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## Polymorphisms and endometriosis: a systematic review and meta-analyses

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1 **Polymorphisms and endometriosis: a systematic review and meta-**  
2 **analyses**

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21 **Running title:** Endometriosis and polymorphisms: updated meta-analyses

22

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## 49 Abstract

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

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

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

67  
68 **OUTCOMES:** The initial selection of 395 publications cited 242 different genes. Sixty-two  
69 genes (corresponding to 265 different polymorphisms) were cited at least in three publications.  
70 After the application of our other selection criteria: an original case-control study of

71 endometriosis; a reported association between endometriosis and at least one polymorphism;  
72 data on women of reproductive age; and a diagnosis of endometriosis in the cases established by  
73 surgery and/or MRI and confirmed by histology, 28 polymorphisms were eligible for meta-  
74 analysis. Only five of the 28 polymorphisms were found to be significantly associated with  
75 endometriosis: interferon gamma (*IFNG*) (CA)repeat, glutathion S-transferase mu 1 (*GSTM1*)  
76 null genotype, glutathion S-transferase pi 1 (*GSTP1*) rs1695 and wingless-type MMTV  
77 integration site family member 4 (*WNT4*) rs16826658 and rs2235529. Six others showed a  
78 significant trend towards an association: progesterone receptor (*PGR*) PROGENS, interCellular  
79 adhesion molecule 1 (*ICAM1*) rs1799969, aryl-hydrocarbon receptor repressor (*AHRR*)  
80 rs2292596, cytochrome family 17 subfamily A polypeptide 1 (*CYP17A1*) rs743572, *CYP2C19*  
81 rs4244285 and peroxisome proliferator-activated receptor gamma (*PPARG*) rs1801282) and 12  
82 showed a significant trend towards the lack of an association: tumor necrosis factor (*TNF*)  
83 rs1799964, interleukin 6 (*IL6*) rs1800796, transforming growth factor beta 1 (*TGFB1*)  
84 rs1800469, estrogen receptor 1 (*ESR1*) rs2234693, *PGR* rs10895068, follicle stimulating  
85 hormone receptor (*FSHR*) rs6166, *ICAM1* rs5498, *CYP11A1* rs4646903, *CYP19A1* rs10046,  
86 tumor protein 53 (TP53) rs1042522, X-ray repair complementing defective repair in Chinese  
87 hamster cells 1 (*XRCC1*) rs25487 and serpin peptidase inhibitor clade E member 1 (*SERPINE1*)  
88 rs1799889); however, for the 18 polymorphisms identified in the latter two groups, further  
89 studies of the potential association with the endometriosis risk are needed. The remaining five of  
90 the 28 polymorphisms were not associated with endometriosis: glutathion S-transferase theta 1  
91 (*GSTT1*) null genotype, vascular endothelial growth factor alpha (*VEGFA*) rs699947, rs833061,  
92 rs2010963 and rs3025039).

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

100

101

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

103

# 104 Introduction

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

118 Even though endometriosis was first described in the early 20<sup>th</sup> century, its aetiology remains  
119 enigmatic. Several theories have been put forward but none fully explains the development of  
120 endometriosis in all the observed sites (Vercellini et al. 2014; Vinatier et al. 2001). The most  
121 widely accepted theory (proposed by Sampson) is based on retrograde menstruation, with the  
122 regurgitation of the endometrial cells in menstrual debris into the peritoneal cavity (Sampson  
123 1927).

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

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

130 The pelvic pain experienced during endometriosis is common in the general population; hence,  
131 the lack of endometriosis-specific symptoms and a first-line assay complicate and lengthen the  
132 diagnostic process in primary care. Indeed, the diagnostic delay (i.e. the time interval between  
133 symptom onset and diagnosis) is considerable: 8 years in the UK (Ballard, Lowton, and Wright  
134 2006), 10.5 years in Austria and Germany (Hudelist et al. 2012), and 7.4 years in The  
135 Netherlands, for example (Staal, van der Zanden, and Nap 2016). There are no reliable blood  
136 screening tests for endometriosis (Vinatier et al. 2001; May et al. 2010; Bedaiwy and Falcone  
137 2004; Nisenblat, Bossuyt, Shaikh, et al. 2016). Similarly, medical imaging procedures (such as  
138 MRI and ultrasound) do not offer satisfactory performance (Nisenblat, Bossuyt, Farquhar, et al.  
139 2016). Even when performed by an experienced physician, ultrasound has insufficient diagnostic  
140 value in the detection of non-ovarian endometriosis, with a false-negative rate of up to 40%  
141 (Guerriero et al. 2015). In another study, MRI was associated with a false-negative rate of 21%,  
142 and gave very heterogeneous results (Nisenblat, Bossuyt, Farquhar, et al. 2016). Hence, the non-  
143 invasive diagnosis of endometriosis is not yet possible. Laparoscopy with a biopsy and  
144 histological analysis of the lesion therefore remain the gold standard for diagnosis (Fassbender et  
145 al. 2015; Rogers et al. 2017). By comparing the incidence rate among women seeking clinical  
146 care with that in a population cohort, it has been demonstrated that about 11% of women have  
147 undiagnosed endometriosis (Buck Louis et al. 2011). Accordingly, there is an urgent need for  
148 new diagnostic tools that can be deployed at the population level.



149 Endometriosis is a complex, heterogeneous disease that involves multiple genetic and  
150 environmental factors (Soave et al. 2015; Saha et al. 2015). Heritable tendencies for  
151 endometriosis were suspected as early as the 1940s, and this hypothesis was confirmed in the  
152 1980s (Simpson and Bischoff 2002; Zondervan et al. 2018). The aggregation of endometriosis  
153 within families means that first-degree relatives of patients have a significantly greater risk of  
154 developing endometriosis (Matalliotakis et al. 2008; Stefansson et al. 2002). In twin studies, it  
155 has been estimated that about 50% of the risk of endometriosis is heritable (Saha et al. 2015;  
156 Treloar et al. 1999). Disease-causing genes can be identified in several ways, some of which  
157 require a candidate gene hypothesis (Bischoff and Simpson 2004). Over the last two decades,  
158 several research groups have investigated the association between endometriosis and  
159 polymorphisms (especially single-nucleotide polymorphisms [SNPs]) primarily in genes  
160 involved in inflammatory and detoxification processes, cell adhesion, and endocrine pathways  
161 (Falconer, D'Hooghe, and Fried 2007).

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

167

## 168 Methods

### 169 Search strategy

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

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

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

177 In order to examine the literature as efficiently and exhaustively as possible, we used the  
178 PubTator text mining tool (Wei, Kao, and Lu 2012) in R (R Core Team 2018) to extract gene  
179 names (Wei et al. 2012). The “pubtator\_function” in the R package “pubmed.mineR” (Shah  
180 2014) extracts specific information from abstracts (*i.e.*, gene names or symbols, in our case).

181

### 182 Study selection

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

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

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

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

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

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

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

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

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

218

## 219 Data extraction

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

227

## 228 Statistical analyses

229 After study selection, we performed a meta-analysis for each polymorphism with at least three  
230 CAT1 “gold standard” studies. For each meta-analysis, all results from CAT1 and CAT2 studies  
231 were included. All statistical analyses were performed using the *meta* (Schwarzer 2007) and  
232 *rmeta* (Lumley 2018) packages in R (version 3.5.1, (R Core Team 2018)). The magnitude of the  
233 association between endometriosis and the polymorphism of interest (for allelic models) was  
234 estimated as the odds ratio (OR) [95% CI]. Meta-analysis was performed by pooling OR  
235 [95%CI] values from the included studies in a fixed-effect or random-effect model. The choice  
236 of the model depended on the result of the between-study heterogeneity test. Thus, a fixed-effect  
237 (Mantel-Haenszel) model was used except when Cochran's Q test was significant (p-value <0.05)  
238 and thus indicated the existence of inter-study heterogeneity: in the latter case, we used a  
239 random-effect (DerSimonian-Laird) model (DerSimonian and Laird 2015).

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

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

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

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

251 minimum number of three studies and without taking account of the study category (Egger et al.  
252 1997).

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

256 The study results were reported in accordance with to the PRISMA statement (Moher et al.  
257 2009). Our study was not eligible for inclusion in the PROSPERO International Prospective  
258 Register of Systematic Reviews because we had already fully extracted the data at the time of  
259 registration; the register is intended to capture this information at the design stage.

## 260 Results

### 261 Search strategy and data selection

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

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

### 270 Meta-analysis results

271 The number of studies included per polymorphism, the numbers of patients and controls, the  
272 model used, the level of heterogeneity, the use of a fixed- or random-effect model, and the OR  
273 [95%CI] are listed in Table I.

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

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

281

282 **Genes and phenotypes:**

283 Mouse/Rat/Chicken genes

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

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

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

290

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

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

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

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

298 The *VEGFA* gene

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



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

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

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

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

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

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

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

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

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

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

326 Seven studies were considered: six CAT1 studies (Cosin et al. 2009; Henidi, Kaabachi, Naouali,  
327 et al. 2015; Liu et al. 2009; Perini et al. 2014; Szczepanska et al. 2015; Vodolazkaia et al. 2016)  
328 and one CAT2 study (Lamp et al. 2010). No associations were observed (OR 1.13; 95% CI 0.89  
329 –1.42) using a random-effect model, and no publication bias was found ( $t = 0.95$ ;  $p = 0.38$ ).

330

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

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

338

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

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

344 Stratification by ASRM stage did not reveal a difference ( $p = 0.90$ ) between the two subgroups,  
345 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:  $\leq 13$  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

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

370

371 *PGR* gene

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

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

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

381 When considering the P2 allele to be the risk allele, we observed an association (OR 1.53; 95%  
382 CI 1.17 – 1.99) using a fixed-effect model, and no publication bias was observed ( $t = 0.36$ ;  $p =$   
383 0.74).

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

385 Of the three CAT1selected studies (van Kaam, Romano, Schouten, et al. 2007; Gentilini,  
386 Vigano, et al. 2008; Cardoso, Machado, et al. 2017), two lacked primary data (Cardoso,  
387 Machado, et al. 2017; Gentilini, Vigano, et al. 2008). However, one CAT2 study was also  
388 considered (Lamp et al. 2011) and meta-analyse was performed on these two studies (Lamp et al.  
389 2011; van Kaam, Romano, Schouten, et al. 2007).

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

393

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

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

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

400

401 *ICAM1* gene

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

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

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

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

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

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

411 Four CAT1 studies (Aghajanzpour, Mashayekhi, and Rajaei 2011; Bessa et al. 2016; Chae et al.  
412 2010; Vigano et al. 2003) were included for this variant.

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

416

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

418 Of the 28 studies dealing with the glutathione S-transferase mu 1 (*GSTM1*) null genotype, 15  
419 studies were included: 11 CAT1 studies (Babu et al. 2005; Hadfield et al. 2001; Hassani et al.  
420 2016; Henidi, Kaabachi, Mbarik, et al. 2015; Huang et al. 2010; Hur et al. 2005; Kim et al. 2007;  
421 Kubiszeski et al. 2015; Matsuzaka, Kikuti, Goya, et al. 2012; Roya, Baludu, and Reddy 2009;  
422 Vichi et al. 2012) and four CAT2 studies (Arvanitis et al. 2003; Baranova et al. 1999; Seifati et  
423 al. 2012; Wu et al. 2012).

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

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

431

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

433 Of the 20 studies dealing with the glutathione S-transferase theta 1 (*GSTT1*) null genotype, nine  
434 CAT1 studies were considered (Babu et al. 2005; Hadfield et al. 2001; Hassani et al. 2016;  
435 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,



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

482 Thus, based on these five remaining studies, no association was identified (OR 0.91; 95% CI  
483 0.79 – 1.05) using a fixed-effect model and no publication bias was observed ( $t = -2.13$ ;  $p =$   
484 0.12).

485

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

487 Of the three selected CAT1 studies for cytochrome P450 family 2 subfamily C polypeptide 19  
488 (*CYP2C19*) rs4244285 (Cardoso, Abrao, Berardo, et al. 2017; Bozdog et al. 2010; Cayan et al.  
489 2009), one lacked a full set of data (Bozdog et al. 2010).

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

493

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

495 Considering the 26 six studies dealing with tumor protein p53 (*TP53*) variants and the  
496 endometriosis risk, only one variant (rs1042522) was examined in nine independent studies.

497 Three CAT1 studies (Gallegos-Arreola, Figuera-Villanueva, et al. 2012; Lattuada, Vigano, et al.  
498 2004; Vietri et al. 2007) and four CAT2 studies (Chang et al. 2002; Hsieh and Lin 2006; Hussain  
499 et al. 2018; Nikbakht Dastjerdi, Aboutorabi, and Eslami Farsani 2013) were considered for meta-  
500 analysis.

