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Abstract

BACKGROUND: Endometriosis is an oestrogen-dependent gynaecological disorder that affects at least 10% of women of reproductive age. It may lead to infertility and non-specific symptoms such as chronic pelvic pain. Endometriosis screening and diagnosis are difficult and time-consuming. Late diagnosis (with a delay ranging from 3.3 to 10.7 years) is a major problem, and may contribute to disease progression and a worse response to treatment once initiated. Efficient screening tests might be reducing this diagnostic delay. As endometriosis is presumed to be a complex disease with several genetic and non-genetic pathogenic factors, many researchers have sought to identify polymorphisms that predispose to this condition.

OBJECTIVE AND RATIONALE: We performed a systematic review and meta-analysis of the most regularly reported polymorphisms in order to identify those that might predispose to endometriosis and might thus be of value in screening.

SEARCH METHODS: The MEDLINE database was searched for English-language publications on DNA polymorphisms in endometriosis, with no date restriction. The PubTator text mining tool was used to extract gene names from the selected publications' abstracts. We only selected polymorphisms reported by at least three studies having applied strict inclusion and exclusion criteria to their control populations. No stratification based on ethnicity was performed. All steps were carried out according to PRISMA guidelines.

OUTCOMES: The initial selection of 395 publications cited 242 different genes. Sixty-two genes (corresponding to 265 different polymorphisms) were cited at least in three publications. After the application of our other selection criteria: an original case-control study of

endometriosis; a reported association between endometriosis and at least one polymorphism; data on women of reproductive age; and a diagnosis of endometriosis in the cases established by surgery and/or MRI and confirmed by histology, 28 polymorphisms were eligible for meta-analysis. Only five of the 28 polymorphisms were found to be significantly associated with endometriosis: interferon gamma (*IFNG*) (CA)repeat, glutathion S-transferase mu 1 (*GSTM1*) null genotype, glutathion S-transferase pi 1 (*GSTP1*) rs1695 and wingless-type MMTV integration site family member 4 (*WNT4*) rs16826658 and rs2235529. Six others showed a significant trend towards an association: progesterone receptor (*PGR*) PROGINS, interCellular adhesion molecule 1 (*ICAM1*) rs1799969, aryl-hydrocarbon receptor repressor (*AHRR*) rs2292596, cytochrome family 17 subfamily A polypeptide 1 (*CYP17A1*) rs743572, *CYP2C19* rs4244285 and peroxisome proliferator-activated receptor gamma (*PPARG*) rs1801282) and 12 showed a significant trend towards the lack of an association: tumor necrosis factor (*TNF*) rs1799964, interleukin 6 (*IL6*) rs1800796, transforming growth factor beta 1 (*TGFB1*) rs1800469, estrogen receptor 1 (*ESR1*) rs2234693, *PGR* rs10895068, follicle stimulating hormone receptor (*FSHR*) rs6166, *ICAM1* rs5498, *CYP1A1* rs4646903, *CYP19A1* rs10046, tumor protein 53 (TP53) rs1042522, X-ray repair complementing defective repair in Chinese hamster cells 1 (*XRCC1*) rs25487 and serpin peptidase inhibitor clade E member 1 (*SERPINE1)* rs1799889); however, for the 18 polymorphisms identified in the latter two groups, further studies of the potential association with the endometriosis risk are needed. The remaining five of the 28 polymorphisms were not associated with endometriosis: glutathion S-transferase theta 1 (*GSTT1*) null genotype, vascular endothelial growth factor alpha (*VEGFA*) rs699947, rs833061, rs2010963 and rs3025039).

WIDER IMPLICATIONS: By carefully taking account of how the control populations were defined, we identified polymorphisms that might be candidates for use in endometriosis screening, and polymorphisms not associated with endometriosis. This might constitute the first step towards identifying polymorphism combinations that predispose to endometriosis in a large cohort of patients with well-defined inclusion criteria. In turn, these results might improve the diagnosis of endometriosis in primary care. Lastly, our present findings may enable a better understanding of endometriosis and improve the management of patients with this disease.

Keywords: endometriosis, polymorphism, predisposition, *IFNG*, *GSTM1*, *GSTP1*, *WNT4*

Introduction

Endometriosis is a chronic inflammatory gynaecological disease characterized by the presence of functional endometrial tissue outside the uterine cavity - mainly in the pelvic cavity (*i.e.*, the ovaries, uterus, uterosacral ligaments and pouch of Douglas) and in the wall of pelvic organs (Chapron et al. 2006; Giudice and Kao 2004). This is a common disease; it has been estimated that 176 million women worldwide suffer from endometriosis (Johnson et al. 2017). The signs and symptoms of endometriosis may vary widely from one woman to another but can include chronic pelvic pain, infertility and even fatigue due to impaired sleep (Zondervan et al. 2018; Ramin-Wright et al. 2018; Fauconnier and Chapron 2005). There is a strong link between endometriosis and infertility; 25 to 50% of infertile women are likely to have endometriosis (Bulletti et al. 2010; Evans and Decherney 2017), and there is an elevated risk of infertility among women with endometriosis (Ballard et al. 2008). However, the mechanism underlying the link between endometriosis and infertility is still poorly understood, and is subject to debate (Somigliana et al. 2017).

Even though endometriosis was first described in the early 20th century, its aetiology remains enigmatic. Several theories have been put forward but none fully explains the development of endometriosis in all the observed sites (Vercellini et al. 2014; Vinatier et al. 2001). The most widely accepted theory (proposed by Sampson) is based on retrograde menstruation, with the regurgitation of the endometrial cells in menstrual debris into the peritoneal cavity (Sampson 1927).

Three main phenotypes of endometriosis have been described: superficial endometriosis, endometrioma, and deep infiltrating endometriosis (Nisolle and Donnez 1997). Even the

classification of this disease is subject to debate (Johnson et al. 2017), however, the revised American Society for Reproductive Medicine (ASRM) classification (Medicine 1997) is widely used. The latter is based on observations during surgery, and the severity is staged from minimal (I) to severe (IV) (Andres, Borrelli, and Abrao 2018).

The pelvic pain experienced during endometriosis is common in the general population; hence, the lack of endometriosis-specific symptoms and a first-line assay complicate and lengthen the diagnostic process in primary care. Indeed, the diagnostic delay (i.e. the time interval between symptom onset and diagnosis) is considerable: 8 years in the UK (Ballard, Lowton, and Wright 2006), 10.5 years in Austria and Germany (Hudelist et al. 2012), and 7.4 years in The Netherlands, for example (Staal, van der Zanden, and Nap 2016). There are no reliable blood screening tests for endometriosis (Vinatier et al. 2001; May et al. 2010; Bedaiwy and Falcone 2004; Nisenblat, Bossuyt, Shaikh, et al. 2016). Similarly, medical imaging procedures (such as MRI and ultrasound) do not offer satisfactory performance (Nisenblat, Bossuyt, Farquhar, et al. 2016). Even when performed by an experienced physician, ultrasound has insufficient diagnostic value in the detection of non-ovarian endometriosis, with a false-negative rate of up to 40% (Guerriero et al. 2015). In another study, MRI was associated with a false-negative rate of 21%, and gave very heterogeneous results (Nisenblat, Bossuyt, Farquhar, et al. 2016). Hence, the non-invasive diagnosis of endometriosis is not yet possible. Laparoscopy with a biopsy and histological analysis of the lesion therefore remain the gold standard for diagnosis (Fassbender et al. 2015; Rogers et al. 2017). By comparing the incidence rate among women seeking clinical care with that in a population cohort, it has been demonstrated that about 11% of women have undiagnosed endometriosis (Buck Louis et al. 2011). Accordingly, there is an urgent need for new diagnostic tools that can be deployed at the population level.

Endometriosis is a complex, heterogeneous disease that involves multiple genetic and environmental factors (Soave et al. 2015; Saha et al. 2015). Heritable tendencies for endometriosis were suspected as early as the 1940s, and this hypothesis was confirmed in the 1980s (Simpson and Bischoff 2002; Zondervan et al. 2018). The aggregation of endometriosis within families means that first-degree relatives of patients have a significantly greater risk of developing endometriosis (Matalliotakis et al. 2008; Stefansson et al. 2002). In twin studies, it has been estimated that about 50% of the risk of endometriosis is heritable (Saha et al. 2015; Treloar et al. 1999). Disease-causing genes can be identified in several ways, some of which require a candidate gene hypothesis (Bischoff and Simpson 2004). Over the last two decades, several research groups have investigated the association between endometriosis and polymorphisms (especially single-nucleotide polymorphisms [SNPs]) primarily in genes involved in inflammatory and detoxification processes, cell adhesion, and endocrine pathways (Falconer, D'Hooghe, and Fried 2007).

The objectives of the present study were, first, to provide an exhaustive review of polymorphisms studied in endometriosis and, second, to estimate the magnitude of the association (using meta-analysis) for the most regularly reported polymorphisms. To this end, we used a text mining approach and applied strict inclusion criteria (notably with regard to the control populations) in our meta-analysis.

Methods

Search strategy

We searched the MEDLINE database for publications on polymorphisms in endometriosis. The following search query was submitted on PubMed on June 1st, 2018:

(((((endometriosis[MeSH Major Topic]) or endometriosis[Title/Abstract]) AND (polymorphism[Title/Abstract] OR polymorphisms[Title/Abstract]))) NOT review[Publication Type]) NOT meta-analysis[Title]) AND English[Language])

No restriction was placed on the publication date. We limited the search to publications in English, and excluded reviews and meta-analyses.

In order to examine the literature as efficiently and exhaustively as possible, we used the PubTator text mining tool (Wei, Kao, and Lu 2012) in R (R Core Team 2018) to extract gene names (Wei et al. 2012). The "pubtator_function" in the R package "pubmed.mineR" (Shah 2014) extracts specific information from abstracts (*i.e.*, gene names or symbols, in our case).

Study selection

We decided to focus solely on genes cited in at least three different publications; we considered that a meta-analysis of two studies was not methodologically relevant. In a second step, this criterion was also applied to the selection of polymorphisms. We decided to focus solely on

genes and polymorphisms cited in at least three different publications in order to increase confidence in our results and limit the number of meta-analyses to be performed.

The publications' eligibility was assessed independently by two investigators (LM and FV). For the meta-analysis, studies had to meet the following inclusion criteria: an original case-control study of endometriosis; a reported association between endometriosis and at least one polymorphism; data on women of reproductive age; and a diagnosis of endometriosis in the cases established by surgery and/or MRI and confirmed by histology. When possible, information on the ASRM stage (Medicine 1997) was used to classify the patients. Studies considering adenomyosis or diseases other than endometriosis were excluded.

We next rated each study's control population with regard to: the World Endometriosis Research Foundation's guidelines; the Endometriosis Phenome and Biobanking Harmonization Project (promoting harmonized, standardized sample collection, and the use of biological sample collection and processing model that reduces inter-study variability (Becker et al. 2014; Fassbender et al. 2014; Rahmioglu et al. 2014; Vitonis et al. 2014); the suggestion that the best controls are pain-free, fertile women in whom the absence of endometriosis has been confirmed by laparoscopy (Greaves et al. 2017); and the ASRM guidelines (Medicine 1997). Three types of study were considered:

- Category 1 (CAT1) studies, in which the absence of endometriosis in the control women has been confirmed during surgery (tubal ligation, hysterectomy, laparoscopy, etc.).

- Category 2 (CAT2) studies, in which the control women had no apparent signs and symptoms of endometriosis (including fertile women and/or women having undergone a Caesarean section). In this category, women may be regarded as a control population, even if inclusion criteria are out of ASRM guidelines.

- Category 3 (CAT3) studies using other sources of controls, such as newborns, volunteers without clinical data, and males. These CAT3 studies were not considered for meta-analysis because males and newborns could not be considered as controls since endometriosis is strictly a female disease.

We also excluded duplicated studies and studies with overlapping data (only the most recent of the studies was considered).

Genome-wide association studies (GWAS) and studies reporting polymorphism haplotypes were assessed on a case-by-case basis to ensure that they were in accordance with our inclusion/exclusion criteria and only those with well-defined SNPs were considered.

Data extraction

For each eligible study, data were extracted by one investigator (LM) using a standardized Microsoft Excel spreadsheet, and checked by a second investigator (FV). Disagreements were resolved by consensus with a third investigator (MH). The following data were extracted for each study: the PubMed identifier (PMID), the title, the authors, the journal, the year of publication, the country in which the research team was based, the study sample size, the diagnostic method, the ASRM stage if available, the type of control population (CAT1-3), and the genotyping method.

Statistical analyses

After study selection, we performed a meta-analysis for each polymorphism with at least three CAT1 “gold standard” studies. For each meta-analysis, all results from CAT1 and CAT2 studies were included. All statistical analyses were performed using the *meta* (Schwarzer 2007) and *rmeta* (Lumley 2018) packages in R (version 3.5.1, (R Core Team 2018)). The magnitude of the association between endometriosis and the polymorphism of interest (for allelic models) was estimated as the odds ratio (OR) [95% CI]. Meta-analysis was performed by pooling OR [95%CI] values from the included studies in a fixed-effect or random-effect model. The choice of the model depended on the result of the between-study heterogeneity test. Thus, a fixed-effect (Mantel-Haenszel) model was used except when Cochran's Q test was significant (p-value <0.05) and thus indicated the existence of inter-study heterogeneity: in the latter case, we used a random-effect (DerSimonian-Laird) model (DerSimonian and Laird 2015).

An OR above 1 with a lower CI boundary above 1 was considered to be statistically significant, as was an OR below 1 with an upper CI boundary below 1.

Heterogeneity in the associations as a function of the study category (CAT1 versus CAT2) was evaluated in a meta-regression analysis. When ASRM stage information was available, a stratification analysis (stages I-II versus stages III-IV) was performed.

However, even though the analysis combined data from studies with different ethnic groups, no stratification based on ethnicity was performed. Indeed, studies included in the present analysis had not systematically specified ethnicity of women, this may lead additional variability in meta-analysis.

Potential publication bias was evaluated with funnel plots, in which the SE of each study was plotted against its OR. Funnel plot asymmetry was estimated using linear regression, with a

minimum number of three studies and without taking account of the study category (Egger et al. 1997).

For each polymorphism included in the present study, a literature search was performed to find potential previous meta-analyses; in order to compare our results with previous ones and identify potential additional records through other sources.

The study results were reported in accordance with to the PRISMA statement (Moher et al. 2009). Our study was not eligible for inclusion in the PROSPERO International Prospective Register of Systematic Reviews because we had already fully extracted the data at the time of registration; the register is intended to capture this information at the design stage.

Results

Search strategy and data selection

After the initial selection procedure (Fig. 1), we identified 28 polymorphisms that were reported in at least three CAT1 studies (i.e. those with the strictest inclusion criteria). A total of 395 individual publications (Supplementary Table SI) mentioned 242 different genes (Supplementary Table SII), of which 62 were cited in more than three publications (Supplementary Table SIII). A total of 265 polymorphisms were cited (Supplementary Table SIV).

We performed a systematic review for each of the 28 remaining polymorphisms studied by at least three CAT1 studies (Table I). For 44 polymorphisms, only two CAT1 studies were identified; hence, these polymorphisms were not considered further (Supplementary Table SIV).

Meta-analysis results

The number of studies included per polymorphism, the numbers of patients and controls, the model used, the level of heterogeneity, the use of a fixed- or random-effect model, and the OR [95%CI] are listed in Table I.

For ease of reference, the relevant flow chart (panel A in supplementary figures), forest plot (figures) and funnel plot for publication bias (panel B in supplementary figures) for each polymorphism are mentioned in the title of the corresponding paragraph. Panel C in supplementary figures shows stratification by stage, when relevant.

Also for ease of reference, publications listed according to the polymorphism(s) studied are shown in Supplementary Data, and only citations of studies included in the meta-analysis are included in the Results section.

Genes and phenotypes:

Mouse/Rat/Chicken genes

Full gene names: not italicised, all letters in lower case, no Greek symbols, hyphens used (e.g. insulin-like growth factor 1).

Gene symbols, mRNA and cDNA: italicised, first letter in upper case, remaining letters in lower case (e.g. *Igf1*), no Greek symbols (e.g. *Tnfa, not Tnf*□), hyphens rarely used.

Protein designations: not italicised, all letters in upper case, no Greek symbols, hyphens rarely used (e.g. IGF1).

Human/non-human primate (and anything else that is not mouse, rat or chicken)

Full gene names: not italicised, all letters in lower case, no Greek symbols, hyphen rarely used (e.g. insulin-like growth factor 1).

Gene symbols, mRNA and cDNA: italicised, all letters are in upper case (e.g. *IGF1*), no Greek symbols (e.g. *TNFA*, not *TNF*□*)*, hyphens rarely used.

Protein designations: not italicised, all letters in upper case, no Greek symbols, hyphens rarely used (e.g. IGF1).

The *VEGFA* gene

Twenty full-text articles on vascular endothelial growth factor alpha *(VEGFA)* SNPs of interest were screened for eligibility. Four of the five main genetic variants of *VEGFA* were analyzed:

rs699947 (Fig. 2A), rs833061 (Fig. 2B), rs2010963 (Fig. 2C) and rs3025039 (Fig. 2D), and none was significantly associated with endometriosis. rs1570360 was not eligible.

