	Europe	Caucasian	PCOS	90/98		PCR and mini-sequencing	9
T. Mahmoudi et al	2015	Iran	Asia	_	PCOS	35/35	19–42/19–44	PCR–RFLP	8
E. Isbilen et al	2020	Turkey	Asia		Idiopathic infertility	101/99	27.45 ± 5.75/ 29.91 ± 4.98	PCR–RFLP	7
J. Djurovic et al	2018	Sebria	Europe		Idiopathic infertility	114/128		PCR–RFLP	6
S. Dasgupta et al	2015	India	Asia		PCOS	251/252		PCR–RFLP	9

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Table 1 (continued)

Study author	Year	Country	Continent	Ethnicity	Disease	Case/control in each SNP	Age case/control (Mean)	Genotyping Method	NOS score
F. L. Vilarino et al	2011	Brazil	America		Endometriosis-associated infertility	132/133	35.1 ± 3.9/ 39.7 ± 3.2	PCR–RFLP	7
F. L. Vilarino et al	2011	Brazil	America		Idiopathic infertility	62/133	35.7 ± 5.0/ 39.7 ± 3.2	PCR–RFLP	7
M Jafari et al	2021	Iran	Asia		Endometriosis-associated infertility	116/114	32 ± 12/ 31 ± 14	ARMS-PCR and PCR–RFLP	9
Bsml (rs1544410)									
E. Wehr et al	2011	Austria	Europe		PCOS	537/137	23–31/ 26–36	NucleoSpin Blood method	8
M. Bagheri et al	2012	Iran	Asia		PCOS	46/46	26.58 ± 3.33/ 28.24 ± 5.25	PCR–RFLP	8
T. Mahmoudi et al	2009	Iran	Asia		PCOS	162/162	28.92 ± 0.41/ 29.91 ± 0.58	PCR	9
D. Jedrzejuk et al	2015	Poland	Europe	Caucasian	PCOS	90/98		PCR and mini-sequencing	9
T. Mahmoudi et al	2015	Iran	Asia		PCOS	35/35	19–42/ 19–44	PCR–RFLP	8
D. K. Song et al	2019	Korea	Asia		PCOS	430/923	24 ± 5/ 27 ± 5	-	8
N. Ramezani et al	2020	Iran	Asia		PCOS	38/40	28.58 ± 5.83/ 31.34 ± 5.5	PCR–RFLP	8
E. Isbilen et al	2020	Turkey	Asia		Idiopathic infertility	101/100	27.45 ± 5.75/ 29.91 ± 4.98	PCR–RFLP	7
J. Djurovic et al	2018	Serbia	Europe		Idiopathic infertility	106/119		PCR–RFLP	6
M. Szczepańska et al	2015	Poland	Europe	Caucasian	Endometriosis-associated infertility	154/346	20–42/ 19–39	PCR–RFLP	8
F. L. Vilarino et al	2011	Brazil	America		Endometriosis-associated infertility	132/133	35.1 ± 3.9/ 39.7 ± 3.2	PCR–RFLP	7
F. L. Vilarino et al	2011	Brazil	America		Idiopathic infertility	62/133	35.7 ± 5.0/ 39.7 ± 3.2	PCR–RFLP	7
Mila W. Regin-atto et al	2018	Brazil	America		Idiopathic infertility	54/86	35 ± 0.5/ 44 ± 0.9	TaqMan qPCR and Sanger sequencing	8
M Jafari et al	2021	Iran	Asia		Endometriosis-associated infertility	116/112	32 ± 12/ 31 ± 14	ARMS-PCR and PCR–RFLP	9
Apal (rs7975232)									
E. Wehr et al	2011	Austria	Europe		PCOS	543/145	23–31/ 26–36	NucleoSpin Blood method	8
A. S. El-Shal et al	2013	Egypt	Africa	Caucasian	PCOS	150/150	29.8 ± 5.6/ 29.3 ± 6.2	PCR–RFLP	9
T. Mahmoudi et al	2009	Iran	Asia		PCOS	162/162	28.92 ± 0.41/ 29.91 ± 0.58	PCR	9
D. Jedrzejuk et al	2015	Poland	Europe	Caucasian	PCOS	90/98		PCR and mini-sequencing-RFLP	9
T. Mahmoudi et al	2015	Iran	Asia		PCOS	35/35	19–42/ 19–44	PCR–RFLP	8
E. Isbilen et al	2020	Turkey	Asia		Idiopathic infertility	101/100	27.45 ± 5.75/ 29.91 ± 4.98	PCR–RFLP	7
J. Djurovic et al	2018	Serbia	Europe		Idiopathic infertility	114/129		PCR–RFLP	6

