Unravelling the Association Between Endometriosis and Immunological Diseases

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Declaration

I declare that this thesis is entirely my own work, and except where otherwise stated, describes my own research.

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Abstract

My D.Phil project investigated if women with endometriosis have an increased risk of immunological diseases, if endometriosis is causal to (any) immunological diseases and if there could be shared genetic risk factors between endometriosis and (any) immunological diseases.

Firstly, existing evidence was summarized by a systematic review of population-based studies that reported an association between endometriosis and (auto)immune diseases. However, many of the studies reviewed were of suboptimal quality. Five studies provided high quality evidence suggesting a significantly increased risk of systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, multiple sclerosis, and inflammatory bowel disease in women with endometriosis as well as a significantly increased risk of endometriosis in women with coeliac disease. Meta-analysis with combinable study results found a significantly increased risk of systemic lupus erythematosus and Sjogren's syndrome in women with endometriosis.

Next, a cross-sectional and a prospective cohort study were conducted analysing UK Biobank data collected from 273,404 UK women. In both cross-sectional study and cohort study analyses, a significantly increased risk was observed for overall immunological diseases, classic autoimmune diseases and for autoinflammatory diseases. A significantly increased risk for mixed-pattern diseases was also observed in cross-sectional study, but this increased risk became non-significant in the prospective cohort study, likely due to a reduced sample size. In the cross-sectional study, women with endometriosis were found to have a significantly increased risk for (systemic) lupus erythematosus, rheumatoid arthritis, coeliac disease, myasthenia gravis, inflammatory bowel disease, osteoarthritis, gout

(including pseudogout, crystal arthropathy), ankylosing spondylitis and a borderline significant risk for type 1 diabetes, ulcerative colitis and psoriasis. Yet the cohort study approach only found a significantly increased risk of incident rheumatoid arthritis (HR [95%CI] = 2.25[1.33-3.79], P = 0.002*) and incident osteoarthritis (HR [95%CI] = 1.26 [1.01-1.58], P = 0.042*) in women with endometriosis aged < 50 years old women and for (systemic) lupus erythematosus (HR [95%CI] = 2.37[1.21-4.65], P = 0.012*) in women of endometriosis aged ≥ 60 years old.

Genome-wide association study (GWAS) data in UKBB were meta-analysed with publicly available GWAS to investigate at genetic level the association between endometriosis and immunological diseases. Endometriosis was found to be significantly genetically correlated with multiple sclerosis (RG[SE] = 0.093[0.034], P = 0.006*), osteoarthritis (RG[SE] = 0.278[0.035], P = 3.248×10^{-15}) and rheumatoid arthritis (RG[SE] = 0.180[0.041], P = 1.25×10^{-5}), but not for other immunological diseases. Mendelian randomisation (MR) analysis did not show endometriosis to be causal to any of the 3 genetically correlated immunological diseases. Multi-trait genetic analysis for endometriosis, multiple sclerosis, osteoarthritis and rheumatoid arthritis identified 10 novel variants for endometriosis, and 4 shared genetic variants between endometriosis and osteoarthritis. Their potential functional roles through eQTL analysis provided insights into key molecular players in disease processes.

Further work could be done to validate my study results by conducting studies with a larger sample size (especially in female-only study population), strict diagnosis criteria and investigation of disease sub-types as well as more robust instrumental variables in MR analysis.

Acknowledgement

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Chapter 1: Research Background and Study Rationale

RESEARCH BACKGROUND

Endometriosis is a chronic gynaecological disorder characterized by the presence of endometrial tissue outside the uterus (1). Symptoms of endometriosis usually include dysmenorrhea (pain with periods), non-menstrual pelvic pain, and infertility (1). These impact greatly on health, life, work productivity, and emotional well-being of affected women and their families (2) resulting in substantial social and economic burden to the individual and society in general (3). The true prevalence of endometriosis is unknown due to the requirement for surgery to establish a diagnosis and a lack of alternative non-invasive effective screening tools. Cross-sectional studies suggest an estimated prevalence of 5-10% in women of reproductive age overall (1) and as high as 20-30% in women suffering from infertility (4).

The gold standard of diagnosis for peritoneal disease is laparoscopy which is an invasive method that cannot be used as a screening method which potentially misses a proportion of patients with relatively mild symptoms. Studies have shown a 7-9 years diagnostic delay for endometriosis in the UK and worldwide, which could potentially aggravate the disease for being left untreated (5).

The main treatment methods of endometriosis include surgical removal of ectopic tissue and/or hormonal treatment to supress ovarian function which are associated with adverse effects such as artificially-derived menopause, low mood, spotty skin and breast tenderness. In addition, treatment medicines are mostly contraceptive which may be counterproductive for some women in this population of reproductive age (1).

Endometriosis is a complex disease caused by a mix of genetic and environmental factors. Family studies showed an aggregation of endometriosis

cases in related versus unrelated female population, indicated the importance of genetic risk factors of endometriosis (6). A large twin study of 3,096 Australian female twins reported a 51% heritability for endometriosis (7). Menstrual and reproductive history has been identified as established risk factor for endometriosis. Earlier age (< 12 years) at menarche (8) and shorter menstrual cycles (< 26 days) (9) were consistently found to be associated with endometriosis in several studies, perhaps through increased exposure to hormones or greater frequencies of menstruation. Also, several studies reported a greater risk of endometriosis in leaner women with a lower body mass index (BMI) (10,11). In a cohort study of 116,430 female nurses with 20 years of follow-up, endometriosis was inversely associated with early adult BMI (body mass index) and may correlate with a peripheral body fat distribution (10). Genetic studies have further reinforced this association (12), consistent with the epidemiological study results. Cigarette smoking was reported as a potential risk factor for endometriosis but the effect might differ in fertile and infertile women (13). Diet was also found to play a role in endometriosis risk but evidence is mixed. For example, a case-control study conducted in an Italian hospital cohort reported that green vegetables (OR [95%CI]: 0.3 [0.2–0.5]) and fruit (OR [95%CI]: 0.6 [0.4–0.8]) were found to be protective for endometriosis while red meat consumption (OR [95%CI]: 2.0 [1.4–2.8]) was found to increase endometriosis risk (14). Yet another case-control study conducted in the US population reported an increased endometriosis risk with higher fruit consumption (OR [95%CI]: 1.5 [1.2–2.3]) and null association with red meat intake (15), perhaps owing to reverse causation. In addition, some studies reported that environmental exposure to endocrine-disrupting chemicals, such as polychlorinated biphenyl and dioxin, might increase the risk of developing endometriosis by disrupting hormone systems and/or

dysregulating immune response (16). However, findings have been inconsistent perhaps owing to small sample sizes, different disease ascertainment methods and varying length/frequency of exposure (17).

While the aetiology of endometriosis is largely unknown, the most widely accepted hypothesis for the pathogenesis of endometriosis is the retrograde menstruation theory proposing the backward flux of menstrual debris that contains endometrial cells flows through the fallopian tubes into the pelvic cavity during menstruation to explain the origin of viable endometrial cells that adhere to peritoneal surfaces and result in endometriotic lesions (18). However, as retrograde menstruation is present in almost all women with fallopian tubes (18) and only a proportion of women develop endometriosis, retrograde menstruation must be regarded as a physiological phenomenon. Aberrations in the immune system of endometriosis patients have been proposed, preventing clearance of ectopic endometrial cells and allowing for their implantation, survival, and maintenance outside the uterus (19). Studies have also shown an escape of cells from immune surveillance by analysing peritoneal environment in endometriosis (20). While the exact mechanisms of immunosurveillance evasion by ectopic endometrial cells remain unclear, several hypotheses have been proposed to explain this phenomenon.

An increased expression of ICAM (intercellular adhesion molecule)-1 was found in ectopic endometrial cells which could bind to leukocyte function antigen-1 (LFA-1) and makes leukocytes less available to recognize the aberrant endometrial cells (21). Also, an overexpression of antiapoptotic factors and a decreased expression of proapoptotic factors was found in ectopic endometrial cells which may interfere in peritoneal homeostasis to aid development of endometriosis (22).

Moreover, an increased FasL expression was found in stromal cells in the peritoneal environment in endometriosis patients which could aid immunosurveillance escape (20).

Abnormalities in almost all types of immune cells have been identified, including increased levels of peritoneal neutrophils and macrophages, reduced cytotoxic function of natural killer cells, and aberrant numbers of T and B lymphocytes that aid endometriotic cell growth, maintenance, invasion, and angiogenesis (23). A significant increase of macrophages was observed in the ectopic endometrium (24,25), which might play a key role in the development of endometrial lesions and concomitant inflammation. Macrophages were identified to co-occur in increased numbers with nerve fibres in and around peritoneal endometrial lesions (26), with the hypothesis that macrophages and nerve fibres interact to promote pain symptoms associated with endometriosis via oestradiol as a key mediator (27,28).

An increased neutrophil infiltration into ectopic uterine tissue was found to be dominant in early stages endometriosis (29,30), which can generate inflammation, particularly through the secretion of IL-17A (23). NK cells were also found to be involved in the pathogenesis of endometriosis with a reduced cytotoxic activity against ectopic endometrial cells. NK cells can eliminate cells that present autoantigens; therefore, their reduced activity in endometriosis may correlate with advanced disease stages (31,32) and may explain the autoimmunity observed in the disease (33).

Additionally, IL-6, IL-15, transforming growth factor (TGF-β) were found to be highly expressed in the peritoneal fluid of women with endometriosis, which has been demonstrated to inhibit NK cell function in vitro (34). Higher levels of IL-17 was

also found in the endometriotic environment, which may contribute to the development of endometriosis by stimulating cytokine production that induce angiogenesis and inflammation (35,36). An imbalance between Th1/Th2 cells was also observed in ectopic endometrial tissues which leads to abnormal cytokine secretion and inflammation, which continues to induce lesion progression (37).

Moreover, an increasing amount of evidence suggested that women with endometriosis are suspectable for immunological disorders. Epidemiological evidence has emerged with a higher prevalence of immunological conditions reported in women with endometriosis, supporting the notion of an aberrant response by the immune system in women with endometriosis (38). Also, numerous candidate gene studies of endometriosis investigated immune-related genes in endometriosis patients and found a higher expression of several immune-related genes in endometriosis patients (39). Moreover, there is growing evidence of increased levels of various serum autoantibodies identified in the serum and peritoneal fluid of endometriosis patients, spurring enthusiasm among researchers to investigate their potential role as biomarkers for endometriosis. Several studies further confirmed the presence of these antibodies. However, a recent series of Cochrane reviews on blood biomarkers and urinary biomarkers for endometriosis found that although several antibodies have been indicated to be increased in women with endometriosis, only anti-endometrial antibodies and interleukin-6 were found to be useful for detecting endometriosis but their accuracy still cannot replace the standard surgical diagnosis (40,41), supporting conclusion from earlier systematic reviews (42) and clinical guidelines (33).

The phenomenon that females have a generally higher prevalence of many immunological diseases is intriguing which could potentially support a potential role

of hormonal and reproductive factors, which are important in the pathogenesis of endometriosis, are also important in the development, activity and severity of several immunological diseases. For example, it is estimated that amongst 80% of the 8.5 million people with autoimmune diseases in the U.S are women (43). Moreover, women were found to have an increased risk of immunological diseases, such as a 2 to 3 times increased risk of developing multiple sclerosis and rheumatoid arthritis (43). This mounting evidence suggests that the reproductive and hormonal factors might play a role in immunological disorders, and also an association with oestrogen-driven diseases including endometriosis. It suggests there may be biological pathways that mediated by hormonal and reproductive factors which could explain the observed increased prevalence of immunological diseases in women with endometriosis.

Given observed disturbances in immune homeostasis of endometriosis patients have been reported by a number of studies, investigating the potential link between endometriosis and immunological disorders in detail is an obvious field of interest that needs to be explored. Concern of immunological disorder risk was one of the top ranked research questions listed by the James Lind Alliance priority setting partnership that endometriosis patients want answering (https://www.jla.nihr.ac.uk/priority-setting-partnerships/endometriosis/). Although there is substantial evidence of an epidemiological link between endometriosis and autoimmune(immunological) diseases (for which I conducted a systemic review detailed in Chapter 2), it is unclear to what extent these links could be explained by selection and diagnostic biases, or can be explained by environmental or genetic risk factors or biological basis.

My DPhil project aims to understand the association between endometriosis and immunological disorders, especially the question if women with endometriosis have a significantly increased risk of developing immunological diseases. This project will analyse data collected from population and to establish potential temporal sequence between the two. Robust quantification of the association as well as the temporal sequence between endometriosis and immunological diseases could facilitate understanding of the causes and consequences of both endometriosis and immunological diseases, providing potential reference to inform scientific discovery and improve clinical practice. For example, considering the current medication for endometriosis is mainly hormonal treatment with considerable side effects due to interference with oestrogen levels. New evidence of a robust, genetically underpinned association between endometriosis and immunological diseases would help to provide novel drug targets such as immuno-modulators and development of new diagnostic tools for endometriosis.

HYPOTHESIS

The primary hypothesis for my thesis project is that women with endometriosis have an increased risk of developing immunological diseases subsequent to their endometriosis diagnosis. In addition, endometriosis might be causal to subsequent development of certain (if not general) immunological diseases. Lastly, that the predisposed risk by endometriosis that potentially leads to immunological diseases could be explained by a shared genetic/biological basis.

RESEARCH OBJECTIVES AND STUDY DESIGNS

My thesis aims to understand if women with endometriosis are more likely to develop immunological diseases subsequently, if endometriosis is causal to immunological diseases, and if there is a genetic/biological basis if any association

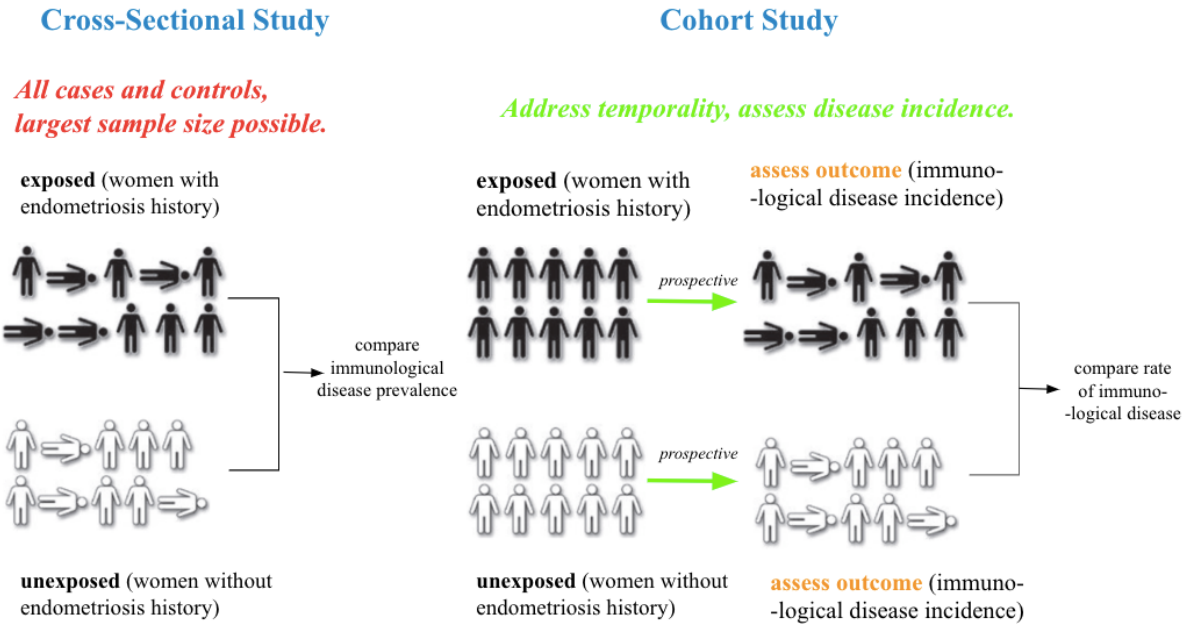
between endometriosis and immunological diseases is be found. The below described research and analysis were conducted to answer my research questions.

Firstly, in Chapter 2, I conduct a systemic review summarizing existing evidence of published literature that studied an association with or without a temporal sequence between endometriosis and auto(immunological) diseases. Also, quality of the reviewed studies was evaluated by GRADE evaluation approach with discussions on study design strengths and limitations. A meta-analysis is conducted for combinable study results on the reported association between endometriosis and auto(immunological) diseases by a fixed or a random effect model. If any reviewed study reported a temporal sequence, this is noted and discussed. This systemic review could facilitate our understanding on the existing evidence and also help direct the phenotypic association analysis on the immunological disease risk in women with endometriosis as detailed in Chapter 3.

In Chapter 3, based on the hypothesis that women with endometriosis have an increased risk to subsequently develop immunological diseases, I conduct phenotypic analysis by analysing one of the largest scale datasets available, UK Biobank (UKBB). A cross-sectional study is conducted first looking at the prevalence of 29 immunological diseases in women with endometriosis versus those without (Figure 1.1 Hypothesis diagram for cross-sectional study and cohort study). A prospective cohort study is also conducted following up two groups of women, those ever diagnosed with endometriosis versus those never diagnosed with endometriosis, to investigate their risk of developing immunological diseases subsequently (Figure 1.1 Hypothesis diagram for cross-sectional study and cohort study). Robustness of the phenotypic association analysis is tested through adjustment for confounders as well as sensitivity analysis of different case

ascertainment methods (self-reports, hospital records, surgeries, severe endometriosis).

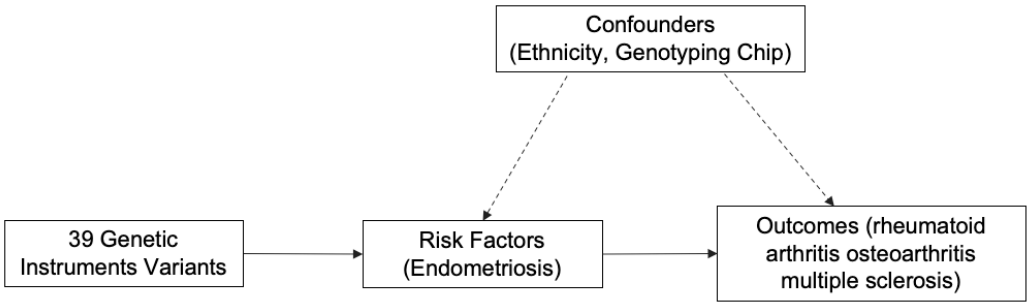
Figure 1.1 Hypothesis diagram for cross-sectional study and cohort study



In Chapter 4, I investigate at the genetic level if endometriosis is causal to (certain) immunological diseases (Figure 1.2 Directed acyclic graph for Mendelian randomisation study). Genome-wide association studies (GWAS) is performed for 8 immunological diseases (ankylosing spondylitis, coeliac disease, inflammatory bowel disease, multiple sclerosis, osteoarthritis, psoriasis, rheumatoid arthritis and systemic lupus erythematosus) with relatively large sample size in UKBB. Publicly available large-scale GWAS results for these 8 immunological diseases are meta-analysed with UKBB GWAS results. Genetic correlation between endometriosis and these 8 immunological diseases by using GWAS meta-analysis results are investigated by LD regression analysis, amongst which, 3 immunological diseases (multiple sclerosis, rheumatoid arthritis, osteoarthritis) found to be genetically correlated with endometriosis. These 3 immunological diseases are studied further

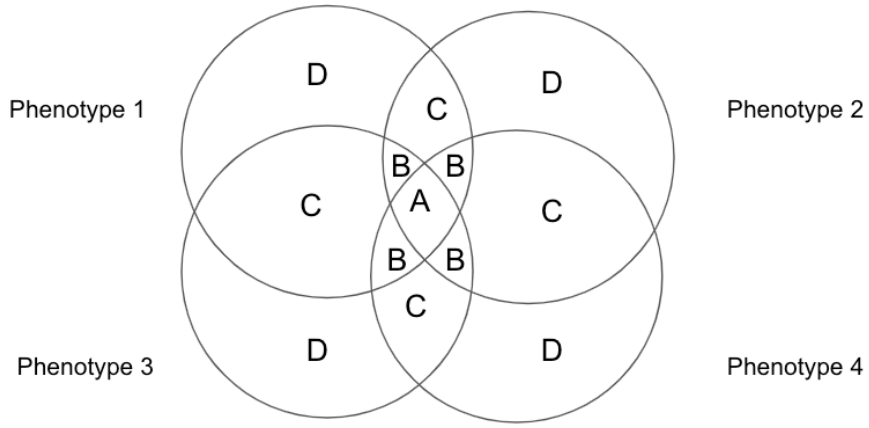
by Mendelian Randomisation analysis to investigate if endometriosis is causal to these 3 immunological diseases.

Figure 1.2 Directed acyclic graph for Mendelian randomisation study



In Chapter 5, based on the hypothesis that there are shared genetic risk factors for genetically correlated endometriosis and immunological diseases, I conduct a multi-trait genetic association analysis (MTAG) for the 3 immunological diseases (multiple sclerosis, rheumatoid arthritis, osteoarthritis) genetically correlated with endometriosis. The potentially shared genetic variants are identified via MTAG analysis by utilising GWAS meta-analysis results for endometriosis and these 3 immunological diseases (Figure 1.3 Hypothesis diagram for multi-trait genetic association analysis). I also research the biological functions for the identified shared genetic variants via eQTL analysis to investigate associated biological pathways that might provide reference for the shared aetiology between endometriosis and the identified immunological diseases.

Figure 1.3 Hypothesis diagram for multi-trait genetic association analysis (genetic risk factors overlap across genetically correlated phenotypes)



*A section: shared genetic risk factors between all 4 phenotypes; B sections: shared genetic risk factors between 3 of the phenotypes; C sections: shared genetic risk factors between 2 of the phenotypes; D sections: genetic risk factors that are not shared by any of the phenotypes.

ROLE OF AUTHOR

I declare that the majority of my DPhil research project is my own work including the statistical analysis, thesis writings, and generation of tables/figures. The research question of the association between endometriosis and immunological diseases was initiated by my supervisor Prof Krina Zondervan. Prof Krina Zondervan also helped to apply and open my access for UKBB data for the statistical analysis of this project. This research project received funding from Wellbeing of Women UK.

For the systematic review, I received help from Ms Shona Kirtley (a librarian worked for the University of Oxford) to develop search strategies for different literature search databases. Ms Shona Kirtley also helped to find the full-text for the identified publications to be included in the systemic review. I received help from Qian Feng for being the 2nd reviewer for screening, Dr Marina Kvaskoff for being the 2nd reviewer for publication quality assessment.

For the phenotypic analysis, I received help from Professor Stacey Missmer and Dr Holly Harris for advice on cohort analysis and the selection of confounders.

For the genetic analysis, I received help from Dr Nilufer Rahmioglu for providing example scripts for conducting GWAS, GWAS meta-analysis, LD regression analysis and MR analysis. Dr Nilufer Rahmioglu also kindly helped to debug and quality check my codes when there were errors. I also received help from Professor Andrew Morris for his advice on the MR analysis methods. Professor Chris Cotsapas kindly shared the large-scale GWAS meta-analysis results for multiple sclerosis from International Multiple Sclerosis Genetic Consortium, which is not publicly available. I received help from Professor Julian Knight and Dr Hai Fang on the definition and classification of immunological diseases. During my Viva, Professor Ruth Travis and Mrs Dorte Rytter provided advice for utilising MR PRESSO for MR sensitivity analysis besides other comments to improve the MR analysis as well as phenotypic association analysis.

PUBLICATIONS AND CONFERENCES

The systemic review (as described in Chapter 2) has been published in Human Reproduction Update (link: https://doi.org/10.1093/humupd/dmz014). This systemic review is mainly my own work. Besides the help I have received as listed in the “ROLE of AUTHORS” section, I have received co-author comments from Professor Stacey Missmer as well as comments from my supervisors Professor Krina Zondervan, Dr Nilufer Rahmioglu and Professor Christian Becker. The phenotypic and genetic analysis described in Chapter 3-5 is manuscript ready to be submitted for Nature Communications. The analysis is mainly my work, my supervisor Dr Nilufer Ruhmioglu drafted the journal manuscript adapting parts from my thesis writings.

Also, I have presented my thesis project work on the below conferences:

- "Do women with endometriosis have an increased risk for immunological diseases? A systematic review of the literature and study of 273,404 women from UK Biobank"; invited oral presentation by European Society of Human Reproduction and Embryology meeting 2019; Vienna, Austria; 24th June 2019.
- "Unravelling the association between endometriosis and immunological diseases: A systematic review of the literature and study of 273,404 women from UK Biobank"; invited oral presentation by National Endometriosis Network Meeting 2019; Edinburgh, UK; 15th September 2019.
- “Unravelling the association between endometriosis and immunological diseases: a large-scale population-based study”; invited oral presentation by 14th World Congress on Endometriosis; Remote; 11th March 2021.
- “Unravelling the association between endometriosis and immunological diseases”; invited oral presentation by 15th World Congress on Endometriosis; Edinburgh, UK; 5th May 2023.

Chapter 2: Systematic Review and Meta-Analysis on Population-Based Studies on Association between Endometriosis and (Auto)immune Diseases

INTRODUCTION

Endometriosis is a chronic gynaecological disorder characterized by the presence of endometrial-like tissue outside the uterus (1). The aetiology of endometriosis is complex and under-explored, yet abnormalities in the immune system of women with endometriosis have been consistently demonstrated and may reflect the chronic inflammatory response to the presence of ectopic endometrium. In addition these abnormalities may imply that the pre-disease milieu is supportive of adherence, survival and maintenance of these ectopic endometrial tissues (23,44–46). it has been hypothesised therefore that women affected by endometriosis have an immunity-associated disorder and an association between endometriosis and immunological diseases has been proposed by several studies (45,47–49). Despite an increasing number of studies reporting an association between endometriosis and immunological diseases, the quality of the evidence from varying analysis methods and mixed study results is unclear. A systemic review is a powerful research tool which can summarize existing studies in an efficient way to present, analyse and critique current evidence and to identify potential knowledge gaps which can lead to further research. In the hierarchy of evidence, systemic reviews and meta-analyses are considered a higher quality of evidence than individual observational studies in supporting clinical decision making processes with less risk of bias (50). However, the quality of the outcome of a systematic review heavily depends on the available evidence.

A systematic review, in comparison to traditional narrative reviews, involves a detailed and comprehensive search strategy, review process and quality appraisal of reported evidence by identifying, assessing and synthesizing all relevant studies on a particular topic. A meta-analysis is, where possible, frequently included in a systemic review which involves statistical synthesisation of numerical study results from all eligible studies into a single quantitative estimate or summary effect size (51). Eligibility for study inclusion should be pre-defined and requires assessment of factors including study design, the risk of bias, type of study and sample size. Also, the heterogeneity between study results is evaluated before combining study results in a meta-analysis (51).

The aim of this chapter is to systematically review and to summarize existing evidence of published literature that studied an association with or without a temporal sequence between endometriosis and auto(immunological) diseases and to conduct a meta-analysis of combinable results. Only population-based studies were included to better represent larger populations. In addition, only peer-reviewed literature was included for scientific rigor and quality. The reported population-based studies were evaluated on their study design, selection of study population, adjustment of confounders, disease ascertainment methods, investigation of temporality, statistical methods, risk of bias to rank the quality of evidence. This systemic review on the association between endometriosis and (auto)immune diseases can facilitate our understanding of the existing evidence and inform future robust population studies. The main results from a literature search until April 2018 were published in 2019 (38). In this chapter, I described the systemic review conducted for literatures published before 7th April 2018 and also described literatures published after 7th April 2018 by a targeted literature review method.

METHODS

Search strategy

This systematic review was registered and accepted for inclusion in PROSPERO in December 2017 (PROSPERO ID Number: CRD42017084175).

A protocol-driven systematic search for articles reporting on an association between endometriosis and autoimmune disease was conducted using the MEDLINE (via OVID), Embase (via OVID), Web of Science Core Collection (Indexes=SCI-Expanded, SSCI, ESCI, CPCI-S, CPCI-SSH), and CINAHL (via EbscoHost) databases. Each database was searched from the database inception date until 7th April, 2018. Search terms included a combination of database-specific controlled vocabulary terms and free-text terms relating to endometriosis (e.g. “endometrio*”) and autoimmune diseases (e.g. “autoimmune diseas*”, “autoimmune response”, “autoimmunit*”, “autoantibod*”). We also included search terms for 23 autoimmune diseases (Addison's disease, autoimmune hepatitis, antiphospholipid syndrome, alopecia areata, coeliac disease, Crohn's disease, dermatitis herpetiformis, Graves' disease, Hashimoto's autoimmune thyroiditis, immune thrombocytopenic purpura, Kawasaki disease, multiple sclerosis, narcolepsy, pernicious anemia, primary biliary cirrhosis, rheumatoid arthritis, rheumatic fever, scleroderma, Sjögren's syndrome, systemic lupus erythematosus, temporal arteritis, type 1 diabetes, ulcerative colitis, vitiligo) that were reported to be most prevalent (i.e. with a worldwide prevalence rate ≥ 10 per 100,000 based on Hayter & Cook (2012)’s review that included a comprehensive list of autoimmune diseases (52)) in combination with terms representing endometriosis to capture other potentially relevant articles. To be as comprehensive as possible, the search was not restricted

to any study types. An example search strategy for the MEDLINE database is described in Appendix Supplementary Document 1.

Inclusion criteria and study selection

Study inclusion criteria comprised peer-reviewed publications with population-based studies that reported an association between endometriosis and any type of autoimmune diseases. Case reports and case series were excluded as their sampling is from limited cases and thus representation of the larger populations is unknown. Review papers, meta-analysis, organisational guidelines, editorial letters, and expert opinions were excluded in order to avoid duplication and erroneous weighting toward more frequently cited or discussed publications. Conference abstracts were also excluded as their full study reports were not obtainable to be assessed and their scientific rigor has not been peer-reviewed. Moreover, only studies published in English language journals were included.

All articles identified by searching the four databases were imported into Mendeley for screening. There were two rounds of screening for study inclusion. In the first round, two reviewers (Nina Shigesi and Qian Fang) performed screening separately by reviewing titles, abstracts and key terms for relevance of both endometriosis and autoimmune diseases. In the second round of screening, full text of the articles identified during initial screening was retrieved and read in detail to assess for eligibility. Possible discordance during study selections were discussed with a third reviewer (Dr Nilufer Rahmioglu) to reach a consensus.

Data extraction

Data from included studies was extracted into a standard form detailing the author(s), publication year, country, time during study conduct, study design,

ascertainment method of diseases and control or comparison group selection, number of study participants, reported risk estimates of endometriosis in association with autoimmune diseases, any adjustment for confounding factors in generating the effect estimates, and any measures taken in addressing temporality for diagnosis of endometriosis and autoimmune diseases. When effect estimates for association between endometriosis and autoimmune diseases were not listed in the original article but enough information was available, their effect estimates were calculated by Reference Man software Version 5.3. Also, where the listed effect estimates in the original article were presented with enough information to be recalculated, such effect estimates were calculated again by Reference Man software to check for accuracy of the original report.

Quality assessment

Quality assessment was performed based on GRADE criteria (53) and carried out separately by two reviewers independently (Nina Shigesi and Dr Marina Kvaskoff). Guided by the Cochrane group, the quality of evidence was assessed for each study outcome of interest (any reported autoimmune diseases in association with endometriosis by at least 3 studies) based on study design and factors that could reduce the quality of evidence (risk of bias, inadequacy or inaccuracy of statistical analyses, inconsistency of results, indirectness, imprecision, publication bias) as well as factors that could increase the quality of evidence (population size, number of outcome events, adjustment for potential confounders, temporality of diagnosis). Any discordance during the assessment of the quality of evidence were discussed with a third reviewer (Professor Christian Becker) to reach consensus.

Data synthesis and meta-analysis

Meta-analyses were performed for each autoimmune disease reported to be associated with endometriosis by at least 3 studies, and were also stratified by study design (cross-sectional, case-control, prospective cohort or retrospective cohort study) for each outcome. For cross-sectional and case-control studies, raw data from each study was extracted to calculate a Mantel Haenszel odds ratio (OR) with 95% confidence intervals (CIs). For cohort studies, an inverse variance probability weighted model was used to pool study results to calculate a rate ratio (RR) with 95% CIs. As almost all of the cohort studies had adjusted for potential confounding variables (albeit not consistent covariates among them), pooling raw data was not possible. Statistical heterogeneity among studies for each outcome was assessed by inspecting the study-specific magnitudes of effect, and the heterogeneity (I^2) statistics. The I^2 statistics for heterogeneity in meta-analysis was interpreted based on the GRADE approach recommended by Cochrane group (54). In meta-analyses of multiple studies for a specific outcome, a fixed-effect estimate was calculated if I^2 heterogeneity = 0%, however, if I^2 heterogeneity ≥ 0% in the meta-analysis, a random-effect estimate and a fixed-effect estimate were both calculated for sensitivity analysis.

Forest plots were constructed to present risk estimates and meta-analysis results for each autoimmune disease reported by at least 3 studies to be associated with endometriosis.

In meta-analyses of cohort studies, hazard ratio (HR) and standardised incidence ratio (SIR) were treated as equal to the rate ratio or relative risk (RR).

In addition, for study results that didn't explicitly specify the type of autoimmune disease but instead used broad terms such as "rheumatic disease",

“arthritis”, “colitis”, or “autoimmune diseases”, their study results and risk estimates were presented in the data extraction characteristics form, but they were not included in the meta-analysis or forest plots.

A sensitivity analysis was performed for the meta-analyses by taking out each study one at a time from the meta-analysis and recalculating the pooled effect size and I^2 to assess for the influence of each study on the pooled effect size if there were at least 3 studies included in the meta-analysis.

Studies published after 7th April 2018

This systemic review and meta-analysis were conducted during the first year of my DPhil study with the search for literature published by 7th April 2018. A rerun of the search conducted in August 2022 showed that there were a few studies published after 7th April 2018, which met the eligibility criteria and could have been included in this review. These later published population-based studies were summarized by a targeted literature review method, their eligibility was checked using the same inclusion/exclusion criteria as detailed above. Data from these newly published studies were similarly extracted into a standard form.

The quality of the additionally available evidence was assessed using the same strict criteria as those used in the published systematic review, including factors that could reduce the quality of evidence (risk of bias, inadequacy or inaccuracy of statistical analyses, inconsistency of results, indirectness, imprecision, publication bias) as well as factors that could increase the quality of evidence (large sample size and number of outcome events, adjustment for potential confounders, temporality of diagnosis). Assessed quality of the later published studies was discussed in the result section, but the risk estimates of the later published studies were not included in the meta-analysis.

RESULTS

Study selection

The initial search retrieved 653 results from MEDLINE, 1,543 from Embase, 49 from CINAHL, and 732 from Web of Science Core Collection. All articles identified in the four databases were imported into Mendeley for screening. After removing duplicates, there were 2,070 papers uploaded to Mendeley for first-stage screening. After the first-stage screening by reviewing titles, abstracts and key terms related to endometriosis or autoimmune diseases, 1,948 publications were excluded for not addressing both endometriosis and autoimmune diseases. During the first round of screening, 122 articles were identified to be potentially relevant and then assessed for eligibility. 96 articles were excluded for not investigating an association between endometriosis and autoimmune diseases at population-level (N = 77), being a review article or meta-analysis (N = 8), a conference abstract (N = 10), expert opinion (N = 1), case report (N = 1). Finally, 26 articles met all the inclusion criteria and were included in this review, 14 of which were included for quantitative synthesis for having calculable risk estimates (Figure 2.1).

Study characteristics

A detailed description of key characteristics for the 26 included studies is shown in Appendix Table x2.1. Briefly, 8 (30.8%) studies were implemented in the population in the United States, 12 (46.2%) in Europe, 3 (11.5%) in South America, and 3 (11.5%) in Asia. With regard to study design, 6 (37.5%) studies were cross-sectional, 12 (46.2%) were case-control studies, and 6 (37.5%) were cohort studies (including 4 prospective cohort studies and 2 retrospective cohort studies). 2 (7.7%) studies did not generate risk estimates for an association between endometriosis

and autoimmune diseases, but instead compared clinical manifestations and serum auto-antibody test results for endometriosis and systematic lupus erythematosus (55) or treatment methods and serum auto-antibody test results for endometriosis and inflammatory bowel disease (56).

For the reported autoimmune diseases in association with endometriosis, one group (48) conducted a nation-wide cross-sectional study in Denmark estimating the prevalence and pairwise comparison of 31 autoimmune diseases (endometriosis was also listed as one of the autoimmune diseases under study). Furthermore, 9 (34.6%) studies reported on systematic lupus erythematosus (SLE), 6 (23.1%) on Sjögren's syndrome (SS), 5 (19.2%) on rheumatoid arthritis (RA), 4 (15.4%) on autoimmune thyroid disorders (ATD), 4 (15.4%) on inflammatory bowel disease (IBD), 4 (15.4%) on coeliac disease (CLD), 3 (11.5%) on multiple sclerosis (MS), 1 on Addison's disease (57), and 1 on rheumatic disease (58).

Ascertainment of endometriosis, immunological diseases and disease-free controls

For the ascertainment of endometriosis diagnosis, 5 studies were based on self-reported data, 1 was based on self-reported data validated by hospital records in some of the study participants, and 20 were based on hospital records, amongst which 6 studies further confirmed endometriosis diagnosed by surgery and/or histology. Four studies categorized endometriosis diagnosis by the Revised American Society for Reproductive Medicine classification of endometriosis (r-ASRM classification) into Stage I/II vs. Stage III/IV endometriosis. For ascertainment of autoimmune disease diagnosis, 6 studies were based on self-reported data, 2 were based on self-reported data validated by hospital records in some of the study

participants, for 18 studies, the disease ascertainment were based on hospital records.

In regards to the selection of the comparator group for women with endometriosis, two (7.7%) studies used prevalence statistics from the general female population identified from the literature as the comparison group. Two (7.7%) studies used age- and period- specific incident rates identified from national statistics as risk estimates for the comparison group, 8 (30.7%) studies identified general female population from nationwide registers. Seven (26.9%) studies selected both women with endometriosis and without endometriosis from the same region/or hospital. Lamb et al. (1986) used friend-controls of recruited endometriosis patients (59). Lee et al. (2016) compared women diagnosed with both endometriosis and IBD and compared them to women with IBD but without endometriosis matched by age and IBD type (56). The other 5 (19.2%) studies recruited women who attended obstetric/gynaecological clinics or a family planning unit.

Of all the included studies, 7 (26.9%) took measures to address the temporal sequence between the diagnosis of endometriosis and autoimmune diseases while 6 of the studies looked at incidence of autoimmune diseases after diagnosis of endometriosis treating autoimmune diseases as the outcome and endometriosis as the exposure, and 1 study looked at incidental endometriosis after diagnosis of autoimmune diseases treating endometriosis as the outcome and autoimmune disease as the exposure. The study design, the number of women with endometriosis, the number of women with autoimmune diseases as well as the selection and number of controls are detailed in Appendix Table x2.1. With regard to the number of autoimmune diseases investigated, 12 studies had a small number of women with autoimmune diseases (≤ 100), 9 had a relatively large number of

women with autoimmune diseases (100-1000), and 4 had a large number of women with autoimmune diseases (≥ 1000). With regard to the number of women with endometriosis investigated, 8 studies had a small number of women with endometriosis (≤ 100), 9 had a relatively large number of women with endometriosis (100-1000), and 8 had a large number of women with endometriosis (≥ 1000). Four studies reported a large effect (OR/RR/SIR/HR ≥ 2) for the association between endometriosis and autoimmune diseases. As for adjustments of confounding factors or stratum-specific evaluation of effect modifiers or interactions in estimating risks, 3 (11.5%) studies included comprehensive adjustment for factors such as age, residence location, hormonal factors or other potential confounding health conditions, 12 (46.2%) studies had made some adjustments of confounding factors such as age, sampling year, location of residence, and the other 11 (42.3%) studies did not adjust for any confounding factors.

Data synthesis and meta-analysis

Of the 26 studies in this systematic review, Eaton et al. (2007) conducted a nationwide cross-sectional study in Denmark using hospital record data to estimate the prevalence and pairwise comparison of 31 autoimmune diseases (endometriosis was also listed as an autoimmune disease) (48). In this study, women with endometriosis were found to have a greater risk of 28 autoimmune diseases including systemic lupus erythematosus, coeliac disease, multiple sclerosis in comparison to the general Danish female population. However, the associated CIs of odds ratios were not reported in the article, hence providing limited evidence. The following paragraphs discuss the other epidemiological studies excluding Eaton et al. (2007)'s study that reported on an association between endometriosis and autoimmune diseases.

Systemic lupus erythematosus (SLE)

Sinaii et al. (2002) reported, in a cross-sectional study of 3,680 U.S. women, a significantly higher prevalence of SLE (the outcome) in women with endometriosis (the exposure) in comparison to the general U.S. female population (prevalence odds ratios (OR) = 20.7 (95% CI: 14.3-29.9), P < 0.001) (47). This exceptionally high risk estimate can probably be explained by the self-reported nature of disease ascertainment from the study participants who were probably very conscious of the health impact by endometriosis as they were all recruited from an endometriosis patient association.

Smith et al. (1993) conducted a small case-control study in 22 women with endometriosis (the exposed group) versus 185 endometriosis-free women with uterine fibroids (the unexposed group), and found that SLE prevalence (the outcome) was higher in women with endometriosis (SLE prevalence: 9.09% versus 0% in women with endometriosis versus fibroids) (60). However, it should be noted that women with endometriosis have been found to be at a significantly increased risk of uterine fibroids (61). Also, considering the small sample size of this study, this study was at a high risk of bias.

Meta-analysis of 3 case-control studies that studied SLE disease outcome in women with endometriosis (the exposed group) and without endometriosis (the unexposed group) by Grimes et al. (1985), Matorras et al. (2007) and Harris et al. (2016a) (62–64) and 2 prospective cohort studies that investigated subsequent SLE risk as the outcome in women with endometriosis (the exposed group) versus those without endometriosis (the unexposed group) by Nielsen et al. (2011) and Harris et al. (2016b) (65,66) has shown a significantly greater risk of SLE in women with endometriosis (OR for case-control studies: 1.36 (95% CI: 1.07-1.73), P = 0.010, I^2 =

44%; Relative risk (RR) for cohort studies: 1.74 (95% CI: 1.10-2.77), P = 0.020, I^2 = 0%) (Figure 2.2a). Among these 5 studies in the meta-analysis, 2 case-control studies (62,67) had a high risk of bias in their study design and a small sample size; the other single case-control study and the 2 prospective cohort studies (64–66) were of higher quality because of their large size and appropriate adjustment for confounders. When restricting to these 2 prospective cohort studies of high quality (65,66), the results were consistent in demonstrating a statistically significant increased SLE risk in women with endometriosis versus those without endometriosis with low heterogeneity in magnitude of effect by meta-analysis (Figure 2.2a). Lastly, Pasoto et al. (2005) compared musculoskeletal and serum immunologic abnormalities in a cross-sectional study comparing 3 groups of women with endometriosis versus SLE versus women without endometriosis or SLE recruited from a hospital in Brazil, but did not find any noticeable similarities among these women possibly because of the indirect study approach and small sample size (55).

Sjögren's syndrome (SS)

Sinaii et al. (2002) reported in a cross-sectional study of U.S. women a greater risk of SS (the outcome) in women with endometriosis (the exposed group) in comparison to the general U.S. female population (prevalence OR = 23.9 (95% CI: 15.5-36.5), P < 0.001), however, as discussed above, there was a high risk of bias in their study design (47). Meta-analysis of 3 case-control studies (67–69) conducted in Norway, Spain and Taiwan revealed a 76% greater risk of SS (outcome of interest) in women with endometriosis (the exposed group) versus those without (the unexposed group) (OR [95%CI]: = 1.76 [1.39-2.21], P < 0.001, I^2 = 0%) (Figure 2.2b). A greater risk of developing SS (outcome of interest) in women with endometriosis (the exposed cohort) was also observed in the previously mentioned

prospective cohort study (65) that followed up 37,661 Danish women through hospital systems (Standardized Incidence Ratio (SIR) = 1.6 (95% CI: 1.3-2.0), P < 0.001).

Rheumatoid arthritis (RA)

Meta-analysis of 2 cross-sectional studies by Sinaii et al. (2002) and by Brouwer et al. (2017) reported a significantly increased RA risk (the outcome of interest) in women with endometriosis (the exposed group) in comparison to the general female population (OR [95%CI]: 1.50 [1.18-1.91], P = 0.002, I^2 = 0%) (Figure 2.2c) (47,70). Yet the poor quality for these 2 studies should be noted. However, in a case-control study (59), the greater risk for endometriosis (the outcome of interest) in women with RA history (the exposed group) and without RA history (the unexposed group) was found largely insignificant with a wide CI (OR [95%CI]: 3.07 [0.12, 77.50], P = 0.46) probably due to its small sample size (43 versus 43 women with and without endometriosis history). Meta-analysis of 2 prospective cohort studies by Merlino et al. (2003) and Harris et al. (2016a) (66,71) also suggested a greater risk of RA (the outcome of interest) among women with endometriosis (the exposed group), but this estimate was not statistically significant (RR [95%CI]: 1.46 [0.70-3.03], P = 0.31, I^2 = 0%) (Figure 2.2c) possibly due to the small sample size and wide CIs in the study conducted by Merlino et al. (2003) as the risk estimate in the study by Harris et al. (2016a) was significant.

Autoimmune thyroid disorder (ATD)

Meta-analysis of 3 case-control studies (72–74) has shown an increased risk of ATD (the outcome of interest) in women with and without endometriosis history (the exposed group), but this risk estimate was not significant with a wide CI and a

high I^2 for heterogeneity (OR [95%CI]: 1.36 [0.54, 3.45], P = 0.52, I^2 = 83%) (Figure 2.2d). The quality of evidence provided by the meta-analysis was low, since 2 of the studies (72,73) had a higher risk of bias in their study design for having a small sample size and unrepresentative control selection, the other study (74) was performed in a large study population (a cross-sectional study in 5,615 Korean women with endometriosis history) but were with no adjustment for confounders, and thus there is a high risk for bias.

Coeliac disease (CLD)

A greater risk of CLD (the outcome of interest) was reported to be associated with endometriosis (the exposure) in 2 case-control studies (OR [95%CI] by meta-analysis: 4.04 [1.53-10.65], P = 0.005, I^2 = 0% (75,76)) (Figure 2.2e). However, these 2 studies had a small sample size and wide CIs in risk estimates. Yet, in a large retrospective cohort study by Stephansson et al. (2011) that followed up 11,097 Swedish women with CLD (the exposure) in comparison to CLD-free female controls (77), a significantly higher risk of endometriosis (the outcome) was found to be associated with CLD (Hazard ratios (HRs) = 1.39 (95% CI: 1.14-1.70), P < 0.001).

Multiple sclerosis (MS)

For MS and endometriosis, the cross-sectional study by Sinaii et al. (2002) reported a 7-fold greater prevalence for MS (the outcome) in women with endometriosis (the exposure) in comparison to the general female population (prevalence OR = 7.1 (95% CI: 4.4-11.3), P < 0.001) (47). However, the issue of selective study population and wide CIs in the study by Sinaii et al. (2002) has been discussed. Nevertheless, in the prospective cohort study by Nielsen et al. (2011), a 20% greater risk for MS (the outcome) was observed in 37,661 Danish women with

hospital-diagnosed endometriosis (the exposure) in comparison to general female controls (SIR = 1.2 (95% CI: 1.1-1.5), P < 0.001) (65).

Inflammatory bowel disease (IBD)

De Silva et al. (2018) conducted a case-control study in 14,279 Danish women with IBD at time of conception and 1,832,732 women without IBD at conception based on hospital records during 1994-2015 and found an increased risk of pregnant women with IBD (the outcome) in women with endometriosis history (the exposure) (ulcerative colitis (UC): OR [95%CI]: 1.97 [1.67-2.31]; Crohn's Disease (CD): OR [95%CI]: 2.16 [1.84-2.55]; IBD: OR [95%CI]: 2.06 [1.83-2.31], P < 0.001) (78). Also, an earlier cohort study (79) during 1977-2007 using hospital records in Danish women reported a significantly increased incidence of IBD (the outcome) in women with endometriosis history (the exposure) in comparison with women without known endometriosis (UC: SIR = 1.5 (95% CI: 1.3-1.7); CD: SIR = 1.6 (95% CI: 1.3-2.0); IBD: SIR = 1.5 (95% CI: 1.4-1.7), P < 0.001). The two studies in Danish women using hospital records during two different periods provided higher quality evidence for an increased risk of IBD in women with endometriosis due to their large sample size, hospital-based disease ascertainment, and the ability to approach temporality between IBD and endometriosis. Lee et al. (2016) studied endometriosis and IBD with an indirect approach by comparing the IBD phenotype, prognosis, treatments among women with IBD and with or without co-morbid endometriosis, and no significant difference between two groups were found except a slightly higher rate of bowel strictures in women with both IBD and endometriosis (56). However, this indirect approach by Lee et al. (2016) and their small sample size (51 women with IBD and endometriosis versus 102 women with IBD alone) should be noted.

Other autoimmune diseases

In addition, Gemmill et al. (2010) reported, in a cross-sectional study, that the prevalence of Addison's disease (the outcome) in U.S. women with endometriosis (the exposure) was higher than the general U.S. females (2.31 per 1,000 population versus 0.09 per 1,000 population), but these prevalence estimates were too low to generate meaningful risk estimates for the studied association (57). Huang et al. (2016) in their retrospective cohort study following up 55,000 Taiwanese women through hospital systems described an increased risk of rheumatic diseases (the outcome) in women with endometriosis (the exposure) (OR [95%CI]: 1.37 [1.28-1.47], $P < 0.001$) compared to the general female population (58). Although rheumatic diseases were often recognized as autoimmune diseases such as SLE, SS, RA, they did not specify which kind of rheumatic diseases were studied.

Sensitivity analysis

A sensitivity analysis for each meta-analysis with at least 3 studies was conducted. Within each meta-analysis, each study was taken out respectively to assess for its influence on the overall risk estimates.

The high heterogeneity in the meta-analysis for studies on SLE risk or SS risk in women with and without endometriosis history mainly comes from the study results by Matorras et al. (2007) (67). In the meta-analysis of 3 case-control studies (72–74) for ATD risk in women with and without endometriosis, each study seemed to account for the high heterogeneity ($I^2 = 83\%$) .

For meta-analysis with a $I^2 = 0\%$ (which indicates there is no evidence of heterogeneity), a fixed-effect model was used for meta-analysis. As the random-effect estimates and fixed-effect estimates would provide different meta-analysis results because of giving different weight to each studies when $I^2 > 0\%$ with evidence

of heterogeneity, a switch between random-effect estimate and fixed-effect estimate for each meta-analysis was performed to assess small-study effects since the included studies in the random-effects meta-analysis, especially small studies, would be weighted relatively more equally than a fixed-effect analysis in the presence of heterogeneity indicated by I^2 of more than 0%.

A switch from a fixed-effect model to a random-effect model for the meta-analysis of 3 case-control studies for SLE risk in women with and without endometriosis history, the pooled OR became largely insignificant (OR [95%CI]: 1.21 [0.61-2.43], P = 0.59) with more weighing towards smaller studies. For the meta-analysis of 3 case-control studies for ATD risk in women with endometriosis history in comparison to those without, a switch from a random-effect model to a fixed-effect model to weight down for smaller studies, the pooled OR became significant with a P value of 0.04 (OR [95%CI]: 1.31 [1.02-1.68]).

Studies published after 7th April 2018

Since 7th April 2018 the date of my systemic review conducted at the 1st year of my DPhil study, later published studies were identified by a targeted literature review via searching key terms of autoimmune/immunological diseases and endometriosis in Pubmed and Google Scholar. 12 studies that were published after 7th April 2018 were identified and fulfilled the study inclusion/exclusion criteria. Information of these 12 studies is summarized in Appendix Table x2.2. Of these, 5 were conducted in European populations and 7 were conducted in Asian populations, amongst which 6 used the same Taiwan national insurance data source (Appendix Table x2.2).

Greenbaum et al., 2019 (80) conducted a cross-sectional analysis using data from a large healthcare plan database covering 2.1 million people in Israel to

investigate the prevalence of and the association between endometriosis, fibromyalgia, and autoimmune diseases. They compared the risk of autoimmune diseases (the outcomes) in women with co-occurrence of both endometriosis and fibromyalgia versus those with either of endometriosis or fibromyalgia, and reported an increased risk of SLE (OR [95%CI]: 1.83 [1.03–3.23], P value = 0.038) in women with co-occurrence of both endometriosis and fibromyalgia versus those with fibromyalgia but not endometriosis (OR [95%CI]: 4.11 [2.02–8.36], P value < 0.001, in women with co-occurrence of both endometriosis and fibromyalgia versus those with endometriosis but not fibromyalgia), SS (OR [95%CI]: 3.08 [1.52–6.20], P value = 0.002, in women with co-occurrence of both endometriosis and fibromyalgia versus those with endometriosis but not fibromyalgia) and IBD (OR [95%CI]: 2.66 [1.75–4.07], P value < 0.001, in women with co-occurrence of both endometriosis and fibromyalgia versus those with fibromyalgia but not endometriosis; OR [95%CI]: 2.97 [1.87–4.72], P value < 0.001, in women with co-occurrence of both endometriosis and fibromyalgia versus those with endometriosis but not fibromyalgia) from a logistic regression model adjusted for age, socioeconomic status, residence district, birth country, BMI. However, the study of autoimmune disease risks in women with both endometriosis and fibromyalgia versus those with either condition cannot directly infer the association between autoimmune diseases with endometriosis alone since co-occurrence of fibromyalgia is a disease closely associated with endometriosis. Also, there was no statistical test or discussion to back up the selection of adjusted confounders in this study, resulting in a risk for over-adjustment.

Harris et al., 2022 (81) conducted a cohort study examining the temporally bidirectional association between endometriosis, psoriasis and psoriatic arthritis

among U.S. women by analysing Women's Health Study data. Women with psoriasis and psoriatic arthritis (the exposures) had a significantly higher risk of developing endometriosis (the outcome) (HR [95%CI] = 2.01[1.23-3.30]). When the temporality was flipped, a greater risk of subsequent psoriasis with psoriatic arthritis (the outcomes) was also observed when endometriosis was examined as the exposure (HR [95%CI] = 1.77[0.89-3.52]). No clear associations were observed between psoriasis without psoriatic arthritis and endometriosis regardless of the temporality between these conditions. This is a well-designed cohort study with 22 years of follow-up of 116,429 U.S. women, however, the study results need to be interpreted with caution due to the small number of psoriasis with psoriatic arthritis cases among women with endometriosis (N = 9), hence this analysis yielded wide confidence intervals.

Porpora et al., 2020 (82) reported a case-control study which included 148 women with laparoscopy and histologically confirmed endometriosis and 150 women without clinical or ultrasound endometriosis diagnosis by analysing data from patients admitted to a hospital in Italy during 2014-2017. They investigated the prevalence and risk of immunological diseases as the outcomes including autoimmune thyroiditis (prevalence 54.4% vs. 9.3% in cases vs. controls, OR [95%CI]: 11.37 [6.00-21.5], P value < 0.001), SLE (5.4% vs. 0.7% in cases vs. controls, OR [95%CI]: 8.63 [1.07-69.91], P value = 0.01), CLD (10.2% vs. 0.7%, OR [95%CI]: 12.04 [2.22-130.79], P value < 0.001) in women with and without endometriosis (the exposure). However, their risk estimates included very wide confidence intervals and their analysis did not include any adjustment of confounders to provide robust evidence.

Shafrir et al., 2021 (83) conducted a cross-sectional analysis investigating the immune-mediated conditions among U.S. women that had a surgical diagnosis of endometriosis (551 surgically confirmed endometriosis cases versus. 652 endometriosis-free controls) by analysing Women's Health Study data. An increased risk of endometriosis (the outcome) (OR [95%CI]: 1.87 [0.92–3.80]) was found in participants with autoimmune and/or inflammatory conditions (the exposure). Also, a positive trend was observed between the number of immune-mediated conditions (the exposure) and the odds of endometriosis (the outcome) (P $value_{trend}$ = 0.0002). Although limited by small sample sizes, this association appeared to be driven by an increased odds of surgically confirmed endometriosis (the outcome) among participants with SLE (OR [95%CI]: 5.39 [0.54– 54.20]), RA (OR [95%CI]: 2.14 [0.54–8.39]), and IBD (OR [95%CI]: 6.78 [1.30–35.5]). This study has the advantage of studying multiple diseases with detailed medical diagnosis records. However, their risk estimates showed very wide confidence intervals and further research with larger sample size and a cohort study design incorporating disease diagnosis date and follow-up time could help better support the observed increased odds of endometriosis in women with autoimmune/inflammatory conditions.

Stella et al., 2021 (84) reported a study of women with endometriosis and concomitant autoimmune disease (cases N = 96) versus women with endometriosis but without autoimmune diseases (controls N = 268, matched by age and study period) who attended an endometriosis outpatient clinic in Italy. In their analysis, endometriosis with concomitant autoimmune diseases (including autoimmune thyroid disorders, type 1 diabetes, inflammatory bowel diseases, coeliac disease, systemic lupus erythematosus, antiphospholipid syndrome, rheumatoid arthritis, systemic sclerosis, multiple sclerosis) was found to have a significant association with stage

IV endometriosis (OR[95%CI]: 2.54 [1.57-4.10], P value = 0.004, with adjustment of the number of laparoscopic surgery performed), suggesting that coexistence of endometriosis and autoimmune diseases is associated with a more severe endometriosis. However, the study design is questionable as endometriosis is treated as both the exposure and the outcome under investigation, hence likely biased the association under study.

Yoshii et al., 2021 (85) reported a case-control study using health insurance claims database in Japan comparing 30,516 women with endometriosis and 120,976 women without endometriosis matched for age and registration month. By conditional logistic regression analyses, a significantly higher incidence of endometriosis (the outcome) was found in women with rheumatoid arthritis (the exposure) (IRR [95%CI]: 1.31 [1.05-1.64]) and systemic lupus erythematosus (the exposure) (IRR: [95%CI]: 1.35 [0.99-1.84]). This study benefits from a large-scale study population in Japan and strict hospital diagnosis data for disease ascertainment. However, their analysis was at risk of over-adjustment with additional adjustment for the number of hospital visits within 3 months after registration, oral contraceptive and levonorgestrel-releasing intrauterine system use within 3 months after registration which were not tested to be contributing to their statistical analysis models.

There were 6 studies which reported an increased risk of SLE, RA, SS and ankylosing spondylitis (the outcome) in women with endometriosis (the exposure) by analysing data from the Taiwan's National Health Insurance Research Database. This dataset is an exciting opportunity to investigate multiple diseases risk as it covers a large-scale population and also has comprehensive hospital medical history record data. However, there were issues in the study design and statistical analysis

of these 6 studies, particularly with the problem of over-adjustment which is present in all of the 6 studies. Amongst these 6 studies that analysed data from Taiwan's National Health Insurance Research Database, Lin and colleagues (86) reported a significantly increased risk of incident SLE in 17,779 women with endometriosis versus 17,779 women. Also, they reported an interesting decreased risk of SLE in women diagnosed with endometriosis with hormonal use (especially long term) (HR [95%CI]: 0.48 [0.30-0.75]). However, their study results need to be interpreted with caution since in their study population, SLE diagnosed before endometriosis was not excluded from the study population. Also, their statistical analyses were over-adjusted as endometriosis-free controls were selected matching age, index year, Charlson Comorbidity Index (CCI) score with the endometriosis cases plus statistical adjustment for age, CCI score besides hormonal and surgical treatments. They also additionally performed stratified analysis by groups of age, CCI score, hormonal and surgical treatments although these factors were already adjusted in their analysis model and that their controls were already matched by age and CCI score to endometriosis cases. The other 5 studies analysing data collected from the same population from Taiwan's National Health Insurance Research Database, also used the same study method as Lin and her colleagues which is with a very high risk of overadjustment to generate valid risk estimates. By analysing this dataset, Fan and colleagues (87) reported a significantly increased SLE risk in women with endometriosis (HR [95%CI]: 2.37 [1.35-4.14]). Xue at al. (88) reported a significantly increased RA risk in women with endometriosis (HR [95%CI]: 1.75 [1.27-2.41]). Chen et al. (89) reported a higher increased risk of RA in women with endometriosis (HR [95%CI]: 3.71 [2.91-5.73]). Chao and colleagues (90) reported an increased risk of SS in women with endometriosis (HR [95%CI]: 1.45 [1.27-1.65]). Yin et al., 2022

(91) reported an increased risk of ankylosing spondylitis in women with endometriosis (HR [95%CI]: 11.61 [1.11-2.35]). These 6 studies that analysed Taiwan's National Health Insurance Research Database were all at a high risk of over-adjustment, although the large nationwide study population, the rich information on patient medical history and 13 years' follow-up time for this database presented an opportunity for high-quality evidence if analysed with a well-designed study approach.

Quality of evidence

Assessment of the risk of bias and quality of the evidence of included studies was conducted based on GRADE criteria (53) (Appendix Table x2.3). Quality assessment was carried out for each study outcome (a specific autoimmune disease reported to be in association with endometriosis, whether to study the autoimmune disease risk in women with endometriosis history or vice versa) if such outcome was reported by at least 3 studies. The overall quality of the evidence for each reported study outcomes generally received a score of "LOW" or "VERY LOW" by GRADE criteria (53) due to potential risk of bias in their study design such as self-reported outcomes, cross-sectional study design, small sample size, unrepresentativeness of the control group or whole study population, limited or no adjustment of confounding factors, and reporting no confidence intervals for risk estimates.

Only 5 of the 26 studies published by April 2018 (65,66,71,77,79) could provide high quality evidence, and 4 of the studies (65,66,77,79) supported a significantly increased risk of SLE, RA, MS, and IBD in women with endometriosis as well as a significantly increased risk of endometriosis in women with CLD. The following five studies provided high quality evidence due to their large sample size, hospital-based disease ascertainment, adjustment of confounders, and the ability to

approach temporality between endometriosis and autoimmune diseases by a cohort study design. Two cohort studies (65,66) by Nielsen et al. (2011) and Harris et al. (2016a) provided high quality evidence that a statistically significant increased SLE risk was found in women with endometriosis versus those without (RR [95%CI]: 1.74 [1.10-2.77], P = 0.020, I^2 = 0%, Figure 2.2a). A prospective cohort study by Harris et al. (2016a) provided high quality evidence that a greater risk of RA was observed among women with endometriosis (HR [95%CI]: 1.41 [1.05-1.89]). Stephansson et al. (2011) (77) in their large retrospective cohort study that followed up 11,097 Swedish women reported a significantly higher risk of endometriosis in women with CLD (HR [95%CI] = 1.39 [1.14-1.70], P < 0.001). In the retrospective cohort study by Nielsen et al. (2011) (65), a 20% greater risk for MS was observed in 37,661 Danish women with hospital-diagnosed endometriosis in comparison to general female controls (SIR [95%CI]= 1.2 [1.1-1.5], P < 0.001). A cohort study by Jess T et al. (2012) (79) in Danish women reported a significantly increased incidence of IBD in women with endometriosis history (UC: SIR [95%CI] = 1.5 [1.3-1.7]; CD: SIR [95%CI] = 1.6 [1.3-2.0]; IBD: SIR [95%CI] = 1.5 [1.4-1.7], P < 0.001).

The significantly increased risks of SLE, RA, MS, IBD in women with endometriosis observed in these high-quality cohort studies were also observed in lower-quality study by a cross-sectional or case-control study that with smaller sample size, unclear disease ascertainment methods, or inability to address temporality as well as in some cohort studies that with smaller sample size but suboptimal study design. Yet, the significantly higher risk of endometriosis in women with CLD in the large cohort study by Stephansson et al. (2011) (77) was not reported in any other study. Later published literatures since April 2018 didn't provide high-quality evidence.

DISCUSSION

In this review of population-based cross-sectional, cohort and case-control studies, endometriosis was suggested to be associated with a range of autoimmune diseases including Addison's disease, ankylosing spondylitis, autoimmune thyroid disorder, coeliac disease, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, psoriasis and psoriatic arthritis. However, due to potential risk of bias in their study design, the quality of the evidence for each reported autoimmune disease in association with endometriosis generally received a score of "LOW" or "VERY LOW" using the GRADE criteria (53). Only 5 of the 26 studies published by April 2018 (65,66,71,77,79) could provide high quality evidence, and 4 of the studies supported a significantly increased risk of systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, multiple sclerosis, and inflammatory bowel disease in women with endometriosis as well as a significantly increased risk of endometriosis in women with coeliac disease. Literature published since April 2018 did not provide high-quality evidence.

Meta-analyses were performed for each autoimmune disease reported to be associated with endometriosis by at least 3 studies, and were also stratified by study design (cross-sectional, case-control, prospective cohort or retrospective cohort studies) for each outcome. In meta-analyses of multiple studies for a specific outcome, a fixed-effect estimate was calculated if I^2 heterogeneity = 0%, however, if I^2 heterogeneity ≥ 0% in the meta-analysis, a random-effect estimate and a fixed-effect estimate were both calculated for sensitivity analysis, but interpretation of results from a random-effect estimate would be more appropriate if I^2 heterogeneity ≥ 0%. A significantly increased risk of SLE was found in women with endometriosis in

the meta-analysis of 3 case-control studies and a cross-sectional study by a fixed effect model (OR [95%CI]: 1.35 [1.06-1.71], P = 0.010), but this meta-analysis result has high heterogeneity (I^2 = 44%) and this increased SLE risk became largely insignificant when switching to a random effect model. Yet the meta-analysis of 2 cohort studies still found a significantly increased risk for SLE in women with endometriosis (RR [95%CI]: 1.74 [1.10-2.77], P = 0.020, I^2 = 0%). In the meta-analysis of 3 case-control studies and a cross-sectional study for SS risk in women with endometriosis, a significantly increased risk of SS was found in women with endometriosis by a fixed effect model with no heterogeneity found (OR [95%CI]: 1.76 [1.39-2.21], P < 0.001, I^2 = 0%). This significantly increased SS risk in women with endometriosis was consistent with another cohort study. Meta-analysis of 2 cross-sectional studies found a significantly increased RA risk in women with endometriosis (OR [95%CI]: 1.50 [1.18-1.91], P = 0.002, I^2 = 0%), however, this increased RA risk became largely insignificant with wide confidence interval in the meta-analysis of 2 cohort studies for RA risk in women with endometriosis (RR [95%CI]: 1.46 [0.70-3.03], P = 0.31, I^2 = 0%) as well as in another case-control study. Meta-analysis of 3 case-control studies found an increased risk for ATD in women with endometriosis by a fixed-effect model (OR[95%CI]: 1.36 [0.54, 3.45], P = 0.52, I^2 = 83%), however, this meta-analysis result had high heterogeneity, and this increased ATD in women with endometriosis became insignificant when switching to a random effect model. Meta-analysis of 2 case-control studies found a significantly increase risk of CLD in women with endometriosis by a fixed effect model with no heterogeneity, yet this risk estimate had with very wide confidence interval to generate meaningful interpretation (OR [95%CI]: 4.04 [1.53-10.65], P = 0.005, I^2 = 0%). Yet in a cohort study following up women with CLD versus those

without CLD, a significantly increased risk of incident endometriosis was found. To summarise findings from meta-analysis of study results with combinable risk estimates, a significantly increased risk of SLE and SS was found in women with endometriosis, but other associations under study were with high heterogeneity between studies, had wide confidence intervals, or not having combinable risk estimates to be meta-analysed.

Whilst there are a number of review articles on the (auto)immunity of endometriosis, these articles mostly discuss the biological or immunological aspects of endometriosis. This systematic review, however, is the first review amalgamating the evidence from available population-based studies with a focus on the association between endometriosis and autoimmune diseases. Our review benefits from a comprehensive search strategy including 23 most common autoimmune diseases (i.e. with a prevalence rate ≥ 10 per 100,000 people worldwide identified by Hayter & Cook (2012)) occurring with endometriosis (52). As a result, I was able to identify 18 additional population-based studies compared to eight studies previously included in a review investigating of risk of chronic disease in endometriosis patients (49). Also, a further 12 studies were identified since April 2018 after I have conducted the systemic review for the publication. Moreover, the current review captures several large-scale and well-designed studies with 5 high quality studies reporting a significant association between endometriosis and autoimmune diseases. Furthermore, meta-analyses were conducted to better evaluate the overall evidence for association of endometriosis and autoimmune disease risks. The meta-analyses were designed carefully with strict subgroup analysis of study results from cross-sectional, case-control or cohort studies. Sensitivity analyses were conducted to examine robustness of the meta-analysis results.

However, some limitations in this review or in the included studies should be noted. The GRADE score for quality assessment for each study outcome were either “LOW” or “VERY LOW”. Many of the included studies were small in size and had limited number of endometriosis and/or autoimmune cases, presenting a high possibility to generate spurious associations. Also, because of the limited statistical power of studies with small samples size included in a meta-analysis, a random-effect estimate would weigh more towards the small studies thus neutralising a significant association found in large and well-conducted studies.

Another issue is the difficulty to establish the temporality between endometriosis and autoimmune diseases, that is, to determine the order of disease development and presentation, and a potential causal relationship or whether they share the same pathophysiology. In cross-sectional and case-control studies, a temporal relationship between these two conditions was impossible to address because the design of the incorporated studies did not include time of diagnosis. However, prospective cohort studies that follow up people with certain exposure(s) prior to the occurrence of the health outcome of interest could provide better evidence on temporality. Moreover, there is an estimated average delay of 7 years between the onset of endometriosis-associated symptoms and its diagnosis (92). In addition, some autoimmune diseases such as coeliac disease could remain undetected for years, thus posing a greater challenge to define the accurate time of disease onset in order to establish the temporal sequence between the two.

In addition, the cross-sectional and case-control studies might be biased because of sub-optimal selection of the comparator group for women with endometriosis. For example, Lamb et al. (1986) recruited friends of endometriosis patients as endometriosis-free controls to compare with women with endometriosis.

Friend-controls might have biased the association under study since friends are more likely to share similar lifestyles or come from the same socio-economic status which could have influenced their health outcomes and likelihood of valid diagnoses (59). Smith et al. (1993) recruited women from hospital records diagnosed with fibroids confirmed by hysterectomy as the comparator group for women with endometriosis but fibroids and endometriosis are correlated diseases (60). Other studies recruited women who attended obstetrical/gynaecological clinics or family planning units as the endometriosis-free comparator group for women with endometriosis, but since endometriosis is a gynaecological disorder, if these women have sought help for obstetric or gynaecological reasons, there exists a risk that their health conditions might be potentially associated with endometriosis. The later published population-based study could not address any of the issues above.

In order to generate the best evidence, we recommend future population-based studies to further investigate the association between endometriosis and autoimmune diseases by adopting a prospective cohort study approach with long follow-up time, clear description of temporal sequence between the exposure and the outcome of study, large study populations, strict disease ascertainment based on hospital diagnosis records (preferably surgical diagnosis for endometriosis and biomarker tests for certain autoimmune disease), carefully selected study population with and without the exposure of interest, and good adjustment for potential confounding factors. Moreover, genome-wide association study and Mendelian randomisation analysis for endometriosis and autoimmune diseases may help to establish a potential causal relationship between the two.

CONCLUSIONS

Evidence from our systematic review of observational population-based studies suggested an increased risk of autoimmune diseases in women with

endometriosis including Addison's disease, ankylosing spondylitis, autoimmune thyroid disorder, coeliac disease, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, psoriasis and psoriatic arthritis. High quality study concluded that a significantly increased risk of systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, multiple sclerosis, and inflammatory bowel disease in women with endometriosis as well as a significantly increased risk of endometriosis in women with coeliac disease. Meta-analysis with combinable study results found a significantly increased risk of SLE and SS in women with endometriosis. However, although there were a few high-quality, well-designed studies with large sample size, many of the included studies in this review were of low quality and with limitations in their study design. It is important to note that the evidence did not allow for accurate estimation of the association between the exposure and the outcome of study, and have no clinical diagnostic utility. Larger follow-up studies would also help understand whether endometriosis is a risk factor or a consequence of autoimmune diseases, or if these two types of disorders share pathological mechanisms and biological pathways resulting in their co-occurrence. For a study on the subsequent risk of developing autoimmune diseases in women with endometriosis history, as most studies of endometriosis include women of reproductive age, longer follow-up studies are needed to ascertain the true risk of auto-immune diseases that may occur after menopause.

The observational evidence also does not exclude the possibility that selection and diagnostic biases in the studies underlie some of the associations observed, or cannot establish any evidence that the observed associations are biologically underpinned. Future genetic and biological studies of immunological

dysfunctions in the context of endometriosis may improve our understanding of the pathogenesis of both conditions, and if shared pathogenic origins are observed, contribute to the identification of novel therapeutic and diagnostic targets.

Figure 2.1 Flowchart for study inclusion and exclusion process

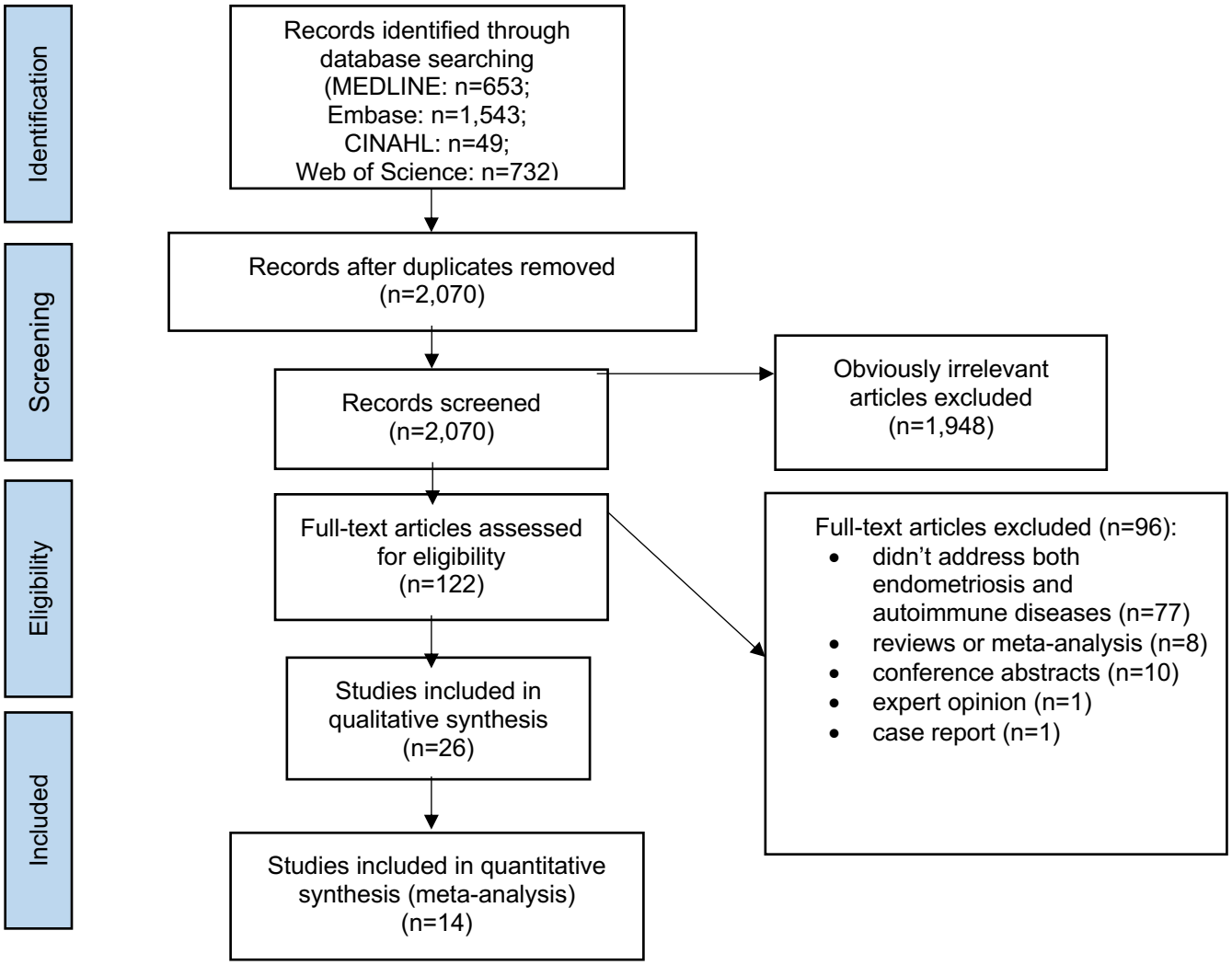


Figure 2.2a Forest plot: studies of endometriosis (ENDO) as the exposure and systemic lupus erythematosus (SLE) as the outcome (high quality studies were marked with "*")

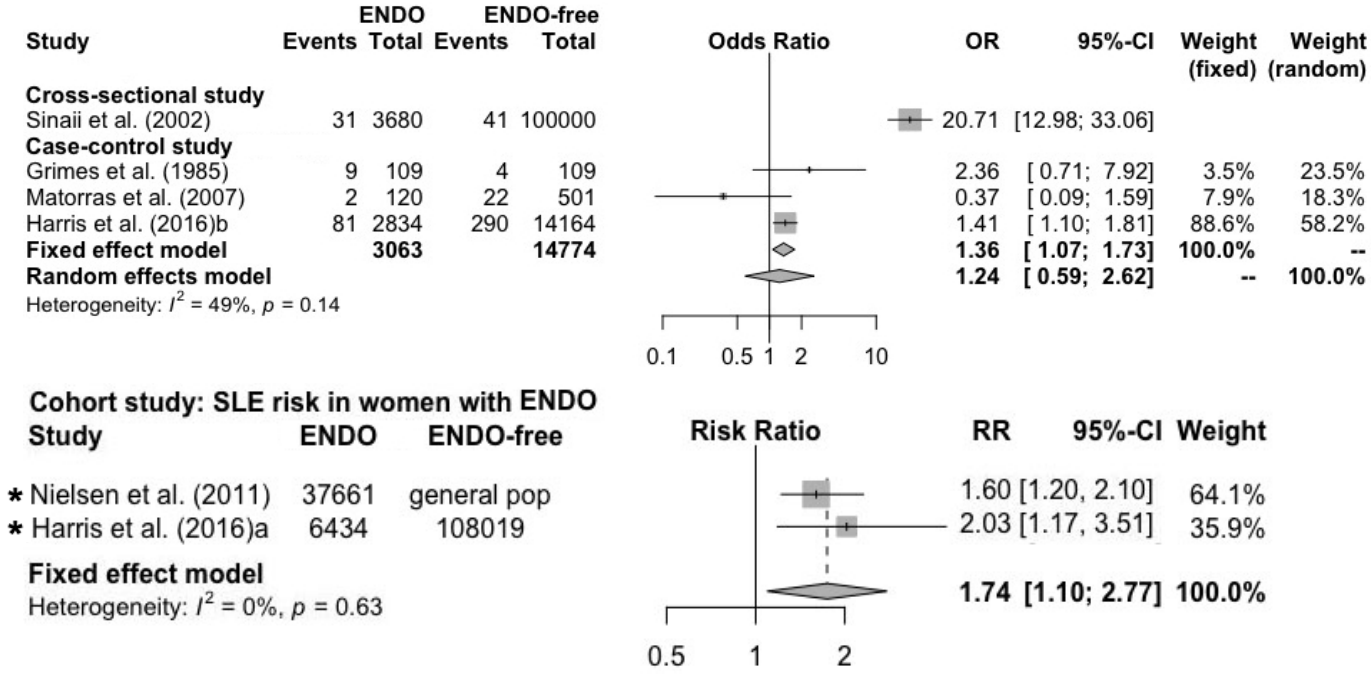


Figure 2.2b Forest plot: studies of endometriosis (ENDO) as the exposure and Sjogren's syndrome (SS, i.e. event) as the outcome

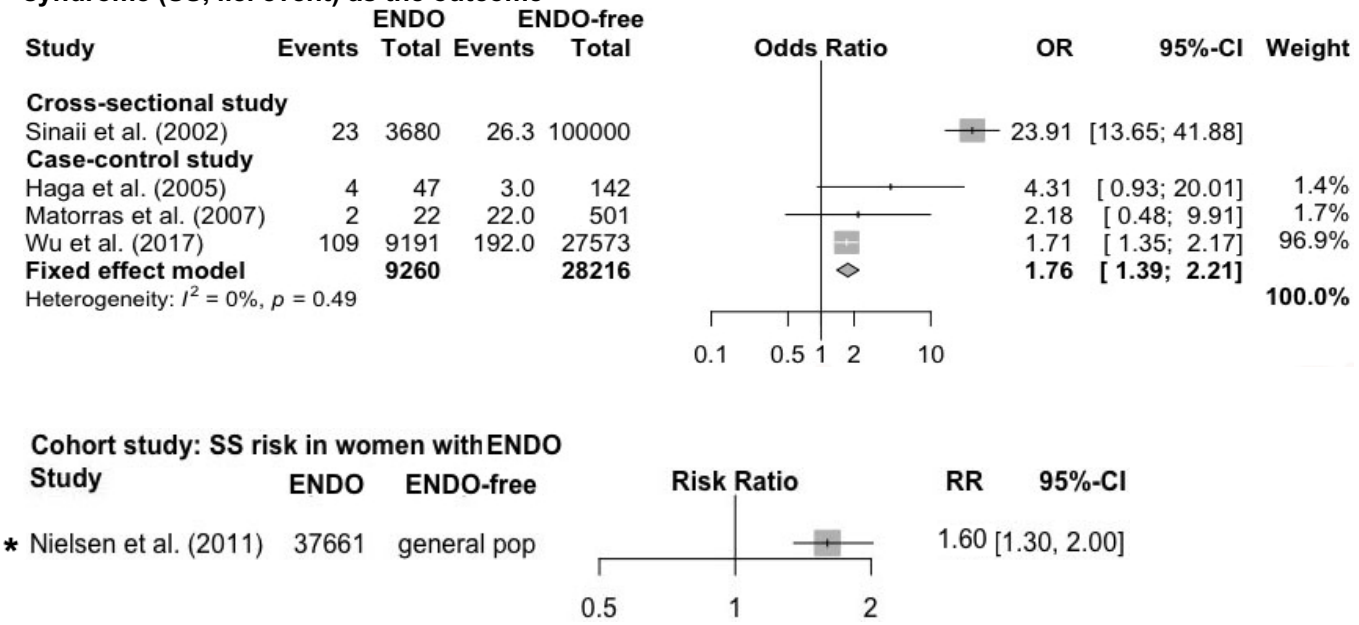


Figure 2.2c Forest plot: studies of endometriosis (ENDO) as the exposure and rheumatoid arthritis (RA) as the outcome

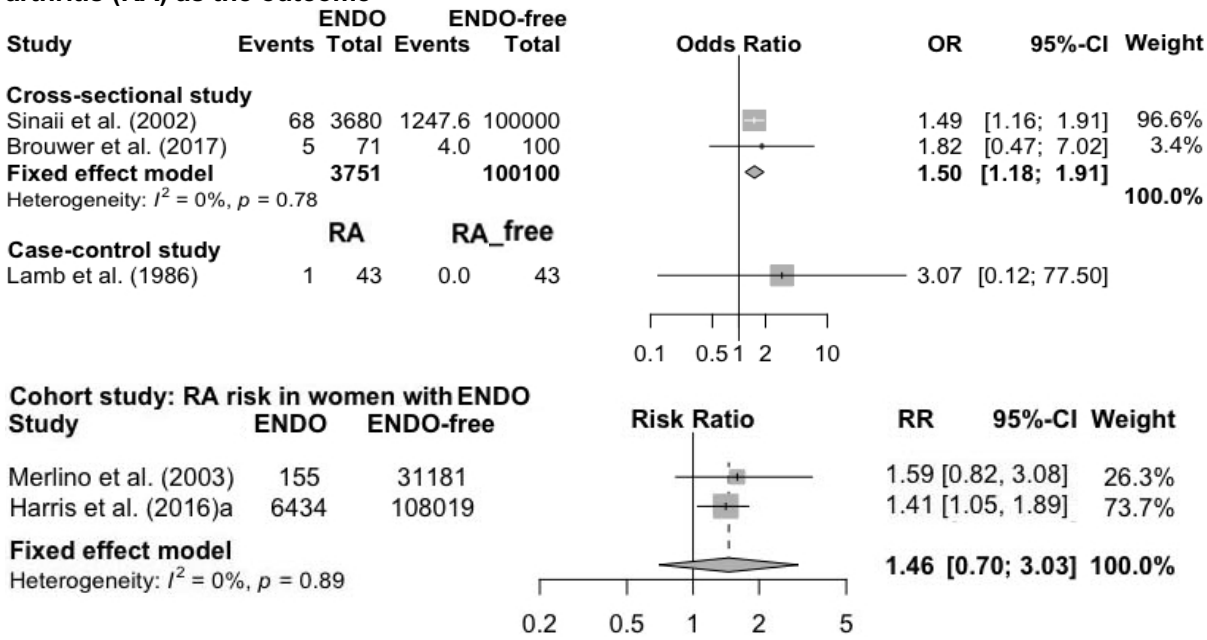


Figure 2.2d Forest plot: studies of endometriosis (ENDO) as the exposure and autoimmune thyroid disorder (ATD) as the outcome

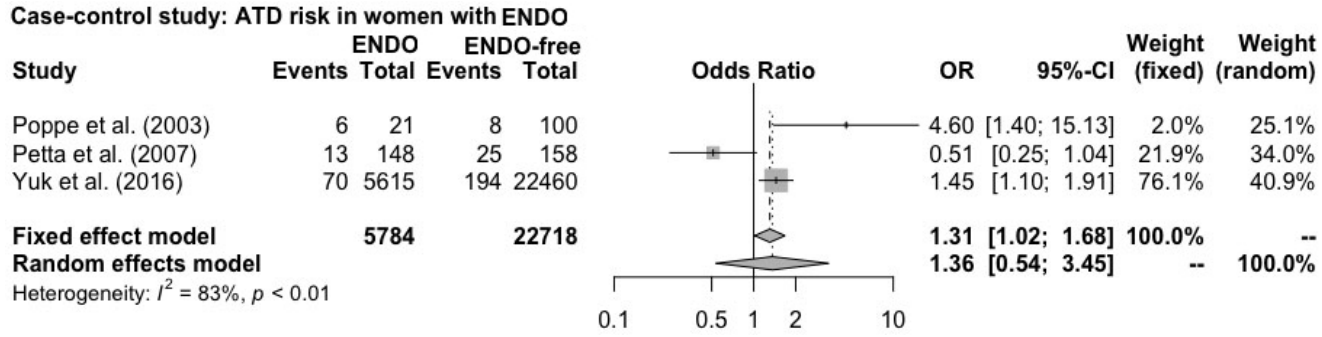
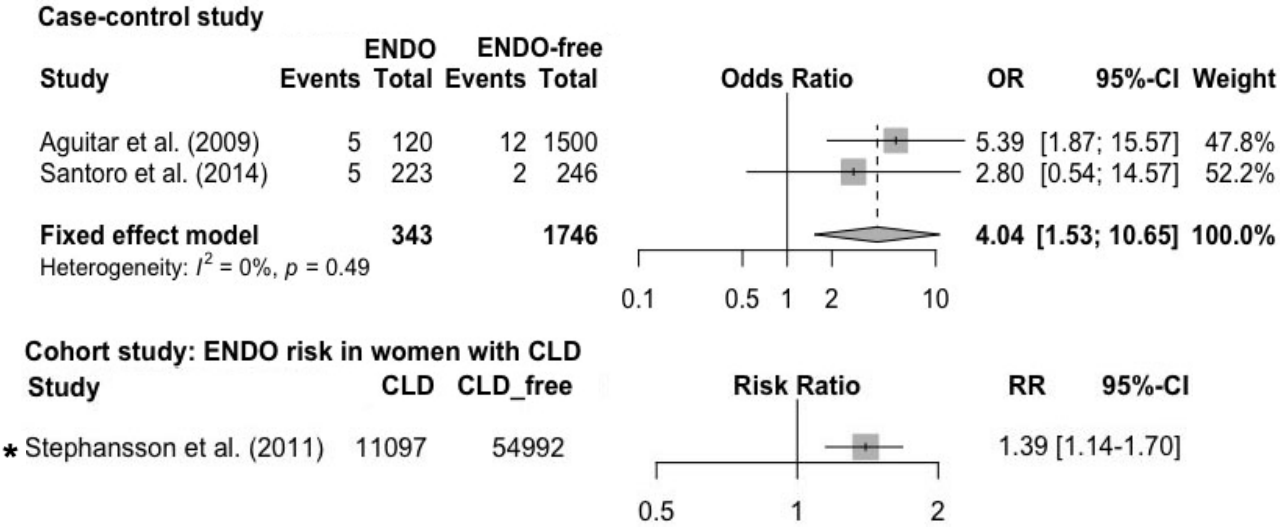


Figure 2.2e Forest plot: case-control studies of endometriosis (ENDO) as the exposure and coeliac disease (CLD) as the outcome and a cohort study of CLD as the exposure and ENDO as the outcome



Chapter 3. Phenotypic Analysis for Immunological Disease Risk in Women with Endometriosis by Analysing UK Biobank Data

INTRODUCTION

The aetiology of endometriosis is complex and under-explored, yet abnormalities in the immune system of women with endometriosis have been consistently demonstrated. Thus, a hypothesis was formed that women affected by endometriosis have an immunity-associated disorder, and an increased risk of immunological diseases in women with endometriosis has been proposed by several studies (38). Epidemiological studies analyse data collected from the population to provide direct and relevant real-world evidence to understand population health and the population at risk. Epidemiological studies use systemic study design, rigid statistical methods, careful interpretation of study results to understand the distribution, determinants of disease as well as associations between an exposure/risk factor and an outcome in populations. Research evidence from epidemiological studies play an important role in forming public policy and clinical practice, hence is essential to understand the association between endometriosis and immunological diseases. Yet the systematic review of existing evidence from population studies in my previous chapter summarized that many epidemiological studies on the association between endometriosis and immunological diseases were of low quality and suffered from study design limitations such as small sample size, sub-optimal study population selection, insufficient adjustment of confounders, unclear disease ascertainment methods, and mixed results.