VEGFA _ rs699947 (-2578C>A): Fig. 2A and Supplementary Figs 1A and B

Four studies were included: three CAT1 studies (Cardoso, Abrao, Vianna-Jorge, et al. 2017; Liu et al. 2009; Vodolazkaia et al. 2016) and one CAT2 study (Lamp et al. 2010). A significant association was not observed (OR 1.07; 95% CI 0.78–1.46) in a random-effect model. No asymmetry was seen in a funnel plot test for bias (t = 0.49; p = 0.67).

VEGFA _ rs833061 (-460T>C): Fig. 2B and Supplementary Figs 2A and B

Nine studies (Altinkaya et al. 2011; Attar, Agachan, et al. 2010; Cosin et al. 2009; Emamifar et al. 2012; Henidi, Kaabachi, Naouali, et al. 2015; Kim, Choi, Choung, et al. 2005; Liu et al. 2009; Perini et al. 2014; Szczepanska et al. 2015) were included in the meta-analysis.

No associations were observed (OR 1.06; 95% CI 0.96 –1.17) in a fixed-effect model (Fig. 2B) with no publication bias (t = 0.45; p = 0.67). When the results were stratified by ASRM stage, there was no difference between subgroups (p = 0.56), and no associations were found (Supplementary Fig. 2C).

VEGFA _ rs2010963 (+405G>C): Fig. 2C and Supplementary Figs 3A and B

Twelve studies (Altinkaya et al. 2011; Attar, Agachan, et al. 2010; Cardoso, Abrao, Vianna-Jorge, et al. 2017; Cosin et al. 2009; Emamifar et al. 2012; Gentilini, Somigliana, et al. 2008; Henidi, Kaabachi, Naouali, et al. 2015; Kim, Choi, Choung, et al. 2005; Saliminejad et al. 2013; Szczepanska et al. 2015; Vanaja et al. 2013; Vodolazkaia et al. 2016) were included (Supplementary Fig. 3A). No associations were observed (OR 0.95; 95% CI 0.69 –1.31) in a random-effect model and no publication bias was observed (t = -1.3; p = 0.21). Stratification by

ASRM stage did not reveal a difference (p = 0.44) between the two subgroups, and no associations were observed (Supplementary Fig. 3C).

VEGFA _ rs3025039 (+936C>T): Fig. 2D and Supplementary Figs 4A and B

Seven studies were considered: six CAT1 studies (Cosin et al. 2009; Henidi, Kaabachi, Naouali, et al. 2015; Liu et al. 2009; Perini et al. 2014; Szczepanska et al. 2015; Vodolazkaia et al. 2016) and one CAT2 study (Lamp et al. 2010). No associations were observed (OR 1.13; 95% CI 0.89 –1.42) using a random-effect model, and no publication bias was found (t = 0.95; p = 0.38).

TNF rs1799964 (-1031T>C) Fig. 3A and Supplementary Figs 5A and B

Of the five tumor necrosis factor *(TNF)* variants evaluated in 14 studies, only *TNF* rs1799964 was considered in the present work. Five full-text articles were included in the meta-analysis: four CAT1 studies (Chae et al. 2008; de Oliveira Francisco et al. 2017; Lee et al. 2008; Saliminejad et al. 2013) and one Cat2 study (Abutorabi et al. 2015). No associations were observed (OR 1.23; 95% CI 0.79–1.92) using a random-effect model, and no publication bias was observed (t = 0.65; p = 0.56).

IL6 _ rs1800796 (-634C>G): Fig. 3B and Supplementary Figs 6A and B

Of the eight studies dealing with interleukin 6 *(IL6)* and endometriosis, three studies (all CAT1) of the rs1800796 polymorphism were included (Bessa et al. 2016; Chae et al. 2010; Kitawaki et al. 2006). No associations were observed (OR 1.16; 95% CI 0.96–1.39) using a fixed-effect model and no publication bias was observed (t = 2.81; p = 0.22).

Stratification by ASRM stage did not reveal a difference (p = 0.90) between the two subgroups, and no associations were found (Supplementary Fig. 6C).

346

347 *TGFB1* rs1800469 (-509C >T): Fig. 3C and Supplementary Figs 7A and B

348 Of the six relevant studies for transforming growth factor beta 1 *(TGFB1)*, four were considered
349 in this meta-analysis, *i.e.*, three CAT1 studies and one CAT2 study (Hsieh, Chang, Tsai, Peng, et
350 al. 2005; Kim et al. 2010; Lee et al. 2011; van Kaam, Romano, Dunselman, et al. 2007).
351 No associations were identified (OR 1.38; 95% CI 0.72–2.64) using a random-effect model, and
352 no publication bias was observed (t = 0.52; p = 0.65).

353

354 *IFNG* (CA) repeat: Fig. 3D and Supplementary Figs 8A and B

355 Of the four studies analysed for interferon gamma *(IFNG)*, three were CAT1 studies (Kim et al.
356 2011; Kitawaki et al. 2004; Rozati, Vanaja, and Nasaruddin 2010). After inspecting, we decided
357 to homogenize our analysis by using a CA dinucleotide repeat length of 13 as a cut-off for
358 classifying alleles as being short (S: ≤13 repeats) or long (L: >13).
359 An association was observed (OR 1.33; 95% CI 1.17–1.52) in a fixed-effect model, and no
360 publication bias was observed (t = 1.67; p = 0.34).
361 After stratification by ASRM stage, a similar association was identified; there was no difference
362 between the subgroups (p = 0.61) (Table I) (Suppl Fig. 8C).

363

364 *ESR1* rs2234693 (PvuII): Fig. 4A and Supplementary Figs 9A and B

365 When considering the 22 studies of estrogen receptor 1 *(ESR1)* variants and endometriosis, only
366 the rs2234693 polymorphism met our inclusion criteria. Pooling the three CAT1 studies (Kim,
367 Choi, Jun, et al. 2005; Kitawaki et al. 2001; Paskulin et al. 2013), no associations were identified

(OR 1.42; 95% IC 0.85 –2.36) using a random-effect model, and no publication bias was observed (t = 1.88; p = 0.31).

PGR gene

Following our data selection process two polymorphisms of progesterone receptor *(PGR)* were analysed. In the 19 studies of endometriosis and *PGR* polymorphisms six *PGR* variants were reported. Only two of them were considered.

PGR _ rs1042838 (PROGINS): Fig. 4B and Supplementary Figs. 10A and B

PROGINS variant (rs1042838) was considered in four CAT1 studies (Christofolini et al. 2011; Lattuada, Somigliana, et al. 2004; van Kaam, Romano, Schouten, et al. 2007; Wieser, Schneeberger, et al. 2002) and one CAT2 study (Costa et al. 2011; Wu et al. 2013). In one study (van Kaam, Romano, Schouten, et al. 2007), we considered the CAT1 controls only (n=101), and excluded the CAT3 controls.

When considering the P2 allele to be the risk allele, we observed an association (OR 1.53; 95% CI 1.17 – 1.99) using a fixed-effect model, and no publication bias was observed (t = 0.36; p = 0.74).

PGR _ rs10895068 (+331G>A) Fig. 4C and Supplementary Figs. 11A and B

Of the three CAT1selected studies (van Kaam, Romano, Schouten, et al. 2007; Gentilini, Vigano, et al. 2008; Cardoso, Machado, et al. 2017), two lacked primary data (Cardoso, Machado, et al. 2017; Gentilini, Vigano, et al. 2008). However, one CAT2 study was also considered (Lamp et al. 2011) and meta-analyse was performed on these two studies (Lamp et al. 2011; van Kaam, Romano, Schouten, et al. 2007).

No associations were identified (OR 0.70; 95% CI 0.41 – 1.18) using a fixed-effect model, and no publication bias was observed on funnel plot; linear regression was not performed since three studies were needed.

FSHR rs6166 (Asn680Ser) Fig. 4D and Supplementary Figs 12A and B

Of the three selected CAT1 studies for follicle stimulating hormone receptor *(FSHR)* rs6166 (Andre et al. 2018; Kerimoglu et al. 2015; Schmitz et al. 2015), one lacked raw data (Schmitz et al. 2015) and only two studies were considered for meta-analysis.

No associations were identified (OR 1.18; 95% CI 0.99 – 1.41) using a fixed-effect model, and no publication bias was observed on funnel plot.

ICAM1 gene

Following our data selection process, both of the main genetic variants of intercellular adhesion molecule 1 *(ICAM1)* were analysed.

ICAM1 rs5498 (K469E): Fig. 5A and Supplementary Figs. 13A and B

Four CAT1 studies (Bessa et al. 2016; Chae et al. 2010; Kitawaki et al. 2006; Vigano et al. 2003) were included in the present meta-analysis.

No associations were identified (OR 1.00; 95% CI 0.86 – 1.16) using a fixed-effect model, and no publication bias was found ($t = 0.95$; $p = 0.44$).

Similar results were found after stratification by ASRM stage (Supplementary Fig 13C).

ICAM1 rs1799969 (G241R): Fig. 5B and Supplementary Figs. 14A and B

Four CAT1 studies (Aghajanpour, Mashayekhi, and Rajaei 2011; Bessa et al. 2016; Chae et al. 2010; Vigano et al. 2003) were included for this variant.

Even though an association was identified (OR 3.31; 95% CI 2.03-5.38), the ORs could not be estimated for two studies (Bessa et al. 2016; Chae et al. 2010) because all the women were homozygotes for the wild-type allele (G).

GSTM1 null genotype: Fig. 6A, Supplementary Fig. 15A and B

Of the 28 studies dealing with the glutathione S-transferase mu 1 *(GSTM1)* null genotype, 15 studies were included: 11 CAT1 studies (Babu et al. 2005; Hadfield et al. 2001; Hassani et al. 2016; Henidi, Kaabachi, Mbarik, et al. 2015; Huang et al. 2010; Hur et al. 2005; Kim et al. 2007; Kubiszeski et al. 2015; Matsuzaka, Kikuti, Goya, et al. 2012; Roya, Baludu, and Reddy 2009; Vichi et al. 2012) and four CAT2 studies (Arvanitis et al. 2003; Baranova et al. 1999; Seifati et al. 2012; Wu et al. 2012).

Using a random-effect model, an association was identified when considering only CAT1 studies (OR 1.31; 95% CI 1.06–1.62), only CAT2 studies (OR 1.66; 95% CI 1.02–2.72) or all studies together (OR 1.40; 95% CI 1.15–1.70). No evidence of significant publication bias across studies ($t = 1.9$; $p = 0.08$) was observed.

After stratification by ASRM stage (Supplementary Fig. 15C), no difference between the subgroups was observed ($p = 0.99$), and the association was confirmed for the stage III/IV subgroup only (OR 1.75; 95% CI 1.26 – 2.44).

GSTT1 null genotype: Fig. 6B, Supplementary Figs. 16A and B

Of the 20 studies dealing with the glutathione S-transferase theta 1 *(GSTT1)* null genotype, nine CAT1 studies were considered (Babu et al. 2005; Hadfield et al. 2001; Hassani et al. 2016; Henidi, Kaabachi, Mbarik, et al. 2015; Hur et al. 2005; Kim et al. 2007; Kubiszeski et al. 2015;

436 Matsuzaka, Kikuti, Goya, et al. 2012; Vichi et al. 2012) and three CAT2 studies (Arvanitis et al.
437 2001; Baranova et al. 1999; Wu et al. 2012) for the meta-analysis.
438 No associations were identified (OR 1.08; 95% CI 0.85–1.38) using the random-effect model.
439 The difference between CAT1 and CAT2 studies was not significant (p = 0.14). The absence of
440 publication bias was confirmed (t = -0.54; p = 0.60).
441
442 *GSTP1* rs1695: Fig. 6C, Supplementary Figs. 17A and B
443 Of the eight studies identified for glutathione S-transferase pi 1 *(GSTP1)*, six CAT1 studies were
444 considered for the meta-analysis step (Ertunc et al. 2005; Hassani et al. 2016; Hur et al. 2005;
445 Jeon et al. 2010; Matsuzaka, Kikuti, Goya, et al. 2012; Vichi et al. 2012).
446 A protective effect was identified (OR 0.80; 95% CI 0.69–0.92) using a fixed-effect model. No
447 publication bias was identified (t = 0.49; p = 0.65).
448
449 *AHRR* rs2292596 (Pro185Ala): Fig. 6D, Supplementary Figs. 18A and B
450 Of the six studies identified for aryl-hydrocarbon receptor repressor *(AHRR)*, three CAT1 studies
451 (Kim et al. 2007; Tsuchiya et al. 2005; Watanabe et al. 2001) were included.
452 A significant association was identified (OR 1.30; 95% CI 1.05 – 1.60) using a fixed-effect
453 model, and no publication bias was observed (t = -0.31; p = 0.80).
454
455 *CYP1A1* rs4646903 (Msp1): Fig 7A Supplementary Figs. 19A and B
456 Of the 20 studies dealing with the cytochrome P450 family 1 subfamily A polypeptide 1
457 *(CYP1A1)* gene, there were three CAT1 studies for rs4646903 polymorphism (Babu et al. 2005;

458 Hadfield et al. 2001; Rozati et al. 2008) and one lacked the raw data (Rozati et al. 2008). One
459 CAT2 studies (Arvanitis et al. 2003) was also considered for the meta-analysis.
460 No association was identified (OR 1.08; 95% CI 0.71 – 1.63) using a random-effect model and
461 no publication bias was observed (t = 0.17; p = 0.89).
462
463 *CYP17A1* _ rs743572 (MspA1): Fig. 7B, Supplementary Figs. 20A and B
464 Of the 17 studies identified for cytochrome P450 family 17 subfamily A polypeptide 1
465 *(CYP17A1),* three CAT1 studies (Bozdag et al. 2010; Cardoso, Machado, et al. 2017;
466 Szczepanska, Wirstlein, Skrzypczak, et al. 2013; Vietri et al. 2009) and two CAT2 studies
467 (Hsieh, Chang, Tsai, Lin, and Tsai 2004; Kado et al. 2002) were included in the meta-analysis
468 step. Raw data were not available for one CAT1 study, and so it was excluded (Cardoso,
469 Machado, et al. 2017).
470 No associations were identified (OR 1.31; 95% CI 0.88 – 1.95) using a random-effect model
471 when all studies were included, while an association was found (OR 1.72; 95% CI 1.13 – 2.62)
472 when only CAT1 studies were considered. No asymmetry was observed suggesting the absence
473 of publication bias (t = 1.08; p = 0.36).
474
475 *CYP19A1* rs10046: Fig 7C Supplementary Figs. 21A and B
476 Of the four CAT1 studies identified for cytochrome P450 family 19 subfamily A polypeptide 1
477 *(CYP19A1)* rs10046, only three were included (Cardoso, Machado, et al. 2017; Szczepanska,
478 Wirstlein, Skrzypczak, et al. 2013; Vietri et al. 2009; Hur et al. 2007), and primary data or raw
479 data (allele frequencies) were not available for one (Cardoso, Machado, et al. 2017). Similarly,

of the two CAT2 studies were included (Wu et al. 2013; Wang et al. 2014; Lamp et al. 2011), one lacked of raw data (Wu et al. 2013).

Thus, based on these five remaining studies, no association was identified (OR 0.91; 95% CI 0.79 – 1.05) using a fixed-effect model and no publication bias was observed (t = -2.13; p = 0.12).

CYP2C19 rs4244285: Fig 7D Supplementary Figs. 22A and B

Of the three selected CAT1 studies for cytochrome P450 family 2 subfamily C polypeptide 19 *(CYP2C19)* rs4244285(Cardoso, Abrao, Berardo, et al. 2017; Bozdag et al. 2010; Cayan et al. 2009), one lacked a full set of data (Bozdag et al. 2010).

Thus, meta-analysis was performed only with data of two studies, and no association was identified (OR 1.91; 95% CI 1.31 – 2.80) using a fixed-effect model and no publication bias was observed on funnel plot.

TP53 rs1042522 (codon 72): Fig. 8A, Supplementary Figs. 23A and 23B

Considering the 26 six studies dealing with tumor protein p53 *(TP53)* variants and the endometriosis risk, only one variant (rs1042522) was examined in nine independent studies. Three CAT1 studies (Gallegos-Arreola, Figuera-Villanueva, et al. 2012; Lattuada, Vigano, et al. 2004; Vietri et al. 2007) and four CAT2 studies (Chang et al. 2002; Hsieh and Lin 2006; Hussain et al. 2018; Nikbakht Dastjerdi, Aboutorabi, and Eslami Farsani 2013) were considered for meta-analysis.

An association was identified when considering CAT2 studies only (OR 1.69; 95% CI: 1.40 – 2.04) or all studies (OR 1.49; 95% CI: 1.16 – 1.90) using the random-effect model, but not when

considering CAT1 studies only (OR 1.22; 95% CI: 0.66 – 2.26). There was no difference between CAT1 and CAT2 studies (p = 0.32). Furthermore, no publication bias was detected (t = -1.64; p = 0.16).

XRCC1 rs25487 (Arg399Gln): Fig. 8B, Supplementary Figs. 24A and B

Of the six studies related to X-ray repair complementing defective repair in Chinese hamster cells 1 *(XRCC1)* polymorphism in endometriosis, three CAT1 studies (Attar, Cacina, et al. 2010; Safan and Ghanem 2015; Saliminejad et al. 2015) and one CAT2 study (Bau et al. 2007) were included in the meta-analysis step.

No associations were identified (OR 1.12; 95% CI 0.70 – 1.77) using the random-effect model, although the result was unsignificant when considering CAT1 studies only (OR 1.33; 95% CI 0.97–1.83). No potential publication bias (t = 0.77; p = 0.52) was identified.