Table 1 (continued)

Study author	Year	Country	Continent	Ethnicity	Disease	Case/control in each SNP	Age case/control (Mean)	Genotyping Method	NOS score
S. Dasgupta et al	2015	India	Asia		PCOS	249/251		PCR–RFLP	9
S. Siddamalla et al	2018	India	Asia		PCOS	95/130		PCR–RFLP	9
M Jafari et al	2021	Iran	Asia		Endometriosis-associated infertility	116/114	32 ± 12/ 31 ± 14	ARMS-PCR and PCR–RFLP	9
D. K. Song et al	2019	Korea	Asia		PCOS	432/927	24 ± 5/ 27 ± 5	-	8
F. L. Vilarino et al	2011	Brazil	America		Endometriosis-associated infertility	132/133	35.1 ± 3.9/ 39.7 ± 3.2	PCR–RFLP	7
F. L. Vilarino et al	2011	Brazil	America		Idiopathic infertility	72/133	35.7 ± 5.0/ 39.7 ± 3.2	PCR–RFLP	7

NR not reported, *PCR* Polymerase chain reaction, *RFLP* restriction fragment length polymorphism

The present study included a total of 22 articles and showed that the VDR gene TaqI polymorphism was associated with infertility susceptibility in women. ApaI and FokI gene polymorphisms were found to be significantly protective SNPs against women's and men's infertility. The published studies related to the association of selected VDR SNPs and recurrent miscarriage were not enough for meta-analysis, therefore, a systematic review was alone performed. The findings were consistent with prior research and may give an entirely novel biomarker in infertility/recurrent miscarriage with diverse etiologies [20, 42–45]. A subgroup analysis was also undertaken to investigate the possible significance of patient ethnicity or infertility etiology on the association between VDR polymorphisms and the risk of infertility. TaqI SNP was shown to be significantly connected with infertility in Africans, while BsmI was found to be associated with the disease mostly in Asians. This finding could be explained by genetic differences between ethnic groupings. Furthermore, due to the procedure of natural selection, functional variations in various groups may differ [26]. Furthermore, VDR ApaI (rs7975232) was found to be associated with infertility susceptibility in the PCOS subgroup, however, a protection association with idiopathic infertility was found.

VDR gene polymorphism could contribute to the pathophysiology of infertility by influencing gene expression and mRNA stability, and hence the cellular and molecular processes associated with infertility etiology. Nevertheless, these polymorphisms are mostly nonfunctional, linkage disequilibrium with another undiscovered functional variant of the VDR gene appears to be the most likely explanation for the observed association. We meta-analyzed the VDR gene TaqI, BsmI, FokI, ApaI

polymorphisms, and women/men infertility for the first time.

The FokI SNP is the only VDR polymorphism leading to a VDR protein with a different structure. Furthermore, it is the only SNP that is not linked to any other VDR polymorphism, implying that it plays a distinct function [46]. The polymorphism, which is a C to T alteration, is located at the 5' end of the gene. This alteration results in a protein of a different size, a 424 amino acid (aa) variant encoded by the major allele form (ACG) and a 427 aa variant expressed by the minor allele form (ATG). The variations are thought to be functionally relevant, with the 424 aa VDR variant having higher transcriptional activity and being associated with lower circulating 25(OH) D levels than the 427 aa variant [46, 47]. Moreover, Yan et al. showed that women with RPL have lower levels of VDR expression in chorionic villi, decidua, and serum compared with normal pregnant women [48]. It has previously been suggested that CC genotype / 424 aa VDR variant has a higher frequency in women with RPL, which leads to lower circulating 25(OH) D levels, respectively. Several studies have demonstrated that high Vitamin D levels might protect against a variety of illnesses, including infertility and recurrent miscarriage. The idea has been suggested in several research that greater prediagnosis plasma levels of 25-hydroxy vitamin D, the predominant circulating form of vitamin D, is related to a significant decrease in pregnancy problems such as PCOS, endometriosis, infertility, and recurrent pregnancy loss [49–52]. Furthermore, comprehensive reviews and meta-analyses revealed a substantial reduction in total pregnancy outcomes in Vitamin D-deficient patients [53, 54]. Our finding revealed a marginally significant association of FokI SNP with infertility under the FF vs.