Robust quantification of the association between endometriosis and immunological diseases could answer the question whether endometriosis is associated with immunological disorders, and if there is an increased risk of developing immunological diseases in women with endometriosis, to facilitate

understanding of both disorders, and potentially provide new avenues for disease diagnosis and treatment methods for endometriosis. This chapter aims to investigate the phenotypic association between endometriosis and a range of immunological diseases, focused on the question if women diagnosed with endometriosis have an increased risk of developing immunological diseases subsequently, by epidemiological analysis of one of the largest datasets available, the UK Biobank (UKBB). Two different methods were used for the association analyses: a cross-sectional study that included the entire available study population to maximise power to detect a phenotypic association between endometriosis and immunological diseases; and a prospective cohort study design to include temporality of disease diagnoses to investigate if women with endometriosis have an increased risk of developing immunological diseases subsequently. The statistical analysis also includes testing robustness of the evidence with adjustment for confounders and sensitivity analysis to evaluate the influence of different disease ascertainment methods.

METHODS

Dataset and study population

The data analysed in this chapter originates from UKBB. Briefly, UKBB comprises a cohort of 502,568 people (including 229,164 men and 273,404 women) aged 40 to 69 years, recruited from across the UK during 2006 and 2010. Only female participants in UKBB were included in this phenotypic association analysis, given that endometriosis is a gynaecological condition affecting biological females. UKBB data were downloaded from the data server on 8th Jan. 2019. In UKBB, information was collected from participants on aspects of medical history, family history, lifestyles, socioeconomic status, and environmental factors during

recruitment using questionnaires. Participants also underwent a range of physical measurements and had samples of blood, urine and saliva collected. Participants were followed up for cause-specific morbidity and mortality through linkage to disease registries, death registries, hospital admission records and primary care data. Quality controlled, imputed, genome-wide genotype data are available for all participants in UKBB. More detailed descriptions of UKBB have been described in details (93).

Disease ascertainment

In UKBB, diagnosed cases of endometriosis and immunological diseases were identified from self-reported questionnaires with information collected at recruitment and/or by ICD-coded hospital records through linkage to hospital systems, where the study participants have been tagged for regular updates of their electronic healthcare records when generated.

Endometriosis

Endometriosis was identified based on self-reports and/or hospital records (ICD10/9 codes as in Appendix Table x3.1). It should be noted that, in UKBB, the earliest date of the hospital record information dates back only to 1995. Cases who received a diagnosis prior to 1995 were not captured in the hospital records data. Moreover, the average age of UKBB women was 56.3 (standard deviation (SD): 8.0) years old at their time of recruitment into UKBB cohort with many of their endometriosis diagnosis date captured in the self-reported data but not in the hospital records data. The main analysis of this study was therefore based on both self-reported and hospital recorded endometriosis diagnosis. As the gold-standard diagnosis method of endometriosis is visualization via surgical laparoscopy,

sensitivity analysis was carried out for assumed surgically confirmed endometriosis (those women who had one or more endometriosis diagnoses plus records of uterus-related surgeries that could further confirm endometriosis (see Appendix Table x3.1 for list of ICD codes used) in association with immunological diseases.

Immunological diseases

The definition and classification of immunological disorders in this analysis are based on the widely-accepted proposal by McGonagle & McDermott (2006) (94). Based on this definition and classification, 29 immunological diseases were identified in UKBB and were investigated for their association with endometriosis. McGonagle and McDermott (94) proposed that all immunological diseases can be categorized into autoinflammatory or autoimmune, or being a combination of autoinflammatory–autoimmune mechanisms. Their classification was based on similar clinical recognition such as neutrophilic inflammation, and presence of autoantibodies, therapeutic insights such as blockage of neutrophil function/inflammasome or lymphocyte function with anti-T cell therapies where all immunological diseases show some degree of disturbances in innate immune cell function and signalling in key cytokine pathways that include TNF and interleukin-1 (IL-1ß). In order to increase the study power and to allow for adequate adjustment for confounding factors or stratification on effect modifiers, immunological diseases were categorized into groups of autoinflammatory diseases; mixed-pattern diseases; classic autoimmune diseases as proposed by McGonagle & McDermott (2006) (94).
The following list denotes the 29 immunological diseases that were identified in UKBB and were grouped accordingly:

1) autoinflammatory diseases: acne, acute respiratory distress syndrome, erythema nodosum, giant cell/Takayasu arteritis, gout/pseudogout, inflammatory

bowel disease (including ulcerative colitis and Crohn's disease), osteoarthritis, sarcoidosis.

2) classic autoimmune diseases: Addison's disease, autoimmune gastritis, autoimmune thyroid disease, celiac disease, dermatomyositis/polymyositis, multiple sclerosis, myasthenia gravis, pemphigus/pemphigoid, primary biliary cirrhosis, rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, systemic sclerosis, type 1 diabetes, vitiligo.

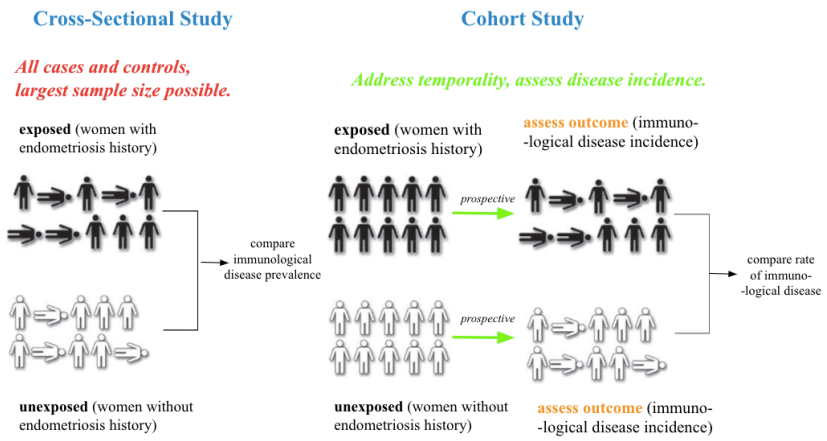
3) mixed-pattern immunological diseases: ankylosing spondylitis, Behcet's syndrome, reactive arthritis, psoriasis/psoriatic arthritis/psoriatic arthropathies.

Analytical study designs

This phenotypic association analysis initially included all women recruited into UKBB (N = 273,404). Two different analysis methods were applied: 1) a cross-sectional study to test for a simple prevalence risk of immunological diseases in women with and without endometriosis with all women population included from the UKBB; 2) a prospective cohort study design to incorporate temporality where entry time was defined as the recruitment date into UKBB. In defining the exposure and outcome for the cohort study analysis, the sequential timing of diagnostic dates of endometriosis and immunological diseases were compared in those women who had both a diagnosis of endometriosis and an immunological disease (1,909 women), among whom 66.8% (1,275 out of 1,909 women) had an immunological disease diagnosis after their endometriosis diagnosis; 2.2% (42 out of 1,909 women) had an immunological disease diagnosis within the same month in which they were diagnosed with endometriosis; and 31.0% women (592 out of 1,909 women) had an immunological disease diagnosis before their endometriosis diagnosis. Considering that the majority of women had immunological diseases diagnosed after

endometriosis, endometriosis was treated as the exposure and immunological diseases as the outcomes in the cohort study, to investigate the risk of immunological diseases in women with and without endometriosis history. This also fits with the hypothesis that many women with endometriosis have symptom onset in their teens or twenties, often many years before their ultimate diagnosis (95). Women with an endometriosis diagnosis at the time of recruitment were classified as exposed, whereas women who had not had an endometriosis diagnosis at the time of recruitment were classified as unexposed. Those women who received an endometriosis diagnosis during follow-up, prior to any immunological disease diagnosis, contributed person-time to the unexposed group until the occurrence of endometriosis diagnosis, if any, and then after diagnosis to the exposed group, subsequently. Women who had one or more immunological diseases diagnosed before endometriosis or those women who had prevalent immunological diseases diagnosed before cohort entry time (at recruitment), were excluded from cohort study analysis. Figure 3.1 illustrated the study design of cross-sectional and cohort study in this chapter.

Figure 3.1 Cross-sectional and cohort study design



Statistical analysis

Descriptive analyses were conducted to summarize baseline characteristics of study participants (assessed at baseline recruitment time), including factors that could be potential confounders in immunological disease risk estimation. A confounder is a variable that biases the estimated effect of the exposure on the outcome under study. A confounder is associated with both the outcome and exposure, but is not an intermediate factor by which the exposure has its effect on the outcome. The potential confounders were identified via literature reviews (1) included: age, ethnicity (British European/Others), menopausal state, age at menarche, number of live births, ever use of hormone replacement therapy or oral contraceptive pills, body mass index, waist-hip ratio, body fat percentage, weight, height, body size or height at age 10, smoking status, alcohol drinking status/frequency, history of infertility, ovarian cancer, myocardial infarction, angina or coronary artery bypass graft. These potential confounders have been described in the baseline characteristics tables.

In the cross-sectional study analysis, the prevalence of each specific and categorized immunological diseases in women with and without a history of endometriosis diagnosis was investigated using logistic regression models with odds ratios (ORs) as risk measure. Cross-sectional study analysis for each specific and categorized immunological diseases was conducted with simple adjustment of age and ethnicity (which are the most important confounders). In the cohort study, the risk of incident immunological diseases in women with and without endometriosis history was investigated using Cox proportional hazards regression models with calculated hazard ratios (HRs). The proportional hazards assumption was tested by function of “cox.zph” in the “survival” R library. In the cohort analysis, time to event

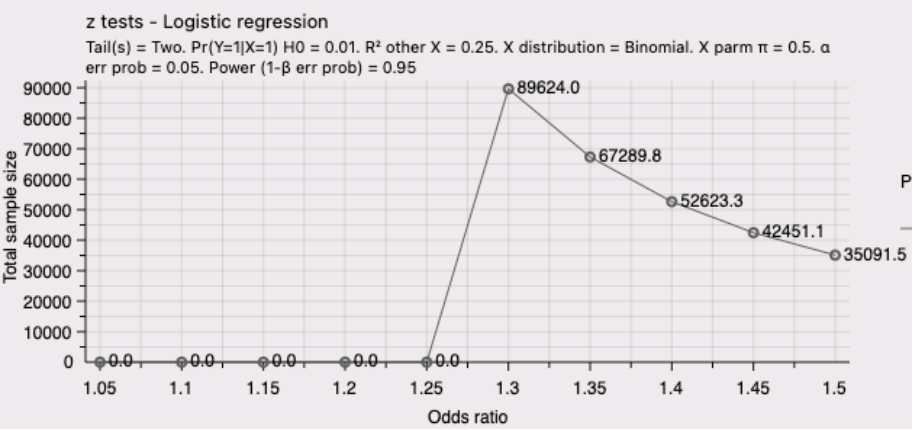
was formulated from entry to the cohort until the end of follow-up time. The follow-up time (rather than age) is used as the underlying time variable, since the date of assessment is described in more detail with information on the exact date and months participants attended the assessment centre (to be used as the index date) in UKBB. The end of follow-up time is the date of incident immunological diseases, death, loss to follow-up or end of follow-up (end date of follow-up is the date of last download of the dataset, which is 8th Jan. 2019), whichever occurred first. Cohort analysis for each specific and categorized immunological diseases was conducted with simple adjustment of age and ethnicity (which are the most important confounders) and also with adjustment of additional confounders that were identified from literature reviews and were tested to be significantly associate with both endometriosis and immunological diseases in UKBB. All risk estimates were reported with 95% confidence intervals (CIs) and two-sided P-values. Person-years and mean follow-up time for each cohort analysis were calculated. A P-value < 0.05 was considered as evidence for significant differences between comparison groups. All analysis was carried out using R software.

Power calculation for the cross-sectional study was conducted using GPower software version 3.1. Z test was selected for power calculation for logistic regression with the option of a priori power analysis to compute required minimum sample size. The power was defined as 80%, α error probability was defined as 0.05. Since age and ethnicity were included in the regression analysis as confounders, which had moderate association with the predictor (endometriosis), the option for "R^2 other X" was selected as 0.25 which was a recommended value for a moderate association. The distribution of predictor (endometriosis) was selected as binomial. Also, in G*Power, "Pr(Y=1|X=1) H0" refers to the probability of the event "Y = 1" (i.e.

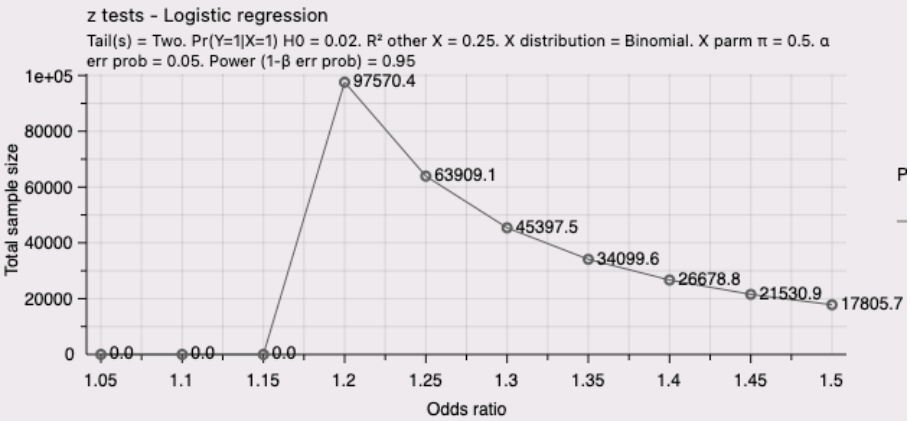
occurrence of immunological diseases) given that "X = 1" (i.e. occurrence of endometriosis) under the null hypothesis. In other words, it represents the estimated probability of a woman had a diagnosis of immunological diseases, assuming there is no effect or association between endometriosis and immunological diseases. In calculating UKBB data, the prevalence rate of an immunological disease in UKBB women ranges between <0.001 to 0.236 (H0 was optioned as 0.01, 0.02, 0.05, 0.15, 0.20 and H0 <0.001 was too small to generate any meaningful power calculation). Figures were drawn with effect sizes of odds ratios ranged from 1.05 to 1.5 in the X-axis and calculated sample sizes plotted in the Y-axis (Figure 3.2). For a relatively rare immunological diseases (prevalent rate = 1%), the minimum required total sample size is 89,624 to observe a relatively large effect size of OR ≥ 1.3 and 35,092 to observe a large effect size of OR ≥ 1.5. For a immunological disease with a 2% prevalent rate, the minimum required total sample size is 97,570 to observe OR ≥ 1.2; 45,398 to observe OR ≥ 1.3 and 17,806 to observe OR ≥ 1.5. For a immunological disease with a 5% prevalent rate, the minimum required total sample size is 70,200 to observe OR ≥ 1.15; 18,892 to observe OR ≥ 1.3 and 7,448 to observe OR ≥ 1.5. For a immunological disease with a 15% prevalent rate, the minimum required total sample size is 57,909 to observe OR ≥ 1.1; 15,375 to observe OR ≥ 1.2; 7,237 to observe an OR ≥ 1.3 and 2,901 to observe OR ≥ 1.5. For a common immunological disease with a 20% prevalent rate such as osteoarthritis, the minimum required total sample size is 46,371 to observe OR ≥ 1.1; 12,368 to observe OR ≥ 1.2; 5,847 to observe an OR ≥ 1.3 and 2,363 to observe OR ≥ 1.5.

Figure 3.2 Power calculation for estimating minimum sample size required by ranges of possible effect size and H0.

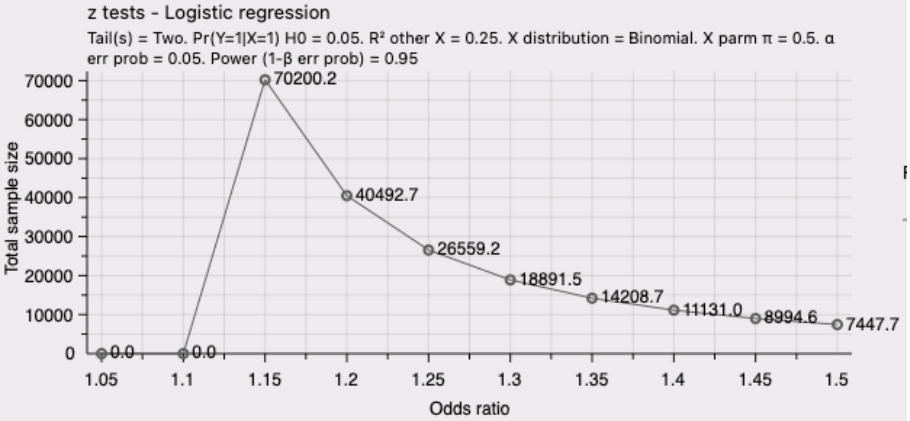
a. H0 = 0.01



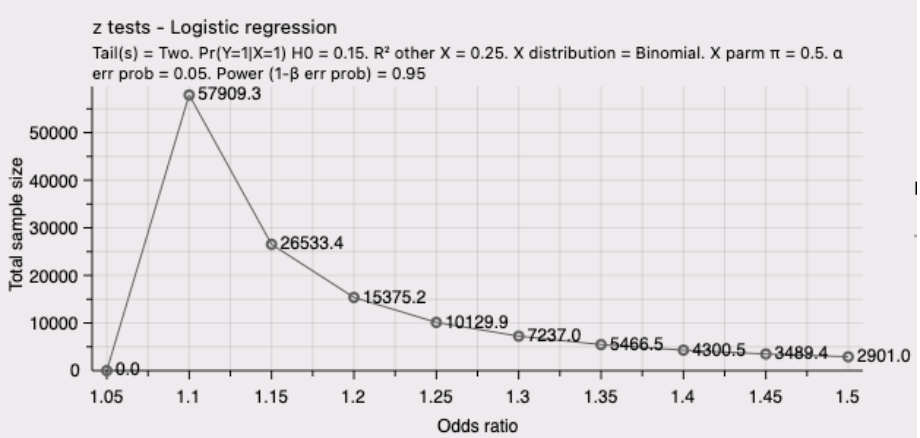
b. H0 = 0.02



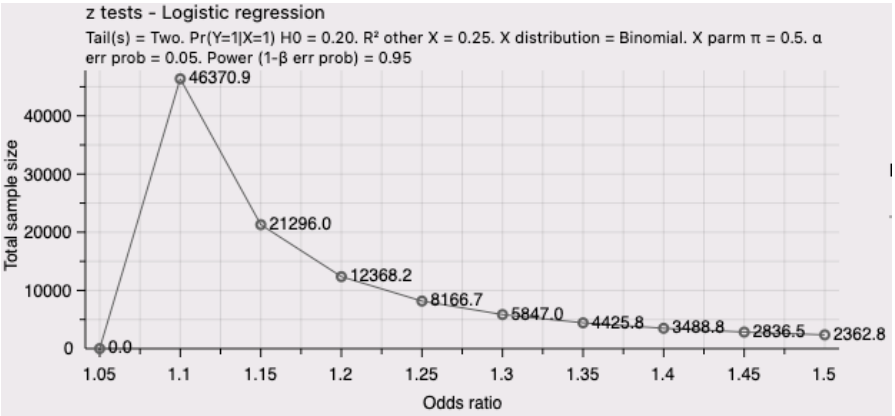
c. H0 = 0.05



d. H0 = 0.15



e. H0 = 0.20



Power calculation for cohort study survival analysis was investigated using "powerSurvEpi package" in R software to calculate minimum sample size required for a 80% study power given α error probability of 0.05. The follow up time was selected as 9.16 years, as shown in Table 3.1 as the shortest follow-up time. The possible HRs ranged 1.10, 1.15, 1.20, 1.25, 1.30, 1.35, 1.40, 1.45, 1.50. The "PVec" refers to the proportion of women with immunological diseases in women with endometriosis and ranged 0.1%, 0.3%, 0.5%, 0.7%, 10.0%, 15.0%. The minimum required sample size for a rare immunological disease with 0.1% prevalence in women with endometriosis is 75,711 to observe HR ≥ 1.10; 20,690 to observe an HR ≥ 1.20; 9,991 to observe HR ≥ 1.30 and 4,183 to observe HR ≥ 1.50. The minimum required sample size for a more common immunological disease with 0.5%

prevalence in women with endometriosis is 15,202 to observe HR ≥ 1.10; 4,154 to observe an HR ≥1.20; 2,006 to observe HR ≥ 1.30 and 840 to observe HR ≥ 1.50. The minimum required sample size for a common immunological disease with 10% prevalence in women with endometriosis is 7,639 to observe HR ≥ 1.10; 2,088 to observe an HR ≥1.20; 1,008 to observe HR ≥ 1.30 and 422 to observe HR ≥ 1.50.

Table 3.1 Power calculations for estimating minimum required sample size by ranges of HRs and proportion of women with immunological diseases in women with endometriosis.

IMD% in ENDO women	HRs for IMD risk in women with endometriosis								
	1.10	**1.15**	**1.20**	**1.25**	**1.30**	**1.35**	**1.40**	**1.45**	**1.50**
0.1%	75,711	35,210	20,690	13,812	9,991	7,636	6,075	4,982	4,183
0.3%	25,285	11,759	6,910	4,613	3,337	2,550	2,029	1,664	1,397
0.5%	15,202	7,069	4,154	2,773	2,006	1,533	1,220	1,000	840
0.7%	10,880	5,060	2,973	1,985	1,436	1,097	873	716	601
10.0%	7,639	3,553	2,088	1,394	1,008	771	613	503	422
15.0%	5,119	2,380	1,399	934	675	516	411	337	283

*IMD: immunological disease; HR: hazard ratio

Sensitivity analysis

Sensitivity analysis was carried out comparing women with self-reported or hospital-based endometriosis diagnoses to assess whether disease ascertainment had an impact on the associations under study. As the gold-standard diagnostic method of endometriosis is surgical inspection, analysis was conducted in women who underwent relevant surgeries (i.e. laparoscopy, hysterectomy, cystoscopy, cystectomy, ovarian/tubal surgery, gynaecological surgery, bladder/bowel surgery, see Appendix Table x3.1) that could confirm endometriosis (based on self-reports or hospital records of these surgeries). Furthermore, the prevalent risk of multiple immunological disease diagnoses (1, 2, 3+) was investigated in women with vs. without endometriosis.

RESULTS

Baseline characteristics

The baseline characteristics of study participants are summarized in Table 3.2 for women with and without endometriosis and Table 3.3 for women with and without immunological diseases. As shown in Table 3.2, women with endometriosis were approximately 3 years younger with a significantly lower proportion of women in the ≥ 60-year old group compared with endometriosis-free controls. There was a slightly higher proportion of women with European ancestry ethnicity in women with endometriosis than the controls. Among women with endometriosis, 60.5% had not yet had menopause at recruitment, while in women without endometriosis, 34.0% had not had menopause at recruitment. In comparison to women without endometriosis, women with endometriosis generally had a lower number of children (27.6% vs. 18.4% women with and without endometriosis had no children, 4.3% vs. 6.5% women with and without endometriosis had ≥ 4 children, P <0.001*), and were more likely to take hormone replacement therapy (49.2% vs. 37.7% in women with and without endometriosis, P value < 0.001*) or oral contraceptive pills (85.2% vs. 80.5% in women with and without endometriosis, P < 0.001*). Women with endometriosis was more likely to be obese at recruitment with an averagely higher body fat percentage (27.6%[5.4] vs. 27.1%[5.2], P < 0.001*). However, there was a higher percentage of women with endometriosis being thinner at age 10 than those without endometriosis (34.9% vs. 31.1%, P < 0.001*). In addition, women with endometriosis were more likely to smoke or drink alcohol. Also, women with endometriosis were more likely to have a history of infertility (5.4% vs. 0.7%, P <0.001*) or diagnosed with ovarian cancer (1.3% vs. 0.4%, P < 0.001*), but there was not a significant difference in their medical history of ever being diagnosed of

cardiovascular disorders including myocardial infarction, angina or ever had coronary artery bypass graft.

As shown in Table 3.3, women with immunological diseases were approximately four years older with a significantly higher proportion of women in the ≥ 60 years old group than the immunological disease-free controls (P < 0.001*). There was a slightly higher proportion of women with European Ancestry ethnicity in women with immunological diseases than those without (83.0% vs. 80.4%, P < 0.001*). In total, 69.0% of those women with immunological diseases had gone through menopause at recruitment while 57.9% women without immunological diseases had gone through menopause. Women with immunological diseases had an earlier age at menarche (P < 0.001*), had had more children (8.2% vs. 5.8% had ≥ 4 children, P < 0.001*), were more likely to take hormone replacement therapy (51.4% vs. 33.9%, P < 0.001*), but less likely to take oral contraceptive pills (77.3% vs. 81.7%, P < 0.001*). Women with immunological diseases than those without were more likely to be obese with a higher waist-hip ratio (28.5 [5.8] vs. 26.6 [4.9], P < 0.001*) and a higher body fat percentage (38.4% [6.9] vs. 36.0% [6.8], P < 0.001*), they were also heavier and taller at age 10 than those without immunological diseases (P = 0.009). In addition, women with immunological diseases were more likely to smoke (P < 0.001*) but less likely to drink alcohol (P < 0.001*). In addition, women with immunological diseases were more likely to have a medical history of myocardial infarction (P < 0.001*), angina (P < 0.001*) or had coronary artery bypass graft (P < 0.001*), but less likely to be infertile (P < 0.001*). There was not a significant difference on ovarian cancer in women with and without immunological diseases.

Table 3.2 Baseline characteristics of women with and without endometriosis (ENDO)

Characteristics	All Women (n=273,404)		Women with ENDO (n=8,223)		ENDO-Free Women (n=265,181)		P Value
Age (year; mean, SD) b	56.3 (8.0)		53.2 (7.9)		56.4 (8.0)		<0.001*
Age group (year; n, %) c							<0.001*
<50	64,676	23.7%	3,081	37.5%	61,595	23.2%	
50-60	94,026	34.4%	2,975	36.2%	91,051	34.3%	
≥60	114,702	42.0%	2,167	26.4%	112,535	42.4%	
Ethnicity (n, %) a							0.17
British European	221,386	81.0%	6,734	81.9%	214,652	80.9%	
Others	43,335	15.9%	1,265	15.4%	42,070	15.9%	
Had menopause (n, %) a							<0.001*
Yes	165,411	60.5%	2,829	34.4%	162,582	61.3%	
No	95,251	34.8%	4,977	60.5%	90,274	34.0%	
Age at menarche (year; n, %) b	13.0 (1.6)		12.8 (1.7)		13.0 (1.6)		<0.001*
Age at menarche group (year; n, %) c							<0.001*
<11	12,365	4.5%	504	6.1%	11,861	4.5%	
11	40,630	14.9%	1,370	16.7%	39,260	14.8%	
12	50,025	18.3%	1,521	18.5%	48,504	18.3%	
13	64,294	23.5%	1,912	23.3%	62,382	23.5%	
>13	97,107	35.5%	2,738	33.3%	94,369	35.5%	
No. of live births (n, %) b	1.8 (1.2)		1.5 (1.2)		1.8 (1.2)		<0.001*
No. of live births (n, %) c							<0.001*
0	51,118	18.7%	2,268	27.6%	48,850	18.4%	
1	36,468	13.3%	1,373	16.7%	35,095	13.2%	
2	119,187	43.6%	3,097	37.7%	116,090	43.8%	
3	48,302	17.7%	1,113	13.5%	47,189	17.8%	
≥4	17,500	6.4%	351	4.3%	17,149	6.5%	
Ever taken hormone replacement therapy (n, %) a							<0.001*
Yes	103,921	38.0%	4,048	49.2%	99,873	37.7%	
No	167,908	61.4%	4,117	50.1%	163,791	61.8%	
Ever taken oral contraceptive pills (n, %) a							<0.001*
Yes	220,453	80.6%	7,009	85.2%	213,444	80.5%	
No	51,532	18.8%	1,172	14.3%	50,360	19.0%	
Body mass index (kg/m²; mean, SD) b	27.1 (5.2)		27.6 (5.4)		27.1 (5.2)		<0.001*
BMI group (kg/m²; n, %) c							<0.001*
<18.5	2,079	0.8%	48	0.6%	2,031	0.8%	
18.5-25	105,672	38.7%	2,861	34.8%	102,811	38.8%	
25-30	99,882	36.5%	3,071	37.3%	96,811	36.5%	
≥30	64,312	23.5%	2,200	26.8%	62,112	23.4%	
Waist-hip ratio	0.82 (0.07)		0.82 (0.07)		0.82 (0.07)		0.96
Waist-hip ratio group							0.62
<0.8	114,374	41.8%	3,485	42.4%	110,889	41.8%	

0.8-0.85	72,752	26.6%	2,133	25.9%	70,619	26.6%	
≥0.85	85,151	31.1%	2,568	31.2%	82,583	31.1%	
Body fat percentage b	36.6 (6.9)		37.3 (6.8)		36.6 (6.9)		<0.001*
Body fat percentage (n, %) c							<0.001*
<32	66,062	24.2%	1,749	21.3%	64,313	24.3%	
32-37	70,379	25.7%	1,999	24.3%	68,380	25.8%	
37-42	71,784	26.3%	2,275	27.7%	69,509	26.2%	
≥42	60,055	22.0%	2,041	24.8%	58,014	21.9%	
Weight	71.5 (14.1)		73.2 (14.6)		71.4 (14.1)		<0.001*
Weight group							<0.001*
<60	53,239	19.5%	1,335	16.2%	51,904	19.6%	
60-70	90,406	33.1%	2,574	31.3%	87,832	33.1%	
70-80	66,879	24.5%	2,075	25.2%	64,804	24.4%	
≥80	61,519	22.5%	2,198	26.7%	59,321	22.4%	
Height	162.4 (6.3)		162.9 (6.3)		162.4 (6.3)		<0.001*
Height group							<0.001*
<160	87,225	31.9%	2,455	29.9%	84,770	32.0%	
160-165	85,192	31.2%	2,565	31.2%	82,627	31.2%	
165-170	64,572	23.6%	1,952	23.7%	62,620	23.6%	
≥170	35,262	12.9%	1,217	14.8%	34,045	12.8%	
Body size at age 10							<0.001*
thinner	85,416	31.2%	2,873	34.9%	82,543	31.1%	
average	135,347	49.5%	3,745	45.5%	131,602	49.6%	
plummer	47,557	17.4%	1,482	18.0%	46,075	17.4%	
Height at age 10							0.47
shorter	56,837	20.8%	1,758	21.4%	55,079	20.8%	
average	142,786	52.2%	4,185	50.9%	138,601	52.3%	
taller	67,874	24.8%	2,135	26.0%	65,739	24.8%	
Smoking status (n, %) a							<0.001*
never smoker	162,066	59.3%	4,937	60.0%	157,129	59.3%	
past smoker	85,458	31.3%	2,420	29.4%	83,038	31.3%	
current smoker	24,367	8.9%	828	10.1%	23,539	8.9%	
Alcohol drinking status (n,%) a							<0.001*
never drinker	15,981	5.8%	422	5.1%	15,559	5.9%	
past drinker	9,983	3.7%	363	4.4%	9,620	3.6%	
current drinker	246,610	90.2%	7,417	90.2%	239,193	90.2%	
Alcohol drinking frequency (n, %) c							<0.001*
never/rarely	67,211	24.6%	2,110	25.7%	65,101	24.5%	
1-3/month	35,509	13.0%	1,283	15.6%	34,226	12.9%	
1-4/week	126,077	46.1%	3,765	45.8%	122,312	46.1%	
≥1/day	43,867	16.0%	1,046	12.7%	42,821	16.1%	
History of infertility (n, %) a							<0.001*
Yes	2,412	0.9%	442	5.4%	1,970	0.7%	
No	270,992	99.1%	7,781	94.6%	263,211	99.3%	

History of ovarian cancer (n, %) a							<0.001*
Yes	1,234	0.5%	105	1.3%	1,129	0.4%	
No	272,170	99.5%	8,118	98.7%	264,052	99.6%	
History of myocardial infarction (n, %) a							0.43
Yes	4,141	1.5%	116	1.4%	4,025	1.5%	
No	269,263	98.5%	8,107	98.6%	261,156	98.5%	
History of angina (n, %) a							0.70
Yes	9,858	3.6%	303	3.7%	9,555	3.6%	
No	263,546	96.4%	7,920	96.3%	255,626	96.4%	
Ever had coronary artery bypass graft (n, %) a							0.93
Yes	779	0.3%	23	0.3%	756	0.3%	
No	272,625	99.7%	8,200	99.7%	264,425	99.7%	

P values <0.05 were considered as evidence of significant difference between comparison groups, and were marked with """".
a P values for categorical variables were derived from chi-square tests.
b P values for continuous variables were derived from t-tests.
c P values linearly-increasing continuous variable were derived from logistic regression models.

Table 3.3 Baseline characteristics of women with and without immunological diseases

Characteristics	Women with Immunological Disease (64,620)		Immunological Disease-Free Women (208,784)		P Value
Age (year; mean, SD) b	59.2 (7.1)		55.5 (8.0)		<0.001*
Age group (year; n, %) c					<0.001*
<50	7,754	12.0%	56,922	27.3%	
50-60	20,130	31.2%	73,896	35.4%	
≥60	36,736	56.8%	77,966	37.3%	
Ethnicity (n, %) a					<0.001*
British European	53,604	83.0%	167,782	80.4%	
Others	8,969	13.9%	34,366	16.5%	
Had menopause (n, %) a					<0.001*
Yes	44,594	69.0%	120,817	57.9%	
No	17,707	27.4%	77,544	37.1%	
Age at menarche (year; n, %) b	12.9 (1.7)		13.0 (1.6)		<0.001*
Age at menarche group (year; n, %) c					<0.001*
<11	3,622	5.6%	8,743	4.2%	
11	10,619	16.4%	30,011	14.4%	
12	11,543	17.9%	38,482	18.4%	
13	13,943	21.6%	50,351	24.1%	
>13	22,828	29.4%	62,434	29.9%	
No. of live births (n, %) b	1.9 (1.2)		1.79 (1.19)		<0.001*
No. of live births (n, %) c					<0.001*
0	10,581	16.4%	40,537	19.4%	
1	8,338	12.9%	28,130	13.5%	
2	27,913	43.2%	91,274	43.7%	
3	12,290	19.0%	36,012	17.2%	
≥4	5,292	8.2%	12,208	5.8%	

Ever taken hormone replacement therapy (n, %) a						<0.001*
	Yes	33,238	51.4%	70,683	33.9%	
	No	30,989	48.0%	136,919	65.6%	
Ever taken oral contraceptive pills (n, %) a						<0.001*
	Yes	49,962	77.3%	170,491	81.7%	
	No	14,270	22.1%	37,262	17.8%	
Body mass index (kg/m²; mean,sd) b			28.5 (5.8)		26.6 (4.9)	<0.001*
BMI group (kg/m²; n, %) c						<0.001*
	<18.5	375	0.6%	1,704	0.8%	
	18.5-25	18,619	28.8%	87,053	41.7%	
	25-30	23,618	36.5%	76,264	36.5%	
	≥30	21,499	33.3%	42,813	20.5%	
Waist-hip ratio			0.83 (0.07)		0.81 (0.07)	<0.001*
Waist-hip ratio group						<0.001*
	<0.8	21,653	33.5%	92,721	44.4%	
	0.8-0.85	17,294	26.8%	55,458	26.6%	
	≥0.85	25,316	39.2%	59,835	28.7%	
Body fat percentage b			38.4 (6.9)		36.0 (6.8)	<0.001*
Body fat percentage (n, %) c						<0.001*
	<32	10,772	16.7%	55,290	26.5%	
	32-37	14,340	22.2%	56,039	26.8%	
	37-42	17,893	27.7%	53,891	25.8%	
	≥42	19,951	30.9%	40,104	19.2%	
Weight			74.7 (15.5)		70.5 (13.5)	<0.001*
Weight group						<0.001*
	<60	9,639	14.9%	43,600	20.9%	
	60-70	18,332	28.4%	72,074	34.5%	
	70-80	16,516	25.6%	50,363	24.1%	
	≥80	19,672	30.4%	41,847	20.0%	
Height			161.8 (6.4)		162.7 (6.3)	<0.001*
Height group						<0.001*
	<160	23,239	36.0%	63,986	30.6%	
	160-165	19,894	30.8%	65,298	31.3%	
	165-170	14,035	21.7%	50,537	24.2%	
	≥170	7,068	10.9%	28,194	13.5%	
Body size at age 10						0.009*
	thinner	20,644	31.9%	64,772	31.0%	
	average	30,593	47.3%	104,754	50.2%	
	plummer	12,105	18.7%	35,452	17.0%	
Height at age 10						0.009*
	shorter	13,452	20.8%	43,385	20.8%	
	average	33,153	51.3%	109,633	52.5%	
	taller	16,444	25.4%	51,430	24.6%	

Smoking status (n, %) a						<0.001*
	never smoker	35,508	54.9%	126,558	60.6%	
	past smoker	22,538	34.9%	62,920	30.1%	
	current smoker	6,119	9.5%	18,248	8.7%	
Alcohol drinking status (n,%) a						<0.001*
	never drinker	4,548	7.0%	11,433	5.5%	
	past drinker	3,480	5.4%	6,503	3.1%	
	current drinker	56,355	87.2%	190,255	91.1%	
Alcohol drinking frequency (n, %) c						<0.001*
	never/rarely	19,840	30.7%	47,371	22.7%	
	1-3/month	8,328	12.9%	27,181	13.0%	
	1-4/week	26,932	41.7%	99,145	47.5%	
	≥1/day	9,320	14.4%	34,547	16.5%	
History of infertility (n, %) a						<0.001*
	Yes	368	0.6%	2,044	1.0%	
	No	64,252	99.4%	206,740	99.0%	
History of ovarian cancer (n, %) a						0.17
	Yes	312	0.5%	922	0.4%	
	No	64,308	99.5%	207,862	80.4%	
History of myocardial infarction (n, %) a						<0.001*
	Yes	1,855	2.9%	2,286	1.1%	
	No	62,765	97.1%	206,498	98.9%	
History of angina (n, %) a						<0.001*
	Yes	4,513	7.0%	5,345	2.6%	
	No	60,107	93.0%	203,439	97.4%	
Ever had coronary artery bypass graft (n, %) a						<0.001*
	Yes	351	0.5%	428	0.2%	
	No	64,269	99.5%	208,356	99.8%	

P values <0.05 were considered as evidence of significant difference between comparison groups, and were marked with """".
a P values for categorical variables were derived from chi-square tests.
b P values for continuous variables were derived from t-tests.
c P values linearly-increasing continuous variable were derived from logistic regression models.

Cross-sectional study

Table 3.4 shows the number of each specific immunological disease diagnosis, and grouped immunological diseases, in women with endometriosis and without. There were 273,404 women in UKBB (at the time of data download), including 8,223 women diagnosed with endometriosis (4,241 by self-reports and 5,026 by hospital diagnosis, accounting for 3.01% of all female participants) and

265,181 women without known endometriosis. In total, 64,620 women had at least one immunological disease diagnosis (42,824 by self-reports and 41,564 by hospital diagnosis, accounting for 23.64% of all female participants).

In the cross-sectional analysis, the prevalence of overall immunological diseases (Table 3.4) was higher in women with endometriosis than those without endometriosis (25.10% vs. 23.59%, odds ratio (OR): 95% confidence interval (CI) = 1.32[1.25-1.39], P < 0.001*). In total, 14,764 women were diagnosed with one or more classic autoimmune diseases in women with and without endometriosis (6.14% vs. 5.38%, OR[95%CI] = 1.24[1.13-1.36], P < 0.001*); 52,027 with autoinflammatory diseases (19.92% vs. 19.00%, OR[95%CI] = 1.33[1.26-1.41], P < 0.001*); and 4,379 women with mixed-pattern diseases (1.90% vs. 1.59%, OR[95%CI] = 1.23[1.10-1.52], P = 0.002*).

In the analysis of prevalent risk for each separate immunological disease in women with vs. without endometriosis, a significantly higher risk was found for: (systemic) lupus erythematosus (OR[95%CI] = 1.62 [1.14-2.24], P = 0.005*), rheumatoid arthritis (OR[95%CI] = 1.22[1.04-1.41], P = 0.011*), coeliac disease (OR[95%CI] = 1.35[1.06-1.70], P = 0.011*), myasthenia gravis (OR[95%CI] = 2.55[1.30-4.49], P = 0.003*), inflammatory bowel disease (OR[95%CI] = 1.28[1.06-1.53], P = 0.009*), osteoarthritis (OR[95%CI] = 1.35[1.27-1.43], P < 0.001*), gout (including pseudogout, crystal arthropathy) (OR[95%CI] = 1.66[1.18-2.26], P = 0.002*), ankylosing spondylitis (OR[95%CI] = 1.59[1.06-2.30], P = 0.019*) and a borderline significant risk for type 1 diabetes (OR[95%CI] = 1.26[0.95-1.64], P = 0.09), ulcerative colitis (OR[95%CI] = 1.24[0.98-1.55], P = 0.06), psoriasis (OR[95%CI] = 1.18[0.97-1.41], P = 0.08). More information on the risk of specific immunological diseases in women with and without endometriosis is shown in Table

3.4. The sample size for this cross-sectional study is 273,404 which includes 8,223 women with endometriosis and 265,181 women without endometriosis. For immunological diseases with a relatively low prevalence rate of 1%, this cross-sectional study is only well-powered to observe a large effect for OR ≥ 1.3 for coeliac disease, inflammatory bowel disease and psoriasis. This cross-sectional study is also well-powered to observe a moderate and relatively large effect for more common immunological diseases such as rheumatoid arthritis, osteoarthritis.

Cohort study results

For the cohort study analysis, prevalent immunological diseases diagnosed before cohort entry time or before endometriosis diagnosis were excluded (see Methods). For overall immunological diseases disease incident risk, 225,452 women were included in the study population including 6,424 women diagnosed with endometriosis as the exposed group; for the classic autoimmune disease incident risk, these numbers were 262,816 and 7,510; for the autoinflammatory disease incident risk, 236,313 and 6,754; and for mixed-pattern disease incident risk, 269,375 and 7,702. For the incident risk analysis of each specific immunological disease in women with vs. without endometriosis, sample sizes for the study population and the number of women included in the exposed group are detailed in Table 3.5.

Cohort analysis was conducted for immunological diseases with a minimum 2,000 immunological disease cases (rheumatoid arthritis, coeliac disease, inflammatory bowel disease, osteoarthritis, psoriasis) to allow enough number of immunological disease cases after excluding prevalent immunological diseases diagnosed before index date or before the endometriosis diagnosis. Cohort analysis was also conducted for (systemic) lupus erythematosus, multiple sclerosis and

psoriasis which has a smaller sample size, since these 3 diseases were selected for genetic analysis in the next chapter prior to this thesis revision, hence were still included in the cohort analysis in this thesis revision for comparison with genetic analysis.

Table 3.5 shows the analysis results with simple adjustment of confounders and with additional full adjustment of confounders. Factors that were both significantly associated with endometriosis and immunological diseases were defined as potential confounders and included: age, ethnicity, menopausal state, age at menarche, number of live births, ever use of hormone replacement therapy, ever taken oral contraceptive pills, body mass index (BMI), body fat percentage, weight, height, body size at age 10, smoking status, alcohol drinking status, alcohol drinking frequency, history of infertility. When adding these potential confounders in a logistic regression analysis model with endometriosis as exposure and overall immunological disease group as the outcome, only age was found to be a confounder that significantly impacted the analysis with a 3% change in the effect size on the association between endometriosis and immunological diseases. While ethnicity was not significantly impacting the analytical results, it was still included in the analytical models as based on literature it is arguable the most important factor to adjust for in the epidemiological studies of endometriosis and/or immunological diseases (1). Subgroup analysis was performed for women of European ancestry, which showed similar association results compared to the model that adjusted for ethnicity as a confounder, hence the latter model was used to include a larger number of study participants. Therefore, the simple-adjusted models that adjusted for age and ethnicity only (Table 3.5). The fully-adjusted models (Table 3.5) additionally adjusted for menopausal state, age at menarche, history of infertility

(while number of live births was also significantly associated with both endometriosis and immunological diseases, this could lead to over-adjustment alongside history of infertility), ever use of HRT, ever taken OCP, BMI, body fat percentage, smoking status and alcohol drinking status. The fully-adjusted models are described as the main cohort analysis results. In checking the proportional hazards (PH) assumption in the cohort analysis, age was found to violate the PH assumption for all analysis, hence stratified cohort analysis by age groups (age < 50, age 50-60, age ≥ 60) are presented (Table 3.5).

In the cohort study analysis, women with endometriosis in comparison to those without were found to have an increased risk of overall immunological diseases in younger women (age < 50: HR[95%CI] = 1.37[1.12-1.67], P = 0.002*; age 50-60: HR[95%CI] = 1.15[0.99-1.35], P = 0.08; age ≥ 60: HR[95%CI] = 0.96[0.80-1.14], P = 0.62), classic autoimmune diseases (age < 50: HR[95%CI] =1.67[1.16-2.42], P = 0.006*; age 50-60: HR [95%CI] =1.07[0.72-1.57], P =0.75; age ≥ 60: HR [95%CI] = 0.80[0.52-1.25], P =0.33), autoinflammatory diseases (age < 50: HR[95%CI] = 1.21[0.97-1.52], P = 0.09; age 50-60: HR[95%CI] =1.18[1.00-1.38], P =0.044*; age ≥ 60: HR[95%CI] = 0.98[0.83-1.16], P =0.83). The significantly increased risk observed in all and categorized immunological disease groups had a significantly increased risk with a larger effect size in younger women, especially in women aged < 50 years old. This largely non-significant risk for grouped immunological diseases in women with endometriosis at an older age (≥ 60 years old) were possibly due to a true null association, and not likely due to a power issue, since there were larger sample sizes in these groups at an older age. Yet an increased risk for mixed-pattern disease group was also observed in women with endometriosis before stratification by age (HR[95%CI]=1.65[1.08-2.53], P = 0.022*),

but this significantly increased risk became non-significant after stratifying by age, likely due to a largely reduced sample size and a reduced study power since all these stratified analysis had a similar and large effect size (age < 50: HR[95%CI] = 1.78[0.80-3.98], P = 0.16; age 50-60: HR[95%CI] = 1.49[0.75-2.95], P = 0.26; age ≥ 60: HR[95%CI] = 1.70[0.80-3.65], P = 0.17). For the specific immunological disease risk, women with endometriosis were found to have an increased risk for rheumatoid arthritis in women of endometriosis aged < 50 years old (HR [95%CI] = 2.25[1.33-3.79], P = 0.002*) and (systemic) lupus erythematosus in women of endometriosis ≥60 years old (HR [95%CI] = 2.37[1.21-4.65], P = 0.012*) with a borderline significantly increased risk for (systemic) lupus erythematosus in women of endometriosis < 50 years old (HR [95%CI] = 1.69 [0.96-2.98], P = 0.07) which is likely due to a reduced power from a smaller sample size in this age group. Also, a significantly increased risk for osteoarthritis was observed in women with endometriosis aged < 50 years old (HR [95%CI] = 1.26 [1.01-1.58], P = 0.042*) and a borderline significantly increased risk for aged 50-60 years old (HR [95%CI] = 1.15 [0.98-1.35], P = 0.09), but the borderline significantly increased risk for osteoarthritis in women with endometriosis aged 50-60 years old and the null association for women with endometriosis aged ≥ 60 years old were not likely due to a power issue, since the sample sizes for these older age groups are even larger than the sample size for the age group < 50 years old.

For cohort analysis results, the mean follow-up time for specific immunological disease risk in women with and without endometriosis ranged between 9.16 to 9.93 years, person-years for simply-adjusted models ranged between 1010.98 to 7,332.22, person-years for fully-adjusted models ranged between 883.40 to 6610.58, which allowed sufficient follow-up time to observe incidence of immunological

disease risk in women with endometriosis in comparison to those women without endometriosis.

Table 3.4 Cross-sectional study of immunological diseases in women with and without endometriosis

Immunological Disease	Immunological Disease					OR (95% CI)	P Value
	Total	in ENDO women (8,223)		in ENDO-free women(265,181)			
Overall	64,620	2,064	25.10%	62,556	23.59%	1.32 (1.25-1.39)	<0.001*
Classic autoimmune disease	14,764	505	6.14%	14,259	5.38%	1.24 (1.13-1.36)	<0.001*
(Systemic) lupus erythematosus	780	36	0.44%	744	0.28%	1.62 (1.14-2.24)	0.005*
Sjogren's syndrome	803	23	0.28%	780	0.29%	1.07 (0.68-1.59)	0.76
Systemic sclerosis	255	10	0.12%	245	0.09%	1.60 (0.79-2.86)	0.15
Multiple sclerosis	1,571	61	0.74%	1,510	0.57%	1.23 (0.93-1.58)	0.13
Rheumatoid arthritis	5,818	187	2.27%	5,631	2.12%	1.22 (1.04-1.41)	0.011*
Coeliac disease	2,023	76	0.92%	1,947	0.73%	1.35 (1.06-1.70)	0.011*
Vitiligo	174	6	0.07%	168	0.06%	1.29 (0.51-2.68)	0.54
Primary biliary cirrhosis	263	8	0.10%	255	0.10%	1.17 (0.53-2.21)	0.67
Addison's disease	180	6	0.07%	174	0.07%	1.21 (0.47-2.50)	0.65
Type 1 diabetes	1,603	57	0.69%	1,546	0.58%	1.26 (0.95-1.64)	0.09
Myasthenia gravis	173	11	0.13%	162	0.06%	2.55 (1.30-4.49)	0.003*
Autoimmune gastritis	1,466	48	0.58%	1,418	0.53%	1.20 (0.88-1.58)	0.22
Pemphigus, Pemphigoid	95	3	0.04%	92	0.03%	--	--
Dermatomyositis,Polymyositis	115	3	0.04%	112	0.04%	0.97 (0.24-2.59)	0.96
Graves' disease	545	23	0.28%	522	0.20%	1.28 (0.80-1.93)	0.27
Hashimoto's disease	244	6	0.07%	238	0.09%	0.89 (0.35-1.84)	0.79
Autoimmune thyroid disease	788	29	0.35%	759	0.29%	1.17 (0.79-1.69)	0.42
Autoinflammatory disease	52,027	1,638	19.92%	50,389	19.00%	1.33 (1.26-1.41)	<0.001*
Crohn's disease	1,382	48	0.58%	1,334	0.50%	1.18 (0.87-1.58)	0.27
Ulcerative colitis	2,365	82	1.00%	2,283	0.86%	1.24 (0.98-1.55)	0.06
Inflammatory bowel disease	3,527	129	1.57%	3,398	1.28%	1.28 (1.06-1.53)	0.009*
Osteoarthritis	47,642	1,493	18.16%	46,149	17.40%	1.35 (1.27-1.43)	<0.001*
Acute respiratory distress syndrome	79	2	0.02%	77	0.03%	--	--
Giant cell, Takayasu cell arteritis	366	10	0.12%	356	0.13%	1.35 (0.67-2.40)	0.35
Sarcoidosis	741	26	0.32%	715	0.27%	1.39 (0.91-2.01)	0.10
Erythema nodosum associated disease	79	5	0.06%	74	0.03%	--	--
Acne, Acne form associated disease	287	8	0.10%	279	0.11%	0.78 (0.35-1.48)	0.50
Gout, Pseudogout, Crystal arthropathy	1,117	41	0.50%	1,076	0.41%	1.66 (1.18-2.26)	0.002*
Mixed-Pattern immunological disease	4,379	156	1.90%	4,223	1.59%	1.23 (1.10-1.52)	0.002*
Ankylosing spondylitis	676	28	0.34%	648	0.24%	1.59 (1.06-2.30)	0.019*
Psoriasis	3,697	121	1.47%	3,576	1.35%	1.18 (0.97-1.41)	0.08
Reactive arthritis	4	1	0.01%	3	0.00%	--	--
Behcet syndrome	27	6	0.07%	21	0.01%	--	--

P values <0.05 were considered as evidence of significant difference between comparison groups, and were marked with """".
*All analysis adjusted for age and ethnicity.

Table 3.5 Cohort analysis results for immunological disease risk in women with and without endometriosis (ENDO)

Immunological Disease	Immunological Disease			Follow-Up Time, Yrs	Simply-Adjusted HR (95%CI)	P Value	Person Yrs	Fully-Adjusted HR (95%CI)	P Value	Person Yrs
	Total	In ENDO women	In ENDO-Free women							
Overall	14,248	472	13,776	9.43	1.31 (1.19-1.44)	<0.001*	5,750.90	1.16 (1.05-1.28)	0.003*	5179.28
Age < 50	1,961	150	1,811	9.72	1.62 (1.36-1.94)	<0.001*	1,558.38	1.37 (1.12-1.67)	0.002*	1364.52
Age 50-60	4,597	186	4,411	9.51	1.33 (1.15-1.55)	<0.001*	2,038.47	1.15 (0.99-1.35)	0.08	1794.70
Age ≥ 60	7,716	162	7,554	9.16	1.09 (0.92-1.29)	0.32	2,154.05	0.96 (0.80-1.14)	0.62	2020.06
Classic Autoimmune Disease	2,627	98	2,529	9.78	1.42 (1.16-1.75)	<0.001*	6,982.99	1.21 (0.96-1.51)	0.10	6302.41
Age < 50	452	50	402	9.89	2.23 (1.61-3.07)	<0.001*	1,681.85	1.67 (1.16-2.42)	0.006*	1469.85
Age 50-60	805	34	771	9.83	1.26 (0.88-1.81)	0.21	2,413.12	1.07 (0.72-1.57)	0.75	2126.90
Age ≥ 60	1,382	26	1,356	9.67	0.98 (0.65-1.48)	0.92	2,888.02	0.80 (0.52-1.25)	0.33	2705.66
Rheumatoid arthritis	1,262	48	1,214	9.81	1.57 (1.18-2.10)	0.002*	7,207.05	1.38 (1.01-1.87)	0.044*	6499.49
Age < 50	166	24	142	9.92	3.19 (2.02- 5.04)	<0.001*	1,731.31	2.2 5(1.33-3.79)	0.002*	1511.40
Age 50-60	369	18	351	9.86	1.52 (0.93-2.47)	0.09	2,491.76	1.25 (0.73-2.11)	0.42	2194.43
Age ≥ 60	732	11	721	9.70	0.80 (0.43-1.50)	0.49	2,983.98	0.76 (0.41-1.43)	0.40	2793.66
Coeliac disease	391	22	369	9.82	1.99 (1.30-3.07)	0.002*	7,299.37	1.73 (1.07-2.81)	0.026*	6580.23
Age < 50	93	12	81	9.92	2.06 (1.00-4.25)	0.051*	1,739.26	1.85 (0.81-4.20)	0.14	1517.48
Age 50-60	139	12	127	9.88	2.39 (1.26-4.55)	0.008*	2,522.21	1.64 (0.75-3.58)	0.21	2220.56
Age ≥ 60	165	4	161	9.73	1.37 (0.51-3.68)	0.54	3,037.89	1.40 (0.51-3.82)	0.51	2842.20
Multiple Sclerosis	149	9	140	9.83	1.84 (0.93-3.61)	0.08	7,309.16	1.86 (0.93-3.71)	0.08	6592.94
Age < 50	65	9	56	9.93	2.60 (1.19-5.70)	0.017*	1,738.29	2.01(0.86-4.68)	0.11	1517.43
Age 50-60	45	1	44	9.88	0.69 (0.09-4.97)	0.71	2,522.59	0.72 (0.10-5.36)	0.75	2222.47
Age ≥ 60	41	1	40	9.73	1.42 (0.19-10.30)	0.73	3,048.27	1.47 (0.20-10.97)	0.71	2853.04
(Systemic) lupus erythematosus	112	5	107	9.83	1.63 (1.14-2.33)	0.007*	7,309.16	1.69 (1.17-2.46)	0.006*	6592.94
Age < 50	18	1	17	9.93	1.54 (0.90-2.65)	0.12	1,738.29	1.69 (0.96-2.98)	0.07	1517.43
Age 50-60	29	2	27	9.88	1.22 (0.60-2.47)	0.58	2,522.59	1.03 (0.48-2.20)	0.94	2222.47
Age ≥ 60	65	3	63	9.73	2.47 (1.32-4.65)	0.005*	3,048.27	2.37 (1.21-4.65)	0.012*	2853.04
Autoinflammatory Disease	13,710	443	13,267	9.46	1.28 (1.16-1.41)	<0.001*	6,080.81	1.13 (1.02-1.26)	0.017*	5472.41

Age < 50	1,679	112	1,567	9.76	1.42 (1.16-1.73)	<0.001*	1,634.81	1.21 (0.97-1.52)	0.09	1429.55
Age 50-60	4,389	182	4,207	9.54	1.37 (1.18-1.60)	<0.001*	2,156.33	1.18 (1.00-1.38)	0.044*	1897.38
Age ≥ 60	7,661	168	7,493	9.19	1.12 (0.94-1.32)	0.20	2,289.67	0.98 (0.83-1.16)	0.83	2145.48
Inflammatory bowel disease	316	12	304	9.82	1.40 (0.79-2.50)	0.25	4,247.05	1.29 (0.70-2.38)	0.41	3828.93
Age < 50	65	2	63	9.92	0.70 (0.17-2.87)	0.62	1,010.98	0.83 (0.20-3.48)	0.79	883.40
Age 50-60	112	8	104	9.87	2.43 (1.18-4.99)	0.016*	1,464.16	1.91 (0.87-4.20)	0.11	1287.00
Age ≥ 60	139	2	137	9.72	0.83 (0.21-3.35)	0.79	1,771.91	0.78 (0.19-3.19)	0.73	1658.53
Osteoarthritis	13,371	416	12,955	9.48	1.31 (1.19-1.44)	<0.001*	6,196.13	1.15 (1.04-1.27)	0.008*	5575.02
Age < 50	1,591	111	1,480	9.77	1.51 (1.23-1.84)	<0.001*	1,662.05	1.26 (1.01-1.58)	0.042*	1452.89
Age 50-60	4,326	177	4,149	9.55	1.36 (1.16-1.58)	<0.001*	2,195.90	1.15 (0.98-1.35)	0.09	1932.13
Age ≥ 60	7,473	147	7,326	9.21	1.16 (0.98-1.36)	0.08	2,338.19	1.02 (0.86-1.21)	0.83	2190.00
Mixed-Pattern Immunological Disease	527	27	500	9.82	1.81 (1.21-2.71)	0.004*	7237.373	1.65 (1.08-2.53)	0.022*	6524.50
Age < 50	92	9	83	9.92	1.81 (0.84-3.92)	0.13	1,723.46	1.78 (0.80-3.98)	0.16	1504.16
Age 50-60	192	11	181	9.87	1.71 (0.91-3.24)	0.10	2,498.64	1.49 (0.75-2.95)	0.26	2199.33
Age ≥ 60	246	10	236	9.72	1.93 (0.95-3.91)	0.07	3,015.28	1.70 (0.80-3.65)	0.17	2821.01
Ankylosing spondylitis	96	4	92	9.83	1.66 (0.61-4.52)	0.32	7,332.22	1.34 (0.48-3.71)	0.58	6610.58
Age < 50	14	1	13	9.93	1.66 (0.22-12.66)	0.63	1,746.27	2.21 (0.27-17.84)	0.46	1523.94
Age 50-60	34	1	33	9.88	0.97 (0.13-7.12)	0.98	2,532.81	0.83 (0.11-6.25)	0.85	2230.05
Age ≥ 60	48	2	46	9.73	2.52 (0.61-10.38)	0.20	3,053.14	1.83 (0.43-7.70)	0.41	2856.60
Psoriasis	427	19	408	9.82	1.67 (1.05-2.65)	0.030*	7,254.40	1.54 (0.94-2.52)	0.09	6539.35
Age < 50	76	7	69	9.92	1.55 (0.63-3.85)	0.34	1,726.77	1.40 (0.55-3.58)	0.48	1506.58
Age 50-60	158	9	149	9.87	1.65 (0.81-3.36)	0.17	2,505.47	1.46 (0.67-3.16)	0.34	2205.45
Age ≥ 60	196	6	190	9.72	1.80 (0.80-4.05)	0.16	3,022.16	1.63 (0.66-4.00)	0.29	2827.32

*For the simply adjusted models, only ethnicity were adjusted.
*For the fully-adjusted models, adjusted confounders include: ethnicity, menopausal stage, age at menarche, ever diagnosed as infertile, ever taken hormone replacement therapy, ever use of oral contraceptive pills, body mass index, body fat percentage, smoking status, alcohol drinking status.
*In the cohort analysis for each immunological disease under study, women with this studied immunological disease occurred before endometriosis diagnosis or cohort entry time (time attended assessment centre) were excluded.
P values <0.05 were considered as evidence of significant difference between comparison groups, and were marked with """".

Risk of multiple immunological diseases

In UKBB, there was a sizable proportion of women diagnosed with more than one immunological disease (N =7,117). Using a cross-sectional study design, women with endometriosis were found to have a 14% increased risk for diagnosis with one immunological disease (OR [95%CI] = 1.14 [1.08-1.21]), 21% increased risk for two immunological diseases (OR [95%CI] = 1.21 [1.05-1.39]), and 30% increased risk for at least three immunological diseases (OR [95%CI] = 1.30 [0.92-1.78], test for trend P value <0.001) in comparison to women without endometriosis (Table 3.6). When looking at subgroups of immunological diseases, there was a 11% increased risk among women with endometriosis of one autoimmune disease (OR [95%CI] = 1.11 [1.00-1.23]), 12% of two autoimmune diseases (OR [95%CI] = 1.12 [0.77-1.59]) and 120% of at least three autoimmune diseases (OR [95%CI] = 2.20 [0.98-4.26], test for trend P value = 0.037). For autoinflammatory diseases, there was a 11% increased risk of one diagnosis (OR [95%CI] = 1.15 [1.08-1.22]), 12% of two disease diagnosis (OR [95%CI] = 1.26 [0.94-1.64]) and 375% of at least three disease diagnosis (OR [95%CI] =3.75 [1.24-9.18], test for trend P value <0.001). For mixed-pattern diseases, there was a 16% increased risk for one diagnosis of mixed-pattern diseases (OR [95%CI] = 1.16 [0.97-1.36]), but there were not enough cases to investigate for more than two mixed-pattern diseases (see Table 3.6). Comparing the number of immunological diseases diagnosed in women with endometriosis and those without, endometriosis appeared to be associated with an increased risk of multiple immunological diseases across all three immunological disease categories. However, due to the reduced sample size for the dose-response analysis on the risk of multiple immunological diseases, study power is low for this dose-response analysis.

Table 3.6 Risks of multiple immunological diseases diagnosed in women with endometriosis

No. of Diseases	Immunological Disease			OR (95%CI)	P value (trend)
	Total	in ENDO women	in ENDO-free women		
Immunological diseases overall					P < 0.001*
1	56,309	1,762	54,547	1.14 (1.08-1.21)	
2	7,117	254	6,863	1.21 (1.05-1.39)	
≥3	1,194	48	1,146	1.30 (0.92-1.78)	
Autoimmune diseases					P = 0.037*
1	13,573	458	13,115	1.11 (1.00-1.23)	
2	1,062	37	1,025	1.12 (0.77-1.58)	
≥3	129	10	119	2.20 (0.98-4.26)	
Autoinflammatory diseases					P < 0.001*
1	50,263	1,569	48,694	1.15 (1.08-1.22)	
2	1,720	64	1,656	1.26 (0.94-1.64)	
≥3	44	5	39	3.75 (1.24-9.18)	
Mixed-pattern diseases					
1	4,354	156	4,198	1.16 (0.97-1.36)	--
2	--	--		--	--
≥3	--	--		--	--

P values <0.05 were considered as evidence of significant difference between comparison groups, and were marked with """".

Sensitivity analysis

In the sensitivity analysis, the disease ascertainment methods for endometriosis by all diagnosis, self-reports or surgically confirmed diagnoses did not materially affect the risk estimates, with their confidence intervals overlapping (Table 3.7). The exception was the hospital diagnosed group for which the risk estimates became largely insignificant owing to a much reduced sample size, hence a reduced study power (Table 3.1).

Table 3.7 Sensitivity analysis: immunological disease risk in women with and without endometriosis with different disease ascertainment methods

	Diagnosis method for endometriosis	IMD prevalence in ENDO-free women(n=265,181)		IMD prevalence in ENDO women		OR (95%CI)	P value
Overall Immunological Disease	All diagnosis	62,556	23.59%	2,064	25.10%	1.09 (1.03-1.14)	0.002*
	Self-reports			1,096	25.84%	1.13 (1.05-1.21)	<0.001*
	Hospital diagnosis			1,191	23.70%	1.01 (0.94-1.07)	0.86
	Surgically confirmed			1,956	28.97%	1.12 (1.06-1.18)	<0.001*
Classic Autoimmune Disease	All diagnosis	14,259	5.38%	505	6.14%	1.15 (1.05-1.26)	0.003*
	Self-reports			256	6.04%	1.13 (0.99-1.28)	0.06
	Hospital diagnosis			307	6.11%	1.14 (1.02-1.28)	0.023*
	Surgically confirmed			478	7.08%	1.18 (1.07-1.29)	<0.001*
Auto-inflammatory Disease	All diagnosis	50,389	19.00%	1,638	19.92%	1.06 (1.00-1.12)	0.037*
	Self-reports			869	20.49%	1.10 (1.02-1.18)	0.014*
	Hospital diagnosis			937	18.64%	0.98 (0.91-1.05)	0.52
	Surgically confirmed			1,556	23.05%	1.09 (1.03-1.16)	0.002*
Mixed-Pattern Disease	All diagnosis	4,223	1.59%	156	1.90%	1.22 (1.03-1.42)	0.018*
	Self-reports			100	2.36%	1.49 (1.21-1.81)	<0.001*
	Hospital diagnosis			76	1.51%	0.95 (0.75-1.18)	0.65
	Surgically confirmed			146	2.16%	1.21 (1.02-1.42)	0.027*
Osteoarthritis	All diagnosis	46,149	17.40%	1,493	18.16%	1.06 (1.00-1.12)	0.06
	Self-reports			790	18.63%	1.09 (1.00-1.17)	0.037*
	Hospital diagnosis			852	16.95%	0.97 (0.90-1.04)	0.40
	Surgically confirmed			1,418	21.00%	1.09 (1.02-1.15)	0.006*

*All results were adjusted for ethnicity and age at recruitment.
P values <0.05 were considered as evidence of significant difference between comparison groups, and were marked with """".
*There are 8,223 women with endometriosis by all diagnosis methods, 4,241 by self-reports, 5,026 by hospital diagnosis, 7,671 by surgical confirmation (self-reported surgeries or hospital recorded surgeries). There are 265,181 women without any diagnosis of endometriosis.

DISCUSSION

This epidemiological study for immunological disease risk in women with endometriosis analysed UKBB data which included 273,404 UK women by a cross-sectional study and a prospective cohort study design. In the cross-sectional study analysis considering risk of immunological diseases based on prevalence in women with endometriosis and without endometriosis, a significantly increased risk for overall immunological diseases, classic autoimmune disease group, autoinflammatory disease group and mixed-pattern disease group was found in women with endometriosis. Also, in the cross-sectional investigation of each separate immunological disease, women with endometriosis were found to have a

significantly increased risk for (systemic) lupus erythematosus, rheumatoid arthritis, coeliac disease, myasthenia gravis, inflammatory bowel disease, osteoarthritis, gout (including pseudogout, crystal arthropathy), ankylosing spondylitis and a borderline significant risk for type 1 diabetes, ulcerative colitis and psoriasis.

The advantage of the cross-sectional study design was that it included the largest sample size possible with the entire available study population included in the analysis, which could potentially increase the study power of association detection. It should be noted that a 80% study power for varied risk estimates in the cross-sectional study, the required minimum sample size was only achieved for a few immunological diseases with large sample size such as osteoarthritis, rheumatoid arthritis, coeliac disease and psoriasis. The disadvantage of a cross-sectional study was that it could only look at a simple association between endometriosis and immunological disease, and was unable to test the temporal sequence between the two diseases/conditions.

Different from the cross-sectional study, all cohort analyses in this chapter were stratified by age due the violation of proportional hazards assumption across age categories. In the cohort analysis, a significantly increased risk for overall immunological diseases, classic autoimmune diseases and autoinflammatory diseases was found in women with endometriosis, especially in women aged < 50 years old. This could fit with the hypothesis such as a cohort effect, that younger women are more likely to get diagnosed with an immunological disease. For specific immunological disease risk, women with endometriosis were found to have a significantly increased risk for rheumatoid arthritis in women of endometriosis aged < 50 years old (HR[95%CI] = 2.37[1.21-4.65], P = 0.012*), for osteoarthritis was observed in women with endometriosis aged < 50 years old (HR[95%CI] =1.26[1.01-

1.58], P =0.042*) and for (systemic) lupus erythematosus in women of endometriosis aged ≥ 60 years old (HR [95%CI] = 2.37[1.21-4.65], P = 0.012*).

In both cross-sectional study and cohort study analyses, a significantly increased risk was observed for overall immunological diseases, classic autoimmune diseases and for autoinflammatory diseases. A significantly increased risk for mixed-pattern diseases was also observed in cross-sectional study, but this increased risk became non-significant in cohort study, likely due to a reduced sample size and hence a reduced study power.

However, in studying specific immunological disease risk in women with vs. without endometriosis, analyses results by the cross-sectional study approach found an increased risk of a range of immunological diseases including (systemic) lupus erythematosus, rheumatoid arthritis, coeliac disease, myasthenia gravis, inflammatory bowel disease, osteoarthritis, gout (including pseudogout, crystal arthropathy), ankylosing spondylitis and a borderline significant risk for type 1 diabetes, ulcerative colitis and psoriasis. Yet the cohort study approach only found a significantly increased risk of incident rheumatoid arthritis and incident osteoarthritis in women with endometriosis aged < 50 years old women and for (systemic) lupus erythematosus in women of endometriosis aged ≥ 60 years old. Differences between the cross-sectional and cohort analysis results might be due to a reduced study power by a reduced sample size in the cohort study design since the effect sizes were in the same direction via cross-sectional and cohort studies.

The main difference between a cross-sectional study and a cohort study is that a cohort study incorporates temporality in investigating the disease occurrence over time, an advantage as it allows potential distinction between causes or consequences of a disease/exposure or a condition of interest. However, the

disadvantage of a cohort study in a sampling source such as UKBB is that the study population is reduced due to the need to exclude prevalent outcomes of interesting (here: immunological diseases) occurring before the index and endometriosis diagnosis dates. Additional adjustment for a range of confounders further reduced the study population, as women with missing information on these factors were excluded from analysis. As discussed in the previous chapter, a prospective cohort study could provide a higher quality evidence than a cross-sectional study, hence the cohort analysis results are treated as the main study findings by epidemiological analysis in this chapter.

The elevated risk of immunological diseases observed in women with endometriosis found in my analysis was consistent with those found in other previous studies that reported a generally increased risk of immunological diseases in women with endometriosis (38). Sinaii et al. in 2002 reported the first large-scale population study of 3,680 women that suggested a higher prevalence of autoimmune disease in women with endometriosis than general female population controls (47). Although there was likely to be selection bias in the study population, as they were recruited from members of an endometriosis patient association, the study was the first population study that raised people's awareness of multiple immunological disease risks in association with endometriosis. Eaton et al., 2007 also reported a generally increased risk of autoimmune diseases in women with endometriosis in a Danish nationwide cross-sectional study that included 5,472,932 persons (48). Using the same Danish national registry data, Jess et al., (2012) and Nielsen et al., (2011) later reported an increased risk of immunological diseases in association with endometriosis via cohort study analysis (65,79). In the systematic review described in Chapter 2, the high quality studies reported that women with endometriosis were

found to have a significantly increased risk of systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, multiple sclerosis and inflammatory bowel disease in women with endometriosis as well as a significantly increased risk of endometriosis in women with coeliac disease. Amongst these previously reported immunological diseases, my cohort analysis observed a significantly increased risk for systemic lupus erythematosus in older women with endometriosis as well as for rheumatoid arthritis and for osteoarthritis in younger women with endometriosis.

In this chapter, I also considered risk of diagnosis of multiple immunological diseases among women with endometriosis and found a significantly increased risk and a larger effect size for risk of multiple immunological diseases in women with vs. without endometriosis across all immunological disease categories. Given the relatively low study power for this dose-response analysis, this warrants replication in a larger study population. The cross-sectional analysis analysing the association between immune-mediated conditions and endometriosis by Shafrir et al. (83) using Women's Health Study data, also observed a positive trend between the number of immune-mediated conditions and the odds of endometriosis (OR[95% CI]=1.87[0.92-3.80], P value for trend =0.0002). This 'dose response' result strengthens the suggestion of there being a biologically plausible association between endometriosis and immunological disease risk, with shared disease mechanisms.

As discussed in the previous chapter, high-quality evidence should come from a study adopting a prospective cohort study approach with long follow-up time, clear description of temporal sequence between the exposure and the outcome of study, large study populations, strict disease ascertainment, carefully selected study population with and without the exposure of interest, and good adjustment for potential confounding factors. The main strength of this phenotypic analysis is the

large study population including 273,404 women from UKBB with rich medical history data which provided an ideal setting in which to the risk of a range of immunological diseases with generally larger case numbers in women with and without endometriosis. To investigate the risk for women with endometriosis developing immunological diseases subsequently, in this analysis, a prospective cohort study approach was adopted with a long follow-up time (> 9 years). This cohort analysis utilised strict definition of the exposure and the outcome. For the outcome of interest, immunological diseases diagnosed before index date or endometriosis diagnosis was excluded. The exposed and unexposed groups were selected carefully looking at women with at least one endometriosis diagnosis record versus women without any endometriosis diagnosis at all time. Also, the detailed information on the lifestyle, physical measurement, demographic information of study participants in UKBB were extracted, which allowed for full adjustment for a range of potential confounders in the cohort analysis. A sensitivity analysis was also conducted to test for robustness of the studied associations by different disease ascertainment methods, which did not materially alter the results in terms of effect sizes.

However, it should be noted that, even with the great efforts by UKBB to record medical history as accurately as possible, there may be recall bias in the self-reported disease diagnostic data, and the analysis was inevitably restricted to the information that was available. Inclusion of self-reported cases is nevertheless important, since the UKBB only incorporates hospital records since 1996. Also, in UKBB, the fact that information of potential confounders were collected at recruitment and don't relate to the same timepoint at which diagnosis was established, have complicated the ability for full adjustment of confounders (e.g. adjustment for BMI at baseline, rather than at time of diagnosis). In addition, while

“temporality” is an important factor to indicate potential “causality” in epidemiological studies, finding the exact time for endometriosis occurrence is always an issue because of the gold-standard surgical diagnosis (i.e. laparoscopy), and the often long delay between women first experiencing symptoms and ultimately receiving a diagnosis. Therefore, in the next chapter, the genetic correlation between endometriosis and immunological diseases and a potential causal relationship testing that if endometriosis is causal to (certain) immunological diseases will be investigated by utilising genetic data available from the UKBB.

Chapter 4: Genetic Basis and Genetic Correlation between Endometriosis and Immunological Diseases

INTRODUCTION

Endometriosis and immunological diseases are common complex conditions caused by multiple genetic and environmental factors. Genetic components have been discussed extensively in their contribution to the pathogenesis of endometriosis (96). Familial aggregation of endometriosis cases has been noted since the 1950s with an increased prevalence of endometriosis reported among related verses unrelated female population, which strongly suggested the presence of a heritable component for endometriosis (97). Indeed in the late 90s, a large twin study of 3,096 Australian female twins reported a 51% heritability for endometriosis (7), whilst a Swedish twin registry study arrived at a similar estimate of 47% in 2015 (98). Similarly, various immunological disorders are widely discussed as heritable diseases with a complex genetic basis. The heritable component for immunological diseases investigated within my thesis range between 44%-77% (Table 4.1). The sizeable heritable components for conditions of interest show that there is a substantial role of genetic variants on disease risk. Identification of genetic variants that influence the risk of endometriosis and immunological diseases could help understand the genetic correlation between endometriosis and immunological diseases, if endometriosis is causal to certain immunological diseases and if there is any potential shared pathogenesis of these conditions.

Genome-wide association studies (GWAS) provide a hypothesis-free genome-wide approach to discover common genetic variants associated with common health conditions. GWAS is based on the “common disease–common variant” hypothesis

where it is hypothesized that common disorders are likely influenced by genetic risk variants that are common in the population (99). The Human Genome Project estimated that the human genome consists of approximately 3 billion base-pairs, of which around 10 millions are common SNPs (population frequency > 5%). These common SNPs across the genome are not independent when tested in a population due to common ancestry between individuals (linkage disequilibrium, LD). Based on LD, several 100,000s of common SNPs with LD can be selected to provide the maximum coverage of the genome (99) without the need to genotype all 10 million SNPs for each individual to capture common variation. In addition, genotype imputation can use short stretches of shared haplotype for individuals with common ancestry to estimate the effects of many variants that are not directly genotyped (100) . Imputation panels such as 1000 Genomes project and HapMap have been developed to provide reference to predict the ungenotyped SNPs (101) to provide maximum coverage of whole genomes with great precision and speed. Thus, by genotyping a few 100,000s of common LD-correlated SNPs and by utilising reference panels to predict ungenotyped variants, all common SNPs can be reliably predicted. Following genotyping, imputation and stringent quality controls checks of the genetic data, association analysis can be conducted by comparing the frequency of SNPs between cases and controls to identify SNPs with significantly different frequency in cases and controls (99). GWAS have been very successful in discovering common genetic variants associated with complex disease. The NHGRI GWAS Catalog collected SNPs documented from 5,931 publications and 415,784 genetic associations as of 26th August 2022 (website: https://www.ebi.ac.uk/gwas/).

The largest GWAS meta-analysis study of endometriosis to date identified 42 genetic loci (3 on chromosome 23) significantly associated with endometriosis (P value < 5×10^{-8}) by meta-analysis of 24 GWAS including 58,961 endometriosis cases and 700,345 controls of European ancestry population (102) (Table 4.1). There have been many large scale GWAS conducted for immunological conditions with multiple genetic risk factors identified (103). The GWAS sample sizes investigated for immunological conditions are much larger which is reflected in the greater number of genetic risk variants identified for these conditions as summarised in Table 4.1. However, the GWAS analyses for immunological conditions have been conducted in sex-combined datasets and no European ancestry female-stratified GWAS meta-analysis results are publicly available to date. Given the epidemiological evidence showing greater prevalence of immunological conditions in females, it would be important to conduct sex-stratified GWAS to identify any female-specific genetic risk variants.

No genetic correlation analysis investigating the potential genetic sharing between endometriosis and immunological disease exist to date. In comparison to the epidemiological study to understand disease correlations, genetic studies could limit the influence of the environment and related information biases from observational studies. In addition, observational studies cannot establish temporality, even in a cohort study design with the exposure and outcome defined based on recorded diagnosis dates to determine the order of disease development where reverse causation might happen, whilst genetic studies, especially summary data-based Mendelian randomisation, which is an analytical method that uses genetic variants as instrumental variables to investigate the effects of modifiable risk factors for diseases, can overcome unmeasured confounding to investigate a potential

causal relationship between diseases as well as the associated temporality (104). However, it should be noted that although genetic studies can overcome some of the challenges of observational studies, results are only valid if several key assumptions are met. Also the interpretation of MR analysis findings with respect to evidence for an causal relationship can be challenging. Prospective phenotypic studies can be useful for shedding light on the temporality of associations and could be compared with MR analysis for temporality.

Here, in this chapter I perform female-only and sex-combined GWAS utilising UKBB European ancestry data. The aim of the female-only GWAS analysis is to identify any female-specific associations with immunological conditions. The sex-combined UKBB GWAS results will be utilised to meta-analyse with publicly available sex-combined large-scale GWAS results that do not already include UKBB GWAS results. Following from the GWAS analyses, I will use the GWAS summary-statistics to estimate the genetic correlation (LD-score regression) between endometriosis and immunological diseases utilising both sex-combined and female-only GWAS results. Lastly, for any immunological condition that shows significant genetic correlation with endometriosis, Mendelian randomisation analyses are implemented to investigate if endometriosis is causal to the respective immunological disease.

METHODS

Dataset and study population

For endometriosis, GWAS meta-analysis results from the International Endometriosis Genome Consortium (IEGC) were used, which included 52,350 cases and 504,157 controls; this included data from 20 GWAS studies excluding UKBB to prevent overlapping study population in genetic correlation and causality analyses.

Table 4.1 Largest existing GWAS for endometriosis and immunological diseases

Conditions	Heritability	Most up to date GWAS results			
		Ancestry	Sample-size cases : controls	No. of risk variants ($5x10^{-8}$)	Variance explained
Endometriosis	51% (7)	European	58,961 : 700,345	42 (Rahmoiglu et al., 2023) (102)	5.01%
Ankylosing spondylitis	77% (105)	European	10,617 : 15,145	113 (Cortes et al., 2013) (106)	24.4%
Coeliac disease	75% (107)	European	12,948 : 14,826	43 (Ricano-Ponce et al., 2020) (108)	Not reported
Inflammatory bowel disease	67% for UC, 75% for CD (109)	European	12,160 : 13,145	240 (De Lange et al., 2017) (110)	Not reported
Multiple sclerosis	46%-71% (111)	European	5,545 : 12,153	233 (Patsopoulos et al., 2019) (112)	19.2%
Osteoarthritis	47% (113)	European Asian	175,803 : 644,862 1,714 vs. 4,311	148 (Boer et al., 2021) (114)	~10%
Psoriasis	68% (115)	European Asian	15,967: 28,194 2,590 : 1,720	89 (Stuart et al., 2022)(116)	Not reported
Rheumatoid arthritis	65% Finnish population, 53% UK population (117)	European Asian	14,361: 43,923 4,873 : 17,642	101 (Okada et al., 2014) (118)	5.5% 4.7%
Systemic lupus erythematosus	44% (119)	European Asian	4,576 : 8,03 4,222 : 8,431	130 (Wang et al., 2021) (120)	9% 13%

The main source of data for immunological conditions was UKBB which includes 502,568 people (including 229,164 males and 273,404 females) aged 40 to 69 years recruited from across the UK during 2006 and 2010. For disease ascertainment in UKBB, cases were identified by self-reports collected by questionnaire at recruitment and/or hospital diagnosis by linkage to the hospital system (as described in Chapter 3). Disease free female controls in all genetic analysis using UKBB data were defined as females without any diagnosis of immunological diseases or endometriosis. GWAS was conducted for eight immunological diseases utilising the European ancestry population within the UKBB data including inflammatory bowel disease (N = 2,869 females; N = 5,751 sex-combined), osteoarthritis (N = 39,866 females; N = 68,878 sex-combined), ankylosing spondylitis (N = 547 females, N = 1,493 sex-combined), psoriasis (N = 3,036 females, N = 6,591 sex-combined), coeliac disease (N = 1,706 females, N = 2,640 sex-combined), multiple sclerosis (N = 1,314 females, N = 1,883 sex-combined), rheumatoid arthritis (N = 4,662 females, N = 7,153 sex-combined) and systemic lupus erythematosus (N = 545 females, N = 673 sex-combined). Furthermore, published GWAS results on these 8 immunological conditions of

European ancestry populations were identified through literature search and the largest ones of European ancestry that were available were requested and downloaded. These if they didn't include UKBB in their results, were meta-analysed with my sex-combined UKBB GWAS results to increase sample size and study power.

Genome-wide association study (GWAS)

DNA samples obtained from UKBB study participants were genotyped utilising UK BiLEVE Axiom Array and UK Biobank Axiom Array (93). Stringent QC was conducted and cleaned data was imputed to Haplotype Reference Consortium (HRC), and merged UK10K and 1000 Genomes phase 3 reference panels (93). Imputations in UKBB were done centrally using the IMPUTE4 program (121). The data was downloaded from the data server on 8th January 2019. Genetic principal components were computed centrally by UKBB to distinguish between European and non-European ancestry population. Only European ancestry population was included in the analysis because of the small number of study population of other ethnic groups. GWAS was conducted analysing UKBB data for females-only and sex-combined study population. In GWAS, an association test for each SNP is performed in relation to the disease of interest yielding a P value and a regression analysis estimate of effect size (beta). The linear mixed model (LMM) implemented in BOLT (122) (software website: https://alkesgroup.broadinstitute.org/ BOLT-LMM/BOLT-LMM_manual.html) was utilised for GWAS analysis to take into account relatedness in the data and to increase power of analysis by a linear mixed effects model. BOLT-LMM employs an LMM to evaluate the association between genetic variants and phenotypic traits whilst accounting for population stratification and cryptic relatedness (123). This approach was shown to provide higher statistical

power in comparison to other methods in large-scale studies (124). The provided reference LD scores for analyses of European-ancestry samples by BOLT-LMM software utilised the 1000 Genomes samples. GWAS results were adjusted for a binary variable denoting the genotyping chip (the UKBB Axiom array or the UK BiLEVE array), with minimum MAF filter of $1x10^{-3}$ and included SNPs with ≤ 60% missingness. The BOLT-LMM GWAS results output for each SNP provide SNP ID, chromosome number, physical (base pair) position, genetic position either from bim file or interpolated from genetic map, effect allele name and the other allele name, frequency of first (effective) allele, fraction of individuals with missing genotype at this SNP, effect size, standard error, infinitesimal (P value of interest) and non-infinitesimal mixed model association test P-value.

Meta-analysis of GWAS

For immunological diseases, published GWAS meta-analysis results were searched via GWAS Atlas (website: https://atlas.ctglab.nl/), GWAS Catalog (website: https://www.ebi.ac.uk/gwas/) and literature review to identify the studies with the largest European study population that is publicly available. The in-house UKBB GWAS results are then meta-analysed with the publicly available GWAS results if UKBB results were not included in each respective GWAS meta-analysis for each immunological condition. Before meta-analysis, GWAS study-level QC was performed and markers absent in the 1000G reference panel, large missing values (≥ 60%) or lack beta/odds ratio estimates were excluded. GWAS meta-analysis for each immunological disease was carried out using METAL software using an inverse variance weighted fixed effect meta-analysis method (125). GWAS meta-analysis results were filtered and excluded those with MAF < 1%, high heterogeneity (HetISquare > 90), present < 50% effective sample size (Neff; Neff =

4NCases*NControls/(NCases + NControls). All genetic analyses were done on genome reference of homo sapiens (human) genome assembly GRCh37 (hg19). Genetic information on chromosome X was excluded. MHC region of Chr6:24000000-35000000 was excluded as it has a dense clustering of immune--relevant genes with extreme polymorphism and very strong long-range linkage disequilibrium, which complicates the determination of the exact genes and alleles that are responsible for signals of disease association in the region (126).

Presentation of GWAS results

For all the eight immunological diseases under study, females-only and sex-combined GWAS as well as meta-analysis of sex-combined GWAS results were presented by Manhattan plots and Q-Q plots using the 'qqman' (127) and 'RColorBrewer' libraries in R (128). In a Manhattan plot, each dot on the plot denotes a SNP, the P values are represented in genomic order by chromosomal position on the x-axis, the value on the y-axis represents the $-\log_{10}$ of the P-value. The red horizontal line denotes genome-wide significance threshold of $5x10^{-8}$ and the blue horizontal line denotes genome-wide nominal significance threshold of $5x10^{-5}$ (129). Q-Q plots graphically present the deviation of the observed P values from the null hypothesis: the observed P-values for each SNP are sorted from largest to smallest and plotted against expected values from a theoretical χ^2-distribution. In a QQ plot, if the dots are on or near the middle line between the x-axis and the y-axis, this means that the observed values correspond to the expected values (i.e. null hypothesis). If the dots move towards the y-axis, the observed P values would be more significant than expected under the null hypothesis (129). Lambda inflation factors were calculated quantifying the extent of the bulk inflation and the excess false positive

rate by calculating the ratio of the median of the empirically observed distribution of the test statistic to the expected median.