501 An association was identified when considering CAT2 studies only (OR 1.69; 95% CI: 1.40 –  
502 2.04) or all studies (OR 1.49; 95% CI: 1.16 – 1.90) using the random-effect model, but not when

503 considering CAT1 studies only (OR 1.22; 95% CI: 0.66 – 2.26). There was no difference  
504 between CAT1 and CAT2 studies ( $p = 0.32$ ). Furthermore, no publication bias was detected ( $t =$   
505  $-1.64$ ;  $p = 0.16$ ).

506

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

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

512 No associations were identified (OR 1.12; 95% CI 0.70 – 1.77) using the random-effect model,  
513 although the result was insignificant when considering CAT1 studies only (OR 1.33; 95% CI  
514 0.97–1.83). No potential publication bias ( $t = 0.77$ ;  $p = 0.52$ ) was identified.

515

516 *WNT4* gene

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

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

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

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

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

527

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

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

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

534

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

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

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

542

## 543 Discussion

544 The objectives of the present study were to provide an exhaustive review of polymorphisms  
545 studied in endometriosis, and perform a meta-analysis for those most regularly reported.  
546 Ultimately, meta-analysis was performed for 28 polymorphisms (in 22 genes); 10 of these  
547 polymorphisms (in nine genes) were found to be significantly associated with endometriosis.  
548 Therefore the study allowed us to identify polymorphisms that could potentially be included in  
549 an endometriosis screening test and we propose a panel of SNPs that could predispose to  
550 endometriosis: *IFNG* (CA)repeat, *GSTMI* null genotype, *GSTP1* rs1695, *WNT4* rs16826658  
551 and *WNT4* rs2235529.

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

564

565 Furthermore, we paid particular attention to the studies' inclusion and exclusion criteria for the  
566 control population; we considered that eligible studies should comply with international  
567 guidelines in general and the benchmark ASRM guidelines in particular. In the absence of  
568 surgery, endometriosis cannot be ruled out; this considerably complicates the selection of the  
569 control population, and constitutes a critical point in many studies. The ideal controls are pain-  
570 free, fertile women in whom the absence of endometriosis has been confirmed by laparoscopy –  
571 although few women fit this profile (Greaves et al. 2017). Next, in line with the guidelines, we  
572 defined three study categories. In CAT1 studies, the control patients were known to be free of  
573 endometriosis, following laparoscopy or other surgical procedures. In CAT2 studies, the controls  
574 were apparently free of endometriosis; they included fertile women and/or women having  
575 undergone Caesarean section (given that endometriosis is a major cause of infertility). Lastly,  
576 controls in CAT3 studies were recruited from the general population; this would necessarily have  
577 included some women with endometriosis, infertile, neonates and men. As our goal was to  
578 identify patients with endometriosis, we considered that only CAT1 studies could reliably probe  
579 a potential association between a polymorphism and the occurrence of endometriosis. Although  
580 CAT2 studies sometimes strengthened the association, they were only considered when the  
581 meta-analysis included three or more CAT1 studies. Of the 10 meta-analyses in which both  
582 CAT1 and CAT2 studies had been included, we found conflicting results for two polymorphisms  
583 (20%): *CYP17A1* rs743572 and *TP53* rs1042522. In the first case, the inclusion of CAT2 studies  
584 meant that *CYP17A1* rs743572 was no longer significantly associated with endometriosis. The  
585 opposite was true in the second case, where the inclusion of CAT2 studies meant that *TP53*  
586 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*

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

634 *PPARG* rs1801282 could have a protective effect for endometriosis (OR 0.52; 95% CI 0.33–  
635 0.82) but this association needs to be confirmed in studies involving more women since only two  
636 studies were include in present analysis.

637

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

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

649 In contrast, no association could be identified for *TNF* rs1799964 (OR 1.01, 95% CI 0.70–1.46),  
650 *IL6* rs1800796 (OR 1.17; 95% CI 0.96–1.41) or *TGFBI* rs1800469 (OR 0.97; 95% CI: 0.82–  
651 1.14). TNF is a pro-inflammatory cytokine involved in inflammation processes. It reportedly  
652 stimulates the proliferation of ectopic endometrial cells (Hornung and von Wussow 2011). Two  
653 meta-analyses (Li et al. 2014; Lyu et al. 2014) have been published but gave contradictory  
654 results: the first (Li et al. 2014) suggested that the presence of the *TNF* rs1799964 polymorphism



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

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

670

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

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

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

684 Many *ESRI* polymorphisms have been assessed studied for their potential link with  
685 endometriosis. However, only rs2234693 was included in a meta-analysis here. Our results were  
686 in line with three previous meta-analyses by Chinese groups (Zhao et al. 2016; Li et al. 2012; Hu  
687 et al. 2012), which included large numbers of studies with less restrictive inclusion criteria (23,  
688 20 and eight studies, respectively, compared with three CAT1 studies here). We did not find an  
689 association between *ESRI* rs2234693 and endometriosis.

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

695

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

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

702 In our text mining procedure, *GSTM1* was the most frequently cited gene (Supplementary Tables  
703 SIV); we included 11 CAT1 and four CAT2 studies in our meta-analysis (Supplementary Fig.  
704 13A). Our results suggest that the *GSTM1* null genotype is associated with a risk of  
705 endometriosis (OR 1.40; 95% IC 1.15–1.70), independent of the selection criteria for controls  
706 (i.e. CAT1 and/or CAT2 studies) (Fig. 6A). The association was significant for advanced-stage  
707 endometriosis (ASRM stage III/IV) but not for ASRM stage I/II (Supplementary Fig. 13C).  
708 Previous meta-analyses (Chen, Xu, et al. 2015; Ding et al. 2014; Guo 2005; Li and Zhang 2015;  
709 Xin et al. 2016; Zhu et al. 2014) also reached the same conclusions (i.e. the *GSTM1* null  
710 genotype is associated with an endometriosis risk), although we did not include precisely the  
711 same studies in our meta-analysis because only some were CAT3 studies (Arvanitis et al. 2001;  
712 Baxter, Thomas, and Campbell 2001; Frare et al. 2013; Hosseinzadeh, Mashayekhi, and Sorouri  
713 2011; Hsieh, Chang, Tsai, Lin, Chen, et al. 2004; Trabert et al. 2011). In light of these results,  
714 the *GSTM1* null genotype is a potentially valuable genetic marker for endometriosis risk.

715 We also found that *AHRR* rs2292596 is associated with endometriosis (OR 1.30; 95% CI 1.05–  
716 1.60) (Fig. 6E). The *AHRR* mediates dioxin toxicity, cell growth, cell differentiation, and the  
717 induction of drug-metabolizing enzymes. It functions as a feedback modulator by repressing aryl  
718 hydrocarbon-dependent gene expression (*CYP1A1*, *SERPINB2*, etc.). The *AHRR* pathway is  
719 also linked to peroxisome proliferator-activated receptor alpha. Although similar results were  
720 obtained in an earlier meta-analysis (Zheng et al. 2015), the small sample size means that these  
721 results must be interpreted with caution (Table I); further investigations are required.

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

726 The *CYP2C19* rs4244285 polymorphism seems to be associated with endometriosis risk (OR  
727 1.91; 95% CI 1.30–2.80), but due to the low number of patients per group confirmation is  
728 needed. Furthermore, a GWAS was identified by our text mining approach but not included in  
729 the meta-analyses due to the control population selection (CAT 3) (Painter et al. 2014).

730 By combining CAT1 and CAT2 studies, none of the remaining polymorphisms in detoxification-  
731 related genes was found to be associated with endometriosis with the exception of *CYP17A1*  
732 rs743572 when considering only CAT1 studies (OR 1.72; 95% CI 1.13–2.62). Earlier meta-  
733 analyses (Hu et al. 2012; Chen, Pang, et al. 2015) of potential links between *CYP17A1* rs743572  
734 and endometriosis included more studies than we did because they used less stringent inclusion  
735 criteria (*i.e.*, CAT3 studies) (Asghar et al. 2005; De Carvalho et al. 2007; Juo et al. 2006; Zhao,  
736 Nyholt, Le, et al. 2008) or because they included articles not written in English (Zhao et al.  
737 2011). None of meta-analyses found a statistically significant relationship between the *CYP17*  
738 rs743572 polymorphism and endometriosis. The results of our CAT1 meta-analysis contrast with  
739 the previous reports, which emphasizes the influence of control selection on the results (Fig. 6D)  
740 and perhaps the value of considering strictly defined CAT1 studies only. As seen above for  
741 *AHRR* rs2292596, studies of larger numbers of patients are required. No association with  
742 endometriosis was identified here for *CYP1A1* rs4646903 and *CYP19A1* rs10046.

743

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 *ICAMI* 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 *ICAMI* rs5498 and endometriosis risk (Fig. 5A). Although an association was found for *ICAMI*  
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 *ICAMI* 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 *ICAMI* 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

790 CAT1 studies included in our meta-analysis assessed Caucasian women (Lattuada, Vigano, et al.  
791 2004; Vietri et al. 2007). Further analysis (with stratification by ethnic group) is required to  
792 explore the underlying link between endometriosis and the *TP53* rs1042522 polymorphism.

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

805  
806 Angiogenesis is also significantly involved in endometriosis in general and vascularization of  
807 ectopic endometrium in particular (Groothuis 2011). *VEGFA* is a key gene in angiogenesis,  
808 which explains why many studies have sought to characterize associations between  
809 endometriosis and *VEGFA* polymorphisms. Five polymorphisms have been studied, and we  
810 performed a meta-analysis on four of these. None was significantly associated with  
811 endometriosis. For rs833061 (Li et al. 2013; Liang, Huang, and Fan 2012; Xu et al. 2012; Zhao,  
812 Nyholt, Thomas, et al. 2008) and rs2010963 (Fang et al. 2015; Li et al. 2013; Liang, Huang, and

813 Fan 2012; Xu et al. 2012; Zhao, Nyholt, Thomas, et al. 2008), our results were similar to those of  
814 earlier meta-analyses. Regarding *VEGFA* rs699947, our results were in line with two previous  
815 meta-analyses, (Liang, Huang, and Fan 2012; Zhao, Nyholt, Thomas, et al. 2008), whereas a  
816 third study concluded that the risk was decreased (Li et al. 2013). Only two published studies  
817 were in line with the results from our meta-analysis (Lamp et al. 2010; Liu et al. 2009) (the  
818 remaining two studies did not meet our inclusion criteria), confirming absence of an association  
819 between this polymorphism and endometriosis. The results for *VEGFA* rs3025039 were  
820 contradictory. Of the four previous meta-analyses (Li et al. 2013; Liang, Huang, and Fan 2012;  
821 Xu et al. 2012; Zhao, Nyholt, Thomas, et al. 2008), three found an association (Li et al. 2013;  
822 Liang, Huang, and Fan 2012; Xu et al. 2012). However, our meta-analysis included four articles  
823 published after the other meta-analyses (Henidi, Kaabachi, Naouali, et al. 2015; Perini et al.  
824 2014; Szczepanska et al. 2015; Vodolazkaia et al. 2016) and excluded three studies (Ikuhashi et  
825 al. 2007; Kim et al. 2008; Zhao, Nyholt, Thomas, et al. 2008). We cannot rule out an association  
826 with specific endometriosis stages because we were unable to stratify by ASRM stage. However,  
827 we consider that further studies of larger samples would probably confirm our present results.  
828 For the fifth *VEGFA* variant (rs1570360, -1154G>A, not included in our meta-analyses), only  
829 two *CAT1* studies were found. Previous meta-analyses did not find an association with  
830 endometriosis (Li et al. 2013; Liang, Huang, and Fan 2012). In summary, none of the *VEGFA*  
831 polymorphisms was associated with endometriosis in the present study; a quite surprising result  
832 considering the large number of studies performed.

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



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

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

848  
849 Finally, our results enabled us to classify polymorphisms into four categories: polymorphisms  
850 associated with endometriosis (n=5) which probably do not require confirmation in a larger  
851 number of studies (*IFNG* (CA)repeat, *GSTM1* null genotype, *GSTP1* rs1695 and *WNT4*  
852 rs16826658 and rs2235529); polymorphisms associated with endometriosis but for which  
853 confirmation is necessary (n=6) (*PGR* PROGINS, *ICAM1* rs1799969, *AHRR* rs2292596,  
854 *CYP17A1* rs743572, *CYP2C19* rs4244285 and *PPARG* rs1801282); polymorphisms not  
855 associated with endometriosis but for which confirmation is necessary (n=12) (*TNF* rs1799964,  
856 *IL6* rs1800796, *TGFBI* rs1800469, *ESR1* rs2234693, *PGR* rs10895068, *FSHR* rs6166, *ICAM1*  
857 rs5498, *CYP1A1* rs4646903, *CYP19A1* rs10046, *TP53* rs1042522, *XRCC1* rs25487 and  
858 *SERPINE1* rs1799889); and polymorphism that definitively do not have an association with

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

864

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

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

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

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

892

## 893 Conclusion

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

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

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

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

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

911 This work constitutes the first step towards identifying potential markers for a genetic screening  
912 test for endometriosis. By combining a patient survey (Fauconnier et al. 2018), a genetic screen  
913 with endometrial or serum biomarkers and an analysis of the family medical history, it may be  
914 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.