Table 2 Characteristics of studies included in the meta-analysis (infertile men)

Study author	Year	Country	Continent	Ethnicity	Disease	Total cases/controls	Case/control in each SNP	Age case/control (Mean)	Genotyping Method	NOS score
FokI (rs2228570)										
M. Mohebi et al	2016	Iran	Asia		infertile men	100/100	100/100	39.1±4.7/ 39.4±5.07	PCR–RFLP	8
M. Mohebi et al	2016	Iran	Asia		infertile men	100/100	100/100	39.3±4.8/ 39.4±5.07	PCR–RFLP	8
R. Bhakat et al	2017	India	Asia		infertile men	50/54	50/54	28.78±4.92/-	PCR–RFLP	7

Table 3 Characteristics of studies (miscarriage)

Study author	Year	Country	Continent	Ethnicity	Disease	Total cases/controls	Case/control in each SNP	Age case/control (Mean)	Genotyping Method	NOS score
TaqI (rs731236)										
A Barisic et al	2019	Slovenia and Croatia	Europe		Recurrent pregnancy loss (RPL) loss of two or more pregnancies before 24 weeks of gestation	160/160	160/160		PCR–RFLP	7
ApaI (rs7975232)										
D. Liu et al	2021	China	Asia		Recurrent pregnancy loss (RPL) loss of two or more pregnancies before 24 weeks of gestation	75/83	71/49	20–45/ 20–45	sequencing PCR	8
FokI (rs2228570)										
V. E. Radzinsky et al	2021	Russia	Asia		Recurrent pregnancy loss (RPL) loss of two or more pregnancies before 24 weeks of gestation	43/77	43/76	18–41/ 18–41	RT-PCR	9
A Barisic et al	2019	Slovenia and Croatia	Europe		Recurrent pregnancy loss (RPL) loss of two or more pregnancies before 24 weeks of gestation	160/160	160/160		PCR–RFLP	7

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Table 4 Distribution of genotype and allele among cases and controls (infertile women)