Identification of lead SNPs

Lead associated SNPs for each immunological disease were identified and compared between UKBB females-only, and sex-combined GWAS results. The lead SNPs were identified by uploading GWAS or GWAS meta-analysis summary statistics into FUMA (website: https://fuma.ctglab.nl/) which is an integrative web-based platform to annotate, prioritize, visualize and interpret GWAS results by utilising information from multiple biological resources (130). The SNP2GENE process in FUMA (https://fuma.ctglab.nl/snp2gene) was used with the following parameters set for lead SNPs identification: 1) specifying sample size column or number; 2) a maximum P-value < $5x10^{-8}$ for lead SNPs identification; 3) $R^2 \leq 0.1$ threshold for LD between a pair of SNP genotypes to define independent significant SNPs; 4) a reference panel population of 1000G Phase3 European; 5) include variants in reference panel (non-GWAS tagged SNPs in LD); 6) a minimum minor allele frequency filter of ≥ 0.01; 7) no maximum distance between LD blocks was specified to merge into a locus to avoid missing potentially independent lead SNPs at close location. Key information of the identified lead SNPs for each immunological diseases are summarized on their effect size, standard error, P value and were compared between UKBB females-only, sex-combined GWAS results as well as sex-combined GWAS meta-analysis results.

Genetic correlation analysis

Genetic correlation analysis between endometriosis and immunological diseases was conducted via linkage disequilibrium score regression (LDSC). The

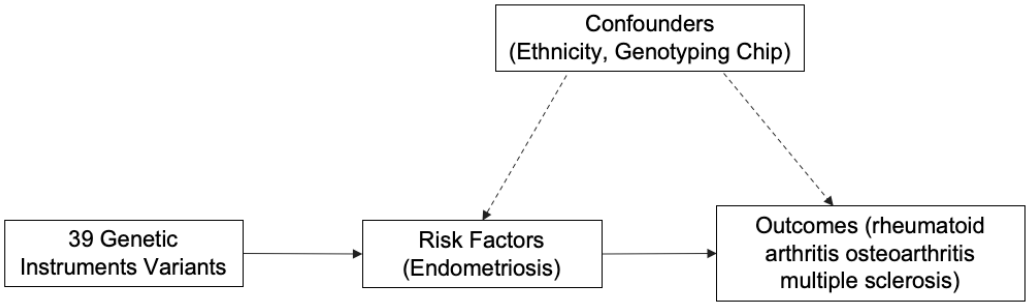
LDSC used GWAS meta-analysis summary statistics for respective disease regressing association test statistics of SNPs on their LD scores (131). The LDSC method does not require individual-level genotype data but instead uses GWAS summary statistics because the LD score of a SNP is the sum of LD r^2 measured with all other SNPs and can be calculated in a reference sample of the same ethnicity when individual genotype data are not available (131). This method calculates genetic correlation by partitioning the SNP heritability based on the fact that the χ^2 association statistic for a given SNP includes the effects of all SNPs that are in LD with it (131). The LD-score was calculated using software available at (http://github.com/bulik/ldsc), which was based on the 1000 Genomes European population and estimated within 1-cM windows, the significance threshold was set as P value = 0.00625 to account for multiple testing of eight immunological diseases. LD reference scores were obtained from (https://data.broadinstitute.org/alkesgroup/LDSCORE/eur_w_ld_chr.tar.bz2, https://data.broadinstitute.org/alkesgroup/LDSCORE/w_hm3.snplist.bz2). Summary statistics from the LDSC analysis including the effect size (RG), standard error (SE), and P value of the genetic correlation estimates under study were presented as well as the partitioned heritability (H^2) and associated standard error (SE) of the diseases under correlation study were summarized.

Mendelian randomisation analysis

The immunological diseases that were identified to be genetically correlated with endometriosis in were further investigated for their potential causal relationship with endometriosis by two-sample Mendelian randomisation (MR) using the TwoSampleMR software (132) (https://mrcieu.github.io/TwoSampleMR/index.html). Mendelian randomization uses genetic variants as instrumental variables (IVs) to

assess whether a risk factor or a condition causally affects a health outcome. Figure 4.1 presents a directed acyclic graph (DAG) to illustrate the Mendelian randomization analysis of this study. There is also no concern of reverse causality in MR as the alleles cannot be altered by disease/trait. For each outcome, variant annotations are retrieved for each SNP instrument, with effects harmonised and reference alleles selected between the endometriosis GWAS meta-analysis and immunological diseases GWAS meta-analysis. Inverse variance weighted MR (MR-IVW) was applied as the initial method as it usually has a higher power to detect causal effect over the other two sample MR methods (133). IVW is equivalent to a weighted regression of SNP-outcome effects on SNP-exposure effects passing through the origin, with the weights being the inverse of the variance of the individual causal effect estimates, and the slope being the estimate of the causal effect (133). Mendelian randomization analysis relies on genetic variants as IVs to explain variation in the exposure, but do not affect the disease outcome except possibly through the exposure (134). A valid IV needs to fulfil the following assumptions (135): 1) the variant is predictive of the exposure; 2) the variant is independent of any confounding factors of the exposure - outcome association under study; 3) the variant is conditionally independent of the outcome given the exposure and the confounding factors. However, conventional inverse-variance weighted method relies on the assumption that all genetic variants analysed are valid IVs to give consistent estimates. IVW causal estimates are biased if there are pleotropic variants (a genetic variant affects the outcome via a different biological pathway from the exposure under investigation) or heterogenetic variants (genetic variants are estimating different quantities for the causal estimates) used as the IVs to affect biological pathways other than the exposure under investigation (136).

Figure 4.1 Directed acyclic graph of Mendelian randomization analysis



As sensitivity analysis, other two-sample MR methods including weighted median MR (137) and MR-Egger regression (136) were implemented in case the assumption of valid IVs was violated. Weighted median MR was shown to have lower Type 1 error rates than the inverse-variance weighted method in a simulation analysis (136). The weighted median MR combines data on multiple genetic variants into a single causal estimate by ordering instrumental variables estimates and take the median. The IVs are assigned weights of their inverse variances of causal effect estimates and SNPs that could be outliers in the causal effect estimates are down weighted. This estimator is consistent even with up to 50% of the genetic variants are invalid instrumental variables. MR Egger provides a sensitivity analysis for the robustness of the findings from a Mendelian randomization investigation and detect evidence of heterogeneity and pleiotropy of IVs. MR Egger adapted Egger regression (a tool to detect small study bias in meta-analysis) to test for bias from pleiotropy with its slope coefficient provides an estimate of the causal effect. Egger's test gives a valid test of the null causal hypothesis and a consistent causal effect estimate even when all the genetic variants are invalid IVs under the assumption that the association of each genetic variant with the exposure is independent of the pleiotropic effect of the variant (not via the exposure) (136). To detect IVs with effect of heterogeneity and pleiotropy, MR PRESSO was applied to identify outliers (138). MR-PRESSO test is a popular tool to evaluate horizontal pleiotropy in MR analysis.

The test is based on a regression analysis in which the variants' (i.e. IV) effects on the outcome (i.e. immunological diseases in my project) are regressed on the same variants' (i.e. IV) effects on exposure (i.e. endometriosis in my project), with the causal effect of the exposure on the outcome estimated by the slope of the regression line (138). MR-PRESSO can generate three types of tests. The MR-PRESSO global test evaluates overall horizontal pleiotropy in all IVs by comparing the observed distance of all the variants to the regression line (residual sum of squares) with the expected distance under the null hypothesis (i.e. no horizontal pleiotropy) (138). The MR-PRESSO outlier test evaluates each of the IV if it is a potential outlier with horizontal pleiotropic outlier by using the observed and expected distributions of the tested variant (138). The MR-PRESSO distortion test evaluates if there is a significant distortion between the causal estimate before and after horizontal pleiotropic outlier variants are removed (138).

Also, scatter plots (139) were generated to present the SNP-outcome association estimates versus the SNP-exposure associations in investigating the causal relationship using the MR models, including IVW, weighted median MR and MR-Egger regression. In the scatter plot, each dot represents an individual SNP with its association with the exposure plotted on the horizontal axis and its association with the outcome on the vertical axis. Horizontal and vertical dotted black lines indicate 95% confidence intervals for the exposure and outcome associations, respectively (139).

In the Mendelian randomisation analysis, endometriosis was treated as the exposure and immunological diseases as the outcomes to investigate if endometriosis is causal to immunological diseases since in the UKBB and many other studies immunological diseases were found to occur typically at an older age

than endometriosis. in UKBB, the mean age of an endometriosis diagnosis was 30.54 (SE: 0.34) while the mean age for osteoarthritis was 52.39 (SE: 0.40), and the mean age for rheumatoid arthritis was 35.07 (SE: 0.46), the mean age for multiple sclerosis was 38.89 (SE: 2.23). Also, review papers have reported that osteoarthritis is most commonly diagnosed at age > 45 years (140), rheumatoid arthritis is most commonly diagnosed at age > 40 years (141). Age at first diagnosis of multiple sclerosis extends from childhood to adult life and mostly ranges between 20-40 years, yet an increased diagnosis age at onset of multiple sclerosis has been observed in recent years (142).

The MR analysis was conducted with the well-established 39 lead endometriosis SNPs identified from the largest endometriosis GWAS meta-analysis results published recently from the IEGC as IVs (102). The 39 lead SNPs for endometriosis were extracted from the endometriosis GWAS meta-analysis results used for the MR analysis in this project (the main difference for the endometriosis GWAS meta-analysis results used for this project and the recently published IEGC endometriosis GWAS meta-analysis results is that the former one doesn't include UKBB cohort or non-European ancestry cohort) and listed in Table 4.2. All statistical analyses were conducted using R software v.3.3.3.

The strength of the 39 IVs used in this analysis was evaluated by calculating R-squared statistics and F statistics for all 39 IVs (a sum of Z statistics for each SNP squared Table 4.2). R^2 is the proportion of variability in the *X (i.e. endometriosis)* that is explained by *G (IV)* which can help to indicate the power for MR studies. F statistics reflects the 'strength' of an IV or a set of IVs (143). R-squared value for each IV were calculated using the "add_rsq()" function in the TwoSampleMR software and the total R-squared statistics for all 39 IVs is 0.298%. F

statistics for all 39 IVs were calculated by a sum of Z-statistics for each SNP squared, and the total F statistics for all 39 IVs is 1656.30. Although the F statistics is relatively large for the 39 IVs, given a low R^2 statistics for the 39 IVs used in the MR analysis, the set of IVs used for the MR analysis in this project is limited in power to assess if endometriosis is causal to certain immunological diseases.

RESULTS

GWAS meta-analysis results

Endometriosis GWAS meta-analysis

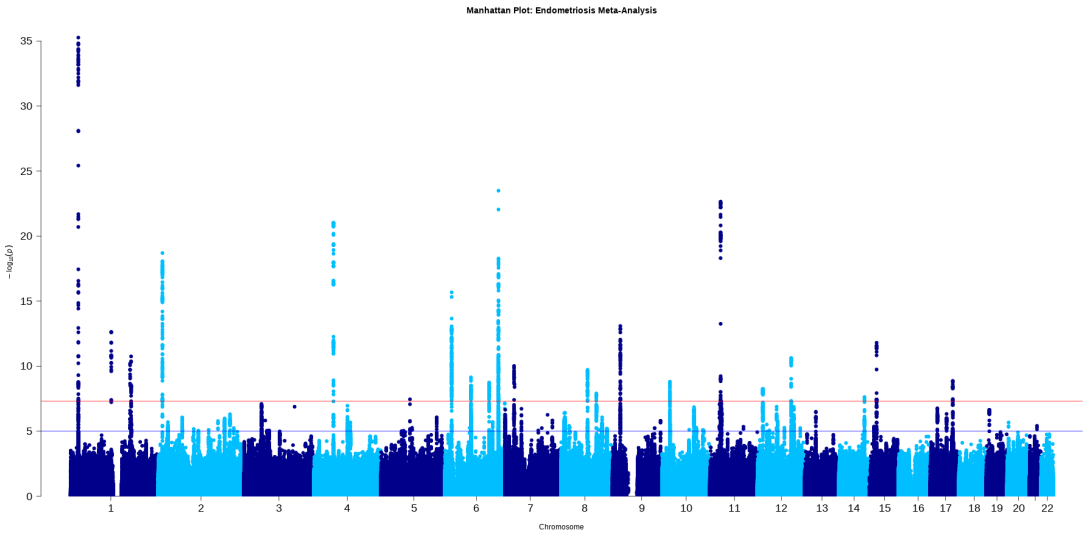
For endometriosis, GWAS meta-analysis results from the IEGC, that included 20 study cohorts but excluded the UKBB cohort, were used for genetic investigation in association with immunological diseases (144). The IEGC GWAS meta-analysis results for endometriosis included a total of 52,350 women diagnosed with endometriosis and 504,157 endometriosis-free controls. The calculated lambda inflation factor was 1.03, which suggested no indication of population stratification. The Manhattan plot and QQ plot for IEGC endometriosis GWAS meta-analysis result are shown in Figure 4.2 The lead SNPs identified from IEGC endometriosis GWAS meta-analysis are summarized in Table 4.3 with a total of 31 lead SNPS identified with P value < $5x10^{-8}$ (144).

Table 4.2 The 39 SNPs extracted from endometriosis GWAS meta-analysis results used as IVs for MR analysis

SNP	CHR	BP	EA	EAF	OR [95%CI]	P-value	Z statistics	R-squared
rs10917151	1	22422721	A	0.15	1.13 [1.11-1.16]	1.14E-34	12.28	2.71E-04
rs12030576	1	115817221	G	0.65	1.06 [1.04-1.08]	2.53E-13	7.32	9.62E-05
rs2040445	1	169216412	G	0.97	1.19 [1.13-1.25]	8.45E-11	6.49	7.57E-05
rs2421985	1	172099136	C	0.49	1.05 [1.04-1.07]	1.77E-11	6.72	8.12E-05
rs11674184	2	11721535	T	0.61	1.07 [1.06-1.09]	2.01E-19	9.01	1.46E-04
rs1430787	2	67868498	A	0.31	1.04 [1.02-1.06]	1.46E-06	4.82	4.17E-05
rs6435157	2	203441224	T	0.77	1.05 [1.03-1.06]	1.26E-06	4.85	4.22E-05
rs1352889	3	49652148	T	0.17	1.05 [1.03-1.07]	7.99E-08	5.37	5.18E-05
rs1903068	4	56008477	A	0.68	1.08 [1.06-1.1]	9.21E-22	9.59	1.65E-04
rs2510770	4	95479372	A	0.32	1.04 [1.02-1.06]	2.66E-06	4.70	3.96E-05
rs2946160	5	157891878	A	0.74	1.04 [1.03-1.06]	1.55E-06	4.80	4.15E-05
rs6456259	6	19761718	G	0.16	1.09 [1.07-1.11]	2.11E-16	8.22	1.21E-04
rs4540228	6	74613060	C	0.67	1.05 [1.03-1.07]	7.25E-10	6.16	6.82E-05
rs2226158	6	125995467	G	0.46	1.05 [1.03-1.06]	2.51E-09	5.96	6.38E-05
rs71575922	6	152554014	G	0.15	1.11 [1.09-1.14]	3.23E-24	10.15	1.85E-04
rs11756073	6	170363580	A	0.17	1.05 [1.03-1.08]	7.29E-08	5.38	5.21E-05
rs1451383	7	25891809	G	0.75	1.06 [1.04-1.08]	9.72E-11	6.47	7.52E-05
rs6970537	7	27217359	G	0.57	1.05 [1.03-1.06]	2.51E-09	5.96	6.38E-05
rs55909142	7	46673774	C	0.59	1.03 [1.02-1.05]	5.37E-05	4.04	2.93E-05
rs17053711	8	25311269	G	0.73	1.04 [1.02-1.06]	5.32E-06	4.55	3.72E-05
rs10090060	8	75257608	A	0.57	1.05 [1.03-1.07]	2.76E-10	6.31	7.16E-05
rs12549438	8	100150371	T	0.20	1.05 [1.04-1.07]	1.26E-08	5.69	5.82E-05
rs10122243	9	22158924	T	0.40	1.06 [1.04-1.08]	8.17E-14	7.47	1.00E-04
rs10983311	9	119470373	T	0.78	1.04 [1.02-1.06]	5.83E-06	4.53	3.69E-05
rs507666	9	136149399	A	0.19	1.05 [1.03-1.07]	1.60E-06	4.80	4.14E-05
rs10828249	10	21824727	A	0.36	1.05 [1.03-1.07]	1.57E-09	6.04	6.55E-05
rs7907732	10	90182764	T	0.38	1.04 [1.02-1.06]	2.90E-07	5.13	4.73E-05
rs3858429	11	30343757	C	0.84	1.11 [1.09-1.14]	2.68E-23	9.94	1.78E-04
rs7924571	11	32350027	C	0.77	1.05 [1.03-1.07]	5.20E-08	5.44	5.33E-05
rs56090796	12	15406228	A	0.33	1.05 [1.03-1.07]	5.57E-09	5.83	6.11E-05
rs3803042	12	54387947	A	0.42	1.04 [1.03-1.06]	1.32E-07	5.28	5.00E-05
rs12320196	12	95645385	G	0.47	1.05 [1.04-1.07]	2.39E-11	6.68	8.02E-05
rs10860864	12	102822862	C	0.82	1.05 [1.03-1.07]	6.04E-07	4.99	4.47E-05
rs7334326	13	50967732	C	0.14	1.06 [1.03-1.08]	3.20E-07	5.11	4.69E-05
rs57281976	14	93112974	G	0.77	1.05 [1.03-1.07]	2.37E-08	5.58	5.60E-05
rs12441483	15	40353416	C	0.47	1.06 [1.04-1.07]	1.60E-12	7.07	8.97E-05
rs66683298	17	46277748	C	0.60	1.04 [1.02-1.06]	4.72E-07	5.04	4.56E-05
rs7214750	17	63903119	C	0.93	1.09 [1.06-1.12]	3.66E-08	5.51	5.45E-05
rs2967684	19	8786624	A	0.16	1.05 [1.03-1.08]	2.98E-07	5.13	4.72E-05
Total							244.40	2.98E-03

Figure 4.2 Endometriosis GWAS meta-analysis results (excluding UKBB)

a. Manhattan plot



b. Q-Q plot

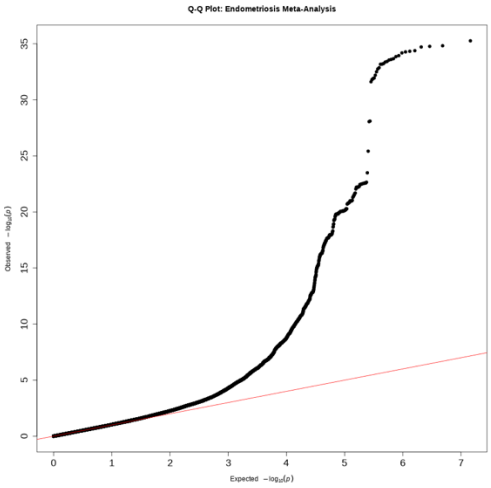


Table 4.3 The 31 Lead endometriosis-associated SNPs (LD R^2 < 0.1, P value < $5x10^{-8}$, MAF ≥ 0.01) identified from endometriosis GWAS meta-analysis for genetic correlation analysis

SNP	CHR	Position (BP)	EA	EAF	OR [95%CI]	P-value	Nearest Gene	Function
rs56319427	1	22396998	A	0.84	1.13 [1.11-1.15]	$5.43x10^{-36}$	*CDC42*	intronic
rs6328	1	115829943	T	0.65	1.06 [1.05-1.08]	$2.31x10^{-13}$	*RP4-663N10.1:NGF*	ncRNA_intronic
rs144737447	1	169160458	A	0.99	1.19 [1.13-1.26]	$6.28x10^{-11}$	*NME7*	intronic
rs2421985	1	172099136	T	0.51	1.05 [1.04-1.07]	$1.77x10^{-11}$	*DNM3*	intronic
rs7580473	2	11658972	T	0.14	1.09 [1.07-1.12]	$1.10x10^{-16}$	*RNA5SP84*	intergenic
rs11674184	2	11721535	T	0.44	1.07 [1.06-1.09]	$2.01x10^{-19}$	*GREB1*	intronic
rs1903068	4	56008477	A	0.31	1.08 [1.06-1.1]	$9.21x10^{-22}$	*KDR*	intergenic
rs4703918	5	82040476	T	0.68	1.05 [1.03-1.06]	$3.54x10^{-8}$	*CTD-2218K11.2*	intergenic
rs6456259	6	19761718	T	0.83	1.09 [1.07-1.11]	$2.11x10^{-16}$	*RP1-167F1.2*	ncRNA_intronic
rs4540228	6	74613060	A	0.67	1.05 [1.03-1.07]	$7.25x10^{-10}$	*CD109*	intergenic
rs1777224	6	126019527	A	0.55	1.05 [1.03-1.06]	$1.82x10^{-9}$	*RP11-624M8.1:RP1-293L8.2*	ncRNA_intronic
rs7759516	6	151838245	A	0.80	1.08 [1.06-1.1]	$3.37x10^{-14}$	*CCDC170*	intronic
rs10484921	6	152042260	A	0.24	1.05 [1.03-1.07]	$4.90x10^{-9}$	*ESR1*	intronic

rs73625113	6	152426433	A	0.95	2.37 [1.11-1.21]	$4.85x10^{-12}$	*ESR1*	intronic
rs71575922	6	152554014	G	0.84	1.11 [1.09-1.14]	$3.23x10^{-24}$	*SYNE1*	intronic
rs74636305	6	152564752	G	0.91	1.14 [1.11-1.17]	$5.32 x10^{-19}$	*SYNE1*	intronic
rs9397093	6	152603624	G	0.72	1.05 [1.03-1.07]	$3.68x10^{-8}$	*SYNE1*	intronic
rs1451383	7	25891809	G	0.73	1.06 [1.04-1.08]	$9.72x10^{-11}$	*CTD-2227E11.1*	intergenic
rs6970537	7	27217359	G	0.56	1.05 [1.03-1.06]	$2.51x10^{-9}$	*RP1-170O19.20: HOXA10*	intronic
rs4471028	8	75294975	T	0.40	1.05 [1.03-1.07]	$1.91x10^{-10}$	*GDAP1*	intergenic
rs12549438	8	100150371	T	0.79	1.05 [1.04-1.07]	$1.26x10^{-8}$	*VPS13B*	intronic
rs10757277	9	22124450	A	0.47	1.05 [1.03-1.06]	$4.76x10^{-9}$	*CDKN2B-AS1*	intergenic
rs10122243	9	22158924	T	0.39	1.06 [1.04-1.08]	$8.17x10^{-14}$	*CDKN2B-AS1*	intergenic
rs10828249	10	21824727	A	0.36	1.05 [1.03-1.07]	$1.57x10^{-9}$	*MLLT10*	intronic
rs10835649	11	30329175	A	0.16	1.11 [1.09-1.13]	$2.23x10^{-23}$	*ARL14EP*	intergenic
rs56090796	12	15406228	A	0.34	1.05 [1.03-1.07]	$5.57x10^{-9}$	*RERG*	intronic
rs12320196	12	95645385	T	0.56	1.05 [1.04-1.07]	$2.39 x10^{-11}$	*VEZT*	intronic
rs57281976	14	93112974	T	0.78	1.05 [1.03-1.07]	$2.37 x10^{-8}$	*RIN3*	intronic
rs12441483	15	40353416	A	0.50	1.06 [1.04-1.07]	$1.60x10^{-12}$	*SRP14-AS1*	ncRNA_intronic
rs9907056	17	63840961	T	0.66	1.05 [1.03-1.07]	$1.35x10^{-9}$	*CEP112*	intronic
rs7214750	17	63903119	A	0.92	1.09 [1.06-1.12]	$3.66x10^{-8}$	*CEP112*	intronic

Abbreviations: CHR: chromosome, BP: Base-pair position, EA: Effective allele, EAF: Effective allele frequency, OR: Odd ratio, 95% CI: 95% confidence interval for the odds ratio.

Immunological diseases GWAS

Eight immunological diseases were included in the genetic analysis. These included ankylosing spondylitis, coeliac disease, inflammatory bowel disease, multiple sclerosis, osteoarthritis, psoriasis, rheumatoid arthritis and systemic lupus erythematosus. Firstly, GWASs were conducted for each condition in UKBB for female-only and sex-combined study populations. Then UKBB sex-combined GWAS results were meta-analysed with the largest publicly available GWAS or GWAS meta-analysis results in European origin population if available to boost study power (Table 4.4).

Ankylosing spondylitis

The overall results for ankylosing spondylitis, from the female-only and sex-combined GWAS in UKBB are shown in Appendix Figure x4.1. The lambda inflation factor for the female-only and sex-combined GWAS was 1.00, which showed no population stratification (Appendix Figure x4.1b). One lead SNP was identified in

female-only GWAS and one lead SNP in sex-combined GWAS in UKBB as summarised in Appendix (Table x4.1).

Table 4.4 Number of cases and controls for immunological diseases UKBB GWAS (female-only and sex-combined) and GWAS meta-analysis (sex-combined)

Immunological diseases	UKBB (cases: controls)		Published sex-combined GWAS (cases: controls)	Sex-combined GWAS meta-analysis (cases: controls)
	Female-only	Sex-combined		
Ankylosing spondylitis	547: 162,403	1,493: 319,532	NA	1,493: 319,532
Coeliac disease	1,706: 162,403	2,640: 319,532	4,533: 10,750 (Dubois et al. 2010)	7,173: 330,282
Inflammatory bowel disease	2,869: 162,403	5,751: 319,532	25,042: 34,915 (Lang et al. 2017)	30,793: 354,447
Multiple sclerosis	1,314: 162,403	1,883: 319,532	14,498: 24,091 (Inter. MS Genet. Consort. 2019)	16,381: 343,623
Osteoarthritis	39,866:162,403	68,878: 319,532	77,052: 378,169* (Tachmazidoul et al. 2019)	77,052: 378,169*
Psoriasis	3,036:162,403	6,591: 319,532	15,967: 28,194 (Stuart et al. 2022)	22,558: 347,726
Rheumatoid arthritis	4,662: 162,403	7,153: 319,532	14,361: 43,923 (Okada et al. 2014)	21,514: 363,455
Systemic Lupus erythematosus	545: 162,403	673: 319,532	5,874: 328,598 (Bentham et al. 2015)	6,547: 648,130

*The GWAS meta-analysis results by Tachmazidoul et al (2019) already included UKBB GWAS results hence was used directly in the genetic correlation and causality analysis.

No GWAS meta-analysis was performed for ankylosing spondylitis as no other suitable publicly available European ancestry GWAS results for this condition was available. There was one study with available GWAS meta-analysis results for ankylosing spondylitis (106), however, their genotyping was performed with the Illumina Immunochip microarray, and the overlap of genetic data in terms of genomic coverage with the UKBB GWAS was low; hence they could not be meta-analysed. Furthermore, an earlier GWAS on ankylosing spondylitis in European population was identified, but their GWAS summary statistics were not publicly available (145). Female-only GWAS results in UKBB, identified one additional novel variant which were not identified in sex-combined analysis (rs7136938, OR [95% CI] = 2.30 [1.74-3.03], P value = 3.60×10^{-9} in female only analysis, OR [95% CI] = 1.40 [1.18-1.66], P = 1.10×10^{-4} in UKBB sex-combined analysis).

Coeliac disease

The overall results for coeliac disease, from the female-only and sex-combined GWAS in UKBB as well as meta-analysed sex-combined GWAS results are shown in Appendix Figure x4.2. The lambda inflation factor for the female-only and sex-combined GWAS was 1.05 and for the GWAS meta-analysis results 0.99. In total, 11 lead SNPs were identified in female-only GWAS analysis in UKBB, 16 lead SNPs in sex-combined GWAS analysis in UKBB and 31 lead SNPs in sex-combined meta-analysis of GWAS results (Appendix Table x4.2). Female-only GWAS results in UKBB, identified one additional novel variant which was not identified in sex-combined analysis (rs10801129: OR [95% CI] = 1.25 [1.16-1.35], P = 5.70 $x10^{-9}$ in female only analysis, OR [95% CI] = 1.18 [1.11-1.25], P = 2.30 $x10^{-7}$ in UKBB sex-combined analysis).

Inflammatory bowel disease

The overall results for inflammatory bowel disease, from the female-only and sex-combined GWAS in UKBB as well as the meta-analysis of sex-combined GWAS are shown in Appendix Figure x4.3. The lambda inflation factor for the female-only UKBB GWAS was 1.05, and sex-combined UKBB GWAS 1.10, for sex-combined GWAS meta-analysis results it was 1.00, which showed no population stratification. In total, 8 lead SNPs were identified in female-only GWAS analysis in UKBB, 21 lead SNPs in sex-combined GWAS analysis in UKBB and 190 lead SNPs in sex-combined meta-analysis of GWAS results (Appendix Table x4.3). Female-only GWAS results in UKBB identified one additional novel variant which was not identified in the sex-combined analysis (rs3867524: OR [95% CI] = 1.18 [1.11-1.25], P = 1.90$x10^{-8}$ in female only analysis, OR [95% CI] = 1.10 [1.06-1.15], P = 5.80$x10^{-6}$ in UKBB sex-combined analysis).

Multiple sclerosis

The overall results for multiple sclerosis, from the female-only and sex-combined GWAS in UKBB as well as meta-analysis GWAS are shown in Appendix Figure x4.4. The lambda inflation factor for the female-only UKBB GWAS was 1.05, for sex-combined UKBB GWAS 1.05, and for GWAS meta-analysis results 1.02, which showed no population stratification. In total, one lead SNP was identified in female-only GWAS analysis in UKBB, 2 lead SNPs in sex-combined GWAS analysis in UKBB and 81 lead SNPs in sex-combined meta-analysis of GWAS results (Appendix Table x4.4). Female-only GWAS results in UKBB, identified one additional novel variant which was not identified in sex-combined analysis (rs143065259: OR [95% CI] = 2.71 [1.90-3.86], P = 3.70×10^{-8} in female only analysis, OR [95% CI] = 2.19 [1.63-2.96], P = 2.70×10^{-7} in UKBB sex-combined analysis).

Osteoarthritis

The overall results for osteoarthritis, from the female-only and sex-combined GWAS in UKBB as well as meta-analysis GWAS are shown in Figure x4.5. The lambda inflation factor for females-only UKBB GWAS was 1.15, for sex-combined UKBB GWAS it was 1.25, and for GWAS meta-analysis results it was 1.29, which exceeded 1.10 as a normal threshold designating evidence for population stratification. However, as lambda increased with sample size, these values are typically seen for GWAS of very large datasets, and were deemed in the acceptable range. In total, 11 lead SNP were identified in female-only GWAS analysis in UKBB, 25 lead SNPs in sex-combined GWAS analysis in UKBB and 43 lead SNPs in sex-combined meta-analysis of GWAS results (Appendix Table x4.5). Female-only GWAS results in the UKBB identified 4 additional novel variants which were not identified in sex-combined analysis (rs11167775: OR [95% CI] = 1.05 [1.04-1.07], P

= 2.40x10^{-8} in female only analysis, OR [95% CI] =1.03 [1.02-1.05], P = 2.90x10^{-5} in UKBB sex-combined analysis; 10:22102104_CCTCTCT_C, OR [95% CI] = 1.05 [1.03-1.07], P = 1.50x10^{-8} in female only analysis, OR [95% CI] = 1.03 [1.01-1.04], P = 2.50 x10^{-5} in UKBB sex-combined analysis; 12:69656876_AT_A, OR [95% CI] = 1.05 [1.03-1.07], P = 3.00 x10^{-8} in female only analysis, OR [95% CI] = 1.04 [1.02-1.05], P = 7.50 x10^{-8} in UKBB sex-combined analysis; rs376354692, OR [95% CI] = 1.05 [1.03-1.06], P = 1.60 x10^{-8} in female only analysis, OR [95% CI] = 1.03 [1.02-1.04], P = 3.40 x10^{-7} in UKBB sex-combined analysis).

Psoriasis

The overall results for psoriasis, from the female-only and sex-combined GWAS in UKBB as well as meta-analysis GWAS are shown in Figure x4.6. The lambda inflation factor for females-only UKBB GWAS was 1.05, for sex-combined UKBB GWAS it was 1.05, and for the GWAS meta-analysis results it was 0.99, which showed no evidence of population stratification. In total, 7 lead SNP were identified in female-only GWAS analysis in UKBB, 41 lead SNPs in sex-combined GWAS analysis in UKBB and 127 lead SNPs in sex-combined meta-analysis of GWAS results (Appendix Table x4.6). Female-only GWAS results in UKBB did not identify any associations that were different from sex-combined results.

Rheumatoid arthritis

The overall results for rheumatoid arthritis, from the female-only and sex-combined GWAS in UKBB as well as meta-analysis GWAS are shown in Appendix Figure x4.7. The lambda inflation factor for the female-only UKBB GWAS was 1.05, for the sex-combined UKBB GWAS it was 1.05, and for GWAS meta-analysis results it was 1.04. In total, 2 lead SNPs were identified in female-only GWAS analysis in

UKBB, 3 lead SNPs in sex-combined GWAS analysis in UKBB and 44 lead SNPs in sex-combined meta-analysis of GWAS results (Appendix Table x4.7). Female-only GWAS results in UKBB, identified one additional novel variant which was not identified in sex-combined analysis (rs6123193: OR [95% CI] = 1.15 [1.10-1.21], P = 6.00×10^{-9} in female only analysis, OR [95% CI] = 1.10 [1.06-1.15], P = 1.10×10^{-6} in sex-combined UKBB analysis).

Systemic lupus erythematosus

The overall results for systemic lupus erythematosus, from the female-only and sex-combined GWAS in UKBB as well as meta-analysis GWAS are shown in Appendix Figure x4.8. The lambda inflation factor for the female-only UKBB GWAS was 1.00, for the sex-combined UKBB GWAS it was 1.00, and for GWAS meta-analysis results it was 0.98, which showed no evidence for population stratification. In total, one lead SNP was identified in the female-only GWAS analysis in UKBB, 2 lead SNPs in sex-combined GWAS analysis in UKBB and 34 lead SNPs in sex-combined meta-analysis of GWAS results (Appendix Table x4.8). Female-only GWAS results in UKBB did not reveal any novel association in comparison to sex-combined results.

Female-specific genome-wide significant novel SNPs

SNPs identified as female-specific novel genetic risk variants were looked up in the eQTL from GTEX portal as summarized in Table 4.5 (those not listed do not have eQTL results in GTEX portal or are pseudogenes or RNA genes with no/limited gene functions discovered, more detailed eQTL analysis results are listed in Appendix Table x4.9).

Rs7136938 is a risk variant identified from female-specific GWAS for ankylosing spondylitis. Rs7136938 regulates expression of B4GALNT3 gene in oesophagus mucosa and sun exposed lower leg skin. B4GALNT3 can promote the synthesis of LacdiNAc, which is an important component for glycoproteins expressed by neurons (146). B4GALNT3 can supress malignant neuroblastoma, reducing cell growth, colony formation, migration, and invasion, likely mediated through suppression of β1 integrin signalling and attenuation of Akt and ERK activation (147).

Table 4.5 Annotation of female-specific genome-wide significant novel SNPs in eQTL data from GTEX

Condition	GWS SNP	eQTL regulated gene and tissue	Gene function
Ankylosing spondylitis	rs7136938	B4GALNT3 in oesophagus mucosa and sun exposed lower leg skin	Predicts prognosis and suppresses cell migration and invasion via β1 integrin signalling in neuroblastoma (147)
Coeliac disease	rs10801129	RGS1 in oesophagus muscularis and gastroesophageal junction, subcutaneous adipose	Desensitizes the chemokine receptors CCR7 and CXCR4 that are critical to the localization of T and B cells in lymphoid organs (148)
Inflammatory bowel disease	rs3867524	MPV17L in colon, thyroid, cells cultured fibroblasts	Deficiency of M-LP/Mpv17L leads to development of β-cell hyperplasia and improved glucose tolerance via activation of the Wnt and TGF-β pathways **(149)**
		NOMO1 in skeletal muscle, heart, adipose, artery	Affects regulation of cell migration and is associated with early-onset colorectal cancer **(150)**
		NTAN1 in skeletal muscle, heart, adipose, skin, thyroid, hear	Regulates endoreplication rates through the N-end rule pathway (151)
		PARN in skin	Causes global poly(A) shortening during Xenopus oocyte maturation); affects mRNA metabolism (152)
		PDXDC1 in whole blood	Enables cadherin binding activity; involved in carboxylic acid metabolic process (153)
		RRN3 in cultured fibroblasts and EBV-transformed lymphocytes, liver, skins, skeletal muscle, heart, artery, oesophagus, brain, colon	Affects DNA-templated transcription, initiation; regulation of intrinsic apoptotic signalling pathway and DNA-templated transcription (154)

Rs10801129 is a risk variant identified from female-specific GWAS for coeliac disease. Rs7136938 regulates expression of RGS1 gene in oesophagus muscularis and gastroesophageal junction, subcutaneous adipose. RGS1 is a member of the regulator of G-protein signalling (RGS) family, has been associated with multiple immune-mediated diseases. RGS1 is regulates T-cell migration within lymphoid tissue, the development and function of TFH cells as well as an indirect effect on B-cell migration and germinal centre formation (148). Rs3867524 is a risk variant identified from female-specific GWAS for inflammatory bowel disease.

Rs7136938 regulates expression of a range of gens in several tissues such as MPV17L in colon, thyroid, cells cultured fibroblasts, NOMO1 in skeletal muscle,

heart, adipose, artery, and NTAN1 in skeletal muscle, heart, adipose, skin, thyroid, hear. Notably, deficiency of MPV17L can trigger β-cell hyperplasia and improve glucose tolerance through activation of the Wnt and TGF-β signalling pathways by an increased levels of phosphorylated β-catenin and glycogen synthase kinase-3β (GSK-3β) (149).

Genetic correlation analysis

The genetic correlation between endometriosis and eight immunological diseases was investigated by LDSC using the generated GWAS datasets. The results are given in Table 4.6 along with the partitioned SNP heritability and the genetic correlation estimates. Endometriosis IEGC GWAS meta-analysis results excluding UKBB were used to represent endometriosis in the genetic correlation analysis with immunological diseases UKBB GWAS females-only and sex-combined results as well as sex-combined GWAS meta-analysed results. Potential sex-specific effects were evaluated by comparing UKBB GWAS females-only results with UKBB sex-combined results.

Nominal genetic correlation (P value < 0.05) was shown between endometriosis and ankylosing spondylitis (female-only RG[SE]: 0.308[0.124], P = 0.013, sex-combined RG[SE]: 0.300[0.124], P = 0.016). There did not seem to be a sex-specific effect since the genetic correlation between endometriosis and ankylosing spondylitis were the same. A nominal genetic correlation was also found between endometriosis and coeliac disease (Female-only RG[SE] = 0.215[0.083], P = 0.010, sex-combined RG[SE] = 0.154[0.068], P = 0.024) with a potential sex-specific effect in UKBB, however, this genetic correlation was not observed in the sex-combined GWAS meta-analysis for coeliac disease (RG[SE] = 0.076 [0.054] ,P

= 0.162) The greater genetic correlation in female-only analysis is intriguing and requires replication in a larger study given that the evidence is nominal.

After correcting for multiple testing ($0.05/8 = 6.25x10^{-3}$) significant genetic correlation between endometriosis and (1) multiple sclerosis (2) osteoarthritis and (3) rheumatoid arthritis was observed (Table 4.6). A significant genetic correlation was observed between endometriosis and multiple sclerosis in sex-combined GWAS meta-analysis results (RG[SE] = 0.093[0.034], P = 0.006*), this genetic correlation was borderline significant in UKBB sex-combined GWAS results (RG[SE] = 0.273[0.116], P = 0.018) or the female-only UKBB GWAS results (RG[SE] = 0.247[0.139], P = 0.076) but with a greater effect size of a genetic correlation observed in UKBB results (Table 4.6).The moderately strong genetic correlation between endometriosis and osteoarthritis was consistent in sex-combined GWAS results from UKBB-only (RG[SE] = 0.278[0.038], $P = 2.41x10^{-13}$) and meta-analysed sex-combined GWAS results (RG[SE] = 0.278[0.035], $P = 3.248x10^{-15}$). A potential sex-specific effect was detected for osteoarthritis as female-only GWAS results had a slightly greater genetic correlation with endometriosis (RG[SE] = 0.322[0.042], $P = 1.85x10^{-14}$*), compared to sex-combined results from UKBB only (RG [SE] = 0.278[0.038], $P = 2.41x10^{-13}$), or meta-analysis (RG [SE] = 0.278[0.035], $P = 3.19x10^{-15}$). For rheumatoid arthritis, a consistent moderately strong genetic correlation was found with endometriosis in sex-combined GWAS meta-analysis results (RG[SE] = 0.180[0.041], P =1.25x10-5) or UKBB sex-combined GWAS results (RG[SE] = 0.284[0.068], $P =2.65x10^{-5}$) and female-only GWAS results (RG[SE]=0.277[0.079], P =0.001*) even with a greater effect size of a genetic correlation observed in UKBB results (Table 4.6). No genetic correlation was observed between endometriosis and inflammatory bowel disease, psoriasis or

systemic lupus erythematosus. For systemic lupus erythematosus this could be due to the small GWAS sample size (number of cases < 10,000) as well as because of true lack of a shared biological link.

Table 4.6 Genetic correlation of immunological diseases and endometriosis within the UKBB female-only and sex-combined results and sex-combined GWAS meta-analysis where available

	UKBB female-only GWAS			UKBB sex-combined GWAS			Sex-combined GWAS meta-analysis		
Immunological Diseases	**H2 (SE)**	**RG (SE)**	**P Value**	**H2 (SE)**	**RG (SE)**	**P Value**	**H2 (SE)**	**RG (SE)**	**P Value**
Ankylosing spondylitis	0.006 (0.003)	0.308 (0.124)	0.013	0.589 (0.310)	0.300 (0.124)	0.016	NA	NA	NA
Coeliac disease	0.013 (0.003)	0.215 (0.083)	0.010	0.009 (0.002)	0.154 (0.068)	0.024	0.301 (0.047)	0.076 (0.054)	0.1619
Inflammatory bowel disease	0.014 (0.003)	0.054 (0.085)	0.521	0.013 (0.002)	0.007 (0.063)	0.910	0.277 (0.028)	-0.041 (0.035)	0.237
Multiple sclerosis	0.004 (0.003)	0.247 (0.139)	0.076	0.003 (0.001)	0.273 (0.116)	0.018	0.260 (0.023)	0.093 (0.033)	0.006*
Osteoarthritis	0.051 (0.004)	0.322 (0.042)	$1.852x10^{-14}$*	0.042 (0.002)	0.278 (0.038)	$2.413x10^{-13}$*	0.046 (0.002)	0.278 (0.035)	3.248x10-15
Psoriasis	0.012 (0.003)	0.043 (0.084)	0.605	0.239 (0.027)	0.066 (0.037)	0.076	0.239 (0.027)	0.066 (0.037)	0.076
Rheumatoid arthritis	0.013 (0.003)	0.277 (0.079)	0.001*	0.011 (0.002)	0.284 (0.068)	$2.646x10^{-5}$*	0.145 (0.017)	0.180 (0.041)	1.252x10-05
Systemic lupus erythematosus	0.003 (0.003)	0.154 (0.154)	0.316	0.002 (0.001)	0.190 (0.165)	0.248	0.332 (0.048)	0.127 (0.071)	0.074

*P value < $6.25x10^{-3}$ as significance level threshold accounting for eight immunological disease tested (0.05/8) to control of multiple testing. Abbreviations: H^2 = proportion of heritability, SE = standard error, RG = genetic correlation coefficient.

Mendelian randomisation analysis

Given the significant genetic correlation between endometriosis with osteoarthritis and rheumatoid arthritis by LDSC analysis, Mendelian randomisation (MR) analysis was utilised to understand the potential causal relationship between endometriosis with osteoarthritis and rheumatoid arthritis. In the MR analysis, endometriosis was used as the exposure, osteoarthritis and rheumatoid arthritis as the outcome (see methods). The MR results are reported from three different models including MR-IVW, weighted median MR and MR-Egger regression. MR-Egger regression tests were also conducted to test for heterogeneity and pleiotropy. MR analysis was conducted utilising 39 genetic variants (IVs) which were endometriosis-associated genome-wide significant signals (P value < $5x10^{-8}$) reported from the

most recent largest available endometriosis GWAS results (102) to represent endometriosis. IVs were extracted from meta-analysed sex-combined GWAS results to represent the outcomes of osteoarthritis, rheumatoid arthritis and multiple sclerosis (Table 4.7).

MR-IVW was used as the main MR analysis since it is the most powerful option, but assumes the absence of horizontal genetic pleiotropy. MR Egger and weighted median estimators relax the strict requirement of no horizontal pleiotropy, but at the cost of decreased statistical power, hence were used as complimentary sensitivity checks. MR analysis was conducted to investigate if endometriosis is causal to any of the genetically associated immunological diseases, including multiple sclerosis, osteoarthritis or rheumatoid arthritis. Outlier IVs were identified by using software MR PRESSO (138). Scatter plots (139) were generated to present the SNP-outcome association estimates versus the SNP-exposure associations in investigating the causal relationship using the MR models, including IVW, weighted median MR and MR-Egger regression before and after outliers removed (Appendix Figure x4.9).

However, the MR analysis utilising 39 IVs did not identify any significant causal relationship for endometriosis's potential causal relationship to any of three immunological diseases. The initial MR analysis found evidence of heterogeneity in the analysis to evaluate if endometriosis is causal to OA or MS. Outliers were identified by MR PRESSO (Table 4.8), 3 SNPs (rs10828249, rs10917151, rs1352889) were identified in the MR analysis investigating if endometriosis was causal to OA, 1 SNP (rs507666) was identified as an outlier in the MR analysis investigating if endometriosis was causal to MS. Test results for potential outliers by MR PRESSO is presented in Table 4.8. MR analysis were repeated after removing

the identified outliers, at which time there was no evidence of heterogeneity or pleiotropy by MR Egger models, and endometriosis was still found to be not causal to OA or MS (Table 4.7).

Table 4.7 MR analysis to investigate if endometriosis (exposure) is causally associated with OA, RA, or MS (outcome)

Immunological Diseases	SNPs	Inverse Variance Weighted		Weighted Median		MR Egger		MR Egger (P Value)	
		OR [95% CI]	P Value	OR [95% CI]	P Value	OR [95% CI]	P Value	Heterogeneity	Pleiotropy
RA	31	1.06 [0.96-1.17]	0.220	1.09 [0.94-1.26]	0.261	1.08 [0.76-1.53]	0.682	0.611	0.435
OA	39	1.02 [0.96-1.07]	0.533	1.02 [0.97-1.08]	0.400	1.08 [0.92-1.26]	0.353	$1.56E^{-05}$	0.229
OA (outlier removed)	36	1.01 [0.97-1.06]	0.495	1.03 [0.98-1.09]	0.281	1.03 [0.9-1.18]	0.655	0.159	0.800
MS	39	1.06 [0.94-1.21]	0.343	1.03 [0.89-1.2]	0.692	1.24 [0.84-1.84]	0.280	0.012*	0.145
MS (outlier removed)	38	1.04 [0.93-1.18]	0.484	1.02 [0.88-1.2]	0.759	1.20 [0.84-1.73]	0.325	0.0626	0.202

P values < 0.05 were considered as evidence of significant difference between comparison groups, and were marked with """".

Table 4.8 MR PRESSO as sensitivity analysis for MR analysis investigating whether endometriosis (exposure) is causally associated with OA, RA or MS (outcome).

Immunological Diseases	Model	Causal Estimate	Standard Deviation	T-statistics	P-value	Global Test (RSS_observed)	Global Test (P-value)
RA	Raw	0.062	0.048	1.296	0.205	28.570	28.570
	Outlier corrected	NA	NA	NA	NA	NA	NA
OA	Raw	0.017	0.027	0.623	0.537	93.230	<0.001
	Outlier corrected	0.014	0.021	0.682	0.500	44.535	44.535
MS	Raw	-0.062	0.066	-0.948	0.349	66.916	0.006
	Outlier corrected	-0.043	0.061	-0.699	0.489	56.016	0.033

*Results by MR PRESSO as sensitivity checks on outliers are presented for MR analysis models before removing outliers (raw model) and after removing outliers (outlier corrected models).
P values < 0.05 were considered as evidence of significant difference between comparison groups, and were marked with """".

DISCUSSION

Following the previous Chapter 3 that investigated the phenotypic association between endometriosis and immunological diseases, the present Chapter 4 explored the association between endometriosis and eight immunological disease at a genetic level. A major advantage of investigating disease association at genetic level is that genetic studies can limit environmental noise and information bias, study population

selection and diagnostic biases as well as unmeasured or unadjusted confounding, and even reverse causation. For endometriosis, a female-specific condition, the largest GWAS meta-analysis to date from IEGC excluding UKBB GWAS results were used. For the immunological conditions, both female-specific and sex-combined GWAS was generated from UKBB data; and for sex-combined GWAS, where possible, UKBB GWAS results were meta-analysed with other available GWAS data to boost analysis power. Female-specific GWAS analysis revealed some novel genetic risk variants for ankylosing spondylitis, coeliac disease, inflammatory bowel disease, multiple sclerosis, osteoarthritis and rheumatoid arthritis, which illustrated the importance of conducting sex-stratified analysis. For example, rs7136938 regulates the expression of B4GALNT3 which can supress malignant neuroblastoma, reducing cell growth, colony formation, migration, and invasion (147). Rs10801129 regulates the expression of RGS1 gene which regulates T-cell migration within lymphoid tissue, the development and function of TFH cells as well as an indirect effect on B-cell migration and germinal centre formation (148).

In the genetic correlation study, significant genetic correlation was observed for osteoarthritis (UKBB female-only RG[SE] = 0.322[0.042], P = 1.85×10^{-14}, UKBB sex-combined RG [SE] = 0.278[0.038], P = 2.41×10^{-13}; sex-combined meta-analysis RG [SE] = 0.278 (0.035), P = 3.248×10^{-15}) and rheumatoid arthritis (UKBB female-only RG [SE] = 0.277 [0.079], P = 0.001*; UKBB sex-combined RG [SE] = 0.284 [0.068], P = 2.65×10^{-5}; sex-combined meta-analysis RG [SE] = 0.180[0.041], P = 1.25×10^{-5}) in analysis regardless of sex-stratification as well as for multiple sclerosis in sex-combined GWAS meta-analysis results (RG [SE] = 0.093[0.034], P = 0.006*). In the genetic correlation analysis with the other immunological diseases, two nominal genetic correlations were observed (1) between endometriosis and

ankylosing spondylitis (UKBB female-only RG[SE] = 0.308[0.124], P = 0.013, sex-combined RG[SE] = 0.300[0.124], P = 0.016), (2) between endometriosis and coeliac disease that was stronger in female-only analysis (UKBB female-only RG[SE] = 0.215[0.083], P = 0.010; UKBB sex-combined RG[SE] = 0.154[0.068], P = 0.024). However, these nominal genetic correlations disappeared after adjusting for multiple testing, possibly due to a smaller study population or a true lack of biologically shared effects. There was no genetic correlation between endometriosis and inflammatory bowel disease, psoriasis or systemic lupus erythematosus. The identified phenotypic association in Chapter 3 could be due to environmental confounders, methodological bias, a smaller study population with reduced power, or possibly the mixed study population with recall bias for self-reported disease diagnosis ascertainment utilised for the genetic study.

In the MR analysis, I followed up the three conditions that showed significant genetic correlation with endometriosis: multiple sclerosis, osteoarthritis and rheumatoid arthritis, however no causal relationship was detected, that is, endometriosis was found not be causal to multiple sclerosis, osteoarthritis or rheumatoid arthritis. It should be noted that the MR analysis in this project is limited in power by the 39 selected IVs to investigate if endometriosis is causal to immunological diseases. Although the F statistics is not small for the 39 IVs, given a low R^2 statistics for the 39 IVs used in the MR analysis, the set of IVs used for the MR analysis in this project has limited power to assess if endometriosis is causal to immunological diseases. The 39 IVs could only explain < 4% of variance for endometriosis (102) and there are many more genetic variants that remain to be discovered for endometriosis. It is possible that endometriosis is causal to these or other immunological diseases, and the potential causal relationship might be

detected if more genetic variants for endometriosis are discovered. Future studies in a larger study population should be conducted, when available, to increase power. It is also possible there are subtypes of these diseases that have a potential causal relationship, and more specified disease diagnosis criteria to investigate the causal relationship in the subtypes of these diseases could provide more information. In addition, although UKBB female-only GWAS results identified 4 female-specific novel risk variants for OA, 1 for RA and 1 for MS, given the small sample size of the female-only GWAS datasets, I have restricted MR analysis to only sex-combined GWAS meta-analysis datasets to maximise statistics power. Future larger female-only GWAS are warranted on these conditions and might reveal further sex-specific genetic risk variants.

A recent study investigating the causal relationship between endometriosis and coeliac disease, systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, multiple sclerosis utilising GWAS summary statistics for these conditions (155) also reported mendelian randomisation (MR) results. However, their results have wide confidence intervals for the risk estimates for all comparisons except for multiple sclerosis which was shown to be protective of endometriosis in the MR weighted median analysis although this result was not confirmed by the other two MR models applied in their study. In contrast to my analysis, the genetic correlation between endometriosis and rheumatoid arthritis was not observed in their analysis, probably due to different GWAS datasets used to represent endometriosis. In their analysis, they utilised FinnGen cohort data (downloaded from https://finngen.gitbook.io/documentation/) to represent endometriosis which only comprised of 3380 endometriosis cases and 31,753 controls, and Okada's GWAS results (118) to represent rheumatoid arthritis (14,361 cases and 43,923 controls),

both with a much smaller study population compared to my analysis (52,350 women with endometriosis and 504,154 endometriosis-free controls; 21,514 rheumatoid arthritis cases versus 363,455 rheumatoid arthritis-free controls). Moreover, their study probably used a different set of IVs than my analysis, yet, they did not publish the list of the IVs in their analysis, hence these cannot be compared with my selected IVs for exploration of differences.

What could explain the observed genetic correlation between endometriosis and or multiple sclerosis, osteoarthritis or rheumatoid arthritis? Although the exact mechanism to account for the link between endometriosis with osteoarthritis, rheumatoid arthritis or multiples sclerosis is unknown, it is likely that endometriosis and osteoarthritis, and rheumatoid arthritis, or multiple sclerosis do have some shared biological pathways or shared risk factors such as those that affect the hormonal system. Endometriosis is an oestrogen-dependent gynaecological condition with female hormonal factors playing an important role in the disease pathology. The role of female hormonal factors in the development of rheumatoid arthritis has also been discussed at length, where factors related to decline in ovarian function and oestrogens bioavailability were found to contribute to rheumatoid arthritis development. Hormonal factors were found to differentially influence the development of rheumatoid arthritis in premenopausal and post-menopausal women, but the role of female hormonal factors in rheumatoid arthritis preclinical phases is yet to be understood (156). Also, the dramatic increase in the prevalence of osteoarthritis in postmenopausal women than pre-menopausal women has drawn a lot of interest to the hypothesis that women are protected by their female sex hormones up until menopause, after which their oestrogen levels decline (157). Yet available data suggest that the role of female reproductive factors in the

pathogenesis and progression of osteoarthritis is complex with inconclusive and mixed evidence (157). It is possible that the downregulation of hormonal pathways in some women as a treatment for endometriosis could impact negatively on their osteoarthritis risk in later life, but only in those that are genetically susceptible. It is also possible that reproductive factors impacting on changing body weight or inflammation processes may contribute to underlying pathogenetic mechanisms and mediate the relationship between endogenous sex hormones and osteoarthritis or rheumatoid arthritis. Obesity and increasing body weight are unprecedented risk factors for osteoarthritis. Gaining weight during menarche, menopause and pregnancy can drastically affect the female reproductive system. Endogenous hormones and reproductive factors through obesity may create an inflammatory environment and thus nurture the development and progression of osteoarthritis and rheumatoid arthritis. In addition, multiple sclerosis is clearly more prevalent in women than in men, with a clear gender differences in earlier disease onset and more frequent relapses in women but faster progression and worse disease prognosis in men (158). Clinical evidence of the impact of sex hormones has been discussed in length on MS. Age at menarche was found to be related to age of MS disease onset (159). A significantly increased relapse rates was observed in women during puerperium, potential reasons might include abrupt drop in oestrogen, progesterone, and glucocorticoids levels (160). This increased relapse rates might also be resulted from rapid normalization of immune function to pre-pregnancy conditions attributed to an immune reconstitution inflammatory syndrome-like phenomenon as a consequence of fetal and placental delivery (160).

Another possibility is that autoimmunity is a yet unrecognised feature of endometriosis, triggered by the misplaced ectopic endometrial cells that have not

been cleared by the immune system. However, no autoimmune mechanisms have been identified in endometriosis to date.

Another question is why endometriosis was found to be associated with some immunological diseases in the phenotypic association study, but this association was not detected at genetic level? One hypothesis is that endometriosis and these immunological diseases share as yet unidentified environmental, not genetic risk factors. Another is that the immunological diseases are diagnosed earlier, and more frequently, due to symptom-related increased health care utility among women with endometriosis. It is possible that the treatment for endometriosis could increase the risk of developing some immunological diseases. For example, women with endometriosis are more likely to take hormonal medicine or oral contraceptives to relieve symptoms, this might affect the development and function of immune response.

The main advantages of my study include (1) the large study population used for sex-combined analysis and unique comparison with newly generated female-only GWAS results for immunological diseases; (2) following up genetic correlation and causality analyses in sex-combined and female-only datasets; (3) application of multiple MR models to test for robust causal relationship between endometriosis and osteoarthritis or rheumatoid or multiple sclerosis; (4) sensitivity analysis in MR analysis which tested for heterogeneity and pleiotropy; and (5) identification of outliers by MR PRESSO analysis and analysis was repeated after removing outliers. However, limitations in my analysis that should be noted include diversity in disease ascertainment methods, which included self-reported data with a risk of disease misclassification in the UKBB. Also, if there are different subtypes of osteoarthritis, rheumatoid arthritis or multiple sclerosis that are associated with different risk-

factors, replication of my analysis might reveal different results. For example, emerging evidence suggests that osteoarthritis at different joints have different risk factors. Obesity-associated inflammation is a strong risk factor for hand osteoarthritis, while in contrast, obesity has a weak or inconsistent associations with hip osteoarthritis (161). Also, early onset disease may have different risk-factors (162). Rheumatoid arthritis that is ACPA-positive and seronegative rheumatoid factor and anti-cyclic citrullinated peptide seronegative also revealed subtype-specific genetic risk variants (163). Amongst multiple sclerosis patients, Patients with relapsing-remitting MS were found to be more likely to respond to immunomodulatory therapy than those with a progressive disease course, this probably reflects different immunopathogenic disease mechanisms (164).

CONCLUSIONS

This is the first study reporting that endometriosis is associated with multiple sclerosis, osteoarthritis and rheumatoid arthritis at genetic level. Although endometriosis was found to be not causal to any of the three genetically correlated immunological diseases (this might be resulted from limited power for the set of IVs), there might be potential shared genetic risk factors which would explain why they are genetically correlated. Investigation of potential shared genetic risk factors could provide valuable reference for the shared biological pathways or disease pathogenesis. In my next chapter, I attempt to identify some of the shared potentially causal genetic variants as well as associated biological functions disease pathogenesis between endometriosis, multiple sclerosis, osteoarthritis and rheumatoid arthritis via multi-trait association analysis.

Chapter 5: Multi-Trait Genetic Analysis for Identification and Annotation of Shared Genetic Variants between Endometriosis and Immunological Diseases

INTRODUCTION

There is evidence from studies showing genetic clustering of multiple immunological conditions in an individual and/or within families which hints at potential shared common genetic factors (165). Moreover, some autoimmune diseases such as rheumatoid arthritis, Sjögren's syndrome and systemic lupus erythematosus show similar clinical manifestations such as pain and inflammation involving connective tissues with overlapping treatment approaches targeting these symptoms indicating shared biological mechanisms (166). Genetic risk variants predisposing across several immune-mediated conditions have been identified, such as the well-known associations of the human leukocyte antigen (HLA) region with all autoimmune diseases, as well as other genetic risk variants associated with multiple autoimmune diseases, such as *IL23R*, *TNFAIP3, IL2RA.25* (167). For example, Zhernakova et al. (168) reviewed 18 published genome-wide association (GWA) and genome-wide non-synonymous SNP scans for 11 immune-related disorders, and found extensive sharing of genetic risk loci with most of these loci mapped to a few shared immunological molecular pathways, including those related to innate immunity, immune signalling, T-cell differentiation, cytokines and chemokines.

In my previous chapter I have shown that endometriosis was found not causal to multiple sclerosis, osteoarthritis or rheumatoid arthritis. However, endometriosis was found to be genetically correlated with multiple sclerosis, osteoarthritis and rheumatoid arthritis, indicating potential shared underlying biological pathway or disease mechanism that could explain the link between endometriosis with multiple sclerosis, osteoarthritis and rheumatoid arthritis.

Multi-trait association analysis (MTAG) can provide additional insights into shared genetic risk variants across genetically correlated traits/conditions (169). By joint analysis of genetically correlated multiple traits, sample size is increased boosting statistical power to detect additional novel genetic variants for each disease highlighting the shared genetic component (169). In this chapter, I will attempt to identify potential shared genetic variants between endometriosis and multiple sclerosis, osteoarthritis or rheumatoid arthritis using multi-trait genetic association analysis of GWAS (MTAG). Furthermore, most of the common genetic variants identified through GWAS whether single or multi-trait, sit in non-coding regions in between genes or in introns of genes. Hence, to understand potential functional roles of identified shared variants, I will annotate these using the expression quantitative traits loci (EQTL) maps from GTEx V8 including 49 tissues from 838 donors (170).

METHODS

Dataset and study population

Multi-trait analysis described in this chapter uses sex-combined GWAS meta-analysis results for IEGC endometriosis GWAS meta-analysis results as presented in Chapter 4, multiple sclerosis (performed inhouse to include UKBB results), osteoarthritis (171) and rheumatoid arthritis (performed inhouse to include UKBB results). All GWAS meta-analysis results are of European ancestry population; sample size and SNP-based heritability of these is reported in Table 5.1. Heritability for these diseases was calculated by via linkage disequilibrium score regression (LDSC) (131). The univariate GWAS results from these conditions are described in detail in Chapter 4.

Table 5.1 GWAS meta-analysis results to input in multi-trait analysis

Traits	Cases vs. Controls	Heritability	Meta-Analysed Published Results
Endometriosis	52,350 : 504,157	0.078 (0.004)	(Rahmioglu et al. 2018) (144) excluded UKBB
Multiple sclerosis	16,381: 343,623	0.260 (0.023)	(Inter. MS Genet. Consort. 2019) meta-analysed with UKBB
Osteoarthritis	77,052 : 378,169	0.046 (0.002)	Tachmazidou et al. 2019 (171) included UKBB
Rheumatoid arthritis	21,514 : 363,455	0.145 (0.017)	Okada et al. 2014 (118) meta-analysed with UKBB

Multi-trait analysis of GWAS (MTAG)

MTAG assumes that the traits included in the analysis are genetically correlated. Genetic correlation analysis between endometriosis and immunological diseases was conducted via linkage disequilibrium score regression (LDSC). The LDSC used GWAS meta-analysis summary statistics for respective disease regressing association test statistics of SNPs on their LD scores (131). This method calculates genetic correlation by partitioning the SNP heritability based on the fact that the χ^2 association statistic for a given SNP includes the effects of all SNPs that are in LD with it (131). The LD-score was calculated using software available at (http://github.com/bulik/ldsc).

In Chapter 4, I reported a moderate genetic correlation between endometriosis and multiple sclerosis (effect size (RG), standard error (SE) = 0.09 (0.03), P value = 0.006* in a sex-combined meta-analysis), osteoarthritis (RG [SE] = 0.28 (0.04), P = 3.25×10^{-15} in a sex-combined meta-analysis) or rheumatoid arthritis (RG [SE] = 0.18 [0.04], P = 1.25×10^{-5} in a sex-combined meta-analysis). Here, I also conducted LDSC to estimate the genetic correlation between multiple sclerosis and rheumatoid arthritis which were strongly genetically correlated (RG [SE]=0.15 (0.04), P = 6×10^{-4}). Rheumatoid arthritis and osteoarthritis were also tested by LDSC and were found to be genetically correlated (RG [SE]= 0.3372 (0.0361), P = 9.1963 x10-

[21]). However, multiple sclerosis and osteoarthritis were not found to be genetically correlated (RG [SE]=0.04 (0.03), P = 0.21).

Prior to MTAG analysis, the GWAS meta-analysis summary results files were filtered by: 1) removing SNPs with a minimum MAF < 1%, or with a MAF differences > 20% among different datasets; 2) restricting all analyses to a common set of SNPs present in the endometriosis, osteoarthritis and rheumatoid arthritis datasets; 3) removing any multiple SNPs that were mapped to an identical chromosomal position among different datasets; 4) removing SNPs with conflict alleles among different datasets.

The MTAG estimator is a generalization of inverse-variance weighted meta-analysis and takes GWAS summary statistics from genetically correlated traits, integrating the information contained in their GWAS results, potentially increasing the study population, and thus boosting statistical power to detect novel causal loci (169). These cross-phenotype analyses estimate the common polygenic structure shared across different traits (i.e. genetic overlap), and the genetic associations of variants from these traits are combined and weighted according to the degree of overlap (169). MTAG outputs trait-specific association statistics, with the assumption that all SNPs share the same variance–covariance matrix of effect sizes across traits; MTAG provides results in terms of P values and effect estimates that can be used like those from a single-trait GWAS (169).

Comparison of multi-trait versus single-trait genetic analysis results

Multi-trait analysis results for endometriosis, osteoarthritis and rheumatoid arthritis were compared with their respective single trait GWAS meta-analysis results. Lead SNPs from MTAG results were identified by uploading trait-specific MTAG results into FUMA via the SNP2GENE process (130) with the same

parameters set for lead SNPs identification (https://fuma.ctglab.nl/snp2gene) (P value < $5x10^{-8}$, LD $R^2 \leq 0.1$ for LD; MAF ≥ 0.01) for the single-trait GWAS analysis as described in Chapter 4.

Identification of shared genetic variants

The identified lead SNPs from endometriosis MTAG results were checked for their pair-wise LD with the lead SNPs identified from osteoarthritis or rheumatoid arthritis MTAG results by using the LDpair tool (via website: https://ldlink.nih.gov/?tab=ldpair). RS number for SNPs were entered into the LDpair tool with the European reference population selected as reference population (which included Utah residents from north and west Europe, Tuscany residents in Italy, populations from Finland, England and Scotland and Spain). The GRCh37 genome build was selected. Two-by-two contingency table was displayed with calculated haplotype genotype counts and allele frequencies for the two query variants. Statistical metrics of linkage disequilibrium were calculated including: D prime (D'), R square (R^2), Chi-square and P-value for goodness-of-fit test (for deviations of expected haplotype frequencies based on allele frequencies). The pair of query variants with a $R^2 \geq 0.6$ were identified as highly correlated genetic variants. Locus zoom plots for the LD-correlated genetic variants between conditions were generated.

Functional annotation of the shared genetic variants

EQTL annotation was performed for the shared genetic variants between endometriosis and osteoarthritis or rheumatoid arthritis utilising Genotype-Tissue Expression (GTEx) portal (website: https://gtexportal.org/home/). Since the identified risk variants in GWAS are mostly in the non-coding regions, eQTL studies can help

to understand the biological effects of such genetic variants in relevant tissues and cells (172). The GTEx project provides a catalogue of genetic effects on gene expression across 49 human tissues from 838 donors with 15,201 samples.

RESULTS

Comparison of multi-trait versus single-trait genetic analysis results

Summary statistics comparing multi-trait MTAG and single-trait GWAS results are in Table 5.2. The MTAG weight factor (average across SNPs) is 1.21 for endometriosis, 1.04 for multiple sclerosis, 0.78 for osteoarthritis and -0.54 for rheumatoid arthritis. The weight factor is calculated from the sum of the GWAS estimates. If a negative weight factor is assigned to one of the trait, it means that the GWAS estimate for this trait contains information about the estimation error in the GWAS estimate for the other trait (169). After running the MTAG analysis, the number of lead SNPs increased from 31 to 47 for endometriosis, from 81 to 101 for multiple sclerosis, from 43 to 61 for osteoarthritis, from 44 to 63 for rheumatoid arthritis. The calculated lambda inflation factor is 1.26 for endometriosis multi-trait analysis results, 1.13 for multiple sclerosis, 1.42 for osteoarthritis, and 1.26 for rheumatoid arthritis. An increased inflation factor indicates increased population structure which could be expected from an increased study population. The Manhattan plot and QQ plot for multi-trait endometriosis results is shown in Figure 5.1, for multiple sclerosis is shown in Figure 5.2, for osteoarthritis is shown in Figure 5.3, for rheumatoid arthritis is shown in Figure 5.4.

Given that the focus of my thesis is understanding the genetic architecture of endometriosis, I present the novel lead SNPs identified for endometriosis in Table 5.3 but for multiple sclerosis, osteoarthritis and rheumatoid arthritis, the lead SNPs

identified from their MTAG analysis are presented in the Appendix Table x5.1, Appendix Table x5.2 and Appendix Table x5.3.

Table 5.2 Statistical summary of MTAG and single-trait GWAS meta-analysis results

	ENDO		MS		OA		RA	
	MTAG	**Single-Trait**	**MTAG**	**Single-Trait**	**MTAG**	**Single-Trait**	**MTAG**	**Single-Trait**
Lead SNPs	47	31	101	81	61	43	63	44
Genomic Locus	35	23	78	60	53	38	52	28
Mean Chi^2	1.34	1.31	1.24	1.23	1.53	1.40	1.35	1.19
Heritability H^2 (SE)	0.103 (0.006)	0.078 (0.004)	0.299 (0.026)	0.260 (0.023)	0.048 (0.002)	0.046 (0.002)	0.215 (0.015)	0.145 (0.017)
Lambda factor	1.26	1.03	1.13	1.02	1.42	1.29	1.26	1.04
Mapped genes	98	68	233	401	208	304	117	138
Sample size	193,551	556,504	47,462	360,004	603,603	455,221	128,571	384,969
Analysed SNPs	3873419							

*Lead SNPs are identified via FUMA: P-value< $5x10^{-8}$; LD $R^2 \leq 0.1$ for LD; MAF ≥ 0.01.
*Genomic risk loci is defined from independent significant SNPs merged by LD blocks. A genomic risk locus can contain multiple lead SNPs and/or independent significant SNPs.
*Mapped genes are defined by nearest genes around independent significant SNPs within LD blocks.

My multi-trait genetic analysis for endometriosis identified 47 lead SNPs, including 16 additional lead SNPs in comparison to the 31 lead SNPs identified from my single-trait GWAS utilising IEGC endometriosis GWAS results excluding UKBB. A recent publication reported 42 lead SNPs for in the single-trait IEGC endometriosis GWAS results including UKBB (102) (lead SNPs listed in Appendix Table x5.4). In comparison to this recent publication, my multi-trait genetic analysis results identified 10 novel genetic risk variants for endometriosis. These 10 novel variants all had borderline endometriosis association P values in single-traits GWAS analysis and when analysed together with a genetic correlated condition they reached genome-wide significance. Given that these are SNPs sitting in non-coding regions of the genome, their functional annotation was checked utilising the eQTL data in GTEx portal. Detailed EQTL analysis results for novel risk variants are listed in Appendix Table x5.5.

Rs12081298 is a novel genetic risk variant for endometriosis identified from multi-trait analysis, it regulates the expression of *CELA3B* and *CELA3A* gene which encode zymogen secreted from the pancreas influencing pancreatic function

(173,174) and. It also regulates the expression of *HSPG2* gene which encodes perlecan protein that forms vascular extracellular matrix to maintain the endothelial barrier (175).

Rs12467319 is another novel risk variant for endometriosis, it regulates the expression of several genes in a wide range of tissues including *KHK* gene which is the principal enzyme responsible for fructose metabolism (176), and may affect fructose consumption and contribute to non-alcoholic fatty liver disease, dyslipidaemia, obesity, and insulin resistance in humans (177). Rs12467319 also regulates the expression of *CGREF1* gene which can inhibit the transcriptional activity of AP-1 and reduce phosphorylation of ERK (extracellular signal-regulated kinases) and p38 MAPK (mitogen-activated protein kinases). AP-1 plays an important role in cell proliferation, survival, differentiation and transformation (178), especially in the process of tumour occurrence, development and metastasis (179).

Rs7613875 is another novel risk variant for endometriosis, it also regulates expression of multiple genes in a wide range of tissues, such as the expression of *MST1R* gene, which is a member of the c-Met family of receptor tyrosine kinase (RTK) and is expressed in epithelial cells and terminally-differentiated macrophages (180,181). Several studies reported that *MST1R* has a strong oncogenic function and was found to overexpressed in numerous solid tumours including breast, prostate, pancreas (182–184). *MST1R* has been shown to support tumorigenesis and progression through cell survival, growth, migration, angiogenesis, anti-inflammatory cytokine production, and more (180,184). Rs7613875 also regulates the expression of *RNF123* gene which encodes E3 ubiquitin-protein ligase influencing cell cycle progression, metabolism of proteins and innate immunity(185).

This gene is recently found to be associated with multisite chronic pain in a UKBB GWAS (186).

Rs1881115 is another novel risk variant for endometriosis, it regulates the expression of *DNAAF5* gene, which has an essential role for the preassembly or stability of axonemal dynein arms (187), recently *DNAAF5* gene was found to promotes the malignant process of hepatocellular carcinoma (188). Rs1881115 also regulates the expression of *ADAP1* gene, which is a neuron-specific phosphatidylinositol 3,4,5-trisphosphate (PIP3) and inositol 1,3,4,5-tetrakisphosphate (IP4)-binding protein (189) and was found to be involved in dendrite branching and spine development (190). *ADAP1* gene was also found to be is a critical mediator of TGF-β-induced cancer invasion, its overexpression could promote invasive tumour progression for invasive squamous cell carcinoma by facilitating cell migration and breakdown of the basement membrane (191).

Rs1401390 is a novel risk variant for endometriosis, it regulates the expression of multiple genes in a wide range of tissues. For example, rs1401390 regulates the expression of *MFHAS1* (Malignant fibrous histiocytoma amplified sequence 1) gene, which has an important role in Toll-like receptor (TLR) ¾-dependent signalling, by influencing the innate immune system in the process of recognizing pathogen-associated molecular patterns (192). *MFHAS1* is also an important oncogene for solid tumours and for hematologic malignancies (193) and is involved in cellular processes such as apoptosis and ubiquitin-related processes (192).

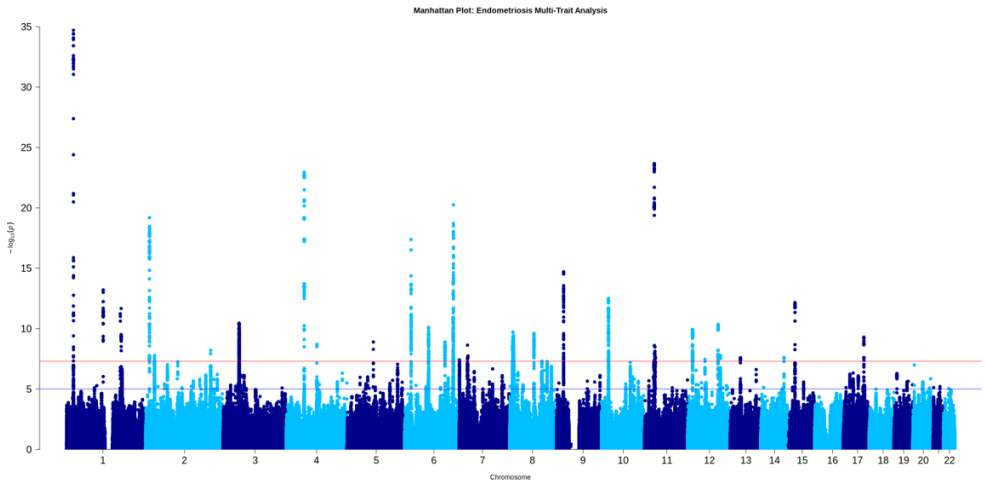
Rs1458942 is a novel risk variant for endometriosis, it regulates the expression of several genes such as *TNKS* gene. *TNKS* participates in various biological processes, such as hyperactivates the Wnt/β-catenin pathway by

destabilizing *AXIN* (194), regulates PARsylation of BLZF1, as well as *CASC3*, thereby recruiting *RNF146* and subsequent ubiquitination (195). *TNKS* also plays important roles in the malignancy of several cancers including lung cancer, breast cancer and hepatocellular cancer (196).

Rs11032350 is a novel risk variant for endometriosis, it regulates the expression of several genes in a wide range of issues. For example, Rs11032350 regulates the expression of *CD59* gene could inhibit the cytolytic activity of complement and to block the assembly of the membrane attack complex (MAC) (197). A low level of *CD59* expression is found to contribute to the pathogenesis of diabetes, multiple sclerosis and acquired immune deficiency syndrome (AIDS), whereas up-regulation of expression of *CD59* is reported in various inflammatory diseases such as Alzheimer's disease, ulcerative colitis and rheumatoid arthritis (198).

Rs72617705, rs851978, rs7834121, rs6539042 are also identified novel variants but these three SNPs are not identified as eQTLs in GTEx data. eQTL look-ups for these novel risk variants are listed in Appendix Table x5.5.

Figure 5.1 Endometriosis multi-trait analysis results: Manhattan plot and Q-Q plot



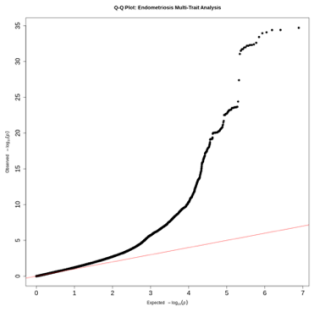
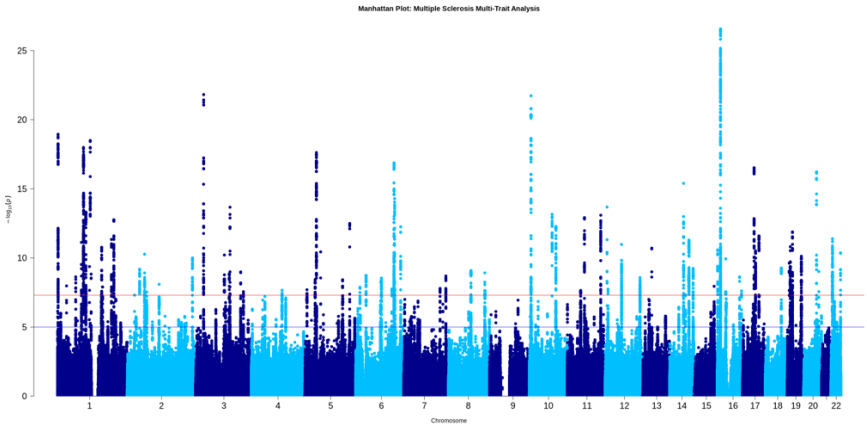


Figure 5.2 Multiple sclerosis multi-trait analysis results: Manhattan plot and Q-Q plot



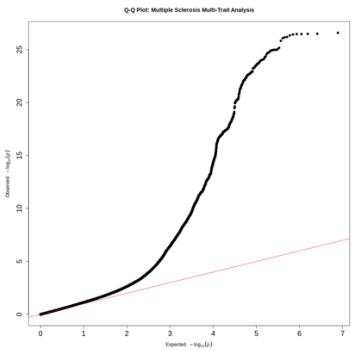
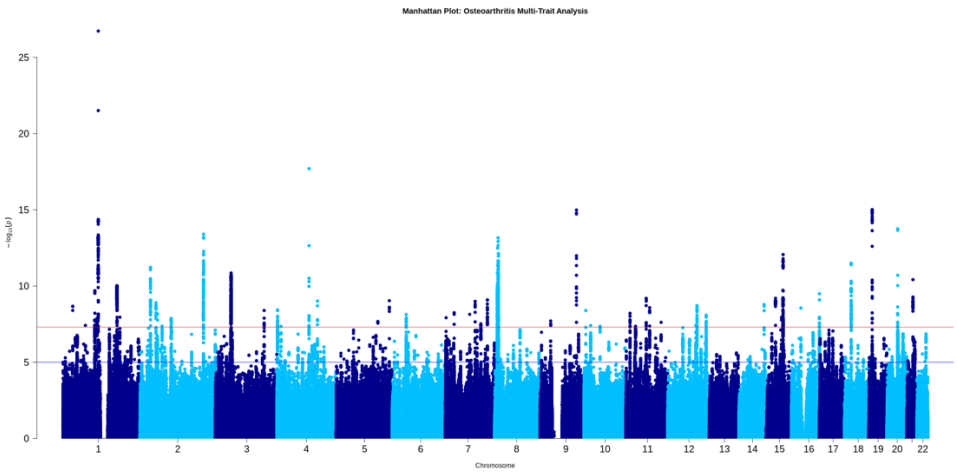


Figure 5.3 Osteoarthritis multi-trait analysis results: Manhattan plot and Q-Q plot



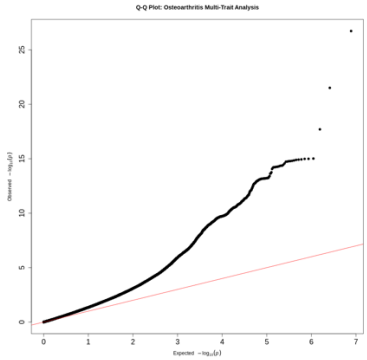
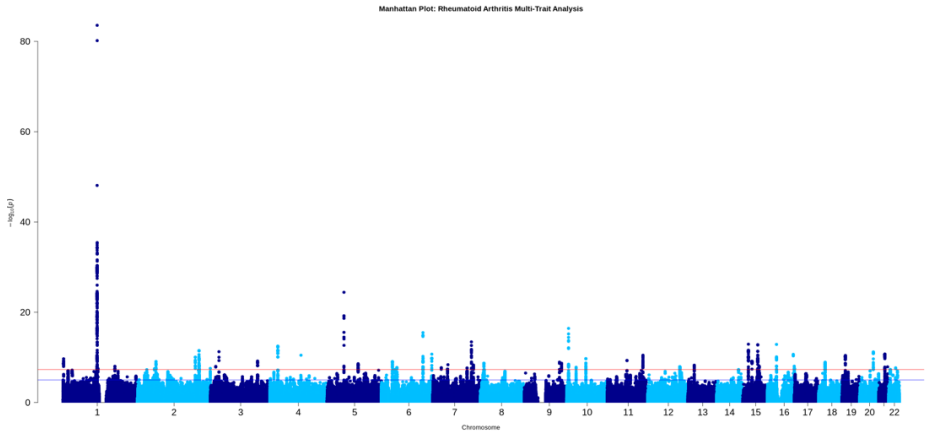


Figure 5.4 Rheumatoid arthritis multi-trait analysis results: Manhattan plot and Q-Q plot



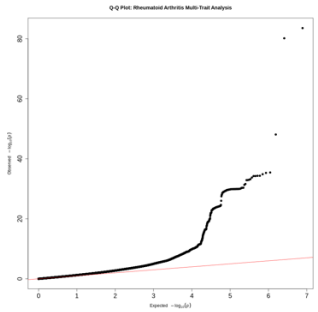


Table 5.3 Lead SNPs (LD R^2 < 0.1, P value < $5x10^{-8}$, MAF ≥ 0.01) identified from endometriosis multi-trait analysis results

MTAG Results									Single-Trait Results		Novel Variant
RSID	CHR	BP	EA	EAF	NrtGene	Function	OR[95%CI]	P value	OR[95%CI]	P value	
rs12081298*	1	22262225	G	0.89	HSPG2	intronic	1.06 [1.04-1.08]	1.83E-08	1.06 [1.04-1.09]	3.13E-07	YES
rs56319427	1	22396998	C	0.84	CDC42	intronic	1.11 [1.1-1.13]	1.98E-35	1.13 [1.11-1.15]	5.43E-36	
rs12030576	1	115817221	G	0.66	RP4-663N10.1	intergenic	1.06 [1.04-1.07]	6.30E-14	1.06 [1.04-1.08]	2.53E-13	
rs2227246	1	169208179	T	0.01	NME7	intronic	1.18 [1.13-1.24]	5.87E-12	1.19 [1.13-1.26]	4.27E-10	
rs2421985	1	172099136	C	0.51	DNM3	intronic	1.05 [1.03-1.06]	2.16E-12	1.05 [1.04-1.07]	1.77E-11	
rs7580473	2	11658972	T	0.14	RNA5SP84	intergenic	1.09 [1.07-1.11]	6.41E-18	1.09 [1.07-1.12]	1.10E-16	
rs11674184	2	11721535	T	0.44	GREB1	intronic	1.07 [1.05-1.08]	6.47E-20	1.07 [1.06-1.09]	2.01E-19	
rs12467319*	2	27348687	T	0.40	ABHD1	intronic	1.04 [1.03-1.05]	1.67E-08	1.04 [1.02-1.05]	6.59E-06	YES
rs72928925	2	203554324	A	0.18	FAM117B	intronic	1.05 [1.04-1.07]	6.07E-09	1.05 [1.03-1.07]	8.59E-07	
rs2131108	3	49665390	G	0.84	BSN	intronic	1.06 [1.04-1.08]	3.55E-11	1.05 [1.03-1.07]	1.12E-07	
rs7613875*	3	49971514	A	0.47	RBM6,MON1A	intergenic	1.04 [1.03-1.06]	1.06E-09	1.03 [1.02-1.05]	6.80E-06	YES
rs1551641	4	55993915	C	0.70	KDR	intergenic	1.08 [1.06-1.09]	1.10E-23	1.08 [1.06-1.1]	1.31E-21	
rs72617705*	4	95620225	T	0.15	RP11-554D13.1	ncRNA_intronic	1.06 [1.04-1.08]	1.98E-09	1.06 [1.04-1.08]	1.11E-07	YES
rs4703918	5	82040476	G	0.68	CTD-2218K11.2	intergenic	1.04 [1.03-1.06]	1.28E-09	1.05 [1.03-1.06]	3.54E-08	
rs6456259	6	19761718	G	0.83	RP1-167F1.2	ncRNA_intronic	1.08 [1.06-1.1]	4.21E-18	1.09 [1.07-1.11]	2.11E-16	
rs3003188	6	74680513	G	0.66	TXNP7	intergenic	1.05 [1.03-1.06]	7.77E-11	1.05 [1.03-1.07]	9.24E-10	
rs1739358	6	126019736	A	0.44	RP11-624M8.1 RP1-293L8.2	ncRNA_intronic	1.04 [1.03-1.06]	1.26E-09	1.05 [1.03-1.06]	1.97E-09	
rs7759516	6	151838245	C	0.80	CCDC170	intronic	1.07 [1.05-1.09]	1.30E-14	1.08 [1.06-1.1]	3.37E-14	
rs851978*	6	152029556	T	0.27	ESR1	intronic	1.04 [1.03-1.06]	1.23E-08	1.04 [1.03-1.06]	2.54E-07	YES

rs9341077	6	152423128	T	0.05	ESR1	UTR3	1.13 [1.09-1.17]	3.37E-11	1.16 [1.11-1.21]	4.85E-12	
rs9397493	6	152542868	G	0.58	SYNE1	intronic	1.05 [1.03-1.06]	2.64E-11	1.05 [1.04-1.07]	5.44E-11	
rs17215781	6	152570274	A	0.09	SYNE1	intronic	1.13 [1.1-1.16]	5.69E-21	1.14 [1.11-1.18]	6.30E-19	
rs584336	6	152616173	A	0.24	SYNE1	intronic	1.07 [1.06-1.09]	3.14E-19	1.08 [1.06-1.1]	1.35E-17	
rs4710796	6	170363029	G	0.82	RP11-302L19.1	intergenic	1.05 [1.03-1.07]	3.67E-08	1.05 [1.03-1.08]	7.71E-08	
rs1881115*	7	921644	C	0.77	SUN1:GET4 RP11-449P15.2	ncRNA_exonic	1.05 [1.03-1.06]	4.17E-08	1.05 [1.03-1.07]	5.42E-07	YES
rs1812673	7	25865542	T	0.48	AC003090.1	intergenic	1.04 [1.03-1.05]	2.35E-09	1.04 [1.03-1.06]	3.94E-08	
rs2071243	7	27208280	T	0.48	HOXA9 RP1-170O19.20 HOXA10-AS	ncRNA_exonic	1.04 [1.02-1.05]	1.85E-08	1.04 [1.02-1.05]	4.05E-07	
rs1401390*	8	8136410	T	0.45	FAM86B3P	intergenic	1.04 [1.02-1.05]	4.66E-08	1.03 [1.02-1.05]	3.82E-05	YES
rs1458942*	8	9406602	G	0.66	RP11-375N15.2	intergenic	1.05 [1.03-1.06]	1.92E-10	1.04 [1.02-1.06]	4.12E-07	YES
rs7834121*	8	10770255	G	0.51	XKR6	intronic	1.04 [1.03-1.06]	3.67E-10	1.04 [1.02-1.05]	1.57E-06	YES
rs10090060	8	75257608	A	0.41	GDAP1	intergenic	1.04 [1.03-1.06]	2.45E-10	1.05 [1.03-1.07]	2.76E-10	
rs13275821	8	100084782	C	0.79	VPS13B	intronic	1.05 [1.03-1.06]	4.87E-08	1.05 [1.04-1.07]	1.79E-08	
rs10757278	9	22124477	A	0.47	CDKN2B-AS1	intergenic	1.04 [1.03-1.06]	3.87E-10	1.05 [1.03-1.06]	5.16E-09	
rs10122243	9	22158924	T	0.39	CDKN2B-AS1	intergenic	1.06 [1.04-1.07]	1.98E-15	1.06 [1.04-1.08]	8.17E-14	
rs11012732*	10	21830104	G	0.65	MLLT10	intronic	1.05 [1.04-1.07]	3.17E-13	1.05 [1.03-1.07]	2.13E-09	YES
rs10835649	11	30329175	A	0.16	ARL14EP	intergenic	1.1 [1.08-1.12]	2.15E-24	1.11 [1.09-1.13]	2.23E-23	
rs7924571	11	32350027	C	0.76	RP1-65P5.1	ncRNA_intronic	1.05 [1.03-1.06]	3.35E-09	1.05 [1.03-1.07]	5.20E-08	
rs11032350	11	33730060	A	0.33	CD59	intronic	1.04 [1.03-1.06]	2.45E-08	1.04 [1.03-1.06]	5.06E-07	
rs7977262	12	15367769	G	0.65	RERG	intronic	1.05 [1.03-1.06]	1.15E-10	1.05 [1.03-1.06]	5.71E-09	
rs3803042	12	54387947	A	0.43	RP11-834C11.12	ncRNA_exonic	1.04 [1.02-1.05]	3.47E-08	1.04 [1.03-1.06]	1.32E-07	

					HOXC6:HOXC-AS2						
rs4762308	12	95649013	A	0.44	VEZT	intronic	1.04 [1.03-1.06]	4.33E-11	1.05 [1.04-1.07]	2.39E-11	
rs6539042*	12	103065503	G	0.74	LINC00485	intergenic	1.04 [1.03-1.06]	1.64E-08	1.05 [1.03-1.07]	1.62E-07	YES
rs1028862	13	51055134	A	0.14	DLEU1	NA	1.05 [1.04-1.07]	2.60E-08	1.05 [1.03-1.08]	8.80E-07	
rs57281976	14	93112974	G	0.78	RIN3	intronic	1.05 [1.03-1.06]	2.44E-08	1.05 [1.03-1.07]	2.37E-08	
rs12441483	15	40353416	C	0.50	SRP14-AS1	ncRNA_intronic	1.05 [1.04-1.06]	7.00E-13	1.06 [1.04-1.07]	1.60E-12	
rs9907056	17	63840961	G	0.66	CEP112	intronic	1.05 [1.03-1.06]	5.05E-10	1.05 [1.03-1.07]	1.35E-09	
rs7214750	17	63903119	C	0.92	CEP112	intronic	1.08 [1.05-1.11]	4.29E-08	1.09 [1.06-1.12]	3.66E-08	

*10 SNPs are novel independent variants from this multi-trait analysis for endometriosis.