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917

## 918 **Authors' roles**

919 Study design: LM, CP, AF and FV

920 Search strategy: LM, CP and FV

921 Study selection: LM and FV

922 Data selection: LM, MH, FV

923 Statistical analysis: LM and MH

924 Manuscript drafting: LM, CP and FV

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

926

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929

## 930 **Conflict of interest**

931 None declared

932

## 933 Figure legends

934 **Figure 1** Selection of polymorphisms for meta-analysis.

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

937

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

940 A) rs699947 (-2578C>A): A allele; B) rs833061 (-460T>C): C allele; C) rs2010963  
941 (+405G>C): C allele; D) rs3025039 (+936C>T): T allele.

942

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

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

948

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

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

954

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

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

958

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

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

964

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

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

969

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

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

974

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



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

981

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

984

985 **Supplementary Figure S1** vascular endothelial growth factor alpha (*VEGFA*) rs699947 (-  
986 2578C>A) polymorphism flow chart and publication bias analysis.

987 A) PRISMA flow chart; B) funnel plot.

988

989 **Supplementary Figure S2** vascular endothelial growth factor alpha (*VEGFA*) rs833061 (-  
990 460T>C) polymorphism flow chart, publication bias analysis and meta-analysis after ASRM  
991 stratification.

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

993

994 **Supplementary Figure S3** vascular endothelial growth factor alpha (*VEGFA*) rs2010963  
995 (+405G>C) polymorphism flow chart, publication bias analysis and meta-analysis after ASRM  
996 stratification.

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

998

999 **Supplementary Figure S4:** vascular endothelial growth factor alpha (*VEGFA*) rs3025039  
1000 (+936C>T) polymorphism flow chart and publication bias analysis.  
1001 A) PRISMA flow chart; B) funnel plot.  
1002  
1003 **Supplementary Figure S5:** tumor necrosis factor (*TNF*) rs1799964 (-1031T/C) polymorphism  
1004 flow chart and publication bias analysis.  
1005 A) PRISMA flow chart; B) funnel plot  
1006  
1007 **Supplementary Figure S6:** interleukin – (*IL6*) rs1800796 (-634C>G) polymorphism flow chart,  
1008 publication bias analysis and meta-analysis after ASRM stratification.  
1009 A) PRISMA flow chart; B) funnel plot, C) forest plot, with stratification by disease stage.  
1010  
1011 **Supplementary Figure S7:** transforming growth factor beta 1 (*TGFB1*) rs1799969 (-509C / T)  
1012 polymorphism flow chart and publication bias analysis.  
1013 A) PRISMA flow chart; B) funnel plot  
1014  
1015 **Supplementary Figure S8:** interferon gamma (*IFNG*) (CA) repeat polymorphism flow chart,  
1016 publication bias analysis and meta-analysis after ASRM stratification.  
1017 A) PRISMA flow chart; B) funnel plot; C) forest plot, with stratification by disease stage.  
1018  
1019 **Supplementary Figure S9:** estrogen receptor 1 (*ESR1*) rs2234693 (PvuII) polymorphism flow  
1020 chart and publication bias analysis.  
1021 A) PRISMA flow chart; B) funnel plot

1022

1023 **Supplementary Figure S10:** progesterone receptor (*PGR*) rs1042838 (PROGINS)

1024 polymorphism flow chart and publication bias analysis.

1025 A) PRISMA flow chart; B) funnel plot

1026

1027 **Supplementary Figure S11:** progesterone receptor (*PGR*) rs 10895068 (+331G>A)

1028 polymorphism flow chart and publication bias analysis.

1029 A) PRISMA flow chart; B) funnel plot

1030

1031 **Supplementary Figure S12:** follicle stimulating hormone receptor (*FSHR*) rs6166 Asn680Ser)

1032 polymorphism flow chart and publication bias analysis.

1033 A) PRISMA flow chart; B) funnel plot

1034

1035 **Supplementary Figure S13:** intercellular adhesion molecule 1 (*ICAM1*) rs5498 (K469E)

1036 polymorphism flow chart, publication bias analysis and meta-analysis after ASRM stratification.

1037 A) PRISMA flow chart; B) funnel plot; C) forest plot, with stratification by disease stage.

1038

1039 **Supplementary Figure S14:** intercellular adhesion molecule 1 (*ICAM1*) rs1799969 (G241R)

1040 polymorphism flow chart and publication bias analysis.

1041 A) PRISMA flow chart; B) funnel plot

1042

1043 **Supplementary Figure S15:** glutathione S-transferase mu 1 (*GSTM1*) null genotype

1044 polymorphism flow chart, publication bias analysis and meta-analysis after ASRM stratification.

1045 A) PRISMA flow chart; B) funnel plot; C) forest plot, with stratification by disease stage.

1046

1047 **Supplementary Figure S16:** glutathione S-transferase theta 1 (*GSTT1*) null genotype  
1048 polymorphism flow chart and publication bias analysis.

1049 A) PRISMA flow chart; B) funnel plot

1050

1051 **Supplementary Figure S17:** glutathione S-transferase pi 1 (*GSTP1*) rs1695 polymorphism flow  
1052 chart and publication bias analysis.

1053 A) PRISMA flow chart; B) funnel plot

1054

1055 **Supplementary Figure S18:** aryl-hydrocarbon receptor repressor (*AHRR*) rs1799969  
1056 (Pro185Ala) polymorphism flow chart and publication bias analysis.

1057 A) PRISMA flow chart; B) funnel plot

1058

1059 **Supplementary Figure S19:** cytochrome P450 family 1 subfamily A polypeptide 1 (*CYP1A1*)  
1060 rs4646909 (Msp1) polymorphism flow chart and publication bias analysis.

1061 A) PRISMA flow chart; B) funnel plot

1062

1063 **Supplementary Figure S20:** cytochrome P450 family 17 subfamily A polypeptide 1 (*CYP17A1*)  
1064 rs743572 (-34A/G) polymorphism flow chart and publication bias analysis.

1065 A) PRISMA flow chart; B) funnel plot

1066

1067 **Supplementary Figure S21:** cytochrome P450 family 19 subfamily A polypeptide 1 (*CYP19A1*)  
1068 rs10046 (1531C>T) polymorphism flow chart and publication bias analysis.  
1069 A) PRISMA flow chart; B) funnel plot  
1070  
1071 **Supplementary Figure S22:** cytochrome P450 family 2 subfamily C polypeptide 19 (*CYP2C19*)  
1072 rs4244285 polymorphism flow chart and publication bias analysis.  
1073 A) PRISMA flow chart; B) funnel plot  
1074  
1075 **Supplementary Figure S23:** tumor protein 53 (*TP53*) rs1042522 (codon 72) polymorphism  
1076 flow chart and publication bias analysis.  
1077 A) PRISMA flow chart; B) funnel plot  
1078  
1079 **Supplementary Figure S24:** X-ray repair complementing defective repair in Chinese hamster  
1080 cells 1 (*XRCC1*) rs25487 (Arg399Gln) polymorphism flow chart and publication bias analysis.  
1081 A) PRISMA flow chart; B) funnel plot  
1082  
1083 **Supplementary Figure S25:** wingless-type MMTV integration site family member 4 (*WNT4*)  
1084 rs16826658 polymorphism flow chart and publication bias analysis.  
1085 A) PRISMA flow chart; B) funnel plot  
1086  
1087 **Supplementary Figure S26:** wingless-type MMTV integration site family member 4 (*WNT4*)  
1088 rs2235529 polymorphism flow chart and publication bias analysis.  
1089 A) PRISMA flow chart; B) funnel plot

1090

1091 **Supplementary Figure S27:** serpin peptidase inhibitor clade E member 1 (*SERPINE1*)

1092 rs1799889 polymorphism flow chart and publication bias analysis.

1093 A) PRISMA flow chart; B) funnel plot

1094

1095 **Supplementary Figure S28:** peroxisome proliferator-activated receptor gamma (*PPARG*)

1096 rs1801282 polymorphism flow chart and publication bias analysis.

1097 A) PRISMA flow chart; B) funnel plot

1098

1099

## 1100 Table legend

1101 **Table I** The main results of the meta-analyses to investigate an association between gene  
1102 polymorphisms and endometriosis.

1103 CAT1: Category 1 studies, in which the absence of endometriosis in the control women has been  
1104 confirmed during surgery (tubal ligation, hysterectomy, laparoscopy, etc.).

1105 CAT2: Category 2 studies, in which the control women had no apparent signs and symptoms of  
1106 endometriosis (including fertile women and/or women having undergone a Caesarean section).

1107 In this category, women may be regarded as a control population, even if inclusion criteria are  
1108 out of ASRM guidelines.

1109 CAT3: Category 3 studies using other sources of controls, such as newborns, volunteers without  
1110 clinical data, and males. These CAT3 studies were not considered for meta-analysis because

1111 males and newborns could not be considered as controls since endometriosis is strictly a female  
1112 disease.

1113 rASRM: revised American Society for Reproductive Medicine classification

1114

## 1115 Supplemental table legend

1116 **Supplementary Table SI** References (the unique identifier number) of the 395 publications  
1117 (PMIDs) identified by the PubMed search.

1118

1119 **Supplementary Table SII** Results of the text mining procedure.

1120

1121 **Supplementary Table SIII** The list of genes cited in one or two different publications.

1122

1123 **Supplementary Table SIV** The list of genes cited in at least three different publications;  
1124 identification of polymorphisms; data selection.

1125

1126 CAT1: Category 1 studies, in which the absence of endometriosis in the control women has been  
1127 confirmed during surgery (tubal ligation, hysterectomy, laparoscopy, etc.).

1128

1129

## 1130 Supplementary Data

1131 List of publications by gene:

1132 vascular endothelial growth factor alpha (*VEGFA*): (Cardoso, Abrao, Vianna-Jorge, et al. 2017;  
1133 Vodolazkaia et al. 2016; Szczepanska et al. 2015; Henidi, Kaabachi, Naouali, et al. 2015; Perini  
1134 et al. 2014; Saliminejad et al. 2013; Vanaja et al. 2013; Emamifar et al. 2012; Lamp et al. 2010;  
1135 Attar, Agachan, et al. 2010; Toktam et al. 2010; Altinkaya et al. 2011; Liu et al. 2009; Cosin et  
1136 al. 2009; Zhao, Nyholt, Thomas, et al. 2008; Gentilini, Somigliana, et al. 2008; Ikuhashi et al.  
1137 2007; Kim et al. 2008; Kim, Choi, Choung, et al. 2005; Bhanoori, Arvind Babu, et al. 2005).  
1138  
1139 tumor necrosis factor (*TNF*): (Abutorabi et al. 2015; Asghar et al. 2004; Chae et al. 2008; de  
1140 Oliveira Francisco et al. 2017; Hsieh et al. 2002; Lakshmi et al. 2010; Lee et al. 2008; Lee, Park,  
1141 and Kim 2002; Mardanian et al. 2014; Saliminejad et al. 2013; Teramoto et al. 2004; Wieser,  
1142 Fabjani, et al. 2002; Zhao et al. 2007; Zhou et al. 2010).  
1143  
1144 interleukin 6 (*IL6*) : (Bessa et al. 2016; Bhanoori, Babu, et al. 2005; Chae et al. 2010; Juo et al.  
1145 2009; Kitawaki et al. 2006; Lee, Park, and Kim 2002; Wieser et al. 2003; Zhou et al. 2010)  
1146  
1147 transforming growth factor beta 1 (*TGFBI*): (Baxter et al. 2002; Hsieh, Chang, Tsai, Peng, et al.  
1148 2005; Kim et al. 2010; Lee et al. 2011; Romano, van Kaam, and Dunselman 2010; van Kaam,  
1149 Romano, Dunselman, et al. 2007)  
1150  
1151 interferon gamma (*IFNG*): (Kim et al. 2011; Kitawaki et al. 2004; Mormile and Vittori 2013;  
1152 Rozati, Vanaja, and Nasaruddin 2010)  
1153