Study author	Cases					Controls					P-HWE	P-HWE adjusted
	FF	Ff	ff	F	f	FF	Ff	ff	F	f		
FokI (rs2228570)												
E. Wehr et al	82	241	215	405	671	22	60	53	104	166	0.473	0.683
E. Isbilen et al	19	17	65	55	147	17	15	67	49	149	0.00	0.551
J. Djurovic et al	21	59	34	101	127	12	64	54	88	172	0.257	0.325
M. Szczepańska et al	37	88	29	162	146	65	189	92	319	373	0.065	0.683
S. Dasgupta et al	10	87	155	107	397	15	85	152	115	389	0.501	0.583
Mila W. Reginatto et al	23	17	9	63	35	29	21	7	79	35	0.311	0.01
M Jafari et al	3	76	37	82	150	5	**65**	43	75	151	0.001	0.972
M. Bagheri et al	4	20	22	28	64	2	15	29	19	73	0.972	0.727
T. Mahmoudi et al	12	67	83	91	233	7	59	96	73	251	0.581	0.965
D. Jedrzejuk et al	11	51	28	73	107	25	50	23	100	96	0.836	0.972
T. Mahmoudi et al	2	17	16	21	49	1	10	24	12	58	0.972	0.768
D. K. Song et al	67	212	153	346	518	159	435	333	753	1101	0.407	0.678
F. L. Vilarino et al	60	61	11	181	83	59	64	10	182	84	0.190	0.475
F. L. Vilarino et al	31	28	3	90	34	59	64	10	182	84	0.190	0.475
F. L. Vilarino et al	65	69	13	199	95	64	77	13	205	103	0.126	0.473
Study author	**Cases**					**Controls**					**P-HWE**	**P-HWE adjusted**
	TT	Tt	tt	T	t	TT	Tt	tt	T	t		
Taql (rs731236)												
E. Wehr et al	226	238	72	690	382	49	65	23	163	111	0.854	0.931
M. Bagheri et al	16	14	8	46	30	17	19	2	53	23	0.255	0.398
A. S. El-Shal et al	40	74	36	154	146	69	61	20	199	101	0.27	0.398
T. Mahmoudi et al	71	71	20	213	111	72	76	14	220	104	0.330	0.398
D. Jedrzejuk et al	37	45	8	119	61	49	37	12	135	61	0.237	0.398
T. Mahmoudi et al	15	14	6	44	26	15	16	4	46	24	0.931	0.931
E. Isbilen et al	44	37	20	125	77	76	15	8	167	31	0.000	0.000
J. Djurovic et al	47	46	21	140	88	54	54	20	162	94	0.296	0.398
S. Dasgupta et al	112	92	47	316	186	110	105	37	325	179	0.151	0.398
F. L. Vilarino et al	55	62	15	172	92	50	71	12	171	95	0.060	0.243
F. L. Vilarino et al	20	30	12	70	54	50	71	12	171	95	0.060	0.243
M Jafari et al	43	64	9	150	82	59	49	6	167	61	0.301	0.398
Study author	**Cases**					**Controls**					**P-HWE**	**P-HWE adjusted**
	BB	Bb	bb	B	b	BB	Bb	bb	B	b		
Bsml (rs1544410)												
E. Wehr et al	77	244	216	398	676	22	66	49	110	164	0.977	0.977
M. Bagheri et al	15	27	4	57	35	20	24	2	64	28	0.115	0.179
T. Mahmoudi et al	24	85	53	133	191	18	91	53	127	197	0.023	0.080
D. Jedrzejuk et al	14	45	31	73	107	13	42	43	68	128	0.591	0.747
T. Mahmoudi et al	10	12	13	32	38	5	23	7	33	37	0.059	0.119
D. K. Song et al	4	40	386	48	812	3	94	826	100	1746	0.851	0.917
N. Ramezani et al	25	10	3	60	16	23	16	1	62	18	0.352	0.493
E. Isbilen et al	39	49	13	127	75	19	59	22	97	103	0.070	0.122
J. Djurovic et al	29	50	27	108	104	36	72	11	144	94	0.003	0.017
M. Szczepańska et al	56	76	22	188	120	147	154	45	448	244	0.640	0.747
F. L. Vilarino et al	10	69	53	89	175	8	66	59	82	184	0.059	0.111
F. L. Vilarino et al	4	34	24	42	82	8	66	59	82	184	0.059	0.111
Mila W. Reginatto et al	23	8	23	54	54	31	8	47	70	102	0.000	0.000
M Jafari et al	17	65	34	99	133	9	71	32	89	135	0.006	0.004

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Table 4 (continued)

Study author	Cases					Controls					P-HWE	P-HWE adjusted
	FF	Ff	ff	F	f	FF	Ff	ff	F	f		
Study author	Cases					Controls					P-HWE	P-HWE adjusted
	AA	Aa	aa	A	a	AA	Aa	aa	A	a		
ApaI (rs7975232)												
E. Wehr et al	127	274	142	528	558	37	60	48	134	156	0.043	0.113
A. S. El-Shal et al	22	65	63	109	191	18	64	68	100	200	0.624	0.737
T. Mahmoudi et al	36	68	58	140	184	23	90	49	136	188	0.073	0.137
D. Jedrzejuk et al	19	52	19	90	90	17	49	32	83	113	0.812	0.812
T. Mahmoudi et al	9	11	15	29	41	6	21	8	33	37	0.227	0.369
E. Isbilen et al	9	85	7	103	99	2	94	4	98	102	0.000	0.000
J. Djurovic et al	12	54	48	78	150	13	77	39	103	155	0.005	0.023
S. Dasgupta et al	12	120	117	144	354	12	117	122	141	361	0.014	0.048
S. Siddamalla et al	32	21	42	85	105	25	35	70	85	175	0.000	0.000
M Jafari et al	18	55	43	91	141	25	59	30	109	119	0.692	0.749
D. K. Song et al	28	164	240	220	644	46	367	514	459	1395	0.056	0.122
F. L. Vilarino et al	44	72	16	160	104	49	67	17	165	101	0.423	0.550
F. L. Vilarino et al	22	29	11	73	51	49	67	17	165	101	0.423	0.550

P-HWE P value for Hardy–Weinberg equilibrium

Table 5 Distribution of genotype and allele among cases and controls (infertile men)