WNT4 gene

Six studies dealing with wingless-type MMTV integration site family member 4 *(WNT4)* and endometriosis were identified.

WNT4 rs16826658: Fig. 9A, Supplementary Figs. 25A and B

Three CAT1 studies (Lee et al. 2014; Mafra et al. 2015; Wu et al. 2015) were considered for meta-analysis. An association was identified (OR 1.27; 95% CI 1.07 – 1.52) using the random-effect model and no publication bias was found (t = 1.43; p = 0.39).

WNT4 _ rs2235529: Fig. 9B, Supplementary Figs. 26A and B

Three CAT1 studies (Li, Hao, et al. 2017; Mafra et al. 2015; Wu et al. 2015) were included. An association was identified (OR 1.21; 95% CI 1.09 – 1.34) using a fixed-effect model and no publication bias was detected (t = 0.1; p = 0.93).

SERPINE1 _ rs1799889 (4G/5G): Fig. 9C, Supplementary Figs. 27A and B

Of the five studies dealing with serpin peptidase inhibitor clade E member 1 (*SERPINE1)* variant rs1799889 and endometriosis, four were considered for meta-analysis (Bedaiwy et al. 2006; Gentilini et al. 2009; Goncalves-Filho et al. 2011; Ramon et al. 2008; Uxa et al. 2010).

No associations were observed (OR 2.03; 95%CI 0.88 – 4.67) using the random-effect model and no publication bias was observed (t = 3.99; p = 0.06).

PPARG rs1801282 (Pro12Ala): Fig. 9D Supplementary Figs. 28A and B

All the three studies identified for peroxisome proliferator-activated receptor gamma *(PPARG)* gene were CAT1 and all dealt with the rs180128 polymorphism (Hwang et al. 2010; Kiyomizu et al. 2006; Dogan et al. 2004). One study lacked primary data (Dogan et al. 2004).

Thus, meta-analysis was performed only with data of two studies. No association was identified (OR 0.52; 95% CI 0.33 – 0.82) using a fixed-effect model and no publication bias was observed on funnel plot.

Discussion

The objectives of the present study were to provide an exhaustive review of polymorphisms studied in endometriosis, and perform a meta-analysis for those most regularly reported. Ultimately, meta-analysis was performed for 28 polymorphisms (in 22 genes); 10 of these polymorphisms (in nine genes) were found to be significantly associated with endometriosis. Therefore the study allowed us to identify polymorphisms that could potentially be included in an endometriosis screening test and we propose a panel of SNPs that could predispose to endometriosis: ***IFNG*** (CA)repeat, ***GSTM1*** null genotype, **GSTP1** rs1695, ***WNT4*** *r*s16826658 and ***WNT4*** rs2235529.

To be as exhaustive as possible, we designed a broad PubMed search query but excluded publications not written in English and meta-analysis. Given that not all authors use the same nomenclature to refer to the same gene, we then used a text-mining procedure (based on the PubTator tool (Wei et al. 2012; Wei, Kao, and Lu 2012, 2013)) to explore a range of gene symbols, names and synonyms. A total of 395 publications (mentioning 242 genes) were considered to be relevant. For greater efficiency, we decided to only include genes cited in three or more publications (n=180). Text mining proved to be effective for data selection: of the 192 studies, only three (Lin et al. 2003; Morizane et al. 2004; Safan and Ghanem 2015) had to be added manually because of the lack of the keyword “polymorphism(s)” in the title or abstract or the lack of a PubMed reference. The manual addition of references was not unexpected (given our chosen search strategy) but our workflow enabled us to identify relevant data rapidly and reliably.

Furthermore, we paid particular attention to the studies' inclusion and exclusion criteria for the control population; we considered that eligible studies should comply with international guidelines in general and the benchmark ASRM guidelines in particular. In the absence of surgery, endometriosis cannot be ruled out; this considerably complicates the selection of the control population, and constitutes a critical point in many studies. The ideal controls are pain-free, fertile women in whom the absence of endometriosis has been confirmed by laparoscopy – although few women fit this profile (Greaves et al. 2017). Next, in line with the guidelines, we defined three study categories. In CAT1 studies, the control patients were known to be free of endometriosis, following laparoscopy or other surgical procedures. In CAT2 studies, the controls were apparently free of endometriosis; they included fertile women and/or women having undergone Caesarean section (given that endometriosis is a major cause of infertility). Lastly, controls in CAT3 studies were recruited from the general population; this would necessarily have included some women with endometriosis, infertile, neonates and men. As our goal was to identify patients with endometriosis, we considered that only CAT1 studies could reliably probe a potential association between a polymorphism and the occurrence of endometriosis. Although CAT2 studies sometimes strengthened the association, they were only considered when the meta-analysis included three or more CAT1 studies. Of the 10 meta-analyses in which both CAT1 and CAT2 studies had been included, we found conflicting results for two polymorphisms (20%): *CYP17A1* rs743572 and *TP53* rs1042522. In the first case, the inclusion of CAT2 studies meant that *CYP17A1* rs743572 was no longer significantly associated with endometriosis. The opposite was true in the second case, where the inclusion of CAT2 studies meant that *TP53* rs1042522 was found to be associated with endometriosis. Hence, to ensure the homogeneity of

587 the meta-analyses, we only considered results obtained with CAT1 studies. Even though this
588 approach restricted the number of studies that could be included, it strengthened our conclusions.
589 Bougie and collaborators suggested that endometriosis prevalence depends on the ethnicity of
590 women and, in particular, appears more frequently in Asian populations (Bougie et al. 2019). In
591 the present work, studies included did not necessary define the ethnic categories of patients
592 included. As this lack of information could represent a new source of variability in our analysis,
593 no stratification based on ethnicity was performed and this limits the scope of the present review,
594 considering the high polymorphism frequency variability between the different ethnic groups.
595
596 GWAS present the advantage of involving a large female population and a recent meta-analysis
597 showed the value of these approaches to identify loci associated with endometriosis (Sapkota et
598 al. 2017). Such studies were not systematically excluded but given our inclusion criteria based on
599 patient and control populations, for all cases, GWAS were not considered in the present analysis.
600 Out of the 11 GWAS available, only four of these could be considered regarding patient
601 inclusion criteria. Of these four, only one included CAT1 control patients, but with no access to
602 details on polymorphisms as only OR were reported.
603
604 According, when considering the 62 eligible genes and the 265 eligible polymorphisms
605 identified by screening abstracts and assessing full-text articles, only 28 polymorphisms were
606 found to have been mentioned in at least three CAT1 studies (Fig. 1). Furthermore, 44
607 polymorphisms had been analysed in only two CAT1 studies (Supplementary Table SIV) and we
608 have considered that, for these polymorphisms, more studies are necessary before meta-analysis.
609 If this arbitrary cut-off of three studies does not introduce selection bias into each polymorphism

610 reviewed, it limits the scope of the present review, focusing on a limited number of
611 polymorphisms. If two studies meet the requirements of homogeneity, with minimal risk of study
612 design bias, then meta-analysis is perfectly possible and should be done in the future. Ultimately,
613 meta-analysis was performed for 28 polymorphisms (in 22 genes); 10 of these polymorphisms
614 (in nine genes) were found to be significantly associated with endometriosis. We could expect a
615 larger number of polymorphisms to be associated with endometriosis considering those excluded
616 using our inclusion criteria.
617
618 To the best of our knowledge, the present study is the first to have highlighted a potential link
619 between endometriosis and the *WNT4* rs16826658 and rs2235529 polymorphisms by meta-
620 analysis of association studies (Fig. 8). The Wnt family protein Wnt-4 is essential for the
621 development of the female reproductive tract (Vainio et al. 1999), and acts as a signalling
622 molecule in cell-cell interactions, proliferation and migration (Liang et al. 2016). Expression
623 levels of WNT4 in the eutopic endometrium appear to be higher in a group of women with
624 endometriosis than in a control group (Liang et al. 2016). Moreover, a GWAS found that a SNP
625 located close to the *WNT4* gene (rs7521902) was associated with the endometriosis risk
626 (Pagliardini et al. 2013). In our meta-analyses, both *WNT4* rs16826658 and rs2235529 were
627 associated with endometriosis (with ORs of 1.27 [95% CI 1.07–1.52] and 1.21 [95% CI 1.09–
628 1.53], respectively). Hence, this finding needs to be validated in other studies – notably in
629 different populations or different disease stages. Although another *WNT4* polymorphism
630 (rs7521902) has been studied in the context of endometriosis, it was evaluated in two CAT1
631 studies and therefore was not included in the present analysis. In contrast to our results for *WNT4*

rs16826658 and rs2235529, the literature data on *WNT4* rs7521902 suggest that it is not significantly associated with the endometriosis risk (Mafra et al. 2015; Wu et al. 2015).

PPARG rs1801282 could have a protective effect for endometriosis (OR 0.52; 95% CI 0.33–0.82) but this association needs to be confirmed in studies involving more women since only two studies were include in present analysis.

Endometriosis is known to be associated with an inflammatory response, and inflammation appears to have an important role in the pathogenesis of this disease (Jiang et al. 2016). We performed meta-analyses for four polymorphisms (*TNF* rs1799964, *IL6* rs1800796, *TGFB1* rs1800469, and *IFNG* (CA) repeat) in genes involved in inflammatory pathways. The cytokine interferon gamma (produced by activated lymphocytes) may be involved in upregulation of soluble ICAM-1 levels during the development of endometriosis (Kyama et al. 2003). To the best of our knowledge, our present meta-analysis was the first to have looked for a correlation between endometriosis risk and the *IFNG* (CA) repeat polymorphism.

Of the four polymorphisms studied, only *IFNG* (CA) repeat was associated with a risk of endometriosis (OR 1.33; 95% CI 1.17–1.52) (Fig. 3D), independent of the disease stage (since an association was identified for stages I/II and for stages III/IV; Supplementary Fig. 8C).

In contrast, no association could be identified for *TNF* rs1799964 (OR 1.01, 95% CI 0.70–1.46), *IL6* rs1800796 (OR 1.17; 95% CI 0.96–1.41) or *TGFB1* rs1800469 (OR 0.97; 95% CI: 0.82–1.14). TNF is a pro-inflammatory cytokine involved in inflammation processes. It reportedly stimulates the proliferation of ectopic endometrial cells (Hornung and von Wussow 2011). Two meta-analyses (Li et al. 2014; Lyu et al. 2014) have been published but gave contradictory results: the first (Li et al. 2014) suggested that the presence of the *TNF* rs1799964 polymorphism

was associated with a reduction in endometriosis risk, whereas the second (Lyu et al. 2014) did not find any association (as in the present study).

The pro-inflammatory cytokine IL-6 is involved in many biological activities. Levels of IL-6 in peritoneal fluid appear to be abnormally high in patients with endometriosis, although this finding is subject to debate (Li, Fu, et al. 2017). Our result was similar to a previous meta-analysis (Li et al. 2014), with an OR of 1.17 (95% CI: 0.96–1.41). Considering the CIs and the fact that the three included CAT1 studies had small numbers of patients (*i.e.*, 692 patients with endometriosis, and 687 controls), well-designed case-control studies in larger cohorts will be required to confirm the absence of correlation between *IL6* rs1800796 and endometriosis. TGF beta-1 (a multifunctional protein encoded by the *TGFB1* gene) is known to be involved in endometriosis. Several studies have described elevated levels of TGF-B1 in the serum, peritoneal fluid, endometrium and peritoneum of patients with endometriosis; this elevation appears to be required for the establishment and development of ectopic endometrium (Young et al. 2017; Soni et al. 2018). However, in line with a previous meta-analysis, our present work did not identify an association between *TGFB1* rs1800469 and endometriosis (Zhang, Yang, and Wang 2012).

Endometriosis is also known to be associated with hormone responses, and hormone receptors are thought to have a major role in the pathogenesis of endometriosis (Jiang et al. 2016). Although many polymorphisms in hormone-related genes have been investigated, the studies' broad inclusion criteria and/or the lack of data meant that we were able to perform a meta-analysis is only two instances (Supplementary Table SIII and SIV).

PGR polymorphisms may be a cause, among others, of the progesterone resistance observed in patients with endometriosis (Patel et al. 2017). Several polymorphisms of PGR were studied in

relation to endometriosis, but only two were considered: PROGINS and rs10895068. PROGINS seems to impact the ligand-binding and affects the entire signaling pathway (Patel et al. 2017). Here, we confirmed the known trend of association previously reported by another meta-analysis (OR = 1.43, 95% CI = 0.99–2.08) (Hu et al. 2012). In contrast, we did not find an association between endometriosis and *PGR* rs10895068 polymorphisms, but since only two studies were considered (one CAT1 and one CAT2) the results need to be confirmed.

Many *ESR1* polymorphisms have been assessed studied for their potential link with endometriosis. However, only rs2234693 was included in a meta-analysis here. Our results were in line with three previous meta-analyses by Chinese groups (Zhao et al. 2016; Li et al. 2012; Hu et al. 2012), which included large numbers of studies with less restrictive inclusion criteria (23, 20 and eight studies, respectively, compared with three CAT1 studies here). We did not find an association between *ESR1* rs2234693 and endometriosis.

Surprising, only one *FSHR* polymorphism (rs6166) met our inclusion criteria, even though FSHR has been studied often in different situations, such as IVF (Boudjenah et al. 2012). Only data for two CAT1 studies (Andre et al. 2018; Kerimoglu et al. 2015) and two CAT2 could be considered for *FSHR* rs6166 explaining the fact that the absence of association needs to be confirmed.

Several studies have focused on genes involved in detoxification mechanisms because it has been hypothesized that dioxin exposure is involved in the pathogenesis of endometriosis although this link is still subject to debate (Soave et al. 2015; Sofo et al. 2015). Among the genes related to detoxification, we found enzymes such as glutathione S-transferase (GST) M1

(*GSTM1*), T1 (*GSTT1*) and P1 (*GSTP1*), together with the *AHRR* gene (Guo 2006), *CYP1A1*, *CYP17A1*, *CYP19A1*, and *CYP2C19*.

In our text mining procedure, *GSTM1* was the most frequently cited gene (Supplementary Tables SIV); we included 11 CAT1 and four CAT2 studies in our meta-analysis (Supplementary Fig. 13A). Our results suggest that the *GSTM1* null genotype is associated with a risk of endometriosis (OR 1.40; 95% IC 1.15–1.70), independent of the selection criteria for controls (i.e. CAT1 and/or CAT2 studies) (Fig. 6A). The association was significant for advanced-stage endometriosis (ASRM stage III/IV) but not for ASRM stage I/II (Supplementary Fig. 13C). Previous meta-analyses (Chen, Xu, et al. 2015; Ding et al. 2014; Guo 2005; Li and Zhang 2015; Xin et al. 2016; Zhu et al. 2014) also reached the same conclusions (i.e. the *GSTM1* null genotype is associated with an endometriosis risk), although we did not include precisely the same studies in our meta-analysis because only some were CAT3 studies (Arvanitis et al. 2001; Baxter, Thomas, and Campbell 2001; Frare et al. 2013; Hosseinzadeh, Mashayekhi, and Sorouri 2011; Hsieh, Chang, Tsai, Lin, Chen, et al. 2004; Trabert et al. 2011). In light of these results, the *GSTM1* null genotype is a potentially valuable genetic marker for endometriosis risk.

We also found that *AHRR* rs2292596 is associated with endometriosis (OR 1.30; 95% CI 1.05–1.60) (Fig. 6E). The AHRR mediates dioxin toxicity, cell growth, cell differentiation, and the induction of drug-metabolizing enzymes. It functions as a feedback modulator by repressing aryl hydrocarbon-dependent gene expression (CYP1A1, SERPINB2, etc.). The AHRR pathway is also linked to peroxisome proliferator–activated receptor alpha. Although similar results were obtained in an earlier meta-analysis (Zheng et al. 2015), the small sample size means that these results must be interpreted with caution (Table I); further investigations are required.

In contrast, *GSTP1* rs1695 polymorphism can reduce the risk of endometriosis as indicated in our results (OR 0.80; 95% CI 0.69–0.92). This result was not in line with the other meta-analysis performed to date (Chen et al. 2013) since they find a lack of association with the endometriosis risk.

The *CYP2C19* rs4244285 polymorphism seems to be associated with endometriosis risk (OR 1.91; 95% CI 1.30–2.80), but due to the low number of patients per group confirmation is needed. Furthermore, a GWAS was identified by our text mining approach but not included in the meta-analyses due to the control population selection (CAT 3) (Painter et al. 2014).

By combining CAT1 and CAT2 studies, none of the remaining polymorphisms in detoxification-related genes was found to be associated with endometriosis with the exception of *CYP17A1* rs743572 when considering only CAT1 studies (OR 1.72; 95% CI 1.13–2.62). Earlier meta-analyses (Hu et al. 2012; Chen, Pang, et al. 2015) of potential links between *CYP17A1* rs743572 and endometriosis included more studies than we did because they used less stringent inclusion criteria (*i.e.,* CAT3 studies) (Asghar et al. 2005; De Carvalho et al. 2007; Juo et al. 2006; Zhao, Nyholt, Le, et al. 2008) or because they included articles not written in English (Zhao et al. 2011). None of meta-analyses found a statistically significant relationship between the *CYP17* rs743572 polymorphism and endometriosis. The results of our CAT1 meta-analysis contrast with the previous reports, which emphasizes the influence of control selection on the results (Fig. 6D) and perhaps the value of considering strictly defined CAT1 studies only. As seen above for *AHRR* rs2292596, studies of larger numbers of patients are required. No association with endometriosis was identified here for *CYP1A1* rs4646903 and *CYP19A1* rs10046.