1154 estradiol receptor 1 (*ESR1*): 21 studies found by our literature search and text mining approach  
1155 (Altmae et al. 2007; Georgiou et al. 1999; Govindan et al. 2009; Hsieh, Chang, Tsai, Lin, et al.  
1156 2005; Huang et al. 2014; Huber et al. 2005; Kim, Choi, Jun, et al. 2005; Kitawaki et al. 2001;  
1157 Lamp et al. 2011; Luisi et al. 2006; Matsuzaka, Kikuti, Izumi, et al. 2012; Oehler et al. 2004;  
1158 Paskulin et al. 2013; Renner et al. 2006; Sato et al. 2008; Seko et al. 2004; Trabert et al. 2011;  
1159 Wang et al. 2013; Wang et al. 2004; Wu et al. 2013; Xie et al. 2009) and an additional study  
1160 (Hsieh et al. 2007) that was incorrectly referenced and listed being as relevant for *ESR2*)  
1161  
1162 progesterone receptor (*PGR*) : (Berchuck et al. 2004; Cardoso, Machado, et al. 2017;  
1163 Christofolini et al. 2011; Costa et al. 2011; D'Amora et al. 2009; De Carvalho et al. 2007;  
1164 Gentilini, Vigano, et al. 2008; Gimenes et al. 2010; Govindan et al. 2007; Lamp et al. 2011;  
1165 Lattuada, Somigliana, et al. 2004; Near et al. 2011; Renner et al. 2008; Silva and Moura 2016;  
1166 Trabert et al. 2011; Treloar et al. 2005; van Kaam, Romano, Schouten, et al. 2007; Wieser,  
1167 Schneeberger, et al. 2002; Wu et al. 2013)  
1168  
1169 follicle stimulating hormone receptor (*FSHR*) : (Andre et al. 2018; Kerimoglu et al. 2015;  
1170 Schmitz et al. 2015)  
1171  
1172 intercellular adhesion molecule 1 (*ICAM1*): (Bessa et al. 2016; Chae et al. 2010; Kitawaki et al.  
1173 2006; Vigano et al. 2003; Aghajanpour, Mashayekhi, and Rajaei 2011)  
1174  
1175 glutathione S-transferase mu 1 (*GSTM1*): 27 studies identified by text mining (Aban et al. 2007;  
1176 Arvanitis et al. 2001; Arvanitis et al. 2003; Babu et al. 2005; Baranova et al. 1997; Baranova et

1177 al. 1999; Baxter, Thomas, and Campbell 2001; Ertunc et al. 2005; Frare et al. 2013; Hadfield et  
1178 al. 2001; Hassani et al. 2016; Henidi, Kaabachi, Mbarik, et al. 2015; Hosseinzadeh, Mashayekhi,  
1179 and Sorouri 2011; Hsieh, Chang, Tsai, Lin, Chen, et al. 2004; Huang et al. 2014; Huang et al.  
1180 2010; Hur et al. 2005; Kim et al. 2007; Kubiszeski et al. 2015; Matsuzaka, Kikuti, Goya, et al.  
1181 2012; Roya, Baludu, and Reddy 2009; Seifati et al. 2012; Silva and Moura 2016; Trabert et al.  
1182 2011; Tuo et al. 2016; Vichi et al. 2012; Wu et al. 2012; Morizane et al. 2004).  
1183 Another publication was added (Morizane et al. 2004); it was cited by previous meta-analyses  
1184 (Ding et al. 2014; Guo 2005; Li and Zhang 2015; Xin et al. 2016; Zhu et al. 2014) but had not  
1185 been identified by our search strategy because the term “polymorphism(s)” was not mentioned in  
1186 the title or the abstract.

1187  
1188 glutathione S-transferase theta 1 (*GSTT1*): (18 studies identified by text miming (Aban et al.  
1189 2007; Arvanitis et al. 2001; Arvanitis et al. 2003; Babu et al. 2005; Baranova et al. 1999; Ertunc  
1190 et al. 2005; Frare et al. 2013; Hadfield et al. 2001; Hassani et al. 2016; Henidi, Kaabachi,  
1191 Mbarik, et al. 2015; Hur et al. 2005; Kim et al. 2007; Kubiszeski et al. 2015; Matsuzaka, Kikuti,  
1192 Goya, et al. 2012; Silva and Moura 2016; Tuo et al. 2016; Vichi et al. 2012; Wu et al. 2012) and  
1193 2 studies (Lin et al. 2003; Morizane et al. 2004) found in previous meta-analyses (Chen, Xu, et  
1194 al. 2015; Ding et al. 2014; Guo 2005; Xin et al. 2016; Zhu et al. 2014))

1195  
1196 glutathione S-transferase pi 1 (*GSTP1*): (Ertunc et al. 2005; Hassani et al. 2016; Hur et al. 2005;  
1197 Jeon et al. 2010; Matsuzaka, Kikuti, Goya, et al. 2012; Tuo et al. 2016; Vichi et al. 2012; Wu et  
1198 al. 2012)

1199

1200 aryl-hydrocarbon receptor repressor (*AHRR*) : (Asada et al. 2009; Kim et al. 2007; Matsuzaka,  
1201 Kikuti, Goya, et al. 2012; Tsuchiya et al. 2005; Watanabe et al. 2001; Wu et al. 2012)  
1202  
1203 cytochrome P450 family 1 subfamily A polypeptide 1 (*CYP1A1*) : 12 studies identified by text  
1204 mining (Silva and Moura 2016; Matsuzaka, Kikuti, Goya, et al. 2012; Wu et al. 2012; Trabert et  
1205 al. 2011; Tsuchiya et al. 2007; Huber et al. 2005; Babu et al. 2005; Arvanitis et al. 2003;  
1206 Arvanitis et al. 2001; Hadfield et al. 2001; Watanabe et al. 2001; Barbosa et al. 2016) and 2  
1207 studies (Juo et al. 2006; Rozati et al. 2008) found in a previous meta-analysis (Fan et al. 2016)  
1208  
1209 *CYP17A1*: (Al-Rubae'i, Naji, and Turki 2017; Asghar et al. 2005; Bozdog et al. 2010; Cardoso,  
1210 Machado, et al. 2017; De Carvalho et al. 2007; Hsieh, Chang, Tsai, Lin, and Tsai 2004; Hsieh,  
1211 Chang, Tsai, Lin, et al. 2005; Huang et al. 2014; Juo et al. 2006; Kado et al. 2002; Szczepanska,  
1212 Wirstlein, Skrzypczak, et al. 2013; Trabert et al. 2011; Vietri et al. 2009; Wu et al. 2013; Zhao,  
1213 Nyholt, Le, et al. 2008)  
1214  
1215 *CYP19A1*: (Cardoso, Machado, et al. 2017; Szczepanska, Wirstlein, Skrzypczak, et al. 2013;  
1216 Vietri et al. 2009; Hur et al. 2007; Wu et al. 2013; Wang et al. 2014; Lamp et al. 2011)  
1217  
1218 *CYP2C19* : (Cardoso, Abrao, Berardo, et al. 2017; Bozdog et al. 2010; Cayan et al. 2009)  
1219  
1220 tumor protein 53 (*TP53*): (Ammendola et al. 2008; Camargo-Kosugi et al. 2014; Chang et al.  
1221 2002; Frare et al. 2013; Gallegos-Arreola, Figuera-Villanueva, et al. 2012; Gallegos-Arreola,  
1222 Valencia-Rodriguez, et al. 2012; Gloria-Bottini et al. 2016; Gloria-Bottini et al. 2013; Govatati et

1223 al. 2012; Hsieh and Lin 2006; Hsieh et al. 2001; Hussain et al. 2018; Lao, Chen, and Qin 2016;  
1224 Lattuada, Vigano, et al. 2004; Nakayama et al. 2001; Nikbakht Dastjerdi, Aboutorabi, and  
1225 Eslami Farsani 2013; Okuda et al. 2003; Omori et al. 2004; Paskulin et al. 2012; Ribeiro Junior  
1226 et al. 2009; Rotman et al. 2013; Silva and Moura 2016; Silva et al. 2011; Vercellini et al. 1994;  
1227 Vietri et al. 2007; Ying et al. 2011)  
1228  
1229 X-ray repair complementing defective repair in Chinese hamster cells 1 (*XRCC1*): 5 were  
1230 identified in our literature search and (Attar, Cacina, et al. 2010; Bau et al. 2007; Hsieh et al.  
1231 2012; Monteiro et al. 2014; Saliminejad et al. 2015), and one study (Safan and Ghanem 2015)  
1232 was cited in a previous meta-analysis only (Lv et al. 2017)  
1233  
1234 wingless-type MMTV integration site family member 4 (*WNT4*): (Lee et al. 2014; Li, Hao, et al.  
1235 2017; Mafra et al. 2015; Matalliotakis, Zervou, Matalliotaki, Arici, et al. 2017; Matalliotakis,  
1236 Zervou, Matalliotaki, Rahmioglu, et al. 2017; Wu et al. 2015)  
1237  
1238 serpin peptidase inhibitor clade E member 1 (*SERPINE1*): (Bedaiwy et al. 2006; Gentilini et al.  
1239 2009; Goncalves-Filho et al. 2011; Ramon et al. 2008; Uxa et al. 2010)  
1240  
1241 peroxisome proliferator-activated receptor gamma (*PPARG*): (Hwang et al. 2010; Kiyomizu et  
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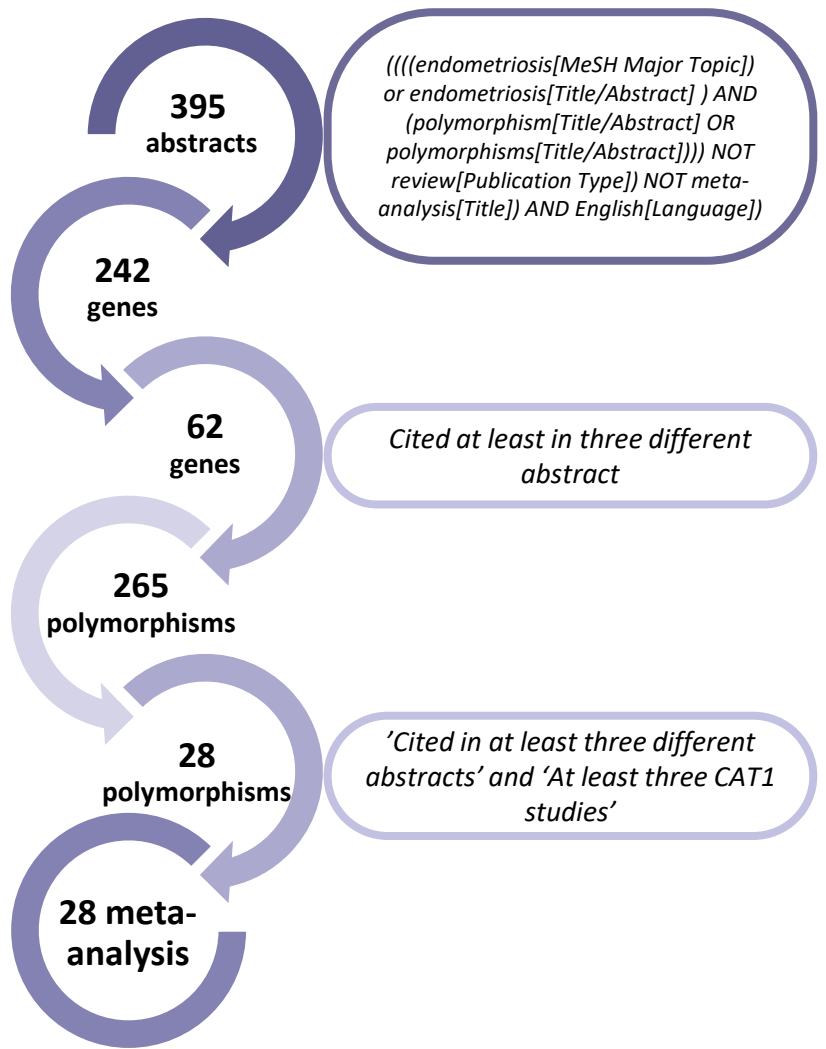


Figure 1: Selection of polymorphisms for meta-analysis.