Shared genetic risk variants between endometriosis and osteoarthritis

Lead SNPs from endometriosis, multiple sclerosis, osteoarthritis and rheumatoid arthritis multi-trait analysis results were checked for their LD correlation. This identified that 4 pairs of genetic variants are in strong LD ($R^2 \geq 0.6$) and are shared genetic variants between endometriosis and osteoarthritis (Table 5.4), no pair of genetic variants in strong LD were found between endometriosis and multiple sclerosis or between endometriosis and rheumatoid arthritis. All 4 of the shared locus have not been previously associated with endometriosis (rs7613875 near *RBM6, MON1A* on chromosome 3, rs1401390 near *FAM86B3P* on chromosome 8, rs7834121 near *XKR6* on chromosome 8, rs11012732 sitting near *MLLT10* on chromosome 8).

The genes nearest to the shared variants are reported in Table 5.4. However, given that these are SNPs sitting in non-coding regions of the genome, I searched for their functional annotation utilising the eQTL data in GTEx portal. Table 5.4 shows a summary of the most potentially interesting genes these variants are eQTLs for and the tissues in which they regulate the respective gene expression. Full eQTL look-ups for these loci are given in the Appendix Table x5.6. The biological functions of the annotated eQTL genes are summarised in the discussion section. Regional plots for the shared genetic loci are presented in Appendix Figure x5.1-x5.4.

Table 5.4 LD-correlated (R2 ≥ 0.6) lead SNPs from endometriosis and osteoarthritis MTAG results

Traits	SNP	Nearest Gene	CHR	BP	EA	EAF	MTAG OR [95%CI]	MTAG P value	LD R^2	GTEx V8 eQTL
ENDO	rs7613875*	*RBM6,*		49971514	A	0.47	1.04 [1.03-1.06]	1.06E-09		*RBM6* in whole blood, adipose tissue, thyroid, tibial nerve, esophagus, arteries, skin, lung, cells, heart, breast, colon, pancreas; *RBM5* in tibial nerve, esophagus; *UBA7* in whole blood, esophagus, pancreas, colon, skin, stomach, arteries, tibial nerve. *FAM212A* in esophagus, brain, skin, muscle, artery, cells; *MST1R* in adipose tissue, arteries, brain, colon, esophagus, heart, lung, muscles, tibial nerve, skin, thyroid, whole blood; *RHOA* in skeletal muscle; *SEMA3F* in adipose, arteries, tibial nerve, cerebellar hemisphere, esophagus, heart;
OA	rs3733135	*MON1A*	3	49939587	A	0.50	1.03 [1.02-1.04]	1.41E-11	0.85	
ENDO	rs1401390*			8136410	T	0.45	1.04 [1.02-1.05]	4.66E-08		*FAM86B3P* in adipose, cells, esophagus, skin, colon, brain, pancreas, breast, lung, heart; *PRAG1* in thyroid, adipose, arteries; *ALG1L13P* in cells, esophagus, skin, colon, adipose, pancreas, brain, kidney, vagina, whole blood, thyroid, stomach; *FAM85B* in testis, tibial nerve, pituitary, brain, arteries, thyroid, lung, uterus, ovary, breast, cells, colon, liver; *PRAG1* in thyroid, testis, adipose, arteries; *ERI1* in cells, testis, arteries.
OA	rs2948308	*FAM86B3P*	8	8097849	T	0.43	1.03 [1.02-1.04]	3.47E-09	0.79	
ENDO	rs7834121*			10770255	G	0.51	1.04 [1.03-1.06]	3.67E-10		*MTMR9* in tibial nerve, colon; *BLK* in blood, cultured fibroblasts; *CTSB* in arteries, oesophagus, stomach, tibial nerve, cultured fibroblasts cells, skin; *FDFT1* in arteries, whole blood, cultured fibroblasts cells, pituitary; *MSRA* in skin, testis, culture fibroblasts cells; *NEIL2* in heart, pituitary, whole blood, arteries, thyroid, tibial nerve; *RP1L1* in tibial nerve, adipose, skin.
OA	rs6985109	*XKR6*	8	10761585	G	0.53	1.04 [1.03-1.05]	6.98E-14	0.79	
ENDO	rs11012732*			21830104	G	0.65	1.05 [1.04-1.07]	3.17E-13		*CASC10* in skin, arteries, brain, esophagus; *MLLT10* in skin; *NEBL* in whole blood.
OA	rs11012726	*MLLT10*	10	21797272	C	0.67	1.03 [1.02-1.04]	3.90E-08	0.79	

*Risk variants identified for endometriosis that are novel from MTAG analysis.
*LD with lead endometriosis SNP is reported.

DISCUSSION

In this chapter, I presented the multi-trait analysis results for endometriosis, osteoarthritis and rheumatoid arthritis using MTAG software. This multi-trait analysis for endometriosis revealed 10 novel genetic variants which regulates the expression of genes such as *CELA3A/CELA3B* which can influence pancreatic function (173), *HSPG2* which encodes perlecan protein that forms vascular extracellular matrix (175), *CGREF1* which can inhibit the transcriptional activity of AP-1 to influence tumour occurrence, development and metastasis (Eferl and Wagner, 2003). In total, 4 shared genetic variants were discovered, which are shared between endometriosis and osteoarthritis.

Rs7613875 and rs3733135 were found to be highly LD-correlated SNPs from endometriosis and osteoarthritis multi-trait analysis results. The eQTL look-up showed rs7613875 and rs3733135 to regulate expression of several gene in a wide range of tissues. For example, rs7613875 and rs3733135 regulate the expression of *RBM5* and *RBM6*, which are located together in 3p21 with highly similar RNA-binding motif proteins. Deletion of 3p21 is associated with lung cancer (199). *RBM5* regulates Fas alternative splice site pairing after exon definition (200) and up-regulate proapoptotic caspase 2 splicing isoform and generates both proapoptotic and antiapoptotic isoforms by alternative splicing (201) while *RBM6* mainly acts as a splicing activator (202). Both downregulation and overexpression of *RBM5* was found in breast cancer samples (203,204) possibly due to growth arrest, induction of apoptosis, and retarded tumour growth (205). *RBM5* was also found to suppress the *Wnt/β-catenin* signalling and to induce cell apoptosis to affect tumour genesis (206). For *RBM6*, its overexpressed level was also found in multiple cancer including breast cancer (204), ovarian cancer (207,208), pancreatic cancer (209). Rs7613875 and rs3733135 also regulates the expression of *MST1R* gene, which has a strong oncogenic function. *MST1R* gene has been shown to support tumorigenesis and progression through cell survival, growth, migration, angiogenesis, anti-inflammatory cytokine production, and more (180,184). *MST1R* was found to be overexpressed in numerous solid tumours including breast, prostate, pancreas (182–184).

Rs1401390 and rs2948308 were found to be highly LD-correlated SNPs from endometriosis and osteoarthritis multi-trait analysis results. In the eQTL searches from GTEx, rs1401390 and rs2948308 were found to regulate expression of several genes such as *FAM86B3P* in adipose, cells, esophagus, skin, colon, brain, pancreas, breast, lung and heart, *CLDN23* in skin, *MFHAS1* in skeletal muscle, heart and esophagus, *PRAG1* in thyroid, adipose and arteries, *ALG1L13P* in cells, esophagus, skin, colon, adipose, pancreas, brain, kidney, vagina, whole blood, thyroid and stomach. Rs1401390 and rs2948308 regulate the expression of *CLDN23* gene, which is a new member of the claudin gene family that are core components for tight junctions and adherent junctions with an essential role in maintaining cell polarity and in the regulation of paracellular permeability (210). Claudins family could downregulate or upregulate of tight junction proteins and trigger malignant transformation and influence cancer progression (211). *CLDN23* is often down-regulated in intestinal-type gastric cancer, *CLDN23* can serve as an independent predictor of patients' survival for gastric cancer patients (212). *CLDN23* is also found to promote the migration of colon cancer cells with studies showed that *CLDN23* can be used as a prognostic marker for colorectal cancer (213,214). Rs1401390 and rs2948308 also regulate the expression of *MFHAS1* gene. which is an oncogene for solid tumours and for hematologic malignancies (193), and is associated with malignant fibrous histiocytomas (215). *MFHAS1* is also found to be and is involved in cellular processes such as apoptosis and ubiquitin-related processes (192). Interestingly, *MFHAS1* is found influence innate immunity. It could inhibit expression of inflammatory factors and negatively regulate Toll-like receptors (TLRs) signalling pathway to influence the process of recognizing pathogen-associated molecular patterns (192).

Rs7834121 and rs6985109 were found to be highly LD-correlated SNPs from endometriosis and osteoarthritis multi-trait analysis results. No eQTL result was found for rs7834121, but rs6985109 was found in eQTL analysis to regulate expression of several genes including *MSRA* in skin, testis and culture fibroblasts; *SOX7* in thyroid, *BLK* in blood and cultured fibroblasts; *NEIL2* in heart, pituitary, whole blood, arteries, thyroid and tibial nerve; *RP1L1* in tibial nerve, adipose and skin. *MSRA* (methionine sulfoxide reductase A) is known to protect proteins

from oxidation and acts as an antioxidant enzyme that scavenges reactive oxygen species (216). *MSRA* can repair oxidative damage to proteins by enzymatic reduction of methionine sulfoxide (217). In a large GWAS meta-analysis, *MSRA* was reported to be associated with central obesity (217), another GWAS study found *MSRA* associated with early-onset extreme obesity in children and adolescents but not in adults (218). The association of *MSRA* and obesity is possibly due to *MSRA* influencing chronic excess ROS production resulting in mitochondrial dysfunction in liver and skeletal muscle cells and contributing to lipid accumulation and insulin resistance in these tissues (219). Various studies have shown that *MSRA* is downregulated in several human tumours including non-small cell lung carcinoma (180), breast cancer cells (220) and endometrial cancer cells (221). A reduced expression of *MSRA* can lead to increased cell proliferation, extracellular matrix degradation and upregulation of *VEGF*, resulting to a more aggressive cellular phenotype (220). *MSRA* was identified as gene that's involved in rheumatoid arthritis in several studies (222,223). *SOX7* belongs to the *SOX* (Sry-related high mobility group box) family, which controls cell fate and differentiation in many cell processes, such as male differentiation, stemness, neurogenesis, and skeletongenesis (224). *SOX7* was found to play a critical role in haematopoiesis (225), and vascular development (226) and angiogenesis (227). *SOX7* was also found to play an important role in tumour genesis, and its decreased expression was reported in renal cell carcinoma (228), breast cancer (229) and endometrial carcinoma (230), likely due to the hypermethylation of the *SOX7* promoter. *SOX7* was found to supress *Wnt/β-catenin* signalling (*Wnt/β-catenin* signalling mainly contributes to embryonic development and adult tissue homeostasis regeneration) in various types of cancer, including breast cancer (229) and gastric cancer (231). *SOX7* can bind with *β-catenin* and *TCF/LEF* to disrupt the functional *β-catenin/BCL9* interaction (232) and to impede the formation of the *β-catenin/TCF/LEF* transcriptional complex (233). Several GWAS studies reported genetic risk variants for endometriosis located in or near to *WNT4* (234,235) which could be linked to the identification of *SOX7* as a genetic risk variant for endometriosis. *SOX7* was also found to impair B lymphopoiesis. *SOX7* downregulates most

pathways involved in B-cell development and receptor signalling (236) which might explain the altered immune system for endometriosis and osteoarthritis.

Rs11012732 and rs11012726 were lead SNPs in high LD with each other in the endometriosis and osteoarthritis multi-trait analysis results. These SNPs regulate the expression of *CASC10* gene in skin, arteries, brain and muscularis of oesophagus, *MLLT10* in skin and *NEBL* in whole blood. *MLLT10* (histone lysine methyltransferase DOT1L cofactor) encodes the *AF10* protein that interacts with *DOT1L* (DOT1-like histone H3K79 methyltransferase). This interaction is essential for *H3K79* demethylation of histone H3 (237,238) a sign of promoter activity (239). Mutations in *MLLT10* have been associated with acute myeloid and acute lymphoblastic leukaemia in many studies (240). A more recent study found *MLLT10* associated with pituitary adenoma, (241) a non-malignant brain tumour frequently associated with hormone over-secretion. An imputation-based fine-mapping study of patients with meningioma (927 cases, 790 controls), female breast cancer (28 108 cases, 22 209 controls), and ovarian cancer (25 509 cases, 40 941 controls) found that a *MLLT10* eQTL was positively associated with risk of oestrogen-mediated cancers including female meningioma, oestrogen receptor positive (ER+) breast cancer, ovarian cancer, and obesity, suggesting a possible oestrogenic mechanism underlying this pleiotropy (242). *CASC10* is an RNA Gene and is affiliated with the lncRNA class. It is an uncharacterized gene located upstream of *MLLT10* (242). *MLLT10* was previously reported to be associated with endometriosis (144) and ovarian cancer (243).

In summary, the multi-trait analysis for endometriosis, osteoarthritis and rheumatoid arthritis identified 10 additional novel causal loci for endometriosis. The 4 identified shared loci revealed a number of interesting shared biological pathways between endometriosis and osteoarthritis; future work on understanding their biological functions in pathogenesis may reveal novel treatment targets for endometrisois and immunolgoical diseases. The identified shared genetic loci could further confirm the observed genetic correlation between endometriosis and osteoarthritis by the LDSC analysis in the previous chapter. Also, as discussed in the previous chapter, although the Mendelian randomisation analysis showed that endometriosis was not causal to osteoarthritis,

multiple sclerosis or rheumatoid arthritis, it may also be possible that there could be a causal basis but since we are limited in the number of genetic variants identified for endometriosis, with current knowledge we do not identify a causal basis. The MR analysis could be replicated when more genetic variants are identified for endometriosis.

In comparison to the many existing multi-trait methods (244–248), MTAG has the advantage of being fast and convenient in computation by utilising GWAS summary statistics without access to individual-level data from different traits; by taking account of possibly unknown sample overlap between traits by bivariate linkage disequilibrium (LD) score (249); by giving a closed-form solution for each analysis step to further improve speed (169). It also generates trait-specific effect estimates for each SNP, similar to GWAS results for convenient result presentation.

However, limitations should be noted that are similar to those described in the single-trait GWAS analysis in the previous chapter: disease ascertainment methods for GWAS included self-reported data with a risk of disease misclassification, which could potentially reduce the power of GWAS to represent respective disease in the MTAG analysis to find shared genetic risk variants. Also different unknown subtypes of endometriosis, multiple sclerosis, osteoarthritis and rheumatoid arthritis may have influenced the results. Hence future replication of my both single-trait and multi-trait genetic analysis in different disease subtypes such as multiple sclerosis, osteoarthritis or rheumatoid arthritis at different location and Stage III/IV endometriosis is important to interpret my current study findings. Moreover, current eQTL analysis was performed in the GTEx portal which does not include the specific isolated tissue most relevant to endometriosis, the endometrium, and only 142 female participants with ‘uterus’ (a mixture of endometrium and myometrium) tissue samples were utilised in the analysis. Replication of my eQTL analysis in eQTL databases based on endometrial and endometriotic tissue and cells are needed to elucidate how genetic variants may drive gene/biological function and the pathogenesis of endometriosis when such a database is publicly available.

Chapter 6 Conclusions and Future Work

Endometriosis is a complex disease thought to be caused by a multitude of genetic and environmental factors, with aberrations in the immune system of endometriosis patients being proposed to explain the survival of ectopic endometrial cells in the pelvic area. However, evidence on the association between endometriosis and immunological diseases, especially the question if women with endometriosis have a significantly increased risk of developing immunological diseases is mixed and inconclusive. Hence, in this thesis, I have 1) conducted systemic review of existing evidence from published literature that studied an association with or without a temporal sequence between endometriosis and auto(immunological) diseases and performed meta-analysis of combinable published risk estimates from population-based studies; 2) performed phenotypic association analysis investigating if women with endometriosis have an increased risk of developing immunological diseases utilising the large-scale population datasets available, the UKBB, through cross-sectional and prospective cohort study approaches; 3) updated evidence for common genetic variants associated with immunological conditions in females only and in sex-combined analyses through genome-wide association studies in UKBB and meta-analysis of these results with large-scale published GWAS data; 4) investigated the genetic correlation between endometriosis and immunological diseases using available and newly generated GWAS data for each respective disease; 5) explored whether endometriosis is causal to multiple sclerosis, osteoarthritis and rheumatoid arthritis which were shown to be significantly genetically correlated with endometriosis; 6) identified shared genetic variants between endometriosis, multiple sclerosis, osteoarthritis and rheumatoid arthritis and performed in silico functional annotations of the novel variants through the use of publicly available eQTL datasets.

In Chapter 2, my systematic review of observational population-based studies summarized existing population studies that reported an association between endometriosis and a range of autoimmune diseases including Addison's disease, ankylosing spondylitis, autoimmune thyroid disorder, coeliac disease, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis,

Sjogren's syndrome, systemic lupus erythematosus, psoriasis and psoriatic arthritis. High quality prospective cohort studies reported a significantly increased risk of systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, multiple sclerosis, and inflammatory bowel disease in women with endometriosis as well as a significantly increased risk of endometriosis in women with coeliac disease. Meta-analysis with combinable study results found a significantly increased risk of systemic lupus erythematosus and Sjogren's syndrome in women with endometriosis. However, although there were a few high-quality, well-designed studies with large sample size, many of the included studies in this review were of low quality and with limitations in their study design.

In Chapter 3, I conducted phenotypic association analysis for endometriosis and 29 immunological diseases in UKBB including 273,404 females by cross-sectional and prospective cohort study approaches. In both cross-sectional study and cohort study analyses, a significantly increased risk was observed for overall immunological diseases (OR [95%CI] = 1.32[1.25-1.39], P < 0.001*; age < 50: HR[95%CI] = 1.37[1.12-1.67], P = 0.002*; age 50-60: HR[95%CI] = 1.15[0.99-1.35], P = 0.08; age ≥ 60: HR[95%CI] = 0.96[0.80-1.14], P = 0.62), classic autoimmune diseases (OR[95%CI] = 1.24[1.13-1.36], P < 0.001*; age < 50: HR[95%CI] =1.67[1.16-2.42], P = 0.006*; age 50-60: HR [95%CI] =1.07[0.72-1.57], P =0.75; age ≥ 60: HR [95%CI] = 0.80[0.52-1.25], P =0.33) and for autoinflammatory diseases (OR [95%CI] = 1.32[1.25-1.39], P < 0.001*; age < 50: HR[95%CI] = 1.21[0.97-1.52], P = 0.09; age 50-60: HR[95%CI] =1.18[1.00-1.38], P =0.044*; age ≥ 60: HR[95%CI] = 0.98[0.83-1.16], P =0.83) in women with endometriosis. A significantly increased risk for mixed-pattern diseases in women with endometriosis was also observed in cross-sectional study (OR[95%CI] = 1.23[1.10-1.52], P = 0.002*), but this increased risk became non-significant in the cohort study (age < 50: HR[95%CI] = 1.78[0.80-3.98], P = 0.16; age 50-60: HR[95%CI] = 1.49[0.75-2.95], P = 0.26; age ≥ 60: HR[95%CI] = 1.70[0.80-3.65], P = 0.17), likely due to a reduced sample size. In the investigation of each separate immunological disease, by the cross-sectional study approach, women with endometriosis were found to have a significantly increased risk for (systemic) lupus erythematosus, coeliac disease, myasthenia gravis, inflammatory bowel disease, osteoarthritis, gout (including pseudogout, crystal arthropathy), ankylosing spondylitis and

a borderline significant risk for type 1 diabetes, ulcerative colitis and psoriasis. Yet the cohort study approach only found a significantly increased risk of incident rheumatoid arthritis (HR [95%CI] = 2.25[1.33-3.79], P = 0.002*) and incident osteoarthritis (HR [95%CI] = 1.26 [1.01-1.58], P = 0.042*) in women with endometriosis aged < 50 years old women and for (systemic) lupus erythematosus (HR [95%CI] = 2.37[1.21-4.65], P = 0.012*) in women of endometriosis aged ≥ 60 years old.

Further to the phenotypic association analyses, in Chapter 4, I investigated at genetic level the association between endometriosis and eight immunological diseases utilising large-scale GWAS data. For the first time, my genetic correlation analysis showed that endometriosis is significantly genetically correlated with multiple sclerosis (RG[SE] = 0.093[0.034], P value = 0.006*), osteoarthritis (RG[SE] = 0.278[0.035], P value = 3.248×10^{-15}) and rheumatoid arthritis (RG[SE] = 0.180[0.041], P value=1.25×10^{-5}). However, MR analysis, did not show endometriosis to be causal to any of the 3 genetically correlated immunological diseases. This may be due to the limited known genome-wide significant endometriosis variants that were utilised as instrumental variables.

In Chapter 5, I have conducted multi-trait genetic analysis combining single-trait GWAS results for endometriosis, multiple sclerosis, osteoarthritis and rheumatoid arthritis which identified 10 novel variants for endometriosis, and 4 shared genetic variants between endometriosis and osteoarthritis. Their potential functional roles through eQTL analysis provided insights into key molecular players in disease processes. The novel genetic risk variants identified for endometriosis from the multi-trait genetic analysis regulates the expression of genes such as *CELA3A/CELA3B* which can influence pancreatic function (173), *HSPG2* which encodes perlecan protein that forms vascular extracellular matrix (175). The 4 shared genetic risk variants between endometriosis and osteoarthritis from multi-trait genetic analysis regulate genes such as *RBM5* and *RBM6* involved in tumorigenesis of several organs, *MSRA* gene which can repair oxidative damage to proteins (217) and are associated with early-onset obesity (218), *SOX7* gene which plays a critical role in haematopoiesis (225), vascular development (226) and angiogenesis (227).

Future directions

This thesis researched on the question of if women with endometriosis are at an increased risk of immunological diseases by a systemic review of existing evidence from population studies, analysing large-scale biobank data through detailed epidemiological and genetic analyses, and interpreting findings through integration with available data on gene expression profiles in tissues. The methods outlined in this study can be applied in future to larger population-based phenotypic analysis and genetic association analysis to test the validity of my study results.

Limitations of this research project included the possibility of disease misclassification which could potentially reduce study power since self-reported data was included, and future studies with strict surgically-confirmed endometriosis and laboratory or radiographically confirmed immunological diseases could help test the validity of my analysis results. Moreover, definition of the diagnosis time has always been an issue for endometriosis since there could be delays between first experiencing symptoms and ultimately receiving a diagnosis. Future studies could incorporate primary care data to include an earlier diagnosis date perhaps based on symptomatology to better define the first disease diagnosis date.

Also, as different subtypes of multiple sclerosis, osteoarthritis and rheumatoid arthritis were previously found to have different risk factors, for example, obesity-associated inflammation is a strong risk factor for hand osteoarthritis, while in contrast, obesity has a weak or inconsistent associations with hip osteoarthritis (161). Hence replication of my analysis utilising these disease subtypes could reveal additional novel results. Furthermore, given that the latest endometriosis GWAS meta-analysis has shown that we are starting to reveal genetic subtypes for endometriosis as well such as ovarian endometriosis having a different genetic basis to peritoneal endometriosis, future studies investigating association with particular subtypes of endometriosis and immune conditions would be important. In addition, there is no published female-specific GWAS results for immunological diseases, future studies with a large female-only study population for immunological diseases might reveal interesting results such as female-specific biological pathways for immune-related disorders.

It is also essential to conduct functional studies to understand the biological mechanisms of these identified novel risk variants for endometriosis and those shared with multiple sclerosis, osteoarthritis, and rheumatoid arthritis. Current in-silico functional annotation included utilisation of eQTL data from GTEX database which does not include the specific isolated tissue most relevant to endometriosis, the endometrium, and only 142 female participants with ‘uterus’ (a mixture of endometrium and myometrium) tissue samples were utilised in the analysis. Replication of my eQTL analysis in eQTL databases based on endometrial and endometriotic tissue and cells are needed to elucidate how genetic variants play a role in pathogenesis of endometriosis.

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APPENDIX

Supplementary document 1. Search strategy for the MEDLINE database

Database & Platform: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search date: 7 April 2018

1. endometriosis/

2. endometrio$.ti,ab,kw.

3. or/1-2

4. Autoimmune diseases/

5. Autoantibodies/

6. Autoimmunity/

7. Multiple Sclerosis/

8. Multiple Sclerosis, Chronic Progressive/

9. Multiple Sclerosis, Relapsing-Remitting/

10. Narcolepsy/

11. Hypersomnolence, Idiopathic/

12. Addison's Disease/

13. Diabetes Mellitus, Type 1/

14. Graves Disease/

15. Hashimoto Disease/

16. Hepatitis, Autoimmune/

17. Coeliac Disease/

18. Crohn Disease/

19. Anemia, Pernicious/

20. Liver Cirrhosis, Biliary/

21. Colitis, Ulcerative/

22. Antiphospholipid Syndrome/

23. Purpura, Thrombocytopenic, Idiopathic/

24. Arthritis, Rheumatoid/

25. Mucocutaneous Lymph Node Syndrome/

26. Rheumatic Fever/

27. Giant Cell Arteritis/

28. Alopecia Areata/

29. Dermatitis Herpetiformis/

30. Vitiligo/

31. Scleroderma, Systemic/

32. Scleroderma, Localized/

33. Scleroderma, Diffuse/

34. Scleroderma, Limited/

35. Sjögren's syndrome/

36. Lupus Erythematosus, Systemic/

37. (autoimmune adj1 (disease$ or response$)).ti,ab,kw.

38. (autoantibod$ or autoimmunit$).ti,ab,kw.

39. ((multiple or disseminated) adj1 scleros$).ti,ab,kw.

40. (MS or narcolepsy or iddm or sprue or ileocolitis or vitiligo or RA).ti,ab,kw.

41. ((gelineau$ or narcoleptic) adj1 syndrome$).ti,ab,kw.

42. (narcolepsy adj2 cataplexy adj1 syndrome$).ti,ab,kw.

43. (paroxysmal adj1 sleep$).ti,ab,kw.

44. (addison$ adj1 disease$).ti,ab,kw.

45. (primary adj1 (adrenal or adrenocortical) adj1 insufficienc$).ti,ab,kw.

46. (primary adj1 hypoadrenalism$).ti,ab,kw.

47. (diabetes adj1 mellitus).ti,ab,kw.

48. (type adj1 ("1" or one) adj1 diabete$).ti,ab,kw.

49. (autoimmune adj2 (diabete$ or hyperthyroidism or hepatitis or hepatitides)).ti,ab,kw.

50. ((grave$ or basedow$) adj1 disease$).ti,ab,kw.

51. (exophthalmic adj1 goiter$).ti,ab,kw.

52. (hashimoto$ adj2 (disease$ or struma or syndrome$ or thyroiditides or thyroiditis)).ti,ab,kw.

53. (chronic adj1 lymphocytic adj1 (thyroiditides or thyroiditis)).ti,ab,kw.

54. (coeliac adj1 (disease$ or sprue)).ti,ab,kw.

55. (gluten adj2 enteropath$).ti,ab,kw.

56. (nontropical adj1 sprue).ti,ab,kw.

57. (crohn$ adj1 (disease$ or enteritis)).ti,ab,kw.

58. (granulomatous adj1 (colitis or enteritis)).ti,ab,kw.

59. ((regional or terminal) adj1 (enteritis or ileitides or ileitis)).ti,ab,kw.

60. (inflammatory adj1 bowel adj1 disease$).ti,ab,kw.

61. ((pernicious or addison$) adj1 (anaemia or anemia)).ti,ab,kw.

62. ((biliary or liver) adj1 (cirrhosis or cirrhoses)).ti,ab,kw.

63. (ulcerative adj1 colitis).ti,ab,kw.

64. (colitis adj1 gravis).ti,ab,kw.

65. (idiopathic adj1 proctocolitis).ti,ab,kw.

66. (antiphospholipid adj3 syndrome$).ti,ab,kw.

67. (hughes adj1 syndrome).ti,ab,kw.

68. ((immune or autoimmune or idiopathic) adj1 thrombocytopen$).ti,ab,kw.

69. (werlhof$ adj1 disease$).ti,ab,kw.

70. ((rheumatoid or rheumatic) adj1 arthritis).ti,ab,kw.

71. (kawasaki adj1 (disease$ or syndrome$)).ti,ab,kw.

72. (rheumatic adj1 (fever$ or arthritides)).ti,ab,kw.

73. ((articular or inflammatory or polyarthritis) adj1 (rheumatism$ or rheumatica$)).ti,ab,kw.

74. ((temporal or cranial) adj1 (arteritis or arteritides)).ti,ab,kw.

75. (giant adj1 cell adj2 (arteritis or aortitides or aortitis)).ti,ab,kw.

76. (horton$ adj3 (disease$ or arteritis)).ti,ab,kw.

77. (alopecia adj1 (areata or circumscripta)).ti,ab,kw.

78. (dermatitis adj1 herpetiformis).ti,ab,kw.

79. (duhring$ adj1 disease$).ti,ab,kw.

80. (scleroderma$ or dermatosclerosis or morphea$).ti,ab,kw.

81. (systemic adj1 sclerosis).ti,ab,kw.

82. ((Sjögren$ or sicca) adj1 syndrome).ti,ab,kw.

83. (lupus adj1 erythematosus).ti,ab,kw.

84. (libman adj1 sacks adj1 disease).ti,ab,kw.

85. (mucocutaneous adj1 lymph adj1 node adj1 syndrome).ti,ab,kw.

86. or/4-85

87. 3 and 86

Table x2.1a Characteristics of included studies in the systematic review published before April 2018 (part 1)

Citation	Country	Study period	Study design	Endometriosis ascertainment and number
Grimes et al. (1985)	U.S.	1973-1982	case-control study	hospital diagnosis (n=12)
Lamb et al. (1986)	U.S.	1980s (not specified)	case-control study	self-reports (n=43)
Smith et al. (1993)	US	1988-1989	case-control study	hospital diagnosis with hysterectomy (n=22)
Sinaii et al. (2002)	U.S., Canada	1998	cross-sectional study	self-reports of laparoscopy/laparotomy (n=3680)
Merlino et al. (2003)	U.S.	1986-1997	prospective cohort study; with 11 years of follow-up	self-reports (n=155)
Poppe et al. (2003)	Belgium	1999-2000	case-control study	hospital diagnosis (n=21)
Haga et al. (2005)	Norway	not specified	case-control study	self-reports (n=7)
Pasoto et al. (2005)	Brazil	not specified	cross-sectional	laparoscopy/laparotomy with hostological analysis (n=45 including13 stage I/II and 32 stage III/IV)
Petta et al. (2007)	Brazil	2005-2006	case-control study (originally reported as cross-sectional study)	surgical and histological diagnosis (n=148)
Eaton et al. (2007)	Denmark	2001	cross-sectional study	hospital diagnosis (prevalence: 4.91 per 1,000 population)
Matorras et al. (2007)	Spain	1990-2004	case-control study	surgical with hostological diagnosis (n=342)
Aguiar et al. (2009)	Brazil	2000-2003	case-control study	laparoscopy with histological diagnosis ≤6 months before blood collection (n=120)
Gemmill et al. (2010)	U.S.	1998	cross-sectional study	self-reports of surgical diagnosis (n=4331)
Stephansson et al. (2011)	Sweden	1969-2008	retrospective cohort study with >5 years of follow-up	hospital diagnosis (n=517)
Nielsen et al. (2011)	Denmark	1977-2007	retrospective cohort study with 1 year of follow-up	hospital diagnosis (n=37,661)
Jess et al. (2012)	Denmark	1977-2007	retrospective cohort study with 13 yeas of follow-up	hospital diagnosis (n=37,661)
Santoro et al. (2014)	Italy	2012	case-control study	laparoscopy with histological diagnosis (n=223)
Caserta et al. (2015)	Italy	2009-2013	case-control study	hospital diagnosis (n=304)
Harris et al. (2016)a	U.S.	1989-2011	prospective cohort study with 22 years of follow-up	self-reports of laparoscopy with hospital records checked in part of the participants (n=6,434)
Harris et al. (2016)b	Sweden	1964-2011	case-control study	hospital diagnosis (n=371)
Yuk et al. (2016)	Korea	2009-2011	cross-sectional study	hospital diagnosis (n=5,615)
Huang et al. (2016)	Taiwan	2000-2010	cross-sectional study (rheumatoid disease)	hospital diagnosis (n=27,973)
Lee et al. (2016)	U.S.	after 2003 (not specified)	case-control study	hospital diagnosis (n=51)
Brouwer et al. (2017)	Netherland	2002-2010	cross-sectional study	hospital diangosis (n=4) and self-reports (n=1)
Wu et al. (2017)	Tailwan	2001-2006	case-control study (Sjogren's syndrome)	hospital diagnosis (n=9,191)
de Silva et al. (2018)	Denmark	1994-2015	retrospective cohort study (ectopic pregnancies) with 11 years of follow-tup; case-control study (IBD)	hospital diagnosis (n=297 in IBD cohort vs. n=18,708 in IBD-free cohort)

Abbreviations: AD:autoimmune disease; ATD:autoimmune thyroid disorder; ENDO:endometriosis; OCP:oral contraceptive pill; SLE:systemic lupus evythmatosus; SS:Sjögren's syndrome; RA:rheumatoid arthritis; TPO:Thyroid peroxidase antibody; CLD:celiac disease; MS:multiple sclerosis; IBD: Irritable bowel disease; CD: Crohn's disease; UC: ulcerative colitis; HRT: hormone replacement therapy.

Table x2.1b Characteristics of included studies in the systematic review published before April 2018 (part 2)

Citation	Autoimmune disease ascertainment and number	Control selection and number
Grimes et al. (1985)	hospital diagnosis: SLE (n=109)	SLE-free women discharged from the same hospital during the same period excluding those admitted for obstetric/gynecologic conditions (n=109)
Lamb et al. (1986)	self-reports: RA (n=1)	Friend-control who self-reported to be without ENDO (n=43)
Smith et al. (1993)	hospital diagnosis with hysterectomy: SLE (n=2), AD other than SLE (n=12), any AD (n=14)	women diagnosed with fibroids by hysterectomy (n=185)
Sinaii et al. (2002)	self-reports of hospital diagnosis: SLE (n=31), MS (n=19), RA (n=68), SS (n=23)	US general female population (prevalence rate identified from literatures)
Merlino et al. (2003)	physician diagnosis: RA (n=158)	women without RA recruited in the study (n=31,178)
Poppe et al. (2003)	hospital diagnosis and serological test: thyroid peroxidase antibodies (aTPO) positive (n=6)	randomly selected, age-matched parous women (n=100)
Haga et al. (2005)	hospital diagnosis: primary Sjogren's syndrome (n=47)	healthy control matched on age, region (n=142)
Pasoto et al. (2005)	hospital diagnosis: SLE (n=15)	healthy women recruited from the same clinical centre underwent laparoscopy (n=21)
Petta et al. (2007)	self-reports (hospital diagnosis validated partly): autoimmune thyroid disorder (n=38)	women without endometriosis from a family planning clinic (n=158)
Eaton et al. (2007)	national registry hospital diagnosis	Danish general population
Matorras et al. (2007)	hospital diagnosis: SLE (n=120), SS (n=22)	asymptomatic women attending gynecology clinic in the same hospital (n=501)
Aguiar et al. (2009)	blood test: CLD (n= 17), biopsy: CLD (n=13)	healthy female donated blood from the same city (n=1,500)
Gemmill et al. (2010)	self-reports: addison disease (n=10)	U.S. general female population (prevalence rate identified from literatures)
Stephansson et al. (2011)	CLD biopsy (n=11,097)	healthy female control selected from national registers: matched to cases based on age, county, calendar period (n=54,992)
Nielsen et al. (2011)	hospital dianogis in END cohort SLE (n=54), SS (n=86), MS (n=130)	Danish general female population (age-/period- specific incident rate identified from national statistics)
Jess et al. (2012)	hospital diagnosis in END cohort: UC (n=228), CD (n=92), IBD (n=320)	Danish general female population (age-/period- specific incidence rates, from national statistics)
Santoro et al. (2014)	serological and histological diagnosis: CLD (n=7);self-reports of ADs (n=37)	female nurses without known ENDO (n=246)
Caserta et al. (2015)	self-reports (?weren't mention), AD (n=41)	female patient from same hospital with no known ENDO or immune disfunction (n=318)
Harris et al. (2016)a	self-reports comfirmed by physician diagnosis: SLE (n=103), RA (n=390)	female nurses reponded to the survey with no known ENDO (n=108,019)
Harris et al. (2016)b	hospital diagnosis: SLE (n=2,834)	female controls selected from national registers mached to cases on birth year, sex, county (n=14,164)
Yuk et al. (2016)	hospital diagnosis: Graves disease (n=105), autoimmune hypothroidism (n=159)	general femal population matched on age, sampling year, sampling weight (n=22,460) identified from national registers
Huang et al. (2016)	hospital diagnosis: rheumatic disease (n=2,891)	healthy female from general population (n=27,937) matched control identified from nationwide registers (nor specified)
Lee et al. (2016)	hospital diagnosis: CD (n=82), UC (n=71)	women with IBD but without ENDO (n=102) matched on age, IBD type
Brouwer et al. (2017)	hospital diagnosis: RA (n=178)	Dutch general females (prevalence rate identified from literatures)
Wu et al. (2017)	hospital diagnosis: sicca syndrome (n=301)	female controls matched on age, income, geographic locaton, first diagnosis year of ENDO (n=27,573) identified from nationwide registers
de Silva et al. (2018)	hospital diagnosis: UC (n=7,548), CD (n=6,731), IBD (n=14,279)	women from the same cohort but without IBD at conception identified from nationwide registers (n=1,832,732)

Table x2.1c Characteristics of included studies in the systematic review published before April 2018 (part 3)

Citation	Risk estimates (in original reports)	Risk estimates (calculated or with correction)
Grimes et al. (1985)	SLE: OR=2.0 (0.6-6.8)	
Lamb et al. (1986)	RA: RR=1.00	RA: OR=3.07 (0.12, 77.50)
Smith et al. (1993)	SLE prevalence was too low to generate ORs	SLE prevalence: 9.09% vs. 0% in women with ENDO vs. fibroids; ADs other than SLE: OR=0.75 (0.09, 6.13); any AIDs: OR=2.50 (0.64, 9.75)
Sinaii et al. (2002)	SLE: POR=20.7 (14.3-29.9)*; MS: POR=7.1 (4.4-11.3)*; RA: POR=1.5 (1.2-1.9)*; SS: POR=23.9 (15.5-36.5)*	
Merlino et al. (2003)	multivariabte-adjusted RA: RR=1.59 (0.82-3.08) all women RA: RR=1.48 (0.71-3.07) ever pregnant women	
Poppe et al. (2003)	TPO-Abs positive: RR=3.57 (1.09-11.8)*	OR=4.60 (1.40, 15.13)
Haga et al. (2005)	---	OR=4.31 (0.93, 20.01)
Pasoto et al. (2005)	musculoskeletal manifestations, mucocutaneous, manifestations and antibodies	
Petta et al. (2007)	ATD: OR=0.52 (0.25-1.06)	ATD: OR=0.51 (0.25-1.04)
Eaton et al. (2007)	pairwise ORs of ENDO in relatoin to: type 1 diabetes:1.0; CLD:1.6;pernicious anemia:1.1; purpura:1.9; MS:1.3; Gulian Barre syndrome:1.3; Crohns's disease:1.5; ulcerative colitis:1.4; primary biliary cirrhosis: 2.0; psoriasis:1.3; vitiligo:2.2; scleroderma:1.5; SLE:1.6; SS:1.6.	
Matorras et al. (2007)	OR for SLE in women with ENDO history: 0.37 (0.09-1.59); OR for ENDO in SLE history: 2.9 (0.27-32.57); OR for SS in ENDO history: 2.17 (0.48-9.90)	ENDO risk in SLE vs. non-SLE: OR=2.94 (0.27-32.56) SS risk in ENDO vs. non-ENDO: OR= 2.18 (0.48, 9.91)
Aguiar et al. (2009)	Positive serology indicative for CLD: OR=5.4 (1.8-15.5)* Bioposy-confirmed CLD: OR=3.8 (1.0-14.1)*	Positive serology indicative for CLD: OR=5.39 (1.87, 15.57) Bioposy-confirmed CLD: OR=3.82 (1.04-14.07)
Gemmill et al. (2010)	addison disease: prevalence: 2.31 per 1000 population in women with ENDO vs. 0.09 per 1000 population in general women population	
Stephansson et al. (2011)	ENDO risk in women with CLD: HR=1.39 (1.14-1.70)*	
Nielsen et al. (2011)	SLE: SIR=1.6 (1.2-2.1)*; SS: SIR=1.6 (1.3-2.0)*; MS: SIR=1.2 (1.05-1.5)*	
Jess et al. (2012)	UC: SIR=1.5 (1.3-1.7)*; CD: SIR=1.6 (1.3-2.0)*; IBD: SIR=1.5 (1.4-1.7)*	
Santoro et al. (2014)		CLD: OR=2.80 (0.54, 14.57); any AD: OR=1.33 (0.68, 2.60)
Caserta et al. (2015)		AD: OR=0.90 (0.48, 1.96)
Harris et al. (2016)a	SLE: HR=2.03 (1.17-3.51)* RA: HR=1.41 (1.05-1.89)*	
Harris et al. (2016)b	SLE: OR=1.39 (1.09-1.78)*	
Yuk et al. (2016)	Graves disease: OR=2.52 (1.30-4.88)* autoimmune hypothyroidism: OR=1.61 (0.88-2.94)	all autoimmune thyroid disorders: OR=1.45 (1.10, 1.91)*
Huang et al. (2016)		rheumatic disease: OR=1.37 (1.28, 1.47)
Lee et al. (2016)	comparison of IBD disease phenotype, the use of immunomodulators, antiTNF agents, combination therapy, and the need for IBD-related surgery	
Brouwer et al. (2017)		RA: OR=1.82 (0.47, 7.02) [control using Thonneau 1991 reference]
Wu et al. (2017)		SS: OR=1.71 (1.35, 2.17)*

de Silva et al. (2018)		UC: OR=1.97 (1.67, 2.31)* ; CD: OR=2.16 (1.84, 2.55)*; IBD: OR=2.06 (1.83, 2.31)*

Table x2.1d Characteristics of included studies in the systematic review published before April 2018 (part 4)

Citation	Risk factors adjusted	Temporality
Grimes et al. (1985)	age, race, parity; control selected randomly from whom discharged from the same hospital as for the cases during the same study interval	investigated risk of newly diagnosed SLE in women with and without ENDO history
Lamb et al. (1986)	--	investigated risk of ENDO in women with and without RA history
Smith et al. (1993)	--	investigated risk of ENDO in women with and without SLE, AD history
Sinaii et al. (2002)	--	prevalence study of AD in women with ENDO vs. general women population (SLE, MS, RA, SS, thyroid disorder)
Merlino et al. (2003)	age, smoking status, age at last pregnancy, drug to stop lactation, age at menopause, polycystic ovary syndrome, use of HRT	prospective cohort study for incident RA occured after 1987 with ENDO exposure Ø
Poppe et al. (2003)	control matched on age	investigated risk of ENDO in women with and without having thyroid auto-immunity
Haga et al. (2005)	control matched on age, region	investigated risk of SS in women with and without ENDO history
Pasoto et al. (2005)	--	clinical menifextations/serological tests for women with ENDO vs. SLE vs. healthy controls; women with laparoscopy/laparotomy after SLE diagnosis was identified as ENDO cases
Petta et al. (2007)	--	investigated risk of ENDO in women with and without thyroid disorder
Eaton et al. (2007)	age, sex	cross-sectional study of ADs prevalence (ENDO was listed as an AD)
Matorras et al. (2007)	--	investigated risk of SLE,SS in women with and without ENDO history; and risk of ENDO in women with and without AD history
Aguiar et al. (2009)	control from same city	investigated risk of ENDO in women with and without CLD history
Gemmill et al. (2010)	--	prevalence study of addison disease in women with ENDO history vs. general women population
Stephansson et al. (2011)	control matched on age, county, period	prospective cohort study for incident ENDO in women with and without CLD history Ø; excluded cases with ENDO diagnosis before CLD diagnosis
Nielsen et al. (2011)	control matched on age, period	prospective cohort study for incident SLE, SS, MS in women with and without ENDO history vs. general women population Ø; women diagnosed with AD before ENDO diagnosis was excluded from analysis
Jess et al. (2012)	control matched on age, period	prospective cohort study for incident IBD in women with and without ENDO history Ø
Santoro et al. (2014)	--	investigated risk of ENDO in women with and without CLD history
Caserta et al. (2015)	--	investigated risk of ENDO in women with and without AD history
Harris et al. (2016)a	age at menarche, parity, mensrual cycle length, BMI, physical activity, smoking, oral contraceptive use, race/ethnicity, infertility and analgesic use. For RA plus parity/total duration of breast feeding.	prospective cohort study for incident SLE, RA in women with and without ENDO history Ø
Harris et al. (2016)b	control matched on age, county	investigated risk of SLE in women with and without ENDO history; selected SLE diagnosis after ENDO diagnosis
Yuk et al. (2016)	control matched on age, sampling year, sampling weight; analysis adjusted for age and sampling year	prevalence study of autoimmune thyroid disorder in women with and without ENDO history
Huang et al. (2016)	matched controls	investigated risk of ENDO in women with and without rheumatoid disease history
Lee et al. (2016)	control matched on age	clinical manifestation, prognosis, and treatment comparing women with IBD and ENDO vs. women with IBD but without ENDO
Brouwer et al. (2017)	--	prevalence study of ENDO in women with RA history vs. general women population
Wu et al. (2017)		case-control study for risk of ENDO in women with and without SS history
de Silva et al. (2018)		investigated risk of IBD at pregnancies in women with and without ENDO history

Table x2.2a Characteristics of included studies in the targeted literature review published after April 2018 (part 1)

Citation	Country	Study period	Study design	Endometriosis ascertainment and number	Autoimmune disease ascertainment and number
Greenbaum et al. (2019)	Israel	2015-2016	cross-sectional study	hospital diagnosis (n=6,647)	hospital diagnosis SLE, IBD
Harris et al. (2022)	U.S.	1991-2013	cohort study	laparoscopically confirmed endometriosis (n=4,112)	physician diagnosis psoriasis, psoriatic arthritis
Porpora et al. (2019)	Italy	2014-2017	case-control study	laparoscopy with histological diagnosis (n=148)	antibody measurement AIR, SLE, CLD
Shafrir et al. (2021)	U.S.	2012-2018	cross-sectional study	surgical diagnosis (n=551)	hospital diagnosis SLE, RA, IBD, Psoriasis
Vanni et al. (2021)	Italy	2015-2019	case-control study	laparoscopically confirmed IV endometriosis with concommitant autoimmune diseases (n=96)	hospital daignosis ATD, T1D, IBD, CLD, SLE, APS, RA, SS, MS, psoriasis, fibromyalgia
Yoshii et al. (2021)	Japan	2011-2018	case-control study	hospital diagnosis (n=30,516)	hospital daignosis SLE, RA

Abbreviations: AIT: autoimmune thyroiditis, PsA: psoriatic arthritis, T2D: type 2 diabetes, CVD: cardiovascular diseases, ATD, autoimmune thyroid disorders, T1D, type 1 diabetes, IBD, infammatory bowel diseases; CLD, coeliac disease, SLE, systemic lupus erythematosus, APS, antiphospholipid syndrome, RA, rheumatoid arthritis, SS, systemic sclerosis, MS, multiple sclerosis, IRR: incidence rate ratio.

Table x2.2b Characteristics of included studies in the targeted literature review published after April 2018 (part 2)

Citation	Control selection and number	Risk estimates (in original reports)
Greenbaum et al. (2019)	women diagnosed with fibromyalgia (n=25,425)	women with endometriosis and fibromyalgia vs. women with fibromyalgia without endometriosis: SLE: OR=1.83 (1.03-3.23), P = 0.038; IBD: OR=2.66 (1.75-4.07), P < 0.001 women with endometriosis and fibromyalgia vs. women with endometriosis without fibromyalgia: SLE: OR=4.11 (2.02–8.36), P < 0.001; IBD: OR=2.97 (1.87-4.72), P < 0.001 SS: OR=3.08 (1.52–6.20), P = 0.002
Harris et al. (2022)	women without endometriosis or without psoriasis	endometriosis as exposure: psoriasis: HR=1.28 (0.95-1.72); psoriasis with PsA: HR=1.77 (0.89-3.52) endometriosis as the outcome: psoriasis without PsA: HR=0.93 (0.68-1.26); psoriasis with PsA: HR=2.01 (1.23-3.30)
Porpora et al. (2019)	women with no clinical or ultrasound endometriosis diagnosis (n=150)	AIT: OR=11.37 (6.00-21.5), P < 0.001; SLE: OR=8.63 (1.07-69.91), P = 0.01; CLD OR=12.04 (2.22-130.79), P < 0.001
Shafrir et al. (2021)	women without autoimmne diagnosis (n=652)	prevalence of AD or AIs: (4.5% vs. 3.4%) in endometriosis cases vs. controls any autoimmune and or inflammatory disease: OR=1.87 (0.92-3.80) SLE: 5.39 (0.54-54.2) for endometriosis risk; RA: 2.14 (0.54-8.39) for endometriosis risk; IBD: 6.78 (1.30-35.5) for endometriosis risk; positive trend for the no. of immune-mediated conditions and the odds of endo (OA=1.29 (1.13-1.48), P-trend = 0.0002)
Vanni et al. (2021)	laparoscopically confirmed stage IV endometriosis without concommitant autoimmune diseases (n=268)	stage IV endometriosis risk in women with endometriosis and concomitant autoimmune diseases (OR 2.54 (1.57-4.10), P = 0.004)
Yoshii et al. (2021)	women without clinically diagnosed endometriosis matched on age and registration date (n=120,976)	SLE: IRR=1.35 (0.99-1.84); RA: IRR=1.31 (1.05-1.64)

Table x2.2c Characteristics of included studies in the targeted literature review published after April 2018 (part 3)

Citation	Risk factors adjusted	Temporality
Greenbaum et al. (2019)	age, socioeconomic status, residence district, birth country, BMI	investigated the risk of prevalent ADs in women with both endometriosis and fibromyalgia vs. those with either endometriosis or fibromyalgia
Harris et al. (2022)	BMI, physical activity, alcohol consumption, smoking status, age at menarche, menstrual cycle length at age 18-22 years, oral contraceptive use, parity and infertility, hypertension, T2D, CVD, hypercholesterolemia, medicine such as acetaminophen, aspiron or ibuprofen)	investigated incident endometriosis as the outcome and psoriasis/PsA as the exposure; incident psoriasis/PsA as the outcome and endometriosis as the exposure
Porpora et al. (2019)	none	investigated the prevalence of ADs in women with and without ENDO
Shafrir et al. (2021)	age, BMI, first-degree family history of endometriosis, age at menarche, oral contraceptive use	investigated the risk of endometriosis in relation to ADs
Vanni et al. (2021)	controls matched on cases by age, study period, number of laparoscopic surgery	investigated the risk of Stage IV endometriosis in women with endometriosis and concomitant autoimmune diseases in comparison to women with endometriosis but without concomitant autoimmune diseases
Yoshii et al. (2021)	number of hospital visits within 3 months after registration, oral contraceptive and levonorgestrelreleasing intrauterine system use within 3 months after registration	investigated the incidence of endometriosis in women with SLE or RA

Table x2.2d Characteristics of included studies in the targeted literature review published after April 2018 (part 4)

Citation	Country	Study period	Study design	Endometriosis ascertainment and number	Autoimmune disease ascertainment and number
Lin et al. (2020)	Taiwan	2000-2013	cohort study	hospital diagnosis (n=17,779)	hospital diagnosis SLE
Xue et al. (2020)	Taiwan	2000-2013	cohort study	hospital diagnosis (n=14,463))	hospital diagnosis RA
Chen et al. (2021)	Taiwan	2000-2015	cohort study	hospital diagnosis (n=17,913))	hospital diagnosis RA
Fan et al. (2021)	Taiwan	1999-2013	cohort study	hospital diagnosis (n=16,758)	hospital diagnosis SLE
Chao et al. (2022)	Taiwan	2000-2013	cohort study	hospital diagnosis (n=14,733)	hospital diagnosis SS
Yin et al. (2022)	Taiwan	1999-2013	cohort study	hospital diagnosis (n=13,092)	hospital diagnosis Ankylosing spondylitis

Table x2.2e Characteristics of included studies in the targeted literature review published after April 2018 (part 5)

Citation	Control selection and number	Risk estimates (in original reports)	Risk factors adjusted	Temporality
Lin et al. (2020)	Endo-free women (n=17,779)	SLE: HR=1.86 (1.36-2.53), P < 0.001	age, index year, CCI score, hormonal and surgical treatment	investigated SLE risk in women with and without ENDO
Xue et al. (2020)	Endo-free women (n=14,463)	RA: HR=1.75 (1.27-2.41)	age, comorbidities, medication and hormonal medication use	investigated RA risk in women with and without ENDO
Chen et al. (2021)	Endo-free women (n=17,913)	RA: HR= 3.71 (2.91-5.73)	age, index year, CCI score, hormonal and surgical treatment	investigated RA risk in women with and without ENDO
Fan et al. (2021)	Endo-free women (n=16,758)	SLE: HR=2.37 (1.35-4.14), P = 0.004	age, comorbidities, corticosteroids use, NSAIDs use and hormonal mediation use	investigated SLE risk in women with and without ENDO
Chao et al. (2022)	Endo-free women (n=58,932)	SS: HR=1.45 (1.27-1.65)	age, diabetes mellitus, hyperlipidemia, coronary artery disease, congestive heart failure, obesity, stroke and chronic kidney disease	investigated SS risk in women with and without ENDO
Yin et al. (2022)	Endo-free women (n=26,184)	AS: HR=1.61 (1.11-2.35), P=0.013	age, index year, comorbidities, corticosteroids use, NSAIDs use	investigated AS risk in women with and without ENDO

Table x2.3a Quality assessment for each study association in the systematic review published before April 2018 (part 1)

Study outcome	No. of studies	GRADE score	Study design		Risk of bias		Inconsistency	
			score	comment	score	comment	score	comment
ENDO and SLE	8	LOW	2	low, non-RCT	-1	4 studies with high risk of bias (self-reported outcomes, small sample size, unrepresentativeness of the control group or whole study population)	0	all studies showed a positive association
ENDO and SS	6	VERY LOW	2	low, non-RCT	-1	3 studies with high risk of bias (self-reported outcomes, small sample size, unrepresentativeness of the control group or whole study population)	0	all studies showed a positive association
ENDO and RA	5	LOW	2	low, non-RCT		3 studies with high risk of bias (self-reported outcomes, small sample size, unrepresentativeness of the control group or whole study population)	0	all studies showed a positive association
ENDO and ATD	4	VERY LOW	2	low, non-RCT		2 studies with higher risk of bias (self-reported outcomes, small sample size, unrepresentativeness of the control group)	0	all studies showed a positive association
ENDO and CLD	4	VERY LOW	2	low, non-RCT	-1	2 studies with high risk of bias (self-reported outcomes, small sample size, unrepresentativeness of the control group)	0	all studies showed a positive association
ENDO and MS	3	VERY LOW	2	low, non-RCT	-1	1 study with high risk of bias (self-reported outcomes, small sample size, unrepresentativeness of the control group)	0	all studies showed a positive association
ENDO and IBD	4	VERY LOW	2	low, non-RCT	-1	1 study with high risk of bias (small sample size, unrepresentativeness of the control group)	0	all studies showed a positive association

Abbreviations: ATD: autoimmune thyroid disorder; ENDO: endometriosis; SLE: systemic lupus evythmatosus; RA: rheumatoid arthritis; SS: Sjögren's syndrome; CLD: celiac disease; MS: multiple sclerosis; IBD: Irritable bowel disease.

Table x2.3b Quality assessment for each study association in the systematic review published before April 2018 (part 2)

Study outcome	Indirectness		Imprecision		Publication bias		Uplifting factors	
	score	comment	score	comment	score	comment	score	comment
ENDO and SLE	0	1 study explored indirect association	-1	4 studies with wide CIs or didn't report a CI	0	--	2	3 studies reported large effect; 2 other studies with good adjustment for confounders and large sample size
ENDO and SS	0	all studies explored the association directly	-1	4 studies with wide CIs or didn't report a CI	0	--	2	3 studies with higher degree of quality: large sample size, adequate disease ascertainment, ability to approach temporality, including 1 study with good adjustment for potential confounders
ENDO and RA	0	all studies explored the association directly	-1	3 studies with wide CIs or didn't report a CI	0	--	2	1 study reported large effect; 2 other studies with good adjustment for confounders and large sample size, adequate disease ascertainment, with 1 study with ability to approach temporality
ENDO and ATD	0	all studies explored the association directly	-2	3 studies with wide CIs or didn't report a CI	0	--	0	--
ENDO and CLD	0	all studies explored the association directly	-2	3 studies with wide CIs or didn't report a CI	0	--	1	1 study with higher degree of quality: large sample size, adequate disease ascertainment, ability to approach temporality
ENDO and MS	0	all studies explored the association directly	-2	2 studies with wide CIs or didn't report a CI	0	--	1	1 study with higher degree of quality: large sample size, adequate disease ascertainment, ability to approach temporality, good adjustment for potential confounders
ENDO and IBD	-1	1 studies explored an indirect association	-1	1 study didn't report a CI	0	--	1	1 study with higher degree of quality: large sample size, adequate disease ascertainment, ability to approach temporality

Table x3.1 Identification codes for endometriosis diagnosis in UKBB

Endometriosis			Surgeries to Confirm Endo	
Self-Reported	ICD9	ICD10	Self-ported	Hospital episodes OPCS data
1402	617, 6170, 6171, 6172, 6173, 6174, 6175, 6176, 6178, 6179	N80, N800, N801, N802, N803, N804, N805, N806, N808, N809	1429,1505, 1506, 1520, 1354,1355, 1356, 1357,1358, 1359, 1363, 1475, 1485, 1508, 1509, 1510, 1519, 1521, 1538, 1600, 1606, 1607, 1609, 1199, 1427, 1461, 1462, 1465, 1466, 1486, 1488, 1547, 1570, 1574, 1577, 1621	Q01, Q011, Q013, Q019, Q09, Q099, Q103, Q108, Q109, Q12, Q121, Q122, Q179,Q18, Q181, Q188, Q189, Q232, Q233, Q234, Q221, Q242, Q243, Q248, Q249,Q25, Q251, Q258, Q259, Q27, Q271, Q201,Q22, Q222, Q223, Q228, Q229, Q23, Q231, Q235, Q236, Q238, Q239, Q24, Q241, Q07, Q074, Q075, Q078, Q079, Q092, Q093, Q094, Q098

Table x4.1 Lead SNPs for ankylosing spondylitis identified from UKBB GWAS (female-only and sex-combined)

GWAS Analysis	SNP	CHR	Position (BP)	EA	EAF	UKBB female-only		UKBB sex-combined		Nearest gene	Function
						OR [95% CI]	P-value	OR [95% CI]	P-value		
Sex-combined	rs61902485	11	59142038	A	0.97	1.78 [1.23-2.58]	2.20×10^{-3}	1.95 [1.56-2.45]	7.70×10^{-9}	OR5AN1	intergenic
Female-only	rs7136938	12	626020	T	0.96	2.30 [1.74-3.03]	3.60×10^{-9}	1.40 [1.18-1.66]	1.10×10^{-4}	B4GALNT3	intronic

Table x4.2.a Lead SNPs for coeliac disease identified from UKBB GWAS (female-only) results

GWAS Analysis	SNP	CHR	BP	EA	EAF	UKBB female-only GWAS		UKBB sex-combined GWAS		Meta-Analysis sex-combined GWAS		Gene	Function
						OR [95% CI]	P-value	OR [95% CI]	P-value	OR [95% CI]	P-value		
Female-only	rs17849501	1	183542323	T	0.94	1.6 [1.37-1.85]	1.20E-09	1.45 [1.28-1.64]	4.40E-09	NA	NA	SMG7:NCF2	exonic
Female-only	rs10801129	1	192521591	T	0.74	1.25 [1.16-1.35]	5.70E-09	1.18 [1.11-1.25]	2.30E-07	NA	NA	RP5-1011O1.2	ncRNA_intronic
Female-only	rs2368187	2	182032501	T	0.56	1.29 [1.2-1.38]	2.40E-13	1.19 [1.12-1.26]	1.60E-09	NA	NA	AC104820.2	ncRNA_intronic
Female-only	rs13079689	3	188102112	T	0.51	1.29 [1.21-1.38]	8.80E-14	1.25 [1.18-1.32]	2.40E-15	NA	NA	LPP	intronic
Female-only	rs13132308	4	123551114	A	0.16	1.42 [1.3-1.55]	4.20E-15	1.39 [1.29-1.49]	3.90E-19	NA	NA	IL21-AS1	ncRNA_intronic
Female-only	rs73407670	6	35206346	A	0.99	2.81 [2.17-3.63]	2.70E-15	2.71 [2.19-3.34]	1.40E-20	NA	NA	SCUBE3	intronic
Female-only	rs9658119	6	35365967	C	0.89	1.39 [1.25-1.56]	3.90E-09	1.35 [1.23-1.47]	1.00E-10	NA	NA	PPARD	intronic
Female-only	rs62432712	6	137964697	G	0.83	1.25 [1.15-1.35]	4.50E-08	1.29 [1.21-1.38]	2.00E-14	NA	NA	RP11-95M15.1	intergenic
Female-only	rs3184504	12	111884608	T	0.46	1.24 [1.16-1.33]	2.40E-10	1.21 [1.14-1.28]	1.30E-11	1.21 [1.16-1.26]	7.92E-22	SH2B3	exonic
Female-only	rs12967678	18	12805388	A	0.91	1.42 [1.28-1.58]	1.90E-11	1.34 [1.23-1.46]	1.40E-11	NA	NA	PTPN2	intronic
Female-only	18:12866436_AAAAAC_A	18	12866436	A	0.50	1.22 [1.14-1.31]	2.10E-08	1.18 [1.11-1.25]	1.20E-08	NA	NA	PTPN2	intronic

Table x4.2.b Lead SNPs for coeliac disease identified from UKBB GWAS (sex-combined) results

GWAS Analysis	SNP	CHR	BP	EA	EAF	UKBB female-only GWAS		UKBB sex-combined GWAS		Meta-Analysis sex-combined GWAS		Gene	Function
						OR [95% CI]	P-value	OR [95% CI]	P-value	OR [95% CI]	P-value		
Sex-combined	rs17849501	1	183542323	T	0.94	1.6 [1.37-1.85]	1.20E-09	1.45 [1.28-1.64]	4.40E-09	NA	NA	SMG7:NCF2	exonic
Sex-combined	rs7535818	1	192545099	A	0.81	1.29 [1.18-1.4]	1.30E-08	1.26 [1.17-1.35]	2.00E-10	NA	NA	RGS1	intronic
Sex-combined	rs4324288	2	182097994	A	0.53	1.26 [1.18-1.35]	1.70E-11	1.2 [1.13-1.27]	1.30E-10	NA	NA	AC104820.2	ncRNA_intron
Sex-combined	rs11904512	2	204642462	C	0.28	1.18 [1.1-1.28]	1.50E-05	1.22 [1.14-1.3]	6.30E-10	NA	NA	NPM1P33	intergenic
Sex-combined	rs4493469	3	46177992	C	0.89	1.37 [1.22-1.54]	1.50E-07	1.37 [1.25-1.51]	1.40E-10	NA	NA	FLT1P1	intergenic
Sex-combined	rs17753641	3	159647674	G	0.91	1.33 [1.2-1.47]	8.70E-08	1.3 [1.2-1.42]	1.30E-09	NA	NA	IL12A-AS1	ncRNA_intron
Sex-combined	rs13079689	3	188102112	T	0.51	1.29 [1.21-1.38]	8.80E-14	1.25 [1.18-1.32]	2.40E-15	NA	NA	LPP	intronic
Sex-combined	rs13132308	4	123551114	A	0.16	1.42 [1.3-1.55]	4.20E-15	1.39 [1.29-1.49]	3.90E-19	NA	NA	IL21-AS1	ncRNA_intron

Sex-combined	rs73407670	6	35206346	A	0.99	2.81 [2.17-3.63]	2.70E-15	2.71 [2.19-3.34]	1.40E-20	NA	NA	SCUBE3	intronic
Sex-combined	rs796898693	6	35304213	C	0.93	1.35 [1.17-1.55]	2.80E-05	1.38 [1.23-1.55]	3.60E-08	NA	NA	PPARD	intergenic
Sex-combined	rs9658119	6	35365967	C	0.89	1.39 [1.25-1.56]	3.90E-09	1.35 [1.23-1.47]	1.00E-10	NA	NA	PPARD	intronic
Sex-combined	rs62432712	6	137964697	G	0.83	1.25 [1.15-1.35]	4.50E-08	1.29 [1.21-1.38]	2.00E-14	NA	NA	RP11-95M15.1	intergenic
Sex-combined	rs3184504	12	111884608	T	0.46	1.24 [1.16-1.33]	2.40E-10	1.21 [1.14-1.28]	1.30E-11	1.21 [1.16-1.26]	7.92E-22	SH2B3	exonic
Sex-combined	rs12967678	18	12805388	A	0.91	1.42 [1.28-1.58]	1.90E-11	1.34 [1.23-1.46]	1.40E-11	NA	NA	PTPN2	intronic
Sex-combined	rs8096327	18	12887750	G	0.61	1.21 [1.13-1.3]	4.50E-08	1.19 [1.12-1.25]	4.60E-09	NA	NA	PTPN2	intronic
Sex-combined	rs17593675	19	32219531	A	0.36	1.19 [1.11-1.27]	1.30E-06	1.17 [1.11-1.24]	4.40E-08	NA	NA	RNU6-967P	intergenic

Table x4.2.c Lead SNPs for coeliac disease identified from meta-analysis GWAS (sex-combined) results

GWAS Analysis	SNP	CHR	BP	EA	EAF	UKBB female-only GWAS		UKBB sex-combined GWAS		Meta-Analysis sex-combined GWAS		Gene	Function
						OR [95% CI]	P-value	OR [95% CI]	P-value	OR [95% CI]	P-value		
Meta-analysis	rs3748816	1	2526746	A	0.33	1.14 [1.06-1.22]	3.40E-04	1.14 [1.08-1.21]	8.20E-06	1.14 [1.1-1.19]	1.42E-10	MMEL1	exonic
Meta-analysis	rs864537	1	167411384	A	0.39	1.08 [1.01-1.16]	2.10E-02	1.12 [1.06-1.19]	3.60E-05	1.14 [1.09-1.18]	1.62E-10	CD247	intronic
Meta-analysis	rs10798176	1	172675525	T	0.19	1.19 [1.09-1.29]	1.20E-04	1.18 [1.1-1.27]	3.90E-06	1.16 [1.1-1.22]	2.96E-08	FASLG	intergenic
Meta-analysis	rs41272536	1	183440531	G	0.94	1.65 [1.4-1.95]	2.00E-09	1.49 [1.3-1.71]	6.80E-09	1.49 [1.3-1.71]	1.94E-08	SMG7-AS1	ncRNA_exonic
Meta-analysis	rs2816316	1	192536813	A	0.18	1.28 [1.17-1.4]	2.20E-08	1.25 [1.17-1.34]	5.70E-10	1.27 [1.21-1.34]	2.96E-19	RP5-1011O1.2	upstream
Meta-analysis	rs10188217	2	61217542	C	0.50	1.1 [1.03-1.17]	6.90E-03	1.1 [1.04-1.16]	7.80E-04	1.12 [1.08-1.17]	8.04E-09	PUS10	intronic
Meta-analysis	rs917997	2	103070568	T	0.22	1.21 [1.12-1.31]	2.60E-06	1.16 [1.09-1.24]	7.70E-06	1.22 [1.16-1.27]	6.25E-17	IL18RAP	intergenic
Meta-analysis	rs1018326	2	182007800	C	0.56	1.28 [1.2-1.37]	1.00E-12	1.17 [1.11-1.24]	2.20E-08	1.17 [1.12-1.21]	6.76E-15	AC104820.2	ncRNA_intronic
Meta-analysis	rs4675374	2	204802578	T	0.22	1.19 [1.09-1.29]	6.80E-05	1.16 [1.08-1.25]	2.00E-05	1.17 [1.12-1.23]	7.10E-11	ICOS	intronic
Meta-analysis	rs13098911	3	46235201	T	0.09	1.36 [1.2-1.54]	2.10E-06	1.39 [1.25-1.54]	6.00E-10	1.35 [1.26-1.44]	5.05E-18	CCR3	intronic
Meta-analysis	rs6806528	3	69252899	T	0.10	1.32 [1.17-1.48]	2.40E-06	1.28 [1.16-1.4]	3.60E-07	1.24 [1.16-1.33]	6.39E-10	FRMD4B	intronic
Meta-analysis	rs11712165	3	119118796	G	0.61	1.06 [0.99-1.14]	7.60E-02	1.12 [1.06-1.18]	1.10E-04	1.13 [1.09-1.18]	2.42E-09	ARHGAP31	intronic
Meta-analysis	rs1353248	3	159623559	C	0.72	1.15 [1.07-1.24]	1.90E-04	1.15 [1.08-1.22]	7.20E-06	1.15 [1.1-1.2]	1.28E-10	IL12A-AS1	intergenic

Meta-analysis	rs17810546	3	159665050	G	0.91	1.3 [1.17-1.44]	4.50E-07	1.28 [1.18-1.39]	8.10E-09	1.33 [1.26-1.41]	1.52E-22	IL12A-AS1	ncRNA_intronic
Meta-analysis	rs1464510	3	188112554	A	0.48	1.26 [1.18-1.35]	1.10E-11	1.24 [1.17-1.31]	2.90E-14	1.27 [1.22-1.32]	4.82E-33	LPP	intronic
Meta-analysis	rs13151961	4	123115502	A	0.16	1.38 [1.27-1.51]	4.00E-13	1.36 [1.27-1.46]	5.10E-17	1.37 [1.3-1.45]	1.53E-30	KIAA1109	intronic
Meta-analysis	rs4288027	4	123183205	C	0.91	1.18 [1.04-1.33]	9.20E-03	1.21 [1.1-1.34]	1.70E-04	1.22 [1.14-1.31]	1.09E-08	KIAA1109	intronic
Meta-analysis	6:35247775_a_at	6	35247775	A	0.32	NA	NA	NA	NA	1.21 [1.13-1.3]	2.40E-08	ZNF76	intronic
Meta-analysis	rs111815981	6	35340115	T	0.01	2.26 [1.81-2.82]	5.60E-13	2.14 [1.78-2.56]	2.00E-16	2.14 [1.77-2.58]	1.79E-15	PPARD	intronic
Meta-analysis	rs802734	6	128278798	G	0.71	1.14 [1.06-1.22]	3.30E-04	1.15 [1.09-1.22]	1.50E-06	1.15 [1.1-1.2]	7.19E-11	PTPRK	intergenic
Meta-analysis	rs2327832	6	137973068	G	0.83	1.25 [1.15-1.35]	5.70E-08	1.29 [1.21-1.38]	2.30E-14	1.27 [1.22-1.33]	3.48E-25	RP11-95M15.1	intergenic
Meta-analysis	rs1738074	6	159465977	T	0.43	1.13 [1.05-1.2]	5.10E-04	1.15 [1.09-1.21]	7.50E-07	1.15 [1.11-1.2]	1.29E-12	RP1-111C20.4:TAGAP	ncRNA_intronic
Meta-analysis	rs501344	8	103114573	G	0.66	1.1 [1.03-1.18]	6.90E-03	1.11 [1.05-1.17]	4.50E-04	1.12 [1.08-1.17]	3.90E-08	NCALD	intronic
Meta-analysis	rs944141	9	5490522	T	0.24	1.16 [1.07-1.26]	2.40E-04	1.15 [1.08-1.23]	2.20E-05	1.15 [1.1-1.2]	3.19E-09	CD274	intergenic
Meta-analysis	rs1250552	10	81058027	A	0.44	1.09 [1.02-1.17]	1.20E-02	1.08 [1.02-1.14]	6.80E-03	1.12 [1.07-1.16]	3.02E-08	ZMIZ1	intronic
Meta-analysis	rs12365699	11	118743286	G	0.84	1.17 [1.07-1.28]	5.70E-04	1.23 [1.14-1.32]	5.80E-08	1.17 [1.11-1.24]	3.08E-08	CXCR5	intergenic
Meta-analysis	rs11221335	11	128385906	C	0.76	1.17 [1.08-1.27]	1.60E-04	1.18 [1.11-1.26]	1.00E-06	1.21 [1.15-1.27]	7.84E-15	ETS1	intronic
Meta-analysis	rs3184504	12	111884608	T	0.46	1.24 [1.16-1.33]	2.40E-10	1.21 [1.14-1.28]	1.30E-11	1.21 [1.16-1.26]	7.92E-22	SH2B3	exonic
Meta-analysis	rs11066320	12	112906415	A	0.43	1.18 [1.1-1.26]	2.90E-06	1.14 [1.08-1.2]	5.30E-06	1.14 [1.1-1.19]	3.36E-11	PTPN11	intronic
Meta-analysis	rs1051533	14	69259662	A	0.21	1.19 [1.1-1.29]	3.10E-05	1.14 [1.07-1.22]	1.20E-04	1.15 [1.1-1.21]	1.14E-08	ZFP36L1	exonic
Meta-analysis	rs1893217	18	12809340	G	0.86	1.31 [1.2-1.43]	4.10E-09	1.25 [1.16-1.35]	2.00E-09	1.21 [1.15-1.28]	1.08E-13	PTPN2	intronic

Table x4.3.a Lead SNPs for inflammatory bowel disease identified from UKBB GWAS (female-only) results

GWAS Analysis	SNP	CHR	BP	EA	EAF	UKBB female-only GWAS		UKBB sex-combined GWAS		Meta-Analysis sex-combined GWAS		Gene	Function
						OR [95% CI]	P-value	OR [95% CI]	P-value	OR [95% CI]	P-value		
Female-only	rs11209026	1	67705958	G	0.06	1.51 [1.36-1.68]	8.20E-15	1.45 [1.35-1.57]	1.30E-22	NA	NA	IL23R	exonic
Female-only	rs34219944	1	67726765	CT	0.71	1.24 [1.17-1.32]	4.40E-13	1.22 [1.17-1.27]	2.60E-20	NA	NA	IL23R	intergenic
Female-only	10:101317836_CT_C	10	101317836	CT	0.46	1.16 [1.1-1.22]	2.30E-08	1.13 [1.09-1.18]	1.40E-10	NA	NA	NKX2-3	intergenic

Female-only	rs7936312	11	76293726	T	0.53	1.17 [1.11-1.23]	5.80E-09	1.13 [1.09-1.17]	4.60E-10	1.15 [1.12-1.17]	4.65E-31	RP11-672A2.7	intergenic
Female-only	rs3867524	16	15379923	G	0.69	1.18 [1.11-1.25]	1.90E-08	1.1 [1.06-1.15]	5.80E-06	NA	NA	NPIPA5	intergenic
Female-only	rs141976787	16	50898940	G	0.98	1.91 [1.53-2.4]	2.20E-08	1.54 [1.31-1.81]	2.40E-07	1.58 [1.42-1.76]	2.26E-17	CTD-2034I21.1	ncRNA_intronic
Female-only	rs6017342	20	43065028	C	0.52	1.17 [1.11-1.23]	4.90E-09	1.15 [1.11-1.2]	7.70E-14	1.13 [1.11-1.16]	1.76E-24	RP5-1013A22.5	intergenic
Female-only	rs2836883	21	40466744	G	0.26	1.22 [1.15-1.29]	8.70E-11	1.23 [1.18-1.28]	9.70E-22	1.2 [1.16-1.23]	5.92E-40	RPL23AP12	intergenic
Female-only	rs11209026	1	67705958	G	0.06	1.51 [1.36-1.68]	8.20E-15	1.45 [1.35-1.57]	1.30E-22	NA	NA	IL23R	exonic
Female-only	rs34219944	1	67726765	CT	0.71	1.24 [1.17-1.32]	4.40E-13	1.22 [1.17-1.27]	2.60E-20	NA	NA	IL23R	intergenic
Female-only	10:101317836_CT_C	10	101317836	CT	0.46	1.16 [1.1-1.22]	2.30E-08	1.13 [1.09-1.18]	1.40E-10	NA	NA	NKX2-3	intergenic
Female-only	rs7936312	11	76293726	T	0.53	1.17 [1.11-1.23]	5.80E-09	1.13 [1.09-1.17]	4.60E-10	1.15 [1.12-1.17]	4.65E-31	RP11-672A2.7	intergenic
Female-only	rs3867524	16	15379923	G	0.69	1.18 [1.11-1.25]	1.90E-08	1.1 [1.06-1.15]	5.80E-06	NA	NA	NPIPA5	intergenic
Female-only	rs141976787	16	50898940	G	0.98	1.91 [1.53-2.4]	2.20E-08	1.54 [1.31-1.81]	2.40E-07	1.58 [1.42-1.76]	2.26E-17	CTD-2034I21.1	ncRNA_intronic
Female-only	rs6017342	20	43065028	C	0.52	1.17 [1.11-1.23]	4.90E-09	1.15 [1.11-1.2]	7.70E-14	1.13 [1.11-1.16]	1.76E-24	RP5-1013A22.5	intergenic
Female-only	rs2836883	21	40466744	G	0.26	1.22 [1.15-1.29]	8.70E-11	1.23 [1.18-1.28]	9.70E-22	1.2 [1.16-1.23]	5.92E-40	RPL23AP12	intergenic

Table x4.3.b Lead SNPs for inflammatory bowel disease identified from UKBB GWAS (sex-combined) results

GWAS Analysis	SNP	CHR	BP	EA	EAF	UKBB female-only GWAS		UKBB sex-combined GWAS		Meta-Analysis sex-combined GWAS		Gene	Function
						OR [95% CI]	P-value	OR [95% CI]	P-value	OR [95% CI]	P-value		
Sex-combined	rs3806310	1	20142681	A	0.37	1.14 [1.08-1.2]	2.00E-06	1.12 [1.08-1.16]	7.10E-09	1.1 [1.08-1.13]	1.48E-16	RP11-91K11.2	ncRNA_intronic
Sex-combined	rs10753575	1	20163868	T	0.61	1.15 [1.09-1.21]	8.10E-07	1.16 [1.12-1.2]	7.90E-14	1.13 [1.1-1.15]	9.40E-23	RP11-91K11.2	intergenic
Sex-combined	1:67663630_AG_A	1	67663630	AG	0.34	1.12 [1.06-1.19]	2.60E-05	1.13 [1.08-1.17]	2.00E-09	NA	NA	C1orf141:IL23R	intronic
Sex-combined	rs779016240	1	67672567	C	0.62	1.16 [1.09-1.23]	9.30E-07	1.13 [1.09-1.18]	5.60E-09	NA	NA	C1orf141:IL23R	intronic
Sex-combined	rs11581607	1	67707690	G	0.06	1.51 [1.36-1.68]	8.90E-15	1.45 [1.35-1.57]	9.40E-23	NA	NA	IL23R	intronic
Sex-combined	rs34219944	1	67726765	CT	0.71	1.24 [1.17-1.32]	4.40E-13	1.22 [1.17-1.27]	2.60E-20	NA	NA	IL23R	intergenic
Sex-combined	1:67766686_TA_T	1	67766686	TA	0.48	1.12 [1.05-1.18]	1.50E-04	1.12 [1.08-1.17]	2.10E-08	NA	NA	IL12RB2	intergenic
Sex-combined	rs10889680	1	67768593	A	0.89	1.24 [1.14-1.35]	7.50E-07	1.24 [1.17-1.32]	6.60E-12	1.23 [1.18-1.28]	6.01E-25	IL12RB2	intergenic
Sex-combined	rs10888436	1	151784994	T	0.55	1.12 [1.06-1.18]	4.80E-05	1.12 [1.08-1.17]	2.60E-09	1.08 [1.05-1.1]	1.46E-09	RORC	intronic
Sex-combined	1:151801454_CAAA_C	1	151801454	C	0.74	1.12 [1.05-1.18]	2.20E-04	1.15 [1.1-1.2]	1.30E-10	NA	NA	RORC	intronic

Sex-combined	rs6671847	1	161478810	G	0.49	1.11 [1.06-1.17]	6.90E-05	1.13 [1.09-1.18]	4.30E-11	1.11 [1.08-1.13]	6.29E-18	FCGR2A	intronic
Sex-combined	rs3024505	1	206939904	A	0.83	1.18 [1.1-1.27]	4.70E-06	1.2 [1.14-1.26]	7.40E-12	1.21 [1.17-1.24]	2.82E-33	IL10	intergenic
Sex-combined	rs11757201	6	138003822	C	0.83	1.13 [1.06-1.21]	8.90E-05	1.13 [1.08-1.19]	4.10E-08	1.1 [1.07-1.13]	1.88E-12	RP11-95M15.1	intergenic
Sex-combined	rs142738614	7	128577914	CG CG GG	0.55	1.13 [1.07-1.19]	8.20E-06	1.12 [1.08-1.16]	7.60E-09	NA	NA	IRF5	intronic
Sex-combined	rs10761659	10	64445564	G	0.50	1.13 [1.07-1.19]	5.10E-06	1.12 [1.08-1.16]	2.50E-09	1.15 [1.13-1.18]	2.98E-34	ZNF365	intergenic
Sex-combined	rs7077040	10	101281014	C	0.48	1.16 [1.1-1.22]	2.90E-08	1.14 [1.1-1.18]	8.90E-12	1.15 [1.13-1.18]	6.44E-35	RP11-129J12.2	intergenic
Sex-combined	rs2212434	11	76281593	T	0.56	1.16 [1.11-1.23]	1.20E-08	1.13 [1.09-1.18]	1.10E-10	1.15 [1.12-1.18]	1.22E-32	C11orf30	intergenic
Sex-combined	rs2066847	16	50763778	GC	0.99	1.58 [1.3-1.93]	5.10E-06	1.54 [1.33-1.77]	2.80E-09	NA	NA	NOD2	exonic
Sex-combined	rs6017342	20	43065028	C	0.52	1.17 [1.11-1.23]	4.90E-09	1.15 [1.11-1.2]	7.70E-14	1.13 [1.11-1.16]	1.76E-24	RP5-1013A22.5	intergenic
Sex-combined	rs1297261	21	16812623	T	0.42	1.11 [1.05-1.17]	9.80E-05	1.13 [1.08-1.17]	9.70E-10	NA	NA	AJ006998.2	intergenic
Sex-combined	rs9977672	21	40463283	G	0.25	1.22 [1.15-1.29]	1.20E-10	1.24 [1.19-1.29]	3.80E-22	1.2 [1.17-1.23]	1.34E-39	RPL23AP12	intergenic

Table x4.3.c Lead SNPs for inflammatory bowel disease identified from meta-analysis GWAS (sex-combined) results

GWAS Analysis	SNP	CHR	BP	EA	EAF	UKBB female-only GWAS		UKBB sex-combined GWAS		Meta-Analysis sex-combined GWAS		Gene	Function
						OR [95% CI]	P-value	OR [95% CI]	P-value	OR [95% CI]	P-value		
Meta-analysis	1:1225641_c_a	1	1225641	C	0.11	NA	NA	NA	NA	1.13 [1.09-1.18]	2.42E-09	SCNN1D	intronic
Meta-analysis	rs72634258	1	8150638	C	0.16	1.03 [0.96-1.1]	4.60E-01	1.05 [1-1.11]	4.40E-02	1.11 [1.08-1.15]	1.99E-11	RP11-431K24.1	ncRNA_intronic
Meta-analysis	rs12041676	1	8273392	A	0.82	1.04 [0.98-1.11]	1.90E-01	1.06 [1.01-1.11]	2.00E-02	1.09 [1.06-1.12]	2.24E-09	RP11-431K24.3	ncRNA_intronic
Meta-analysis	1:20110838_c_t	1	20110838	T	0.64	NA	NA	NA	NA	1.09 [1.06-1.12]	3.45E-11	TMCO4	intronic
Meta-analysis	rs1317209	1	20140036	G	0.18	1.12 [1.05-1.2]	9.60E-04	1.13 [0.84-0.93]	2.40E-06	1.12 [1.09-1.16]	7.17E-15	RNF186	upstream:downstream
Meta-analysis	rs3820328	1	20142447	G	0.37	1.14 [1.08-1.2]	2.20E-06	1.12 [1.08-1.16]	1.00E-08	1.1 [1.08-1.13]	1.38E-16	RP11-91K11.2	ncRNA_intronic
Meta-analysis	rs4654925	1	20227723	C	0.56	1.14 [1.08-1.2]	6.10E-07	1.15 [1.1-1.19]	7.70E-13	1.13 [1.11-1.16]	1.37E-26	OTUD3	intronic
Meta-analysis	rs79453445	1	20242739	A	0.98	1.37 [1.17-1.61]	7.50E-05	1.31 [1.17-1.47]	2.10E-06	1.25 [1.16-1.34]	1.07E-09	OTUD3	intergenic
Meta-analysis	rs34963268	1	22710877	C	0.84	1.09 [1.01-1.16]	1.80E-02	1.13 [1.07-1.19]	1.50E-06	1.14 [1.1-1.17]	1.48E-16	RP11-415K20.1	intergenic
Meta-analysis	rs116068903	1	67498721	T	0.99	1.18 [0.95-1.45]	1.30E-01	1.17 [1.01-1.36]	4.30E-02	1.34 [1.21-1.49]	1.50E-08	SLC35D1	intronic