744 No association was also identified for the *GSTT1* null genotype. In contrast, five earlier studies
745 concluded that the *GSTT1* null genotype is associated with endometriosis susceptibility (Chen,
746 Xu, et al. 2015; Ding et al. 2014; Guo 2005; Xin et al. 2016; Zhu et al. 2014). However, we
747 included more recent data in the meta-analysis (including three case-control studies (Hassani et
748 al. 2016; Henidi, Kaabachi, Mbarik, et al. 2015; Kubiszeski et al. 2015)), and excluded the CAT3
749 studies (Frare et al. 2013; Lin et al. 2003; Morizane et al. 2004) and studies not published in
750 English (Ding et al. 2004; Ivashchenko et al. 2003) that were taken into account in the earlier
751 meta-analyses. However, it is clear that the selection of control participants influences the overall
752 result, as discussed above for *CYP17A1* rs743572, nor the disease stage for understanding the
753 differences observed between the various meta-analyses.
754
755 Cell adhesion molecules are cell surface proteins that mediate cell adherence, inflammatory and
756 immune responses, and cancer-related biological processes. Changes in the expression of various
757 cell adhesion proteins (such as ICAM-1) have been investigated in the context of endometriosis
758 (Kuessel et al, 2017). Significantly elevated serum levels of soluble ICAM-1 are observed in
759 women with endometriosis, and especially in patients with late-stage disease (Hornung and von
760 Wussow 2011). To the best of our knowledge, our present work constitutes the second meta-
761 analysis of *ICAM1* polymorphisms (rs5498 and rs1799969) in endometriosis (Pabalan et al.
762 2015). We included an additional study (Bessa et al. 2016) and excluded another (due to the
763 selection of control population) (Yamashita et al. 2005). We did not find an association between
764 *ICAM1* rs5498 and endometriosis risk (Fig. 5A). Although an association was found for *ICAM1*
765 rs1799969 (OR=3.31; 95% CI: 2.03-5.38), ORs could be calculated in two studies only
766 (Aghajanpour, Mashayekhi, and Rajaei 2011; Vigano et al. 2003) (Fig. 5B). Although all the

767 studies tend to conclude that the *ICAM1* rs1799969 polymorphism is associated with the
768 endometriosis risk, it is impossible to draw firm conclusions at this stage. Additional large cohort
769 studies and well-designed case-control studies of *ICAM1* rs1799969 are required.
770
771 Endometriosis is an invasive process, and many studies have focused on the impact of the
772 *tumour suppressor gene p53* (*TP53*). This sequence-specific DNA-binding transcription factor
773 has been referred to as a guardian of genome integrity, and is involved in the response to a
774 variety of physiologic cellular stressors through its ability to induce cell cycle arrest and
775 apoptosis (Aubrey, Strasser, and Kelly 2016). *TP53* is one of the most frequently mutated genes
776 in all types of human cancers. The most common polymorphism (rs1042522, in codon 72) has
777 been studied extensively in the context of endometriosis. When considering CAT1 studies only,
778 we did not observe an association with endometriosis (OR 1.22; 95% CI 0.66–2.26). However,
779 the opposite result was found after pooling CAT1 and CAT2 studies (OR 1.49; 95% CI 1.16–
780 1.90) (Fig. 7B). This result is in line with previous meta-analyses (Feng et al. 2015; Lao, Chen,
781 and Qin 2016; Yan et al. 2015) that included many more studies than we did (*i.e.*, 15, 11 and 15,
782 respectively, compared with seven in our meta-analysis). We excluded these studies because they
783 did not meet our inclusion criteria for the control participants (Ammendola et al. 2008; Camargo-
784 Kosugi et al. 2014; Govatati et al. 2012; Omori et al. 2004; Paskulin et al. 2012; Ying et al.
785 2011), lacked raw data (Rotman et al. 2013) or were not published in English (Bianco et al.
786 2011; Huang et al. 2013). Previous meta-analyses have suggested an association between the
787 *TP53* rs1042522 polymorphism and endometriosis risk in Asian populations, in particular. When
788 examining our results and the literature data in more detail, one can reasonably hypothesize that
789 the heterogeneity might be due to ethnicity and not the control criteria. Indeed, two of the three

CAT1 studies included in our meta-analysis assessed Caucasian women (Lattuada, Vigano, et al. 2004; Vietri et al. 2007). Further analysis (with stratification by ethnic group) is required to explore the underlying link between endometriosis and the *TP53* rs1042522 polymorphism.

We also analysed another polymorphism (*XRCC1* rs25487) in a gene considered to be a guardian of genome integrity. The *XRCC1* gene encodes a protein which is thought to detect DNA breaks and repair base excisions, in co-operation with other proteins (London 2015). The loss of *XRCC1* destabilizes the genome and leads to chromosome translocations and/or deletions. Our meta-analysis suggested that the *XRCC1* rs25487 polymorphism is not associated with endometriosis (Fig. 7B); this contrasts with the previous meta-analysis, where allele A was found to protect against endometriosis (Lv et al. 2017). We excluded two CAT3 studies (Hsieh et al. 2012; Monteiro et al. 2014), which was enough to change the random forest results and the overall results. Once again, the selection of the control population appears to be critical. Considering the limited number of patients included in both meta-analyses, further work is needed to obtain a more comprehensive conclusion and thus confirm or refute the potential link between endometriosis and the *XRCC1* rs25487 polymorphism.

Angiogenesis is also significantly involved in endometriosis in general and vascularization of ectopic endometrium in particular (Groothuis 2011). *VEGFA* is a key gene in angiogenesis, which explains why many studies have sought to characterize associations between endometriosis and *VEGFA* polymorphisms. Five polymorphisms have been studied, and we performed a meta-analysis on four of these. None was significantly associated with endometriosis. For rs833061 (Li et al. 2013; Liang, Huang, and Fan 2012; Xu et al. 2012; Zhao, Nyholt, Thomas, et al. 2008) and rs2010963 (Fang et al. 2015; Li et al. 2013; Liang, Huang, and

Fan 2012; Xu et al. 2012; Zhao, Nyholt, Thomas, et al. 2008), our results were similar to those of earlier meta-analyses. Regarding *VEGFA* rs699947, our results were in line with two previous meta-analyses, (Liang, Huang, and Fan 2012; Zhao, Nyholt, Thomas, et al. 2008), whereas a third study concluded that the risk was decreased (Li et al. 2013). Only two published studies were in line with the results from our meta-analysis (Lamp et al. 2010; Liu et al. 2009) (the remaining two studies did not meet our inclusion criteria), confirming absence of an association between this polymorphism and endometriosis. The results for VEGFA rs3025039 were contradictory. Of the four previous meta-analyses (Li et al. 2013; Liang, Huang, and Fan 2012; Xu et al. 2012; Zhao, Nyholt, Thomas, et al. 2008), three found an association (Li et al. 2013; Liang, Huang, and Fan 2012; Xu et al. 2012). However, our meta-analysis included four articles published after the other meta-analyses (Henidi, Kaabachi, Naouali, et al. 2015; Perini et al. 2014; Szczepanska et al. 2015; Vodolazkaia et al. 2016) and excluded three studies (Ikuhashi et al. 2007; Kim et al. 2008; Zhao, Nyholt, Thomas, et al. 2008). We cannot rule out an association with specific endometriosis stages because we were unable to stratify by ASRM stage. However, we consider that further studies of larger samples would probably confirm our present results. For the fifth VEGFA variant (rs1570360, -1154G>A, not included in our meta-analyses), only two CAT1 studies were found. Previous meta-analyses did not find an association with endometriosis (Li et al. 2013; Liang, Huang, and Fan 2012). In summary, none of the *VEGFA* polymorphisms was associated with endometriosis in the present study; a quite surprising result considering the large number of studies performed.

The last polymorphism included in our meta-analyses - for the first time, to the best of our knowledge - was *SERPINE1* rs1799889. The plasminogen activator inhibitor 1 protein encoded by *SERPINE1* is a serine protease inhibitor involved in fibrinolysis. The fibrinolytic system

appears to be involved in the pathogenesis of endometriosis in general and disease onset and progression in particular (Zorio et al. 2008; Gilabert-Estelles et al. 2006). Although we did not find an association (OR 2.03; 95% CI 0.88–4.67) (Fig. 8C), the marked heterogeneity and the small number of included studies mean that a large, well-designed case-control study of the potential relationship between *SERPINE1* rs1799889 and endometriosis is justified.

We found that additional studies are required for several of the genes included in our review. One must also consider genes with only two CAT1 series. Of the 44 such polymorphisms, two have been discussed above; no association was found for *VEGFA* rs1570360 and *WNT4* rs7521902, and further studies are not deemed necessary. In contrast, the two CAT1 studies of the the *Fc receptor-like 3* (*FCRL3)* rs7528684 polymorphism (Barbosa et al. 2012; Szczepanska, Wirstlein, Holysz, et al. 2013) indicate an association with endometriosis. Thus, *FCRL3* rs7528684 is another worthwhile candidate for additional studies.

Finally, our results enabled us to classify polymorphisms into four categories: polymorphisms associated with endometriosis (n=5) which probably do not require confirmation in a larger number of studies (*IFNG* (CA)repeat, *GSTM1* null genotype, GSTP1 rs1695 and *WNT4* rs16826658 and rs2235529); polymorphisms associated with endometriosis but for which confirmation is necessary (n=6) (*PGR* PROGINS, *ICAM1* rs1799969, *AHRR* rs2292596, *CYP17A1* rs743572, *CYP2C19* rs4244285 and *PPARG* rs1801282); polymorphisms not associated with endometriosis but for which confirmation is necessary (n=12) (*TNF* rs1799964, *IL6* rs1800796, *TGFB1* rs1800469, *ESR1* rs2234693, *PGR* rs10895068, *FSHR* rs6166, *ICAM1* rs5498, *CYP1A1* rs4646903, *CYP19A1* rs10046, *TP53* rs1042522, *XRCC1* rs25487 and *SERPINE1* rs1799889); and polymorphism that definitively do not have an association with

endometriosis (n=5) (*GSTT1* null genotype, *VEGFA* rs699947, *VEGFA* rs833061, *VEGFA* rs2010963 and *VEGFA* rs3025039). The selection criteria to decide which polymorphisms require confirmation are the following: low number of studies (CAT1 <3) and/or low patients number included (<1000) or divergence in the results among studies due to inclusion criteria for controls.

Could the nature of significantly associated polymorphisms provide us with information on the aetiology of endometriosis? Along with detoxification, inflammation, and endocrine processes, cell cycle control and cell adhesion might be major factors in the development of ectopic endometrial lesions. Surprisingly, no polymorphisms in *VEGFA* - the key factor in angiogenesis – appeared to predispose to endometriosis. Hence, we hypothesize that local angiogenesis is a consequence of the development of ectopic endometrium and not a cause of cell proliferation. With regard to inflammation, only the *IFNG* (CA) repeat polymorphism appeared to predispose to endometriosis. Similar observations apply to endocrine processes and *PGR* PROGINS. We therefore further hypothesize that endocrine pathways are not greatly involved in the development of endometriosis. In contrast, cell adhesion and detoxification seem to be linked to a predisposition to endometriosis. There are two possible explanations. First, an environmental predisposition to endometriosis may explain familial variations. Second, cell adhesion is an important factor in invasive processes. Hence, further studies are required to evaluate the association between the frequency of polymorphisms and the endometriosis stage.

Finally, the present review has some limitations mainly related to our inclusion criteria. First, it focused solely on polymorphisms studied in at least three different publications. Second, we only included studies with controls where endometriosis was excluded at surgery or from clinical data

and excluded probably larger studies using populations with undiagnosed endometriosis. Third, ethnicity was not considered despite high polymorphism frequency variability according to ethnic origin.

Few stratifications were performed in the present analysis, and a difference was only observed for the *GSTM1* null genotype (i.e. a stronger association for stage III/IV endometriosis than for stage I/II). It is also important to bear in mind that SNP studies require a candidate gene hypothesis; this explains why most of our genes of interest come from pathways already known to be involved in the pathogenesis or development of endometriosis (Falconer, D'Hooghe, and Fried 2007). Understanding the potential effects of these associations on the physiopathology of endometriosis will require further functional research (Zondervan et al. 2018).

Conclusion

To the best our knowledge, this is the first meta-analysis to have been performed for *IFNG* (CA repeats), *WNT4* (rs16826658 and rs2235529) and *SERPINE1* (rs1799889) polymorphisms in the context of endometriosis. Our study confirmed the importance of being cautious with regard to the criteria for selecting the control population. The control population may be influencing meta-analysis results, and thus highlight the rationale for stratifying by control category. Although CAT1 studies may be not representative of the general population, potential genetic markers of endometriosis should be investigated in well-designed case-control studies before the research is extended.

As mentioned above, we classified 28 polymorphisms into several categories (Fig. 10).

Five of the polymorphisms (Fig. 10, panel on right) probably do not require further study as none were associated with endometriosis.

Five of the polymorphisms could be analyzed simultaneously after the design of a large, collaborative CAT1/2 study, as associated with endometriosis (Fig. 10, left panel).

For the remaining polymorphisms, further studies will be necessary, even though there is at present some evidence of an association for six polymorphisms, and no association for 12 of them. Further studies will also be necessary for a few polymorphisms not included in the present work, *i.e.*, those polymorphisms with a positive association on the basis of two CAT1 studies.

This work constitutes the first step towards identifying potential markers for a genetic screening test for endometriosis. By combining a patient survey (Fauconnier et al. 2018), a genetic screen with endometrial or serum biomarkers and an analysis of the family medical history, it may be possible to identify women with a high predisposition to endometriosis. The combination of

915 these polymorphisms presents the potential for developing a diagnostic tool in primary care for
916 symptomatic patients and should thus decrease the time needed to diagnose endometriosis.

Authors' roles

Study design: LM, CP, AF and FV

Search strategy: LM, CP and FV

Study selection: LM and FV

Data selection: LM, MH, FV

Statistical analysis: LM and MH

Manuscript drafting: LM, CP and FV

Critical discussion: LM, MH, AF, CP and FV

Funding

Endofrance (www.endofrance.org), Endomind (www.endomind.org), IRSF (www.irsf.fr)

Conflict of interest

None declared

Figure legends

Figure 1 Selection of polymorphisms for meta-analysis.

CAT1: Category 1 studies, in which the absence of endometriosis in the control women has been confirmed during surgery (tubal ligation, hysterectomy, laparoscopy, etc.).

Figure 2 Forest plots for vascular endothelial growth factor alpha (*VEGFA)* polymorphisms (allelic model; events = allele studied, total = number of alleles in total).

A) rs699947 (-2578C>A): A allele; B) rs833061 (-460T>C): C allele; C) rs2010963 (+405G>C): C allele; D) rs3025039 (+936C>T): T allele.

Figure 3 Forest plots for polymorphisms involved in inflammation pathways (allelic model events = allele studied, total = number of alleles in total).

A) tumor necrosis factor (*TNF)* (rs1799964): C allele; B) interleukin 6 (*IL6)* (rs1800796): G allele; C) transforming growth factor beta 1 (*TGFB1)* (rs1800469): T allele; D) interferon gamma (*IFNG)* ((CA) repeats): S ≤ 13 repeats.

Figure 4 Forest plots for polymorphisms involved in endocrine pathways (allelic model events = allele studied, total = number of alleles in total).

A) estrogen receptor 1 (*ESR1)* (rs2234693): C allele; B) progesterone receptor (*PGR)* (rs1042838; PROGINS): P2 allele, C) *PGR* (rs10895068): A allele, D) follicle stimulating hormone receptor (*FSHR)* (rs6166): G allele.

Figure 5 Forests plot for intercellular adhesion molecule 1 (*ICAM1)* polymorphisms (allelic model events = allele studied, total = number of alleles in total).

A) rs5498 (K469E): G allele; B) rs1799969 (G241R): A allele.

Figure 6 Forest plots for polymorphisms involved in detoxification processes (allelic model events = allele studied, total = number of alleles in total).

A) glutathione S-transferase mu 1 (*GSTM1)* (null genotype): null; B) glutathione S-transferase theta 1 (*GSTT1)* (null genotype): null; C) glutathione S-transferase pi 1 (*GSTP1)* (rs1695): G allele; D) aryl-hydrocarbon receptor repressor (*AHRR)* (rs2292596): G allele.

Figure 7 Forest plots for polymorphisms of cytochrome P450 family (allelic model events = allele studied, total = number of alleles in total).

A) cytochrome P450 family 1 subfamily A polypeptide 1 (*CYP1A1)* (rs4646909): C allele; B) *CYP17A1* (rs743572): C allele; C) *CYP19A1* (rs10046): T; D) *CYP2C19* (rs4244285)

Figure 8 Forest plots for polymorphisms involved in genome regulation (allelic model events = allele studied, total = number of alleles in total).

A) tumor protein (*TP53)* (rs1042522): Pro; B) X-ray repair complementing defective repair in Chinese hamster cells 1 (*XRCC1)* (rs25487): A allele.

Figure 9 Forest plots for *WNT4*, *SERPINE1* and *PPARG* polymorphisms (allelic model events = allele studied, total = number of alleles in total).