Study author	cases					controls					P-HWE	P-HWE adjusted
	FF	Ff	ff	F	f	FF	Ff	ff	F	f		
FokI (rs2228570)												
M. Mohebi et al	1	21	78	23	177	0	18	82	18	182	0.322	0.322
M. Mohebi et al	3	23	74	29	171	0	18	82	18	182	0.322	0.322
R. Bhakat et al	8	13	29	29	71	3	6	45	12	96	0.001	0.003

Table 6 Distribution of genotype and allele among cases and controls (miscarriage)

Study author	Cases					Controls					P-HWE	P-HWE adjusted
	FF	Ff	ff	F	f	FF	Ff	ff	F	f		
FokI (rs2228570)												
V. E. Radzinsky et al	16	21	6	53	33	21	37	18	79	73	0.828	0.832
A Barisic et al	17	75	68	109	211	26	87	47	139	181	0.177	0.355
Study author	Cases					Controls					P-HWE	P-HWE adjusted
	AA	Aa	aa	A	a	AA	Aa	aa	A	a		
ApaI (rs7975232)												
D. Liu et al	48	20	3	116	26	30	17	2	77	21	0.832	0.832
Study author	Cases					Controls					P-HWE	P-HWE adjusted
	TT	Tt	tt	T	t	TT	Tt	tt	T	t		
TaqI (rs731236)												
A Barisic et al	23	64	73	110	210	34	67	59	135	185	0.073	0.293

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Table 7 Main results of pooled ORs in the meta-analysis of *VDR* gene polymorphisms (infertile women)

Comparisons		Number of studies	Test of association				Test of heterogeneity		Publication bias
			OR	95% CI	*p*-value	Model	*p*-value	I^2	*p*-value (Egger's test)
FokI (rs2228570)									
f vs. F	Allele contrast	14	0.939	[0.861; 1.023]	0.151	Fixed	0.083	0.356	0.220
ff vs. Ff + FF	Recessive model	14	0.887	[0.780; 1.008]	0.067	Fixed	0.336	0.104	0.354
ff + Ff vs. FF	Dominant model	14	0.971	[0.831; 1.134]	0.712	Fixed	0.270	0.163	0.650
Ff vs. FF + ff	Over dominant	14	1.090	[0.970; 1.225]	0.145	Fixed	0.948	0.000	0.213
ff vs. FF	Homozygote	14	0.944	[0.777; 1.147]	0.564	Fixed	0.094	0.341	0.516
FF vs. Ff		14	0.876	[0.765; 1.003]	0.056	Fixed	0.776	0.000	0.439
Ff vs. ff		14	1.001	[0.849; 1.180]	0.985	Fixed	0.650	0.000	0.961
TaqI (rs731236)									
t vs. T	Allele contrast	11	1.206	[1.084; 1.342]	0.000	Fixed	0.000	0.704	0.148
tt vs. Tt + TT	Recessive model	11	1.383	[1.119; 1.709]	0.002	Fixed	0.165	0.285	0.160
tt + Tt vs. TT	Dominant model	11	1.214	[0.048; 1.407]	0.009	Fixed	0.000	0.698	0.270
Tt vs. TT + tt	Over dominant	11	1.0325	[0.892; 1.195]	0.668	Fixed	0.009	0.558	0.489
tt vs. TT	Homozygote	11	1.459	[1.162; 1.832]	0.001	Fixed	0.019	0.514	0.169
TT vs. Tt		11	1.285	[1.024; 1.611]	0.029	Fixed	0.479	0.000	0.350
Tt vs. tt		11	1.134	[0.969; 1.327]	0.115	Fixed	0.001	0.649	0.325
BsmI (rs1544410)									
b vs. B	Allele contrast	13	1.030	[0.929; 1.141]	0.570	Fixed	0.076	0.375	0.448
bb vs. Bb + BB	Recessive model	13	1.131	[0.938; 1.365]	0.195	Fixed	0.103	0.340	0.044
bb + Bb vs. BB	Dominant model	13	0.986	[0.844; 1.151]	0.859	Fixed	0.046	0.424	0.367
Bb vs. BB + bb	Over dominant	13	0.915	[0.795; 1.053]	0.216	Fixed	0.114	0.325	0.445
bb vs. BB	Homozygote	13	1.095	[0.864; 1.388]	0.449	Fixed	0.038	0.442	0.805
BB vs. Bb		13	1.161	[0.950; 1.419]	0.142	Fixed	0.116	0.323	0.085
Bb vs. bb		13	0.936	[0.794; 1.103]	0.434	Fixed	0.055	0.408	0.342
ApaI (rs7975232)									
a vs. A	Allele contrast	12	0.953	[0.872; 1.042]	0.299	Fixed	0.212	0.229	0.898
aa vs. Aa + AA	Recessive model	12	1.000	[0.879; 1.138]	0.992	Fixed	0.060	0.411	0.353
aa + Aa vs. AA	Dominant model	12	0.837	[0.703; 0.997]	0.046	Fixed	0.197	0.243	0.168
Aa vs. AA + aa	Over dominant	12	0.913	[0.807; 1.033]	0.149	Fixed	0.008	0.553	0.079
aa vs. AA	Homozygote	12	0.842	[0.688; 1.031]	0.097	Fixed	0.458	0.000	0.704
AA vs. Aa		12	1.056	[0.921; 1.210]	0.432	Fixed	0.031	0.468	0.260
Aa vs. aa		12	0.833	[0.691; 1.004]	0.055	Fixed	0.090	0.365	0.042