Meta-analysis	rs7540900	1	67597295	A	0.83	1.04 [0.96-1.13]	3.50E-01	1.02 [0.97-1.09]	4.10E-01	1.1 [1.07-1.14]	8.33E-09	C1orf141	intronic
Meta-analysis	rs10789224	1	67605134	C	0.28	1.08 [1.02-1.14]	9.00E-03	1.09 [1.05-1.13]	3.00E-05	1.13 [1.1-1.16]	4.18E-22	C1orf141	intronic
Meta-analysis	rs77138986	1	67630990	C	0.02	1.41 [1.16-1.7]	4.60E-04	1.33 [1.16-1.52]	4.80E-05	1.52 [1.39-1.67]	7.43E-20	C1orf141	intronic
Meta-analysis	rs72676064	1	67656684	C	0.04	1.45 [1.28-1.64]	4.50E-09	1.41 [1.29-1.54]	3.00E-14	1.53 [1.44-1.63]	7.03E-43	C1orf141:IL23R	intronic
Meta-analysis	rs10889669	1	67675728	T	0.70	1.22 [1.15-1.29]	1.60E-11	1.2 [0.8-0.87]	8.60E-19	1.25 [1.22-1.28]	5.24E-73	C1orf141:IL23R	intronic
Meta-analysis	1:67691201_c_ct	1	67691201	CT	0.83	NA	NA	NA	NA	1.18 [1.11-1.25]	2.56E-08	C1orf141:IL23R	intronic
Meta-analysis	rs148911931	1	67758729	G	0.03	1.21 [1.02-1.45]	3.20E-02	1.36 [0.65-0.84]	2.80E-06	1.25 [1.16-1.35]	3.11E-09	RP4-763G1.1	intergenic
Meta-analysis	rs10889680	1	67768593	T	0.11	1.24 [1.14-1.35]	7.50E-07	1.24 [0.76-0.86]	6.60E-12	1.23 [1.18-1.28]	6.01E-25	IL12RB2	intergenic
Meta-analysis	rs1109918	1	67862482	G	0.01	1.25 [1.05-1.49]	1.10E-02	1.29 [1.13-1.46]	8.30E-05	1.34 [1.22-1.46]	3.68E-10	IL12RB2	UTR3
Meta-analysis	rs11590963	1	67906429	C	0.39	1.11 [1.05-1.17]	1.40E-04	1.09 [0.88-0.95]	4.80E-06	1.1 [1.08-1.13]	8.24E-17	SERBP1	intergenic
Meta-analysis	rs11209112	1	68018455	G	0.15	1.1 [1.02-1.17]	7.50E-03	1.08 [0.88-0.97]	2.50E-03	1.09 [1.06-1.12]	3.21E-08	RP11-393N21.1	intergenic
Meta-analysis	rs1336900	1	150679033	A	0.59	1.04 [0.98-1.1]	1.70E-01	1.03 [0.99-1.07]	8.90E-02	1.07 [1.05-1.1]	1.46E-08	HORMAD1	exonic
Meta-analysis	rs10888436	1	151784994	C	0.45	1.12 [1.06-1.18]	4.80E-05	1.12 [0.86-0.93]	2.60E-09	1.08 [1.05-1.1]	1.46E-09	RORC	intronic
Meta-analysis	rs76990585	1	151795777	C	0.19	1.01 [0.94-1.08]	8.30E-01	1.06 [0.9-0.99]	1.30E-02	1.08 [1.05-1.11]	2.88E-08	RORC	intronic
Meta-analysis	rs4845604	1	151801680	A	0.86	1.15 [1.06-1.24]	3.60E-04	1.13 [1.07-1.19]	6.60E-06	1.14 [1.11-1.18]	5.59E-15	RORC	intronic
Meta-analysis	rs41264285	1	155033918	C	0.19	1.04 [0.97-1.11]	2.50E-01	1.06 [0.9-0.98]	8.20E-03	1.08 [1.05-1.11]	4.11E-08	ADAM15	exonic
Meta-analysis	rs4276914	1	155142229	G	0.49	1.04 [0.99-1.1]	1.00E-01	1.06 [0.91-0.98]	1.60E-03	1.08 [1.05-1.1]	6.09E-10	KRTCAP2:RP11-201K10.3	intronic
Meta-analysis	rs6658353	1	161469054	C	0.51	1.11 [1.06-1.17]	6.80E-05	1.13 [1.09-1.17]	1.70E-10	1.12 [1.09-1.14]	9.73E-21	FCGR2A	intergenic
Meta-analysis	rs11578245	1	161499460	A	0.89	1.14 [1.05-1.24]	2.70E-03	1.14 [0.82-0.93]	1.70E-05	1.16 [1.12-1.2]	8.28E-15	RP11-25K21.6	ncRNA_intronic
Meta-analysis	rs10753788	1	169606273	A	0.56	1.09 [1.03-1.14]	2.30E-03	1.09 [0.88-0.95]	1.00E-05	1.07 [1.05-1.1]	3.89E-09	SELP	intergenic
Meta-analysis	rs16841904	1	197701992	C	0.19	1.08 [1.01-1.15]	2.20E-02	1.09 [0.88-0.96]	3.20E-04	1.1 [1.07-1.13]	1.99E-11	DENND1B	intronic
Meta-analysis	rs2816972	1	200085004	A	0.88	1.15 [1.06-1.25]	9.50E-04	1.18 [0.8-0.9]	6.40E-08	1.14 [1.1-1.18]	5.89E-12	NR5A2	intronic
Meta-analysis	rs35730213	1	200874229	C	0.73	1.13 [1.07-1.2]	1.60E-05	1.12 [1.08-1.17]	5.60E-08	1.14 [1.11-1.17]	8.30E-23	C1orf106	intronic

Meta-analysis	rs79474100	1	206914649	T	0.04	1.32 [0.66-0.87]	7.80E-05	1.19 [0.76-0.93]	5.70E-04	1.25 [1.17-1.34]	5.83E-12	Y_RNA	intergenic
Meta-analysis	rs3024505	1	206939904	G	0.17	1.18 [0.79-0.91]	4.70E-06	1.2 [0.79-0.88]	7.40E-12	1.21 [1.17-1.24]	2.82E-33	IL10	intergenic
Meta-analysis	rs6702254	1	206964952	T	0.69	1.06 [0.89-1]	4.30E-02	1.07 [0.9-0.97]	1.50E-03	1.08 [1.05-1.1]	6.16E-09	IL19	intergenic
Meta-analysis	rs10910476	1	234734956	C	0.45	1.08 [0.88-0.98]	6.10E-03	1.07 [0.9-0.97]	2.00E-04	1.07 [1.05-1.1]	4.68E-09	IRF2BP2	intergenic
Meta-analysis	rs2891409	2	25017357	T	0.75	1.03 [0.97-1.1]	3.00E-01	1.05 [1-1.09]	4.00E-02	1.08 [1.05-1.11]	6.23E-09	CENPO	intronic
Meta-analysis	rs56159942	2	25242274	G	0.20	1.07 [0.88-1]	3.90E-02	1.05 [0.91-1]	4.30E-02	1.09 [1.06-1.12]	7.16E-09	DNAJC27-AS1	ncRNA_intronic
Meta-analysis	rs11677002	2	28614401	C	0.46	1.05 [1-1.11]	6.10E-02	1.07 [1.03-1.11]	7.30E-04	1.09 [1.06-1.11]	1.16E-12	AC104695.3	ncRNA_intronic
Meta-analysis	rs7605725	2	43641627	G	0.37	1.05 [1-1.11]	7.10E-02	1.04 [1-1.09]	3.90E-02	1.07 [1.05-1.1]	2.88E-08	THADA	intronic
Meta-analysis	rs55946629	2	43851246	C	0.12	1.12 [0.83-0.96]	3.70E-03	1.09 [0.87-0.97]	1.70E-03	1.12 [1.09-1.16]	5.95E-12	Y_RNA	intergenic
Meta-analysis	rs7608697	2	61204641	A	0.64	1.06 [0.89-0.99]	3.20E-02	1.09 [0.89-0.96]	2.80E-05	1.13 [1.1-1.16]	1.95E-24	PUS10	intronic
Meta-analysis	rs4671401	2	61473148	C	0.23	1.08 [1.02-1.15]	9.10E-03	1.07 [1.02-1.11]	2.70E-03	1.08 [1.05-1.11]	4.47E-09	USP34	intronic
Meta-analysis	rs13022757	2	102613546	C	0.55	1.03 [0.98-1.09]	2.00E-01	1.06 [1.02-1.1]	2.90E-03	1.07 [1.05-1.1]	1.29E-09	IL1R2	intronic
Meta-analysis	2:103065522_ag_a	2	103065522	AG	0.22	NA	NA	NA	NA	1.09 [1.06-1.12]	9.45E-10	IL18RAP	intronic
Meta-analysis	rs1468789	2	103092503	T	0.79	1.1 [1.04-1.17]	1.70E-03	1.11 [1.07-1.16]	8.00E-07	1.1 [1.07-1.13]	4.90E-13	SLC9A4	intronic
Meta-analysis	rs72837849	2	111989858	T	0.87	1.13 [0.81-0.96]	4.30E-03	1.12 [0.84-0.95]	2.00E-04	1.11 [1.07-1.15]	2.06E-08	MIR4435-1HG	ncRNA_intronic
Meta-analysis	rs6740847	2	182308352	G	0.46	1.08 [1.03-1.14]	2.80E-03	1.08 [1.04-1.12]	1.10E-04	1.09 [1.07-1.12]	1.18E-13	ITGA4	intergenic
Meta-analysis	2:187576378_at_a	2	187576378	AT	0.10	NA	NA	NA	NA	1.12 [1.08-1.16]	4.03E-09	FAM171B	intronic
Meta-analysis	rs10931830	2	199621633	C	0.36	1.07 [1.01-1.13]	1.60E-02	1.07 [1.03-1.11]	7.50E-04	1.08 [1.05-1.1]	1.08E-09	AC019330.1	ncRNA_intronic
Meta-analysis	rs1456536	2	199826222	C	0.28	1.08 [0.88-0.98]	1.00E-02	1.09 [0.88-0.96]	7.30E-05	1.08 [1.05-1.11]	1.40E-09	AC018717.1	ncRNA_intronic
Meta-analysis	rs62183956	2	219046122	T	0.50	1.06 [1.01-1.12]	2.50E-02	1.07 [1.03-1.11]	5.50E-04	1.08 [1.05-1.1]	2.40E-10	snoU13	intergenic
Meta-analysis	rs1811711	2	228670476	G	0.18	1.08 [1.01-1.16]	1.90E-02	1.09 [1.04-1.14]	4.00E-04	1.09 [1.06-1.13]	1.65E-08	AC073065.3	intergenic
Meta-analysis	rs10192579	2	234146302	T	0.61	1.02 [0.93-1.03]	4.00E-01	1.04 [0.92-1]	2.90E-02	1.1 [1.07-1.12]	1.73E-14	ATG16L1	intronic
Meta-analysis	rs7595856	2	234193274	G	0.17	1.06 [0.99-1.13]	9.70E-02	1.05 [1-1.1]	5.10E-02	1.1 [1.07-1.14]	2.14E-11	ATG16L1	intronic

Meta-analysis	rs34236350	2	241568326	C	0.18	1.13 [0.83-0.95]	5.80E-04	1.12 [0.85-0.94]	8.20E-06	1.13 [1.1-1.17]	2.60E-16	GPR35	intronic
Meta-analysis	rs6724516	2	241586810	G	0.28	1.11 [0.85-0.96]	6.30E-04	1.11 [0.86-0.94]	2.70E-06	1.1 [1.07-1.12]	5.69E-12	GPR35	intergenic
Meta-analysis	rs34638686	3	48682658	C	0.11	1.15 [0.8-0.95]	2.30E-03	1.11 [0.85-0.96]	1.40E-03	1.15 [1.11-1.19]	8.66E-13	CELSR3	intronic
Meta-analysis	rs1131095	3	49714225	T	0.68	1.14 [0.83-0.93]	1.10E-05	1.1 [0.87-0.94]	3.20E-06	1.15 [1.13-1.18]	6.23E-31	APEH	exonic
Meta-analysis	rs6762648	3	188400858	A	0.79	1.05 [0.99-1.12]	1.30E-01	1.06 [1.01-1.11]	1.10E-02	1.09 [1.06-1.12]	1.08E-08	LPP	intronic
Meta-analysis	4:123504329_at_a	4	123504329	AT	0.20	NA	NA	NA	NA	1.09 [1.06-1.12]	1.56E-08	IL21	intergenic
Meta-analysis	rs62324212	4	123560939	C	0.46	1.14 [0.83-0.93]	1.70E-06	1.1 [0.87-0.94]	5.50E-07	1.1 [1.07-1.12]	1.02E-14	IL21-AS1	ncRNA_intronic
Meta-analysis	rs7715399	5	10682230	T	0.60	1.1 [0.86-0.96]	8.00E-04	1.09 [0.88-0.95]	1.30E-05	1.08 [1.05-1.1]	2.18E-09	DAP	intronic
Meta-analysis	rs395157	5	38867732	C	0.48	1.04 [0.91-1.01]	1.00E-01	1.05 [0.92-0.99]	9.90E-03	1.07 [1.05-1.1]	4.54E-09	OSMR	intronic
Meta-analysis	rs1039653	5	40041437	T	0.62	1.1 [1.04-1.16]	9.20E-04	1.08 [1.04-1.12]	1.90E-04	1.07 [1.04-1.09]	1.98E-08	LINC00603	intergenic
Meta-analysis	rs4957256	5	40207142	T	0.77	1.1 [1.03-1.17]	3.30E-03	1.09 [1.04-1.15]	1.40E-04	1.11 [1.08-1.15]	4.64E-14	LINC00604	intergenic
Meta-analysis	rs351649	5	40217845	A	0.52	1.07 [0.89-0.98]	8.70E-03	1.07 [0.9-0.97]	1.80E-04	1.08 [1.05-1.1]	1.33E-10	LINC00604	intergenic
Meta-analysis	rs115419645	5	40323417	T	0.97	1.14 [1.02-1.28]	2.10E-02	1.2 [1.1-1.3]	1.30E-05	1.23 [1.16-1.29]	2.03E-13	AC108105.1	intergenic
Meta-analysis	rs6451494	5	40411291	T	0.59	1.11 [0.85-0.95]	8.80E-05	1.1 [0.88-0.95]	1.20E-06	1.16 [1.13-1.18]	4.15E-34	AC108105.1	intergenic
Meta-analysis	rs56309786	5	40433227	C	0.14	1.14 [0.81-0.95]	8.00E-04	1.1 [0.86-0.96]	8.30E-04	1.19 [1.15-1.22]	2.45E-24	AC108105.1	intergenic
Meta-analysis	rs10076944	5	40496951	G	0.33	1.08 [0.87-0.98]	5.40E-03	1.08 [0.89-0.96]	1.20E-04	1.12 [1.09-1.15]	9.44E-20	SNORA63	intergenic
Meta-analysis	5:40936082_c_ct	5	40936082	C	0.06	NA	NA	NA	NA	1.14 [1.09-1.19]	2.34E-08	C7	intronic
Meta-analysis	rs4705885	5	130423559	G	0.32	1.1 [0.86-0.96]	9.80E-04	1.11 [0.87-0.94]	5.00E-07	1.11 [1.08-1.14]	9.41E-17	HINT1	intergenic
Meta-analysis	rs35260072	5	131630852	A	0.61	1.08 [0.88-0.97]	3.20E-03	1.1 [0.88-0.95]	1.60E-06	1.13 [1.1-1.16]	2.23E-25	P4HA2:SLC22A4	intronic
Meta-analysis	5:131737385_g_a	5	131737385	G	0.15	NA	NA	NA	NA	1.11 [1.07-1.14]	7.22E-11	SLC22A5	intergenic
Meta-analysis	rs77335401	5	131759825	C	0.13	1.08 [0.99-1.17]	6.90E-02	1.08 [1.02-1.14]	1.40E-02	1.12 [1.08-1.16]	1.97E-09	C5orf56:AC116366.5	ncRNA_intronic
Meta-analysis	rs17622517	5	131803537	T	0.93	1.16 [0.79-0.95]	2.90E-03	1.13 [0.82-0.95]	3.60E-04	1.14 [1.09-1.19]	2.59E-08	C5orf56	intronic
Meta-analysis	rs254559	5	134444982	C	0.41	1.11 [0.85-0.95]	1.10E-04	1.09 [0.88-0.95]	5.20E-06	1.07 [1.05-1.1]	3.67E-09	C5orf66	intronic

Meta-analysis	rs9637870	5	150227615	G	0.11	1.17 [0.77-0.94]	1.50E-03	1.14 [0.82-0.94]	2.80E-04	1.18 [1.13-1.23]	3.97E-15	IRGM	UTR5
Meta-analysis	rs11747112	5	158774609	G	0.16	1.03 [0.96-1.11]	4.70E-01	1.04 [0.99-1.1]	1.30E-01	1.1 [1.06-1.13]	1.31E-08	AC008697.1	ncRNA_exonic
Meta-analysis	rs10060969	5	158820061	T	0.66	1.09 [0.87-0.97]	2.60E-03	1.09 [0.88-0.95]	2.00E-05	1.12 [1.1-1.15]	1.43E-20	AC008697.1	intergenic
Meta-analysis	rs918521	5	158826247	A	0.84	1.04 [0.9-1.02]	1.90E-01	1.07 [0.89-0.98]	3.80E-03	1.11 [1.08-1.15]	7.03E-13	AC008697.1	intergenic
Meta-analysis	5:158827769_c_a	5	158827769	C	0.34	NA	NA	NA	NA	1.16 [1.13-1.19]	2.67E-32	AC008697.1	intergenic
Meta-analysis	rs62377655	5	158871681	A	0.92	1.14 [1.04-1.26]	6.80E-03	1.16 [1.08-1.25]	2.90E-05	1.21 [1.16-1.27]	2.63E-18	AC008703.1	intergenic
Meta-analysis	rs10051765	5	176799992	T	0.66	1.03 [0.92-1.03]	3.10E-01	1.05 [0.91-0.99]	1.40E-02	1.08 [1.05-1.1]	4.52E-09	RGS14	downstream
Meta-analysis	rs1267496	6	14716017	G	0.23	1.1 [0.85-0.97]	6.70E-03	1.09 [0.88-0.96]	4.30E-04	1.1 [1.07-1.14]	2.46E-11	RNU6-793P	intergenic
Meta-analysis	rs4712528	6	20678430	G	0.21	1.06 [0.89-1.01]	9.00E-02	1.07 [0.89-0.98]	2.60E-03	1.1 [1.07-1.13]	5.52E-11	CDKAL1	intronic
Meta-analysis	rs9466056	6	21384613	G	0.40	1.07 [1.01-1.12]	2.10E-02	1.07 [1.03-1.12]	2.40E-04	1.08 [1.06-1.11]	6.24E-11	RP1-135L22.1	intergenic
Meta-analysis	rs67289879	6	42007403	C	0.21	1.07 [0.87-1]	4.20E-02	1.09 [0.87-0.96]	2.00E-04	1.09 [1.06-1.13]	1.67E-09	CCND3	intronic
Meta-analysis	rs78727630	6	90985296	A	0.82	1.08 [1.01-1.16]	2.80E-02	1.08 [1.03-1.14]	2.40E-03	1.1 [1.06-1.13]	4.35E-08	BACH2	intronic
Meta-analysis	rs6568423	6	106442096	G	0.29	1.13 [0.84-0.94]	3.60E-05	1.07 [0.9-0.97]	1.10E-03	1.09 [1.07-1.12]	6.12E-12	RN7SKP211	intergenic
Meta-analysis	rs34659678	6	111888540	C	0.07	1.04 [0.86-1.08]	5.10E-01	1.14 [0.81-0.95]	1.60E-03	1.17 [1.11-1.23]	1.52E-10	TRAF3IP2-AS1:TRAF3IP2	ncRNA_intronic
Meta-analysis	rs6920220	6	138006504	G	0.17	1.14 [0.83-0.94]	5.40E-05	1.13 [0.84-0.92]	5.80E-08	1.1 [1.07-1.13]	1.52E-12	RP11-95M15.1	intergenic
Meta-analysis	rs6456143	6	167415440	C	0.45	1.06 [0.9-1]	3.20E-02	1.05 [0.92-0.99]	1.10E-02	1.09 [1.07-1.12]	1.29E-14	FGFR1OP:RP11-517H2.6	ncRNA_intronic
Meta-analysis	rs798502	7	2789880	C	0.28	1.09 [1.03-1.15]	4.20E-03	1.09 [1.04-1.13]	6.70E-05	1.08 [1.05-1.11]	2.76E-09	AMZ1:GNA12	intronic
Meta-analysis	7:20577298_g_a	7	20577298	A	0.92	NA	NA	NA	NA	1.13 [1.08-1.18]	3.12E-08	EEF1A1P27	intergenic
Meta-analysis	rs4917129	7	50323174	T	0.59	1.09 [0.87-0.96]	1.00E-03	1.1 [0.88-0.94]	9.20E-07	1.09 [1.07-1.12]	1.82E-13	AC020743.4	intergenic
Meta-analysis	rs6969140	7	98753900	A	0.71	1.06 [1-1.13]	4.90E-02	1.07 [1.02-1.11]	3.20E-03	1.08 [1.05-1.11]	7.96E-09	SMURF1	intergenic
Meta-analysis	7:107437615_c_a	7	107437615	A	0.52	NA	NA	NA	NA	1.08 [1.06-1.11]	1.03E-10	SLC26A3	intronic
Meta-analysis	rs4380874	7	107480315	C	0.41	1.1 [1.04-1.16]	6.00E-04	1.1 [1.05-1.14]	2.60E-06	1.1 [1.08-1.13]	8.85E-17	PIGCP2	intergenic

Meta-analysis	rs3757387	7	128576086	T	0.55	1.12 [0.84-0.94]	1.40E-05	1.12 [0.86-0.93]	1.10E-08	1.07 [1.04-1.09]	1.43E-08	IRF5	intergenic
Meta-analysis	7:148398271_taactta_t	7	148398271	T	0.59	NA	NA	NA	NA	1.08 [1.05-1.11]	3.07E-10	CUL1	intronic
Meta-analysis	rs4380956	8	126529074	G	0.37	1.05 [0.9-1.01]	8.60E-02	1.04 [0.93-1]	5.30E-02	1.08 [1.05-1.1]	5.59E-10	RP11-136O12.2	ncRNA_intronic
Meta-analysis	rs543379	9	265469	G	0.48	1.07 [1.02-1.13]	7.90E-03	1.08 [1.04-1.12]	1.30E-04	1.07 [1.04-1.09]	4.29E-08	DOCK8	intronic
Meta-analysis	rs7035464	9	4875652	A	0.75	1.12 [0.84-0.95]	4.20E-04	1.11 [0.86-0.94]	3.40E-06	1.08 [1.06-1.11]	3.83E-09	RCL1	intergenic
Meta-analysis	9:4984530_g_c	9	4984530	C	0.63	NA	NA	NA	NA	1.15 [1.13-1.18]	4.14E-32	JAK2	upstream
Meta-analysis	rs10114470	9	117547772	T	0.68	1.08 [0.88-0.98]	7.10E-03	1.1 [0.87-0.94]	2.10E-06	1.14 [1.11-1.17]	7.71E-25	TNFSF15	UTR3
Meta-analysis	rs7872350	9	117594017	C	0.13	1.08 [0.86-1]	6.10E-02	1.12 [0.84-0.94]	5.00E-05	1.14 [1.1-1.17]	1.24E-13	RP11-78H18.2	intergenic
Meta-analysis	rs3829110	9	139269198	A	0.61	1.13 [0.84-0.93]	2.50E-06	1.09 [0.88-0.95]	8.90E-06	1.14 [1.12-1.17]	1.87E-30	SNAPC4	downstream
Meta-analysis	rs7870145	9	139401565	G	0.12	1.19 [1.1-1.29]	3.60E-05	1.1 [1.04-1.17]	1.50E-03	1.15 [1.11-1.19]	3.08E-13	NOTCH1	intronic
Meta-analysis	rs12722489	10	6102012	T	0.86	1.06 [0.99-1.13]	1.20E-01	1.1 [1.04-1.15]	3.90E-04	1.1 [1.06-1.13]	1.16E-08	IL2RA	intronic
Meta-analysis	rs2480277	10	30703513	A	0.60	1.11 [0.86-0.95]	2.00E-04	1.07 [0.9-0.98]	1.20E-03	1.09 [1.06-1.11]	7.03E-12	RP11-449I17.5	intergenic
Meta-analysis	10:35355402_at_a	10	35355402	A	0.64	NA	NA	NA	NA	1.09 [1.07-1.12]	5.15E-13	CUL2	intronic
Meta-analysis	rs2393902	10	64369001	T	0.66	1.08 [0.87-0.98]	6.70E-03	1.07 [0.9-0.97]	1.30E-03	1.07 [1.05-1.1]	2.82E-08	ZNF365	intronic
Meta-analysis	rs79829650	10	64380124	T	0.89	1.2 [1.09-1.32]	1.30E-04	1.17 [1.09-1.25]	7.20E-06	1.17 [1.12-1.21]	2.98E-13	ZNF365	intronic
Meta-analysis	rs10761659	10	64445564	A	0.50	1.13 [0.84-0.93]	5.10E-06	1.12 [0.86-0.93]	2.50E-09	1.15 [1.13-1.18]	2.98E-34	ZNF365	intergenic
Meta-analysis	rs224136	10	64470675	T	0.82	1.06 [0.99-1.14]	1.10E-01	1.07 [1.02-1.13]	1.10E-02	1.12 [1.08-1.16]	6.33E-12	ALDH7A1P4	intergenic
Meta-analysis	rs10822056	10	64514111	T	0.51	1.05 [1-1.11]	6.20E-02	1.04 [1-1.08]	3.80E-02	1.07 [1.04-1.09]	1.27E-08	ALDH7A1P4	intergenic
Meta-analysis	rs1250573	10	81042475	A	0.71	1.04 [0.98-1.1]	1.60E-01	1.04 [1-1.08]	5.40E-02	1.08 [1.05-1.11]	9.47E-10	ZMIZ1	intronic
Meta-analysis	10:82267945_c_a	10	82267945	A	0.81	NA	NA	NA	NA	1.11 [1.08-1.14]	2.40E-13	TSPAN14	intronic
Meta-analysis	rs11814780	10	90826390	A	0.92	1.2 [1.09-1.32]	2.60E-04	1.2 [1.12-1.29]	2.20E-07	1.14 [1.09-1.19]	1.76E-09	MIR4679-2	intergenic
Meta-analysis	rs6584282	10	101286495	G	0.49	1.15 [1.09-1.21]	9.10E-08	1.14 [1.09-1.18]	3.20E-11	1.15 [1.13-1.18]	2.45E-35	RP11-129J12.2	ncRNA_intronic
Meta-analysis	rs112679028	11	76293230	A	0.91	1.18 [0.77-0.92]	1.20E-04	1.13 [0.83-0.94]	1.10E-04	1.12 [1.08-1.16]	1.33E-08	RP11-672A2.7	intergenic

Meta-analysis	rs11236791	11	76295598	G	0.45	1.16 [0.82-0.91]	4.70E-08	1.13 [0.85-0.92]	4.30E-10	1.15 [1.12-1.18]	1.22E-32	RP11-672A2.7	intergenic
Meta-analysis	rs11564146	12	40754308	T	0.98	1.01 [0.81-1.24]	9.60E-01	1.04 [0.83-1.12]	6.30E-01	1.29 [1.19-1.39]	7.77E-10	LRRK2	intronic
Meta-analysis	rs7134599	12	68500075	G	0.37	1.1 [0.86-0.96]	4.60E-04	1.1 [0.88-0.95]	2.80E-06	1.13 [1.1-1.15]	6.45E-24	IFNG-AS1	ncRNA_intronic
Meta-analysis	12:68585235_g_a	12	68585235	G	0.47	NA	NA	NA	NA	1.08 [1.05-1.1]	3.94E-10	IFNG-AS1	ncRNA_intronic
Meta-analysis	rs315143	12	69792025	G	0.27	1.08 [1.02-1.15]	1.20E-02	1.09 [1.04-1.14]	1.10E-04	1.08 [1.05-1.11]	5.12E-09	RN7SL804P	intergenic
Meta-analysis	rs3897234	13	27542030	T	0.77	1.01 [0.94-1.07]	8.60E-01	1.06 [0.91-0.99]	1.60E-02	1.09 [1.06-1.12]	7.19E-10	RPS21P8	intergenic
Meta-analysis	13:40836270_c_t	13	40836270	C	0.04	NA	NA	NA	NA	1.21 [1.15-1.28]	5.17E-12	RNY3P9	intergenic
Meta-analysis	rs3764147	13	44457925	A	0.77	1.07 [0.88-0.99]	3.40E-02	1.06 [0.9-0.98]	8.60E-03	1.08 [1.05-1.11]	4.66E-08	LACC1	exonic
Meta-analysis	13:99770328_t_a	13	99770328	T	0.21	NA	NA	NA	NA	1.09 [1.06-1.12]	2.45E-08	DOCK9-AS2	intergenic
Meta-analysis	rs4902651	14	69272125	T	0.52	1.04 [0.99-1.1]	1.10E-01	1.05 [1.02-1.09]	5.90E-03	1.08 [1.05-1.1]	3.88E-10	ZFP36L1	intergenic
Meta-analysis	rs4462528	14	88426297	T	0.89	1.06 [0.86-1.03]	2.00E-01	1.09 [0.86-0.98]	8.40E-03	1.14 [1.1-1.18]	1.15E-11	GALC	intronic
Meta-analysis	rs2033785	15	67441866	G	0.23	1.09 [1.02-1.16]	7.30E-03	1.07 [1.02-1.12]	4.40E-03	1.09 [1.06-1.12]	5.59E-09	SMAD3	intronic
Meta-analysis	rs56375023	15	67448363	G	0.22	1.08 [0.87-0.98]	1.30E-02	1.08 [0.89-0.97]	9.50E-04	1.12 [1.1-1.16]	4.96E-18	SMAD3	intronic
Meta-analysis	rs1864239	15	80205354	A	0.98	NA	NA	NA	NA	3.81 [2.56-5.66]	4.28E-11	ST20-MTHFS:ST20	intronic
Meta-analysis	rs2021511	16	11344903	T	0.70	1.06 [1-1.13]	4.40E-02	1.07 [1.02-1.11]	2.30E-03	1.08 [1.05-1.11]	8.34E-09	RMI2	intronic
Meta-analysis	rs34835672	16	11700100	C	0.45	1.1 [0.87-0.96]	6.30E-04	1.08 [0.89-0.96]	2.20E-05	1.08 [1.05-1.1]	1.31E-09	LITAF	intronic
Meta-analysis	16:28489342_g_a	16	28489342	A	0.54	NA	NA	NA	NA	1.11 [1.08-1.13]	1.33E-15	CLN3:CLN3	intronic
Meta-analysis	16:28899411_c_t	16	28899411	T	0.63	NA	NA	NA	NA	1.07 [1.05-1.1]	4.05E-08	ATP2A1	intronic
Meta-analysis	rs13334400	16	50398483	C	0.48	1.07 [0.88-0.98]	7.90E-03	1.06 [0.91-0.98]	2.10E-03	1.08 [1.05-1.1]	5.47E-10	BRD7	intronic
Meta-analysis	rs9673419	16	50661273	A	0.78	1.06 [0.89-1]	5.10E-02	1.07 [0.9-0.98]	3.90E-03	1.1 [1.07-1.13]	9.35E-13	NKD1	intronic
Meta-analysis	rs113593463	16	50719743	G	0.01	1.38 [0.59-0.89]	1.90E-03	1.35 [0.64-0.86]	6.90E-05	1.44 [1.32-1.57]	1.46E-17	SNX20	intergenic
Meta-analysis	rs75489898	16	50723618	A	0.94	1.07 [0.96-1.2]	2.10E-01	1.08 [1-1.17]	6.40E-02	1.17 [1.11-1.23]	9.53E-09	NOD2	intergenic
Meta-analysis	rs2066844	16	50745926	C	0.05	1.32 [0.67-0.86]	9.50E-06	1.19 [0.77-0.91]	7.30E-05	1.35 [1.28-1.42]	3.90E-31	NOD2	exonic

Meta-analysis	16:50763778_gc_g	16	50763778	G	0.99	NA	NA	NA	NA	1.81 [1.66-1.97]	2.58E-42	NOD2	exonic
Meta-analysis	rs2160683	16	50829853	T	0.44	1.06 [1.01-1.12]	2.30E-02	1.05 [1.01-1.09]	7.10E-03	1.11 [1.08-1.13]	1.83E-17	CYLD:RP11-327F22.4	ncRNA_intronic
Meta-analysis	rs67921626	16	50898377	T	0.96	1.12 [0.77-1.04]	1.40E-01	1.11 [0.81-1.01]	7.00E-02	1.24 [1.16-1.32]	1.84E-11	CTD-2034I21.1	ncRNA_intronic
Meta-analysis	16:50926947_gc_g	16	50926947	GC	0.02	NA	NA	NA	NA	1.25 [1.16-1.35]	1.21E-09	RP11-883G14.1	ncRNA_intronic
Meta-analysis	rs55709012	16	51002618	A	0.95	1.04 [0.84-1.09]	5.00E-01	1.11 [0.82-0.99]	2.20E-02	1.17 [1.11-1.24]	3.41E-08	RP11-883G14.2	intergenic
Meta-analysis	rs78299226	16	51029186	C	0.05	1.15 [0.78-0.97]	1.50E-02	1.13 [0.82-0.96]	4.20E-03	1.16 [1.1-1.21]	1.49E-08	RP11-883G14.2	intergenic
Meta-analysis	rs11548656	16	81916912	G	0.04	1.13 [0.99-1.3]	7.80E-02	1.12 [1.02-1.24]	2.20E-02	1.21 [1.14-1.29]	3.71E-09	PLCG2	exonic
Meta-analysis	rs16940186	16	86009740	T	0.83	1.11 [0.84-0.97]	5.80E-03	1.09 [0.87-0.97]	2.30E-03	1.11 [1.07-1.14]	1.76E-10	RP11-542M13.2	intergenic
Meta-analysis	16:86017663_g_a	16	86017663	A	0.78	NA	NA	NA	NA	1.09 [1.05-1.12]	1.40E-08	RP11-542M13.2	ncRNA_intronic
Meta-analysis	17:7007622_g_a	17	7007622	A	0.91	NA	NA	NA	NA	1.15 [1.09-1.2]	4.12E-08	ASGR2	intronic
Meta-analysis	17:32582997_acagctcctccttct_a	17	32582997	A	0.68	NA	NA	NA	NA	1.1 [1.07-1.13]	9.00E-13	CCL2	intronic
Meta-analysis	rs41338755	17	32688713	A	0.96	1.1 [0.97-1.25]	1.30E-01	1.16 [1.06-1.26]	1.70E-03	1.19 [1.12-1.27]	2.81E-08	CCL1	intronic
Meta-analysis	rs12936409	17	38043649	C	0.47	1.1 [0.86-0.96]	2.80E-04	1.08 [0.89-0.96]	7.50E-05	1.13 [1.1-1.15]	5.78E-25	ZPBP2	intergenic
Meta-analysis	rs730086	17	40271757	A	0.67	1.06 [1-1.12]	6.30E-02	1.05 [1.01-1.09]	1.60E-02	1.08 [1.05-1.1]	1.11E-08	KAT2A:CTD-2132N18.3	intronic
Meta-analysis	rs3736162	17	40497839	C	0.72	1.09 [1.03-1.16]	3.70E-03	1.09 [1.04-1.13]	1.10E-04	1.11 [1.09-1.14]	3.59E-16	STAT3	intronic
Meta-analysis	rs56143576	17	40644674	A	0.85	1.12 [0.83-0.96]	1.80E-03	1.09 [0.87-0.97]	1.00E-03	1.11 [1.07-1.14]	1.62E-10	ATP6V0A1	intronic
Meta-analysis	17:70611194_c_cg	17	70611194	CG	0.86	NA	NA	NA	NA	1.11 [1.07-1.15]	4.56E-10	LINC00511	ncRNA_intronic
Meta-analysis	rs80262450	18	12818922	G	0.09	1.11 [0.83-0.98]	1.10E-02	1.12 [0.84-0.94]	7.00E-05	1.16 [1.12-1.2]	4.13E-16	PTPN2	intronic
Meta-analysis	rs2024092	19	1124031	G	0.20	1.08 [0.87-0.99]	1.70E-02	1.11 [0.86-0.95]	1.50E-05	1.13 [1.1-1.16]	4.26E-17	SBNO2	intronic
Meta-analysis	rs72977586	19	1186316	G	0.12	1.11 [0.84-0.97]	6.30E-03	1.08 [0.88-0.98]	5.10E-03	1.1 [1.06-1.14]	2.12E-08	STK11	intergenic
Meta-analysis	19:1189173_gt_g	19	1189173	GT	0.17	NA	NA	NA	NA	1.1 [1.07-1.14]	6.40E-09	STK11	intergenic

Meta-analysis	rs12720356	19	10469975	A	0.91	1.18 [0.78-0.92]	2.10E-04	1.15 [0.82-0.93]	1.20E-05	1.16 [1.12-1.21]	1.68E-14	TYK2	exonic
Meta-analysis	rs144309607	19	10492274	T	0.97	1.2 [1.06-1.36]	3.70E-03	1.2 [1.1-1.31]	6.30E-05	1.25 [1.17-1.33]	2.39E-12	TYK2	upstream
Meta-analysis	rs62131887	19	10587596	T	0.76	1.11 [1.04-1.17]	6.50E-04	1.08 [1.03-1.13]	3.60E-04	1.09 [1.06-1.12]	1.91E-10	PDE4A	intergenic
Meta-analysis	rs10408351	19	33754044	G	0.22	1.06 [0.88-1]	5.40E-02	1.1 [0.87-0.95]	6.20E-05	1.13 [1.09-1.16]	2.70E-16	CTD-2540B15.12	intergenic
Meta-analysis	rs12609705	19	33756284	C	0.77	1.08 [1.02-1.15]	1.20E-02	1.09 [1.05-1.14]	6.20E-05	1.1 [1.07-1.13]	3.31E-12	CTD-2540B15.12	intergenic
Meta-analysis	rs6017342	20	43065028	A	0.52	1.17 [0.81-0.9]	4.90E-09	1.15 [0.83-0.9]	7.70E-14	1.13 [1.11-1.16]	1.76E-24	RP5-1013A22.5	intergenic
Meta-analysis	rs4811031	20	48956954	G	0.40	1.08 [1.03-1.15]	4.00E-03	1.06 [1.02-1.11]	2.50E-03	1.07 [1.05-1.1]	2.51E-08	RP11-290F20.2	intergenic
Meta-analysis	rs4812068	20	57843903	C	0.33	1.12 [1.06-1.18]	1.20E-04	1.08 [1.04-1.12]	2.30E-04	1.08 [1.06-1.11]	1.51E-10	ZNF831	intergenic
Meta-analysis	rs310669	20	62212154	G	0.35	1.05 [0.9-1.01]	1.10E-01	1.06 [0.91-0.98]	2.80E-03	1.08 [1.06-1.11]	1.20E-10	HELZ2	intergenic
Meta-analysis	rs6089956	20	62308364	A	0.87	1.08 [1.01-1.16]	2.70E-02	1.11 [1.05-1.16]	1.50E-04	1.13 [1.09-1.17]	5.48E-12	RTEL1:RTEL1-TNFRSF6B	intronic
Meta-analysis	rs55765053	20	62328480	C	0.08	1.18 [0.77-0.94]	1.70E-03	1.13 [0.82-0.95]	7.80E-04	1.16 [1.1-1.22]	8.67E-09	RTEL1-TNFRSF6B:TNFRSF6B	exonic
Meta-analysis	rs6062496	20	62329099	G	0.40	1.09 [0.87-0.97]	2.10E-03	1.07 [0.9-0.97]	3.60E-04	1.12 [1.09-1.15]	1.24E-21	RTEL1-TNFRSF6B:TNFRSF6B	intronic
Meta-analysis	rs1297271	21	16823163	T	0.56	1.1 [1.05-1.16]	3.10E-04	1.12 [1.08-1.16]	1.00E-08	1.14 [1.12-1.17]	3.18E-30	CYCSP42	intergenic
Meta-analysis	rs992242	21	40252033	C	0.36	1.05 [0.9-1]	7.30E-02	1.07 [0.9-0.97]	7.50E-04	1.07 [1.04-1.09]	3.46E-08	AF064858.6	ncRNA_exonic
Meta-analysis	rs4817986	21	40465512	T	0.74	1.21 [1.14-1.29]	1.40E-10	1.23 [1.18-1.28]	1.20E-21	1.2 [1.16-1.23]	2.36E-40	RPL23AP12	intergenic
Meta-analysis	rs12627242	21	40467879	C	0.15	1.09 [0.85-0.99]	2.70E-02	1.1 [0.86-0.96]	4.10E-04	1.12 [1.09-1.16]	7.80E-12	RPL23AP12	intergenic
Meta-analysis	21:40476413_c_t	21	40476413	C	0.23	NA	NA	NA	NA	1.1 [1.07-1.13]	6.69E-10	RPL23AP12	intergenic
Meta-analysis	rs2838517	21	45613825	C	0.38	1.15 [1.09-1.21]	4.60E-07	1.11 [1.07-1.15]	1.10E-07	1.13 [1.1-1.15]	1.76E-24	AP001057.1	intergenic
Meta-analysis	rs5754467	22	21985094	A	0.80	1.13 [0.83-0.95]	4.70E-04	1.08 [0.89-0.97]	2.70E-03	1.11 [1.08-1.14]	1.36E-12	YDJC	upstream

Meta-analysis	rs1978083	22	30570443	C	0.73	1.07 [0.88-0.99]	2.90E-02	1.05 [0.91-0.99]	2.10E-02	1.08 [1.05-1.11]	9.65E-09	HORMAD2	intronic
Meta-analysis	rs9611131	22	39662480	C	0.15	1.16 [1.08-1.25]	6.40E-05	1.14 [1.08-1.2]	2.10E-06	1.18 [1.14-1.22]	7.70E-23	AL031590.1	intergenic
Meta-analysis	rs5757584	22	39662550	C	0.17	1.09 [0.85-0.98]	1.10E-02	1.11 [0.86-0.95]	2.90E-05	1.14 [1.11-1.18]	1.35E-17	AL031590.1	intergenic

Table x4.4.a Lead SNPs for multiple sclerosis identified from UKBB GWAS (female-only) results

GWAS Analysis	SNP	CHR	BP	EA	EAF	UKBB female-only GWAS		UKBB sex-combined GWAS		Meta-Analysis sex-combined GWAS		Gene	Function
						OR [95% CI]	P-value	OR [95% CI]	P-value	OR [95% CI]	P-value		
Female-only	rs143065259	13	19811782	T	0.99	2.71 [1.9-3.86]	3.70E-08	2.19 [1.63-2.96]	2.70E-07	NA	NA	PSPC1P1	intergenic

Table x4.4.b Lead SNPs for multiple sclerosis identified from UKBB GWAS (sex-combined) results

GWAS Analysis	SNP	CHR	BP	EA	EAF	UKBB female-only GWAS		UKBB sex-combined GWAS		Meta-Analysis sex-combined GWAS		Gene	Function
						OR [95% CI]	P-value	OR [95% CI]	P-value	OR [95% CI]	P-value		
Sex-combined	rs7341635	8	1721643	A	0.68	1.22 [1.12-1.33]	3.80E-06	1.23 [1.15-1.33]	9.60E-09	1.06 [1.03-1.10]	3.70E-04	CLN8	intronic
Sex-combined	15:60909858_CAGAG_C	15	60909858	C	0.93	1.45 [1.23-1.72]	1.10E-05	1.5 [1.3-1.72]	1.70E-08	NA	NA	RP11-219B17.1:RORA	ncRNA_intronic

Table x4.4.c Lead SNPs for multiple sclerosis identified from meta-analysis GWAS (sex-combined) results

GWAS Analysis	SNP	CHR	BP	EA	EAF	UKBB female-only GWAS		UKBB sex-combined GWAS		Meta-Analysis sex-combined GWAS		Gene	Function
						OR [95%CI]	P-value	OR [95%CI]	P-value	OR [95%CI]	P-value		
Meta-analysis	rs10914539	1	32715641	T	0.18	1.15 [1.09-1.2]	1.35E-08	1.12 [1.03-1.21]	5.60E-03	1.1 [1.03-1.18]	5.20E-03	FAM167B	intergenic
Meta-analysis	rs12743302	1	85714805	T	0.09	1.15 [1.09-1.21]	2.64E-08	1.14 [1.03-1.26]	1.00E-02	1.15 [1.06-1.25]	7.10E-04	C1orf52	intergenic
Meta-analysis	rs11809700	1	93152635	T	0.29	1.15 [1.12-1.2]	4.94E-16	1.18 [1.04-1.34]	9.20E-03	1.23 [1.1-1.37]	1.50E-04	EVI5	intronic
Meta-analysis	rs483180	1	120267505	C	0.32	1.11 [1.07-1.14]	4.16E-09	1.09 [0.96-1.23]	1.90E-01	1.08 [0.98-1.2]	1.30E-01	PHGDH	intronic
Meta-analysis	rs17676381	1	157681898	T	0.20	1.14 [1.09-1.19]	2.55E-09	1.16 [1.07-1.26]	2.00E-04	1.15 [1.07-1.23]	5.00E-05	RP11-367J7.4	intergenic
Meta-analysis	rs1323292	1	192541021	A	0.18	1.14 [1.1-1.19]	1.38E-10	1.18 [1.06-1.3]	1.50E-03	1.17 [1.08-1.28]	2.50E-04	RGS1	intergenic
Meta-analysis	rs7588193	2	43360947	A	0.25	1.12 [1.08-1.16]	1.20E-09	1.15 [1.06-1.26]	1.40E-03	1.15 [1.07-1.24]	1.70E-04	AC093609.1	intergenic
Meta-analysis	rs2371108	3	27757018	T	0.40	1.12 [1.09-1.16]	1.73E-12	1.2 [1.03-1.39]	1.60E-02	1.21 [1.07-1.36]	2.90E-03	EOMES	downstream

Meta-analysis	rs4683959	3	101748902	T	0.35	1.1 [1.07-1.14]	3.23E-09	1.1 [1.02-1.19]	1.20E-02	1.07 [1.01-1.15]	3.30E-02	RP11-221J22.1:RP11-221J22.2	intergenic
Meta-analysis	rs11749040	5	40396425	A	0.14	1.21 [1.15-1.26]	1.06E-16	1.23 [1.09-1.39]	5.70E-04	1.26 [1.14-1.39]	8.70E-06	AC108105.1	intergenic
Meta-analysis	rs1992661	5	40414989	A	0.41	1.14 [1.1-1.17]	5.83E-14	1.07 [0.98-1.16]	1.20E-01	1.08 [1.01-1.16]	3.30E-02	AC108105.1	intergenic
Meta-analysis	rs2546890	5	158759900	A	0.49	1.12 [1.08-1.15]	1.12E-12	1.08 [0.98-1.2]	1.30E-01	1.12 [1.03-1.22]	8.00E-03	AC008697.1	ncRNA_exonic
Meta-analysis	rs3757247	6	90957463	T	0.49	1.09 [1.06-1.13]	1.00E-08	1.19 [1.08-1.31]	6.10E-04	1.18 [1.09-1.29]	8.30E-05	BACH2	intronic
Meta-analysis	rs6903449	6	135492408	A	0.23	1.13 [1.08-1.17]	3.13E-09	1.2 [1.11-1.31]	1.40E-05	1.15 [1.07-1.23]	1.50E-04	MYB	intergenic
Meta-analysis	rs212409	6	159470058	A	0.44	1.11 [1.07-1.14]	1.05E-10	1.07 [0.98-1.17]	1.20E-01	1.09 [1.01-1.17]	3.20E-02	RP1-111C20.4	ncRNA_intronic
Meta-analysis	rs67256453	7	149314756	T	0.26	1.11 [1.07-1.15]	1.57E-08	1.05 [0.97-1.13]	2.10E-01	1.11 [1.04-1.19]	1.50E-03	ZNF767	ncRNA_intronic
Meta-analysis	rs1483573	8	79623617	A	0.29	1.1 [1.07-1.14]	2.12E-08	1.1 [1.02-1.19]	1.60E-02	1.14 [1.07-1.22]	1.00E-04	ZC2HC1A:IL7	intronic
Meta-analysis	rs3134883	10	6100725	A	0.29	1.11 [1.08-1.15]	1.65E-10	1.02 [0.93-1.12]	7.10E-01	1.07 [0.99-1.15]	1.10E-01	IL2RA	intronic
Meta-analysis	rs1250565	10	81047015	A	0.33	1.12 [1.09-1.16]	2.67E-12	1.09 [1-1.19]	6.30E-02	1.03 [0.96-1.12]	4.10E-01	ZMIZ1	intronic
Meta-analysis	rs1112718	10	94479107	A	0.39	1.12 [1.08-1.15]	4.98E-12	1.16 [1.07-1.25]	2.30E-04	1.13 [1.06-1.21]	2.10E-04	Y_RNA	intergenic
Meta-analysis	rs175120	11	60829495	T	0.38	1.12 [1.08-1.16]	1.04E-11	1.15 [1.07-1.25]	2.80E-04	1.16 [1.09-1.24]	4.10E-06	RP11-881M11.8	ncRNA_intronic
Meta-analysis	rs7977720	12	9866349	T	0.47	1.09 [1.06-1.13]	1.30E-08	1.07 [0.99-1.16]	9.40E-02	1.08 [1.01-1.16]	2.00E-02	CLECL1	intergenic
Meta-analysis	rs1633360	12	58108052	T	0.40	1.1 [1.07-1.14]	1.97E-09	1.07 [0.97-1.18]	1.80E-01	1.06 [0.98-1.15]	1.50E-01	OS9:RP11-571M6.7	ncRNA_intronic
Meta-analysis	rs7975763	12	123604053	T	0.22	1.13 [1.08-1.17]	1.74E-09	1.16 [1.07-1.25]	3.10E-04	1.14 [1.06-1.21]	2.20E-04	PITPNM2	intronic
Meta-analysis	rs1706477	12	123913697	T	0.44	1.12 [1.07-1.16]	3.54E-08	1.07 [0.99-1.16]	8.20E-02	1.11 [1.04-1.18]	2.10E-03	RILPL2	intronic
Meta-analysis	rs9591325	13	50811220	T	0.05	1.22 [1.15-1.3]	3.42E-10	1.19 [1.04-1.37]	1.20E-02	1.16 [1.03-1.3]	1.40E-02	DLEU1	NA
Meta-analysis	rs12434551	14	69253364	A	0.47	1.12 [1.09-1.16]	7.04E-14	1.05 [0.97-1.14]	2.10E-01	1.07 [1-1.14]	5.80E-02	ZFP36L1	intergenic

Meta-analysis	rs408667	14	88417821	A	0.48	1.1 [1.06-1.13]	2.05E-09	1.06 [0.98-1.16]	1.60E-01	1.05 [0.98-1.13]	1.80E-01	GALC	intronic
Meta-analysis	rs2432301	16	1073028	T	0.20	1.13 [1.09-1.18]	1.10E-09	1.18 [1.05-1.32]	4.80E-03	1.16 [1.05-1.27]	2.80E-03	RP11-161M6.3	intergenic
Meta-analysis	rs12932240	16	11020831	A	0.27	1.11 [1.07-1.16]	1.00E-08	1.1 [1.02-1.19]	1.60E-02	1.11 [1.03-1.18]	2.90E-03	CIITA	UTR3
Meta-analysis	rs8051340	16	11041413	C	0.14	1.16 [1.1-1.22]	3.96E-08	1.07 [0.99-1.16]	8.00E-02	1.1 [1.03-1.17]	5.30E-03	CLEC16A	intronic
Meta-analysis	rs7200786	16	11177801	A	0.49	1.18 [1.14-1.22]	7.30E-26	1.09 [1-1.19]	5.80E-02	1.09 [1.01-1.17]	2.80E-02	CLEC16A	intronic
Meta-analysis	rs117714844	16	11221596	T	0.10	1.52 [1.38-1.67]	1.78E-17	1.06 [0.97-1.16]	1.80E-01	1.09 [1.01-1.17]	2.70E-02	CLEC16A	intronic
Meta-analysis	rs243329	16	11352313	A	0.48	1.11 [1.08-1.14]	4.04E-11	1.14 [1.04-1.24]	3.10E-03	1.11 [1.04-1.19]	3.30E-03	RMI2	intronic
Meta-analysis	rs1026916	17	40529835	A	0.37	1.14 [1.1-1.17]	1.74E-14	1.07 [0.99-1.16]	9.20E-02	1.08 [1.01-1.15]	2.70E-02	STAT3	intronic
Meta-analysis	rs2777899	17	57832391	T	0.46	1.11 [1.08-1.14]	3.49E-11	1.04 [0.96-1.13]	3.20E-01	1.08 [1.01-1.16]	2.40E-02	VMP1	intronic
Meta-analysis	rs28834106	19	10592144	T	0.24	1.12 [1.08-1.16]	3.24E-09	1.14 [1.03-1.26]	8.90E-03	1.14 [1.05-1.23]	2.40E-03	KEAP1	intergenic
Meta-analysis	rs62120363	19	18297608	A	0.28	1.12 [1.08-1.16]	8.98E-11	1.06 [0.97-1.15]	2.20E-01	1.09 [1.01-1.17]	2.80E-02	MPV17L2	intergenic
Meta-analysis	rs1465697	19	49837246	T	0.24	1.12 [1.08-1.16]	4.77E-10	1.12 [1.04-1.21]	4.60E-03	1.14 [1.06-1.22]	1.70E-04	CTC-301O7.4	ncRNA_intronic
Meta-analysis	rs2248137	20	52789743	C	0.40	1.11 [1.08-1.15]	9.83E-11	1.16 [1.07-1.26]	1.80E-04	1.14 [1.06-1.21]	1.30E-04	CYP24A1	intronic
Meta-analysis	rs9610458	22	22205353	T	0.46	1.11 [1.08-1.14]	5.49E-11	1.15 [1.06-1.25]	7.40E-04	1.12 [1.04-1.19]	1.70E-03	MAPK1	intronic
Meta-analysis	rs361725	22	50971047	T	0.36	1.11 [1.07-1.15]	3.32E-10	1.12 [1.04-1.21]	3.90E-03	1.09 [1.02-1.17]	8.10E-03	ODF3B	upstream
Meta-analysis	rs10797431	1	2501222	G	0.66	1.14 [1.11-1.18]	1.07E-15	1.07 [0.99-1.16]	7.80E-02	1.08 [1.01-1.15]	3.00E-02	RP3-395M20.7	ncRNA_exonic
Meta-analysis	rs12408934	1	65423447	G	0.91	1.17 [1.1-1.23]	4.88E-08	1.07 [0.96-1.18]	2.20E-01	1.11 [1.02-1.21]	1.90E-02	JAK1	intronic
Meta-analysis	rs10873698	1	85756250	G	0.62	1.11 [1.08-1.15]	2.93E-11	1.15 [0.92-1.43]	2.30E-01	1.26 [1.04-1.52]	1.70E-02	RP11-131L23.1	ncRNA_intronic
Meta-analysis	rs12133753	1	92222089	C	0.85	1.14 [1.1-1.19]	3.50E-10	1.07 [0.99-1.16]	7.50E-02	1.1 [1.03-1.17]	6.20E-03	TGFBR3	intronic
Meta-analysis	rs139244879	1	93226096	C	0.93	1.23 [1.15-1.32]	5.75E-09	1.01 [0.94-1.1]	7.20E-01	1.04 [0.97-1.11]	2.50E-01	EVI5	intronic

Meta-analysis	rs12047382	1	101319255	T	0.57	1.12 [1.09-1.16]	2.76E-13	1.05 [0.97-1.13]	2.60E-01	1.04 [0.97-1.11]	2.80E-01	EXTL2	intergenic
Meta-analysis	rs4143029	1	117048330	C	0.86	1.25 [1.19-1.31]	4.82E-18	1.1 [1-1.21]	5.30E-02	1.13 [1.04-1.22]	4.00E-03	RP5-1086K13.1	intergenic
Meta-analysis	rs296546	1	200891091	C	0.71	1.13 [1.09-1.17]	1.77E-12	1.1 [1.02-1.19]	1.30E-02	1.12 [1.05-1.19]	9.80E-04	MROH3P	ncRNA_intronic
Meta-analysis	rs2420518	2	61054980	C	0.56	1.1 [1.07-1.13]	3.76E-09	1.22 [1.05-1.42]	1.10E-02	1.19 [1.04-1.35]	9.60E-03	AC010733.4	ncRNA_intronic
Meta-analysis	rs7562347	2	61209875	G	0.57	1.1 [1.07-1.14]	1.19E-09	1.12 [1.04-1.21]	4.50E-03	1.18 [1.11-1.26]	5.90E-07	PUS10	intronic
Meta-analysis	rs57116599	2	112770799	G	0.76	1.11 [1.07-1.16]	2.09E-08	1.13 [1.04-1.22]	2.50E-03	1.12 [1.05-1.19]	9.20E-04	MERTK	intronic
Meta-analysis	rs35540610	2	231121829	C	0.79	1.12 [1.08-1.16]	1.08E-09	1.14 [0.95-1.37]	1.70E-01	1.22 [1.05-1.43]	1.00E-02	SP140	intronic
Meta-analysis	rs432888	3	28072443	C	0.51	1.15 [1.12-1.19]	4.50E-19	1.06 [0.98-1.15]	1.40E-01	1.06 [1-1.14]	6.20E-02	AC092415.1	intergenic
Meta-analysis	rs1131265	3	119222456	G	0.84	1.12 [1.08-1.17]	8.67E-09	1.21 [1.09-1.33]	2.00E-04	1.2 [1.1-1.3]	2.60E-05	TIMMDC1	exonic
Meta-analysis	rs4676756	3	121532639	G	0.61	1.11 [1.08-1.15]	7.12E-11	1.09 [1-1.19]	6.10E-02	1.06 [0.98-1.14]	1.20E-01	IQCB1	intronic
Meta-analysis	rs2255214	3	121770539	G	0.51	1.12 [1.09-1.16]	1.66E-13	1.1 [0.97-1.23]	1.30E-01	1.09 [0.98-1.2]	9.90E-02	CD86	intergenic
Meta-analysis	rs9282641	3	121796768	G	0.91	1.21 [1.15-1.29]	2.27E-11	1.13 [1.04-1.22]	2.60E-03	1.18 [1.1-1.26]	7.40E-07	CD86	UTR5
Meta-analysis	rs1014486	3	159691112	C	0.54	1.1 [1.07-1.14]	7.92E-10	1.25 [1.09-1.45]	1.90E-03	1.24 [1.1-1.4]	5.20E-04	IL12A-AS1	ncRNA_intronic
Meta-analysis	rs6881270	5	35879095	C	0.73	1.1 [1.07-1.14]	2.42E-08	1.09 [1.01-1.18]	2.30E-02	1.07 [1-1.14]	4.00E-02	IL7R	UTR3
Meta-analysis	rs9647635	6	135841056	C	0.64	1.14 [1.1-1.17]	2.27E-15	1.07 [0.99-1.16]	8.00E-02	1.11 [1.04-1.18]	2.30E-03	LINC00271	ncRNA_intronic
Meta-analysis	rs276554	6	137410516	G	0.80	1.14 [1.1-1.19]	2.18E-11	1.12 [1.04-1.21]	3.30E-03	1.11 [1.04-1.18]	2.70E-03	IL20RA	intergenic
Meta-analysis	rs498549	6	137984935	G	0.57	1.12 [1.08-1.15]	4.03E-12	1.08 [1-1.17]	5.60E-02	1.13 [1.05-1.21]	5.90E-04	RP11-95M15.1	intergenic
Meta-analysis	rs6990534	8	128814091	G	0.67	1.11 [1.08-1.15]	7.50E-10	1.08 [1-1.17]	5.10E-02	1.06 [0.99-1.13]	1.00E-01	PVT1	ncRNA_intronic
Meta-analysis	rs12253981	10	6092346	G	0.59	1.11 [1.08-1.15]	9.86E-11	1.14 [1.06-1.24]	6.00E-04	1.13 [1.06-1.21]	1.90E-04	IL2RA	intronic
Meta-analysis	rs41295055	10	6111622	C	0.84	1.21 [1.16-1.26]	9.94E-20	1.1 [1.01-1.21]	3.60E-02	1.09 [1.01-1.17]	3.60E-02	RP11-414H17.2	intergenic

Meta-analysis	rs35335304	10	6187416	G	0.67	1.12 [1.08-1.17]	4.88E-08	1.13 [1.02-1.25]	2.20E-02	1.07 [0.98-1.16]	1.50E-01	PFKFB3	intronic
Meta-analysis	rs2269434	11	47360412	C	0.65	1.1 [1.06-1.13]	2.98E-08	1.01 [0.93-1.11]	7.40E-01	1.05 [0.97-1.12]	2.30E-01	MYBPC3	intronic
Meta-analysis	rs4939490	11	60793651	G	0.59	1.13 [1.1-1.17]	2.13E-14	1.02 [0.94-1.11]	5.90E-01	1.05 [0.98-1.13]	1.90E-01	CD6	intergenic
Meta-analysis	rs12365699	11	118743286	G	0.84	1.14 [1.1-1.19]	4.93E-10	1.03 [0.94-1.13]	5.10E-01	1.07 [0.99-1.15]	7.50E-02	CXCR5	intergenic
Meta-analysis	rs77841686	11	118762073	G	0.98	1.33 [1.21-1.46]	6.33E-09	1.1 [1-1.2]	4.10E-02	1.1 [1.02-1.18]	1.60E-02	CXCR5	intronic
Meta-analysis	rs1800693	12	6440009	C	0.57	1.13 [1.09-1.16]	1.78E-13	1.05 [0.97-1.14]	1.90E-01	1.09 [1.02-1.16]	1.20E-02	TNFRSF1A	intronic
Meta-analysis	rs117822168	14	88504511	G	0.95	1.33 [1.23-1.45]	1.24E-11	1.04 [0.97-1.13]	2.80E-01	1.07 [1-1.14]	5.20E-02	LINC01146	ncRNA_intronic
Meta-analysis	rs9989163	14	103235012	G	0.54	1.1 [1.06-1.13]	1.70E-08	1.06 [0.98-1.14]	1.80E-01	1.09 [1.02-1.16]	1.30E-02	RP11-661D19.3	intergenic
Meta-analysis	rs3809627	16	30103160	C	0.58	1.1 [1.07-1.14]	3.19E-09	1.1 [1.02-1.19]	1.50E-02	1.09 [1.02-1.16]	1.10E-02	TBX6	UTR5
Meta-analysis	rs12925972	16	79111297	C	0.53	1.1 [1.07-1.14]	3.35E-09	1.14 [1.03-1.25]	9.10E-03	1.11 [1.03-1.21]	9.50E-03	WWOX:RP11-556H2.4	ncRNA_exonic
Meta-analysis	rs12943464	17	45690351	T	0.53	1.1 [1.07-1.13]	7.56E-10	1.17 [1.08-1.27]	8.40E-05	1.16 [1.08-1.24]	2.20E-05	NPEPPS:RP11-580I16.2	ncRNA_intronic
Meta-analysis	rs12962126	18	56351448	G	0.79	1.11 [1.07-1.15]	3.27E-08	1.06 [0.96-1.16]	2.70E-01	1.07 [0.98-1.16]	1.10E-01	MALT1:RP11-126O1.4	ncRNA_intronic
Meta-analysis	rs12461821	19	6671369	G	0.80	1.15 [1.1-1.2]	1.41E-10	1.08 [1-1.17]	5.30E-02	1.1 [1.03-1.17]	4.20E-03	TNFSF14	upstream
Meta-analysis	rs6074022	20	44740196	C	0.74	1.13 [1.09-1.17]	1.71E-12	1.06 [0.99-1.15]	1.10E-01	1.08 [1.01-1.15]	2.00E-02	CD40	intergenic

Table x4.5.a Lead SNPs for osteoarthritis identified from UKBB GWAS (female-only) results

GWAS Analysis	SNP	CHR	BP	EA	EAF	UKBB female-only GWAS		UKBB sex-combined GWAS		Meta-Analysis sex-combined GWAS		Gene	Function
						OR [95% CI]	P-value	OR [95% CI]	P-value	OR [95% CI]	P-value		
Female-only	rs785113	1	40154983	C	0.80	1.05 [1.03-1.07]	1.40E-08	1.04 [1.03-1.06]	3.00E-09	1.04 [1.02-1.05]	7.76E-08	HPCAL4	intronic
Female-only	rs2862851	2	70712802	T	0.47	1.05 [1.03-1.06]	1.60E-08	1.04 [1.03-1.06]	4.80E-13	1.05 [1.03-1.06]	4.35E-16	TGFA	intronic
Female-only	rs78617107	2	204435946	C	0.13	1.07 [1.04-1.09]	3.40E-08	1.06 [1.04-1.08]	3.90E-09	1.05 [1.03-1.07]	5.98E-09	RAPH1	intergenic

Female-only	rs34811474	4	25408838	G	0.22	1.06 [1.04-1.08]	2.10E-09	1.05 [1.03-1.06]	6.00E-11	1.04 [1.03-1.05]	2.17E-09	ANAPC4	exonic
Female-only	rs13107325	4	103188709	T	0.92	1.11 [1.08-1.15]	2.60E-12	1.1 [1.07-1.12]	2.40E-16	1.1 [1.07-1.12]	8.29E-19	SLC39A8	exonic
Female-only	rs11167775	5	141807507	A	0.79	1.05 [1.04-1.07]	2.40E-08	1.03 [1.02-1.05]	2.90E-05	NA	NA	AC005592.2	ncRNA_intronic
Female-only	10:22102104_CCTCTCT_C	10	22102104	CCTCTCT	0.42	1.05 [1.03-1.07]	1.50E-08	1.03 [1.01-1.04]	2.50E-05	NA	NA	DNAJC1	intronic
Female-only	12:69656876_AT_A	12	69656876	AT	0.34	1.05 [1.03-1.07]	3.00E-08	1.04 [1.02-1.05]	7.50E-08	NA	NA	CPSF6	intronic
Female-only	rs194479	16	89694431	C	0.74	1.05 [1.04-1.07]	8.00E-09	1.04 [1.02-1.05]	5.90E-08	1.04 [1.02-1.05]	8.02E-09	DPEP1	intronic
Female-only	19:10763214_ATT_A	19	10763214	ATT	0.40	1.05 [1.03-1.07]	1.00E-09	1.04 [1.03-1.05]	7.90E-11	NA	NA	ILF3-AS1	ncRNA_exonic
Female-only	rs376354692	21	40709007	A	0.39	1.05 [1.03-1.06]	1.60E-08	1.03 [1.02-1.04]	3.40E-07	NA	NA	HMGN1	intergenic

Table x4.5.b Lead SNPs for osteoarthritis identified from UKBB GWAS (sex-combined) results

GWAS Analysis	SNP	CHR	BP	EA	EAF	UKBB female-only GWAS		UKBB sex-combined GWAS		Meta-Analysis sex-combined GWAS		Gene	Function
						OR [95% CI]	P-value	OR [95% CI]	P-value	OR [95% CI]	P-value		
Sex-combined	rs785113	1	40154983	C	0.80	1.40E-08	1.04 [1.03-1.06]	3.00E-09	1.04 [1.02-1.05]	7.76E-08	1.40E-08	HPCAL4	intronic
Sex-combined	rs11809524	1	103459537	T	0.84	2.60E-06	1.05 [1.03-1.07]	3.90E-09	1.05 [1.04-1.07]	2.24E-11	2.60E-06	COL11A1	intronic
Sex-combined	1:150214028_CT_C	1	150214028	C	0.61	9.40E-06	1.04 [1.02-1.05]	4.60E-08	NA	NA	9.40E-06	RNU2-17P	intergenic
Sex-combined	rs139958868	2	33414257	T	0.43	3.20E-07	1.04 [1.03-1.05]	6.80E-10	NA	NA	3.20E-07	LTBP1	intronic
Sex-combined	rs2862851	2	70712802	T	0.47	1.60E-08	1.04 [1.03-1.06]	4.80E-13	1.05 [1.03-1.06]	4.35E-16	1.60E-08	TGFA	intronic
Sex-combined	rs78617107	2	204435946	C	0.13	3.40E-08	1.06 [1.04-1.08]	3.90E-09	1.05 [1.03-1.07]	5.98E-09	3.40E-08	RAPH1	intergenic
Sex-combined	rs377609499	3	50022069	A	0.56	6.00E-04	1.04 [1.02-1.05]	2.00E-08	NA	NA	6.00E-04	RBM6	intronic
Sex-combined	rs798726	4	1685211	C	0.79	1.80E-03	1.05 [1.03-1.06]	3.10E-09	1.04 [1.03-1.06]	1.56E-09	1.80E-03	FAM53A:Y_RNA	ncRNA_exonic
Sex-combined	rs34811474	4	25408838	G	0.22	2.10E-09	1.05 [1.03-1.06]	6.00E-11	1.04 [1.03-1.05]	2.17E-09	2.10E-09	ANAPC4	exonic
Sex-combined	rs13107325	4	103188709	T	0.92	2.60E-12	1.1 [1.07-1.12]	2.40E-16	1.1 [1.07-1.12]	8.29E-19	2.60E-12	SLC39A8	exonic
Sex-combined	rs72688751	4	130256802	T	0.85	3.00E-05	1.05 [1.03-1.07]	8.90E-09	1.04 [1.03-1.06]	2.05E-07	3.00E-05	RP11-419L4.1	intergenic
Sex-combined	rs111810959	6	44709460	A	0.67	1.50E-06	1.04 [1.02-1.05]	3.10E-08	NA	NA	1.50E-06	SUPT3H	intergenic

Sex-combined	rs6966540	7	95727967	C	0.62	1.60E-05	1.04 [1.03-1.05]	1.60E-09	1.04 [1.03-1.05]	2.56E-10	1.60E-05	DYNC1I1	intronic
Sex-combined	8:9088524_GA_G	8	9088524	GA	0.47	1.40E-06	1.04 [1.02-1.05]	1.60E-09	NA	NA	1.40E-06	RP11-10A14.8	intergenic
Sex-combined	rs919642	9	116911147	T	0.74	3.00E-07	1.05 [1.04-1.07]	3.70E-14	NA	NA	3.00E-07	COL27A1	intergenic
Sex-combined	rs4978572	9	116943302	G	0.65	3.10E-06	1.04 [1.02-1.05]	4.40E-09	1.04 [1.02-1.05]	8.07E-10	3.10E-06	COL27A1	intronic
Sex-combined	rs35741412	11	47431764	A	0.97	8.50E-05	1.11 [1.07-1.16]	3.40E-08	1.1 [1.06-1.14]	2.25E-07	8.50E-05	SLC39A13	exonic
Sex-combined	rs553809825	11	48795664	A	0.98	5.70E-05	1.12 [1.08-1.17]	1.40E-08	NA	NA	5.70E-05	RP11-56P9.5	intergenic
Sex-combined	rs2930291	15	74604834	G	0.38	3.90E-03	1.04 [1.02-1.05]	1.60E-08	1.03 [1.02-1.05]	5.82E-09	3.90E-03	CCDC33	intronic
Sex-combined	rs12917376	15	75116167	T	0.53	6.50E-05	1.04 [1.03-1.05]	1.10E-10	1.04 [1.03-1.05]	5.41E-12	6.50E-05	LMAN1L:RP11-414J4.2	ncRNA_exonic
Sex-combined	rs1126464	16	89704365	G	0.25	6.60E-08	1.04 [1.03-1.06]	4.90E-09	1.04 [1.03-1.06]	1.56E-10	6.60E-08	DPEP1	exonic
Sex-combined	19:10763214_ATT_A	19	10763214	ATT	0.40	1.00E-09	1.04 [1.03-1.05]	7.90E-11	NA	NA	1.00E-09	ILF3-AS1	ncRNA_exonic
Sex-combined	rs75621460	19	41833784	A	0.97	2.50E-07	1.15 [1.11-1.2]	1.70E-12	1.16 [1.12-1.2]	1.62E-15	2.50E-07	TGFB1	intronic
Sex-combined	rs1886693	20	33986566	C	0.58	3.00E-07	1.04 [1.03-1.05]	2.10E-10	NA	NA	3.00E-07	UQCC1	intronic
Sex-combined	rs553943792	20	34133155	C	0.09	5.40E-08	1.07 [1.04-1.09]	4.40E-08	NA	NA	5.40E-08	ERGIC3	intronic

Table x4.5.c Lead SNPs for osteoarthritis identified from meta-analysis GWAS (sex-combined) results

GWAS Analysis	SNP	CHR	BP	EA	EAF	UKBB female-only GWAS		UKBB sex-combined GWAS		Meta-Analysis sex-combined GWAS		Gene	Function
						OR [95% CI]	P-value	OR [95% CI]	P-value	OR [95% CI]	P-value		
Meta-analysis	rs2622873	1	103466053	T	0.13	1.05 [1.02-1.07]	1.50E-04	1.05 [1.03-1.07]	1.90E-08	1.06 [1.04-1.07]	9.50E-12	COL11A1	intronic
Meta-analysis	1:150214028_ct_c	1	150214028	C	0.61	NA	NA	NA	NA	1.03 [1.02-1.05]	2.54E-08	RNU2-17P	intergenic
Meta-analysis	1:174192402_t_taaaaaaaaaaaaaaaaa	1	174192402	TAAAAAAAAAAAAAAAAA	0.57	NA	NA	NA	NA	1.03 [1.02-1.05]	1.05E-08	RABGAP1L	intronic

Meta-analysis	rs2785988	1	219744138	A	0.29	1.03 [1.02-1.05]	1.50E-04	1.03 [1.02-1.04]	4.90E-06	1.04 [1.02-1.05]	1.97E-09	RP11-95P13.2	intergenic
Meta-analysis	rs10218792	1	245750932	G	0.76	1.04 [1.02-1.06]	4.90E-05	1.04 [1.02-1.05]	3.50E-07	1.04 [1.02-1.05]	2.03E-08	KIF26B	intronic
Meta-analysis	rs2061027	2	33434336	A	0.48	1.04 [1.02-1.06]	1.20E-06	1.04 [1.02-1.05]	3.70E-09	1.04 [1.03-1.05]	3.16E-13	LTBP1	intronic
Meta-analysis	rs858936	2	50940168	C	0.89	1.03 [1.01-1.06]	9.40E-03	1.04 [1.03-1.06]	3.80E-06	1.05 [1.03-1.06]	4.73E-08	NRXN1	intronic
Meta-analysis	rs3771501	2	70717653	A	0.47	1.05 [1.03-1.06]	1.60E-08	1.04 [1.03-1.06]	5.10E-13	1.05 [1.03-1.06]	4.24E-16	TGFA	intronic
Meta-analysis	rs72810664	2	78817318	C	0.71	1.03 [1.02-1.05]	1.50E-04	1.03 [1.02-1.04]	5.70E-07	1.03 [1.02-1.04]	4.89E-08	AC092660.1	intergenic
Meta-analysis	rs62182810	2	204387482	A	0.46	1.04 [1.03-1.06]	3.80E-08	1.03 [1.02-1.05]	4.40E-08	1.03 [1.02-1.05]	1.65E-09	RAPH1	intronic
Meta-analysis	3:50022049_a_g	3	50022049	A	0.48	NA	NA	NA	NA	1.04 [1.03-1.05]	9.09E-11	RBM6	intronic
Meta-analysis	rs1867924	4	1671772	A	0.47	1.02 [1.01-1.04]	4.30E-03	1.03 [1.02-1.05]	5.00E-08	1.03 [1.02-1.04]	4.18E-09	FAM53A	intronic
Meta-analysis	rs798726	4	1685211	C	0.79	1.03 [1.01-1.05]	1.80E-03	1.05 [1.03-1.06]	3.10E-09	1.04 [1.03-1.06]	1.56E-09	FAM53A:Y_RNA	ncRNA_exonic
Meta-analysis	rs1913707	4	13039440	A	0.38	1.03 [1.01-1.05]	3.90E-04	1.03 [1.02-1.04]	4.30E-07	1.04 [1.02-1.05]	2.53E-10	RNU6-962P	intergenic
Meta-analysis	rs34811474	4	25408838	G	0.78	1.06 [1.04-1.08]	2.10E-09	1.05 [1.03-1.06]	6.00E-11	1.04 [1.03-1.05]	2.17E-09	ANAPC4	exonic
Meta-analysis	rs13107325	4	103188709	T	0.08	1.11 [1.08-1.15]	2.60E-12	1.1 [1.07-1.12]	2.40E-16	1.1 [1.07-1.12]	8.29E-19	SLC39A8	exonic
Meta-analysis	rs12154055	6	44449697	G	0.65	1.04 [1.02-1.05]	1.20E-05	1.03 [1.02-1.05]	1.50E-07	1.03 [1.02-1.04]	2.71E-08	CDC5L	intergenic
Meta-analysis	rs10948196	6	44959384	T	0.59	1.04 [1.02-1.06]	1.80E-06	1.03 [1.02-1.05]	1.50E-07	1.03 [1.02-1.04]	4.10E-08	SUPT3H	intronic
Meta-analysis	rs113471597	7	6532167	G	0.75	1.03 [1.01-1.05]	5.00E-04	1.04 [1.02-1.05]	1.50E-07	1.04 [1.02-1.05]	4.14E-08	AC072052.7	intergenic
Meta-analysis	rs1990577	7	78119199	C	0.54	1.04 [1.02-1.06]	1.30E-06	1.03 [1.02-1.04]	4.30E-07	1.03 [1.02-1.04]	3.92E-08	MAGI2	intronic
Meta-analysis	7:95711593_t_taa	7	95711593	T	0.11	NA	NA	NA	NA	1.04 [1.02-1.05]	6.38E-09	DYNC1I1	intronic
Meta-analysis	7:95719833_t_ta	7	95719833	TA	0.65	NA	NA	NA	NA	1.04 [1.03-1.05]	2.13E-10	DYNC1I1	intronic
Meta-analysis	rs330050	8	9087679	G	0.53	1.04 [1.02-1.05]	2.10E-06	1.04 [1.02-1.05]	3.50E-09	1.04 [1.03-1.05]	1.93E-11	RP11-10A14.8	intergenic
Meta-analysis	rs11784455	8	11540724	T	0.63	1.04 [1.02-1.05]	6.00E-06	1.03 [1.02-1.05]	1.40E-07	1.04 [1.03-1.05]	2.18E-10	GATA4	intronic
Meta-analysis	rs10974438	9	4291928	A	0.38	1.03 [1.02-1.05]	6.00E-05	1.03 [1.01-1.04]	3.30E-05	1.03 [1.02-1.05]	1.34E-08	GLIS3	intronic

Meta-analysis	9:116911147_a_t	9	116911147	T	0.74	NA	NA	NA	NA	1.05 [1.04-1.06]	8.55E-15	COL27A1	intergenic
Meta-analysis	rs4978572	9	116943302	G	0.65	1.04 [1.02-1.05]	3.10E-06	1.04 [1.02-1.05]	4.40E-09	1.04 [1.02-1.05]	8.07E-10	COL27A1	intronic
Meta-analysis	11:13237519_ca_c	11	13237519	CA	0.48	NA	NA	NA	NA	1.03 [1.02-1.04]	3.94E-08	ARNTL	intergenic
Meta-analysis	rs11031191	11	30774280	T	0.31	1.02 [1.01-1.04]	3.00E-03	1.03 [1.02-1.05]	2.40E-07	1.03 [1.02-1.05]	1.42E-08	DCDC1	intergenic
Meta-analysis	rs1149620	11	76506572	T	0.57	1.03 [1.01-1.04]	2.00E-03	1.03 [1.02-1.05]	8.60E-08	1.04 [1.02-1.05]	6.93E-10	TSKU	intronic
Meta-analysis	rs317630	12	69637847	T	0.31	1.05 [1.03-1.07]	1.10E-07	1.04 [1.02-1.05]	2.10E-07	1.04 [1.02-1.05]	1.97E-08	CPSF6	intronic
Meta-analysis	rs2171126	12	94167220	T	0.49	1.03 [1.01-1.05]	2.50E-04	1.03 [1.02-1.04]	3.20E-06	1.03 [1.02-1.05]	9.07E-10	CRADD	intronic
Meta-analysis	12:123703422_a_agtt	12	123703422	AGTT	0.78	NA	NA	NA	NA	1.04 [1.03-1.06]	7.16E-09	MPHOSPH9	intronic
Meta-analysis	15:50731131_a_at	15	50731131	AT	0.81	NA	NA	NA	NA	1.04 [1.03-1.06]	4.23E-08	USP8	intronic
Meta-analysis	rs35206230	15	75097780	T	0.40	1.03 [1.01-1.05]	3.00E-04	1.04 [1.03-1.05]	5.50E-10	1.04 [1.03-1.05]	1.48E-12	CSK	intergenic
Meta-analysis	rs1126464	16	89704365	G	0.75	1.05 [1.03-1.07]	6.60E-08	1.04 [1.03-1.06]	4.90E-09	1.04 [1.03-1.06]	1.56E-10	DPEP1	exonic
Meta-analysis	17:7450868_ctt_c	17	7450868	CTT	0.37	NA	NA	NA	NA	1.03 [1.02-1.05]	3.83E-08	TNFSF12	intergenic
Meta-analysis	17:29427026_t_ta	17	29427026	T	0.49	NA	NA	NA	NA	1.03 [1.02-1.04]	4.72E-08	NF1	intronic
Meta-analysis	rs10502437	18	20970706	G	0.60	1.02 [1.01-1.04]	4.40E-03	1.03 [1.02-1.04]	2.90E-06	1.03 [1.02-1.04]	2.50E-08	TMEM241	intronic
Meta-analysis	rs1560707	19	10750738	T	0.41	1.05 [1.03-1.07]	3.60E-09	1.04 [1.03-1.05]	1.10E-10	1.04 [1.03-1.05]	1.35E-13	SLC44A2	intronic
Meta-analysis	rs75621460	19	41833784	A	0.03	1.15 [1.09-1.21]	2.50E-07	1.15 [1.11-1.2]	1.70E-12	1.16 [1.12-1.2]	1.62E-15	TGFB1	intronic
Meta-analysis	rs2248393	20	33926103	C	0.38	1.04 [1.02-1.06]	2.00E-06	1.04 [1.03-1.05]	1.10E-09	1.04 [1.03-1.06]	3.73E-14	UQCC1	intronic
Meta-analysis	rs2741377	20	52097121	T	0.59	1.03 [1.02-1.05]	4.50E-05	1.03 [1.02-1.04]	1.00E-06	1.03 [1.02-1.04]	3.21E-08	TSHZ2:RP4-678D15.1:RP5-823G15.5	ncRNA_intronic

Table x4.6.a Lead SNPs for psoriasis identified from UKBB GWAS (female-only) results

GWAS Analysis	SNP	CHR	BP	EA	EAF	UKBB female-only GWAS		UKBB sex-combined GWAS		Meta-Analysis sex-combined GWAS		Gene	Function
						OR [95% CI]	P-value	OR [95% CI]	P-value	OR [95% CI]	P-value		

Female-only	rs7540520	1	152619739	G	0.58	1.17 [1.11-1.23]	1.70E-09	1.12 [1.08-1.16]	1.70E-09	1.14 [1.11-1.17]	1.13E-22	RP1-52J10.9	intergenic
Female-only	rs8177833	5	150466690	G	0.93	1.49 [1.34-1.67]	1.80E-12	1.47 [1.36-1.59]	1.70E-22	NA	NA	TNIP1	UTR5
Female-only	rs1549922	5	158731548	G	0.47	1.22 [1.16-1.29]	6.50E-15	1.25 [1.2-1.29]	1.60E-34	1.27 [1.24-1.3]	3.61E-77	AC008697.1	intergenic
Female-only	rs1433048	5	158755845	G	0.19	1.24 [1.16-1.32]	8.90E-11	1.25 [1.19-1.31]	2.40E-22	1.26 [1.22-1.3]	7.64E-48	AC008697.1:IL12B	ncRNA_intronic
Female-only	rs918519	5	158826357	A	0.18	1.31 [1.23-1.39]	8.40E-19	1.34 [1.29-1.4]	2.10E-44	1.37 [1.33-1.41]	1.20E-100	AC008697.1	intergenic
Female-only	rs73818525	5	158863387	T	0.95	1.36 [1.22-1.51]	1.10E-08	1.39 [1.29-1.49]	9.60E-19	1.39 [1.32-1.46]	6.28E-35	AC008703.1	intergenic
Female-only	rs34536443	19	10463118	G	0.03	1.42 [1.25-1.61]	2.60E-08	1.43 [1.31-1.55]	4.30E-16	NA	NA	TYK2	exonic

Table x4.6.b Lead SNPs for psoriasis identified from UKBB GWAS (sex-combined) results

GWAS Analysis	SNP	CHR	BP	EA	EAF	UKBB female-only GWAS		UKBB sex-combined GWAS		Meta-Analysis sex-combined GWAS		Gene	Function
						OR [95% CI]	P-value	OR [95% CI]	P-value	OR [95% CI]	P-value		
Sex-combined	rs2063111	1	25303944	G	0.57	1.08 [1.03-1.14]	2.00E-03	1.12 [1.08-1.16]	9.10E-10	1.13 [1.1-1.16]	7.45E-21	RP11-84D1.2	intergenic
Sex-combined	rs4385674	1	67684934	C	0.06	1.26 [1.13-1.4]	4.00E-05	1.27 [1.18-1.37]	4.40E-10	1.35 [1.28-1.43]	1.16E-24	C1orf141:IL23R	intronic
Sex-combined	rs12033764	1	67734482	T	0.67	1.15 [1.09-1.21]	6.50E-07	1.12 [1.08-1.16]	2.40E-09	1.13 [1.1-1.16]	1.11E-18	RNU4ATAC4P	intergenic
Sex-combined	rs4112787	1	152551325	T	0.64	1.17 [1.11-1.24]	5.40E-09	1.14 [1.1-1.18]	6.50E-12	1.17 [1.14-1.21]	1.61E-32	LCE3D	downstream
Sex-combined	rs2488401	1	197702401	T	0.82	1.11 [1.04-1.18]	1.40E-03	1.14 [1.09-1.19]	3.70E-09	1.1 [1.07-1.14]	4.88E-10	DENND1B	intronic
Sex-combined	rs842636	2	61091950	G	0.45	1.1 [1.04-1.16]	2.60E-04	1.11 [1.07-1.15]	2.30E-08	1.14 [1.11-1.17]	2.97E-25	AC010733.4	ncRNA_intronic
Sex-combined	rs2111485	2	163110536	G	0.60	1.09 [1.04-1.15]	1.00E-03	1.12 [1.08-1.16]	8.20E-10	1.15 [1.12-1.18]	2.08E-26	FAP	intergenic
Sex-combined	rs469758	5	96121715	C	0.35	1.15 [1.09-1.21]	5.00E-07	1.11 [1.07-1.15]	3.10E-08	1.12 [1.09-1.15]	6.90E-18	ERAP1	intronic
Sex-combined	rs848	5	131996500	C	0.79	1.16 [1.08-1.23]	1.30E-05	1.14 [1.09-1.19]	2.30E-08	1.17 [1.13-1.2]	3.18E-21	AC004041.2:IL13	ncRNA_intronic
Sex-combined	rs8177833	5	150466690	G	0.93	1.49 [1.34-1.67]	1.80E-12	1.47 [1.36-1.59]	1.70E-22	NA	NA	TNIP1	UTR5
Sex-combined	rs62385094	5	157652029	T	0.94	1.28 [1.16-1.41]	7.30E-07	1.21 [1.13-1.29]	3.50E-08	1.19 [1.13-1.26]	2.17E-10	CTC-436K13.6	downstream
Sex-combined	rs115254282	5	158591510	T	0.99	1.48 [1.23-1.79]	3.00E-05	1.63 [1.43-1.85]	8.60E-14	1.54 [1.4-1.7]	5.09E-18	RNF145	intronic
Sex-combined	rs1473247	5	158603571	T	0.26	1.15 [1.08-1.22]	2.80E-06	1.18 [1.13-1.23]	2.00E-15	1.2 [1.16-1.23]	1.33E-33	RNF145	intronic
Sex-combined	rs776291103	5	158617689	C	0.65	1.08 [1.02-1.14]	1.00E-02	1.12 [1.07-1.16]	3.40E-08	NA	NA	RNF145	intronic