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



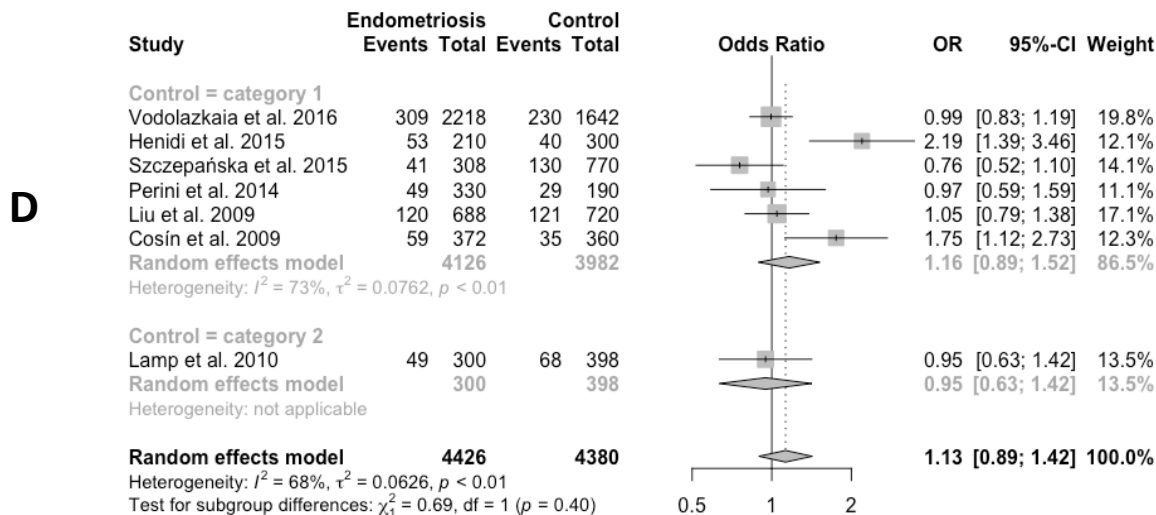
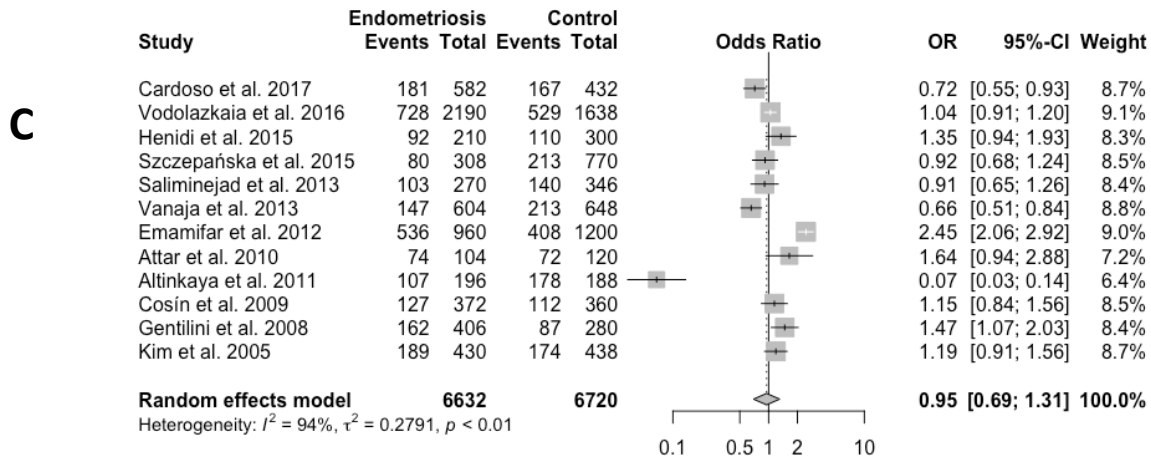
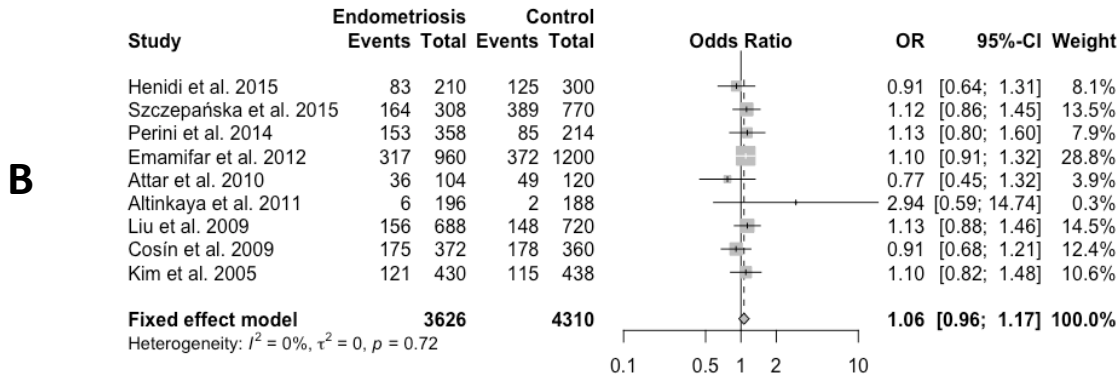
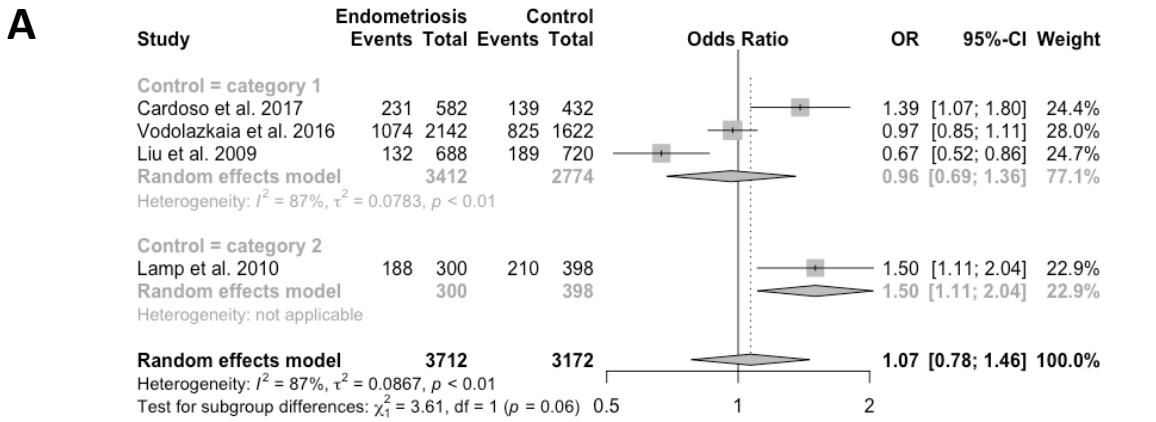
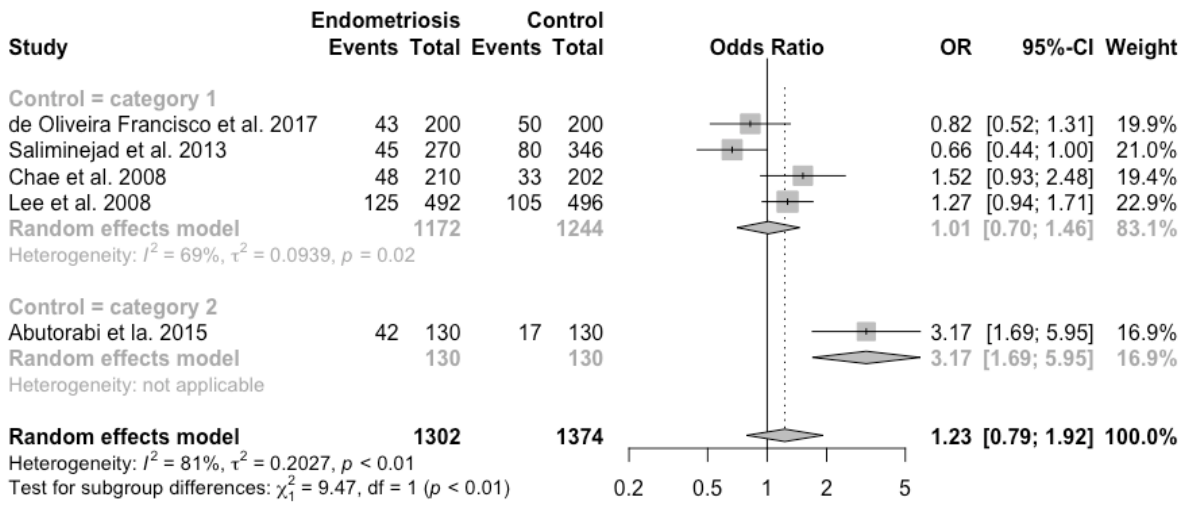


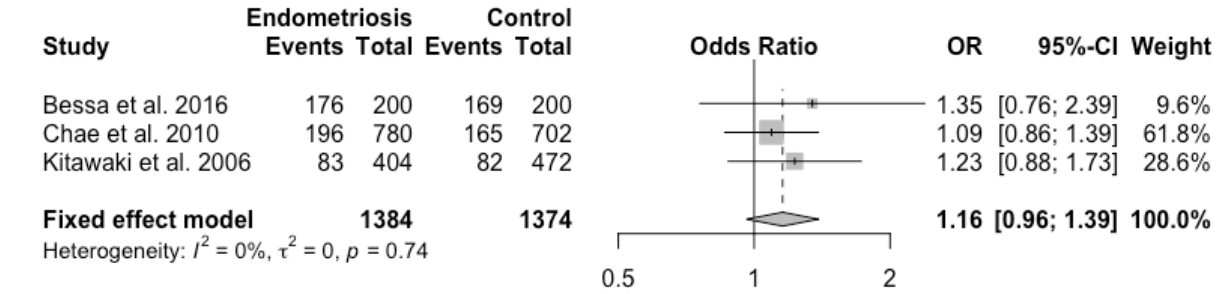
Figure 2: Forest plot for vascular endothelial growth factor alpha (VEGFA) polymorphisms. (allelic model; events = studied allele, total = allele number)

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

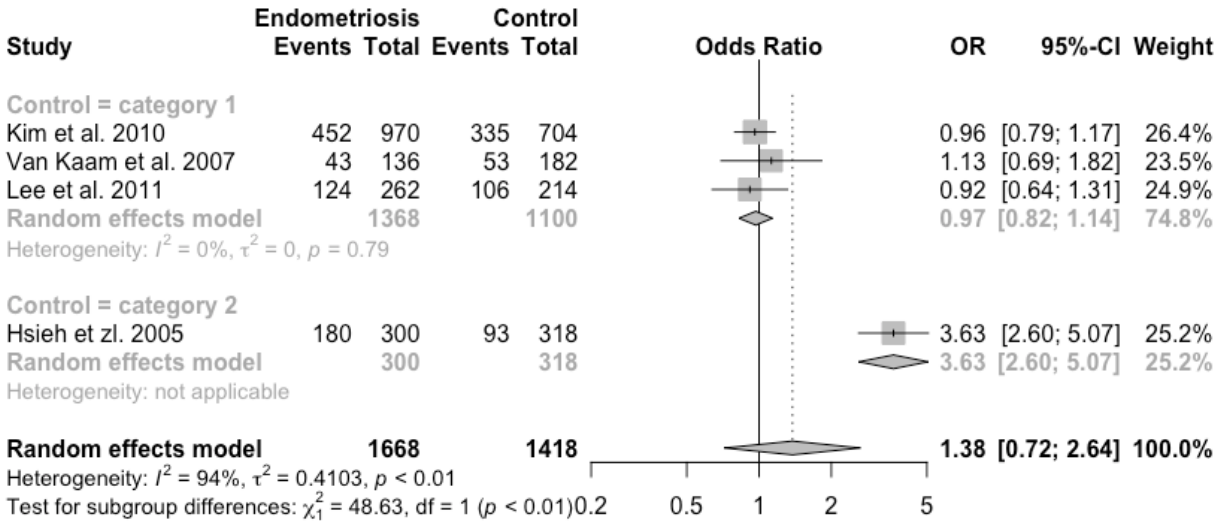
**A**



**B**



**C**



**D**

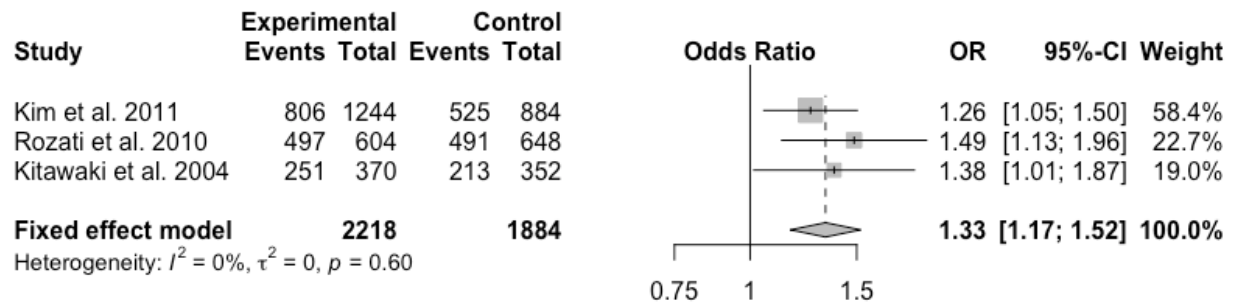


Figure 3 : Forest plot for polymorphisms involved in inflammation pathway

(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.