Table 8 Main results of pooled ORs in the meta-analysis of *VDR* gene polymorphisms (infertile men)

Comparisons		Number of studies	Test of association				Test of heterogeneity		Publication bias
			OR	95% CI	*p*-value	Model	*p*-value	I^2	*p*-value (Egger's test)
FokI (rs2228570)									
f vs. F	Allele contrast	2	0.980	[0.667; 1.439]	0.918	Fixed	0.001	0.850	0.053
ff vs. Ff + FF	Recessive model	2	0.421	[0.182; 0.976]	0.043	Fixed	0.055	0.653	0.140
ff + Ff vs. FF	Dominant model	2	1.216	[0.768; 1.923]	0.402	Fixed	0.110	0.545	0.111
Ff vs. FF + ff	Over dominant	2	1.476	[0.945; 2.307]	0.086	Fixed	0.410	0.000	0.133
ff vs. FF	Homozygote	2	0.590	[0.181; 1.928]	0.383	Fixed	0.065	0.633	0.162
FF vs. Ff		2	0.484	[0.184; 1.273]	0.141	Fixed	0.117	0.533	0.143
Ff vs. ff		2	1.267	[0.790; 2.031]	0.325	Fixed	0.823	0.000	0.291

Table 9 Main results of pooled ORs in the meta-analysis of *VDR* gene polymorphisms (miscarriage)

Comparisons		Number of studies	Test of association				Test of heterogeneity		Publication bias
			OR	95% CI	*p*-value	Model	*p*-value	I^2	*p*-value (Egger's test)
FokI (rs2228570)									
f vs. F	Allele contrast	4	1.238	[1.016; 1.508]	0.034	Fixed	0.187	0.373	0.934
ff vs. Ff + FF	Recessive model	4	1.476	[1.096; 1.986]	0.010	Fixed	0.626	0.000	0.657
ff + Ff vs. FF	Dominant model	4	1.139	[0.792; 1.638]	0.481	Fixed	0.164	0.411	0.418
Ff vs. FF + ff	Over dominant	4	0.774	[0.587; 1.020]	0.068	Fixed	0.886	0.000	0.144
ff vs. FF	Homozygote	4	1.462	[0.966; 2.212]	0.072	Fixed	0.188	0.372	0.693
FF vs. Ff		4	1.469	[1.074; 2.011]	0.016	Fixed	0.898	0.000	0.328
Ff vs. ff		4	0.992	[0.675; 1.456]	0.968	Fixed	0.294	0.190	0.379

Ff genetic model (OR = 0.8763, 95% CI [0.7651–1.0036], $P = 0.05$). This indicates that the FokI f allele might be a risk factor for infertility, future studies with larger sample sizes and considering other confounder variables still need to confirm these findings though.