Sex-combined	5:158631394_TG_T	5	158631394	T	0.82	1.15 [1.08-1.23]	4.90E-05	1.2 [1.14-1.26]	3.10E-14	NA	NA	RNF145	intronic
Sex-combined	rs2853694	5	158749088	G	0.47	1.22 [1.16-1.28]	1.70E-14	1.25 [1.2-1.29]	1.40E-34	1.27 [1.24-1.3]	1.44E-78	AC008697.1:IL12B	ncRNA_intronic
Sex-combined	rs148653348	5	158763058	T	0.99	1.36 [1.12-1.67]	2.30E-03	1.71 [1.49-1.97]	2.80E-14	1.77 [1.62-1.94]	7.35E-37	AC008697.1	ncRNA_intronic
Sex-combined	rs12657636	5	158810793	T	0.16	1.31 [1.23-1.4]	2.30E-15	1.29 [1.23-1.36]	2.70E-27	1.6 [1.54-1.67]	2.61E-109	AC008697.1	intergenic
Sex-combined	rs138384115	5	158812487	T	0.13	1.21 [1.11-1.31]	8.20E-06	1.21 [1.15-1.28]	3.20E-11	NA	NA	AC008697.1	intergenic
Sex-combined	rs12188300	5	158829527	T	0.94	1.41 [1.3-1.54]	3.70E-15	1.54 [1.45-1.63]	1.30E-45	NA	NA	AC008697.1	intergenic
Sex-combined	rs563517676	5	158840459	A	0.42	1.14 [1.08-1.2]	2.60E-06	1.17 [1.13-1.22]	3.00E-17	NA	NA	AC008703.1	intergenic
Sex-combined	rs73818525	5	158863387	T	0.95	1.36 [1.22-1.51]	1.10E-08	1.39 [1.29-1.49]	9.60E-19	1.39 [1.32-1.46]	6.28E-35	AC008703.1	intergenic
Sex-combined	rs5872600	5	158863412	G	0.02	1.51 [1.25-1.83]	2.50E-05	1.77 [1.55-2.02]	3.00E-17	NA	NA	AC008703.1	intergenic
Sex-combined	rs2059133	5	158863536	C	0.35	1.13 [1.06-1.19]	3.40E-05	1.13 [1.09-1.17]	9.90E-10	NA	NA	AC008703.1	intergenic
Sex-combined	rs4921506	5	158938919	T	0.28	1.09 [1.03-1.15]	2.60E-03	1.12 [1.08-1.17]	3.90E-09	NA	NA	AC008703.2	intergenic
Sex-combined	rs11153299	6	111895914	C	0.46	1.12 [1.06-1.18]	1.80E-05	1.11 [1.07-1.15]	1.80E-08	1.11 [1.08-1.14]	1.58E-16	TRAF3IP2-AS1:TRAF3IP2	ncRNA_exonic
Sex-combined	rs33980500	6	111913262	T	0.91	1.22 [1.11-1.34]	5.40E-05	1.35 [1.26-1.44]	1.50E-18	1.42 [1.36-1.49]	6.61E-54	TRAF3IP2-AS1:TRAF3IP2	exonic
Sex-combined	rs13203885	6	111995127	C	0.87	1.15 [1.07-1.24]	2.20E-04	1.16 [1.1-1.23]	1.50E-08	1.14 [1.1-1.18]	1.01E-12	FYN	intronic
Sex-combined	rs582757	6	138197824	C	0.27	1.13 [1.06-1.19]	3.90E-05	1.12 [1.08-1.17]	8.90E-09	1.17 [1.13-1.2]	4.85E-28	TNFAIP3	intronic
Sex-combined	6:138230038_GT_G	6	138230038	GT	0.02	1.31 [1.13-1.52]	2.80E-04	1.34 [1.21-1.48]	1.50E-08	NA	NA	TNFAIP3	intergenic
Sex-combined	rs2485361	6	159500004	A	0.35	1.08 [1.03-1.14]	2.30E-03	1.11 [1.07-1.15]	8.60E-09	1.1 [1.07-1.13]	1.93E-13	RP1-111C20.3	intergenic
Sex-combined	rs11795343	9	32523737	T	0.42	1.06 [1.01-1.12]	2.30E-02	1.11 [1.07-1.15]	8.50E-09	1.11 [1.08-1.14]	4.00E-16	DDX58	intronic
Sex-combined	rs10790962	11	128385169	G	0.47	1.12 [1.07-1.18]	1.40E-05	1.13 [1.09-1.17]	9.50E-11	NA	NA	ETS1	intronic
Sex-combined	rs7310615	12	111865049	C	0.47	1.13 [1.07-1.19]	2.40E-06	1.12 [1.08-1.16]	3.60E-10	1.1 [1.07-1.13]	4.97E-12	SH2B3	intronic
Sex-combined	rs8016947	14	35832666	G	0.53	1.07 [1.02-1.13]	8.40E-03	1.12 [1.08-1.16]	9.10E-11	1.14 [1.11-1.17]	1.42E-25	RP11-561B11.3	ncRNA_intronic
Sex-combined	rs28998802	17	26124908	A	0.84	1.06 [0.98-1.14]	1.30E-01	1.18 [1.12-1.24]	3.00E-10	1.21 [1.17-1.25]	2.49E-26	NOS2	intronic

Sex-combined	rs10459953	17	26127518	G	0.64	1.07 [1.01-1.13]	1.30E-02	1.11 [1.07-1.15]	2.20E-08	1.13 [1.1-1.16]	2.77E-19	NOS2:RP1-66C13.4	UTR5
Sex-combined	18:51786991_GA_G	18	51786991	G	0.75	1.15 [1.09-1.22]	3.30E-06	1.14 [1.09-1.19]	7.00E-10	NA	NA	POLI	intergenic
Sex-combined	rs34536443	19	10463118	G	0.03	1.42 [1.25-1.61]	2.60E-08	1.43 [1.31-1.55]	4.30E-16	NA	NA	TYK2	exonic
Sex-combined	rs280519	19	10472933	A	0.50	1.07 [1.01-1.12]	1.30E-02	1.11 [1.07-1.15]	8.20E-09	1.13 [1.1-1.16]	3.49E-22	TYK2	intronic
Sex-combined	rs6063454	20	48590791	G	0.39	1.1 [1.05-1.16]	1.80E-04	1.12 [1.08-1.16]	2.20E-09	1.14 [1.11-1.17]	1.16E-24	RNU6-147P	intergenic

Table x4.6.c Lead SNPs for psoriasis identified from meta-analysis GWAS (sex-combined) results

GWAS Analysis	SNP	CHR	BP	EA	EAF	UKBB female-only GWAS		UKBB sex-combined GWAS		Meta-Analysis sex-combined GWAS		Gene	Function
						OR [95% CI]	P-value	OR [95% CI]	P-value	OR [95% CI]	P-value		
Meta-analysis	rs112147823	1	8206827	T	0.09	1.21 [1.1-1.32]	3.00E-05	1.15 [1.08-1.22]	9.50E-06	1.17 [1.11-1.22]	3.90E-11	RP11-431K24.1	intergenic
Meta-analysis	rs438650	1	8290082	C	0.78	1.07 [1.01-1.13]	3.40E-02	1.09 [1.04-1.13]	1.10E-04	1.11 [1.08-1.15]	5.37E-12	RP11-431K24.4	intergenic
Meta-analysis	1:24513154_a_aaac	1	24513154	AAAC	0.85	NA	NA	NA	NA	1.26 [1.19-1.33]	2.97E-16	IFNLR1	intronic
Meta-analysis	rs6600249	1	25305160	C	0.55	1.08 [1.03-1.14]	1.70E-03	1.11 [1.07-1.15]	6.10E-09	1.13 [1.1-1.16]	1.02E-21	RP11-84D1.2	intergenic
Meta-analysis	rs12044149	1	67600686	T	0.24	1.02 [0.96-1.08]	4.80E-01	1.06 [1.02-1.1]	5.10E-03	1.09 [1.06-1.12]	7.61E-10	C1orf141	intronic
Meta-analysis	rs11581607	1	67707690	G	0.94	1.22 [1.11-1.35]	9.10E-05	1.23 [1.15-1.32]	4.60E-09	1.33 [1.26-1.4]	2.39E-26	IL23R	intronic
Meta-analysis	rs6698141	1	67741314	C	0.33	1.15 [1.09-1.21]	6.20E-07	1.12 [1.08-1.16]	2.90E-09	1.13 [1.1-1.16]	1.04E-18	RP4-763G1.1	intergenic
Meta-analysis	rs148911931	1	67758729	A	0.03	1.34 [1.13-1.59]	8.10E-04	1.23 [1.09-1.39]	7.40E-04	1.26 [1.16-1.37]	2.60E-08	RP4-763G1.1	intergenic
Meta-analysis	rs11585473	1	67906292	C	0.61	1.03 [0.98-1.09]	1.90E-01	1.05 [1.02-1.09]	4.90E-03	1.08 [1.05-1.1]	2.86E-08	SERBP1	intergenic
Meta-analysis	rs34517439	1	78450517	A	0.09	1.09 [1.01-1.18]	2.60E-02	1.12 [1.06-1.18]	7.20E-05	1.12 [1.08-1.17]	1.86E-08	DNAJB4:GIPC2	intronic
Meta-analysis	rs10494269	1	151782334	G	0.78	1.06 [1-1.13]	5.90E-02	1.11 [1.06-1.16]	9.40E-06	1.09 [1.06-1.13]	4.62E-08	RORC	intronic
Meta-analysis	rs4112788	1	152551276	G	0.64	1.17 [1.11-1.24]	6.30E-09	1.14 [1.1-1.18]	7.60E-12	1.17 [1.14-1.21]	1.61E-32	LCE3D	downstream
Meta-analysis	rs41268476	1	152692803	A	0.05	1.18 [1.04-1.34]	1.00E-02	1.2 [1.1-1.32]	3.20E-05	1.23 [1.15-1.31]	4.31E-10	C1orf68	UTR3

Meta-analysis	1:152774515_g_ga	1	152774515	G	0.47	NA	NA	NA	NA	1.08 [1.05-1.11]	2.35E-08	LCE1C	intergenic
Meta-analysis	rs17641524	1	197704717	T	0.18	1.1 [1.03-1.17]	2.50E-03	1.14 [1.09-1.19]	4.60E-09	1.11 [1.07-1.14]	5.71E-11	DENND1B	exonic
Meta-analysis	rs2151222	1	206654268	G	0.75	1.09 [1.02-1.15]	5.60E-03	1.09 [1.04-1.13]	5.10E-05	1.1 [1.07-1.13]	9.43E-11	IKBKE	intronic
Meta-analysis	2:60979956_t_ta	2	60979956	TA	0.73	NA	NA	NA	NA	1.12 [1.08-1.15]	3.21E-12	PAPOLG	intergenic
Meta-analysis	rs1177203	2	61074686	G	0.55	1.1 [1.04-1.16]	2.90E-04	1.1 [1.06-1.14]	5.90E-08	1.14 [1.11-1.17]	2.82E-25	AC010733.4	ncRNA_intronic
Meta-analysis	rs77775761	2	61088295	G	0.92	1.19 [1.08-1.31]	4.10E-04	1.14 [1.06-1.22]	1.70E-04	1.15 [1.1-1.21]	1.37E-09	AC010733.4	ncRNA_intronic
Meta-analysis	2:62552321_a_g	2	62552321	A	0.39	NA	NA	NA	NA	1.1 [1.07-1.13]	2.16E-13	RP11-642D6.1	intergenic
Meta-analysis	2:162995222_t_g	2	162995222	G	0.60	NA	NA	NA	NA	1.1 [1.07-1.13]	1.05E-11	GCG	intergenic
Meta-analysis	rs2111485	2	163110536	G	0.60	1.09 [1.04-1.15]	1.00E-03	1.12 [1.08-1.16]	8.20E-10	1.15 [1.12-1.18]	2.08E-26	FAP	intergenic
Meta-analysis	rs78456138	2	163132346	C	0.99	1.12 [0.95-1.32]	1.90E-01	1.21 [1.08-1.36]	9.90E-04	1.35 [1.23-1.48]	3.49E-10	IFIH1	intronic
Meta-analysis	rs17783344	2	163208893	T	0.16	1.1 [1.02-1.19]	1.00E-02	1.12 [1.06-1.17]	2.50E-05	1.13 [1.09-1.17]	1.14E-10	GCA	exonic
Meta-analysis	2:231175549_t_c	2	231175549	C	0.73	NA	NA	NA	NA	1.08 [1.05-1.11]	1.89E-08	SP140	exonic
Meta-analysis	rs6796868	3	17003529	A	0.36	1.1 [1.04-1.16]	4.40E-04	1.1 [1.06-1.14]	2.70E-07	1.11 [1.08-1.14]	1.28E-13	PLCL2	intronic
Meta-analysis	rs4683946	3	101615826	G	0.81	1.01 [0.95-1.07]	8.20E-01	1.07 [1.03-1.12]	1.50E-03	1.1 [1.07-1.14]	3.58E-09	NFKBIZ	intergenic
Meta-analysis	3:101654840_a_at	3	101654840	AT	0.78	NA	NA	NA	NA	1.11 [1.07-1.14]	3.26E-09	RP11-221J22.1	intergenic
Meta-analysis	3:189662658_g_gt	3	189662658	GT	0.82	NA	NA	NA	NA	1.13 [1.09-1.17]	3.30E-10	LEPREL1	intergenic
Meta-analysis	5:96120198_t_taaac	5	96120198	TAAAC	0.71	NA	NA	NA	NA	1.14 [1.11-1.18]	1.10E-21	ERAP1	intronic
Meta-analysis	rs17622656	5	131820997	A	0.35	1.1 [1.04-1.16]	3.40E-04	1.07 [1.03-1.11]	1.40E-04	1.08 [1.06-1.11]	5.98E-10	IRF1	intronic
Meta-analysis	rs848	5	131996500	C	0.79	1.16 [1.08-1.23]	1.30E-05	1.14 [1.09-1.19]	2.30E-08	1.17 [1.13-1.2]	3.18E-21	AC004041.2:IL13	ncRNA_intronic
Meta-analysis	rs17111727	5	150455442	G	0.93	1.11 [0.99-1.24]	7.10E-02	1.12 [1.03-1.21]	5.10E-03	1.16 [1.1-1.23]	2.99E-08	TNIP1	intronic
Meta-analysis	5:150466690_g_gc	5	150466690	G	0.07	NA	NA	NA	NA	1.56 [1.48-1.64]	5.82E-66	TNIP1	UTR5

Meta-analysis	5:150472094_a_g	5	150472094	G	0.55	NA	NA	NA	NA	1.08 [1.05-1.1]	1.29E-08	TNIP1	intronic
Meta-analysis	rs4958894	5	150487174	T	0.30	1.11 [1.05-1.18]	1.40E-04	1.11 [1.06-1.15]	3.30E-07	1.11 [1.08-1.14]	4.46E-14	ANXA6	intronic
Meta-analysis	rs79427955	5	150492548	A	0.01	1.56 [1.23-1.98]	2.80E-04	1.41 [1.2-1.67]	4.60E-05	1.55 [1.38-1.74]	1.62E-13	ANXA6	intronic
Meta-analysis	rs62385130	5	157704997	T	0.04	1.31 [1.17-1.46]	1.90E-06	1.24 [1.15-1.33]	4.20E-08	1.22 [1.14-1.3]	4.17E-10	CTC-436K13.2	ncRNA_intronic
Meta-analysis	rs77343625	5	158208927	T	0.08	1.15 [1.05-1.27]	2.80E-03	1.16 [1.08-1.23]	1.40E-05	1.17 [1.12-1.23]	2.91E-11	EBF1	intronic
Meta-analysis	rs31864	5	158220193	A	0.45	1.07 [1.02-1.13]	9.50E-03	1.1 [1.06-1.13]	4.40E-07	1.08 [1.05-1.11]	2.28E-09	EBF1	intronic
Meta-analysis	rs116278653	5	158534851	G	0.95	1.19 [1.03-1.38]	1.90E-02	1.16 [1.05-1.29]	3.10E-03	1.28 [1.18-1.38]	4.28E-10	RP11-175K6.1	ncRNA_intronic
Meta-analysis	rs115254282	5	158591510	T	0.01	1.48 [1.23-1.79]	3.00E-05	1.63 [1.43-1.85]	8.60E-14	1.54 [1.4-1.7]	5.09E-18	RNF145	intronic
Meta-analysis	rs72813995	5	158620521	T	0.17	1.15 [1.08-1.24]	3.60E-05	1.2 [1.15-1.26]	9.90E-15	1.23 [1.19-1.27]	5.09E-34	RNF145	intronic
Meta-analysis	5:158623237_g_gt	5	158623237	G	0.35	NA	NA	NA	NA	1.13 [1.1-1.17]	2.68E-18	RNF145	intronic
Meta-analysis	rs7715173	5	158664631	T	0.21	1.18 [1.1-1.25]	6.60E-07	1.19 [1.14-1.24]	2.00E-14	1.22 [1.18-1.26]	4.28E-34	CTB-11I22.1:CTB-11I22.2	ncRNA_intronic
Meta-analysis	rs12513881	5	158725325	C	0.97	1.28 [1.1-1.47]	9.60E-04	1.3 [1.17-1.43]	3.70E-07	1.35 [1.27-1.43]	4.09E-21	UBLCP1	intergenic
Meta-analysis	rs2546890	5	158759900	A	0.49	1.21 [1.15-1.27]	3.50E-13	1.23 [1.19-1.27]	3.50E-31	1.28 [1.25-1.31]	4.05E-82	AC008697.1	ncRNA_exonic
Meta-analysis	rs148653348	5	158763058	T	0.01	1.36 [1.12-1.67]	2.30E-03	1.71 [1.49-1.97]	2.80E-14	1.77 [1.62-1.94]	7.35E-37	AC008697.1	ncRNA_intronic
Meta-analysis	5:158810793_t_c	5	158810793	T	0.16	NA	NA	NA	NA	1.31 [1.27-1.35]	1.73E-60	AC008697.1	intergenic
Meta-analysis	rs12188300	5	158829527	T	0.94	1.41 [1.3-1.54]	3.70E-15	1.54 [1.45-1.63]	1.30E-45	1.6 [1.54-1.67]	2.61E-109	AC008697.1	intergenic
Meta-analysis	rs4921492	5	158832277	C	0.65	1.11 [1.05-1.17]	1.90E-04	1.16 [1.12-1.2]	6.40E-15	1.2 [1.16-1.23]	3.17E-39	AC008697.1	intergenic
Meta-analysis	rs13188027	5	158841639	C	0.80	1.12 [1.04-1.19]	1.20E-03	1.11 [1.06-1.16]	1.10E-05	1.13 [1.09-1.16]	9.05E-12	AC008703.1	intergenic
Meta-analysis	rs73818525	5	158863387	T	0.05	1.36 [1.22-1.51]	1.10E-08	1.39 [1.29-1.49]	9.60E-19	1.39 [1.32-1.46]	6.28E-35	AC008703.1	intergenic
Meta-analysis	5:158863412_g_gc	5	158863412	G	0.02	NA	NA	NA	NA	1.71 [1.55-1.88]	2.56E-26	AC008703.1	intergenic

Meta-analysis	5:158863536_t_c	5	158863536	C	0.65	NA	NA	NA	NA	1.13 [1.09-1.16]	1.78E-13	AC008703.1	intergenic
Meta-analysis	rs12516325	5	158879190	T	0.35	1.08 [1.02-1.14]	5.80E-03	1.12 [1.08-1.16]	2.30E-09	1.13 [1.1-1.16]	2.39E-18	AC008703.1	ncRNA_intronic
Meta-analysis	5:158944457_a_g	5	158944457	A	0.33	NA	NA	NA	NA	1.09 [1.06-1.12]	2.56E-10	AC008703.2	intergenic
Meta-analysis	rs76192477	5	158958236	G	0.98	1.3 [1.09-1.54]	3.60E-03	1.29 [1.14-1.45]	4.30E-05	1.33 [1.2-1.46]	1.37E-08	AC008703.2	intergenic
Meta-analysis	rs12187831	5	159133593	G	0.99	1.52 [1.27-1.83]	7.60E-06	1.28 [1.12-1.45]	1.70E-04	1.35 [1.22-1.5]	1.18E-08	AC008691.1	intergenic
Meta-analysis	6:577820_a_g	6	577820	A	0.50	NA	NA	NA	NA	1.09 [1.06-1.12]	1.34E-10	EXOC2	intronic
Meta-analysis	rs7748720	6	20689945	A	0.21	1.05 [0.99-1.12]	1.10E-01	1.08 [1.03-1.12]	7.30E-04	1.12 [1.08-1.15]	1.06E-12	CDKAL1	intronic
Meta-analysis	6:111842161_a_ac	6	111842161	AC	0.79	NA	NA	NA	NA	1.12 [1.09-1.16]	3.75E-12	TRAF3IP2-AS1	ncRNA_intronic
Meta-analysis	rs6912112	6	111880904	G	0.96	1.08 [0.95-1.24]	2.30E-01	1.13 [1.03-1.23]	1.10E-02	1.21 [1.14-1.29]	1.53E-09	TRAF3IP2-AS1:TRAF3IP2	ncRNA_intronic
Meta-analysis	6:111896777_t_c	6	111896777	C	0.54	NA	NA	NA	NA	1.12 [1.09-1.14]	2.56E-17	TRAF3IP2-AS1:TRAF3IP2	ncRNA_intronic
Meta-analysis	rs33980500	6	111913262	T	0.09	1.22 [1.11-1.34]	5.40E-05	1.35 [1.26-1.44]	1.50E-18	1.42 [1.36-1.49]	6.61E-54	TRAF3IP2-AS1:TRAF3IP2	exonic
Meta-analysis	rs13203885	6	111995127	C	0.87	1.15 [1.07-1.24]	2.20E-04	1.16 [1.1-1.23]	1.50E-08	1.14 [1.1-1.18]	1.01E-12	FYN	intronic
Meta-analysis	6:138054863_ct_c	6	138054863	CT	0.44	NA	NA	NA	NA	1.09 [1.06-1.12]	1.59E-09	RP11-356I2.1	ncRNA_intronic
Meta-analysis	rs1416172	6	138104861	C	0.88	1.17 [1.08-1.26]	5.90E-05	1.11 [1.06-1.17]	6.20E-05	1.15 [1.11-1.2]	3.67E-14	Y_RNA	upstream
Meta-analysis	rs139691717	6	138194425	G	0.97	1.09 [0.87-1.37]	4.40E-01	1.24 [1.06-1.45]	5.90E-03	1.43 [1.26-1.61]	1.03E-08	TNFAIP3	intronic
Meta-analysis	rs582757	6	138197824	C	0.73	1.13 [1.06-1.19]	3.90E-05	1.12 [1.08-1.17]	8.90E-09	1.17 [1.13-1.2]	4.85E-28	TNFAIP3	intronic
Meta-analysis	6:138230038_g_gt	6	138230038	GT	0.98	NA	NA	NA	NA	1.28 [1.19-1.39]	2.08E-10	TNFAIP3	intergenic
Meta-analysis	rs4585576	6	138281021	A	0.06	1.22 [1.1-1.35]	2.10E-04	1.17 [1.09-1.26]	2.10E-05	1.16 [1.1-1.21]	1.97E-08	RP11-240M16.1	ncRNA_intronic
Meta-analysis	rs79715597	6	159366373	C	0.96	1.16 [1.05-1.29]	4.20E-03	1.16 [1.08-1.24]	7.70E-05	1.17 [1.11-1.23]	1.09E-08	RNU6-293P	intergenic

Meta-analysis	rs2451258	6	159506600	C	0.65	1.07 [1.02-1.13]	7.50E-03	1.11 [1.07-1.15]	4.40E-08	1.1 [1.08-1.13]	4.51E-14	RP1-111C20.3	intergenic
Meta-analysis	rs77801025	7	37403192	A	0.10	1.22 [1.12-1.32]	3.10E-06	1.12 [1.06-1.18]	1.30E-04	1.13 [1.08-1.17]	5.90E-09	ELMO1	intronic
Meta-analysis	rs4728141	7	128567032	C	0.53	1.08 [1.03-1.14]	2.50E-03	1.1 [1.06-1.14]	2.40E-07	1.08 [1.05-1.11]	1.79E-09	IRF5	intergenic
Meta-analysis	rs11795343	9	32523737	T	0.42	1.06 [1.01-1.12]	2.30E-02	1.11 [1.07-1.15]	8.50E-09	1.11 [1.08-1.14]	4.00E-16	DDX58	intronic
Meta-analysis	rs10816608	9	110778738	G	0.56	1.07 [1.01-1.12]	1.30E-02	1.06 [1.02-1.1]	1.70E-03	1.09 [1.06-1.11]	4.06E-10	RP11-240E2.2	intergenic
Meta-analysis	rs2675662	10	75599127	A	0.41	1.09 [1.04-1.15]	5.00E-04	1.09 [1.06-1.13]	8.30E-07	1.11 [1.08-1.14]	8.02E-16	CAMK2G	intronic
Meta-analysis	rs2802372	10	81047575	A	0.38	1.1 [1.05-1.16]	2.20E-04	1.08 [1.05-1.12]	8.20E-06	1.1 [1.07-1.12]	1.25E-12	ZMIZ1	intronic
Meta-analysis	rs510372	11	64115137	C	0.62	1.09 [1.03-1.15]	1.50E-03	1.07 [1.03-1.11]	4.30E-04	1.09 [1.06-1.12]	2.14E-10	CCDC88B	intronic
Meta-analysis	rs12801731	11	65549606	C	0.53	1.09 [1.04-1.15]	9.80E-04	1.09 [1.05-1.13]	1.40E-06	1.08 [1.05-1.1]	9.79E-09	AP5B1	intergenic
Meta-analysis	rs2231884	11	65656564	T	0.16	1.1 [1.03-1.18]	5.70E-03	1.14 [1.09-1.19]	7.30E-08	1.12 [1.09-1.16]	7.19E-12	FIBP	upstream
Meta-analysis	11:109959102_a_agcaggt	11	109959102	AGCAGGT	0.70	NA	NA	NA	NA	1.12 [1.09-1.15]	1.32E-15	ZC3H12C	intergenic
Meta-analysis	rs7933433	11	128194450	T	0.39	1.09 [1.03-1.15]	1.30E-03	1.09 [1.05-1.13]	8.60E-06	1.09 [1.06-1.12]	2.80E-11	RP11-702B10.1	intergenic
Meta-analysis	11:128385169_a_g	11	128385169	G	0.53	NA	NA	NA	NA	1.12 [1.09-1.15]	5.56E-18	ETS1	intronic
Meta-analysis	12:907801_t_ttaa	12	907801	T	0.48	NA	NA	NA	NA	1.08 [1.05-1.11]	4.91E-08	WNK1	intronic
Meta-analysis	12:6468303_t_c	12	6468303	T	0.40	NA	NA	NA	NA	1.08 [1.05-1.11]	1.57E-08	SCNN1A	intronic
Meta-analysis	12:10582739_t_c	12	10582739	T	0.20	NA	NA	NA	NA	1.12 [1.08-1.17]	1.61E-08	NKG2-E:KLRC2	intronic
Meta-analysis	12:56449875_a_c	12	56449875	A	0.48	NA	NA	NA	NA	1.11 [1.08-1.14]	1.82E-12	RPS26	intergenic
Meta-analysis	rs4759017	12	56691600	C	0.63	1.05 [0.99-1.1]	7.70E-02	1.07 [1.03-1.1]	4.40E-04	1.08 [1.05-1.11]	3.55E-09	CS:RP11-977G19.10	intronic
Meta-analysis	rs11575224	12	56752154	C	0.94	1.14 [1.03-1.26]	1.10E-02	1.19 [1.11-1.27]	2.00E-06	1.29 [1.22-1.35]	3.87E-21	STAT2	intronic

Meta-analysis	rs3184504	12	111884608	T	0.46	1.13 [1.07-1.19]	2.40E-06	1.12 [1.08-1.16]	6.10E-10	1.1 [1.07-1.13]	6.38E-14	SH2B3	exonic
Meta-analysis	12:112896840_a_ag	12	112896840	A	0.41	NA	NA	NA	NA	1.08 [1.05-1.11]	2.17E-09	PTPN11	intronic
Meta-analysis	rs4772186	13	99957987	A	0.15	1.05 [0.98-1.12]	1.70E-01	1.07 [1.02-1.12]	9.10E-03	1.1 [1.06-1.14]	1.01E-08	UBAC2:GPR183	intronic
Meta-analysis	14:35403344_ca_c	14	35403344	C	0.63	NA	NA	NA	NA	1.09 [1.06-1.12]	8.14E-09	RP11-85K15.2	ncRNA_intronic
Meta-analysis	rs8007822	14	35724997	A	0.07	1.09 [0.99-1.21]	8.30E-02	1.13 [1.06-1.22]	4.70E-04	1.15 [1.1-1.21]	9.99E-09	KIAA0391:KIAA0391	intronic
Meta-analysis	rs8016947	14	35832666	G	0.53	1.07 [1.02-1.13]	8.40E-03	1.12 [1.08-1.16]	9.10E-11	1.14 [1.11-1.17]	1.42E-25	RP11-561B11.3	ncRNA_intronic
Meta-analysis	14:35843209_a_g	14	35843209	G	0.55	NA	NA	NA	NA	1.08 [1.05-1.1]	1.20E-08	RP11-561B11.3	intergenic
Meta-analysis	rs7148066	14	35847810	G	0.84	1.1 [1.02-1.18]	9.20E-03	1.14 [1.08-1.19]	1.50E-07	1.17 [1.13-1.21]	8.64E-19	RP11-561B11.1	intergenic
Meta-analysis	rs2233409	14	35874270	A	0.23	1.05 [0.99-1.12]	8.20E-02	1.06 [1.02-1.11]	3.60E-03	1.09 [1.06-1.12]	5.05E-09	NFKBIA	upstream
Meta-analysis	rs28510484	15	31637569	G	0.83	1.05 [0.98-1.13]	1.40E-01	1.05 [1-1.1]	3.10E-02	1.1 [1.06-1.14]	3.92E-08	KLF13	intronic
Meta-analysis	rs11644510	16	11277358	T	0.35	1.07 [1.01-1.12]	1.90E-02	1.07 [1.03-1.11]	6.20E-04	1.08 [1.05-1.11]	1.79E-08	CLEC16A	intergenic
Meta-analysis	rs2021511	16	11344903	C	0.70	1.12 [1.06-1.18]	9.20E-05	1.09 [1.05-1.14]	8.80E-06	1.11 [1.08-1.14]	2.67E-13	RMI2	intronic
Meta-analysis	16:31070782_a_attat	16	31070782	A	0.37	NA	NA	NA	NA	1.1 [1.07-1.12]	3.94E-12	ZNF668	intergenic
Meta-analysis	rs28998802	17	26124908	A	0.16	1.06 [0.98-1.14]	1.30E-01	1.18 [1.12-1.24]	3.00E-10	1.21 [1.17-1.25]	2.49E-26	NOS2	intronic
Meta-analysis	rs6505483	17	26126345	G	0.64	1.07 [1.02-1.13]	8.70E-03	1.11 [1.07-1.15]	2.70E-08	1.13 [1.1-1.16]	1.31E-19	NOS2:RP1-66C13.4	intronic
Meta-analysis	17:40536575_a_at	17	40536575	A	0.40	NA	NA	NA	NA	1.1 [1.07-1.13]	3.56E-11	STAT3	intronic
Meta-analysis	rs75524028	17	40810228	T	0.05	1.23 [1.09-1.38]	5.20E-04	1.17 [1.08-1.27]	1.10E-04	1.18 [1.11-1.25]	2.99E-08	TUBG2	intergenic
Meta-analysis	rs58587945	17	73920219	T	0.14	1.08 [1-1.17]	5.30E-02	1.13 [1.07-1.19]	1.20E-05	1.14 [1.09-1.18]	4.08E-11	RP11-552F3.	intronic

												12:FBF1	
Meta-analysis	rs11653893	17	78178830	A	0.49	1.06 [1.01-1.11]	3.00E-02	1.07 [1.04-1.11]	9.10E-05	1.08 [1.05-1.1]	5.87E-09	CARD14:RP11-334C17.5	ncRNA_exonic
Meta-analysis	rs559406	18	12857002	G	0.54	1.06 [1.01-1.12]	2.30E-02	1.08 [1.04-1.11]	4.60E-05	1.09 [1.06-1.12]	5.88E-11	PTPN2	intronic
Meta-analysis	18:51786412_t_c	18	51786412	T	0.27	NA	NA	NA	NA	1.11 [1.08-1.14]	3.71E-13	POLI	intergenic
Meta-analysis	19:10408279_ca_c	19	10408279	C	0.57	NA	NA	NA	NA	1.09 [1.06-1.12]	7.28E-11	ICAM5	downstream
Meta-analysis	rs2278442	19	10444826	A	0.34	1.08 [1.03-1.14]	2.90E-03	0.91 [0.87-0.94]	1.50E-07	1.12 [1.09-1.15]	6.78E-17	ICAM3	intronic
Meta-analysis	19:10448774_ca_c	19	10448774	CA	0.24	NA	NA	NA	NA	1.11 [1.08-1.15]	5.65E-11	ICAM3	intronic
Meta-analysis	rs11085725	19	10462513	C	0.73	1.11 [1.05-1.17]	2.20E-04	1.15 [1.11-1.2]	1.30E-12	1.18 [1.14-1.21]	1.65E-29	TYK2	intronic
Meta-analysis	19:10516937_g_ga	19	10516937	G	0.17	NA	NA	NA	NA	1.11 [1.08-1.15]	1.61E-09	CDC37	intronic
Meta-analysis	rs45524632	19	10596988	C	0.99	1.53 [1.31-1.79]	1.20E-07	1.48 [1.32-1.65]	3.20E-12	1.56 [1.42-1.7]	6.90E-22	KEAP1	UTR3
Meta-analysis	rs8111338	19	10635838	T	0.05	1.11 [0.99-1.25]	6.20E-02	1.16 [1.07-1.26]	2.10E-04	1.19 [1.12-1.26]	3.52E-09	S1PR5	intergenic
Meta-analysis	rs4804520	19	10811667	T	0.48	1 [0.95-1.05]	9.60E-01	1.05 [1.01-1.09]	6.80E-03	1.09 [1.06-1.12]	8.45E-11	QTRT1	upstream
Meta-analysis	19:18519997_ctt_c	19	18519997	C	0.67	NA	NA	NA	NA	1.09 [1.06-1.12]	5.13E-09	AC008397.1	downstream
Meta-analysis	rs516316	19	49206145	C	0.44	1.06 [1.01-1.11]	2.40E-02	1.05 [1.02-1.09]	4.10E-03	1.08 [1.05-1.11]	3.05E-09	FUT2	intronic
Meta-analysis	20:31353564_t_c	20	31353564	T	0.37	NA	NA	NA	NA	1.08 [1.05-1.1]	3.41E-08	DNMT3B	intronic
Meta-analysis	rs6063454	20	48590791	G	0.61	1.1 [1.05-1.16]	1.80E-04	1.12 [1.08-1.16]	2.20E-09	1.14 [1.11-1.17]	1.16E-24	RNU6-147P	intergenic
Meta-analysis	rs6020157	20	48591758	A	0.17	1.13 [1.06-1.21]	2.60E-04	1.14 [1.09-1.19]	6.10E-08	1.15 [1.11-1.19]	4.33E-17	RNU6-147P	intergenic
Meta-analysis	rs131656	22	21917450	A	0.19	1.12 [1.05-1.19]	7.60E-04	1.1 [1.06-1.15]	1.30E-05	1.11 [1.08-1.15]	1.91E-11	UBE2L3	intronic

Table x4.7.a Lead SNPs for rheumatoid arthritis identified from UKBB GWAS (female-only) results

GWAS Analysis	SNP					UKBB female-only GWAS		UKBB sex-combined GWAS		Meta-Analysis sex-combined GWAS			
		CHR	BP	EA	EAF	OR [95% CI]	P-value	OR [95% CI]	P-value	OR [95% CI]	P-value	Gene	Functio
Female-only	rs7731626	5	55444683	G	0.38	1.14 [1.1-1.19]	5.50E-10	1.13 [1.09-1.17]	2.10E-12	1.16 [1.13-1.20]	1.50E-26	ANKRD55	intronic

Female-only	rs6123193	20	51237903	C	0.24	1.15 [1.1-1.21]	6.00E-09	1.1 [1.06-1.15]	1.10E-06	NA	NA	RP4-723E3.1	ncRNA_ntronic

Table x4.7.b Lead SNPs for rheumatoid arthritis identified from UKBB GWAS (sex-combined) results

GWAS Analysis	SNP	CHR	BP	EA	EAF	UKBB female-only GWAS		UKBB sex-combined GWAS		Meta-Analysis sex-combined GWAS		Gene	Function
						OR [95% CI]	P-value	OR [95% CI]	P-value	OR [95% CI]	P-value		
Sex-combined	rs6679677	1	114303808	A	0.91	1.2 [1.12-1.29]	9.80E-08	1.23 [1.17-1.3]	1.00E-13	1.52 [1.47-1.58]	1.03E-109	RSBN1	downstream
Sex-combined	rs10065637	5	55438851	C	0.22	1.15 [1.1-1.21]	3.60E-08	1.16 [1.11-1.21]	1.60E-12	1.17 [1.14-1.21]	5.90E-23	ANKRD55	intronic
Sex-combined	rs34536443	19	10463118	G	0.03	1.28 [1.15-1.41]	2.10E-06	1.28 [1.18-1.39]	2.10E-09	1.35 [1.26-1.44]	2.88E-19	TYK2	exonic

Table x4.7.c Lead SNPs for rheumatoid arthritis identified from meta-analysis GWAS (sex-combined) results

GWAS Analysis	SNP	CHR	BP	EA	EAF	UKBB female-only GWAS		UKBB sex-combined GWAS		Meta-Analysis sex-combined GWAS		Gene	Function
						OR [95%CI]	P-value	OR [95%CI]	P-value	OR [95%CI]	P-value		
Meta-analysis	rs1635578	1	17666095	T	0.35	1.08 [1.05-1.1]	7.69E-09	1.1 [1.05-1.15]	3.20E-05	1.09 [1.05-1.13]	7.50E-06	PADI4:AC004824.2	intronic
Meta-analysis	rs773566	1	113821584	C	0.58	1.09 [1.06-1.11]	4.75E-10	1.03 [0.99-1.08]	1.30E-01	1.05 [1.02-1.09]	3.60E-03	RP11-389O22.5	intergenic
Meta-analysis	rs12061333	1	113860779	A	0.78	1.12 [1.09-1.15]	1.26E-13	1.04 [0.99-1.1]	8.60E-02	1.07 [1.03-1.11]	1.20E-03	MAGI3	intergenic
Meta-analysis	rs12128454	1	113910209	C	0.89	1.17 [1.13-1.22]	4.01E-17	1.06 [1-1.13]	6.80E-02	1.06 [1.01-1.12]	3.10E-02	MAGI3	intergenic
Meta-analysis	rs72687965	1	114073152	C	0.97	1.27 [1.19-1.37]	4.08E-12	1.08 [0.97-1.21]	1.40E-01	1.19 [1.09-1.29]	1.30E-04	MAGI3	intronic
Meta-analysis	chr1:114154300	1	114154300	C	0.99	1.58 [1.41-1.77]	7.00E-16	NA	NA	NA	NA	MAGI3	intronic
Meta-analysis	rs1217195	1	114178764	T	0.41	1.1 [1.07-1.12]	7.76E-13	1.06 [1.02-1.1]	6.50E-03	1.05 [1.01-1.08]	7.10E-03	MAGI3	intronic
Meta-analysis	rs6679677	1	114303808	A	0.91	1.52 [1.47-1.58]	1.03E-103	1.2 [1.12-1.29]	9.80E-08	1.23 [1.17-1.3]	1.00E-13	RSBN1	downstream
Meta-analysis	rs2476600	1	114369734	A	0.45	1.13 [1.11-1.16]	1.10E-23	1.03 [0.99-1.08]	1.30E-01	1.05 [1.01-1.08]	6.90E-03	RP51073O3.2: PTPN22	ncRNA_intronic
Meta-analysis	rs12729894	1	114481962	G	0.53	1.08 [1.05-1.11]	1.96E-08	1.04 [1-1.09]	6.70E-02	1.02 [0.99-1.06]	2.10E-01	HIPK1	intronic
Meta-analysis	rs1158912	1	114527534	T	0.90	1.2 [1.16-1.25]	1.98E-19	1.05 [0.98-1.13]	1.30E-01	1.08 [1.02-1.14]	1.20E-02	OLFML3	intergenic
Meta-analysis	rs906868	2	30448344	T	0.63	1.08 [1.05-1.11]	5.73E-09	1.08 [1.03-1.13]	4.20E-04	1.07 [1.03-1.11]	1.60E-04	LBH	intergenic
Meta-analysis	rs67574266	2	61108829	A	0.64	1.08 [1.05-1.1]	3.55E-09	1.04 [0.99-1.08]	8.60E-02	1.03 [1-1.07]	8.50E-02	REL	UTR5

Meta-analysis	rs9653442	2	100825367	C	0.45	1.07 [1.05-1.1]	1.37E-08	1.04 [1-1.08]	8.20E-02	1.04 [1-1.07]	4.40E-02	LINC01104	ncRNA_intronic
Meta-analysis	rs72837868	2	112010094	G	0.87	1.14 [1.09-1.19]	3.05E-08	1.13 [1.06-1.2]	3.90E-04	1.13 [1.07-1.19]	7.10E-06	MIR4435-1HG	ncRNA_intronic
Meta-analysis	rs11889341	2	191943742	T	0.77	1.11 [1.08-1.14]	4.06E-13	1.12 [1.07-1.18]	3.70E-06	1.09 [1.05-1.14]	1.70E-05	STAT4	intronic
Meta-analysis	rs3087243	2	204738919	G	0.47	1.09 [1.06-1.11]	1.00E-11	1.06 [1.02-1.1]	7.20E-03	1.03 [0.99-1.06]	9.50E-02	CTLA4	downstream
Meta-analysis	rs4416363	3	17025606	G	0.68	1.08 [1.05-1.11]	6.02E-09	1.04 [0.99-1.09]	8.60E-02	1.05 [1.02-1.09]	4.20E-03	PLCL2	intronic
Meta-analysis	rs16878091	4	26088128	A	0.70	1.11 [1.09-1.14]	3.59E-16	1.08 [1.03-1.13]	1.20E-03	1.09 [1.05-1.13]	1.10E-05	RP11-324H7.1	intergenic
Meta-analysis	rs188841	5	55421384	G	0.66	1.08 [1.05-1.11]	1.18E-08	1.09 [1.04-1.14]	2.20E-04	1.08 [1.04-1.12]	2.10E-05	ANKRD55	intronic
Meta-analysis	rs7731626	5	55444683	G	0.38	1.16 [1.13-1.2]	1.50E-26	1.14 [1.1-1.19]	5.50E-10	1.13 [1.09-1.17]	2.10E-12	ANKRD55	intronic
Meta-analysis	rs556560	5	102623924	A	0.34	1.08 [1.05-1.1]	1.67E-08	1.07 [1.02-1.12]	2.30E-03	1.05 [1.01-1.09]	5.60E-03	C5orf30	intergenic
Meta-analysis	rs617328	6	138000398	G	0.69	1.09 [1.06-1.12]	3.05E-10	1.09 [1.05-1.15]	9.40E-05	1.08 [1.04-1.12]	6.80E-05	RP11-95M15.1	intergenic
Meta-analysis	rs6920220	6	138006504	A	0.83	1.13 [1.1-1.16]	1.94E-16	1.11 [1.06-1.16]	4.00E-05	1.08 [1.04-1.13]	9.30E-05	RP11-95M15.1	intergenic
Meta-analysis	rs58721818	6	138243739	T	0.98	1.26 [1.18-1.35]	6.41E-12	1.13 [1.01-1.27]	3.50E-02	1.1 [1-1.21]	5.40E-02	RP11-10J5.1	intergenic
Meta-analysis	rs3093017	6	167541258	C	0.42	1.1 [1.07-1.13]	2.58E-14	1.07 [1.03-1.12]	8.30E-04	1.07 [1.04-1.11]	6.50E-05	RP11-517H2.6:CCR6	ncRNA_intronic
Meta-analysis	rs10261758	7	50353192	G	0.31	1.08 [1.05-1.11]	1.38E-08	1.07 [1.02-1.12]	3.00E-03	1.1 [1.06-1.14]	5.10E-07	IKZF1	intronic
Meta-analysis	rs3757387	7	128576086	C	0.55	1.1 [1.07-1.13]	1.40E-13	1.1 [1.06-1.15]	6.50E-06	1.08 [1.05-1.12]	2.20E-06	IRF5	intergenic
Meta-analysis	rs13242075	7	128708939	A	0.89	1.12 [1.08-1.16]	4.08E-09	1.12 [1.05-1.2]	4.40E-04	1.08 [1.02-1.14]	4.00E-03	RP11-128A6.3	intergenic
Meta-analysis	rs706778	10	6098949	T	0.59	1.09 [1.06-1.11]	2.52E-11	1.05 [1-1.09]	3.70E-02	1.06 [1.03-1.1]	4.50E-04	IL2RA	intronic
Meta-analysis	chr10:63813790	10	63813790	T	0.77	1.12 [1.08-1.15]	1.35E-12	NA	NA	NA	NA	ARID5B	intronic
Meta-analysis	rs7119044	11	118738298	C	0.81	1.1 [1.07-1.13]	1.44E-09	1.03 [0.98-1.09]	2.30E-01	1.04 [1-1.09]	5.90E-02	CXCR5	intergenic
Meta-analysis	rs7310615	12	111865049	C	0.47	1.08 [1.05-1.11]	2.50E-09	1.09 [1.05-1.14]	4.10E-05	1.07 [1.04-1.11]	3.80E-05	SH2B3	intronic
Meta-analysis	rs9603618	13	40371377	C	0.28	1.08 [1.05-1.12]	1.08E-08	1.05 [1.01-1.1]	2.60E-02	1.06 [1.02-1.1]	1.90E-03	COG6	intergenic
Meta-analysis	rs72727387	15	38843476	A	0.75	1.1 [1.07-1.13]	6.73E-12	1.06 [1.01-1.11]	1.20E-02	1.08 [1.04-1.12]	1.00E-04	RASGRP1	intronic
Meta-analysis	rs7181071	15	69997342	C	0.07	1.15 [1.11-1.2]	1.42E-11	1.1 [1.03-1.17]	6.90E-03	1.11 [1.05-1.17]	3.00E-04	RP11-279F6.3	intergenic

Meta-analysis	rs7170107	15	70010647	T	0.72	1.11 [1.08-1.15]	1.97E-14	1.08 [1.03-1.14]	7.30E-04	1.07 [1.03-1.11]	4.30E-04	AC009677.1	intergenic
Meta-analysis	rs12941333	17	38040534	T	0.53	1.07 [1.04-1.1]	2.67E-08	1.04 [1-1.08]	6.00E-02	1.05 [1.01-1.08]	6.90E-03	ZPBP2	intergenic
Meta-analysis	rs2278442	19	10444826	A	0.66	1.09 [1.06-1.12]	2.48E-10	1.08 [1.03-1.12]	7.90E-04	1.08 [1.04-1.12]	2.40E-05	ICAM3	intronic
Meta-analysis	rs34536443	19	10463118	G	0.03	1.35 [1.26-1.44]	2.88E-19	1.28 [1.15-1.41]	2.10E-06	1.28 [1.18-1.39]	2.10E-09	TYK2	exonic
Meta-analysis	rs12985305	19	10599132	T	0.57	1.08 [1.05-1.1]	3.13E-08	1.08 [1.04-1.13]	1.40E-04	1.06 [1.02-1.1]	8.20E-04	KEAP1	intronic
Meta-analysis	rs4810485	20	44747947	G	0.74	1.09 [1.06-1.12]	9.29E-09	1.05 [1-1.1]	4.00E-02	1.04 [1-1.08]	7.40E-02	CD40	intronic
Meta-analysis	rs2409493	21	34808289	A	0.44	1.08 [1.05-1.1]	1.04E-08	1.08 [1.03-1.12]	4.70E-04	1.08 [1.04-1.12]	6.80E-06	IFNGR2:TMEM50B	intronic
Meta-analysis	rs909685	22	39747671	A	0.70	1.08 [1.05-1.11]	1.81E-08	1.05 [1-1.1]	3.80E-02	1.05 [1.01-1.09]	1.20E-02	SYNGR1	intronic

Table x4.8.a Lead SNPs for systemic lupus erythematosus identified from UKBB GWAS (female-only) results

GWAS Analysis	SNP	CHR	BP	EA	EAF	UKBB female-only GWAS		UKBB sex-combined GWAS		Meta-Analysis sex-combined GWAS		Gene	Function
						OR [95% CI]	P-value	OR [95% CI]	P-value	OR [95% CI]	P-value		
Female-only	rs17849501	1	183542323	T	0.94	2.14 [1.64-2.8]	2.50E-08	2 [1.57-2.55]	2.30E-08	2.2 [1.98-2.45]	3.70E-48	SMG7:NCF2	exonic

Table x4.8.b Lead SNPs for systemic lupus erythematosus identified from UKBB GWAS (sex-combined) results

GWAS Analysis	SNP	CHR	BP	EA	EAF	UKBB female-only GWAS		UKBB sex-combined GWAS		Meta-Analysis sex-combined GWAS		Gene	Function
						OR [95% CI]	P-value	OR [95% CI]	P-value	OR [95% CI]	P-value		
Sex-combined	rs17849501	1	183542323	T	0.94	2.14 [1.64-2.8]	2.50E-08	2.00 [1.57-2.55]	2.30E-08	2.2 [1.98-2.45]	3.70E-48	SMG7:NCF2	exonic
Sex-combined	rs139284140	19	8310127	T	0.98	3.74 [2.12-6.62]	5.70E-06	4.21 [2.52-7.03]	4.10E-08	NA	NA	CERS4	intronic

Table x4.8.c Lead SNPs for systemic lupus erythematosus identified from meta-analysis GWAS (sex-combined) results

GWAS Analysis	SNP	CHR	BP	EA	EAF	UKBB female-only GWAS		UKBB sex-combined GWAS		Meta-Analysis sex-combined GWAS		Gene	Function
						OR [95% CI]	P-value	OR [95% CI]	P-value	OR [95% CI]	P-value		
Meta-analysis	rs6679677	1	114303808	A	0.09	1.06 [0.87-1.29]	5.40E-01	1.12 [0.93-1.33]	2.30E-01	1.32 [1.2-1.45]	6.63E-09	RSBN1	downstream
Meta-analysis	rs6671847	1	161478810	A	0.49	1.14 [1.01-1.28]	3.30E-02	1.11 [1-1.24]	5.20E-02	1.19 [1.12-1.26]	4.22E-09	FCGR2A	intronic
Meta-analysis	rs10912578	1	173251856	A	0.30	1.01 [0.89-1.15]	8.40E-01	1 [0.89-1.13]	9.70E-01	1.2 [1.13-1.28]	1.10E-08	snoU13	intergenic
Meta-analysis	rs2422349	1	173340809	T	0.26	1.16 [1.02-1.33]	2.70E-02	1.17 [1.03-1.32]	1.20E-02	1.23 [1.15-1.31]	3.36E-09	RP11-296O14.2	intergenic
Meta-analysis	rs80087370	1	183224185	T	0.98	1.78 [1.12-2.82]	1.40E-02	1.42 [0.94-2.16]	9.60E-02	1.77 [1.44-2.17]	4.46E-08	NMNAT2	intronic
Meta-analysis	rs17849501	1	183542323	T	0.06	2.14 [1.64-2.8]	2.50E-08	2 [1.57-2.55]	2.30E-08	2.2 [1.98-2.45]	3.70E-48	SMG7:NCF2	exonic
Meta-analysis	rs13019891	2	113829869	G	0.55	1.01 [0.9-1.14]	8.60E-01	1 [0.9-1.12]	9.70E-01	1.51 [1.43-1.6]	5.82E-44	IL1F10	intronic
Meta-analysis	rs2293765	2	191520845	C	0.56	1.16 [1.03-1.31]	1.50E-02	1.12 [1.01-1.25]	3.40E-02	1.25 [1.18-1.33]	1.01E-13	NAB1	UTR5

Meta-analysis	rs11693463	2	191869911	G	0.93	1.21 [0.96-1.53]	1.10E-01	1.18 [0.96-1.46]	1.20E-01	1.39 [1.24-1.55]	4.02E-09	STAT1	intronic
Meta-analysis	rs7601754	2	191940451	A	0.18	1.14 [0.97-1.33]	1.20E-01	1.14 [0.99-1.32]	6.80E-02	1.38 [1.28-1.49]	1.28E-16	STAT4	intronic
Meta-analysis	rs4853458	2	191959489	A	0.23	1.45 [1.25-1.67]	3.80E-07	1.35 [1.19-1.54]	5.00E-06	1.64 [1.54-1.76]	2.81E-48	STAT4	intronic
Meta-analysis	rs2573219	2	233288667	C	0.91	1.06 [0.86-1.3]	6.00E-01	1.03 [0.86-1.25]	7.40E-01	1.58 [1.45-1.73]	1.22E-23	AC068134.6	intergenic
Meta-analysis	rs9852014	3	129084581	G	0.93	1.09 [0.86-1.38]	4.70E-01	1.12 [0.9-1.38]	3.10E-01	1.59 [1.44-1.76]	6.17E-19	RP11-529F4.1	intergenic
Meta-analysis	rs1464446	3	146601295	G	0.82	1.03 [0.88-1.19]	7.50E-01	1.01 [0.88-1.16]	8.70E-01	1.26 [1.17-1.37]	6.51E-09	RP11-649A16.1	intergenic
Meta-analysis	rs13136219	4	102743687	C	0.62	1.13 [1-1.28]	5.20E-02	1.16 [1.03-1.29]	1.10E-02	1.18 [1.12-1.25]	8.79E-09	BANK1	intronic
Meta-analysis	rs1078324	5	149202268	C	0.95	1.01 [0.78-1.31]	9.30E-01	1.06 [0.84-1.34]	6.20E-01	1.54 [1.33-1.79]	6.29E-09	PPARGC1B	intronic
Meta-analysis	rs6889239	5	150457771	C	0.74	1.19 [1.03-1.37]	1.60E-02	1.16 [1.02-1.32]	2.20E-02	1.28 [1.2-1.37]	8.70E-14	TNIP1	intronic
Meta-analysis	rs2431697	5	159879978	T	0.43	1.1 [0.98-1.24]	1.10E-01	1.14 [1.02-1.27]	2.10E-02	1.22 [1.15-1.29]	4.50E-11	MIR146A	intergenic
Meta-analysis	rs75424836	6	138229183	C	0.98	1.71 [1.17-2.52]	6.00E-03	1.55 [1.09-2.2]	1.40E-02	1.85 [1.57-2.17]	1.63E-13	TNFAIP3	intergenic
Meta-analysis	rs2004640	7	128578301	T	0.47	1.3 [1.15-1.46]	1.70E-05	1.23 [1.11-1.37]	1.50E-04	1.36 [1.28-1.44]	2.27E-24	IRF5	splicing
Meta-analysis	rs35000415	7	128585616	T	0.10	1.51 [1.25-1.82]	2.40E-05	1.47 [1.24-1.74]	1.20E-05	1.72 [1.58-1.87]	2.91E-35	IRF5	intronic
Meta-analysis	rs12155244	7	128710988	C	0.82	1.17 [1.01-1.36]	3.90E-02	1.15 [1-1.31]	5.20E-02	1.24 [1.15-1.34]	3.21E-08	RP11-128A6.3	intergenic
Meta-analysis	rs4840568	8	11351019	A	0.27	1.16 [1.01-1.33]	3.00E-02	1.16 [1.02-1.31]	2.00E-02	1.27 [1.19-1.35]	1.66E-13	BLK	upstream
Meta-analysis	rs7823055	8	55511676	G	0.58	1.02 [0.9-1.15]	7.60E-01	1.03 [0.92-1.14]	6.50E-01	1.31 [1.23-1.38]	1.56E-19	RP1	intergenic
Meta-analysis	rs58688157	11	625085	A	0.27	1.31 [1.15-1.5]	5.50E-05	1.24 [1.1-1.4]	4.00E-04	1.25 [1.17-1.33]	7.14E-11	CDHR5	UTR5
Meta-analysis	rs10794329	11	648251	C	0.45	1.28 [1.13-1.44]	7.30E-05	1.26 [1.13-1.41]	2.90E-05	1.19 [1.13-1.27]	2.74E-09	DEAF1	intronic
Meta-analysis	rs597808	12	111973358	A	0.47	1.19 [1.06-1.34]	4.50E-03	1.2 [1.07-1.33]	1.20E-03	1.18 [1.11-1.25]	2.94E-08	ATXN2	intronic
Meta-analysis	16:31282098_t_c	16	31282098	C	0.63	1 [1-1]		1 [1-1]		1.2 [1.13-1.28]	2.40E-09	ITGAM	intronic
Meta-analysis	rs35472514	16	31283323	G	0.86	1.51 [1.25-1.84]	2.60E-05	1.52 [1.27-1.81]	3.20E-06	1.7 [1.57-1.85]	1.59E-37	ITGAM	intronic
Meta-analysis	rs13332649	16	85966683	A	0.20	1.21 [1.05-1.39]	1.00E-02	1.26 [1.11-1.43]	4.30E-04	1.34 [1.24-1.44]	1.40E-14	RP11-542M13.3	intergenic
Meta-analysis	rs74956615	19	10427721	T	0.97	1.35 [1.04-1.75]	2.40E-02	1.33 [1.05-1.69]	1.70E-02	1.56 [1.33-1.83]	3.38E-08	CTD-2369P2.12:RAVER1	UTR3
Meta-analysis	rs2278442	19	10444826	A	0.34	1.27 [1.12-1.43]	1.80E-04	1.29 [1.16-1.45]	7.00E-06	1.21 [1.14-1.28]	1.08E-09	ICAM3	intronic
Meta-analysis	rs35251378	19	10459969	G	0.73	1.14 [1-1.3]	4.80E-02	1.13 [1.01-1.28]	4.00E-02	1.23 [1.15-1.31]	5.56E-10	TYK2	intergenic
Meta-analysis	rs3747093	22	21984379	A	0.20	1.21 [1.04-1.41]	1.20E-02	1.21 [1.06-1.39]	6.50E-03	1.28 [1.19-1.37]	9.69E-12	YDJC	upstream

Table x4.9 EQTL look-ups for female-specific genetic risk variants

Trait	Gencode Id	Gene Symbol	Variant Id	SNP Id	P-Value	NES	Tissue
Ankylosing spondylitis	ENSG00000139044.10	B4GALNT3	chr12_516854_C_T_b38	rs7136938	0.000034	-0.23	Esophagus - Mucosa

	ENSG00000139044.10	B4GALNT3	chr12_516854_C_T_b38	rs7136938	0.000074	-0.16	Skin - Sun Exposed (Lower leg)
Coeliac Disease	ENSG00000090104.11	RGS1	chr1_192552461_G_T_b38	rs10801129	1.90E-24	-0.44	Esophagus - Muscularis
	ENSG00000090104.11	RGS1	chr1_192552461_G_T_b38	rs10801129	1.40E-07	-0.26	Esophagus - Gastroesophageal Junction
	ENSG00000090104.11	RGS1	chr1_192552461_G_T_b38	rs10801129	0.000077	-0.13	Adipose - Subcutaneous
	ENSG00000232498.1	RP5-1011O1.2	chr1_192552461_G_T_b38	rs10801129	3.80E-13	-0.44	Esophagus - Muscularis
	ENSG00000232498.1	RP5-1011O1.2	chr1_192552461_G_T_b38	rs10801129	3.00E-10	-0.44	Esophagus - Gastroesophageal Junction
	ENSG00000232498.1	RP5-1011O1.2	chr1_192552461_G_T_b38	rs10801129	0.000001	-0.44	Uterus
Inflammatory bowel disease	ENSG00000255277.3	ABCC6P2	chr16_15286066_C_G_b38	rs3867524	2.20E-07	0.25	Thyroid
	ENSG00000255277.3	ABCC6P2	chr16_15286066_C_G_b38	rs3867524	0.000038	0.39	Minor Salivary Gland
	ENSG00000156968.8	MPV17L	chr16_15286066_C_G_b38	rs3867524	7.90E-07	0.21	Colon - Transverse
	ENSG00000156968.8	MPV17L	chr16_15286066_C_G_b38	rs3867524	0.000013	0.12	Thyroid
	ENSG00000156968.8	MPV17L	chr16_15286066_C_G_b38	rs3867524	0.00015	0.2	Cells - Cultured fibroblasts
	ENSG00000103512.14	NOMO1	chr16_15286066_C_G_b38	rs3867524	4.20E-09	0.15	Muscle - Skeletal
	ENSG00000103512.14	NOMO1	chr16_15286066_C_G_b38	rs3867524	4.90E-09	-0.21	Heart - Left Ventricle
	ENSG00000103512.14	NOMO1	chr16_15286066_C_G_b38	rs3867524	5.30E-07	-0.21	Heart - Atrial Appendage
	ENSG00000103512.14	NOMO1	chr16_15286066_C_G_b38	rs3867524	0.0000012	-0.17	Adipose - Subcutaneous
	ENSG00000103512.14	NOMO1	chr16_15286066_C_G_b38	rs3867524	0.00011	-0.16	Artery - Aorta
	ENSG00000103512.14	NOMO1	chr16_15286066_C_G_b38	rs3867524	0.0002	-0.13	Artery - Tibial
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	9.50E-40	-0.54	Adipose - Subcutaneous
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	2.10E-30	-0.48	Adipose - Visceral (Omentum)
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	1.50E-28	-0.47	Nerve - Tibial
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	1.70E-25	-0.39	Skin - Sun Exposed (Lower leg)

	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	1.10E-23	-0.34	Skin - Not Sun Exposed (Suprapubic)
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	1.20E-23	-0.38	Artery - Tibial
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	6.70E-23	-0.25	Whole Blood
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	2.00E-21	-0.41	Heart - Atrial Appendage
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	9.10E-20	-0.28	Muscle - Skeletal
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	5.50E-19	-0.29	Esophagus - Mucosa
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	7.20E-19	-0.28	Thyroid
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	1.50E-18	-0.4	Breast - Mammary Tissue
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	7.10E-18	-0.3	Lung
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	1.60E-15	-0.3	Cells - Cultured fibroblasts
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	2.10E-14	-0.26	Heart - Left Ventricle
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	4.60E-12	-0.42	Brain - Caudate (basal ganglia)
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	7.60E-11	-0.37	Pancreas
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	4.10E-10	-0.21	Stomach
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	1.40E-08	-0.25	Esophagus - Gastroesophageal Junction
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	2.20E-08	-0.38	Uterus
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	2.30E-08	-0.28	Brain - Nucleus accumbens (basal ganglia)
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	2.50E-08	-0.18	Esophagus - Muscularis
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	2.70E-08	-0.32	Spleen
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	5.10E-08	-0.32	Testis
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	5.40E-08	-0.34	Brain - Hypothalamus
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	7.20E-08	-0.32	Pituitary

	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	8.70E-08	-0.21	Artery - Aorta
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	9.60E-08	-0.43	Brain - Amygdala
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	1.40E-07	-0.34	Brain - Cerebellum
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	1.70E-07	-0.16	Colon - Transverse
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	1.70E-07	-0.18	Colon - Sigmoid
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	6.90E-07	-0.32	Brain - Hippocampus
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	9.20E-07	-0.23	Adrenal Gland
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	0.0000016	-0.3	Liver
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	0.000003	-0.48	Minor Salivary Gland
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	0.000003	-0.32	Brain - Frontal Cortex (BA9)
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	0.0000031	-0.29	Brain - Anterior cingulate cortex (BA24)
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	0.0000075	-0.29	Brain - Cortex
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	0.0000081	-0.31	Artery - Coronary
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	0.000016	-0.36	Brain - Spinal cord (cervical c-1)
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	0.000027	-0.24	Prostate
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	0.000042	-0.28	Ovary
	ENSG00000188599.17	NPIPP1	chr16_15286066_C_G_b38	rs3867524	0.000047	-0.22	Small Intestine - Terminal Ileum
	ENSG00000157045.8	NTAN1	chr16_15286066_C_G_b38	rs3867524	1.50E-12	-0.17	Muscle - Skeletal
	ENSG00000157045.8	NTAN1	chr16_15286066_C_G_b38	rs3867524	3.00E-07	-0.19	Heart - Left Ventricle
	ENSG00000157045.8	NTAN1	chr16_15286066_C_G_b38	rs3867524	0.000001	-0.14	Adipose - Visceral (Omentum)
	ENSG00000157045.8	NTAN1	chr16_15286066_C_G_b38	rs3867524	0.0000012	-0.13	Skin - Not Sun Exposed (Suprapubic)
	ENSG00000157045.8	NTAN1	chr16_15286066_C_G_b38	rs3867524	0.0000044	-0.11	Thyroid
	ENSG00000157045.8	NTAN1	chr16_15286066_C_G_b38	rs3867524	0.000018	-0.17	Heart - Atrial Appendage

	ENSG00000140694.16	PARN	chr16_15286066_C_G_b38	rs3867524	0.00029	-0.1	Skin - Sun Exposed (Lower leg)
	ENSG00000179889.18	PDXDC1	chr16_15286066_C_G_b38	rs3867524	0.00017	0.07	Whole Blood
	ENSG00000250251.6	PKD1P6	chr16_15286066_C_G_b38	rs3867524	4.00E-23	-0.33	Adipose - Subcutaneous
	ENSG00000250251.6	PKD1P6	chr16_15286066_C_G_b38	rs3867524	7.90E-13	-0.27	Adipose - Visceral (Omentum)
	ENSG00000250251.6	PKD1P6	chr16_15286066_C_G_b38	rs3867524	3.10E-10	-0.17	Skin - Sun Exposed (Lower leg)
	ENSG00000250251.6	PKD1P6	chr16_15286066_C_G_b38	rs3867524	9.10E-10	-0.25	Heart - Atrial Appendage
	ENSG00000250251.6	PKD1P6	chr16_15286066_C_G_b38	rs3867524	2.90E-09	-0.15	Skin - Not Sun Exposed (Suprapubic)
	ENSG00000250251.6	PKD1P6	chr16_15286066_C_G_b38	rs3867524	1.10E-07	-0.1	Whole Blood
	ENSG00000250251.6	PKD1P6	chr16_15286066_C_G_b38	rs3867524	1.40E-07	-0.15	Artery - Tibial
	ENSG00000250251.6	PKD1P6	chr16_15286066_C_G_b38	rs3867524	2.00E-07	-0.18	Nerve - Tibial
	ENSG00000250251.6	PKD1P6	chr16_15286066_C_G_b38	rs3867524	4.90E-07	-0.21	Breast - Mammary Tissue
	ENSG00000250251.6	PKD1P6	chr16_15286066_C_G_b38	rs3867524	0.0000021	-0.15	Esophagus - Mucosa
	ENSG00000250251.6	PKD1P6	chr16_15286066_C_G_b38	rs3867524	0.0000043	-0.16	Lung
	ENSG00000250251.6	PKD1P6	chr16_15286066_C_G_b38	rs3867524	0.000032	-0.11	Muscle - Skeletal
	ENSG00000250251.6	PKD1P6	chr16_15286066_C_G_b38	rs3867524	0.000044	-0.2	Spleen
	ENSG00000261819.1	RP11-680G24.4	chr16_15286066_C_G_b38	rs3867524	0.0000077	0.47	Brain - Frontal Cortex (BA9)
	ENSG00000261819.1	RP11-680G24.4	chr16_15286066_C_G_b38	rs3867524	0.000064	0.21	Lung
	ENSG00000261819.1	RP11-680G24.4	chr16_15286066_C_G_b38	rs3867524	0.000093	0.21	Adipose - Subcutaneous
	ENSG00000261819.1	RP11-680G24.4	chr16_15286066_C_G_b38	rs3867524	0.00019	0.17	Muscle - Skeletal
	ENSG00000275910.1	RP11-680G24.6	chr16_15286066_C_G_b38	rs3867524	0.0000026	0.43	Brain - Frontal Cortex (BA9)
	ENSG00000275910.1	RP11-680G24.6	chr16_15286066_C_G_b38	rs3867524	0.00015	0.18	Lung

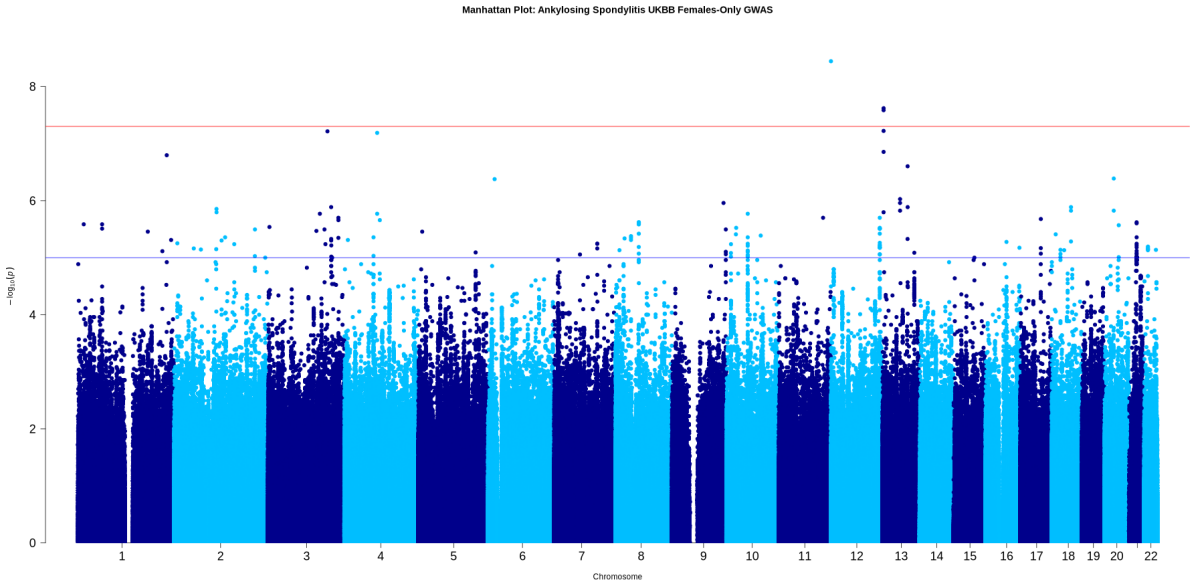
	ENSG00000254609.1	RP11-719K4.3	chr16_15286066_C_G_b38	rs3867524	0.000066	-0.2	Colon - Transverse
	ENSG00000260735.1	RP11-72I8.1	chr16_15286066_C_G_b38	rs3867524	4.20E-31	-0.61	Adipose - Subcutaneous
	ENSG00000260735.1	RP11-72I8.1	chr16_15286066_C_G_b38	rs3867524	2.30E-27	-0.54	Skin - Sun Exposed (Lower leg)
	ENSG00000260735.1	RP11-72I8.1	chr16_15286066_C_G_b38	rs3867524	8.70E-25	-0.53	Nerve - Tibial
	ENSG00000260735.1	RP11-72I8.1	chr16_15286066_C_G_b38	rs3867524	2.30E-24	-0.55	Skin - Not Sun Exposed (Suprapubic)
	ENSG00000260735.1	RP11-72I8.1	chr16_15286066_C_G_b38	rs3867524	1.50E-20	-0.42	Artery - Tibial
	ENSG00000260735.1	RP11-72I8.1	chr16_15286066_C_G_b38	rs3867524	7.10E-20	-0.54	Cells - Cultured fibroblasts
	ENSG00000260735.1	RP11-72I8.1	chr16_15286066_C_G_b38	rs3867524	7.60E-20	-0.58	Heart - Atrial Appendage
	ENSG00000260735.1	RP11-72I8.1	chr16_15286066_C_G_b38	rs3867524	9.60E-20	-0.57	Breast - Mammary Tissue
	ENSG00000260735.1	RP11-72I8.1	chr16_15286066_C_G_b38	rs3867524	8.30E-19	-0.57	Colon - Sigmoid
	ENSG00000260735.1	RP11-72I8.1	chr16_15286066_C_G_b38	rs3867524	1.30E-18	-0.4	Muscle - Skeletal
	ENSG00000260735.1	RP11-72I8.1	chr16_15286066_C_G_b38	rs3867524	4.50E-18	-0.42	Thyroid
	ENSG00000260735.1	RP11-72I8.1	chr16_15286066_C_G_b38	rs3867524	4.80E-18	-0.52	Artery - Aorta
	ENSG00000260735.1	RP11-72I8.1	chr16_15286066_C_G_b38	rs3867524	1.20E-17	-0.49	Adipose - Visceral (Omentum)
	ENSG00000260735.1	RP11-72I8.1	chr16_15286066_C_G_b38	rs3867524	5.90E-17	-0.45	Esophagus - Mucosa
	ENSG00000260735.1	RP11-72I8.1	chr16_15286066_C_G_b38	rs3867524	9.00E-16	-0.4	Lung
	ENSG00000260735.1	RP11-72I8.1	chr16_15286066_C_G_b38	rs3867524	3.00E-14	-0.41	Esophagus - Muscularis
	ENSG00000260735.1	RP11-72I8.1	chr16_15286066_C_G_b38	rs3867524	1.20E-13	-0.42	Colon - Transverse
	ENSG00000260735.1	RP11-72I8.1	chr16_15286066_C_G_b38	rs3867524	2.40E-13	-0.45	Esophagus - Gastroesophageal Junction
	ENSG00000260735.1	RP11-72I8.1	chr16_15286066_C_G_b38	rs3867524	7.40E-13	-0.58	Pituitary
	ENSG00000260735.1	RP11-72I8.1	chr16_15286066_C_G_b38	rs3867524	6.00E-11	-0.62	Brain - Cerebellum
	ENSG00000260735.1	RP11-72I8.1	chr16_15286066_C_G_b38	rs3867524	1.40E-10	-0.57	Artery - Coronary
	ENSG00000260735.1	RP11-72I8.1	chr16_15286066_C_G_b38	rs3867524	2.60E-10	-0.41	Heart - Left Ventricle

	ENSG00000260735.1	RP11-72I8.1	chr16_15286066_C_G_b38	rs3867524	8.80E-10	-0.58	Ovary
	ENSG00000260735.1	RP11-72I8.1	chr16_15286066_C_G_b38	rs3867524	4.70E-09	-0.56	Brain - Cerebellar Hemisphere
	ENSG00000260735.1	RP11-72I8.1	chr16_15286066_C_G_b38	rs3867524	5.60E-09	-0.52	Prostate
	ENSG00000260735.1	RP11-72I8.1	chr16_15286066_C_G_b38	rs3867524	6.60E-08	-0.45	Testis
	ENSG00000260735.1	RP11-72I8.1	chr16_15286066_C_G_b38	rs3867524	1.60E-07	-0.32	Stomach
	ENSG00000260735.1	RP11-72I8.1	chr16_15286066_C_G_b38	rs3867524	0.000003	-0.41	Spleen
	ENSG00000260735.1	RP11-72I8.1	chr16_15286066_C_G_b38	rs3867524	0.0000033	-0.35	Pancreas
	ENSG00000260735.1	RP11-72I8.1	chr16_15286066_C_G_b38	rs3867524	0.0000046	-0.53	Minor Salivary Gland
	ENSG00000260735.1	RP11-72I8.1	chr16_15286066_C_G_b38	rs3867524	0.000012	-0.41	Vagina
	ENSG00000260735.1	RP11-72I8.1	chr16_15286066_C_G_b38	rs3867524	0.000019	-0.43	Uterus
	ENSG00000260735.1	RP11-72I8.1	chr16_15286066_C_G_b38	rs3867524	0.000053	-0.42	Brain - Cortex
	ENSG00000183458.13	RP11-958N24.1	chr16_15286066_C_G_b38	rs3867524	1.20E-11	-0.23	Adipose - Subcutaneous
	ENSG00000183458.13	RP11-958N24.1	chr16_15286066_C_G_b38	rs3867524	4.70E-10	-0.2	Esophagus - Muscularis
	ENSG00000183458.13	RP11-958N24.1	chr16_15286066_C_G_b38	rs3867524	5.20E-10	-0.25	Nerve - Tibial
	ENSG00000183458.13	RP11-958N24.1	chr16_15286066_C_G_b38	rs3867524	5.40E-09	-0.24	Colon - Sigmoid
	ENSG00000183458.13	RP11-958N24.1	chr16_15286066_C_G_b38	rs3867524	5.80E-09	-0.2	Esophagus - Gastroesophageal Junction
	ENSG00000183458.13	RP11-958N24.1	chr16_15286066_C_G_b38	rs3867524	0.0000016	-0.22	Heart - Left Ventricle
	ENSG00000183458.13	RP11-958N24.1	chr16_15286066_C_G_b38	rs3867524	0.0000026	-0.16	Thyroid
	ENSG00000183458.13	RP11-958N24.1	chr16_15286066_C_G_b38	rs3867524	0.0000034	-0.21	Breast - Mammary Tissue
	ENSG00000183458.13	RP11-958N24.1	chr16_15286066_C_G_b38	rs3867524	0.000004	-0.18	Adipose - Visceral (Omentum)
	ENSG00000183458.13	RP11-958N24.1	chr16_15286066_C_G_b38	rs3867524	0.0000083	-0.21	Artery - Aorta
	ENSG00000183458.13	RP11-958N24.1	chr16_15286066_C_G_b38	rs3867524	0.000024	-0.22	Heart - Atrial Appendage
	ENSG00000183458.13	RP11-958N24.1	chr16_15286066_C_G_b38	rs3867524	0.000037	-0.29	Ovary

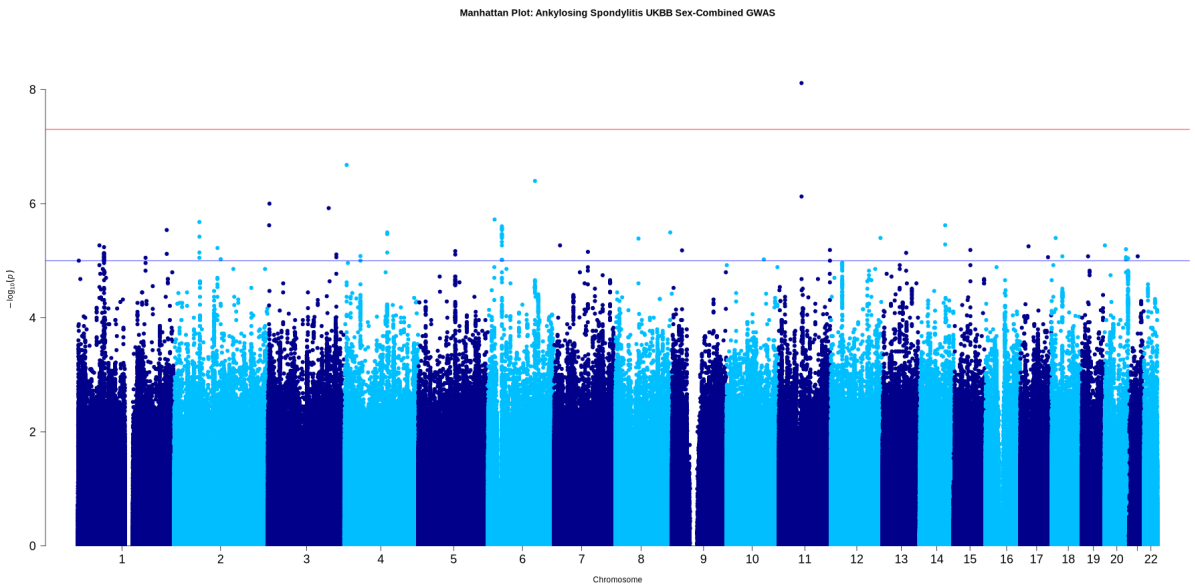
	ENSG00000183458.13	RP11-958N24.1	chr16_15286066_C_G_b38	rs3867524	0.000056	-0.22	Pancreas
	ENSG00000183458.13	RP11-958N24.1	chr16_15286066_C_G_b38	rs3867524	0.000086	-0.2	Testis
	ENSG00000183458.13	RP11-958N24.1	chr16_15286066_C_G_b38	rs3867524	0.000091	-0.15	Lung
	ENSG00000183458.13	RP11-958N24.1	chr16_15286066_C_G_b38	rs3867524	0.00011	-0.08	Whole Blood
	ENSG00000183458.13	RP11-958N24.1	chr16_15286066_C_G_b38	rs3867524	0.00012	-0.11	Cells - Cultured fibroblasts
	ENSG00000085721.12	RRN3	chr16_15286066_C_G_b38	rs3867524	2.10E-20	-0.21	Cells - Cultured fibroblasts
	ENSG00000085721.12	RRN3	chr16_15286066_C_G_b38	rs3867524	3.20E-11	0.4	Liver
	ENSG00000085721.12	RRN3	chr16_15286066_C_G_b38	rs3867524	1.40E-10	-0.22	Skin - Sun Exposed (Lower leg)
	ENSG00000085721.12	RRN3	chr16_15286066_C_G_b38	rs3867524	4.80E-10	0.17	Muscle - Skeletal
	ENSG00000085721.12	RRN3	chr16_15286066_C_G_b38	rs3867524	1.30E-08	-0.19	Skin - Not Sun Exposed (Suprapubic)
	ENSG00000085721.12	RRN3	chr16_15286066_C_G_b38	rs3867524	7.40E-08	0.25	Heart - Left Ventricle
	ENSG00000085721.12	RRN3	chr16_15286066_C_G_b38	rs3867524	0.0000013	-0.13	Artery - Tibial
	ENSG00000085721.12	RRN3	chr16_15286066_C_G_b38	rs3867524	0.0000019	-0.17	Esophagus - Mucosa
	ENSG00000085721.12	RRN3	chr16_15286066_C_G_b38	rs3867524	0.0000098	-0.3	Brain - Cerebellum
	ENSG00000085721.12	RRN3	chr16_15286066_C_G_b38	rs3867524	0.000033	-0.32	Cells - EBV-transformed lymphocytes
	ENSG00000085721.12	RRN3	chr16_15286066_C_G_b38	rs3867524	0.00006	0.15	Colon - Transverse
	ENSG00000207425.1	Y_RNA	chr16_15286066_C_G_b38	rs3867524	0.00014	0.22	Thyroid
Rheumatoid arthritis	ENSG00000234948.1	LINC01524	chr20_52621364_C_T_b38	rs6123193	0.0000016	-0.26	Testis
Multiple sclerosis	no EQTL result						
Osteoarthritis	no EQTL result						
	no EQTL result						
	no EQTL result						
	no EQTL result						

Figure x4.1 Ankylosing spondylitis GWAS results
A. Manhattan plots for i. female-only and ii. sex-combined UKBB GWAS

i. Female-only UKBB GWAS



ii. Sex-combined UKBB GWAS



B. Q-Q plots for i. female-only and ii. sex-combined UKBB GWAS

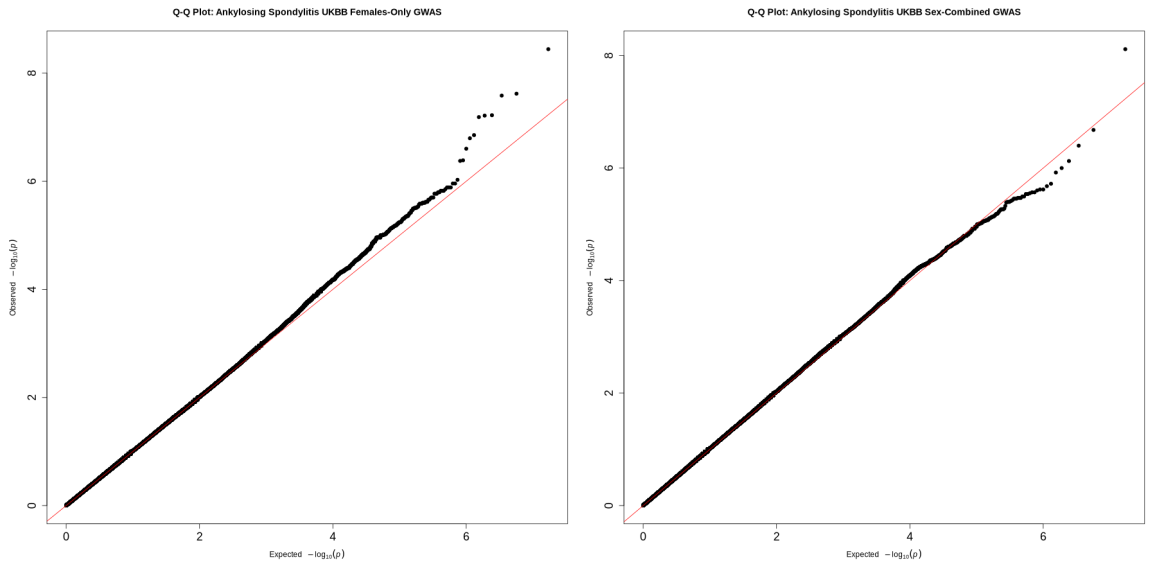
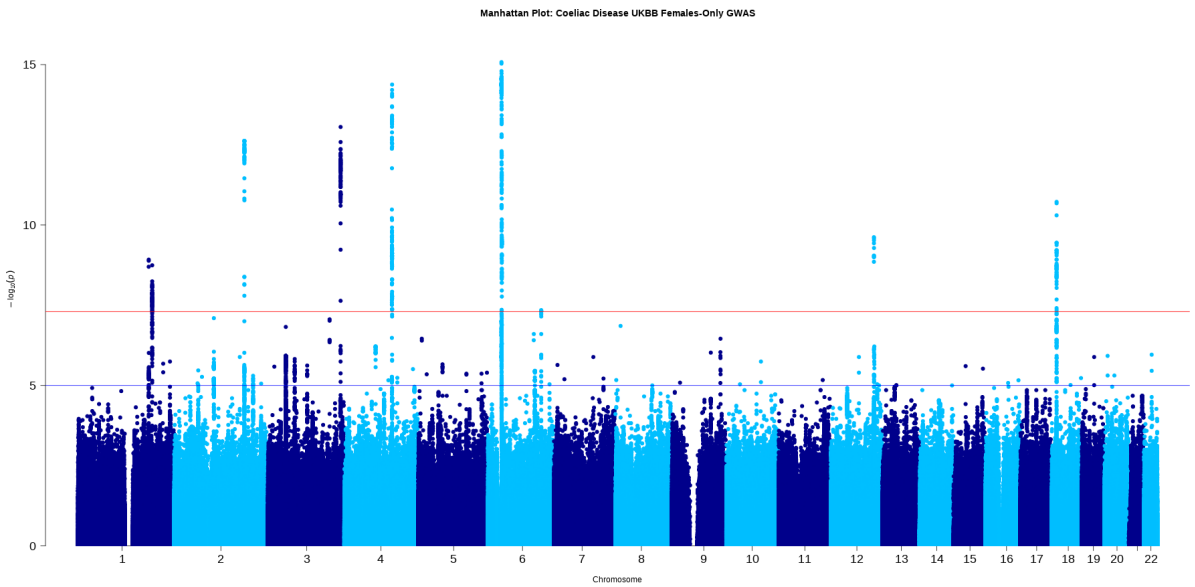


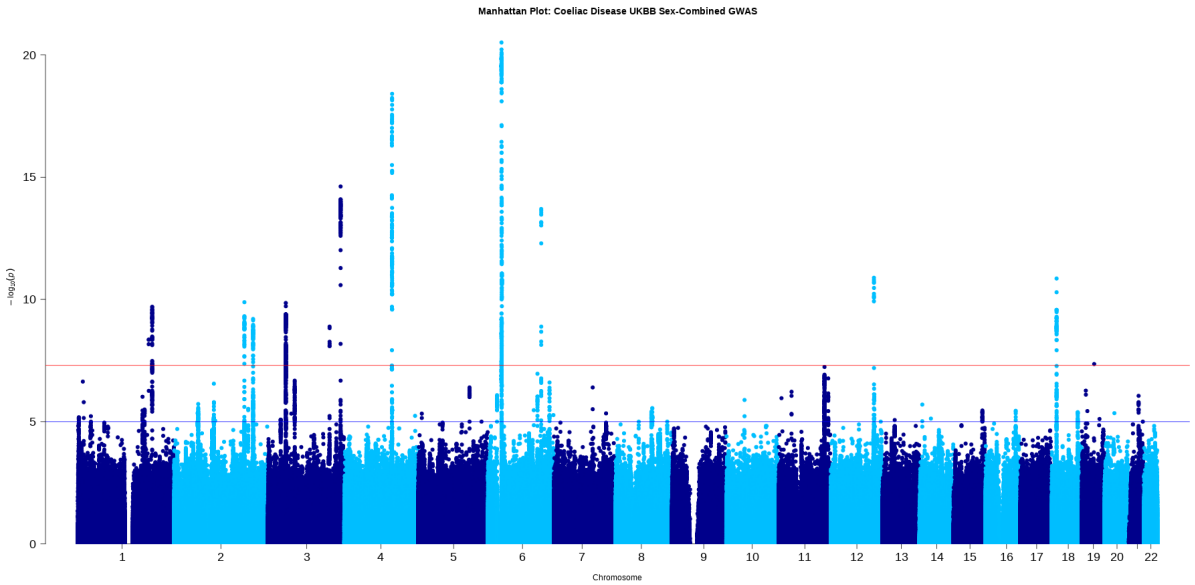
Figure x4.2 Coeliac disease GWAS results