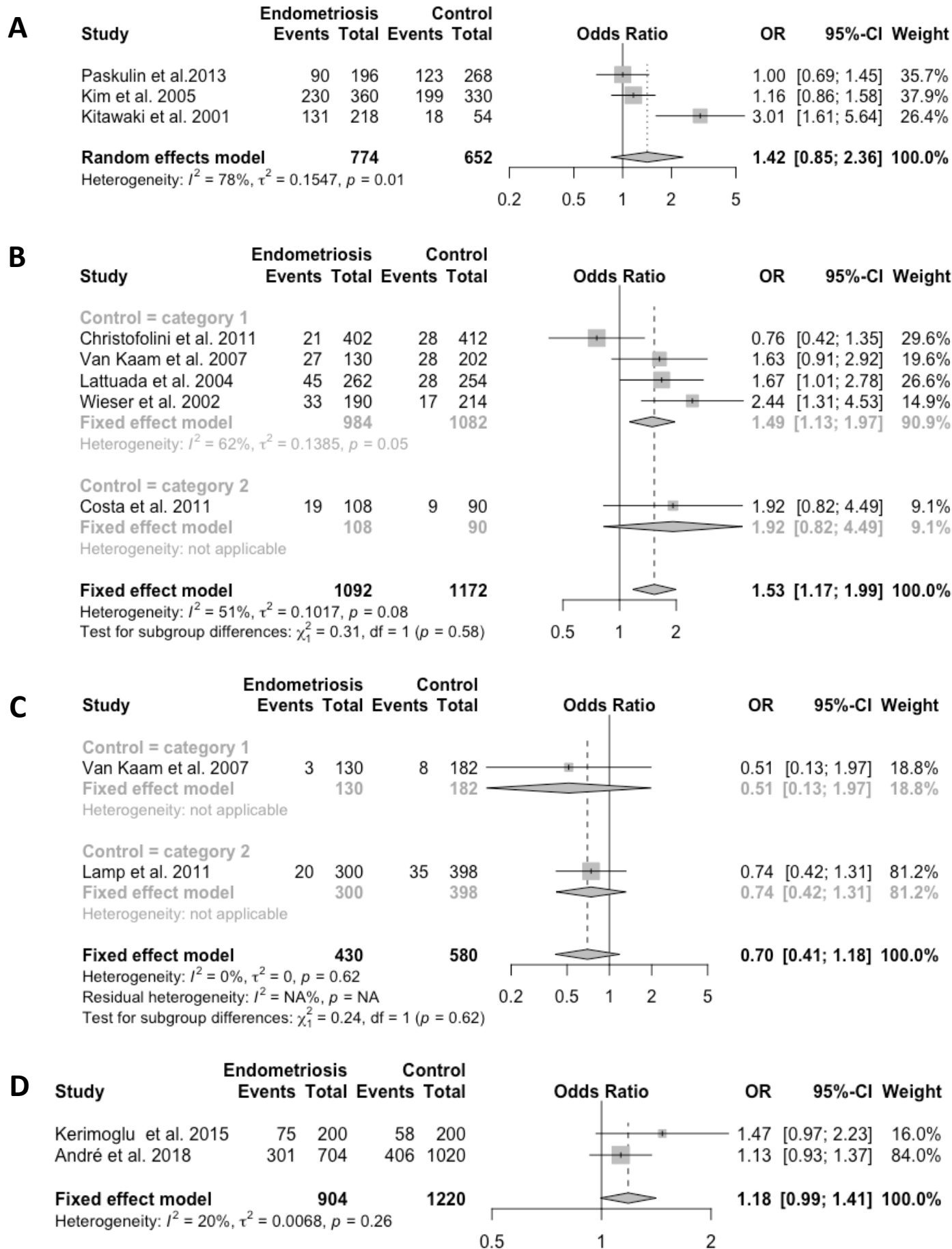
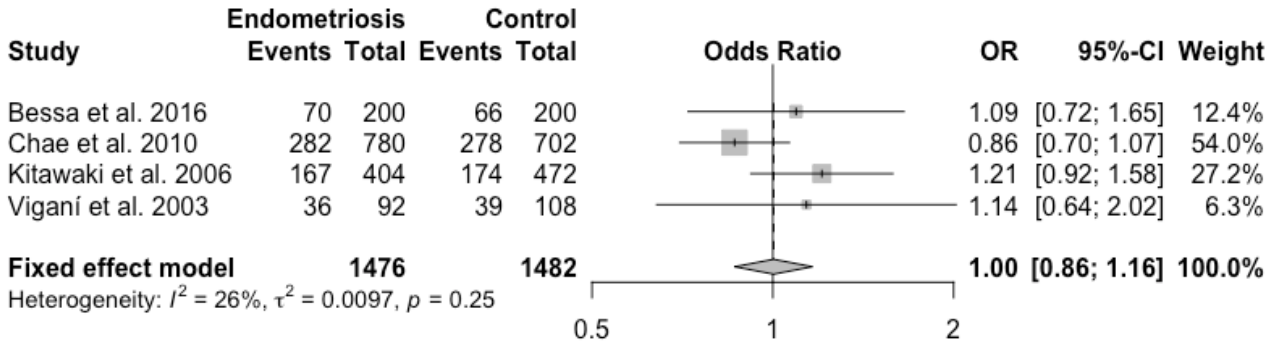


Figure 4: Forest plot for polymorphisms involved in Hormonal pathway.

(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) follicle stimulating hormone receptor (FSHR) (rs6166): G allele.

**A**



**B**

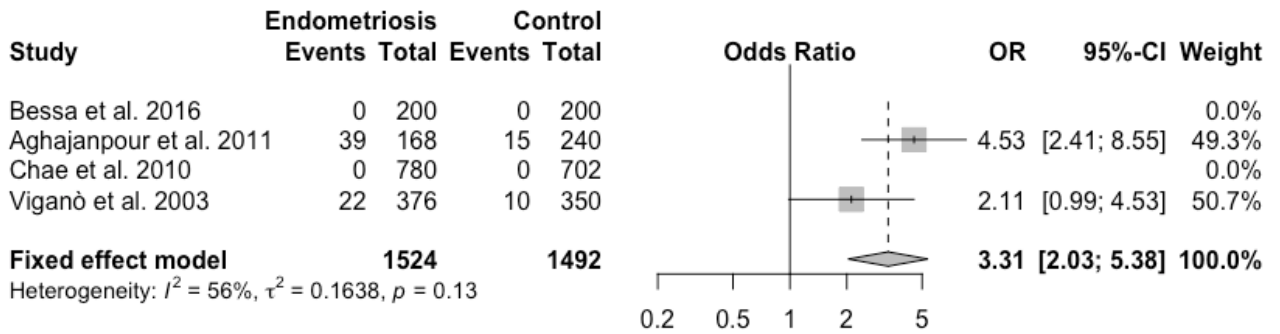
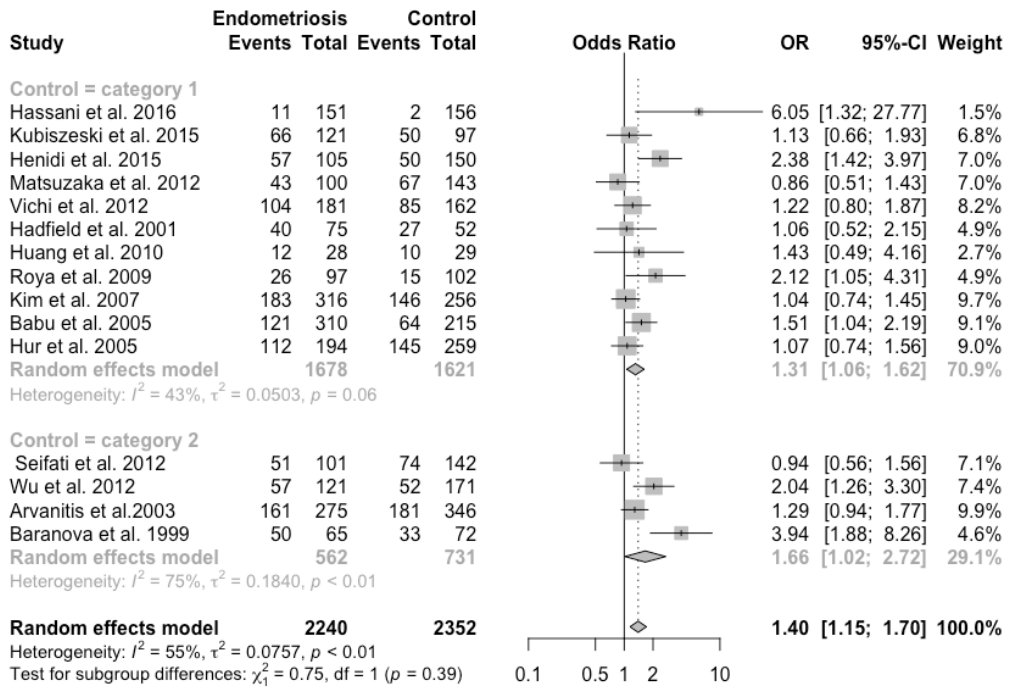


Figure 5 : Forest plot for intercellular adhesion molecule 1 (ICAM1) polymorphisms.

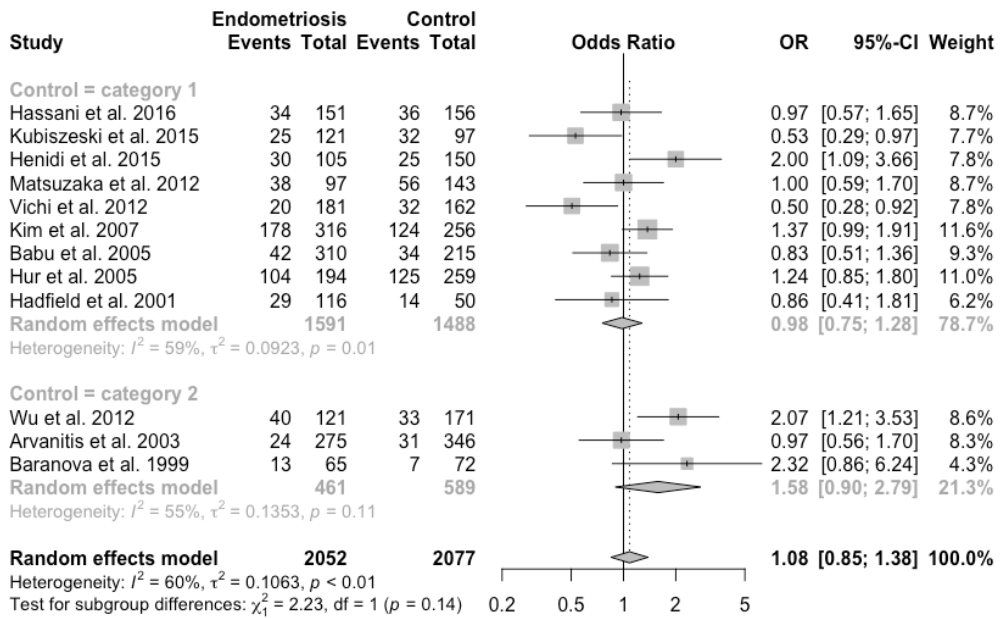
(allelic model events = studied allele, total = allele number)