A) wingless-type MMTV integration site family member 4 (*WNT4)* (rs16826658): allele G; B) *WNT4* (rs2235529): allele A; C) serpin peptidase inhibitor clade E member 1 (*SERPINE1)* (rs1799889): 4G allele, D) peroxisome proliferator-activated receptor gamma (*PPARG)* (rs1801282): allele G.

Figure 10 Schematic illustration summarizing the main relevant gene polymorphisms identified in this study.

Supplementary Figure S1 vascular endothelial growth factor alpha (*VEGFA)* rs699947 (-2578C>A) polymorphism flow chart and publication bias analysis.
A) PRISMA flow chart; B) funnel plot.

Supplementary Figure S2 vascular endothelial growth factor alpha (*VEGFA)* rs833061 (-460T>C) polymorphism flow chart, publication bias analysis and meta-analysis after ASRM stratification.
A) PRISMA flow chart; B) funnel plot; C) forest plot, with stratification by disease stage.

Supplementary Figure S3 vascular endothelial growth factor alpha (*VEGFA)* rs2010963 (+405G>C) polymorphism flow chart, publication bias analysis and meta-analysis after ASRM stratification.
A) PRISMA flow chart; B) funnel plot; C) forest plot, with stratification by disease stage.

Supplementary Figure S4: vascular endothelial growth factor alpha (*VEGFA)* rs3025039 (+936C>T) polymorphism flow chart and publication bias analysis.

A) PRISMA flow chart; B) funnel plot.

Supplementary Figure S5: tumor necrosis factor (*TNF)* rs1799964 (-1031T/C) polymorphism flow chart and publication bias analysis.

A) PRISMA flow chart; B) funnel plot

Supplementary Figure S6: *interleukin – (IL6*) rs1800796 (-634C>G) polymorphism flow chart, publication bias analysis and meta-analysis after ASRM stratification.

A) PRISMA flow chart; B) funnel plot, C) forest plot, with stratification by disease stage.

Supplementary Figure S7: transforming growth factor beta 1 (*TGFB1)* rs1799969 (-509C / T) polymorphism flow chart and publication bias analysis.

A) PRISMA flow chart; B) funnel plot

Supplementary Figure S8: interferon gamma (*IFNG)* (CA) repeat polymorphism flow chart, publication bias analysis and meta-analysis after ASRM stratification.

A) PRISMA flow chart; B) funnel plot; C) forest plot, with stratification by disease stage.

Supplementary Figure S9: estrogen receptor 1 (*ESR1)* rs2234693 (PvuII) polymorphism flow chart and publication bias analysis.

A) PRISMA flow chart; B) funnel plot

Supplementary Figure S10: progesterone receptor (*PGR)* rs1042838 (PROGINS) polymorphism flow chart and publication bias analysis.
A) PRISMA flow chart; B) funnel plot

Supplementary Figure S11: progesterone receptor (*PGR)* rs 10895068 (+331G>A) polymorphism flow chart and publication bias analysis.
A) PRISMA flow chart; B) funnel plot

Supplementary Figure S12: follicle stimulating hormone receptor (*FSHR)* rs6166 Asn680Ser) polymorphism flow chart and publication bias analysis.
A) PRISMA flow chart; B) funnel plot

Supplementary Figure S13: intercellular adhesion molecule 1 (*ICAM1)* rs5498 (K469E) polymorphism flow chart, publication bias analysis and meta-analysis after ASRM stratification.
A) PRISMA flow chart; B) funnel plot; C) forest plot, with stratification by disease stage.

Supplementary Figure S14: intercellular adhesion molecule 1 (*ICAM1)* rs1799969 (G241R) polymorphism flow chart and publication bias analysis.
A) PRISMA flow chart; B) funnel plot

Supplementary Figure S15: glutathione S-transferase mu 1 (*GSTM1)* null genotype polymorphism flow chart, publication bias analysis and meta-analysis after ASRM stratification.

A) PRISMA flow chart; B) funnel plot; C) forest plot, with stratification by disease stage.

Supplementary Figure S16: glutathione S-transferase theta 1 (*GSTT1)* null genotype polymorphism flow chart and publication bias analysis.
A) PRISMA flow chart; B) funnel plot

Supplementary Figure S17: glutathione S-transferase pi 1 (*GSTP1)* rs1695 polymorphism flow chart and publication bias analysis.
A) PRISMA flow chart; B) funnel plot

Supplementary Figure S18: aryl-hydrocarbon receptor repressor (*AHRR)* rs1799969 (Pro185Ala) polymorphism flow chart and publication bias analysis.
A) PRISMA flow chart; B) funnel plot

Supplementary Figure S19: cytochrome P450 family 1 subfamily A polypeptide 1 (*CYP1A1)* rs4646909 (Msp1) polymorphism flow chart and publication bias analysis.
A) PRISMA flow chart; B) funnel plot

Supplementary Figure S20: cytochrome P450 family 17 subfamily A polypeptide 1 (*CYP17A1)* rs743572 (-34A/G) polymorphism flow chart and publication bias analysis.
A) PRISMA flow chart; B) funnel plot

Supplementary Figure S21: cytochrome P450 family 19 subfamily A polypeptide 1 (*CYP19A1)* rs10046 (1531C>T) polymorphism flow chart and publication bias analysis.
A) PRISMA flow chart; B) funnel plot

Supplementary Figure S22: cytochrome P450 family 2 subfamily C polypeptide 19 (*CYP2C19)* rs4244285 polymorphism flow chart and publication bias analysis.
A) PRISMA flow chart; B) funnel plot

Supplementary Figure S23: tumor protein 53 (*TP53)* rs1042522 (codon 72) polymorphism flow chart and publication bias analysis.
A) PRISMA flow chart; B) funnel plot

Supplementary Figure S24: X-ray repair complementing defective repair in Chinese hamster cells 1 (*XRCC1)* rs25487 (Arg399Gln) polymorphism flow chart and publication bias analysis.
A) PRISMA flow chart; B) funnel plot

Supplementary Figure S25: wingless-type MMTV integration site family member 4 (*WNT4)* rs16826658 polymorphism flow chart and publication bias analysis.
A) PRISMA flow chart; B) funnel plot

Supplementary Figure S26: wingless-type MMTV integration site family member 4 (*WNT4)* rs2235529 polymorphism flow chart and publication bias analysis.
A) PRISMA flow chart; B) funnel plot

Supplementary Figure S27: serpin peptidase inhibitor clade E member 1 (*SERPINE1)* rs1799889 polymorphism flow chart and publication bias analysis.

A) PRISMA flow chart; B) funnel plot

Supplementary Figure S28: peroxisome proliferator-activated receptor gamma *(PPARG)* rs1801282 polymorphism flow chart and publication bias analysis.

A) PRISMA flow chart; B) funnel plot

Table legend

Table I The main results of the meta-analyses to investigate an association between gene polymorphisms and endometriosis.

CAT1: Category 1 studies, in which the absence of endometriosis in the control women has been confirmed during surgery (tubal ligation, hysterectomy, laparoscopy, etc.).

CAT2: Category 2 studies, in which the control women had no apparent signs and symptoms of endometriosis (including fertile women and/or women having undergone a Caesarean section). In this category, women may be regarded as a control population, even if inclusion criteria are out of ASRM guidelines.

CAT3: Category 3 studies using other sources of controls, such as newborns, volunteers without clinical data, and males. These CAT3 studies were not considered for meta-analysis because

males and newborns could not be considered as controls since endometriosis is strictly a female disease.

rASRM: revised American Society for Reproductive Medicine classification

Supplemental table legend

Supplementary Table SI References (the unique identifier number) of the 395 publications (PMIDs) identified by the PubMed search.

Supplementary Table SII Results of the text mining procedure.

Supplementary Table SIII The list of genes cited in one or two different publications.

Supplementary Table SIV The list of genes cited in at least three different publications; identification of polymorphisms; data selection.

CAT1: Category 1 studies, in which the absence of endometriosis in the control women has been confirmed during surgery (tubal ligation, hysterectomy, laparoscopy, etc.).

Supplementary Data

List of publications by gene:

vascular endothelial growth factor alpha *(VEGFA)*: (Cardoso, Abrao, Vianna-Jorge, et al. 2017; Vodolazkaia et al. 2016; Szczepanska et al. 2015; Henidi, Kaabachi, Naouali, et al. 2015; Perini et al. 2014; Saliminejad et al. 2013; Vanaja et al. 2013; Emamifar et al. 2012; Lamp et al. 2010; Attar, Agachan, et al. 2010; Toktam et al. 2010; Altinkaya et al. 2011; Liu et al. 2009; Cosin et al. 2009; Zhao, Nyholt, Thomas, et al. 2008; Gentilini, Somigliana, et al. 2008; Ikuhashi et al. 2007; Kim et al. 2008; Kim, Choi, Choung, et al. 2005; Bhanoori, Arvind Babu, et al. 2005).

tumor necrosis factor *(TNF)*: (Abutorabi et al. 2015; Asghar et al. 2004; Chae et al. 2008; de Oliveira Francisco et al. 2017; Hsieh et al. 2002; Lakshmi et al. 2010; Lee et al. 2008; Lee, Park, and Kim 2002; Mardanian et al. 2014; Saliminejad et al. 2013; Teramoto et al. 2004; Wieser, Fabjani, et al. 2002; Zhao et al. 2007; Zhou et al. 2010).

interleukin 6 *(IL6)* : (Bessa et al. 2016; Bhanoori, Babu, et al. 2005; Chae et al. 2010; Juo et al. 2009; Kitawaki et al. 2006; Lee, Park, and Kim 2002; Wieser et al. 2003; Zhou et al. 2010)

transforming growth factor beta 1 *(TGFB1)*: (Baxter et al. 2002; Hsieh, Chang, Tsai, Peng, et al. 2005; Kim et al. 2010; Lee et al. 2011; Romano, van Kaam, and Dunselman 2010; van Kaam, Romano, Dunselman, et al. 2007)

interferon gamma *(IFNG):* (Kim et al. 2011; Kitawaki et al. 2004; Mormile and Vittori 2013; Rozati, Vanaja, and Nasaruddin 2010)

estradiol receptor 1 *(ESR1)*: 21 studies found by our literature search and text mining approach (Altmae et al. 2007; Georgiou et al. 1999; Govindan et al. 2009; Hsieh, Chang, Tsai, Lin, et al. 2005; Huang et al. 2014; Huber et al. 2005; Kim, Choi, Jun, et al. 2005; Kitawaki et al. 2001; Lamp et al. 2011; Luisi et al. 2006; Matsuzaka, Kikuti, Izumi, et al. 2012; Oehler et al. 2004; Paskulin et al. 2013; Renner et al. 2006; Sato et al. 2008; Seko et al. 2004; Trabert et al. 2011; Wang et al. 2013; Wang et al. 2004; Wu et al. 2013; Xie et al. 2009) and an additional study (Hsieh et al. 2007) that was incorrectly referenced and listed being as relevant for *ESR2*))

progesterone receptor *(PGR)* : (Berchuck et al. 2004; Cardoso, Machado, et al. 2017; Christofolini et al. 2011; Costa et al. 2011; D'Amora et al. 2009; De Carvalho et al. 2007; Gentilini, Vigano, et al. 2008; Gimenes et al. 2010; Govindan et al. 2007; Lamp et al. 2011; Lattuada, Somigliana, et al. 2004; Near et al. 2011; Renner et al. 2008; Silva and Moura 2016; Trabert et al. 2011; Treloar et al. 2005; van Kaam, Romano, Schouten, et al. 2007; Wieser, Schneeberger, et al. 2002; Wu et al. 2013)

follicule stimulating hormone receptor *(FSHR) :* (Andre et al. 2018; Kerimoglu et al. 2015; Schmitz et al. 2015)

intercellular adhesion molecule 1 *(ICAM1)*: (Bessa et al. 2016; Chae et al. 2010; Kitawaki et al. 2006; Vigano et al. 2003; Aghajanpour, Mashayekhi, and Rajaei 2011)

glutathione S-transferase mu 1 *(GSTM1)*: 27 studies identified by text miming (Aban et al. 2007; Arvanitis et al. 2001; Arvanitis et al. 2003; Babu et al. 2005; Baranova et al. 1997; Baranova et

al. 1999; Baxter, Thomas, and Campbell 2001; Ertunc et al. 2005; Frare et al. 2013; Hadfield et al. 2001; Hassani et al. 2016; Henidi, Kaabachi, Mbarik, et al. 2015; Hosseinzadeh, Mashayekhi, and Sorouri 2011; Hsieh, Chang, Tsai, Lin, Chen, et al. 2004; Huang et al. 2014; Huang et al. 2010; Hur et al. 2005; Kim et al. 2007; Kubiszeski et al. 2015; Matsuzaka, Kikuti, Goya, et al. 2012; Roya, Baludu, and Reddy 2009; Seifati et al. 2012; Silva and Moura 2016; Trabert et al. 2011; Tuo et al. 2016; Vichi et al. 2012; Wu et al. 2012; Morizane et al. 2004).
Another publication was added (Morizane et al. 2004); it was cited by previous meta-analyses (Ding et al. 2014; Guo 2005; Li and Zhang 2015; Xin et al. 2016; Zhu et al. 2014) but had not been identified by our search strategy because the term "polymorphism(s)" was not mentioned in the title or the abstract.

glutathione S-transferase theta 1 *(GSTT1)*: (18 studies identified by text miming (Aban et al. 2007; Arvanitis et al. 2001; Arvanitis et al. 2003; Babu et al. 2005; Baranova et al. 1999; Ertunc et al. 2005; Frare et al. 2013; Hadfield et al. 2001; Hassani et al. 2016; Henidi, Kaabachi, Mbarik, et al. 2015; Hur et al. 2005; Kim et al. 2007; Kubiszeski et al. 2015; Matsuzaka, Kikuti, Goya, et al. 2012; Silva and Moura 2016; Tuo et al. 2016; Vichi et al. 2012; Wu et al. 2012) and 2 studies (Lin et al. 2003; Morizane et al. 2004) found in previous meta-analyses (Chen, Xu, et al. 2015; Ding et al. 2014; Guo 2005; Xin et al. 2016; Zhu et al. 2014))

glutathione S-transferase pi 1 *(GSTP1):* (Ertunc et al. 2005; Hassani et al. 2016; Hur et al. 2005; Jeon et al. 2010; Matsuzaka, Kikuti, Goya, et al. 2012; Tuo et al. 2016; Vichi et al. 2012; Wu et al. 2012)

*a*ryl-hydrocarbon receptor repressor *(AHRR)* : (Asada et al. 2009; Kim et al. 2007; Matsuzaka, Kikuti, Goya, et al. 2012; Tsuchiya et al. 2005; Watanabe et al. 2001; Wu et al. 2012)

cytochrome P450 family 1 subfamily A polypeptide 1 *(CYP1A1)* : 12 studies identified by text miming (Silva and Moura 2016; Matsuzaka, Kikuti, Goya, et al. 2012; Wu et al. 2012; Trabert et al. 2011; Tsuchiya et al. 2007; Huber et al. 2005; Babu et al. 2005; Arvanitis et al. 2003; Arvanitis et al. 2001; Hadfield et al. 2001; Watanabe et al. 2001; Barbosa et al. 2016) and 2 studies (Juo et al. 2006; Rozati et al. 2008) found in a previous meta-analysis (Fan et al. 2016)

CYP17A1: (Al-Rubae'i, Naji, and Turki 2017; Asghar et al. 2005; Bozdag et al. 2010; Cardoso, Machado, et al. 2017; De Carvalho et al. 2007; Hsieh, Chang, Tsai, Lin, and Tsai 2004; Hsieh, Chang, Tsai, Lin, et al. 2005; Huang et al. 2014; Juo et al. 2006; Kado et al. 2002; Szczepanska, Wirstlein, Skrzypczak, et al. 2013; Trabert et al. 2011; Vietri et al. 2009; Wu et al. 2013; Zhao, Nyholt, Le, et al. 2008)

CYP19A1: (Cardoso, Machado, et al. 2017; Szczepanska, Wirstlein, Skrzypczak, et al. 2013; Vietri et al. 2009; Hur et al. 2007; Wu et al. 2013; Wang et al. 2014; Lamp et al. 2011)

CYP2C19 : (Cardoso, Abrao, Berardo, et al. 2017; Bozdag et al. 2010; Cayan et al. 2009)

tumor protein 53 *(TP53)*: (Ammendola et al. 2008; Camargo-Kosugi et al. 2014; Chang et al. 2002; Frare et al. 2013; Gallegos-Arreola, Figuera-Villanueva, et al. 2012; Gallegos-Arreola, Valencia-Rodriguez, et al. 2012; Gloria-Bottini et al. 2016; Gloria-Bottini et al. 2013; Govatati et

al. 2012; Hsieh and Lin 2006; Hsieh et al. 2001; Hussain et al. 2018; Lao, Chen, and Qin 2016; Lattuada, Vigano, et al. 2004; Nakayama et al. 2001; Nikbakht Dastjerdi, Aboutorabi, and Eslami Farsani 2013; Okuda et al. 2003; Omori et al. 2004; Paskulin et al. 2012; Ribeiro Junior et al. 2009; Rotman et al. 2013; Silva and Moura 2016; Silva et al. 2011; Vercellini et al. 1994; Vietri et al. 2007; Ying et al. 2011)