A. Manhattan plots for i. female-only, ii. sex-combined, iii. meta-analysis sex-combined GWAS

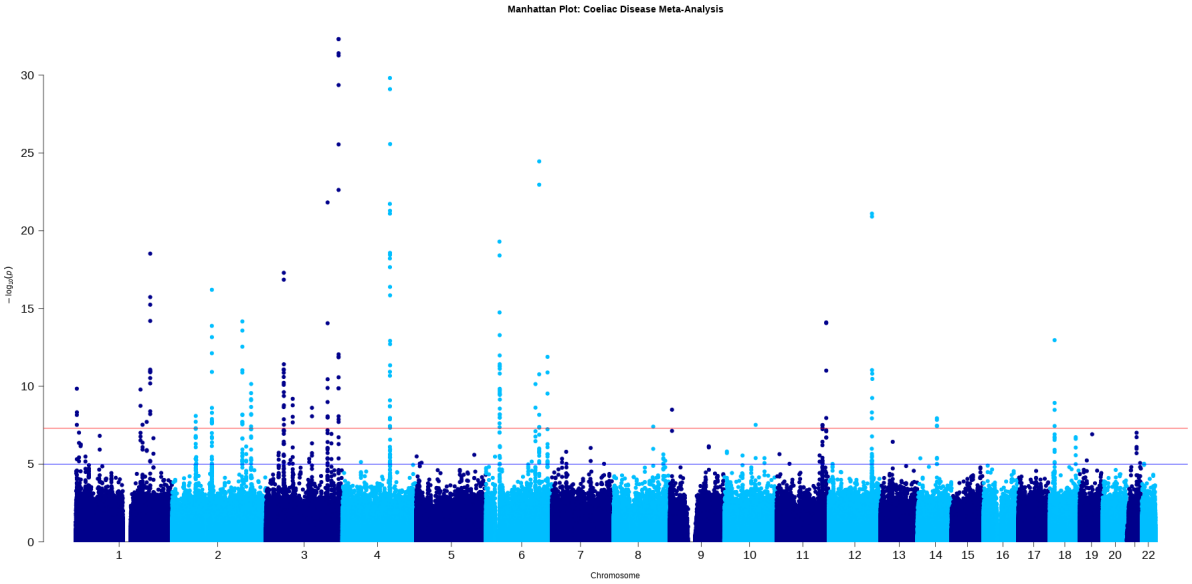
i. Female-only UKBB GWAS



ii. Sex-combined UKBB GWAS



iii. Meta-analysis sex-combined GWAS



B. Q-Q plots for i. female-only, ii. sex-combined, iii. meta-analysis sex-combined GWAS

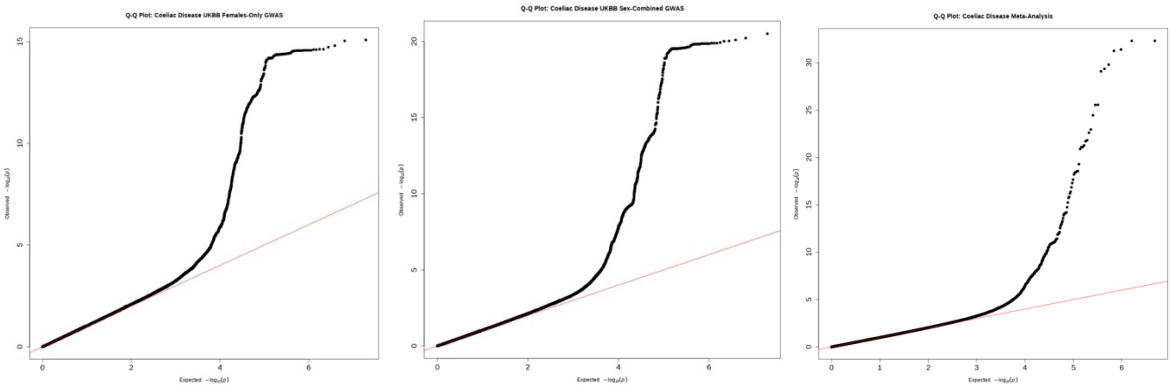
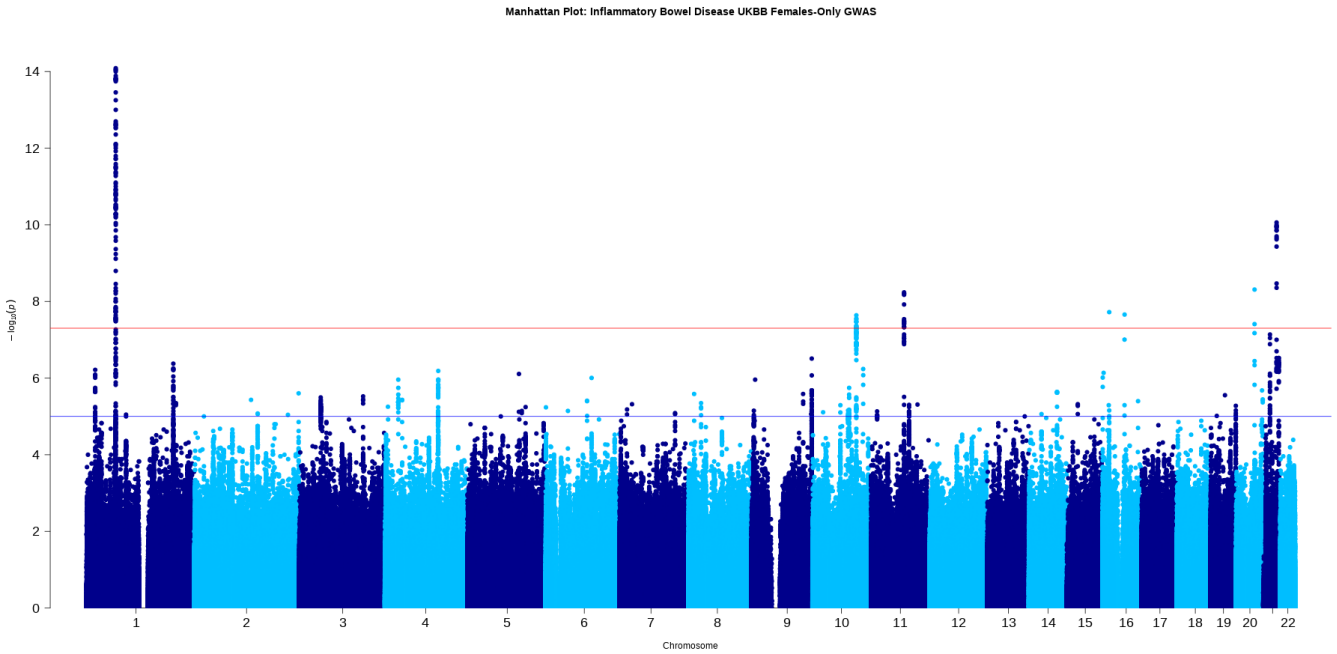


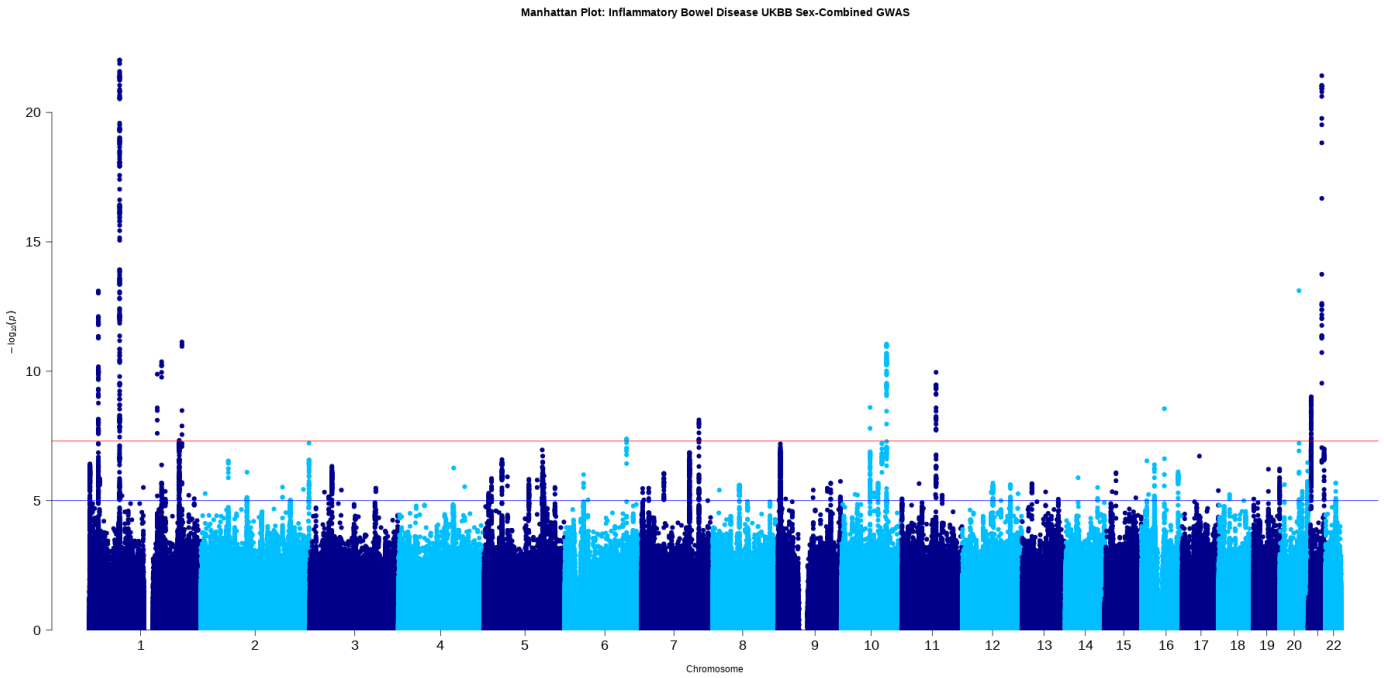
Figure x4.3 Inflammatory bowel disease GWAS results

A. Manhattan plots for i. female-only, ii. sex-combined, iii. meta-analysis sex-combined GWAS

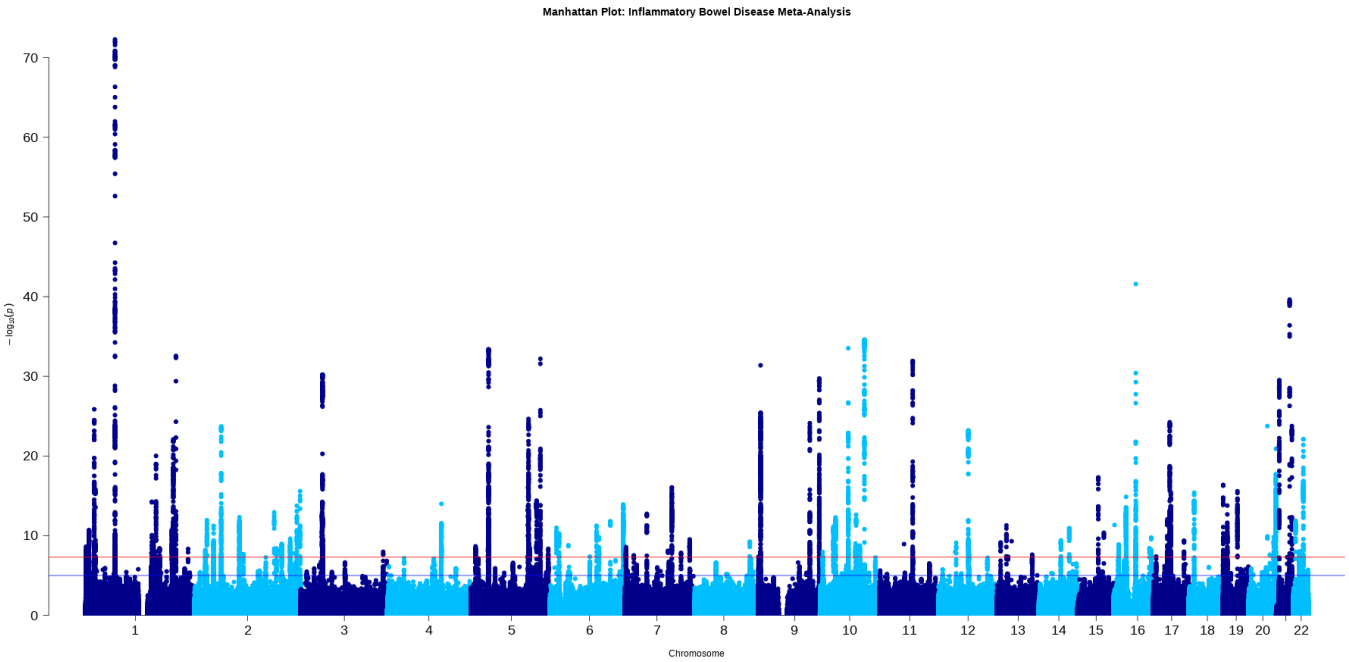
i. Female-only UKBB GWAS



ii. Sex-combined UKBB GWAS



iii. Meta-analysis sex-combined GWAS



B. Q-Q plots for i. female-only, ii. sex-combined, iii. meta-analysis sex-combined GWAS

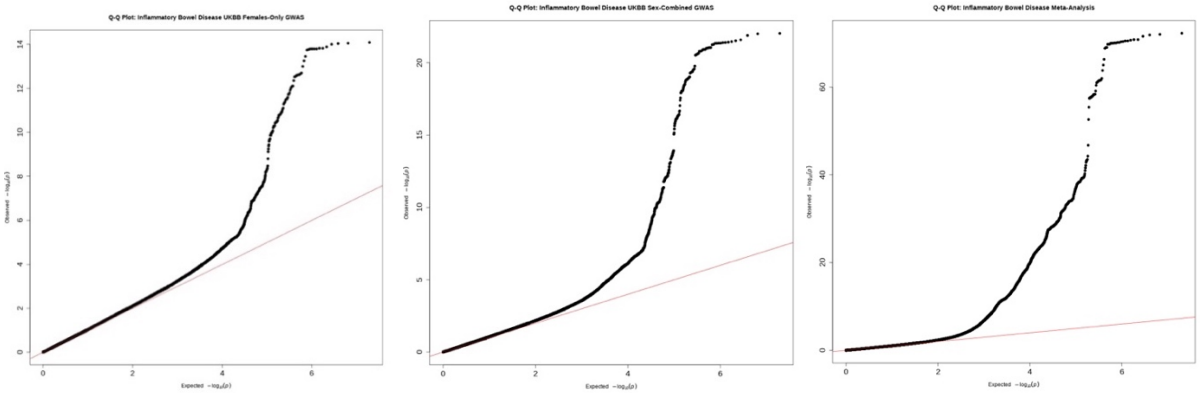
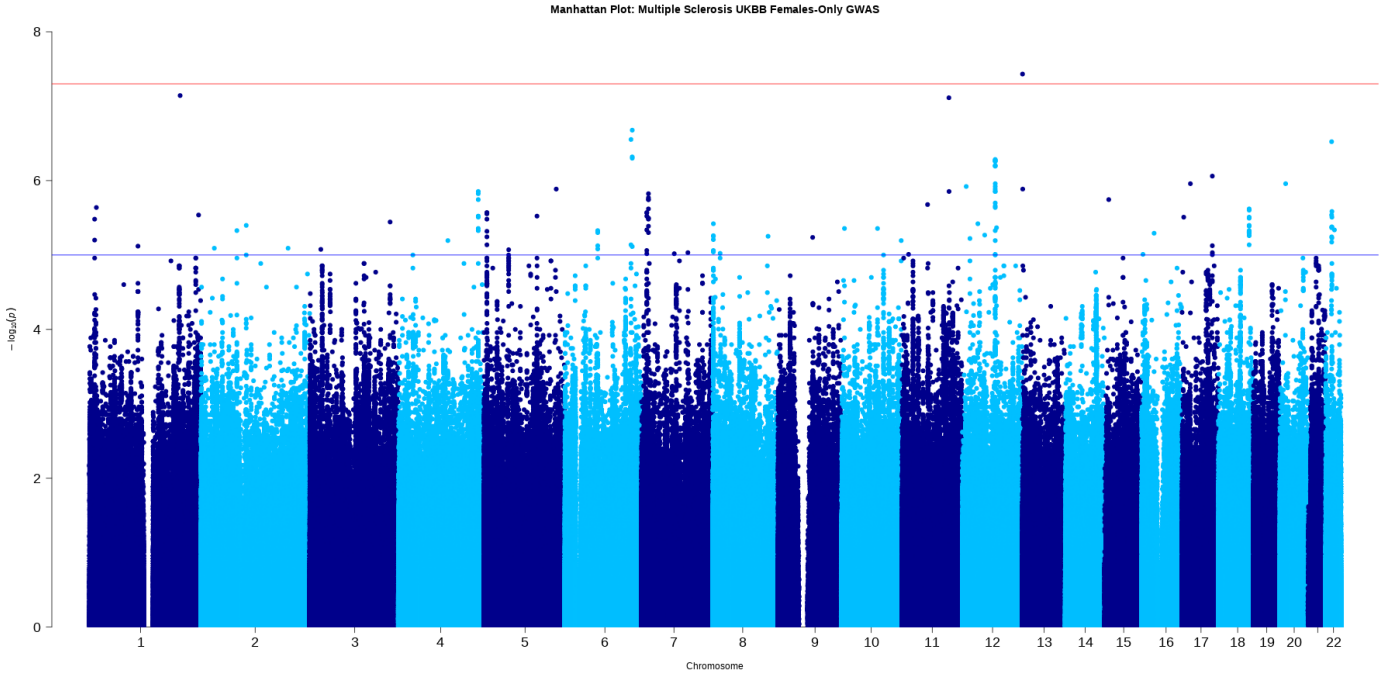


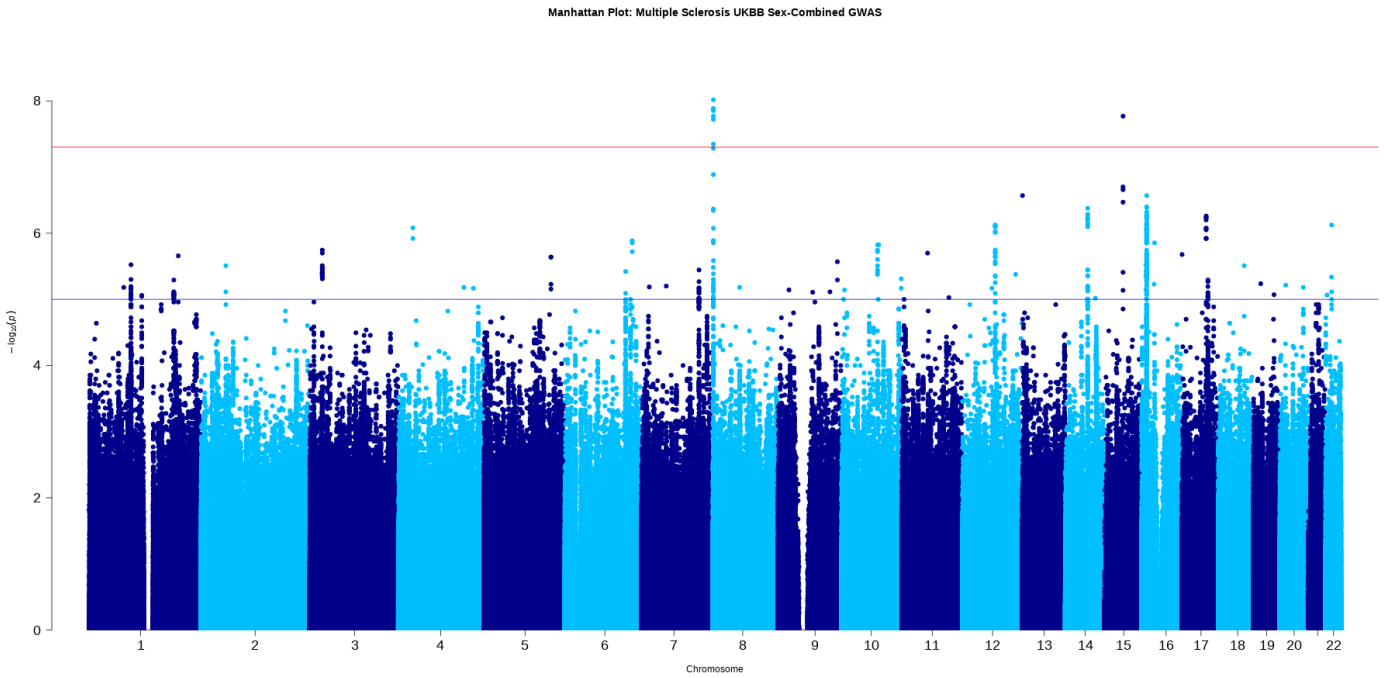
Figure x4.4 Multiple sclerosis GWAS results

A. Manhattan plots for i. female-only, ii. sex-combined, iii. meta-analysis sex-combined GWAS

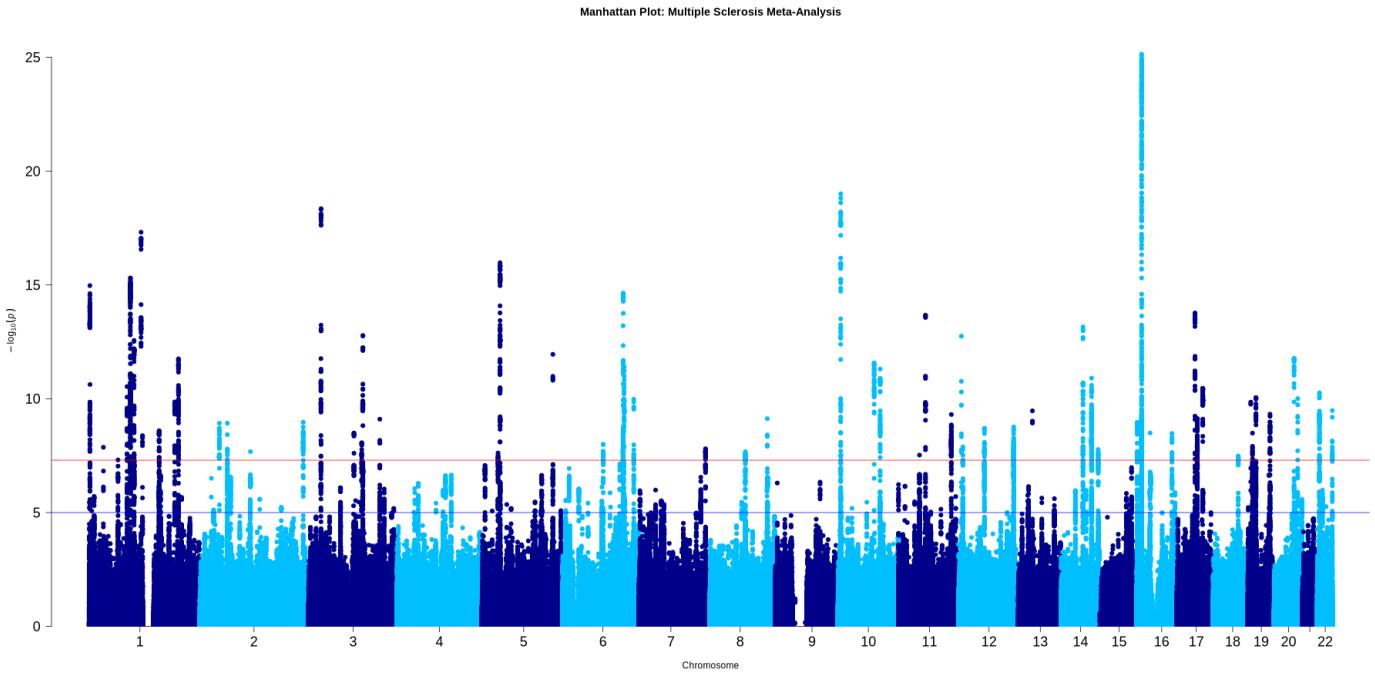
i. Female-only UKBB GWAS



ii. Sex-combined UKBB GWAS



iii. Meta-analysis sex-combined GWAS



B. Q-Q plots for i. female-only, ii. sex-combined, iii. meta-analysis sex-combined GWAS

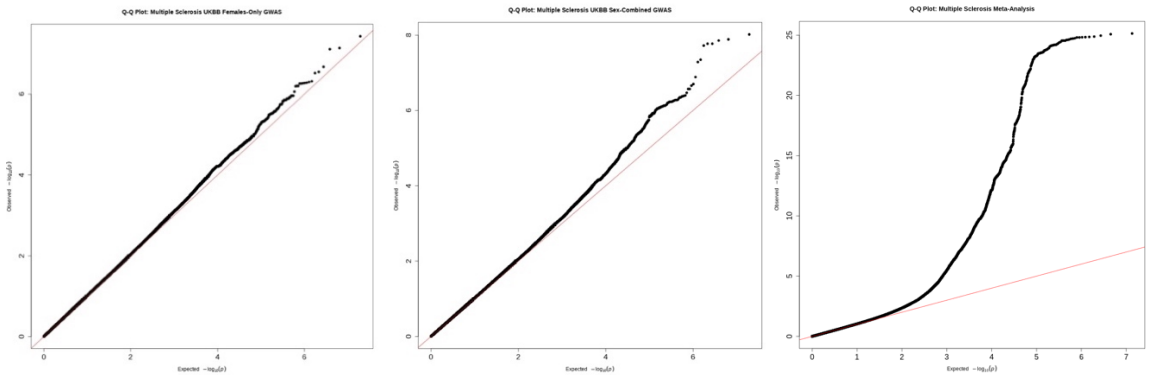
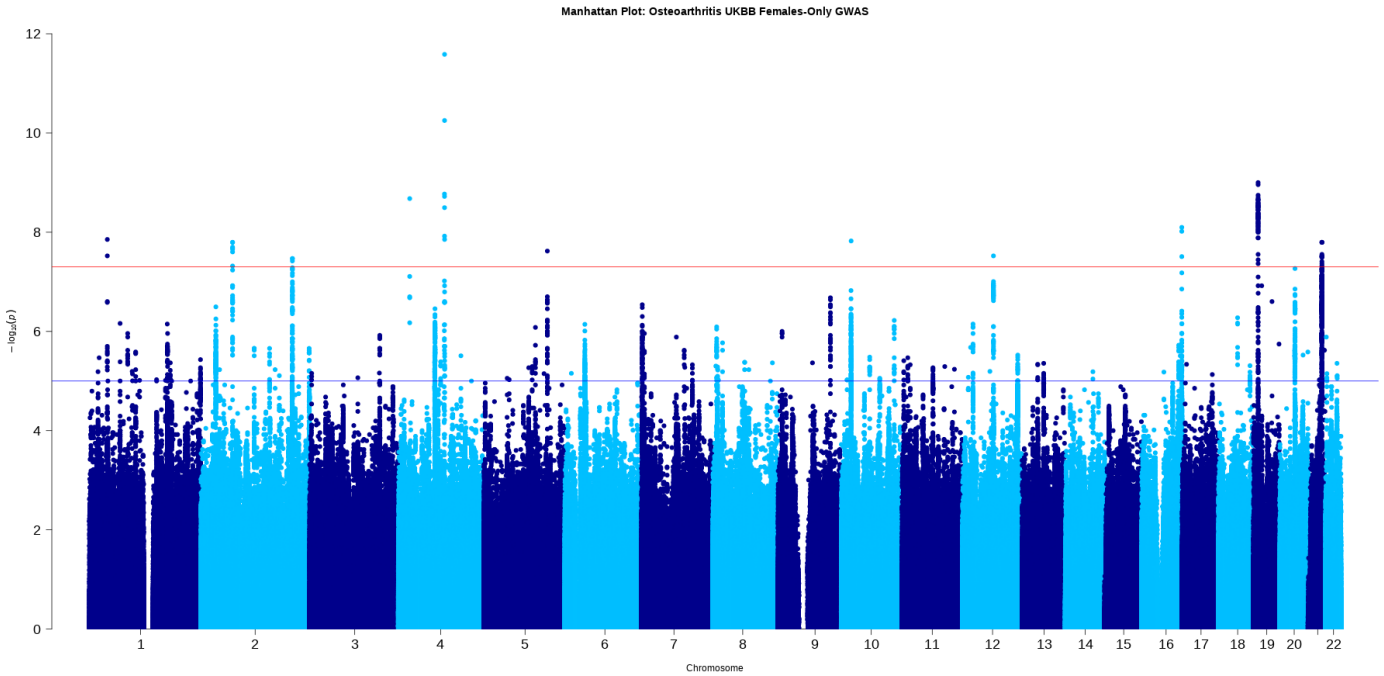


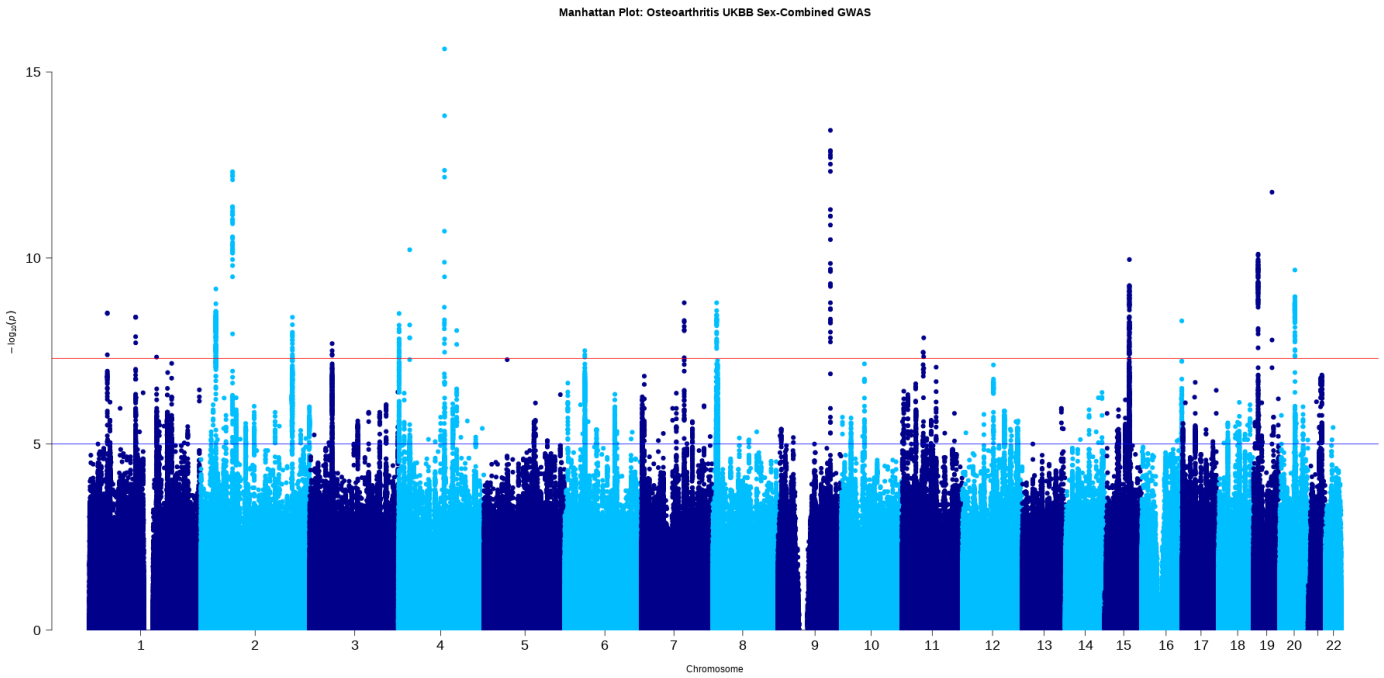
Figure x4.5 Osteoarthritis GWAS results

A. Manhattan plots for i. female-only, ii. sex-combined, iii. meta-analysis sex-combined GWAS

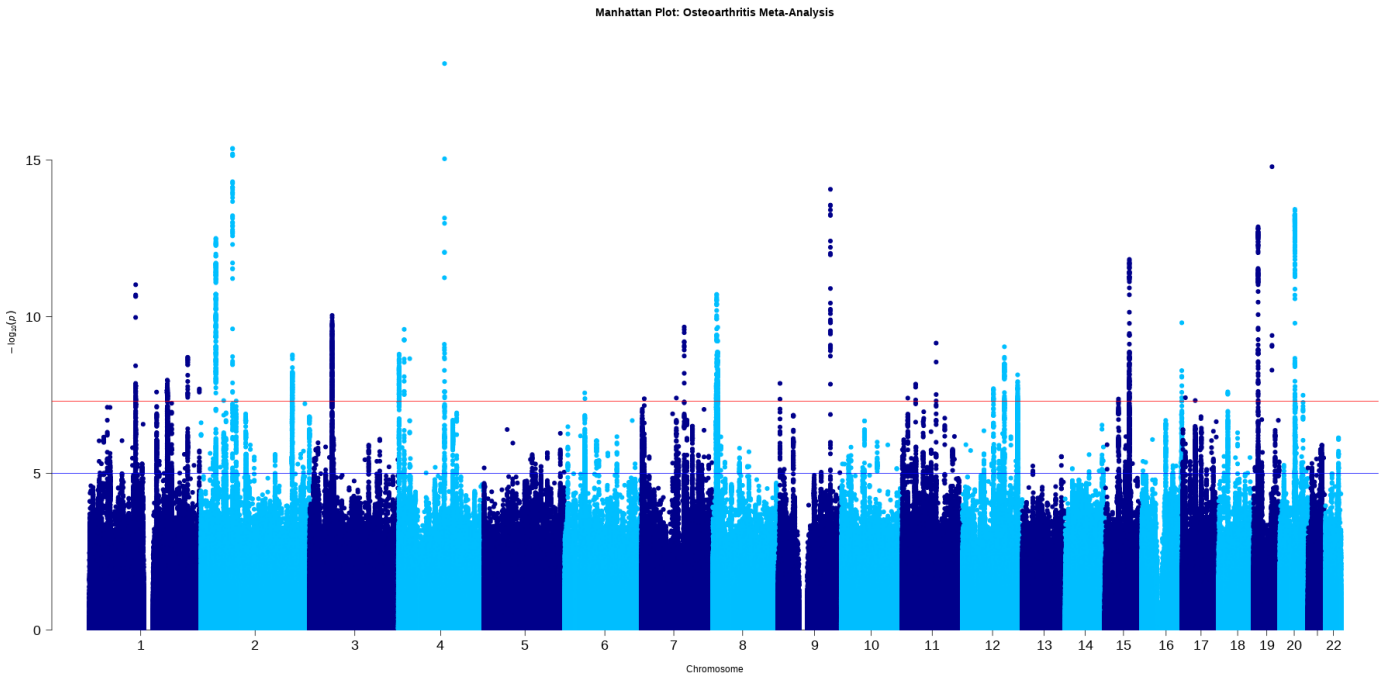
i. Female-only UKBB GWAS



ii. Sex-combined UKBB GWAS



iii. Meta-analysis sex-combined GWAS



B. Q-Q plots for i. female-only, ii. sex-combined, iii. meta-analysis sex-combined GWAS

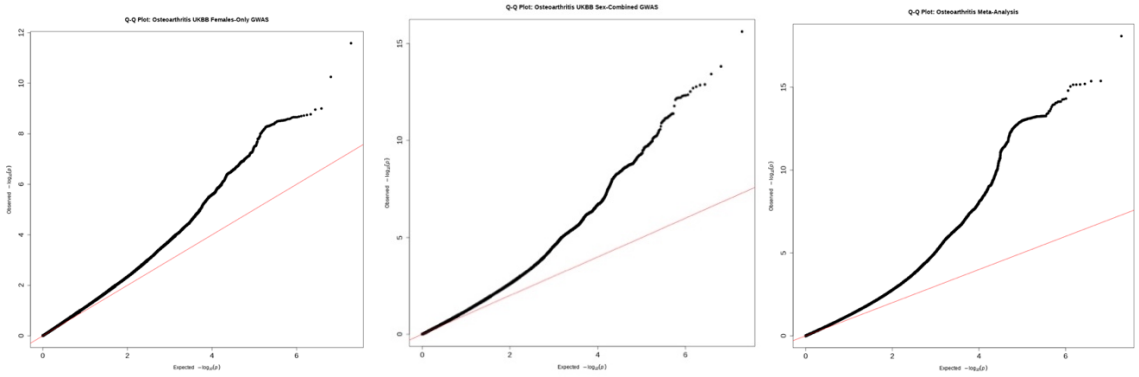
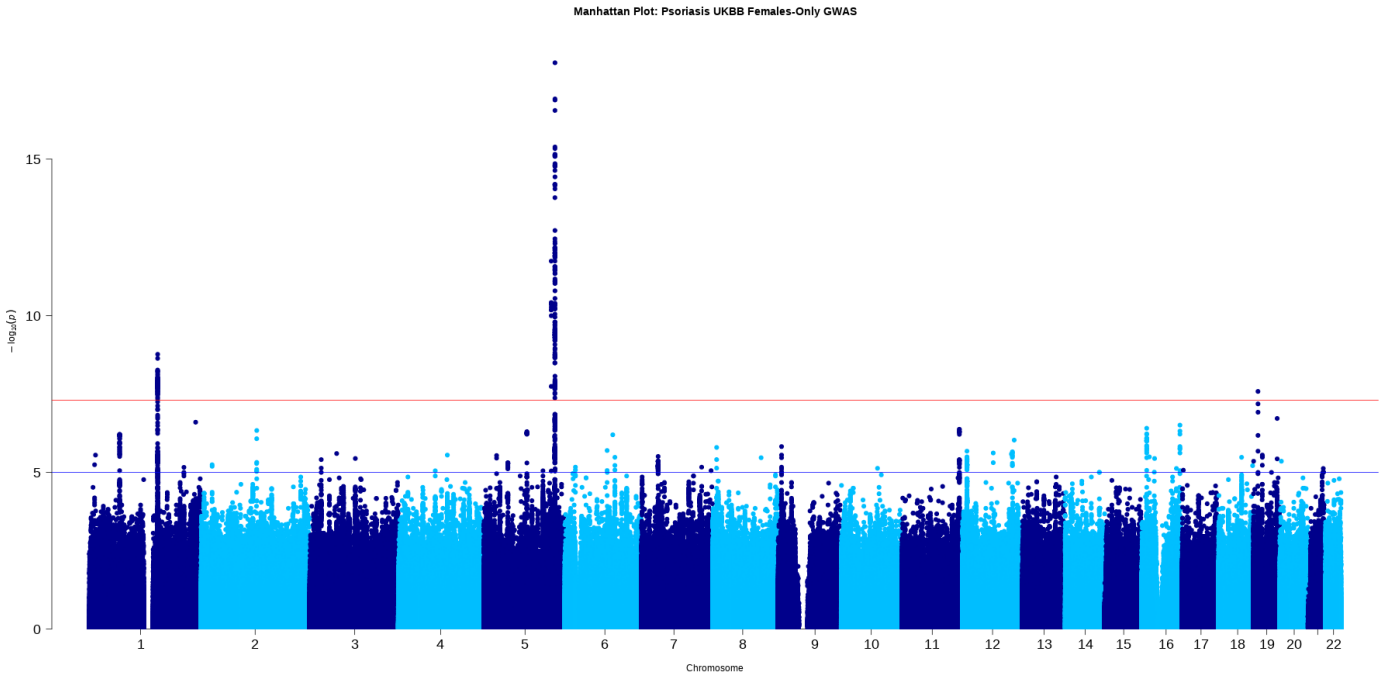


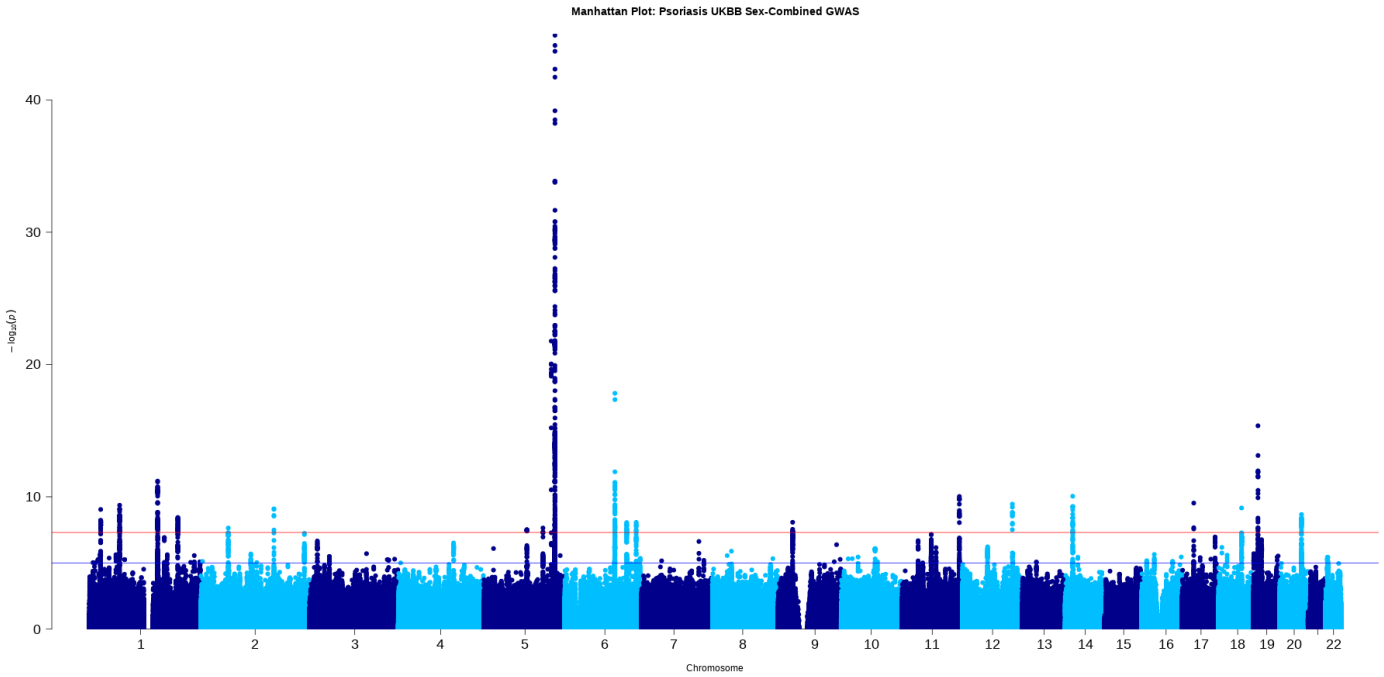
Figure x4.6 Psoriasis GWAS results

A. Manhattan plots for i. female-only, ii. sex-combined, iii. meta-analysis sex-combined GWAS

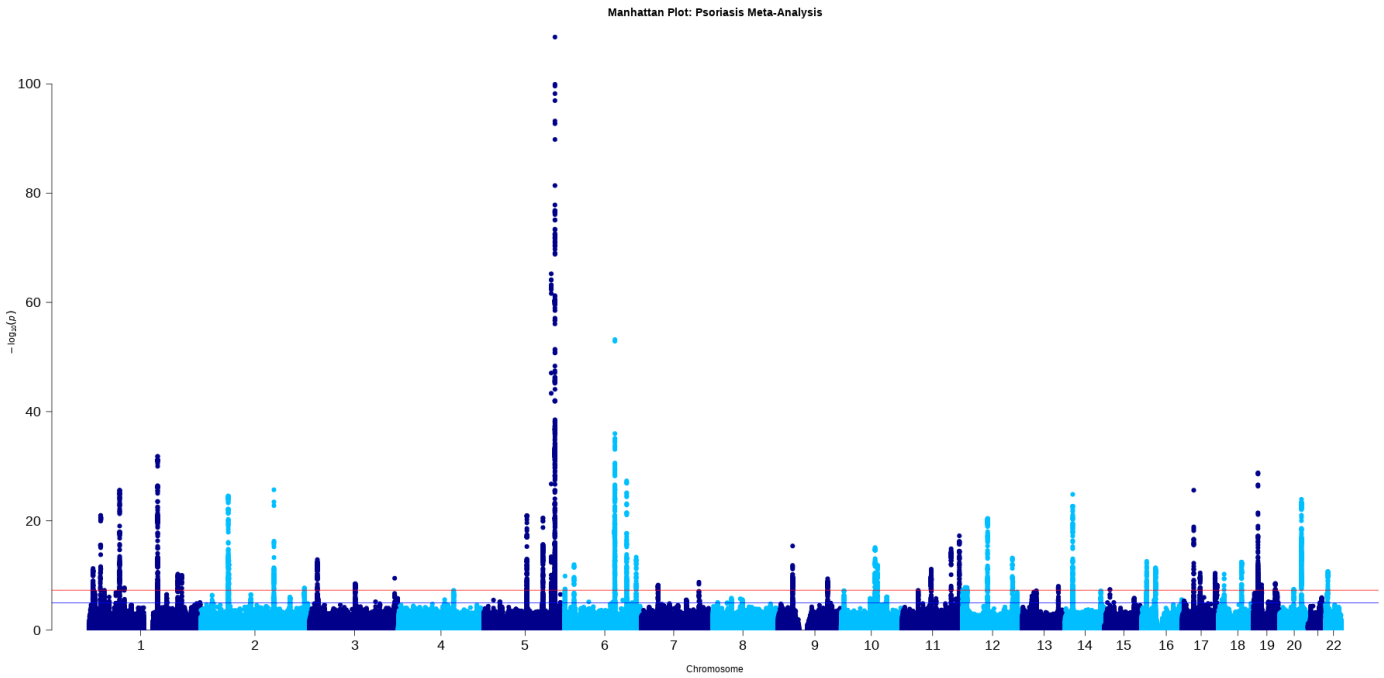
i. Female-only UKBB GWAS



ii. Sex-combined UKBB GWAS



iii. Meta-analysis sex-combined GWAS



B. Q-Q plots for i. female-only, ii. sex-combined, iii. meta-analysis sex-combined GWAS

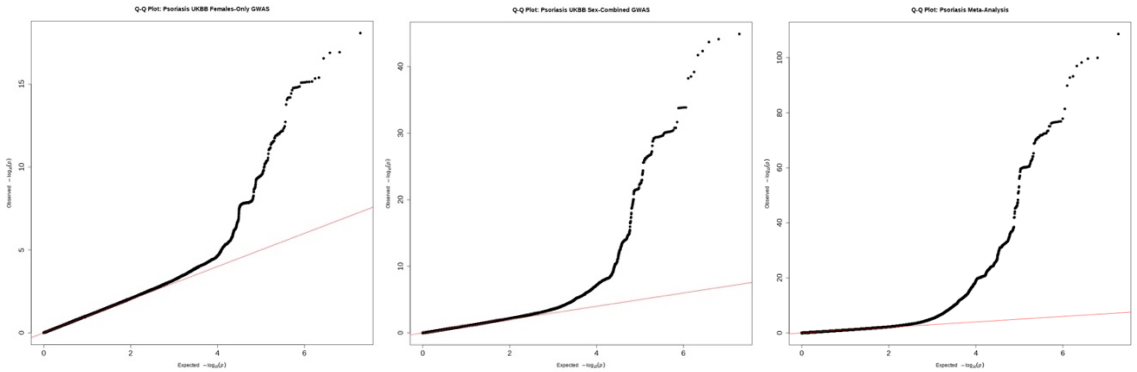
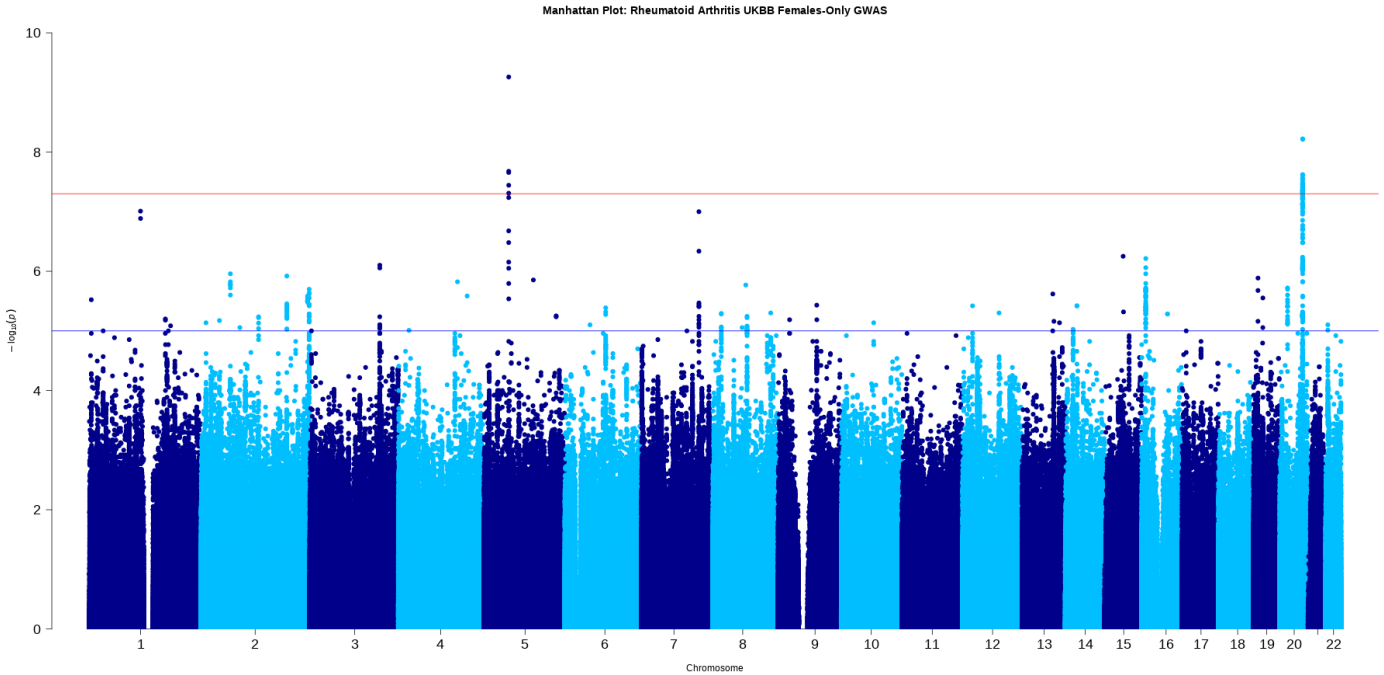


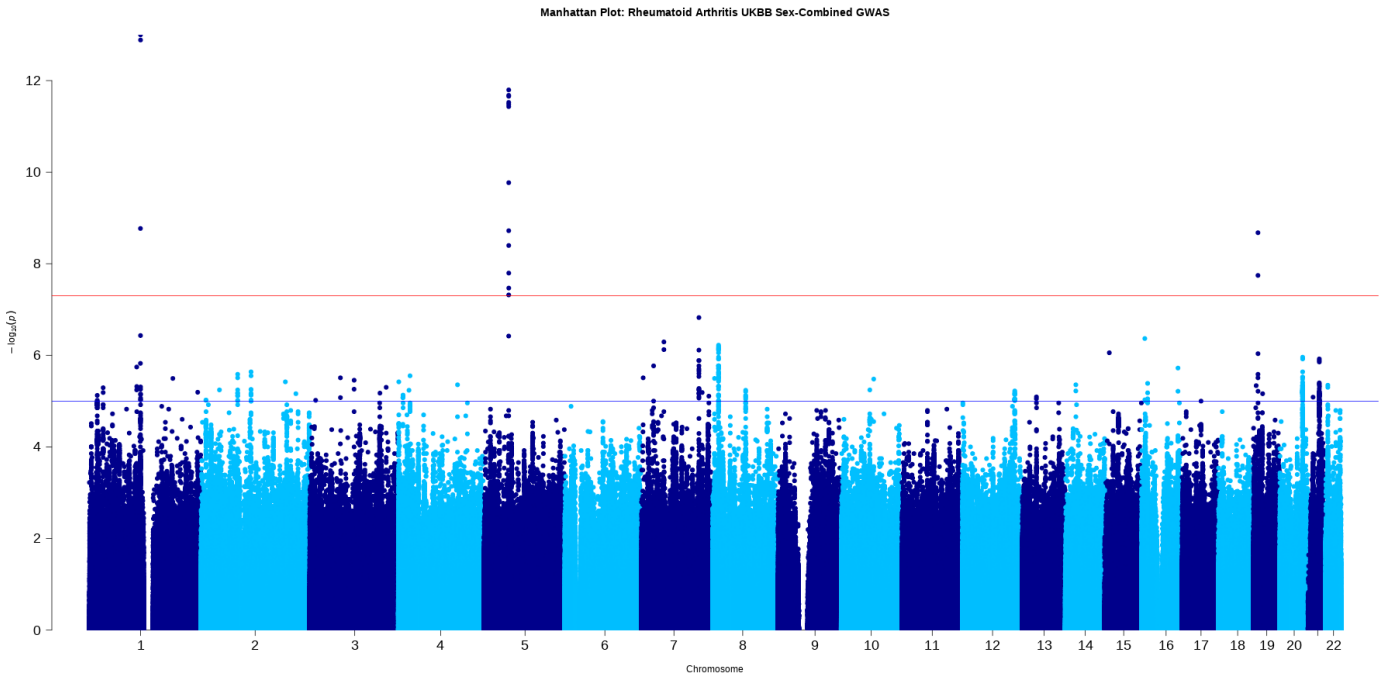
Figure x4.7 Rheumatoid arthritis GWAS results

A. Manhattan plots for i. female-only, ii. sex-combined, iii. meta-analysis sex-combined GWAS

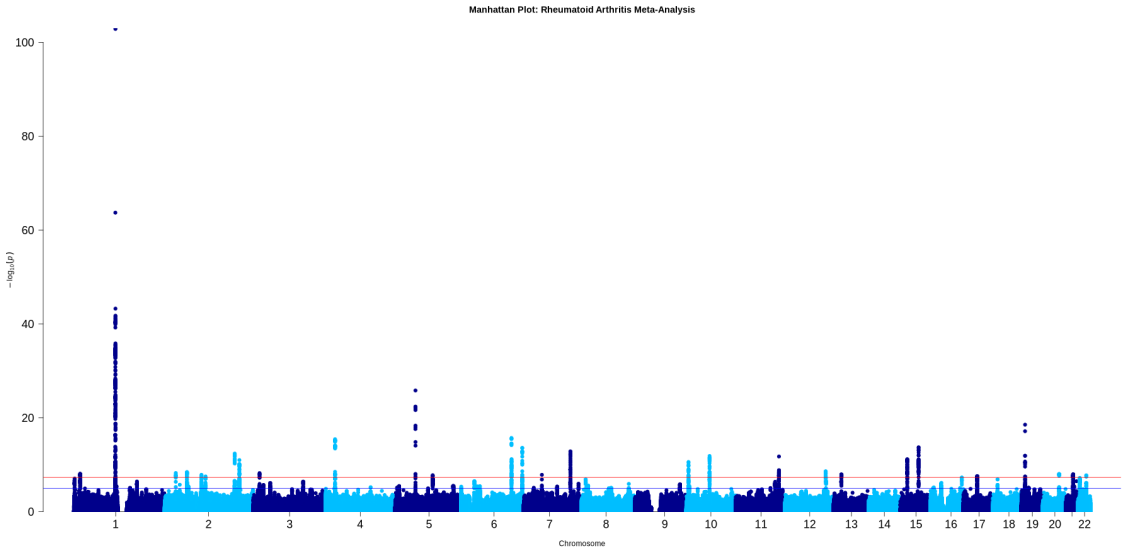
i. Female-only UKBB GWAS



ii. Sex-combined UKBB GWAS



iii. Meta-analysis sex-combined GWAS



B. Q-Q plots for i. female-only, ii. sex-combined, iii. meta-analysis sex-combined GWAS

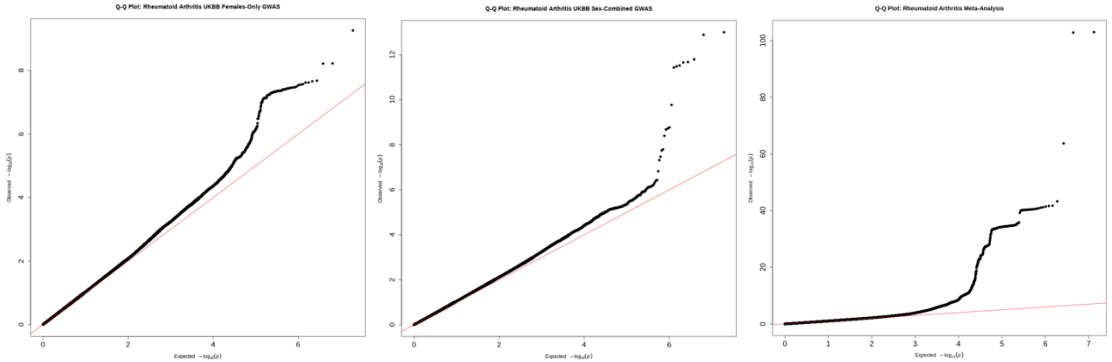
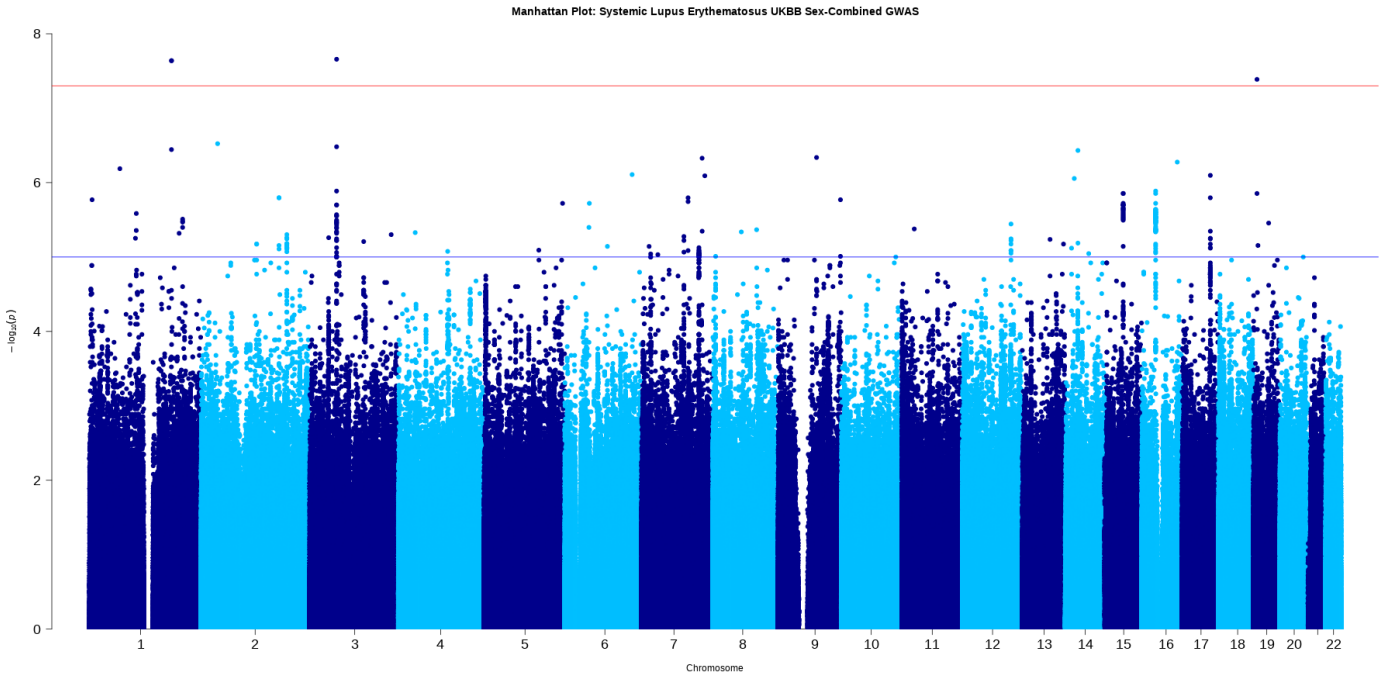


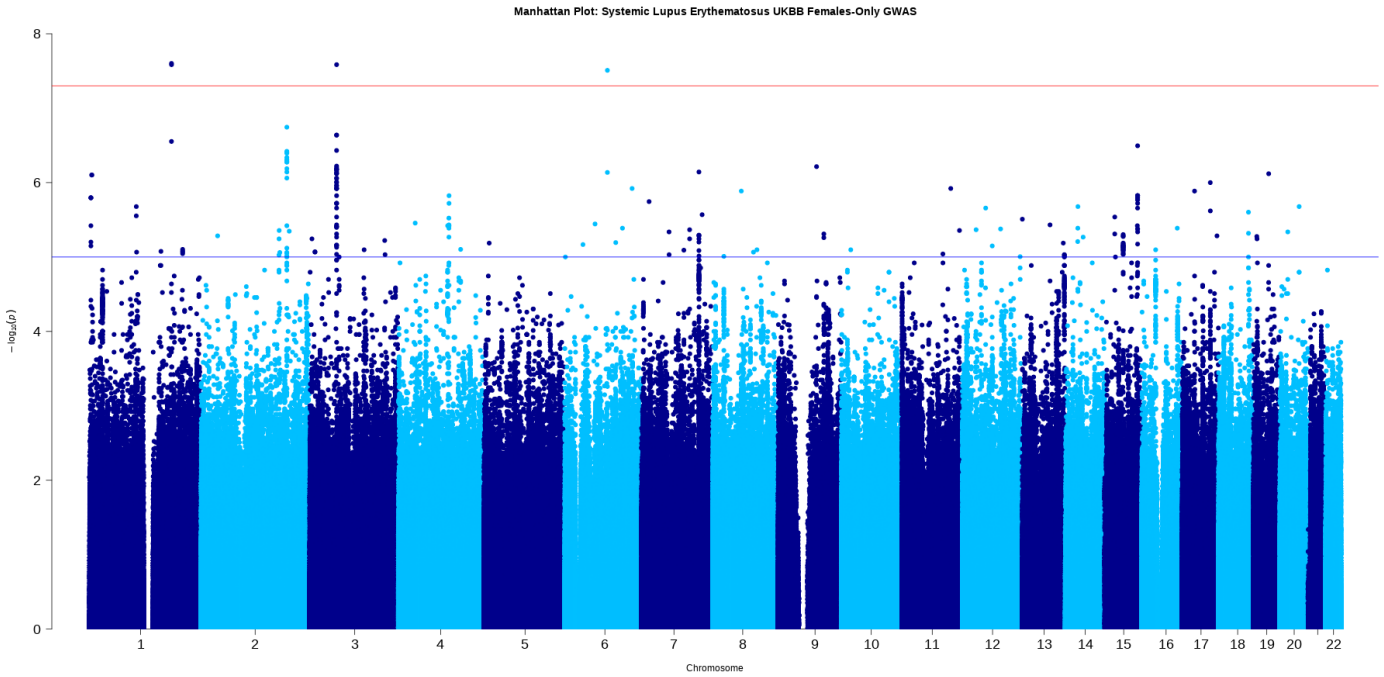
Figure x4.8 Systemic lupus erythematosus GWAS results

A. Manhattan plots for i. female-only, ii. sex-combined, iii. meta-analysis sex-combined GWAS

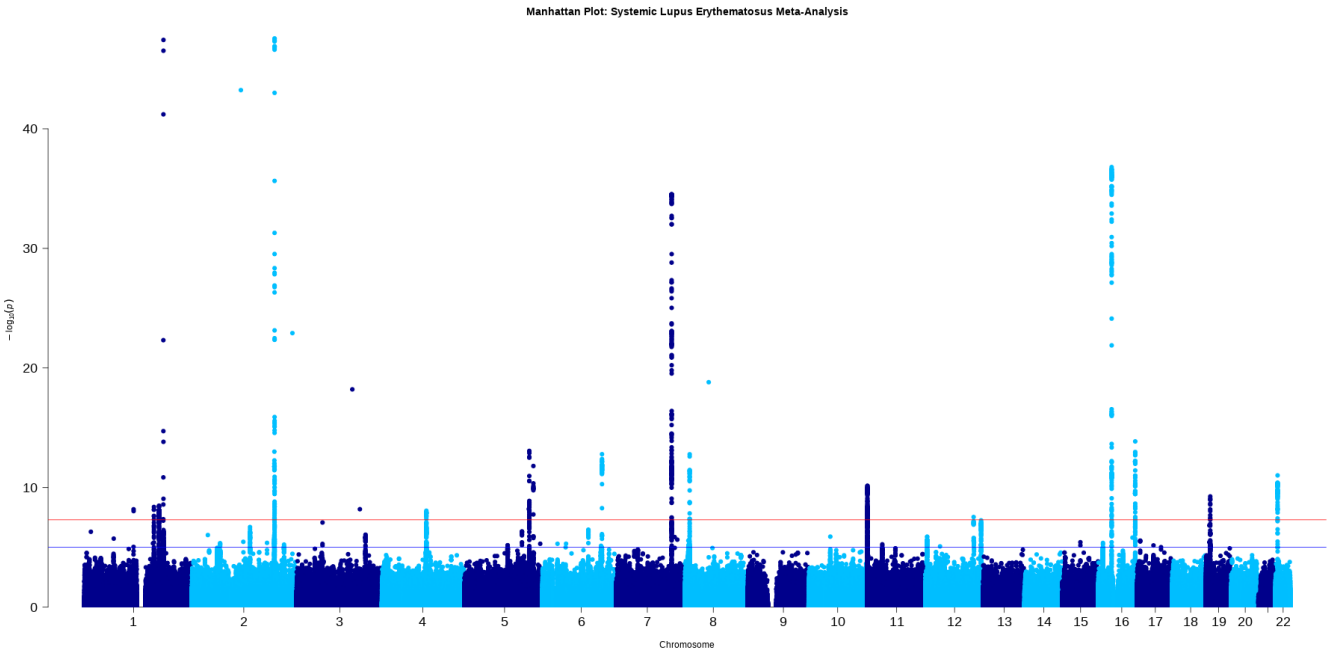
i. Female-only UKBB GWAS



ii. Sex-combined UKBB GWAS



iii. Meta-analysis sex-combined GWAS



B. Q-Q plots for i. female-only, ii. sex-combined, iii. meta-analysis sex-combined GWAS

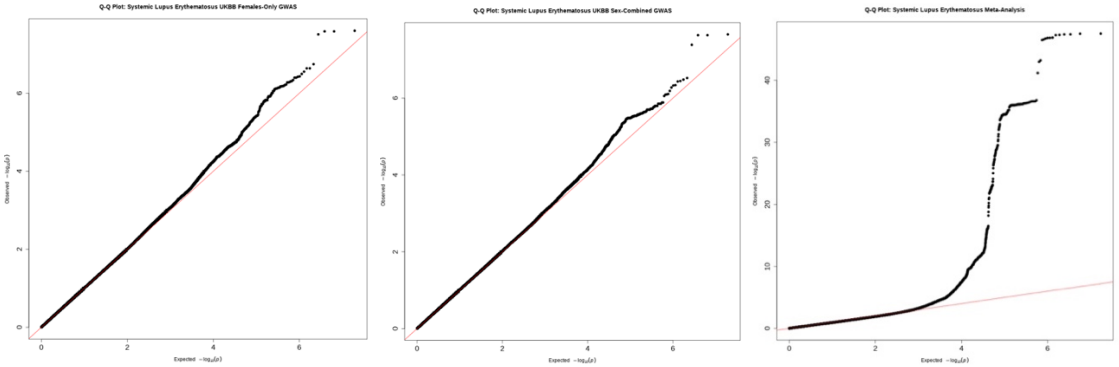
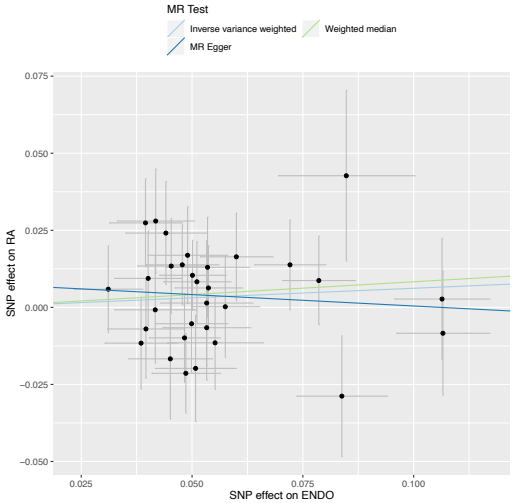


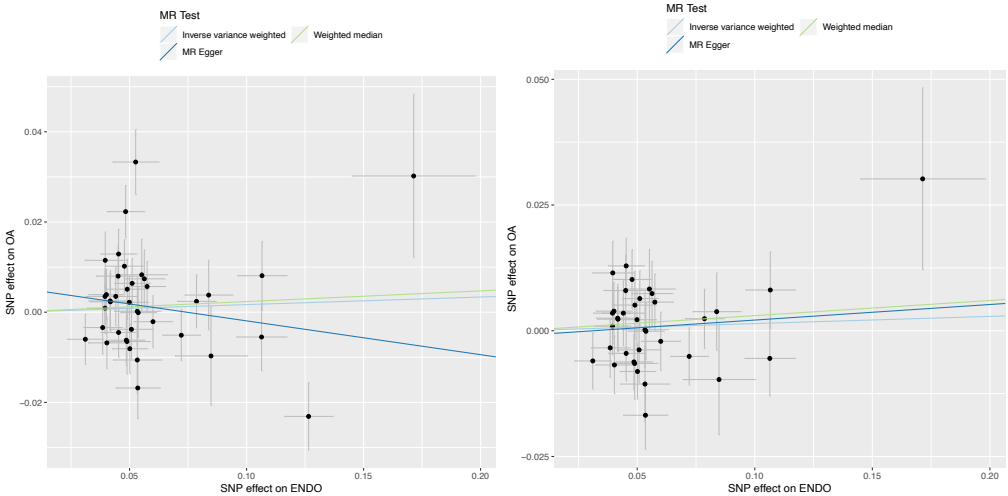
Figure x4.9 MR analysis plots

A. plots for RA



B. plots for OA

i. Before outliers removed ii. After outliers removed



C. plots for MS

i. Before outliers removed ii. After outliers removed

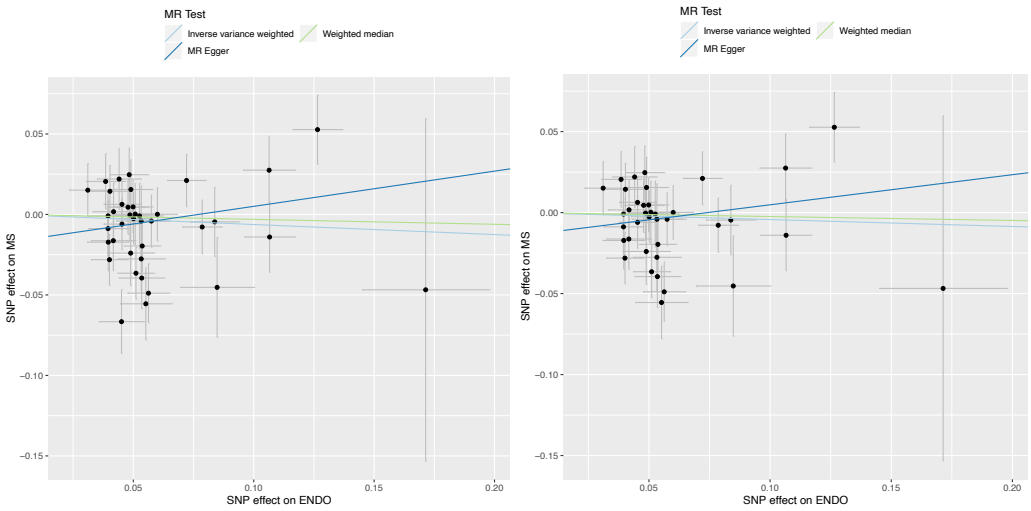


Figure x5.1a Regional plot for shared genetic risk variants of rs7613875 in endometriosis

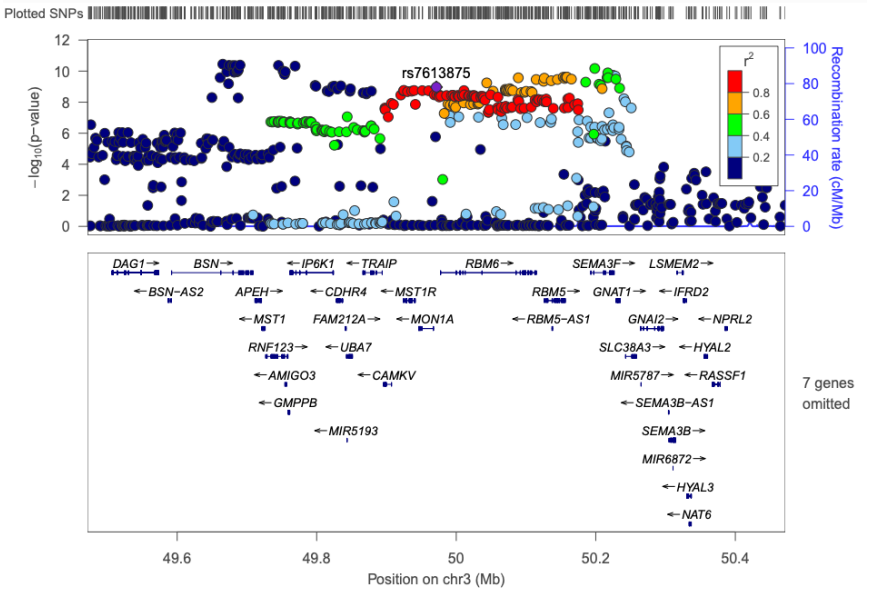


Figure x5.1b Regional plot for shared genetic risk variants of rs3733135 in osteoarthritis

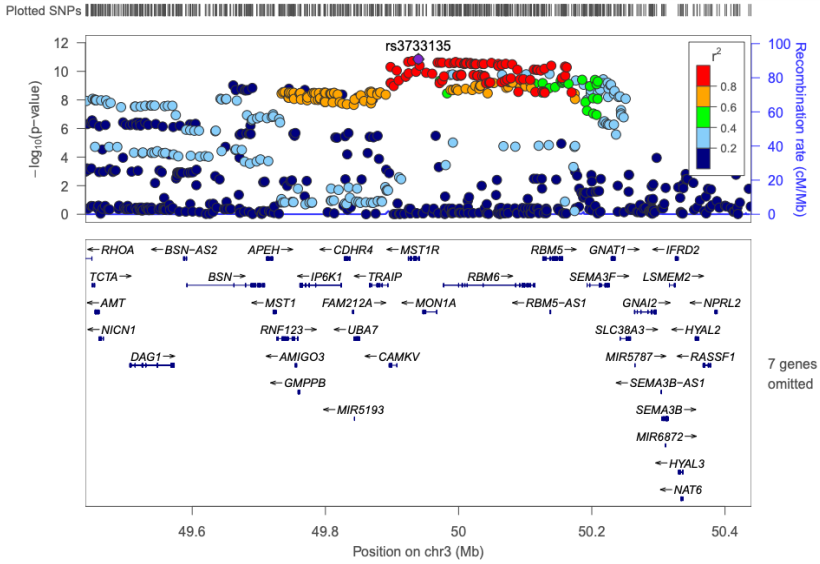


Figure x5.2a Regional plot for shared genetic risk variants of rs1401390 in endometriosis

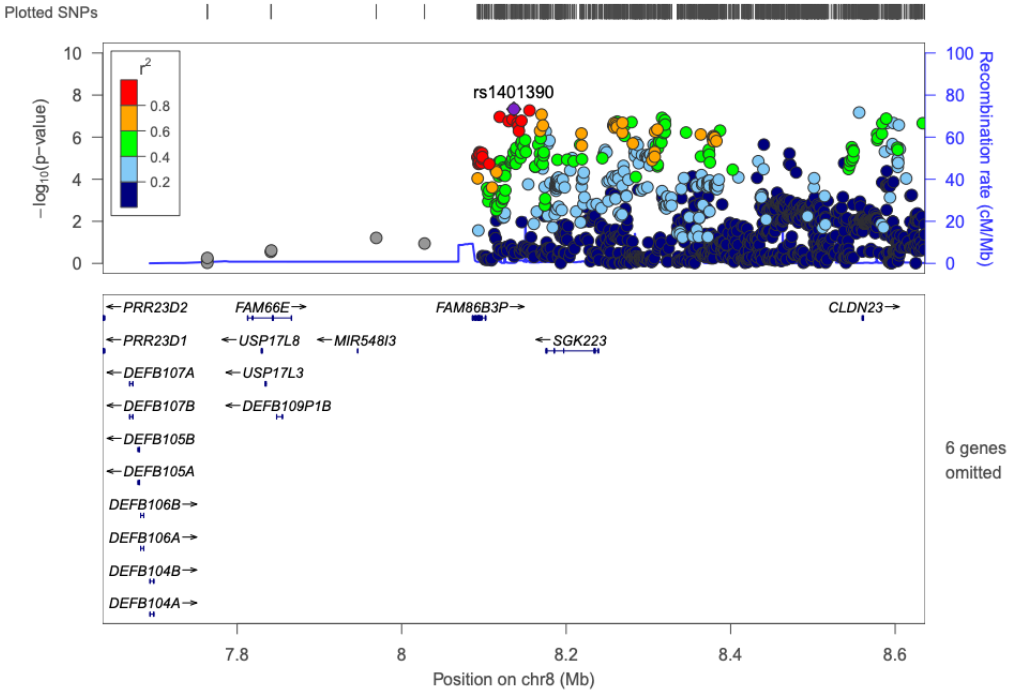


Figure x5.2b Regional plot for shared genetic risk variants of rs2948308 in osteoarthritis

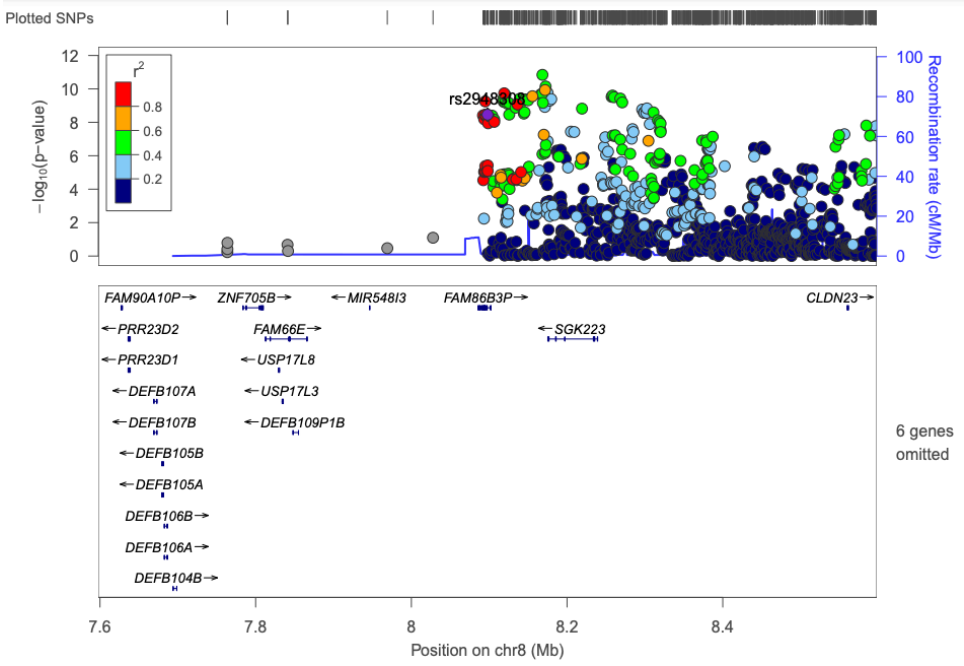


Figure x5.3a Regional plot for shared genetic risk variants of rs7834121 in endometriosis

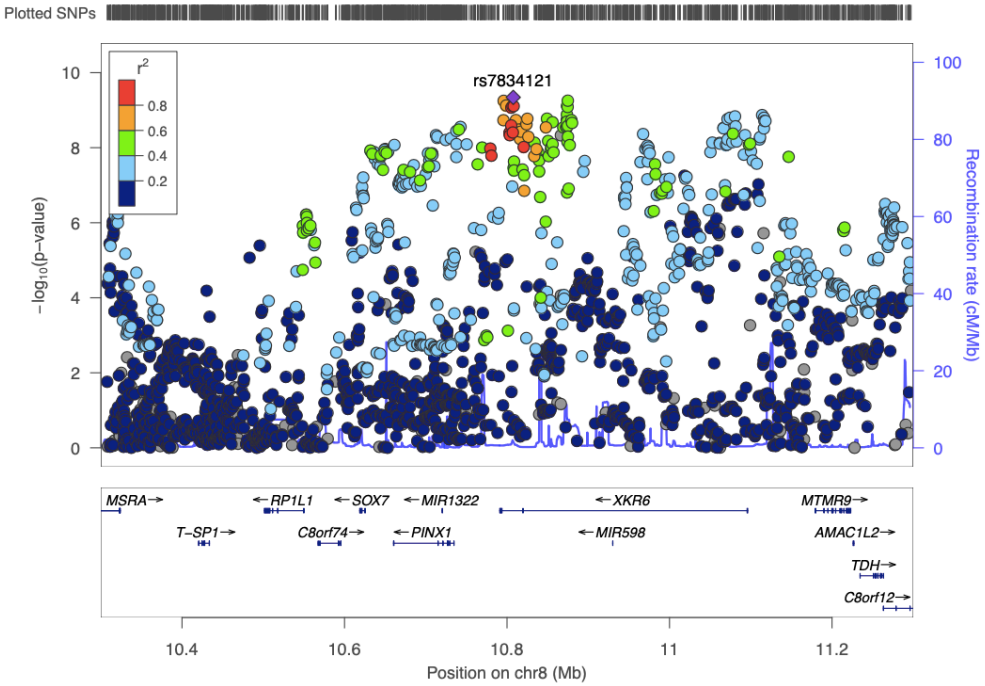


Figure x5.3b Regional plot for shared genetic risk variants of rs6985109 in osteoarthritis

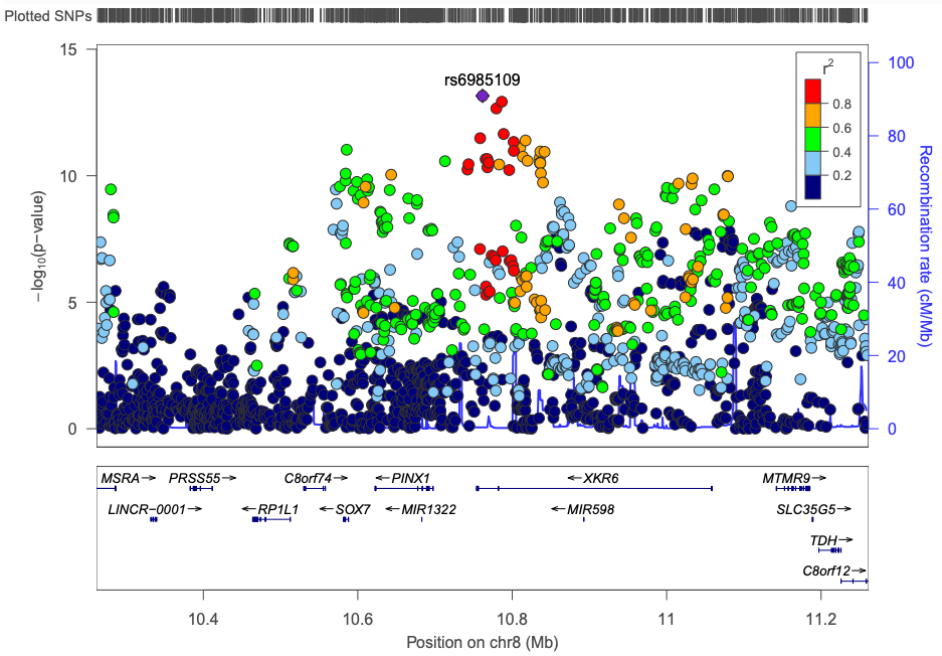


Figure x5.4a Regional plot for shared genetic risk variants of rs11012732 in endometriosis

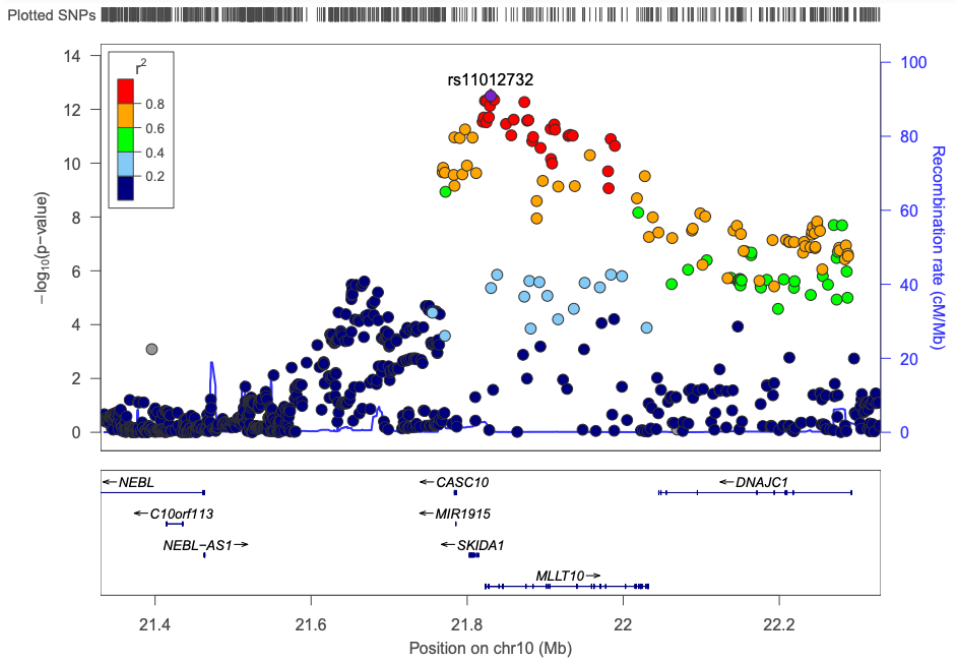


Figure x5.4b Regional plot for shared genetic risk variants of rs11012726 in osteoarthritis