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

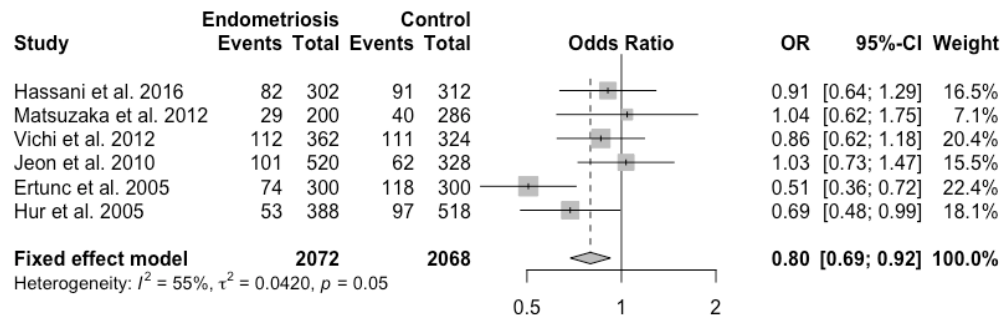
**A**



**B**



**C**



**D**

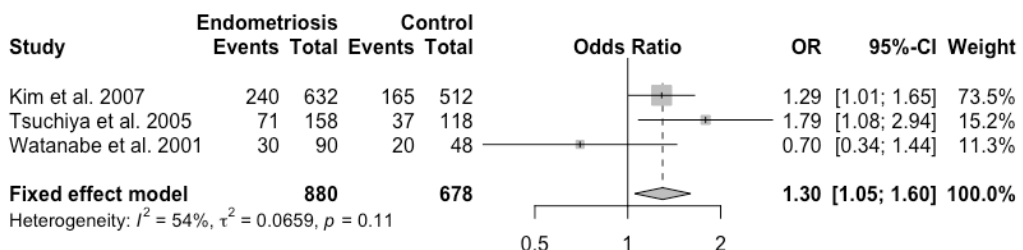
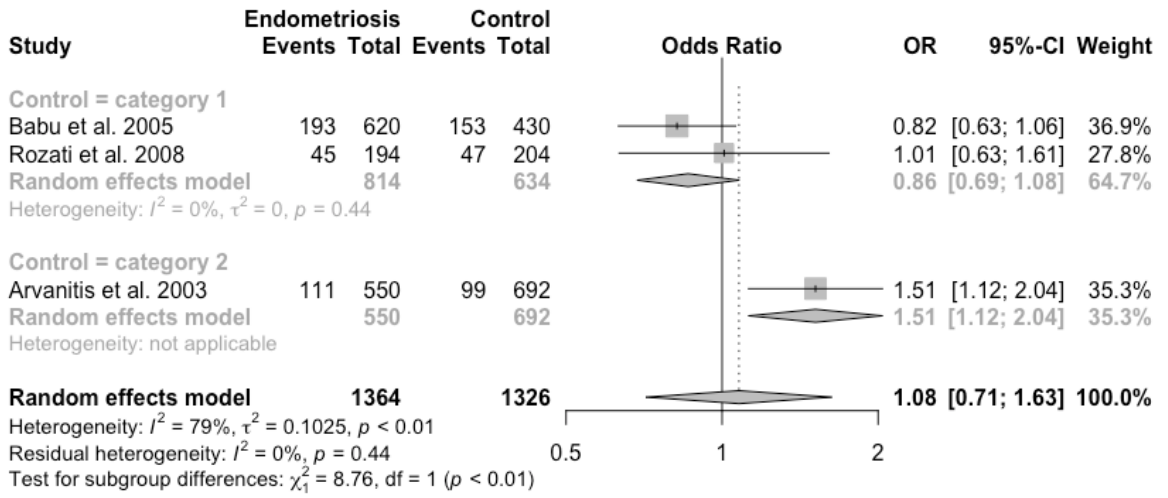


Figure 6: Forest plot for polymorphisms involved in detoxification process.

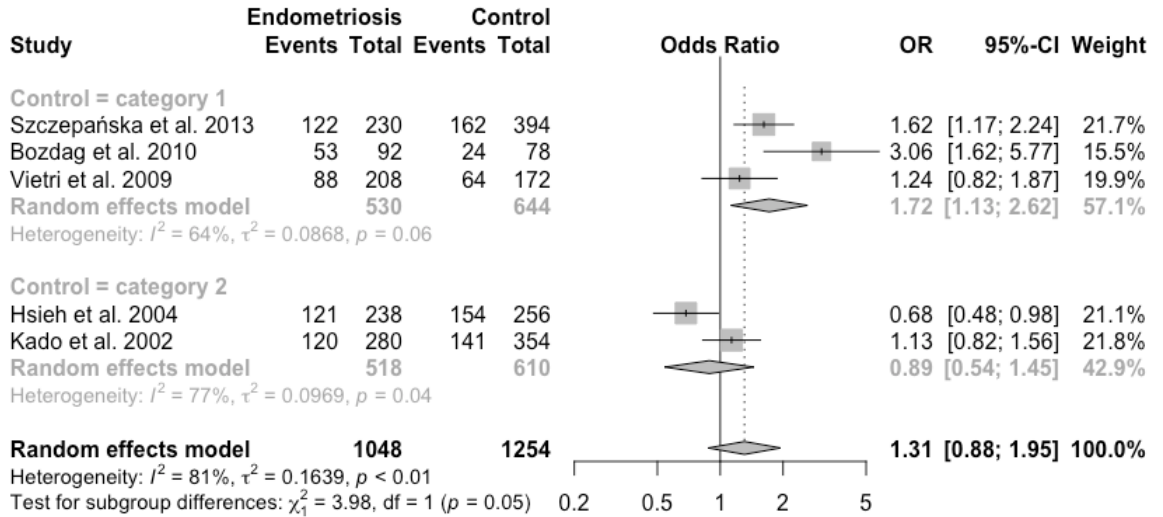
(allelic model events = studied allele, total = allele number)

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.

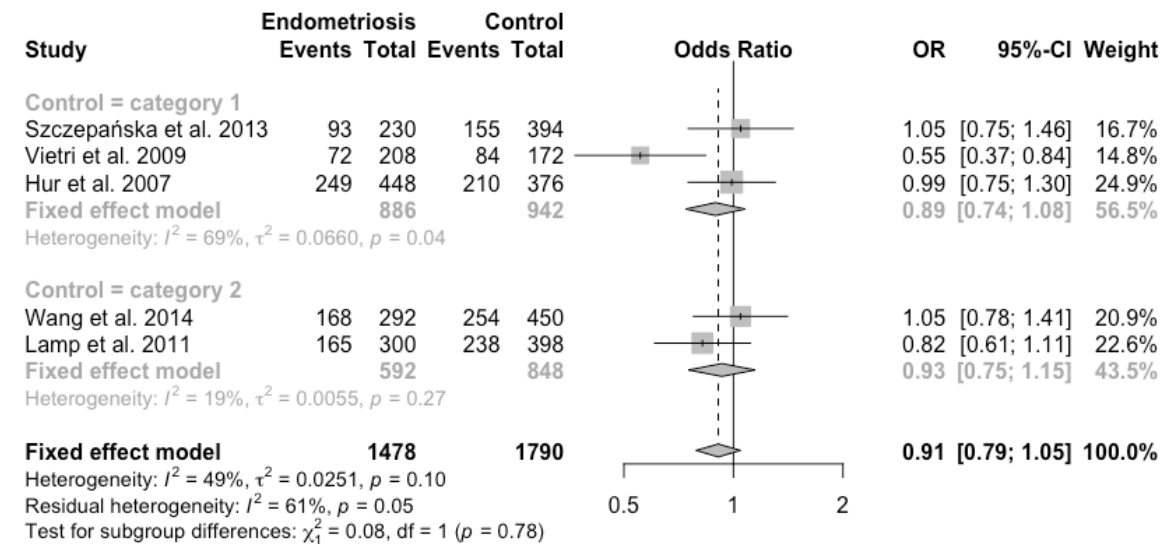
**A**



**B**



**C**



**D**

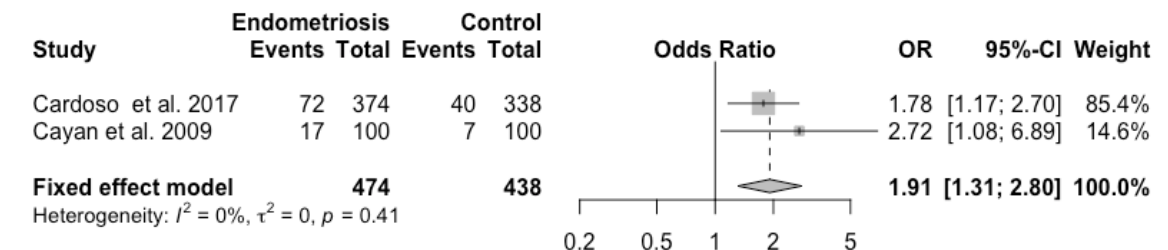
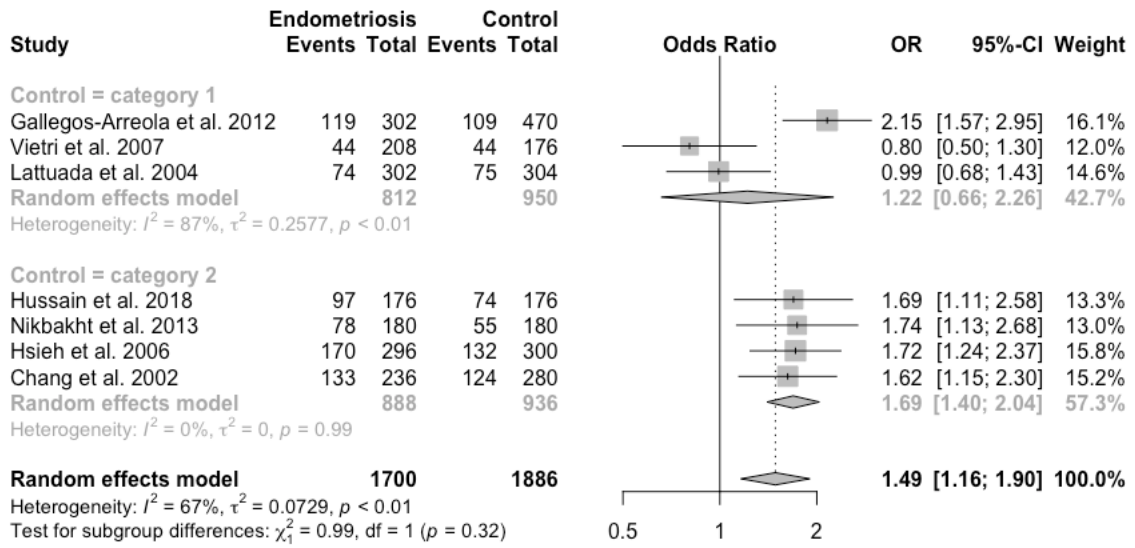


Figure 7: Forest plot for polymorphisms of cytochrome P450 family.

(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**



**B**

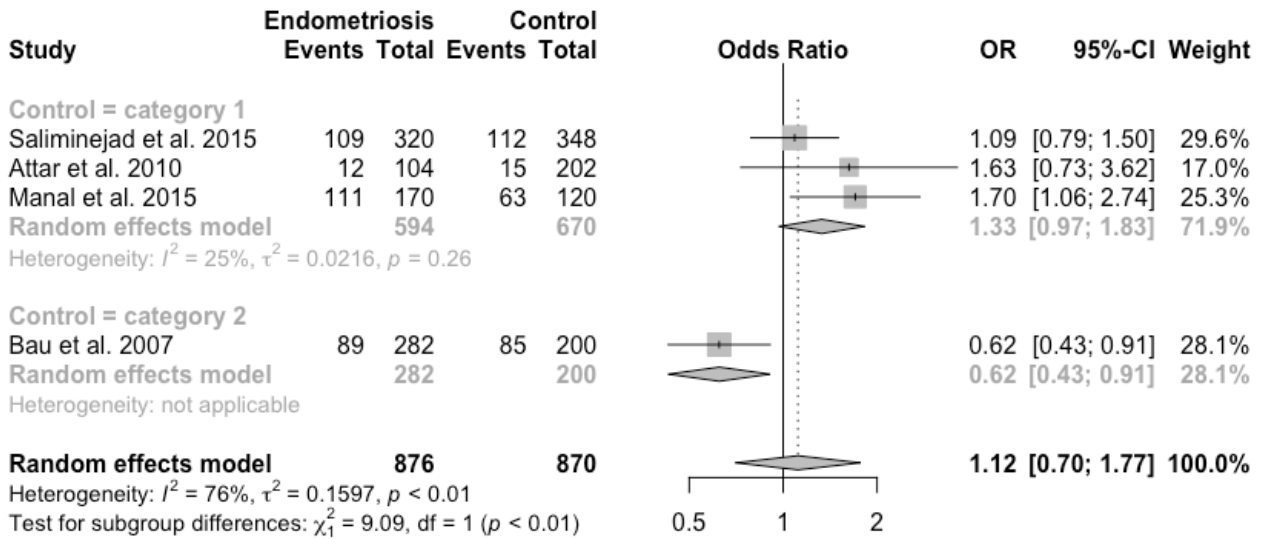
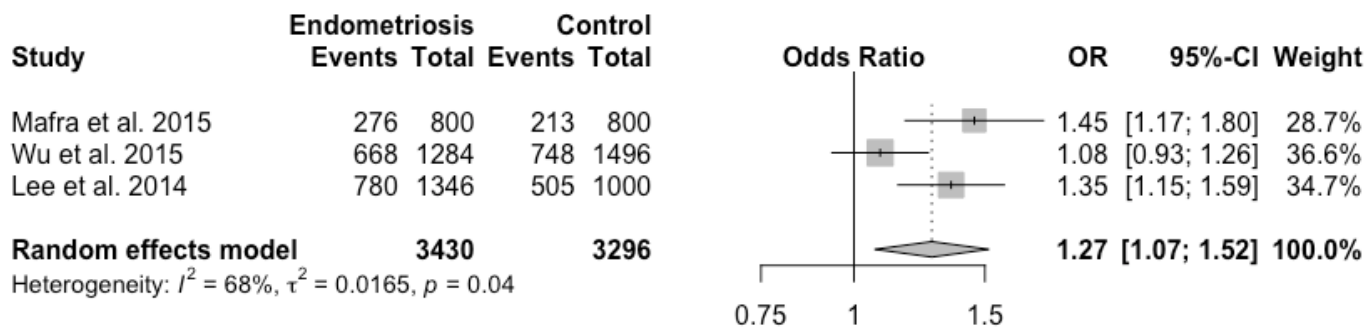


Figure 8: Forest plot for polymorphisms involved in genome regulation.