X-ray repair complementing defective repair in Chinese hamster cells 1 *(XRCC1)*: 5 were identified in our literature search and (Attar, Cacina, et al. 2010; Bau et al. 2007; Hsieh et al. 2012; Monteiro et al. 2014; Saliminejad et al. 2015), and one study (Safan and Ghanem 2015) was cited in a previous meta-analysis only (Lv et al. 2017)

wingless-type MMTV integration site family member 4 *(WNT4)*: (Lee et al. 2014; Li, Hao, et al. 2017; Mafra et al. 2015; Matalliotakis, Zervou, Matalliotaki, Arici, et al. 2017; Matalliotakis, Zervou, Matalliotaki, Rahmioglu, et al. 2017; Wu et al. 2015)

serpin peptidase inhibitor clade E member 1 *(SERPINE1)*: (Bedaiwy et al. 2006; Gentilini et al. 2009; Goncalves-Filho et al. 2011; Ramon et al. 2008; Uxa et al. 2010)

peroxisome proliferator-activated receptor gamma *(PPARG):* (Hwang et al. 2010; Kiyomizu et al. 2006; Dogan et al. 2004)

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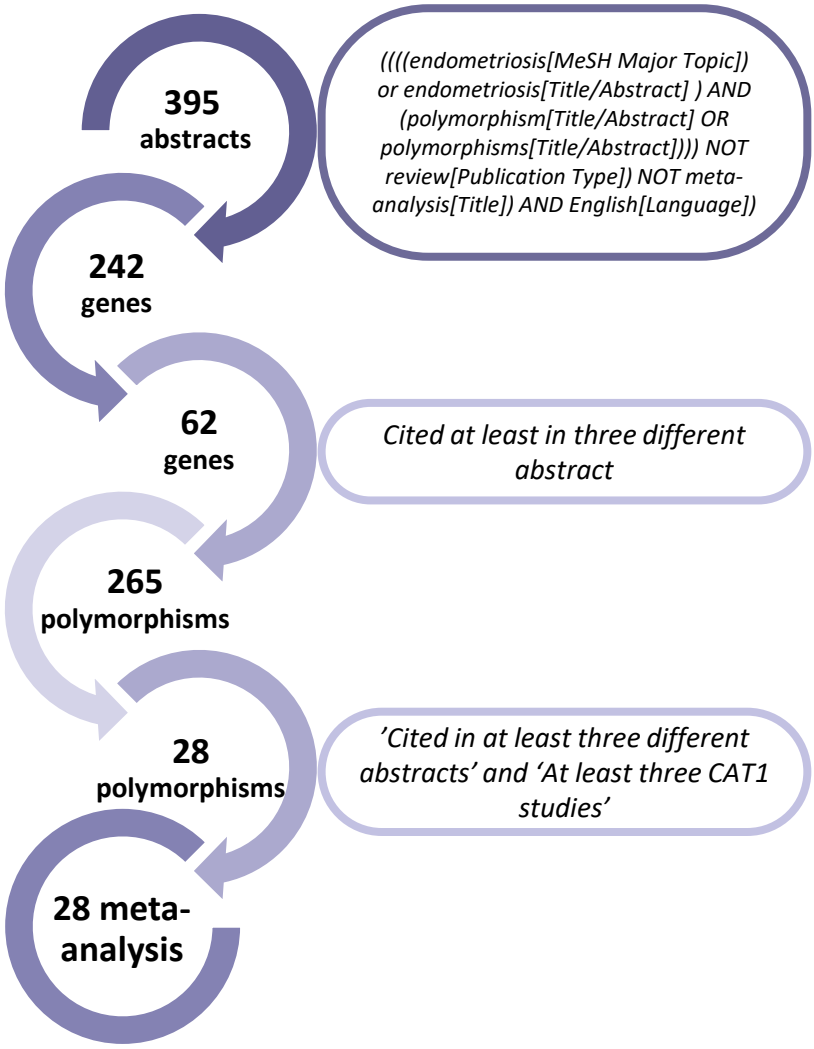


Figure 1: Selection of polymorphisms for meta-analysis.

CAT1: Category 1 studies, in which the absence of endometriosis in the control women has been confirmed during surgery (tubal ligation, hysterectomy, laparoscopy, etc.).

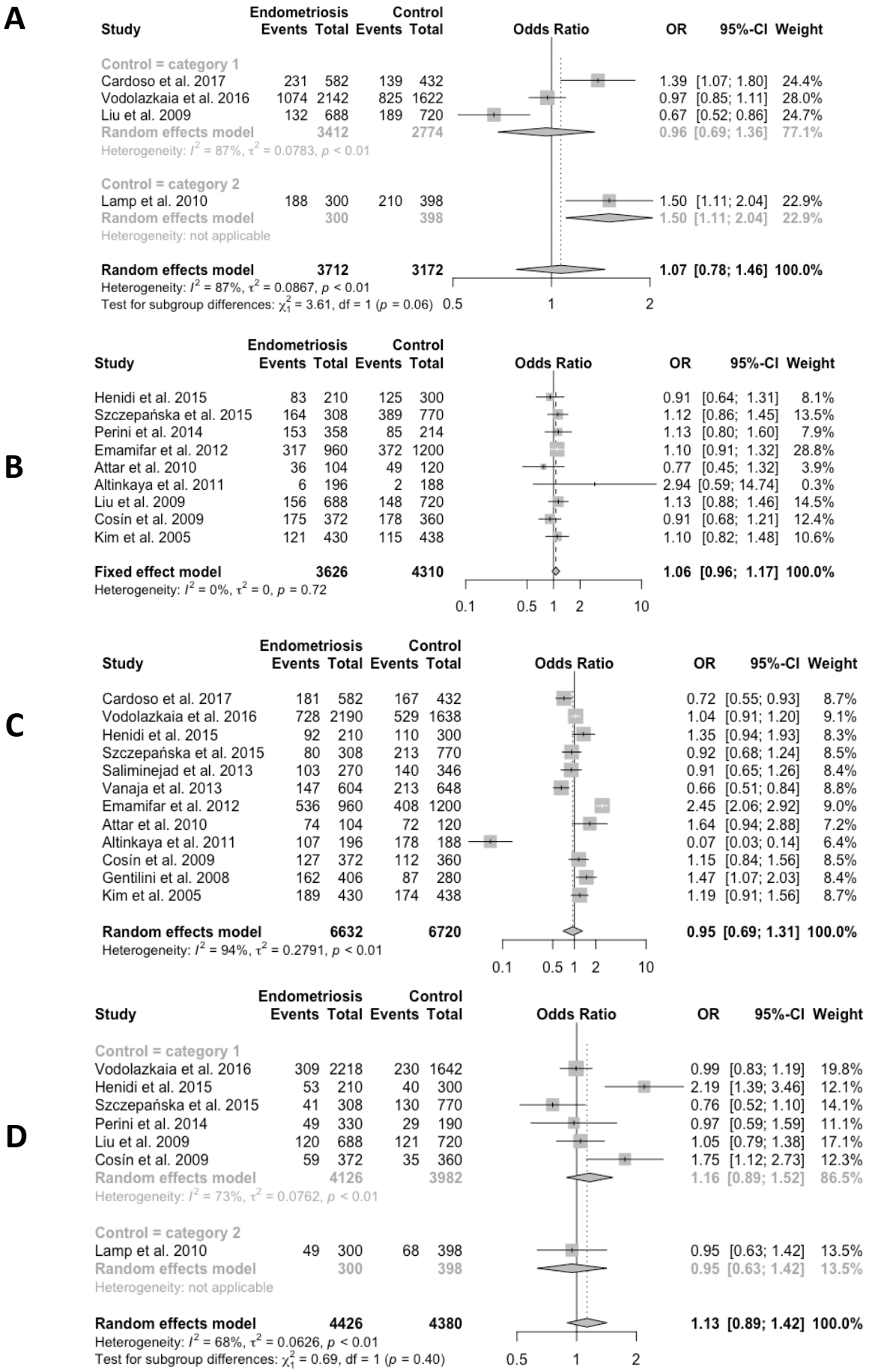


Figure 2: Forest plot for vascular endothelial growth factor alpha (VEGFA) polymorphisms.
(allelic model; events = studied allele, total = allele number)
A) rs699947 (-2578C>A): A allele; B) rs833061 (-460T>C): C allele; C) rs2010963 (+405G>C): C allele; D) rs3025039 (+936C>T): T allele

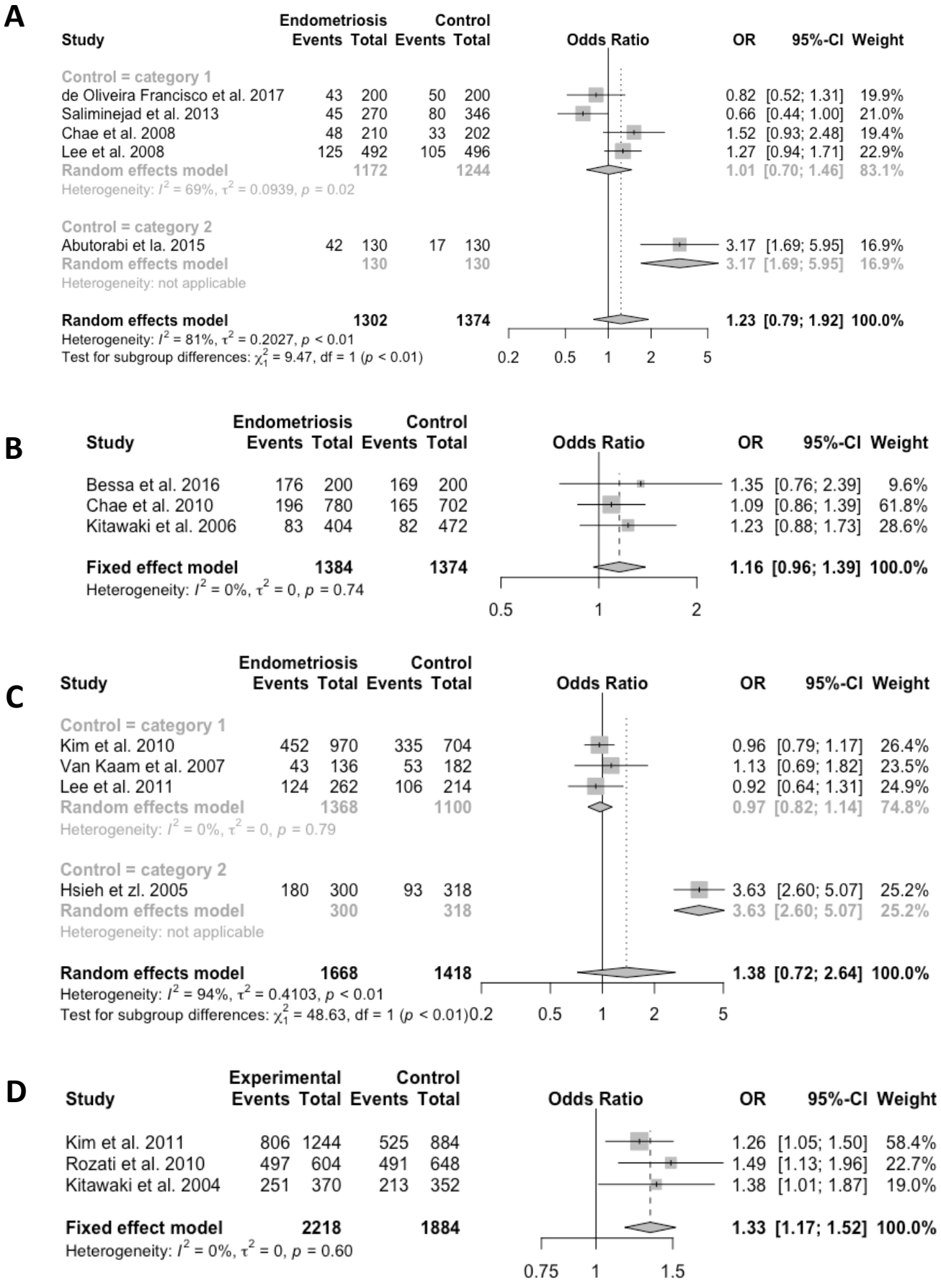


Figure 3 : Forest plot for polymorphisms involved in inflammation pathway

(allelic model events = studied allele, total = allele number)

A) tumor necrosis factor (TNF) (rs1799964): C allele; B) interleukin 6 (IL6) (rs1800796): G allele; C) transforming growth factor beta 1 (TGFB1) (rs1800469): T allele; D) interferon gamma (IFNG) ((CA) repeats): S ≤ 13 repeats.

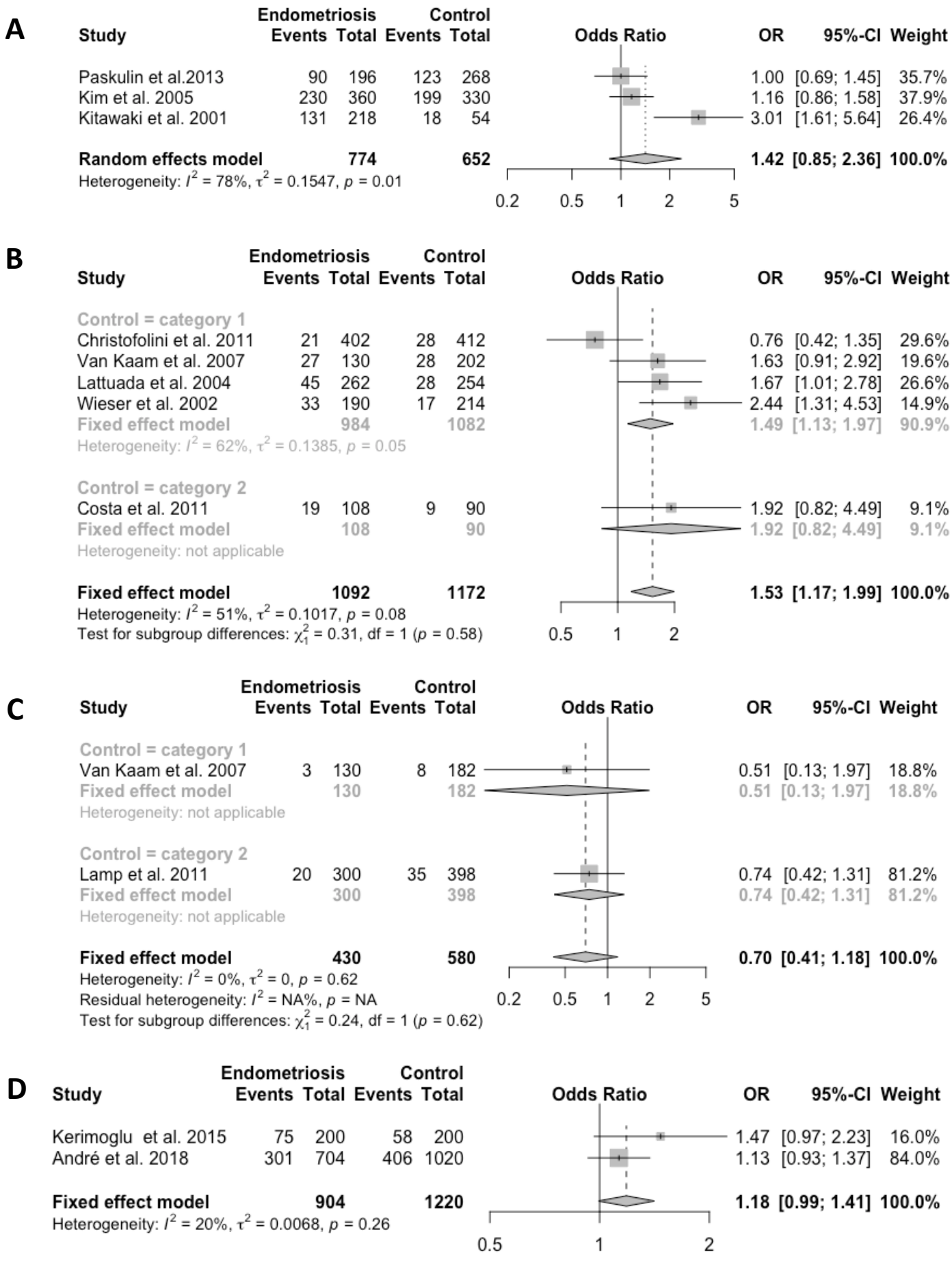
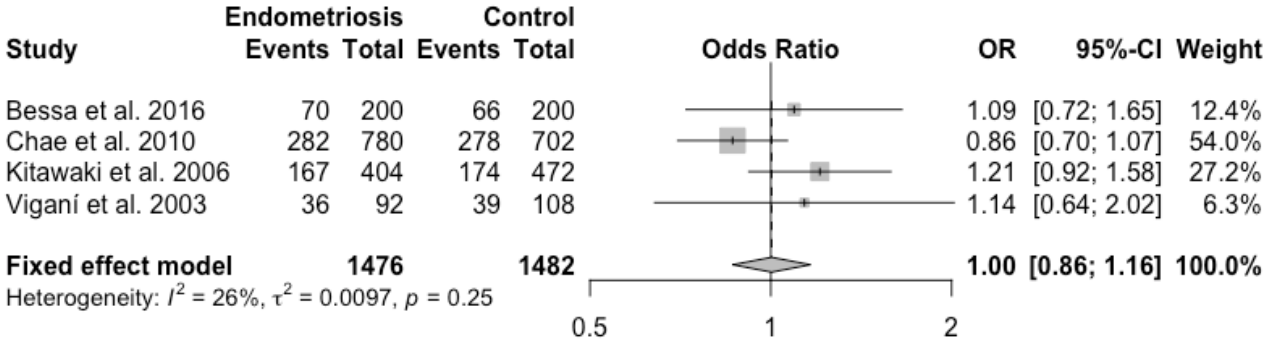


Figure 4: Forest plot for polymorphisms involved in Hormonal pathway.
(allelic model events = studied allele, total = allele number)
A) estrogen receptor 1 (ESR1) (rs2234693): C allele; B) progesterone receptor (PGR) (rs1042838; PROGINS): P2 allele, C) PGR (rs10895068): A allele, D) follicule stimulating hormone receptor (FSHR) (rs6166): G allele.