The functional evaluation of the three significant noncoding VDR SNPs (BsmI, TaqI, and ApaI) examined in this meta-analysis revealed contradictory findings from prior studies regarding their biological implications. Even if these SNPs are nonfunctional, the impacts identified in this meta-analysis and other studies could be driven by other, actually important SNPs in significant LD located elsewhere in the VDR gene. Some studies aimed at characterizing differences in VDR expression for SNPs in the 3' end of the VDR gene found that the BsmI-ApaI-TaqI haplotype BAt (rs1544410-A/rs7975232-A/rs731236-C) had higher levels of VDR mRNA expression than the baT (rs1544410-G/rs7975232-C/rs731236-T). These SNPs could be implicated in gene expression control, specifically by mRNA stability modulation. To be more specific, the existence of the TaqI G allele improves VDR mRNA stability and half-life, leading to an increased VDR synthesis and therefore directly altering vitamin D levels and consequently subsequent effects of vitamin D [55, 56].

A significant association was found between ApaI and infertility in the present meta-analysis. We observed a borderline and a significant protective association for the Aa vs. aa model (OR = 0.83, $P = 0.05$) and the dominant model (OR = 0.84, $P < 0.05$), however, no significant association was reported in other genetic model contrasts. These findings show that individuals who inherited ApaI SNP in a dominant form might be more protected against infertility. This polymorphism is in strong linkage disequilibrium with the poly(A) microsatellite located in the 3′ untranslated region [45] of the VDR gene, which appears to influence VDR messenger RNA stability and VDR translational activity (9). Sub-group analysis,

however, showed a protective association against infertility in the PCOS subgroup under dominant (AA + Aa vs. aa), over-dominant, (Aa vs. AA + aa, AA vs. aa, and Aa vs. aa genetic models and a susceptibility association under the recessive genetic model in idiopathic infertility sub-group.

In our study, we noted a higher frequency of the genotype containing a mutated t allele of TaqI polymorphism. Interestingly, TaqI polymorphism was the only SNP that showed significant association with infertility overall and based on the etiology, excluding Over dominant genetic model. Our results showed that TaqI polymorphism may increase susceptibility to infertility under the allele contrast, recessive, dominant, homozygote, TT vs. Tt, Tt vs. tt genetic models. This indicates the If Taq t allele is a protective factor for infertility, then the infertility chance of patients with Taq t allele will be lower than that of patients with Taq T allele (OR > 1, $P < 0.05$). These data suggested the role of these genetic variants might be attributed with infertility due to the influence on the VDR function and consequently disturbed vitamin D metabolism or might be due to the LD with other VDR SNPs. These results suggest the special role of maternal setting genetic variants of the VDR gene in the etiology of this pregnancy complication. However, further research is required to determine what exactly FokI is acting as a marker for infertility.

As ~ 50% of patients with recurrent pregnancy loss (RPL) do not have a definite etiology, we further aimed to perform the meta-analysis of the association between VDR polymorphisms and recurrent miscarriage. The potential association of VDR polymorphisms with the etiology of recurrent miscarriages has been indicated in several studies [31, 45, 57]. Although with conflicting results, most of them suggested VDR SNPs association with RM in women. A study reported lower expression of VDR in trophoblastic, decidua, and serum villi in

the RM group compared to the control, suggesting that impaired VDR expression in the first trimester of pregnancy may be associated with the occurrence of RM [48]. Accordingly, it could be suggested that VDR SNPs might be involved in the susceptibility and protection against RPL through influence on the VDR mRNA expression level and stability or due to the LD with other SNPs. In our study, we only found the association of FokI, and RPL in more than two studies, therefore the meta-analysis was performed for FokI polymorphism. Our data showed that FokI is significantly associated with a lower risk of RPL in allele contrast 9OR = 1.23, $P = 0.034$), recessive model (OR = 1.47, $P = 0.010$), and FF vs. Ff (OR = 1.46, OR = 0.016) genetic models. This indicates that carriers of FokI SNP might be more protected against RPL, however, it is required to be studied in larger sample sizes and to examine the exact functional effect of this SNP on the RPL etiology.