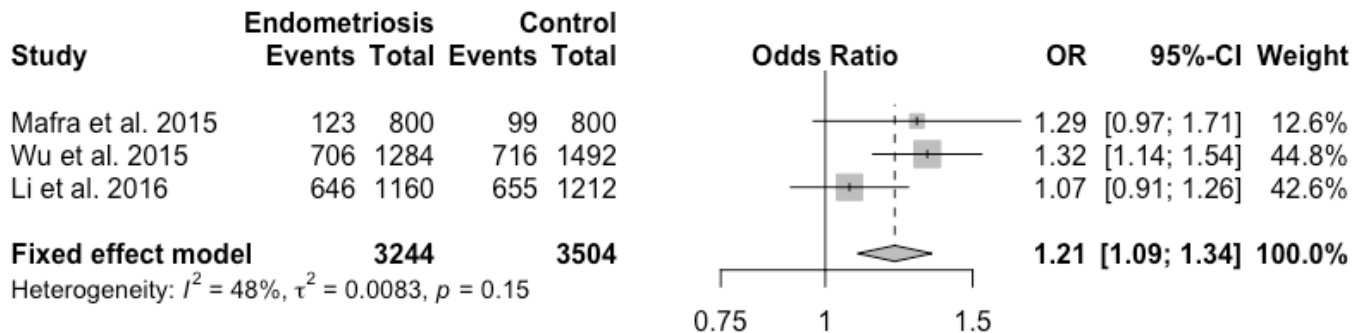
(allelic model events = studied allele, total = allele number)

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

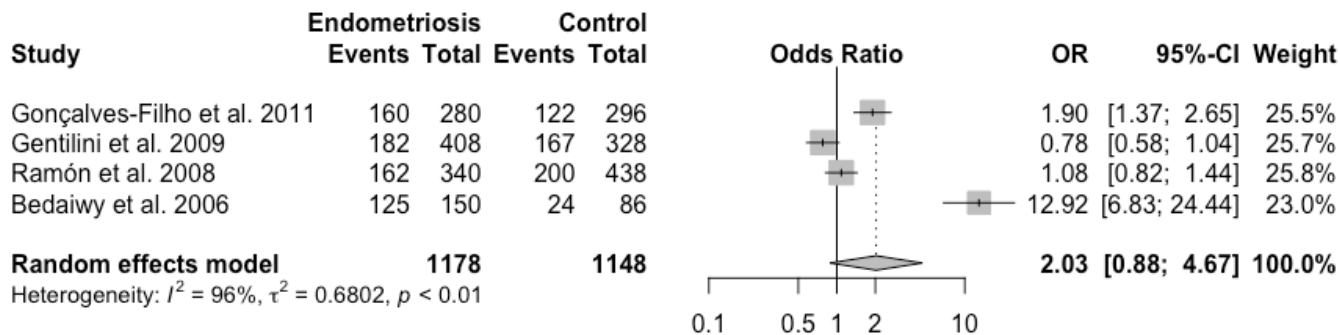
A



B



C



D

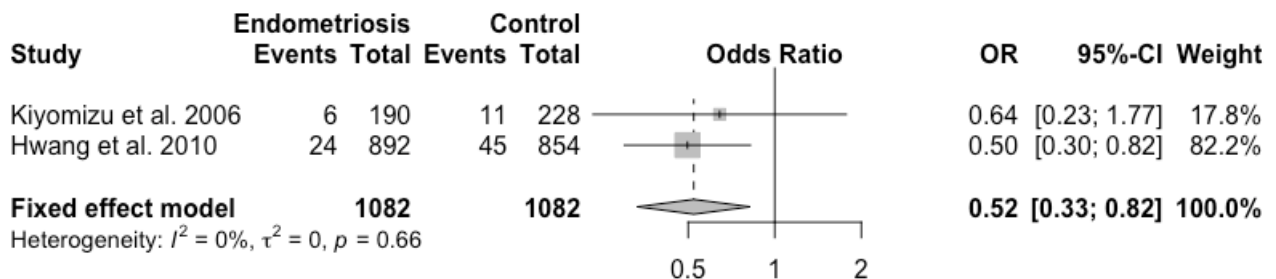


Figure 9 : Forest plot for WNT4, SERPINE1 and PPARG polymorphisms

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

A) wingless-type MMTV integration site family member 4 (WNT4) (rs16826658): allele G; B) WNT4 (rs223529): allele A;

C) serpin peptidase inhibitor clade E member 1 (SERPINE1) (rs1799889): 4G allele, D) peroxisome proliferator-activated receptor gamma (PPARG) (rs1801282): allele G.



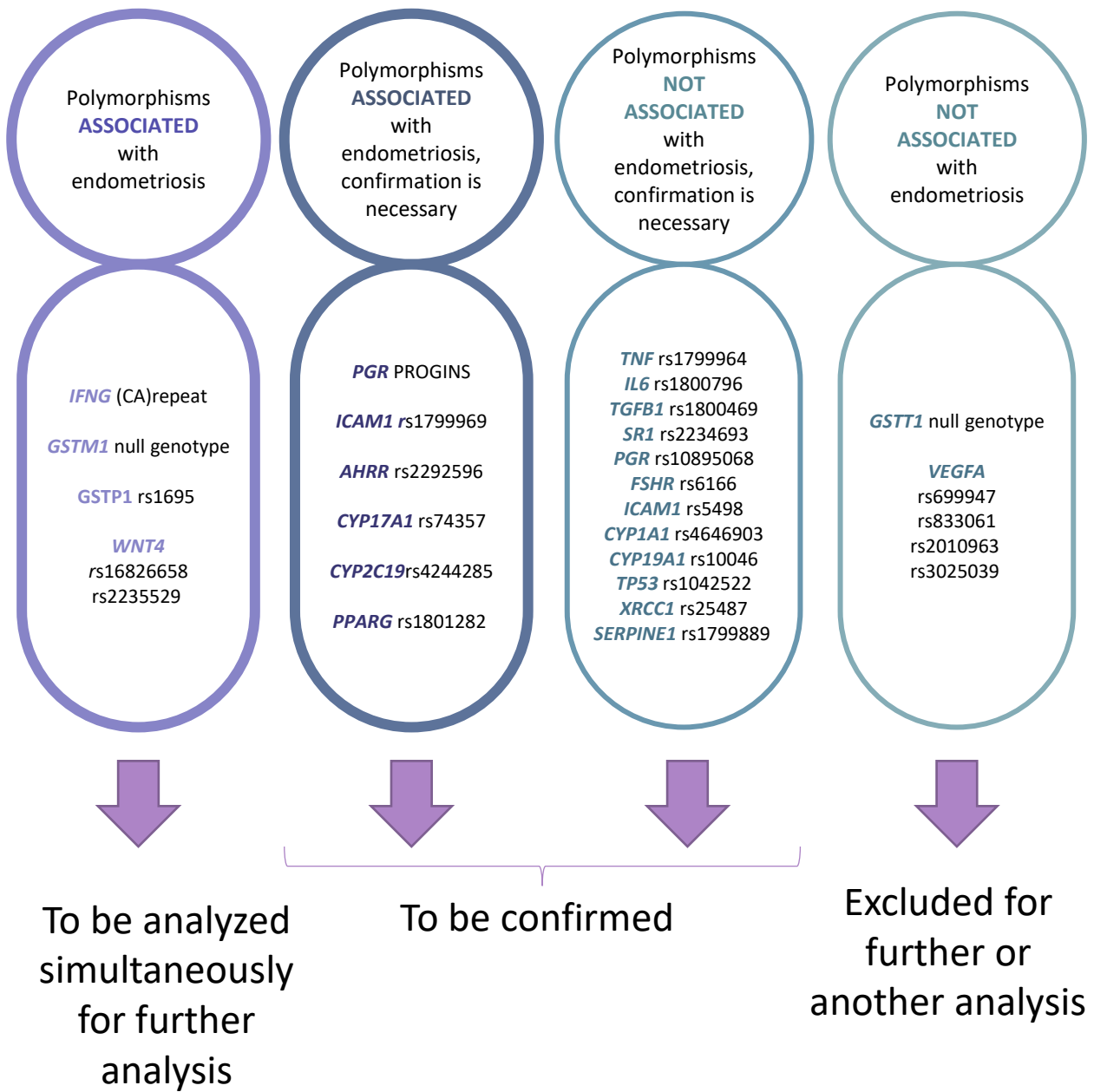


Figure 10: Final results

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

Gene Name	Symbol	Polymorphisms	Minor allele	Endometriosis stage (rASRM)	Studies						Number of patients		Model	heterogeneity test	Fixed or random effects model	OR	CI	p-value	p-value (subgroup differences)	Association yes/no	tumor protocol summary linear regression test					
					Total	Excluded			Included			Endometriosis									Control	allelic/genomic	p-value	t	df	p-value
						CAT3	Lack of Raw data	Overlapped data	Total	CAT1	CAT2															
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		
		rs833061 (-460T>C)	C	All	13	3	0	1	9	9	0	1813	2155	allelic	0,72	fixed	CAT1	0,96	[0.69; 1.36]	0,2326	no	0,45	7	0,67		
		rs2010963 (+405G>C)	C	I-II	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		
		rs3025039 (+936C>T)	T	III-IV	7	7	0	0	7	7	0	1315	2227	allelic	< 0.0001	random		0,94	[0.54; 1.66]	0,67	no					
tumor necrosis factor	TNF	rs1799964 (-1031T>C)	C	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		
		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		
		rs1800796 (-634C>G)	G	I-II	2	2	0	0	2	2	0	79	336	allelic	0,925	fixed		1,13	[0.71; 1.79]	0,9	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		
		rs1800469 (-509C>T)	T	All	3	0	0	0	3	3	0	1109	1884	allelic	0,595	fixed	CAT1	0,97	[0.82; 1.14]	0,97	no					
interferon gamma	IFNG	(CA)repeat	S	All	3	0	0	0	3	3	0	299	1884	allelic	0,1633	fixed		1,33	[1.17; 1.52]	< 0.0001	yes	1,67	1	0,34		
		(CA)repeat	S	I-II	3	3	0	0	3	3	0	299	1884	allelic	0,1633	fixed		1,28	[1.05; 1.57]	0,61	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		
		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		
progesterone receptor	PGR	rs10895068	A	All	7	3	2	0	2	1	1	215	290	allelic	0,6237	fixed	CAT1	1,49	[1.13; 1.97]	0,1792	yes	NA	NA	NA		
		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		
		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		
		rs5498 (K469E)	G	I-II	2	2	0	0	2	2	0	79	336	allelic	0,2582	fixed		1,19	[0.84; 1.70]	0,32	no					
		rs5498 (K469E)	G	III-IV	3	3	0	0	3	3	0	613	687	allelic	0,2582	fixed		0,98	[0.83; 1.15]	0,32	no					
glutathione S-transferase mu 1	GSTM1	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		
		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		
		Null genotype	absence	I-II	4	2	2	2	223	466	null genotype	0,0001	random	CAT1	1,31	[1.06; 1.62]	0,39	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		
		Null genotype	absence	All	15	3	0	0	12	9	3	2052	2077	null genotype	0,0039	random	CAT1	0,98	[0.75; 1.28]	<0.01	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		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		
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		
		rs10046	T	All	8	1	2	0	5	3	2	739	895	allelic	0,0987	fixed	CAT1	0,9	[0.73; 1.08]	0,1809	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		
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	1,22	[0.66; 2.26]	0,6424	no	0,77	2	0,52		
		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					
		rs25487 (Arg399Gln)	A	All	6	2	0	0	4	3	1	438	435	allelic	0,006	random	CAT2	1,33	[0.97; 1.83]	<0.01	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		