A



B

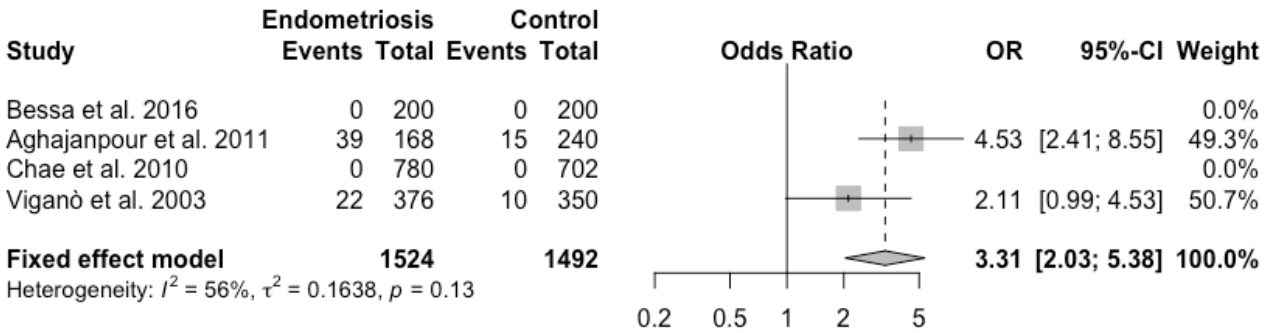


Figure 5 : Forest plot for intercellular adhesion molecule 1 (ICAM1) polymorphisms.

(allelic model events = studied allele, total = allele number)

A) rs5498 (K469E): G allele; B) rs1799969 (G241R): A allele

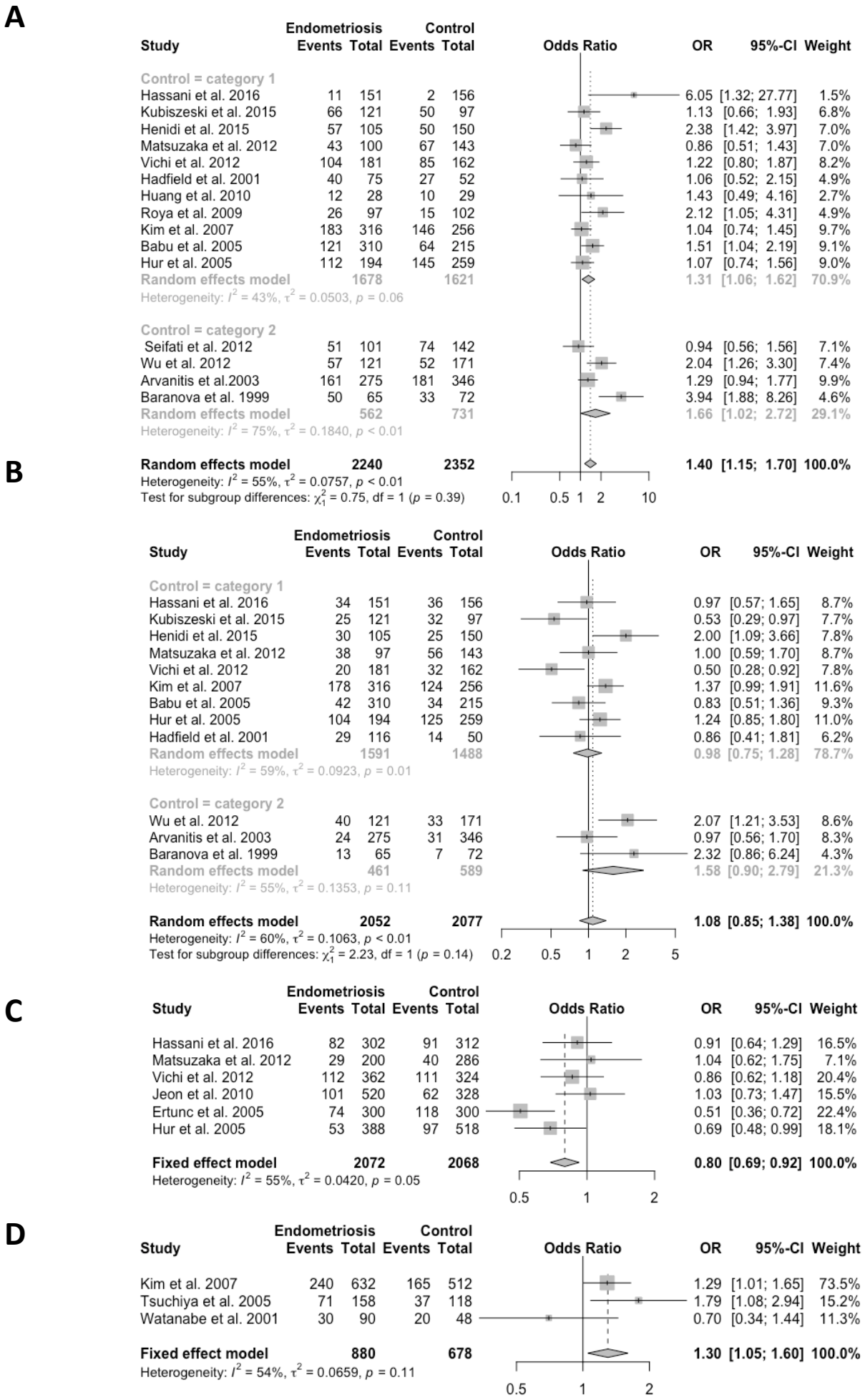


Figure 6: Forest plot for polymorphisms involved in detoxification process.

(allelic model events = studied allele, total = allele number)

A) glutathione S-transferase mu 1 (GSTM1) (null genotype): null; B) glutathione S-transferase theta 1 (GSTT1) (null genotype): null; C) glutathione S-transferase pi 1 (GSTP1) (rs1695): G allele; D) aryl-hydrocarbon receptor repressor (AHRR) (rs2292596): G allele.

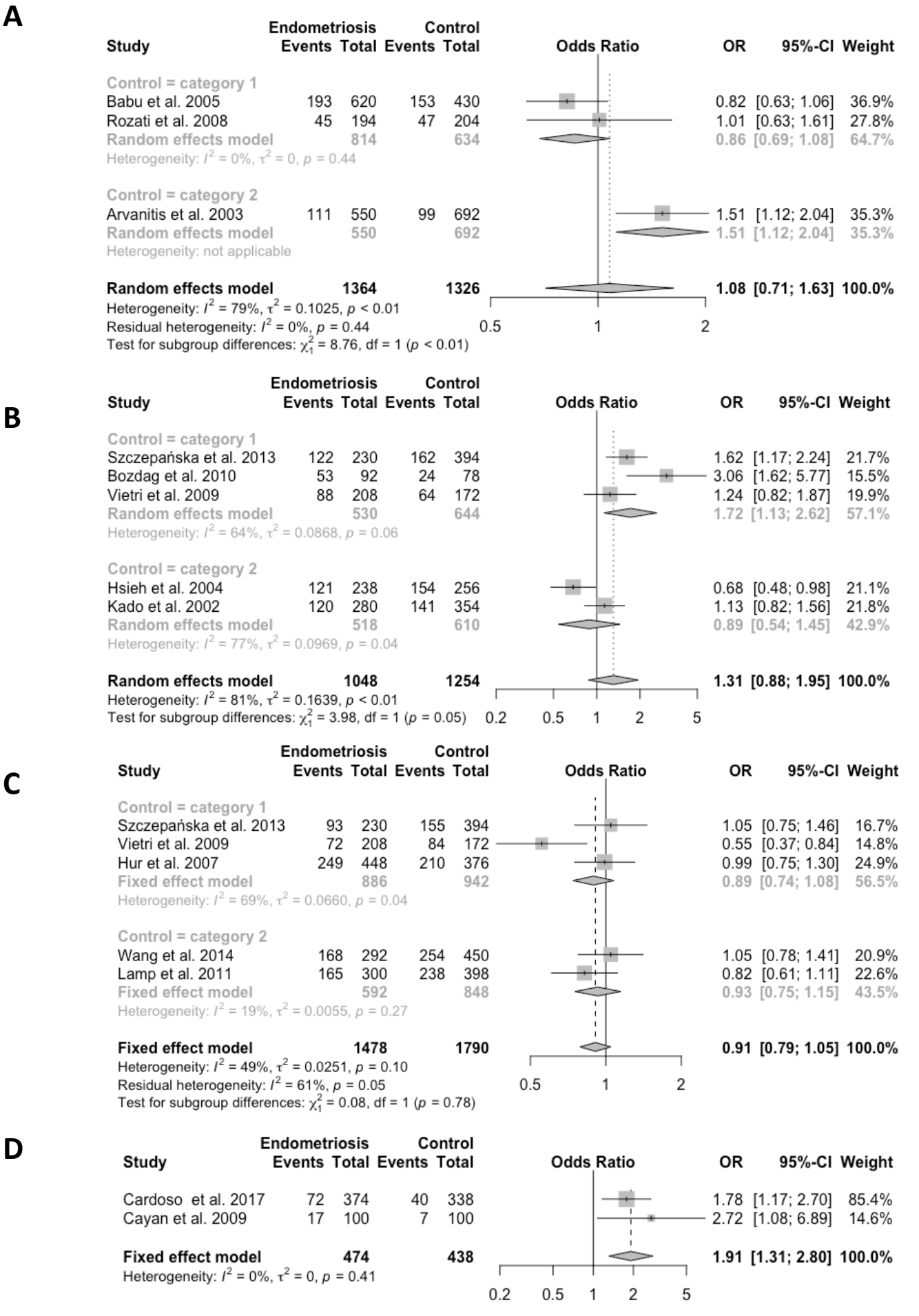
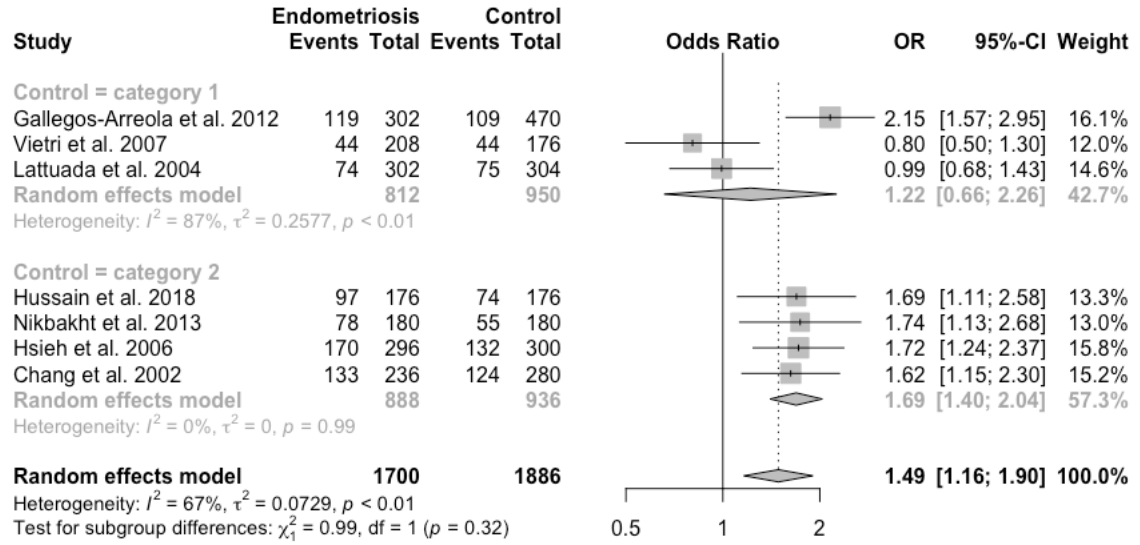


Figure 7: Forest plot for polymorphisms of cytochrome P450 family.
(allelic model events = studied allele, total = allele number)
A) cytochrome P450 family 1 subfamily A polypeptide 1 CYP1A1 (rs4646909): C allele; B) CYP17A1 (rs743572): C allele ; C) CYP19A1 (rs10046): T; D) CYP2C19 (rs4244285)

A



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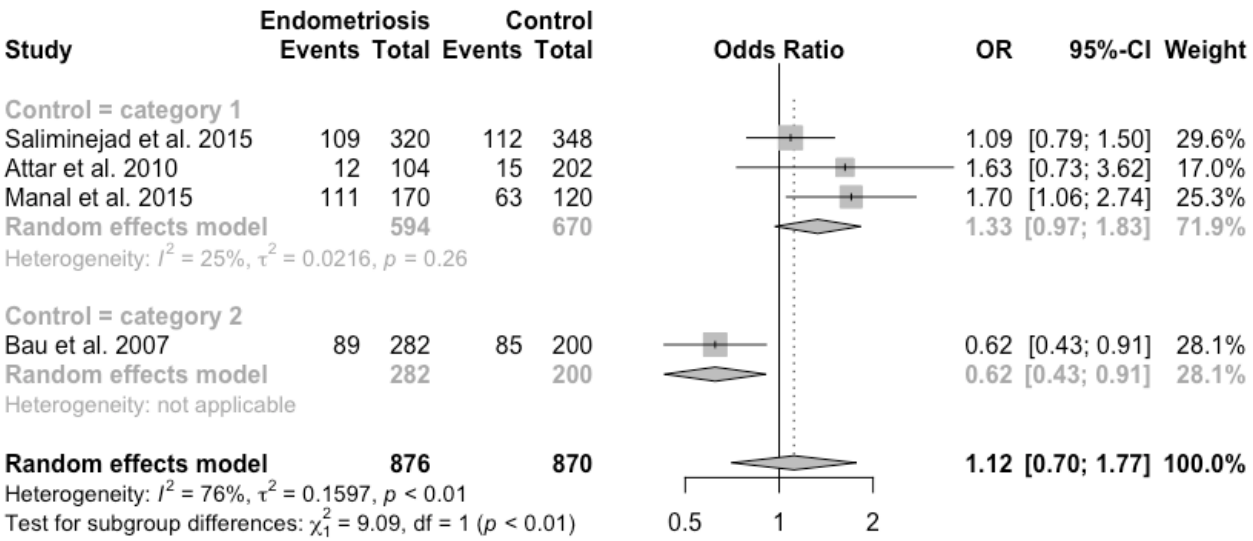
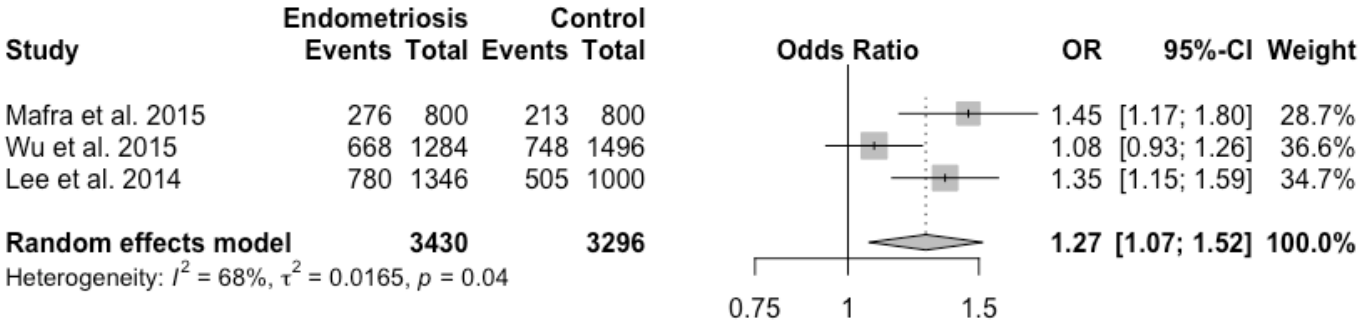


Figure 8: Forest plot for polymorphisms involved in genome regulation.

(allelic model events = studied allele, total = allele number)

A) tumor protein (TP53) (rs1042522): Pro; B) X-ray repair complementing defective repair in Chinese hamster cells 1 (XRCC1) (rs25487): A allele.