Because of racial differences, evidence of disease occurrence is not always accurate. This shows that various races have distinct effects on genetic background [58]. Therefore, based on subgroup analysis of different races, it can be found that the same polymorphisms in disease susceptibility in different populations play different roles. In our study, subgroup analysis suggested that the VDR gene BsmI polymorphism was significantly associated with susceptibility to infertility for the comparison of (AA vs. aa), (AA vs. Aa), and recessive model, and was protective SNP in the over-dominant genetic model in Asian population. For VDR gene TaqI polymorphism, it was significantly associated with susceptibility to infertility under the comparison of allele contrast (A vs. a), recessive model (AA vs. Aa + aa), dominant model (AA + Aa vs. aa), over-dominant (Aa vs. AA + aa), AA vs. aa, AA vs. Aa, Aa vs. aa genetic models in African and Asian population. However, for VDR gene ApaI polymorphism, it was protectively associated with infertility under dominant model (AA + Aa vs. aa), over-dominant (Aa vs. AA + aa), AA vs. aa, AA vs. Aa, Aa vs. aa genetic models and a susceptibility association was observed under recessive model (aa vs. Aa + AA) in Asian. FokI polymorphism was not significantly associated with infertility under any genetic models in any geographic population. The opposite association in different populations for an SNP in subgroup analysis might be due to ethnic differences. Of course, it also may be the difference in results caused by the insufficient number of studies included. We certainly need more and better research to get more reliable results.

Our study contains certain characteristics linked to study design that can help to strengthen the conclusions. The criteria for study selection were stringent, and such

an exact selection guaranteed the right degree of analysis. Both groups (patients and controls) had participants who were similar in terms of age, ethnic background, and area of residence, reducing the impact of known confounders. In the genetic models, statistical power was adequate for genotype and allele frequencies of reported gene polymorphisms, as well as relationships between individual VDR polymorphisms and the probability of infertility/RPL. A drawback of this research is that we did not have original data, so we were unable to control for other factors such as circulating vitamin D levels, sun exposure, aspirin/NSAID use, stage disease, calcium, and vitamin D intake. The main drawback of the current study is the relatively small sample size and a lack of enough publications on the association of VDR SNPs and RPL. Finally, only four single nucleotide variations of the VDR gene were studied in this study, while, there are several more genetic variations that influence VD metabolism.

The limitation lies in the incapacity to explore diverse age groups through subgroup analyses, relying on the specified age range of 20 to 40 years in the primary studies. This constraint was underscored within the study's delineation of limitations regarding subgroup analyses grounded on age. Also, this study relied on secondary data sources, limiting our ability to control for potential confounding factors, including circulating vitamin D levels, sun exposure, aspirin/NSAID use, stage of disease, calcium, and vitamin D intake. The relatively small sample size in the current study reduced both statistical power and the generalizability of the results. Furthermore, insufficient publications on the association of VDR SNPs and RPL hindered comparison with previous studies. The examination in this study was confined to four single nucleotide variations of the VDR gene—FokI, BsmI, ApaI, and TaqI. However, numerous other genetic variations, such as CYP2R1, CYP27B1, CYP24A1, and GC, influence vitamin D metabolism. Consequently, our findings may not fully capture the genetic effects of vitamin D on RPL.

Conclusion

Some comparisons revealed heterogeneity, but it was somewhat addressed by ethnicity-based subgroup analysis. According to our findings, VDR ApaI and FokI can have a role in infertility/recurrent miscarriage. These SNPs might be utilized to assess the risk of infertility/recurrent miscarriage. The observed relationships should be replicated in a bigger meta-analysis. Furthermore, expression studies are essential for fully comprehending the function of VDR polymorphisms in the etiology of infertility/recurrent miscarriage. Finally, investigations should be conducted to determine whether nutritional therapies such as vitamin D can provide a possible

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response to the hereditary propensity. Finally, our findings imply that VDR FokI and ApaI polymorphisms may be linked to infertility/recurrent miscarriage. However, more research with a larger sample size and considering other confounding factors is required in the future to reach a conclusive conclusion.

Authors' contributions
AM, MA, and AA wrote the paper, and, along with YM, contributed to the design and analysis of the data, while SA and MGh gathered data and assisted in writing the manuscript. YM and AA critically reviewed it, YM gave final approval to the published version. All authors have read and given their approval to the manuscript. Every writer should have made significant input in the creation and design of the work; SA, MGh, and MA should have been involved in collecting, analyzing, and interpreting data, as well as developing new software for the project; AM must have prepared the initial draft and AA, YA should have made substantial revisions to it. YA and AA have given their approval to the version that was submitted (as well as any significantly modified versions that include the author's contributions to the study).

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was reviewed and approved by the Research Ethics Committees of Kurdistan University of Medical Sciences Medicine. The project was found to be by the ethical principles and the national norms and standards for conducting Medical Research in Iran. Consent to participate was not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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