A



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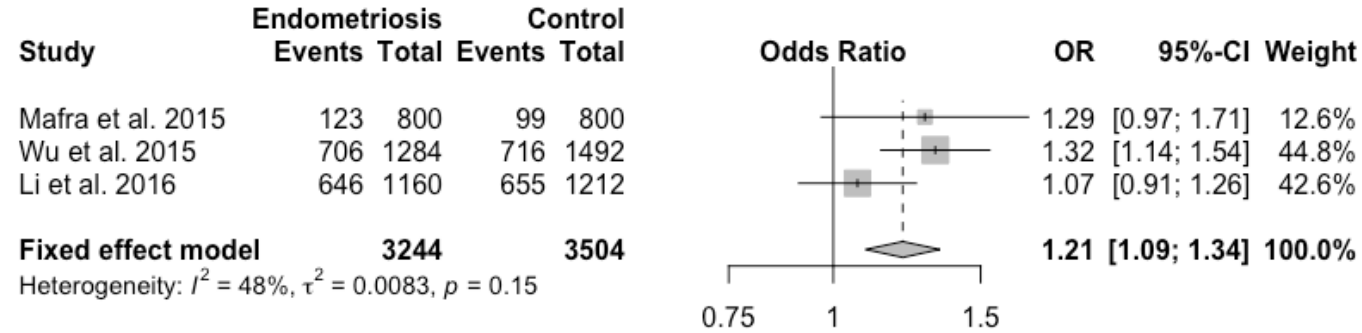
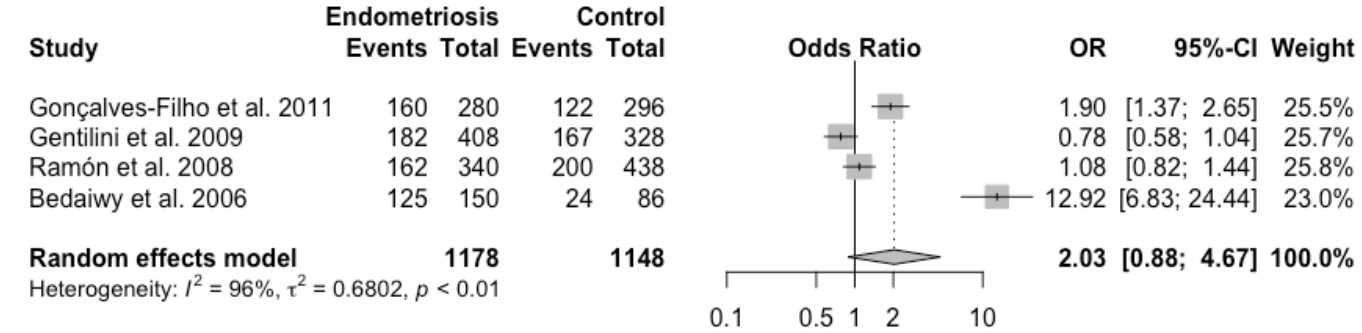


C



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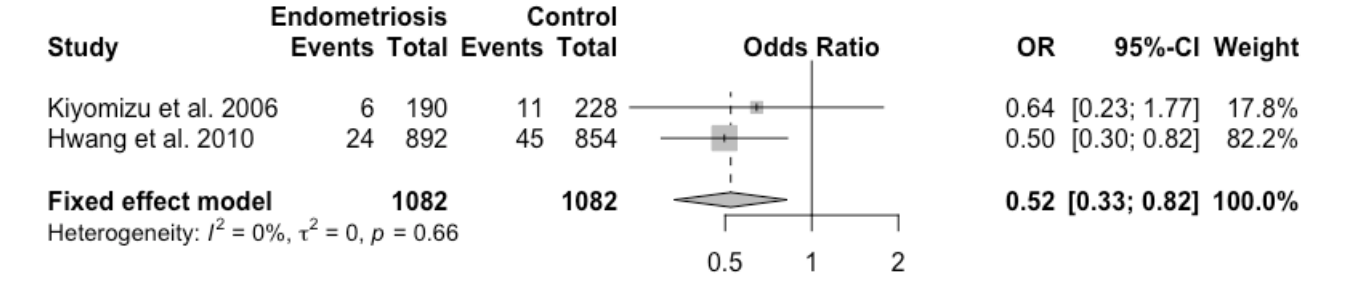

Figure 9 : Forest plot for WNT4, SERPINE1 and PPARG polymorphisms

(allelic model events = studied allele, total = allele number)

A) wingless-type MMTV integration site family member 4 (WNT4) (rs16826658): allele G; B) WNT4 (rs2235529): allele A; C) serpin peptidase inhibitor clade E member 1 (SERPINE1) (rs1799889): 4G allele, D) peroxisome proliferator-activated receptor gamma (PPARG) (rs1801282): allele G.

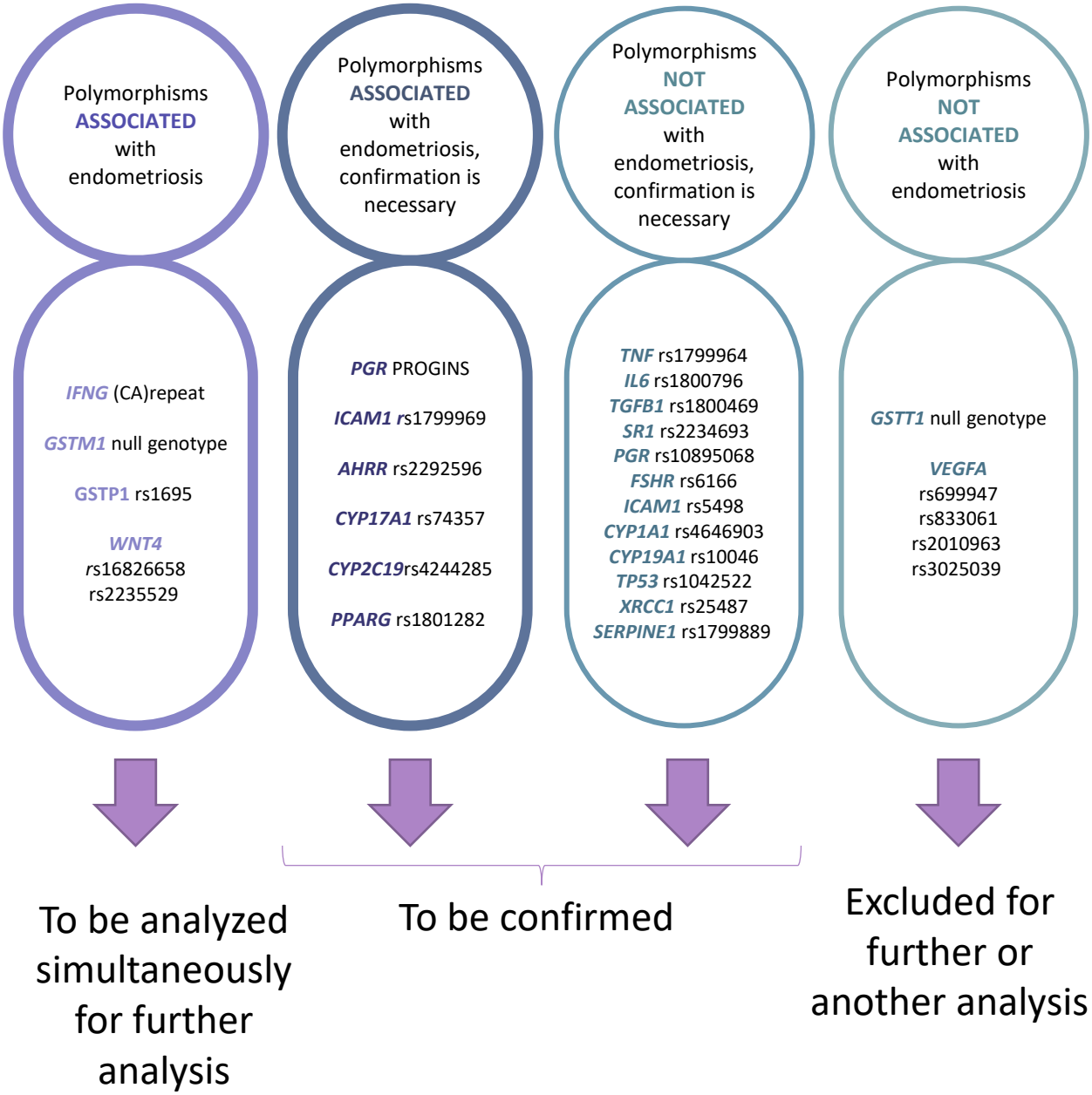

Figure 10: Final results

Table I The main results of the meta-analyses to investigate an association between gene polymorphisms and endometriosis.

Gene		Polymorphisms	Minor allele	Endometriosis stage (rASRM)	Studies							Number of patients		Model	heterogenity test	Fixed or random effects model		OR	CI	p.value	p.value (subgroup differences)	Association	Funnel plot asymmetry linear regression test		
						Excluded			Included																
Name	Symbol			All/I-II/III-IV	Total	CAT3	Lack of Raw data	Overlappped data	Total	CAT1	CAT2	Endometriosis	Control	allelic/genomic	p.value							yes/no	t	df	p.value
vascular endothelial growth factor alpha	*VEGFA*	rs699947 (-2578C>A)	A	All	6	1	0	1	4	3	1	1856	1586	allelic	< 0.001	random	CAT1+CAT2	1,07	[0.78; 1.46]	0,6827		no	0,49	2	0,67
																	CAT1	0,96	[0.69; 1.36]			no			
		rs833061 (-460T>C)	C	All	13	3	0	1	9	9	0	1813	2155	allelic	0,72	fixed		1,06	[0.96; 1.17]	0,2326		no	0,45	7	0,67
				I-II					5	5	0	595	1084	allelic	0,78	fixed		1,03	[0.88; 1.21]		0,78	no			
				III-IV					5	5	0	541	703	allelic	0,78	fixed		1	[0.83; 1.20]			no			
		rs2010963 (+405G>C)	C	All	17	4	0	1	12	12	0	3316	3360	allelic	< 0.0001	random		0,95	[0.69; 1.31]	0,7616		no	-1,35	10	0,21
				I-II					7	7	0	1315	2227	allelic	< 0.0001	random		0,94	[0.54; 1.66]		0,67	no			
				III-IV					7	7	0	1201	1846	allelic	< 0.0001	random		0,8	[0.53; 1.23]			no			
		rs3025039 (+936C>T)	T	All	11	2	1	1	7	6	1	2213	2190	allelic	0,0049	random	CAT1+CAT2	1,13	[0.89; 1.42]	0,3116		no	0,95	5	0,38
																	CAT1	1,16	[0.89; 1.52]			no			
tumor necrosis factor	*TNF*	rs1799964 (-1031T>C)	C	All	7	2	0	0	5	4	1	651	687	allelic	0,0004	random	CAT1+CAT2	1,23	[0.79; 1.92]	0,366		no	0,65	3	0,56
interleukin 6	*IL6*	rs1800796 (-634C>G)	G	All	3	0	0	0	3	3	0	692	687	allelic	0,7354	fixed		1,16	[0.96; 1.39]	0,1235		no	2,81	1	0,22
				I-II					2	2	0	79	336	allelic	0,925	fixed		1,13	[0.71; 1.79]		0,9	no			
				III-IV					3	3	0	613	687	allelic				1,17	[0.96; 1.41]			no			
transforming growth factor beta 1	*TGFB1*	rs1800469 (-509C >T)	T	All	4	0	0	0	4	3	1	834	709	allelic	< 0.0001	random	CAT1+CAT2	1,38	[0.72; 2.64]	0,336		no	0,52	2	0,65
																	CAT1	0,97	[0.82; 1.14]			no			
interferon gamma	*IFNG*	(CA)repeat	S	All	3	0	0	0	3	3	0	1109	1884	allelic	0,595	fixed		1,33	[1.17; 1.52]	< 0.0001		yes	1,67	1	0,34
				I-II					3	3	0	299	1884	allelic	0,1633	fixed		1,28	[1.05; 1.57]		0,61	yes			
				III-IV					3	3	0	810	1884	allelic				1,37	[1.18; 1.58]			yes			
estrogen receptor 1	*ESR1*	rs2234693 (PvuII)	C	All	11	8	0	0	3	3	0	387	326	allelic	0,0104	random		1,42	[0.85; 2.36]	0,1802		no	1,88	1	0,31
progesterone receptor	*PGR*	rs1042838 (PROGINS)	P2	All	10	4	0	1	5	4	1	546	586	allelic	0,0843	fixed	CAT1+CAT2	1,53	[1.17; 1.99]	0,0017		yes	0,36	3	0,74
																	CAT1	1,49	[1.13; 1.97]			yes			
		rs10895068	A	All	7	3	2	0	2	1	1	215	290	allelic	0,6237	fixed	CAT1+CAT2	0,7	[0.41; 1.18]	0,1792		no	NA	NA	NA
follicle stimulating hormone receptor	*FSHR*	rs6166	G	All	5	1	1	1	2	2	0	452	904	allelic	0,2648	fixed		1,18	[0.99; 1.41]	0,0608		no	NA	NA	NA
intercellular adhesion molecule 1	*ICAM1*	rs5498 (K469E)	G	All	5	1	0	0	4	4	0	738	741	allelic	0,2544	fixed		1	[0.86; 1.16]	0,9698		no	0,95	2	0,44
				I-II					2	2	0	79	336	allelic	0,2582	fixed		1,19	[0.84; 1.70]		0,32	no			
				III-IV					3	3	0	613	687	allelic				0,98	[0.83; 1.15]			no			
		rs1799969 (G241R)	A	All	5	1	0	0	4	4	0	762	746	allelic	0,131	fixed		3,31	[2.03; 5.38]	< 0.0001		yes	NA	NA	NA
glutathione S-transferase mu 1	*GSTM1*	Null genotype	absence	All	23	7	0	1	15	11	4	2240	2352	null genotype	0,0054	random	CAT1+CAT2	1,4	[1.15; 1.70]	0,0009		yes	1,93	13	0,08
																	CAT1	1,31	[1.06; 1.62]		0,39	yes			
																	CAT2	1,66	[1.02; 2.72]			yes			
				I-II					4	2	2	223	466	null genotype	0,0001	random	CAT1+CAT2	1,75	[0.90; 3.41]		0,99	no			
				III-IV					9	6	3	1161	1494	null genotype	0,0001	random	CAT1+CAT2	1,76	[1.18; 2.62]			yes			
glutathione S-transferase theta 1	*GSTT1*	Null genotype	absence	All	15	3	0	0	12	9	3	2052	2077	null genotype	0,0039	random	CAT1+CAT2	1,08	[0.85; 1.38]	0,5236		no	-0,54	10	0,6
																	CAT1	0,98	[0.75; 1.28]		<0.01	no			
																	CAT2	1,58	[0.90; 2.79]			no			
glutathione S-transferase pi 1	*GSTP1*	rs1695	G	All	8	1	1	0	6	6	0	1036	1034	allelic	0,0507	fixed		0,8	[0.69; 0.92]	0,0025		yes	0,49	4	0,65
aryl-hydrocarbon receptor repressor	*AHRR*	rs2292596 (Pro185Ala)	G	All	4	0	1	0	3	3	0	440	339	allelic	0,1116	fixed		1,3	[1.05; 1.6]	0,0153		yes	-0,32	1	0,8
cytochrome P450 family 1 subfamily A polypeptide 1	*CYP1A1*	rs4646903	C	All	9	4	2	0	3	2	1	682	663	allelic	0,0093	random	CAT1+CAT2	1,08	[0.71; 1.63]	0,7216		no	0,17	1	0,89
cytochrome P450 family 17 subfamily A polypeptide 1	*CYP17A1*	rs743572 (MspA1)	A2	All	14	6	1	2	5	3	2	524	527	allelic	0,0003	random	CAT1+CAT2	1,31	[0.88; 1.95]	0,1902		no	1,08	3	0,36
																	CAT1	1,72	[1.13; 2.62]			yes			
cytochrome P450 family 19 subfamily A polypeptide 1	*CYP19A1*	rs10046	T	All	8	1	2	0	5	3	2	739	895	allelic	0,0987	fixed	CAT1+CAT2	0,91	[0.79; 1.05]	0,1809		no	-2,13	3	0,12
																	CAT1	0,9	[0.73; 1.08]			no			
cytochrome P450 family 2 subfamily C polypeptide 19	*CYP2C19*	rs4244285		All	4	1	1	0	2	2	0	237	474	allelic	0,4116	fixed		1,91	[1.30; 2.80]	0,0008		yes	NA	NA	NA
tumor protein 53	*TP53*	rs1042522 (codon 72)	Pro	All	15	7	1	0	7	3	4	850	943	allelic	0,0063	random	CAT1+CAT2	1,49	[1.16; 1.90]	0,0016		yes	-1,64	5	0,16
																	CAT1	1,22	[0.66; 2.26]		0,32	no			
																	CAT2	1,69	[1.40; 2.04]			yes			
X-ray repair complementing defective repair in Chinese hamster cells 1	*XRCC1*	rs25487 (Arg399Gln)	A	All	6	2	0	0	4	3	1	438	435	allelic	0,006	random	CAT1+CAT2	1,12	[0.70; 1.77]	0,6424		no	0,77	2	0,52
																	CAT1	1,33	[0.97; 1.83]		<0.01	no			
																	CAT2	0,62	[0.43; 0.91]			yes			
wingless-type MMTV integration site family member 4	*WNT4*	rs16826658	G	All	3	0	0	0	3	3	0	1715	1648	allelic	0,0448	random		1,27	[1.07; 1.52]	0,0077		yes	1,43	1	0,39
		rs2235529	A	All	3	0	0	0	3	3	0	1622	1752	allelic	0,1478	fixed		1,21	[1.09; 1.34]	0,0003		yes	0,1	1	0,93
serpin peptidase inhibitor clade E member 1	*SERPINE1*	rs1799889 (4G/5G)	4G	All	4	0	0	0	4	4	0	589	574	allelic	< 0.0001	random		2,03	[0.88; 4.67]	0,096		no	3,99	2	0,06
peroxisome proliferator-activated receptor gamma	*PPARG*	rs1801282	G	All	3	0	1	0	2	2	0	541	541	allelic	0,6555	fixed		0,52	[0.33; 0.82]	0,0049		yes	NA	NA	NA