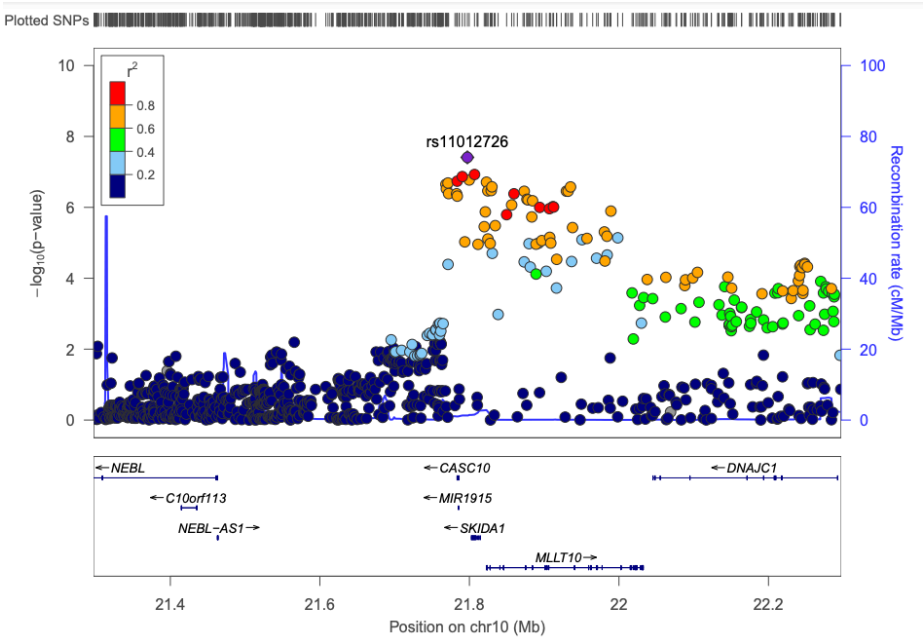


Table x5.1 Lead SNPs for multiple sclerosis identified from MTAG

MTAG Results									Single-Trait Results	
RSID	CHR	BP	EA	EAF	NrtGene	Function	OR[95%CI]	P value	OR[95%CI]	P value
rs10797431	1	2501222	G	0.66	RP3-395M20.7	ncRNA_exonic	1.15 [1.12-1.19]	1.15E-19	1.14 [1.11-1.18]	1.07E-15
rs10914539	1	32715641	T	0.18	FAM167B	intergenic	1.14 [1.09-1.19]	1.07E-08	1.15 [1.09-1.2]	1.35E-08
rs12408934	1	65423447	G	0.91	JAK1	intronic	1.16 [1.11-1.22]	2.37E-09	1.17 [1.1-1.23]	4.88E-08
rs11161564	1	85712918	C	0.91	C1orf52	intergenic	1.14 [1.09-1.19]	2.10E-08	1.15 [1.09-1.21]	2.70E-08
rs10873698	1	85756250	G	0.62	RP11-131L23.1	ncRNA_intronic	1.11 [1.08-1.14]	7.54E-12	1.11 [1.08-1.15]	2.93E-11
rs12133753	1	92222089	C	0.85	TGFBR3	intronic	1.14 [1.1-1.18]	3.00E-11	1.14 [1.1-1.19]	3.50E-10
rs41286801	1	92975464	T	0.18	EVI5	UTR3	1.19 [1.15-1.24]	1.03E-18	1.18 [1.13-1.23]	6.38E-15
rs12404778	1	93248983	C	0.80	EVI5	intronic	1.18 [1.12-1.24]	2.56E-11	1.18 [1.12-1.25]	3.21E-10
rs34731154	1	101293350	T	0.42	EXTL2	intergenic	1.12 [1.09-1.15]	4.95E-14	1.12 [1.09-1.15]	6.43E-13
rs6679677	1	114303808	A	0.09	RSBN1	downstream	1.19 [1.12-1.25]	4.26E-10	1.01 [0.95-1.07]	7.41E-01
rs1414273	1	117102649	C	0.86	CD58:MIR548AC	ncRNA_exonic	1.23 [1.17-1.28]	3.22E-19	1.24 [1.18-1.3]	8.80E-18
rs532303	1	120265444	G	0.68	PHGDH	intronic	1.1 [1.07-1.14]	1.50E-09	1.11 [1.07-1.14]	5.31E-09
rs17676381	1	157681898	T	0.20	RP11-367J7.4	intergenic	1.14 [1.1-1.19]	1.71E-11	1.14 [1.09-1.19]	2.55E-09
rs2090756	1	160707404	G	0.79	SLAMF7	intergenic	1.11 [1.07-1.14]	1.27E-08	1.1 [1.06-1.14]	2.94E-07
rs1323292	1	192541021	A	0.18	RGS1	intergenic	1.14 [1.1-1.19]	4.63E-12	1.14 [1.1-1.19]	1.38E-10
rs55838263	1	200874728	A	0.28	C1orf106	intronic	1.13 [1.09-1.17]	1.77E-13	1.13 [1.09-1.17]	3.25E-12
rs34914018	2	25405374	C	0.95	POMC	intergenic	1.31 [1.19-1.44]	4.98E-08	1.32 [1.18-1.46]	3.13E-07
rs6741704	2	43343806	G	0.73	AC093609.1	intergenic	1.11 [1.07-1.15]	6.54E-10	1.11 [1.07-1.15]	1.31E-08
rs2420518	2	61054980	C	0.56	AC010733.4	ncRNA_intronic	1.1 [1.07-1.14]	5.41E-11	1.1 [1.07-1.13]	3.76E-09
rs7562347	2	61209875	G	0.57	PUS10	intronic	1.09 [1.06-1.12]	4.08E-09	1.1 [1.07-1.14]	1.19E-09
rs12613194	2	68646467	C	0.57	PLEK	intergenic	1.09 [1.05-1.12]	2.98E-08	1.08 [1.05-1.12]	1.03E-06
rs57116599	2	112770799	G	0.76	MERTK	intronic	1.11 [1.07-1.15]	8.15E-09	1.11 [1.07-1.16]	2.09E-08
rs35256947	2	231161026	C	0.75	SP140	intronic	1.11 [1.08-1.15]	1.02E-10	1.11 [1.07-1.15]	3.30E-09
rs2371108	3	27757018	T	0.40	EOMES	downstream	1.13 [1.1-1.17]	4.72E-16	1.12 [1.09-1.16]	1.73E-12
rs427289	3	28073021	T	0.49	AC092415.1	intergenic	1.16 [1.12-1.19]	1.54E-22	1.15 [1.12-1.19]	4.76E-19

rs4683959	3	101748902	T	0.35	RP11-221J22.1:RP11-221J22.2	intergenic	1.1 [1.07-1.14]	6.23E-11	1.1 [1.07-1.14]	3.23E-09
rs2293370	3	119219934	G	0.84	TIMMDC1	intronic	1.12 [1.08-1.17]	1.41E-09	1.12 [1.08-1.17]	8.67E-09
rs4285028	3	121660664	A	0.28	SLC15A2	UTR3	1.1 [1.06-1.14]	1.25E-08	1.1 [1.06-1.14]	6.58E-08
rs2255214	3	121770539	G	0.51	CD86	intergenic	1.12 [1.09-1.15]	2.16E-14	1.12 [1.09-1.16]	1.66E-13
rs9282641	3	121796768	G	0.91	CD86	UTR5	1.2 [1.14-1.26]	3.24E-11	1.21 [1.15-1.29]	2.27E-11
rs2366408	3	159696099	T	0.35	IL12A-AS1	ncRNA_intronic	1.1 [1.07-1.13]	1.04E-09	1.1 [1.06-1.13]	8.69E-09
rs4955575	3	169534538	A	0.26	LRRC34	intergenic	1.1 [1.06-1.14]	2.80E-08	1.09 [1.06-1.13]	9.22E-07
rs6854803	4	109095552	G	0.55	LEF1-AS1	ncRNA_exonic	1.09 [1.06-1.12]	2.19E-08	1.09 [1.05-1.12]	2.45E-07
rs274668	5	6711630	T	0.35	PAPD7	intergenic	1.09 [1.06-1.13]	2.02E-08	1.09 [1.06-1.13]	8.55E-08
rs6881270	5	35879095	C	0.73	IL7R	UTR3	1.1 [1.07-1.14]	3.69E-09	1.1 [1.07-1.14]	2.42E-08
rs11749040	5	40396425	A	0.14	AC108105.1	intergenic	1.2 [1.15-1.25]	2.42E-18	1.21 [1.15-1.26]	1.06E-16
rs6878370	5	40433552	A	0.41	AC108105.1	intergenic	1.13 [1.09-1.16]	8.36E-16	1.13 [1.09-1.16]	9.58E-14
rs7731626	5	55444683	G	0.62	ANKRD55	intronic	1.12 [1.08-1.16]	3.67E-11	1.09 [1.05-1.13]	4.43E-06
rs244658	5	133432632	C	0.85	CTB-113I20.1	intergenic	1.14 [1.09-1.19]	3.82E-09	1.13 [1.08-1.18]	2.81E-07
rs4921213	5	158733619	G	0.53	AC008697.1	intergenic	1.11 [1.08-1.14]	3.24E-13	1.11 [1.08-1.15]	1.04E-11
rs9349957	6	14723743	C	0.78	RNU6-793P	intergenic	1.12 [1.08-1.17]	1.33E-08	1.12 [1.07-1.17]	3.02E-07
rs879036	6	36349890	T	0.14	ETV7	intronic	1.14 [1.09-1.19]	1.88E-09	1.12 [1.07-1.17]	9.63E-07
rs17504727	6	88241110	C	0.91	RARS2	intronic	1.25 [1.16-1.35]	5.49E-09	1.23 [1.13-1.34]	7.61E-07
rs3757247	6	90957463	T	0.49	BACH2	intronic	1.09 [1.06-1.12]	2.87E-09	1.09 [1.06-1.13]	1.00E-08
rs802730	6	128280104	T	0.28	PTPRK	intergenic	1.1 [1.06-1.13]	1.77E-08	1.1 [1.06-1.14]	7.24E-08
rs9494167	6	135489069	C	0.77	MYB	intergenic	1.12 [1.08-1.17]	2.17E-10	1.12 [1.08-1.17]	3.55E-09
rs9647635	6	135841056	C	0.64	LINC00271	ncRNA_intronic	1.14 [1.1-1.17]	1.33E-17	1.14 [1.1-1.17]	2.27E-15
rs17066096	6	137452908	G	0.77	IL22RA2	intergenic	1.13 [1.09-1.16]	2.91E-12	1.13 [1.09-1.17]	3.54E-11
rs62432712	6	137964697	A	0.17	RP11-95M15.1	intergenic	1.11 [1.07-1.15]	1.78E-08	1.08 [1.04-1.12]	5.68E-05
rs12525643	6	138011151	G	0.72	RP11-95M15.2	intergenic	1.14 [1.1-1.17]	5.17E-15	1.12 [1.08-1.16]	3.18E-11
rs212409	6	159470058	A	0.44	RP1-111C20.4	ncRNA_intronic	1.11 [1.08-1.15]	5.68E-13	1.11 [1.07-1.14]	1.05E-10
rs13238352	7	128647942	T	0.10	TNPO3	intronic	1.14 [1.09-1.19]	1.63E-08	1.11 [1.06-1.17]	1.04E-05
rs67256453	7	149314756	T	0.26	ZNF767	ncRNA_intronic	1.11 [1.07-1.14]	2.05E-09	1.11 [1.07-1.15]	1.57E-08

rs4609182	8	79557227	C	0.71	ZC2HC1A	intergenic	1.11 [1.07-1.14]	8.35E-10	1.1 [1.07-1.14]	2.85E-08
rs6990534	8	128814091	G	0.67	PVT1	ncRNA_intronic	1.1 [1.07-1.14]	1.23E-09	1.11 [1.08-1.15]	7.50E-10
rs4733845	8	129188457	G	0.79	MIR1208	intergenic	1.1 [1.07-1.14]	2.28E-08	1.1 [1.06-1.14]	2.92E-07
rs2228150	10	6067969	T	0.02	IL2RA:RP11-536K7.5	exonic	1.26 [1.17-1.37]	4.57E-09	1.24 [1.13-1.35]	5.87E-06
rs12722552	10	6071347	C	0.91	IL2RA:RP11-536K7.5	ncRNA_intronic	1.15 [1.09-1.2]	1.08E-08	1.13 [1.07-1.19]	6.10E-06
rs11256497	10	6087794	A	0.41	IL2RA	intronic	1.1 [1.07-1.14]	3.16E-11	1.11 [1.07-1.14]	1.17E-10
rs3134883	10	6100725	A	0.29	IL2RA	intronic	1.13 [1.1-1.17]	5.67E-15	1.11 [1.08-1.15]	1.65E-10
rs41295055	10	6111622	C	0.84	RP11-414H17.2	intergenic	1.21 [1.17-1.26]	1.88E-22	1.21 [1.16-1.26]	9.94E-20
rs1250565	10	81047015	A	0.33	ZMIZ1	intronic	1.12 [1.09-1.16]	6.95E-14	1.12 [1.09-1.16]	2.67E-12
rs7923866	10	94482076	C	0.63	Y_RNA	intergenic	1.11 [1.08-1.15]	5.31E-13	1.12 [1.08-1.15]	1.29E-11
rs2269434	11	47360412	C	0.65	MYBPC3	intronic	1.09 [1.06-1.12]	2.27E-08	1.1 [1.06-1.13]	2.98E-08
rs4939491	11	60793722	A	0.41	CD6	intergenic	1.12 [1.09-1.16]	1.23E-13	1.13 [1.1-1.17]	2.34E-14
rs650258	11	60832282	C	0.63	RP11-881M11.8	ncRNA_intronic	1.12 [1.08-1.15]	1.09E-12	1.12 [1.08-1.16]	1.05E-11
rs12365699	11	118743286	G	0.84	CXCR5	intergenic	1.16 [1.12-1.21]	8.24E-14	1.14 [1.1-1.19]	4.93E-10
rs11217081	11	118769032	A	0.46	BCL9L	UTR3	1.09 [1.06-1.12]	1.91E-08	1.09 [1.05-1.12]	1.94E-07
rs1800693	12	6440009	C	0.57	TNFRSF1A	intronic	1.12 [1.09-1.16]	2.09E-14	1.13 [1.09-1.16]	1.78E-13
rs7977720	12	9866349	T	0.47	CLECL1	intergenic	1.09 [1.06-1.12]	1.83E-08	1.09 [1.06-1.13]	1.30E-08
rs1633360	12	58108052	T	0.40	OS9:RP11-571M6.7	ncRNA_intronic	1.11 [1.08-1.14]	1.07E-11	1.1 [1.07-1.14]	1.97E-09
rs7975763	12	123604053	T	0.22	PITPNM2	intronic	1.12 [1.08-1.16]	2.69E-09	1.13 [1.08-1.17]	1.74E-09
rs9596267	13	50820238	C	0.94	DLEU1	NA	1.21 [1.15-1.28]	1.98E-11	1.22 [1.14-1.29]	1.15E-09
rs12435329	14	69250891	T	0.46	ZFP36L1	intergenic	1.13 [1.09-1.16]	4.06E-16	1.12 [1.09-1.16]	1.04E-13
rs175697	14	75962977	C	0.52	JDP2	intergenic	1.09 [1.06-1.12]	4.68E-08	1.08 [1.05-1.12]	1.65E-06
rs8012190	14	88452441	A	0.39	GALC	intronic	1.1 [1.07-1.13]	5.97E-10	1.1 [1.06-1.13]	4.73E-09
rs17124032	14	88546009	G	0.92	LINC01146	ncRNA_intronic	1.21 [1.14-1.27]	5.18E-12	1.21 [1.14-1.29]	2.19E-10
rs12436513	14	103269755	C	0.65	TRAF3	intronic	1.1 [1.07-1.13]	5.87E-10	1.09 [1.06-1.13]	2.49E-08
rs7183707	15	90883733	T	0.31	GABARAPL3	intergenic	1.1 [1.06-1.13]	1.14E-08	1.1 [1.06-1.13]	1.72E-07
rs396920	16	1067171	T	0.19	RP11-161M6.3	intergenic	1.14 [1.09-1.18]	2.64E-11	1.13 [1.09-1.18]	1.23E-09
rs12708713	16	11072459	C	0.82	CLEC16A	intronic	1.12 [1.08-1.17]	2.42E-09	1.13 [1.08-1.18]	5.98E-09

rs2160042	16	11158232	G	0.86	CLEC16A	intronic	1.15 [1.1-1.2]	6.87E-10	1.16 [1.1-1.22]	2.02E-09
rs794426	16	11242858	C	0.63	CLEC16A	intronic	1.18 [1.15-1.22]	2.71E-27	1.18 [1.15-1.22]	2.51E-25
rs367569	16	11365500	C	0.71	RMI2	intronic	1.1 [1.07-1.14]	1.54E-09	1.1 [1.06-1.13]	2.13E-07
rs7191700	16	11406803	C	0.66	RMI2	intronic	1.11 [1.08-1.15]	3.53E-12	1.11 [1.08-1.15]	1.97E-10
rs3809627	16	30103160	C	0.58	TBX6	UTR5	1.11 [1.07-1.14]	1.18E-10	1.1 [1.07-1.14]	3.19E-09
rs12925972	16	79111297	C	0.53	WWOX:RP11-556H2.4	ncRNA_exonic	1.09 [1.06-1.13]	2.37E-09	1.1 [1.07-1.14]	3.35E-09
rs9939427	16	86016091	A	0.23	RP11-542M13.2	ncRNA_intronic	1.11 [1.07-1.15]	2.46E-08	1.09 [1.05-1.14]	6.88E-06
rs8071537	17	40530895	T	0.36	STAT3	intronic	1.14 [1.11-1.17]	3.00E-17	1.14 [1.1-1.17]	1.91E-14
rs7223029	17	45701731	C	0.53	RP11-580I16.2	ncRNA_intronic	1.1 [1.07-1.13]	3.10E-11	1.1 [1.07-1.13]	7.88E-10
rs1292061	17	57911230	A	0.43	VMP1	intronic	1.11 [1.08-1.14]	2.59E-12	1.11 [1.08-1.15]	3.59E-11
rs12962126	18	56351448	G	0.79	MALT1:RP11-126O1.4	ncRNA_intronic	1.12 [1.08-1.16]	5.40E-10	1.11 [1.07-1.15]	3.27E-08
rs1077667	19	6668972	C	0.77	TNFSF14	intronic	1.13 [1.09-1.17]	2.42E-10	1.14 [1.09-1.18]	1.74E-10
rs2043330	19	10553618	C	0.71	PDE4A	intronic	1.11 [1.08-1.15]	1.55E-11	1.1 [1.07-1.14]	1.54E-08
rs10421112	19	16525391	T	0.30	EPS15L1	intronic	1.09 [1.06-1.13]	1.56E-08	1.09 [1.06-1.13]	1.45E-07
rs1044821	19	18307108	C	0.72	MPV17L2	UTR3	1.13 [1.09-1.16]	1.33E-12	1.12 [1.08-1.16]	8.98E-11
rs1465697	19	49837246	T	0.24	CTC-301O7.4	ncRNA_intronic	1.12 [1.08-1.15]	7.69E-11	1.12 [1.08-1.16]	4.77E-10
rs2024568	20	44732089	T	0.26	RPL13P2	intergenic	1.15 [1.11-1.19]	6.04E-17	1.13 [1.09-1.17]	1.93E-12
rs2259735	20	52788314	T	0.42	CYP24A1	UTR5	1.1 [1.07-1.13]	9.62E-10	1.1 [1.07-1.14]	3.21E-09
rs9610458	22	22205353	T	0.46	MAPK1	intronic	1.11 [1.08-1.14]	4.17E-12	1.11 [1.08-1.14]	5.49E-11
rs361725	22	50971047	T	0.36	ODF3B	upstream	1.11 [1.07-1.14]	4.34E-11	1.11 [1.07-1.15]	3.32E-10

Table x5.2 Lead SNPs for osteoarthritis identified from MTAG

MTAG Results									Single-Trait Results	
RSID	CHR	BP	EA	EAF	NrtGene	Function	OR[95%CI]	P value	OR[95%CI]	P value
rs3766823	1	32197257	A	0.16	BAI2	intronic	1.04 [1.03-1.05]	2.15E-09	1.04 [1.02-1.05]	7.09E-07
rs7551627	1	72960531	A	0.19	RPL31P12	intergenic	1.03 [1.02-1.04]	3.85E-08	1.03 [1.02-1.05]	9.02E-07
rs4098282	1	103470547	A	0.17	COL11A1	intronic	1.04 [1.03-1.06]	2.02E-10	1.05 [1.04-1.07]	2.02E-11

rs904023	1	110606675	A	0.43	STRIP1:ALX3	intronic	1.03 [1.02-1.04]	1.26E-08	1.02 [1.01-1.03]	2.49E-04
rs6679677	1	114303808	A	0.09	RSBN1	downstream	1.09 [1.07-1.11]	1.90E-27	1.00 [0.99-1.02]	6.82E-01
rs61624206	1	174547512	G	0.72	RABGAP1L	intronic	1.04 [1.02-1.05]	9.64E-11	1.03 [1.02-1.05]	2.70E-08
rs17504460	1	183913540	C	0.80	COLGALT2	intronic	1.03 [1.02-1.05]	1.12E-08	1.04 [1.02-1.05]	5.76E-08
rs58774073	2	33431618	C	0.52	LTBP1	intronic	1.03 [1.02-1.04]	5.98E-12	1.04 [1.03-1.05]	4.56E-13
rs17502934	2	50994255	T	0.15	NRXN1	intronic	1.04 [1.03-1.06]	1.26E-09	1.04 [1.02-1.06]	6.23E-07
rs59985551	2	56106928	C	0.77	EFEMP1	intronic	1.03 [1.02-1.04]	6.63E-09	1.04 [1.02-1.05]	1.17E-07
rs3755378	2	70720603	C	0.65	TGFA	intronic	1.03 [1.02-1.04]	4.29E-08	1.03 [1.02-1.04]	2.44E-08
rs55815229	2	99944392	T	0.43	TXNDC9	intronic	1.03 [1.02-1.04]	1.35E-08	1.03 [1.02-1.04]	2.11E-07
rs13394110	2	100873975	G	0.82	LINC01104	intergenic	1.03 [1.02-1.05]	2.53E-08	1.04 [1.02-1.05]	6.84E-07
rs2443798	2	204394236	T	0.42	RAPH1	intronic	1.04 [1.03-1.05]	3.96E-14	1.03 [1.02-1.05]	1.83E-09
rs9831648	3	49214303	G	0.79	KLHDC8B	downstream	1.03 [1.02-1.05]	3.77E-09	1.03 [1.02-1.04]	8.12E-06
rs3733135	3	49939587	A	0.50	MST1R:CTD-2330K9.2	ncRNA_intronic	1.03 [1.02-1.04]	1.41E-11	1.03 [1.02-1.05]	5.27E-10
rs2171542	3	156429651	T	0.47	METTL15P1	intergenic	1.03 [1.02-1.04]	4.03E-09	1.03 [1.02-1.04]	8.82E-07
rs798748	4	1716770	C	0.63	TMEM129	downstream	1.03 [1.02-1.04]	3.70E-09	1.03 [1.02-1.05]	5.08E-09
rs2056117	4	13010092	C	0.65	RNU6-962P	intergenic	1.03 [1.02-1.04]	4.46E-08	1.03 [1.02-1.04]	3.04E-08
rs13107325	4	103188709	T	0.08	SLC39A8	exonic	1.08 [1.07-1.1]	2.01E-18	1.10 [1.07-1.12]	8.29E-19
rs72688751	4	130256802	T	0.15	RP11-419L4.1	intergenic	1.04 [1.03-1.06]	9.69E-10	1.04 [1.03-1.06]	2.05E-07
rs329122	5	133864599	G	0.57	JADE2	intronic	1.03 [1.02-1.04]	2.13E-08	1.02 [1.01-1.03]	1.31E-04
rs4076077	5	170863509	C	0.52	FGF18	intronic	1.03 [1.02-1.04]	9.25E-10	1.03 [1.02-1.04]	2.53E-06

rs1482883	6	44638566	C	0.51	SUPT3H	intergenic	1.03 [1.02-1.04]	7.46E-09	1.03 [1.02-1.04]	4.47E-07
rs1558461	7	2121156	A	0.11	MAD1L1	intronic	1.04 [1.03-1.06]	1.21E-08	1.04 [1.03-1.06]	1.12E-06
rs481806	7	28207300	G	0.74	JAZF1	intronic	1.03 [1.02-1.04]	5.69E-09	1.03 [1.01-1.04]	4.50E-05
rs10246978	7	78147094	T	0.42	MAGI2	intronic	1.03 [1.02-1.04]	7.24E-09	1.03 [1.02-1.04]	2.23E-07
rs12672406	7	95710662	T	0.32	DYNC1I1	intronic	1.03 [1.02-1.04]	1.02E-09	1.04 [1.02-1.05]	8.44E-10
rs4730633	7	113992074	G	0.52	FOXP2	intronic	1.03 [1.02-1.04]	3.05E-08	1.03 [1.02-1.04]	3.66E-07
rs2551760	7	135169414	C	0.72	CNOT4	intronic	1.03 [1.02-1.04]	8.14E-10	1.03 [1.02-1.04]	7.01E-06
rs2948308	8	8097849	T	0.43	FAM86B3P:ALG1L13P	ncRNA_exonic	1.03 [1.02-1.04]	3.47E-09	1.03 [1.02-1.04]	2.86E-07
rs1825100	8	9146270	C	0.52	RP11-115J16.1	ncRNA_intronic	1.04 [1.03-1.05]	3.25E-13	1.04 [1.02-1.05]	3.85E-10
rs6985109	8	10761585	G	0.53	XKR6	intronic	1.04 [1.03-1.05]	6.98E-14	1.03 [1.02-1.05]	1.33E-09
rs34960871	8	11584549	A	0.11	GATA4	intronic	1.04 [1.03-1.06]	2.24E-09	1.04 [1.02-1.06]	1.62E-06
rs12676145	8	11856583	A	0.47	RP11-481A20.4	upstream	1.04 [1.03-1.05]	7.39E-13	1.03 [1.02-1.04]	2.91E-09
rs16935971	9	33803111	A	0.25	RP11-133O22.6	ncRNA_intronic	1.03 [1.02-1.04]	1.97E-08	1.03 [1.02-1.05]	1.09E-06
rs4979341	9	116905543	T	0.26	COL27A1	intergenic	1.04 [1.03-1.06]	1.04E-15	1.05 [1.04-1.06]	2.83E-14
rs706778	10	6098949	T	0.41	IL2RA	intronic	1.03 [1.02-1.04]	4.06E-09	1.02 [1.01-1.03]	3.38E-03
rs11012726	10	21797272	C	0.67	SKIDA1	intergenic	1.03 [1.02-1.04]	3.90E-08	1.03 [1.01-1.04]	1.75E-05
rs7081577	10	52011840	A	0.48	ASAH2	intergenic	1.03 [1.02-1.04]	4.39E-08	1.03 [1.02-1.04]	4.78E-07
rs12808129	11	13246222	G	0.51	ARNTL	intergenic	1.03 [1.02-1.04]	6.18E-09	1.03 [1.02-1.04]	2.03E-07
rs273556	11	30866279	C	0.70	DCDC1	intronic	1.03 [1.02-1.04]	4.39E-08	1.03 [1.01-1.04]	1.20E-05
rs34789990	11	65252477	G	0.93	MALAT1	intergenic	1.06 [1.04-1.08]	6.43E-10	1.06 [1.03-1.08]	4.67E-07

rs644740	11	65561468	C	0.54	OVOL1	UTR5	1.03 [1.02-1.04]	7.55E-10	1.03 [1.02-1.04]	1.81E-06
rs1224954	11	76488545	G	0.60	TSKU	intergenic	1.03 [1.02-1.04]	2.62E-09	1.03 [1.02-1.04]	1.26E-07
rs7940164	11	113451765	G	0.69	DRD2	intergenic	1.03 [1.02-1.04]	2.43E-08	1.03 [1.02-1.04]	2.25E-06
rs11105401	12	90150382	G	0.76	RNU6-148P	intergenic	1.03 [1.02-1.04]	3.76E-08	1.03 [1.02-1.04]	6.42E-06
rs2363081	12	94168926	A	0.49	CRADD	intronic	1.03 [1.02-1.04]	1.94E-09	1.03 [1.02-1.04]	3.33E-09
rs28372579	12	123881176	A	0.23	SETD8	intronic	1.03 [1.02-1.05]	8.22E-09	1.04 [1.02-1.05]	9.47E-08
rs72698727	14	101189019	T	0.18	DLK1	intergenic	1.04 [1.03-1.05]	1.64E-09	1.04 [1.02-1.05]	3.89E-07
rs4380013	15	50759428	A	0.22	USP8	intronic	1.04 [1.03-1.05]	6.40E-10	1.04 [1.02-1.05]	3.52E-07
rs17374222	15	69995344	A	0.47	RP11-279F6.3	intergenic	1.03 [1.02-1.04]	1.17E-08	1.01 [1.00-1.02]	3.44E-02
rs11072508	15	75062397	T	0.39	CSK	intergenic	1.04 [1.03-1.05]	8.66E-13	1.04 [1.03-1.05]	5.29E-12
rs7201780	16	30147265	C	0.52	MAPK3	intergenic	1.03 [1.02-1.04]	2.78E-09	1.02 [1.01-1.03]	4.41E-05
rs72821332	16	89318271	C	0.93	RP11-46C24.5	intergenic	1.06 [1.04-1.09]	2.69E-08	1.06 [1.03-1.08]	1.19E-05
rs3803689	16	89800058	C	0.59	ZNF276	intronic	1.03 [1.02-1.04]	3.22E-10	1.03 [1.02-1.04]	1.60E-08
rs10502437	18	20970706	G	0.60	TMEM241	intronic	1.04 [1.03-1.05]	3.20E-12	1.03 [1.02-1.04]	2.50E-08
rs11085743	19	10759442	G	0.60	ILF3-AS1	intergenic	1.04 [1.03-1.05]	9.77E-16	1.04 [1.03-1.05]	1.57E-13
rs56280929	20	33825157	C	0.90	EDEM2:MMP24-AS1:MMP24	ncRNA_intronic	1.05 [1.03-1.06]	2.36E-08	1.05 [1.03-1.07]	1.81E-07
rs224333	20	34023962	G	0.63	GDF5	intronic	1.04 [1.03-1.05]	1.75E-14	1.04 [1.03-1.06]	1.40E-13
rs8128364	21	34867525	C	0.50	DNAJC28	intergenic	1.03 [1.02-1.04]	3.82E-11	1.02 [1.01-1.04]	8.23E-06

Table x5.3 Lead SNPs for rheumatoid arthritis identified from MTAG

MTAG Results									Single-Trait Results	
RSID	CHR	BP	EA	EAF	NrtGene	Function	OR[95%CI]	P value	OR[95%CI]	P value
rs867436	1	2523723	T	0.33	MMEL1	intronic	1.06 [1.04-1.08]	2.02E-10	1.07 [1.04-1.1]	8.72E-08
rs12086096	1	113856853	G	0.78	MAGI3	intergenic	1.07 [1.05-1.1]	5.16E-11	1.12 [1.09-1.15]	1.32E-13
rs12128454	1	113910209	C	0.89	MAGI3	intergenic	1.12 [1.09-1.15]	5.40E-16	1.17 [1.13-1.22]	4.01E-17
rs1230675	1	114175770	A	0.27	MAGI3	intronic	1.07 [1.05-1.09]	4.03E-11	1.09 [1.06-1.12]	6.74E-11
rs6679677	1	114303808	C	0.91	RSBN1	downstream	1.33 [1.29-1.37]	2.75E-84	1.52 [1.47-1.58]	1.03E-103
rs1158912	1	114527534	C	0.90	OLFML3	intergenic	1.12 [1.09-1.16]	3.94E-14	1.2 [1.16-1.25]	1.98E-19
rs12137270	1	117264336	C	0.74	GAPDHP64	intergenic	1.06 [1.04-1.08]	3.12E-08	1.07 [1.04-1.1]	3.62E-06
rs2105325	1	173349725	C	0.75	RP11-296O14.2	intergenic	1.06 [1.04-1.08]	9.43E-09	1.07 [1.04-1.1]	1.20E-06
rs59985551	2	56106928	T	0.23	EFEMP1	intronic	1.06 [1.04-1.08]	3.11E-08	1.04 [1.01-1.06]	1.11E-02
rs13026755	2	61160619	C	0.66	REL: RP11-373L24.1	intergenic	1.06 [1.04-1.08]	7.98E-10	1.08 [1.05-1.11]	9.44E-09
rs7574865	2	191964633	T	0.23	STAT4	intronic	1.07 [1.05-1.09]	8.94E-11	1.11 [1.08-1.14]	5.50E-13
rs62182810	2	204387482	G	0.54	RAPH1	intronic	1.07 [1.05-1.09]	3.12E-12	1.05 [1.02-1.08]	4.07E-04
rs3087243	2	204738919	A	0.47	CTLA4	downstream	1.06 [1.04-1.08]	4.51E-10	1.09 [1.06-1.11]	1.00E-11
rs4073150	2	241865415	G	0.51	AC104809.3	intronic	1.06 [1.04-1.08]	2.76E-08	1.06 [1.03-1.09]	4.23E-05
rs12491516	3	17075768	C	0.71	PLCL2	intronic	1.06 [1.04-1.08]	9.86E-09	1.08 [1.05-1.11]	5.75E-08
rs9880772	3	27777779	G	0.53	EOMES	intergenic	1.06 [1.05-1.08]	5.43E-12	1.06 [1.03-1.09]	3.44E-06
rs345985	3	156397174	T	0.39	TIPARP	intronic	1.06 [1.04-1.08]	6.45E-10	1.06 [1.03-1.08]	2.06E-05
rs4473645	4	26091198	G	0.70	RP11-324H7.1	intergenic	1.07 [1.05-1.1]	3.08E-13	1.12 [1.09-1.15]	6.83E-16

rs13107325	4	103188709	C	0.92	SLC39A8	exonic	1.14 [1.09-1.18]	3.27E-11	1.02 [0.97-1.08]	4.20E-01
rs4865631	5	55370715	A	0.34	CTD-2227I18.1	intergenic	1.06 [1.04-1.08]	8.51E-09	1.06 [1.03-1.09]	5.48E-05
rs7731626	5	55444683	A	0.38	ANKRD55	intronic	1.11 [1.09-1.13]	3.81E-25	1.16 [1.13-1.2]	1.50E-26
rs556560	5	102623924	A	0.34	C5orf30	intergenic	1.06 [1.04-1.08]	2.46E-09	1.08 [1.05-1.1]	1.67E-08
rs2234067	6	36355654	C	0.86	ETV7 RP1-50J22.4	ncRNA_intronic	1.09 [1.06-1.12]	8.14E-10	1.1 [1.06-1.14]	3.28E-07
rs9472362	6	44751285	C	0.56	SUPT3H	intergenic	1.05 [1.03-1.07]	4.86E-08	1.04 [1.01-1.07]	5.37E-03
rs1342622	6	51330756	C	0.60	SNORD66	intergenic	1.05 [1.03-1.07]	1.75E-08	1.06 [1.03-1.08]	5.09E-06
rs617328	6	138000398	G	0.69	RP11-95M15.1	intergenic	1.07 [1.05-1.09]	5.91E-11	1.09 [1.06-1.12]	3.05E-10
rs17264332	6	138005515	G	0.83	RP11-95M15.1	intergenic	1.09 [1.07-1.12]	3.32E-16	1.13 [1.1-1.16]	2.97E-16
rs6932056	6	138242437	C	0.98	RP11-10J5.1	intergenic	1.18 [1.12-1.24]	1.35E-10	1.26 [1.18-1.35]	1.63E-11
rs1571878	6	167540842	T	0.42	RP11-517H2.6:CCR6	ncRNA_intronic	1.06 [1.04-1.08]	1.93E-11	1.1 [1.07-1.13]	2.58E-14
rs481806	7	28207300	T	0.26	JAZF1	intronic	1.06 [1.04-1.08]	1.88E-08	1.05 [1.02-1.08]	2.16E-04
rs6960408	7	48963932	A	0.47	AC006024.4	ncRNA_intronic	1.05 [1.03-1.07]	3.80E-08	1.06 [1.03-1.08]	6.14E-05
rs10261758	7	50353192	A	0.31	IKZF1	intronic	1.06 [1.04-1.08]	4.23E-09	1.08 [1.05-1.11]	1.38E-08
rs9969232	7	114158954	G	0.61	FOXP2	intronic	1.06 [1.04-1.08]	2.17E-08	1.06 [1.03-1.09]	1.72E-04
rs3823536	7	128579666	G	0.53	IRF5	intronic	1.07 [1.05-1.09]	3.60E-14	1.09 [1.07-1.12]	5.05E-13
rs2551760	7	135169414	T	0.28	CNOT4	intronic	1.06 [1.04-1.09]	5.00E-09	1.06 [1.03-1.09]	2.73E-04
rs2736340	8	11343973	C	0.76	BLK	intergenic	1.06 [1.04-1.08]	1.88E-09	1.07 [1.05-1.1]	1.82E-07
rs4979341	9	116905543	C	0.74	COL27A1	intergenic	1.07 [1.05-1.09]	1.11E-09	1.03 [1-1.06]	4.62E-02
rs1930785	9	123691237	T	0.42	TRAF1	intronic	1.06 [1.04-1.08]	1.92E-09	1.06 [1.04-1.09]	1.92E-06

rs12722522	10	6078553	A	0.08	IL2RA	intronic	1.09 [1.06-1.12]	1.50E-08	1.08 [1.04-1.13]	1.16E-04
rs706778	10	6098949	C	0.59	IL2RA	intronic	1.08 [1.06-1.1]	3.77E-17	1.09 [1.06-1.11]	2.52E-11
rs793095	10	31385974	C	0.53	AL359546.1	intergenic	1.05 [1.03-1.07]	1.52E-08	1.05 [1.03-1.08]	2.99E-05
rs11593907	10	63786554	C	0.76	ARID5B	intronic	1.07 [1.05-1.1]	1.84E-10	1.11 [1.08-1.14]	3.10E-12
rs644740	11	65561468	T	0.46	OVOL1	UTR5	1.06 [1.04-1.08]	4.61E-10	1.05 [1.02-1.07]	1.22E-03
rs4938573	11	118741842	C	0.81	CXCR5	intergenic	1.08 [1.06-1.1]	3.28E-11	1.1 [1.07-1.14]	1.63E-09
rs2374606	12	106789172	G	0.80	POLR3B	intronic	1.07 [1.05-1.09]	1.12E-08	1.07 [1.03-1.1]	8.34E-05
rs9603618	13	40371377	T	0.28	COG6	intergenic	1.06 [1.04-1.08]	5.39E-09	1.08 [1.05-1.12]	1.08E-08
rs7141996	14	93094298	A	0.18	RIN3	intronic	1.07 [1.04-1.09]	4.81E-08	1.06 [1.03-1.1]	2.58E-04
rs72727387	15	38843476	G	0.75	RASGRP1	intronic	1.08 [1.06-1.1]	1.19E-13	1.1 [1.07-1.13]	6.73E-12
rs11070778	15	50738876	G	0.82	USP8	intronic	1.08 [1.05-1.11]	7.28E-10	1.06 [1.03-1.1]	4.08E-04
rs17374222	15	69995344	C	0.53	RP11-279F6.3	intergenic	1.07 [1.05-1.09]	1.51E-13	1.1 [1.07-1.12]	9.48E-14
rs12913522	15	74599765	G	0.62	CCDC33	intronic	1.06 [1.04-1.08]	8.39E-09	1.05 [1.01-1.08]	3.69E-03
rs7201780	16	30147265	T	0.48	MAPK3	intergenic	1.07 [1.05-1.09]	1.33E-13	1.07 [1.04-1.1]	7.21E-07
rs12232384	16	86009760	C	0.78	RP11-542M13.2	intergenic	1.08 [1.05-1.1]	2.12E-11	1.08 [1.05-1.12]	1.63E-07
rs72821332	16	89318271	T	0.07	RP11-46C24.5	intergenic	1.14 [1.09-1.19]	8.92E-09	1.11 [1.05-1.19]	7.94E-04
rs4785746	16	90006179	T	0.44	TUBB3	intergenic	1.06 [1.04-1.08]	2.73E-08	1.06 [1.03-1.09]	2.48E-04
rs62095889	18	21069068	A	0.33	RIOK3	intergenic	1.06 [1.04-1.08]	1.14E-09	1.06 [1.03-1.09]	1.19E-04
rs11085727	19	10466123	T	0.27	TYK2	intronic	1.07 [1.05-1.09]	2.35E-10	1.1 [1.07-1.13]	2.08E-11
rs3843751	19	10748121	T	0.37	SLC44A2	intronic	1.07 [1.05-1.09]	3.71E-11	1.05 [1.02-1.08]	2.97E-04

rs6032663	20	44735263	G	0.74	RPL13P2	intergenic	1.07 [1.05-1.1]	6.24E-12	1.09 [1.06-1.12]	1.02E-08
rs4816452	21	34810330	A	0.44	IFNGR2:TMEM50B	intronic	1.06 [1.04-1.08]	1.88E-11	1.07 [1.05-1.1]	1.60E-08
rs1893592	21	43855067	A	0.28	UBASH3A	intronic	1.06 [1.04-1.08]	1.24E-08	1.07 [1.05-1.1]	3.16E-07
rs11089637	22	21979096	C	0.83	UBE2L3	downstream	1.07 [1.04-1.1]	4.60E-08	1.09 [1.05-1.12]	1.04E-06
rs2069235	22	39747780	G	0.70	SYNGR1	intronic	1.06 [1.04-1.08]	2.04E-08	1.08 [1.05-1.11]	1.89E-08

Table x5.4 Lead SNPs for endometriosis identified in the recent IEGC publication

Locus	Lead SNP	CHR	BP	RA (RAFEUR; RAFJPT)	OR (95% CI)	P value
WNT4/1p36.12	rs10917151	1	22422721	A (0.17; 0.57)	1.14 (1.12-1.16)	5.08x10 -44
NGF/1p13.2	rs12030576	1	115817221	G (0.65; 0.41)	1.06 (1.04-1.07)	3.34x10-13
SLC19A2/1q24.2	rs2040445	1	169216412	G (0.97; N/A)	1.17 (1.12-1.23)	1.40x10-10
DNM3/1q24.3	rs2421985	1	172099136	C (0.49; 0.77)	1.05 (1.04-1.07)	6.73x10-14
GREB1/2p25.1	rs11674184	2	11721535	T (0.61; 0.54)	1.08 (1.07-1.10)	3.16x10-26
ETAA1/2p14	rs1430787	2	67868498	A (0.31; 0.22)	1.14 (1.12-1.16)	9.65x10-9
BMPR2/2q33.1	rs6435157	2	203441224	T (0.77; 0.97)	1.05 (1.03-1.06)	4.97x10-8
BSN/3p21.31	rs1352889	3	49652148	T (0.17; N/A)	1.05 (1.03-1.07)	2.79x10-8
KDR/4q12	rs1903068	4	56008477	A (0.68; 0.88)	1.08 (1.06-1.10)	1.55x10-24
PDLIM5/4q22.3	rs2510770	4	95479372	A (0.32; 0.49)	1.04 (1.03-1.06)	7.64x10-9
EBF1/5q33.3	rs2946160	5	157891878	A (0.74; 0.69)	1.05 (1.03-1.06)	1.99x10-8
ID4/6p22.3	rs6456259	6	19761718	G (0.16; N/A)	1.08 (1.06-1.10)	4.23x10-17
CD109/6q13	rs4540228	6	74613060	C (0.66; 0.58)	1.05 (1.04-1.07)	1.66x10-11
HEY2/6q22.31	rs2226158	6	125995467	G (0.46; 0.27)	1.05 (1.03-1.06)	3.35x10-10
SYNE1/6q25.1	rs71575922	6	152554014	G (0.15; N/A)	1.12 (1.10-1.14)	1.21x10-31
FAM120B/6q27	rs11756073	6	170363580	A (0.17; 0.26)	1.06 (1.04-1.08)	3.13x10-9
7p15.2/7p15.2	rs1451383	7	25891809	G (0.74; 0.20)	1.06 (1.04-1.07)	8.66x10-12
HOXA10/7p15.2	rs6970537	7	27217359	G (0.57; 0.75)	1.05 (1.03-1.06)	6.98x10-11
7p12.3/7p12.3	rs55909142	7	46673774	C (0.59; 0.50)	1.04 (1.03-1.06)	8.92x10-9
KCTD9/8p21.2	rs17053711	8	25311269	G (0.73; 0.54)	1.05 (1.03-1.06)	9.61x10-9
GDAP1/8q21.11	rs10090060	8	75257608	A (0.57; 0.68)	1.06 (1.04-1.07)	6.61x10-15
VPS13B/8q22.2	rs12549438	8	100150371	T (0.21; 0.39)	1.05 (1.04-1.07)	8.36x10-10
CDKN2B-AS1/9p21.3	rs10122243	9	22158924	T (0.41; 0.39)	1.06 (1.05-1.08)	1.49x10-17

ASTN2/9q33.1	rs10983311	9	119470373	T (0.77; 0.61)	1.05 (1.03-1.07)	2.20x10-8
ABO/9q34.2	rs507666	9	136149399	A (0.20; 0.27)	1.05 (1.03-1.07)	1.04x10-8
MLLT10/10p12.31	rs10828249	10	21824727	A (0.35; N/A)	1.05 (1.04-1.07)	3.74x10-12
RNLS/10q23.31	rs7907732	10	90182764	T (0.39; 0.51)	1.05 (1.03-1.06)	2.19x10-10
FSHB/11p14.1	rs3858429	11	30343757	C (0.84; 0.98)	1.12 (1.10-1.14)	2.23x10-30
WT1/11p14.1	rs7924571	11	32350027	C (0.76; 0.23)	1.05 (1.04-1.07)	6.00x10-10
PTPRO/12p12.3	rs56090796	12	15406228	A (0.33; 0.18)	1.05 (1.03-1.06)	3.46x10-9
HOXC10/12p13.13	rs3803042	12	54387947	A (0.42; 0.55)	1.04 (1.03-1.06)	6.97x10-9
VEZT/12q22	rs12320196	12	95645385	G (0.47; 0.49)	1.05 (1.04-1.07)	6.74x10-14
IGF1/12q23.2	rs10860864	12	102822862	C (0.82; 0.80)	1.06 (1.04-1.08)	3.69x10-10
DLEU1/13q14.2	rs7334326	13	50967732	C (0.16; 0.77)	1.06 (1.04-1.08)	1.29x10-8
RIN3/14q32.12	rs57281976	14	93112974	G (0.77; 0.81)	1.05 (1.03-1.07)	3.53x10-9
SRP14-AS1/15q15.1	rs12441483	15	40353416	C (0.47; 0.78)	1.05 (1.04-1.07)	1.58x10-13
SKAP1/17q21.32	rs66683298	17	46277748	C (0.60; 0.78)	1.05 (1.03-1.06)	7.18x10-10
CEP112/17q24.1	rs7214750	17	63903119	C (0.93; 0.94)	1.09 (1.06-1.12)	9.80x10-10
ACTL9/19p13.2	rs2967684	19	8786624	A (0.16; N/A)	1.06 (1.04-1.08)	1.29x10-8
TEX11/Xq13.1	rs13441059	X	70108889	--	1.05 (1.04-1.07)	1.58x10-11
FRMD7/Xq26.2	rs5933091	X	131278107	--	1.05 (1.03-1.07)	1.05x10-9
LINC00629/Xq26.3	rs73241342	X	133691738	--	1.14 (1.10-1.19)	1.39x10-10

***** Abbreviations. RA: Risk allele, RAF: Risk allele frequency, EUR: European, JPT: Japanese.

Table x5.5 EQTL look-ups for 10 novel risk variants for endometriosis from multi-trait analysis

Gencode Id	Gene Symbol	Variant Id	SNP Id	P-Value	NES	Tissue
ENSG00000219073.7	CELA3B	chr1_21935732_G_A_b38	rs12081298	1.10E-08	0.31	Pancreas
ENSG00000219073.7	CELA3B	chr1_21935732_G_A_b38	rs12081298	1.90E-07	0.43	Stomach
ENSG00000142789.19	CELA3A	chr1_21935732_G_A_b38	rs12081298	3.00E-07	-0.3	Pancreas
ENSG00000283234.1	RP11-26H16.4	chr1_21935732_G_A_b38	rs12081298	3.80E-07	0.59	Pancreas
ENSG00000201919.1	RNU6-1022P	chr1_21935732_G_A_b38	rs12081298	2.30E-06	0.37	Pancreas
ENSG00000142798.17	HSPG2	chr1_21935732_G_A_b38	rs12081298	4.30E-05	-0.36	Pituitary
ENSG00000138030.12	KHK	chr2_27125819_T_C_b38	rs12467319	1.00E-32	0.41	Skin - Sun Exposed (Lower leg)
ENSG00000138030.12	KHK	chr2_27125819_T_C_b38	rs12467319	4.10E-31	0.41	Muscle - Skeletal
ENSG00000138030.12	KHK	chr2_27125819_T_C_b38	rs12467319	8.90E-26	0.39	Adipose - Subcutaneous
ENSG00000138030.12	KHK	chr2_27125819_T_C_b38	rs12467319	3.60E-22	0.36	Skin - Not Sun Exposed (Suprapubic)
ENSG00000138030.12	KHK	chr2_27125819_T_C_b38	rs12467319	6.60E-22	0.28	Nerve - Tibial

ENSG00000138030.12	KHK	chr2_27125819_T_C_b38	rs12467319	8.00E-21	0.35	Adipose - Visceral (Omentum)
ENSG00000084764.10	MAPRE3	chr2_27125819_T_C_b38	rs12467319	2.50E-16	0.19	Skin - Sun Exposed (Lower leg)
ENSG00000138030.12	KHK	chr2_27125819_T_C_b38	rs12467319	1.20E-15	0.26	Whole Blood
ENSG00000138030.12	KHK	chr2_27125819_T_C_b38	rs12467319	2.60E-15	0.25	Thyroid
ENSG00000138030.12	KHK	chr2_27125819_T_C_b38	rs12467319	9.60E-14	0.2	Artery - Tibial
ENSG00000084764.10	MAPRE3	chr2_27125819_T_C_b38	rs12467319	1.10E-13	0.19	Skin - Not Sun Exposed (Suprapubic)
ENSG00000138030.12	KHK	chr2_27125819_T_C_b38	rs12467319	1.50E-13	0.34	Breast - Mammary Tissue
ENSG00000138030.12	KHK	chr2_27125819_T_C_b38	rs12467319	9.00E-13	0.36	Testis
ENSG00000138030.12	KHK	chr2_27125819_T_C_b38	rs12467319	2.00E-11	0.24	Esophagus - Gastroesophageal Junction
ENSG00000138030.12	KHK	chr2_27125819_T_C_b38	rs12467319	3.10E-11	0.23	Lung
ENSG00000138028.15	CGREF1	chr2_27125819_T_C_b38	rs12467319	5.30E-11	0.2	Cells - Cultured fibroblasts
ENSG00000138030.12	KHK	chr2_27125819_T_C_b38	rs12467319	1.70E-10	0.22	Esophagus - Mucosa
ENSG00000138030.12	KHK	chr2_27125819_T_C_b38	rs12467319	7.90E-10	0.34	Heart - Left Ventricle
ENSG00000138030.12	KHK	chr2_27125819_T_C_b38	rs12467319	8.70E-10	0.2	Esophagus - Muscularis
ENSG00000138030.12	KHK	chr2_27125819_T_C_b38	rs12467319	8.90E-10	0.32	Heart - Atrial Appendage
ENSG00000138030.12	KHK	chr2_27125819_T_C_b38	rs12467319	1.00E-09	0.32	Stomach
ENSG00000084764.10	MAPRE3	chr2_27125819_T_C_b38	rs12467319	9.70E-09	0.11	Muscle - Skeletal
ENSG00000138028.15	CGREF1	chr2_27125819_T_C_b38	rs12467319	1.00E-08	0.22	Muscle - Skeletal
ENSG00000138028.15	CGREF1	chr2_27125819_T_C_b38	rs12467319	1.80E-08	0.23	Esophagus - Mucosa
ENSG00000138030.12	KHK	chr2_27125819_T_C_b38	rs12467319	7.60E-08	0.37	Ovary
ENSG00000138080.13	EMILIN1	chr2_27125819_T_C_b38	rs12467319	1.30E-07	-0.18	Whole Blood
ENSG00000138030.12	KHK	chr2_27125819_T_C_b38	rs12467319	1.70E-07	0.23	Cells - Cultured fibroblasts
ENSG00000143994.13	ABHD1	chr2_27125819_T_C_b38	rs12467319	4.00E-07	0.15	Nerve - Tibial
ENSG00000084764.10	MAPRE3	chr2_27125819_T_C_b38	rs12467319	5.50E-07	0.27	Ovary
ENSG00000138030.12	KHK	chr2_27125819_T_C_b38	rs12467319	6.60E-07	0.19	Colon - Sigmoid
ENSG00000138030.12	KHK	chr2_27125819_T_C_b38	rs12467319	1.10E-06	0.28	Prostate
ENSG00000138030.12	KHK	chr2_27125819_T_C_b38	rs12467319	1.30E-06	0.18	Artery - Aorta
ENSG00000143994.13	ABHD1	chr2_27125819_T_C_b38	rs12467319	1.50E-06	0.23	Colon - Sigmoid
ENSG00000138030.12	KHK	chr2_27125819_T_C_b38	rs12467319	1.50E-06	0.23	Colon - Transverse
ENSG00000143994.13	ABHD1	chr2_27125819_T_C_b38	rs12467319	3.20E-06	0.15	Adipose - Visceral (Omentum)
ENSG00000084764.10	MAPRE3	chr2_27125819_T_C_b38	rs12467319	6.90E-06	0.14	Esophagus - Mucosa
ENSG00000115155.16	OTOF	chr2_27125819_T_C_b38	rs12467319	9.70E-06	0.19	Brain - Caudate (basal ganglia)
ENSG00000084764.10	MAPRE3	chr2_27125819_T_C_b38	rs12467319	1.30E-05	0.17	Cells - Cultured fibroblasts
ENSG00000138030.12	KHK	chr2_27125819_T_C_b38	rs12467319	2.10E-05	0.18	Pancreas

ENSG00000138030.12	KHK	chr2_27125819_T_C_b38	rs12467319	2.50E-05	0.23	Adrenal Gland
ENSG00000084764.10	MAPRE3	chr2_27125819_T_C_b38	rs12467319	4.80E-05	0.11	Artery - Tibial
ENSG00000157851.16	DPYSL5	chr2_27125819_T_C_b38	rs12467319	7.40E-05	-0.24	Brain - Cerebellar Hemisphere
ENSG00000157851.16	DPYSL5	chr2_27125819_T_C_b38	rs12467319	1.10E-04	-0.21	Brain - Cerebellum
ENSG00000138030.12	KHK	chr2_27125819_T_C_b38	rs12467319	1.30E-04	0.28	Spleen
ENSG00000143994.13	ABHD1	chr2_27125819_T_C_b38	rs12467319	1.80E-04	0.12	Muscle - Skeletal
ENSG00000084693.15	AGBL5	chr2_27125819_T_C_b38	rs12467319	3.20E-04	0.12	Cells - Cultured fibroblasts
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.00E-130	-0.59	Whole Blood
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	5.00E-109	-0.57	Adipose - Subcutaneous
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.20E-102	-0.51	Thyroid
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	3.10E-97	-0.45	Nerve - Tibial
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	4.20E-96	-0.49	Esophagus - Mucosa
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.80E-92	-0.47	Artery - Tibial
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	3.00E-86	-0.44	Skin - Sun Exposed (Lower leg)
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.40E-82	-0.5	Esophagus - Muscularis
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	2.10E-78	-0.4	Lung
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.50E-74	-0.5	Cells - Cultured fibroblasts
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	2.10E-72	-0.48	Adipose - Visceral (Omentum)
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.20E-70	-0.5	Heart - Atrial Appendage
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.30E-66	-0.5	Artery - Aorta
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	7.90E-66	-0.42	Skin - Not Sun Exposed (Suprapubic)
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	8.60E-64	-0.56	Breast - Mammary Tissue
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	7.80E-63	-0.6	Colon - Transverse
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.70E-57	-0.4	Muscle - Skeletal
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	2.70E-56	-0.58	Pancreas
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.40E-54	-0.52	Esophagus - Gastroesophageal Junction
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	5.00E-54	-0.46	Heart - Left Ventricle
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	4.30E-49	-0.55	Stomach
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	6.90E-46	-0.42	Testis
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	5.10E-40	-0.52	Colon - Sigmoid
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	7.50E-39	-0.64	Brain - Cerebellum
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.00E-37	-0.59	Spleen
ENSG00000234667.1	ACTBP13	chr3_49934081_C_A_b38	rs7613875	3.60E-37	-0.41	Skin - Sun Exposed (Lower leg)

ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.50E-33	-0.65	Pituitary
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	7.00E-30	-0.55	Brain - Cortex
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.20E-29	-0.5	Prostate
ENSG00000182179.12	UBA7	chr3_49934081_C_A_b38	rs7613875	4.10E-29	-0.2	Whole Blood
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.40E-28	-0.63	Small Intestine - Terminal Ileum
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	8.40E-27	-0.42	Brain - Nucleus accumbens (basal ganglia)
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.20E-25	-0.46	Artery - Coronary
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.70E-23	-0.44	Brain - Cerebellar Hemisphere
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	4.20E-21	-0.38	Brain - Caudate (basal ganglia)
ENSG00000185614.4	FAM212A	chr3_49934081_C_A_b38	rs7613875	7.20E-21	0.27	Esophagus - Mucosa
ENSG00000182179.12	UBA7	chr3_49934081_C_A_b38	rs7613875	3.80E-20	-0.21	Esophagus - Mucosa
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	4.60E-20	-0.39	Brain - Frontal Cortex (BA9)
ENSG00000234667.1	ACTBP13	chr3_49934081_C_A_b38	rs7613875	5.10E-20	-0.37	Skin - Not Sun Exposed (Suprapubic)
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	2.10E-19	-0.33	Adrenal Gland
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	1.20E-17	0.53	Brain - Cerebellum
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	3.00E-17	-0.42	Brain - Putamen (basal ganglia)
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	3.70E-17	0.23	Adipose - Subcutaneous
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	4.20E-17	0.2	Skin - Not Sun Exposed (Suprapubic)
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	2.20E-16	0.26	Nerve - Tibial
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	2.50E-16	-0.43	Liver
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	2.00E-15	-0.33	Ovary
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	2.70E-15	-0.57	Minor Salivary Gland
ENSG00000182179.12	UBA7	chr3_49934081_C_A_b38	rs7613875	4.50E-15	-0.34	Pancreas
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	6.30E-15	-0.33	Brain - Hypothalamus
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	2.00E-14	-0.31	Brain - Hippocampus
ENSG00000182179.12	UBA7	chr3_49934081_C_A_b38	rs7613875	2.60E-14	-0.26	Colon - Transverse
ENSG00000185614.4	FAM212A	chr3_49934081_C_A_b38	rs7613875	4.20E-14	0.48	Brain - Cerebellum
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	8.50E-14	0.17	Skin - Sun Exposed (Lower leg)
ENSG00000182179.12	UBA7	chr3_49934081_C_A_b38	rs7613875	1.30E-13	-0.19	Skin - Not Sun Exposed (Suprapubic)
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	2.50E-13	-0.47	Brain - Spinal cord (cervical c-1)
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	4.80E-13	-0.43	Vagina
ENSG00000185614.4	FAM212A	chr3_49934081_C_A_b38	rs7613875	6.60E-13	0.16	Skin - Not Sun Exposed (Suprapubic)

ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	8.10E-13	0.28	Adipose - Subcutaneous
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	8.40E-13	0.17	Artery - Tibial
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	2.30E-12	-0.47	Brain - Anterior cingulate cortex (BA24)
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	2.40E-12	0.29	Brain - Cerebellum
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	2.40E-12	0.48	Brain - Cerebellar Hemisphere
ENSG00000187492.8	CDHR4	chr3_49934081_C_A_b38	rs7613875	2.90E-12	0.36	Testis
ENSG00000182179.12	UBA7	chr3_49934081_C_A_b38	rs7613875	3.60E-12	-0.18	Artery - Aorta
ENSG00000185614.4	FAM212A	chr3_49934081_C_A_b38	rs7613875	6.60E-12	0.44	Brain - Cerebellar Hemisphere
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	6.90E-12	-0.57	Cells - EBV-transformed lymphocytes
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	1.70E-11	0.29	Nerve - Tibial
ENSG00000164076.16	CAMKV	chr3_49934081_C_A_b38	rs7613875	2.10E-11	0.49	Stomach
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	3.40E-11	0.2	Nerve - Tibial
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	3.80E-11	0.25	Muscle - Skeletal
ENSG00000185614.4	FAM212A	chr3_49934081_C_A_b38	rs7613875	6.00E-11	0.18	Muscle - Skeletal
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	8.50E-11	0.18	Artery - Tibial
ENSG00000182179.12	UBA7	chr3_49934081_C_A_b38	rs7613875	9.80E-11	-0.19	Stomach
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	1.50E-10	0.2	Skin - Sun Exposed (Lower leg)
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	2.40E-10	0.17	Thyroid
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	3.20E-10	0.21	Thyroid
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	3.50E-10	0.43	Brain - Nucleus accumbens (basal ganglia)
ENSG00000182179.12	UBA7	chr3_49934081_C_A_b38	rs7613875	3.60E-10	-0.13	Skin - Sun Exposed (Lower leg)
ENSG00000228008.1	CTD-2330K9.3	chr3_49934081_C_A_b38	rs7613875	4.50E-10	0.4	Artery - Aorta
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	7.70E-10	0.2	Skin - Not Sun Exposed (Suprapubic)
ENSG00000182179.12	UBA7	chr3_49934081_C_A_b38	rs7613875	8.70E-10	-0.096	Nerve - Tibial
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	1.20E-09	0.31	Artery - Tibial
ENSG00000185614.4	FAM212A	chr3_49934081_C_A_b38	rs7613875	1.70E-09	0.12	Skin - Sun Exposed (Lower leg)
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	2.00E-09	0.19	Cells - Cultured fibroblasts
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	2.20E-09	0.24	Brain - Cerebellar Hemisphere
ENSG00000182179.12	UBA7	chr3_49934081_C_A_b38	rs7613875	3.00E-09	-0.27	Spleen
ENSG00000001617.11	SEMA3F	chr3_49934081_C_A_b38	rs7613875	4.90E-09	-0.22	Nerve - Tibial
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	8.60E-09	0.18	Breast - Mammary Tissue
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	1.10E-08	0.23	Heart - Atrial Appendage

ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.10E-08	-0.37	Brain - Substantia nigra
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.30E-08	-0.49	Kidney - Cortex
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	2.00E-08	0.17	Artery - Aorta
ENSG00000182179.12	UBA7	chr3_49934081_C_A_b38	rs7613875	2.40E-08	-0.099	Cells - Cultured fibroblasts
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	3.70E-08	0.29	Cells - Cultured fibroblasts
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	4.00E-08	0.099	Thyroid
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	4.60E-08	0.19	Esophagus - Muscularis
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	6.20E-08	0.15	Brain - Cortex
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	6.90E-08	-0.4	Uterus
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	7.90E-08	0.28	Pituitary
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	1.20E-07	0.39	Brain - Cortex
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	1.30E-07	0.17	Artery - Aorta
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	1.30E-07	0.12	Esophagus - Muscularis
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	1.30E-07	0.15	Pancreas
ENSG00000182179.12	UBA7	chr3_49934081_C_A_b38	rs7613875	1.40E-07	-0.088	Artery - Tibial
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	3.30E-07	0.15	Lung
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	3.40E-07	0.11	Colon - Transverse
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	3.70E-07	0.14	Adipose - Visceral (Omentum)
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	4.30E-07	0.14	Brain - Nucleus accumbens (basal ganglia)
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	6.30E-07	0.16	Esophagus - Muscularis
ENSG00000182179.12	UBA7	chr3_49934081_C_A_b38	rs7613875	7.40E-07	-0.095	Lung
ENSG00000164076.16	CAMKV	chr3_49934081_C_A_b38	rs7613875	7.40E-07	0.18	Testis
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	7.70E-07	0.17	Breast - Mammary Tissue
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	8.10E-07	0.15	Colon - Sigmoid
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	8.10E-07	0.23	Esophagus - Gastroesophageal Junction
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	9.70E-07	0.15	Adipose - Visceral (Omentum)
ENSG00000001617.11	SEMA3F	chr3_49934081_C_A_b38	rs7613875	9.90E-07	-0.18	Heart - Atrial Appendage
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	1.10E-06	-0.25	Whole Blood
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	1.10E-06	0.32	Brain - Cerebellar Hemisphere
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	1.20E-06	0.29	Brain - Cerebellum
ENSG00000186792.16	HYAL3	chr3_49934081_C_A_b38	rs7613875	1.20E-06	-0.2	Cells - Cultured fibroblasts
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	1.20E-06	0.17	Heart - Atrial Appendage
ENSG00000001617.11	SEMA3F	chr3_49934081_C_A_b38	rs7613875	1.40E-06	-0.14	Adipose - Subcutaneous

ENSG00000182179.12	UBA7	chr3_49934081_C_A_b38	rs7613875	1.50E-06	-0.17	Small Intestine - Terminal Ileum
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	1.60E-06	0.13	Adipose - Subcutaneous
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	2.10E-06	0.19	Artery - Coronary
ENSG00000182179.12	UBA7	chr3_49934081_C_A_b38	rs7613875	2.20E-06	-0.085	Esophagus - Muscularis
ENSG00000164077.13	MON1A	chr3_49934081_C_A_b38	rs7613875	2.40E-06	-0.16	Testis
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	2.90E-06	0.17	Brain - Hypothalamus
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	6.00E-06	0.13	Colon - Transverse
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	6.90E-06	0.12	Lung
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	7.00E-06	0.13	Esophagus - Gastroesophageal Junction
ENSG00000164077.13	MON1A	chr3_49934081_C_A_b38	rs7613875	8.80E-06	-0.095	Whole Blood
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	1.00E-05	0.11	Stomach
ENSG00000228008.1	CTD-2330K9.3	chr3_49934081_C_A_b38	rs7613875	1.00E-05	0.25	Lung
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	1.10E-05	0.18	Artery - Coronary
ENSG00000186792.16	HYAL3	chr3_49934081_C_A_b38	rs7613875	1.20E-05	-0.31	Pituitary
ENSG00000185614.4	FAM212A	chr3_49934081_C_A_b38	rs7613875	1.30E-05	-0.15	Artery - Aorta
ENSG00000228008.1	CTD-2330K9.3	chr3_49934081_C_A_b38	rs7613875	1.30E-05	0.27	Esophagus - Muscularis
ENSG00000185614.4	FAM212A	chr3_49934081_C_A_b38	rs7613875	1.40E-05	-0.1	Cells - Cultured fibroblasts
ENSG00000176095.11	IP6K1	chr3_49934081_C_A_b38	rs7613875	1.60E-05	0.1	Nerve - Tibial
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	1.70E-05	0.18	Prostate
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	1.80E-05	0.43	Brain - Anterior cingulate cortex (BA24)
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	2.00E-05	0.14	Brain - Anterior cingulate cortex (BA24)
ENSG00000001617.11	SEMA3F	chr3_49934081_C_A_b38	rs7613875	2.30E-05	0.17	Artery - Aorta
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	2.30E-05	0.13	Esophagus - Mucosa
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	2.30E-05	0.11	Esophagus - Mucosa
ENSG00000001617.11	SEMA3F	chr3_49934081_C_A_b38	rs7613875	2.30E-05	-0.15	Adipose - Visceral (Omentum)
ENSG00000003756.16	RBM5	chr3_49934081_C_A_b38	rs7613875	2.50E-05	-0.091	Esophagus - Mucosa
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	2.70E-05	0.19	Colon - Sigmoid
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	2.70E-05	0.13	Muscle - Skeletal
ENSG00000088538.12	DOCK3	chr3_49934081_C_A_b38	rs7613875	3.30E-05	0.14	Skin - Sun Exposed (Lower leg)
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	3.40E-05	0.32	Brain - Caudate (basal ganglia)
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	3.50E-05	0.097	Adipose - Visceral (Omentum)
ENSG00000001617.11	SEMA3F	chr3_49934081_C_A_b38	rs7613875	4.60E-05	-0.13	Heart - Left Ventricle

ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	5.30E-05	0.16	Heart - Left Ventricle
ENSG00000233276.3	GPX1	chr3_49934081_C_A_b38	rs7613875	5.40E-05	-0.19	Adrenal Gland
ENSG00000007402.11	CACNA2D2	chr3_49934081_C_A_b38	rs7613875	5.50E-05	-0.15	Pancreas
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	5.50E-05	0.21	Artery - Aorta
ENSG00000003756.16	RBM5	chr3_49934081_C_A_b38	rs7613875	6.00E-05	-0.061	Nerve - Tibial
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	7.40E-05	0.15	Esophagus - Gastroesophageal Junction
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	7.40E-05	0.091	Skin - Sun Exposed (Lower leg)
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	8.50E-05	0.33	Brain - Hippocampus
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.30E-04	-0.25	Brain - Amygdala
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	1.30E-04	0.098	Skin - Not Sun Exposed (Suprapubic)
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	1.40E-04	0.17	Testis
ENSG00000187492.8	CDHR4	chr3_49934081_C_A_b38	rs7613875	1.40E-04	0.12	Artery - Tibial
ENSG00000235016.1	SEMA3F-AS1	chr3_49934081_C_A_b38	rs7613875	1.40E-04	0.22	Brain - Cerebellar Hemisphere
ENSG00000228008.1	CTD-2330K9.3	chr3_49934081_C_A_b38	rs7613875	1.40E-04	0.26	Colon - Sigmoid
ENSG00000281691.1	RBM5-AS1	chr3_49934081_C_A_b38	rs7613875	1.60E-04	0.13	Skin - Sun Exposed (Lower leg)
ENSG00000182179.12	UBA7	chr3_49934081_C_A_b38	rs7613875	1.70E-04	-0.16	Liver
ENSG00000228008.1	CTD-2330K9.3	chr3_49934081_C_A_b38	rs7613875	1.80E-04	0.19	Thyroid
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	1.80E-04	0.09	Heart - Left Ventricle
ENSG00000178252.17	WDR6	chr3_49934081_C_A_b38	rs7613875	1.90E-04	-0.15	Skin - Sun Exposed (Lower leg)
ENSG00000001617.11	SEMA3F	chr3_49934081_C_A_b38	rs7613875	2.40E-04	-0.11	Lung
ENSG00000186792.16	HYAL3	chr3_49934081_C_A_b38	rs7613875	2.90E-04	-0.24	Brain - Cerebellum
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	2.90E-04	0.16	Heart - Left Ventricle
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	3.20E-04	0.23	Brain - Cortex
ENSG00000164062.12	APEH	chr3_49934081_C_A_b38	rs7613875	3.20E-04	-0.074	Cells - Cultured fibroblasts
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	3.30E-04	0.13	Colon - Sigmoid
ENSG00000185614.4	FAM212A	chr3_49934081_C_A_b38	rs7613875	3.30E-04	-0.096	Artery - Tibial
ENSG00000187492.8	CDHR4	chr3_49934081_C_A_b38	rs7613875	3.40E-04	0.18	Esophagus - Mucosa
ENSG00000164062.12	APEH	chr3_49934081_C_A_b38	rs7613875	3.70E-04	-0.063	Adipose - Subcutaneous
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	3.80E-04	0.083	Lung
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	4.00E-04	0.072	Colon - Transverse
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	4.10E-04	0.077	Heart - Atrial Appendage
ENSG00000233276.3	GPX1	chr3_49934081_C_A_b38	rs7613875	4.10E-04	-0.11	Cells - Cultured fibroblasts

ENSG00000164077.13	MON1A	chr3_49934081_C_A_b38	rs7613875	4.80E-04	-0.083	Esophagus - Muscularis
ENSG00000188338.14	SLC38A3	chr3_49934081_C_A_b38	rs7613875	5.60E-04	-0.13	Thyroid
ENSG00000187492.8	CDHR4	chr3_49934081_C_A_b38	rs7613875	6.00E-04	0.13	Thyroid
ENSG00000001617.11	SEMA3F	chr3_49934081_C_A_b38	rs7613875	6.30E-04	-0.12	Esophagus - Muscularis
ENSG00000067560.10	RHOA	chr3_49934081_C_A_b38	rs7613875	6.60E-04	0.078	Muscle - Skeletal
ENSG00000186792.16	HYAL3	chr3_49934081_C_A_b38	rs7613875	7.60E-04	-0.14	Adipose - Subcutaneous
ENSG00000145020.15	AMT	chr3_49934081_C_A_b38	rs7613875	7.70E-04	-0.073	Esophagus - Mucosa
ENSG00000188191.14	PRKAR1B	chr7_882007_T_C_b38	rs1881115	1.40E-35	0.56	Esophagus - Mucosa
ENSG00000188191.14	PRKAR1B	chr7_882007_T_C_b38	rs1881115	6.20E-30	0.49	Cells - Cultured fibroblasts
ENSG00000188191.14	PRKAR1B	chr7_882007_T_C_b38	rs1881115	3.70E-21	0.34	Skin - Sun Exposed (Lower leg)
ENSG00000188191.14	PRKAR1B	chr7_882007_T_C_b38	rs1881115	2.50E-17	0.33	Skin - Not Sun Exposed (Suprapubic)
ENSG00000188191.14	PRKAR1B	chr7_882007_T_C_b38	rs1881115	2.00E-15	0.66	Liver
ENSG00000188191.14	PRKAR1B	chr7_882007_T_C_b38	rs1881115	1.60E-12	0.29	Thyroid
ENSG00000188191.14	PRKAR1B	chr7_882007_T_C_b38	rs1881115	6.00E-12	0.34	Lung
ENSG00000188191.14	PRKAR1B	chr7_882007_T_C_b38	rs1881115	4.70E-11	0.36	Colon - Transverse
ENSG00000188191.14	PRKAR1B	chr7_882007_T_C_b38	rs1881115	1.50E-09	0.4	Small Intestine - Terminal Ileum
ENSG00000164818.15	DNAAF5	chr7_882007_T_C_b38	rs1881115	4.70E-09	0.2	Lung
ENSG00000164818.15	DNAAF5	chr7_882007_T_C_b38	rs1881115	5.40E-09	0.29	Nerve - Tibial
ENSG00000164818.15	DNAAF5	chr7_882007_T_C_b38	rs1881115	5.80E-09	0.25	Thyroid
ENSG00000105963.13	ADAP1	chr7_882007_T_C_b38	rs1881115	9.00E-09	0.27	Skin - Sun Exposed (Lower leg)
ENSG00000164818.15	DNAAF5	chr7_882007_T_C_b38	rs1881115	1.00E-08	0.31	Artery - Aorta
ENSG00000164818.15	DNAAF5	chr7_882007_T_C_b38	rs1881115	2.40E-08	0.22	Artery - Tibial
ENSG00000188191.14	PRKAR1B	chr7_882007_T_C_b38	rs1881115	3.60E-08	0.32	Stomach
ENSG00000188191.14	PRKAR1B	chr7_882007_T_C_b38	rs1881115	2.10E-07	0.43	Minor Salivary Gland
ENSG00000164818.15	DNAAF5	chr7_882007_T_C_b38	rs1881115	7.70E-07	0.41	Liver
ENSG00000188191.14	PRKAR1B	chr7_882007_T_C_b38	rs1881115	1.40E-06	0.34	Pancreas
ENSG00000164828.17	SUN1	chr7_882007_T_C_b38	rs1881115	1.60E-06	0.1	Skin - Sun Exposed (Lower leg)
ENSG00000188191.14	PRKAR1B	chr7_882007_T_C_b38	rs1881115	2.30E-06	0.27	Esophagus - Gastroesophageal Junction
ENSG00000105963.13	ADAP1	chr7_882007_T_C_b38	rs1881115	3.30E-06	0.25	Skin - Not Sun Exposed (Suprapubic)
ENSG00000237181.1	AC147651.4	chr7_882007_T_C_b38	rs1881115	4.80E-06	0.2	Whole Blood
ENSG00000164828.17	SUN1	chr7_882007_T_C_b38	rs1881115	5.60E-06	0.13	Cells - Cultured fibroblasts
ENSG00000188191.14	PRKAR1B	chr7_882007_T_C_b38	rs1881115	9.40E-06	0.14	Adipose - Subcutaneous
ENSG00000164818.15	DNAAF5	chr7_882007_T_C_b38	rs1881115	1.70E-05	0.42	Brain - Cerebellum

ENSG00000164828.17	SUN1	chr7_882007_T_C_b38	rs1881115	1.80E-05	0.09	Skin - Not Sun Exposed (Suprapubic)
ENSG00000105963.13	ADAP1	chr7_882007_T_C_b38	rs1881115	2.10E-05	0.078	Whole Blood
ENSG00000188191.14	PRKAR1B	chr7_882007_T_C_b38	rs1881115	2.50E-05	0.18	Adipose - Visceral (Omentum)
ENSG00000164828.17	SUN1	chr7_882007_T_C_b38	rs1881115	6.20E-05	-0.099	Artery - Tibial
ENSG00000188191.14	PRKAR1B	chr7_882007_T_C_b38	rs1881115	8.00E-05	0.18	Esophagus - Muscularis
ENSG00000164818.15	DNAAF5	chr7_882007_T_C_b38	rs1881115	1.30E-04	0.14	Skin - Sun Exposed (Lower leg)
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	4.50E-88	0.87	Cells - Cultured fibroblasts
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	7.60E-71	0.83	Esophagus - Mucosa
ENSG00000253981.5	ALG1L13P	chr8_8278888_C_T_b38	rs1401390	9.30E-52	0.77	Cells - Cultured fibroblasts
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	1.30E-46	-1	Testis
ENSG00000275342.4	PRAG1	chr8_8278888_C_T_b38	rs1401390	2.00E-42	-0.48	Thyroid
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	1.70E-35	0.63	Adipose - Visceral (Omentum)
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	2.70E-34	-0.71	Nerve - Tibial
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	5.20E-34	0.54	Skin - Not Sun Exposed (Suprapubic)
ENSG00000104626.14	ERI1	chr8_8278888_C_T_b38	rs1401390	3.40E-32	-0.27	Cells - Cultured fibroblasts
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	9.30E-32	-0.91	Pituitary
ENSG00000249188.1	ENPP7P1	chr8_8278888_C_T_b38	rs1401390	5.90E-30	-0.82	Testis
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	4.60E-29	-0.9	Brain - Cortex
ENSG00000254153.1	CTA-398F10.2	chr8_8278888_C_T_b38	rs1401390	1.60E-28	0.45	Skin - Sun Exposed (Lower leg)
ENSG00000254153.1	CTA-398F10.2	chr8_8278888_C_T_b38	rs1401390	3.80E-27	0.49	Skin - Not Sun Exposed (Suprapubic)
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	1.30E-26	-0.9	Brain - Cerebellum
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	1.70E-26	0.61	Colon - Transverse
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	3.00E-26	-0.62	Artery - Tibial
ENSG00000253981.5	ALG1L13P	chr8_8278888_C_T_b38	rs1401390	2.60E-25	0.6	Esophagus - Mucosa
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	1.40E-24	-0.91	Brain - Anterior cingulate cortex (BA24)
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	1.00E-23	-0.83	Brain - Nucleus accumbens (basal ganglia)
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	1.60E-23	-0.7	Brain - Cerebellar Hemisphere
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	1.80E-23	-0.54	Thyroid
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	3.30E-23	-0.6	Brain - Cerebellum
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	4.30E-23	-0.84	Brain - Frontal Cortex (BA9)
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	1.20E-21	0.63	Pancreas
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	2.30E-21	-0.73	Brain - Cortex
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	2.80E-21	-0.81	Brain - Caudate (basal ganglia)

ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	2.80E-20	-0.89	Brain - Cerebellar Hemisphere
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	7.30E-20	0.36	Skin - Sun Exposed (Lower leg)
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	2.10E-19	-0.71	Brain - Frontal Cortex (BA9)
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	4.10E-19	-0.86	Brain - Hypothalamus
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	8.90E-19	-0.88	Brain - Hippocampus
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	1.50E-18	0.28	Breast - Mammary Tissue
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	2.40E-18	0.36	Lung
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	4.90E-18	-0.84	Brain - Putamen (basal ganglia)
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	4.40E-17	-0.53	Lung
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	1.20E-16	-0.87	Brain - Amygdala
ENSG00000233609.3	RPL10P19	chr8_8278888_C_T_b38	rs1401390	2.20E-16	0.36	Thyroid
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	2.90E-16	-0.91	Brain - Substantia nigra
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	9.30E-16	-0.96	Brain - Spinal cord (cervical c-1)
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	1.40E-15	-0.68	Brain - Anterior cingulate cortex (BA24)
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	1.70E-15	-0.93	Uterus
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	2.00E-15	0.33	Adipose - Subcutaneous
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	4.80E-15	0.42	Heart - Left Ventricle
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	1.40E-14	-0.52	Artery - Aorta
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	1.90E-14	0.42	Colon - Sigmoid
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	2.80E-14	0.75	Vagina
ENSG00000249188.1	ENPP7P1	chr8_8278888_C_T_b38	rs1401390	1.20E-13	-0.68	Brain - Cerebellum
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	1.40E-13	-0.75	Ovary
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	1.50E-13	-0.6	Esophagus - Gastroesophageal Junction
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	2.20E-12	-0.46	Breast - Mammary Tissue
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	3.80E-12	-0.39	Adipose - Subcutaneous
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	5.10E-12	0.24	Thyroid
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	6.80E-12	-0.44	Pituitary
ENSG00000233609.3	RPL10P19	chr8_8278888_C_T_b38	rs1401390	2.90E-11	0.26	Lung
ENSG00000253981.5	ALG1L13P	chr8_8278888_C_T_b38	rs1401390	4.00E-11	0.38	Skin - Not Sun Exposed (Suprapubic)
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	4.20E-10	0.25	Esophagus - Muscularis
ENSG00000253981.5	ALG1L13P	chr8_8278888_C_T_b38	rs1401390	6.40E-10	0.44	Colon - Transverse
ENSG00000248538.6	RP11-10A14.5	chr8_8278888_C_T_b38	rs1401390	7.50E-10	-0.42	Testis
ENSG00000104626.14	ERI1	chr8_8278888_C_T_b38	rs1401390	2.00E-09	0.26	Testis

ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	2.10E-09	0.77	Kidney - Cortex
ENSG00000254153.1	CTA-398F10.2	chr8_8278888_C_T_b38	rs1401390	2.10E-09	0.3	Esophagus - Mucosa
ENSG00000248538.6	RP11-10A14.5	chr8_8278888_C_T_b38	rs1401390	2.20E-09	0.3	Whole Blood
ENSG00000253981.5	ALG1L13P	chr8_8278888_C_T_b38	rs1401390	2.70E-09	0.33	Adipose - Subcutaneous
ENSG00000147324.10	MFHAS1	chr8_8278888_C_T_b38	rs1401390	3.00E-09	0.2	Muscle - Skeletal
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	3.90E-09	0.36	Stomach
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	4.20E-09	-0.64	Cells - EBV-transformed lymphocytes
ENSG00000254153.1	CTA-398F10.2	chr8_8278888_C_T_b38	rs1401390	4.90E-09	-0.25	Thyroid
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	1.00E-08	-0.4	Brain - Hippocampus
ENSG00000233609.3	RPL10P19	chr8_8278888_C_T_b38	rs1401390	1.60E-08	0.52	Brain - Cortex
ENSG00000233609.3	RPL10P19	chr8_8278888_C_T_b38	rs1401390	1.90E-08	0.28	Adipose - Visceral (Omentum)
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	1.90E-08	-0.38	Esophagus - Muscularis
ENSG00000249188.1	ENPP7P1	chr8_8278888_C_T_b38	rs1401390	2.10E-08	-0.47	Pituitary
ENSG00000253981.5	ALG1L13P	chr8_8278888_C_T_b38	rs1401390	4.20E-08	0.43	Pancreas
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	4.70E-08	0.27	Heart - Atrial Appendage
ENSG00000147324.10	MFHAS1	chr8_8278888_C_T_b38	rs1401390	5.50E-08	0.26	Heart - Atrial Appendage
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	6.10E-08	0.24	Nerve - Tibial
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	6.20E-08	-0.44	Colon - Sigmoid
ENSG00000253958.1	CLDN23	chr8_8278888_C_T_b38	rs1401390	7.00E-08	-0.22	Skin - Sun Exposed (Lower leg)
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	7.00E-08	0.2	Muscle - Skeletal
ENSG00000275342.4	PRAG1	chr8_8278888_C_T_b38	rs1401390	8.30E-08	-0.3	Testis
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	8.40E-08	-0.47	Liver
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	9.40E-08	-0.37	Adipose - Visceral (Omentum)
ENSG00000253981.5	ALG1L13P	chr8_8278888_C_T_b38	rs1401390	1.50E-07	-0.45	Brain - Cerebellar Hemisphere
ENSG00000253981.5	ALG1L13P	chr8_8278888_C_T_b38	rs1401390	2.90E-07	0.72	Kidney - Cortex
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	4.10E-07	-0.52	Spleen
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	5.30E-07	0.46	Minor Salivary Gland
ENSG00000253981.5	ALG1L13P	chr8_8278888_C_T_b38	rs1401390	5.30E-07	0.55	Vagina
ENSG00000233609.3	RPL10P19	chr8_8278888_C_T_b38	rs1401390	5.70E-07	0.34	Pancreas
ENSG00000253981.5	ALG1L13P	chr8_8278888_C_T_b38	rs1401390	5.70E-07	-0.37	Brain - Cerebellum
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	5.80E-07	-0.29	Skin - Sun Exposed (Lower leg)
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	5.90E-07	-0.3	Cells - Cultured fibroblasts
ENSG00000233609.3	RPL10P19	chr8_8278888_C_T_b38	rs1401390	1.40E-06	0.13	Whole Blood

ENSG00000233609.3	RPL10P19	chr8_8278888_C_T_b38	rs1401390	1.40E-06	0.45	Brain - Hippocampus
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	1.50E-06	0.26	Esophagus - Gastroesophageal Junction
ENSG00000254153.1	CTA-398F10.2	chr8_8278888_C_T_b38	rs1401390	1.50E-06	0.28	Stomach
ENSG00000253981.5	ALG1L13P	chr8_8278888_C_T_b38	rs1401390	1.50E-06	0.12	Whole Blood
ENSG00000253981.5	ALG1L13P	chr8_8278888_C_T_b38	rs1401390	1.80E-06	0.23	Thyroid
ENSG00000253130.1	CTD-3023L14.2	chr8_8278888_C_T_b38	rs1401390	1.90E-06	-0.25	Thyroid
ENSG00000249188.1	ENPP7P1	chr8_8278888_C_T_b38	rs1401390	2.00E-06	-0.52	Brain - Cerebellar Hemisphere
ENSG00000248538.6	RP11-10A14.5	chr8_8278888_C_T_b38	rs1401390	2.10E-06	-0.26	Nerve - Tibial
ENSG00000104626.14	ERI1	chr8_8278888_C_T_b38	rs1401390	2.20E-06	-0.16	Artery - Aorta
ENSG00000253981.5	ALG1L13P	chr8_8278888_C_T_b38	rs1401390	2.30E-06	0.29	Adipose - Visceral (Omentum)
ENSG00000254153.1	CTA-398F10.2	chr8_8278888_C_T_b38	rs1401390	2.30E-06	0.46	Minor Salivary Gland
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	2.50E-06	-0.57	Minor Salivary Gland
ENSG00000254597.1	FAM90A10P	chr8_8278888_C_T_b38	rs1401390	2.50E-06	-0.35	Testis
ENSG00000233609.3	RPL10P19	chr8_8278888_C_T_b38	rs1401390	2.60E-06	0.47	Brain - Anterior cingulate cortex (BA24)
ENSG00000253981.5	ALG1L13P	chr8_8278888_C_T_b38	rs1401390	2.70E-06	0.37	Stomach
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	3.40E-06	-0.3	Skin - Not Sun Exposed (Suprapubic)
ENSG00000173281.4	PPP1R3B	chr8_8278888_C_T_b38	rs1401390	4.30E-06	0.12	Artery - Tibial
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	4.60E-06	-0.46	Artery - Coronary
ENSG00000233609.3	RPL10P19	chr8_8278888_C_T_b38	rs1401390	5.90E-06	0.39	Brain - Caudate (basal ganglia)
ENSG00000233609.3	RPL10P19	chr8_8278888_C_T_b38	rs1401390	6.00E-06	0.45	Brain - Putamen (basal ganglia)
ENSG00000253981.5	ALG1L13P	chr8_8278888_C_T_b38	rs1401390	6.50E-06	0.32	Colon - Sigmoid
ENSG00000233609.3	RPL10P19	chr8_8278888_C_T_b38	rs1401390	8.00E-06	0.19	Adipose - Subcutaneous
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	1.20E-05	-0.35	Stomach
ENSG00000233609.3	RPL10P19	chr8_8278888_C_T_b38	rs1401390	1.50E-05	0.24	Breast - Mammary Tissue
ENSG00000253958.1	CLDN23	chr8_8278888_C_T_b38	rs1401390	1.60E-05	-0.18	Skin - Not Sun Exposed (Suprapubic)
ENSG00000253981.5	ALG1L13P	chr8_8278888_C_T_b38	rs1401390	1.80E-05	-0.41	Brain - Cortex
ENSG00000253981.5	ALG1L13P	chr8_8278888_C_T_b38	rs1401390	2.20E-05	0.38	Liver
ENSG00000275342.4	PRAG1	chr8_8278888_C_T_b38	rs1401390	2.50E-05	-0.14	Adipose - Visceral (Omentum)
ENSG00000233609.3	RPL10P19	chr8_8278888_C_T_b38	rs1401390	2.50E-05	0.23	Colon - Transverse
ENSG00000147324.10	MFHAS1	chr8_8278888_C_T_b38	rs1401390	3.20E-05	-0.13	Esophagus - Gastroesophageal Junction
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	3.60E-05	-0.32	Colon - Transverse
ENSG00000275342.4	PRAG1	chr8_8278888_C_T_b38	rs1401390	5.50E-05	-0.16	Artery - Aorta

ENSG00000233609.3	RPL10P19	chr8_8278888_C_T_b38	rs1401390	5.60E-05	0.22	Heart - Left Ventricle
ENSG00000233609.3	RPL10P19	chr8_8278888_C_T_b38	rs1401390	6.70E-05	0.22	Nerve - Tibial
ENSG00000233609.3	RPL10P19	chr8_8278888_C_T_b38	rs1401390	1.10E-04	0.22	Esophagus - Mucosa
ENSG00000104626.14	ERI1	chr8_9549092_G_A_b38	rs1458942	3.10E-09	0.15	Cells - Cultured fibroblasts
ENSG00000254237.5	RP11-115J16.2	chr8_9549092_G_A_b38	rs1458942	1.70E-08	-0.29	Testis
ENSG00000233609.3	RPL10P19	chr8_9549092_G_A_b38	rs1458942	2.50E-08	-0.24	Thyroid
ENSG00000253958.1	CLDN23	chr8_9549092_G_A_b38	rs1458942	4.00E-08	0.23	Skin - Sun Exposed (Lower leg)
ENSG00000272267.2	RP11-375N15.2	chr8_9549092_G_A_b38	rs1458942	1.40E-07	-0.29	Colon - Transverse
ENSG00000233609.3	RPL10P19	chr8_9549092_G_A_b38	rs1458942	1.50E-06	-0.47	Brain - Anterior cingulate cortex (BA24)
ENSG00000272267.2	RP11-375N15.2	chr8_9549092_G_A_b38	rs1458942	1.80E-06	0.45	Brain - Putamen (basal ganglia)
ENSG00000233609.3	RPL10P19	chr8_9549092_G_A_b38	rs1458942	2.40E-06	-0.45	Brain - Cortex
ENSG00000233609.3	RPL10P19	chr8_9549092_G_A_b38	rs1458942	3.20E-06	-0.29	Pancreas
ENSG00000272505.1	RP11-981G7.6	chr8_9549092_G_A_b38	rs1458942	4.50E-06	-0.45	Brain - Spinal cord (cervical c-1)
ENSG00000253735.1	RP11-115J16.3	chr8_9549092_G_A_b38	rs1458942	5.30E-06	0.25	Testis
ENSG00000261451.1	RP11-981G7.1	chr8_9549092_G_A_b38	rs1458942	7.40E-06	-0.24	Thyroid
ENSG00000233609.3	RPL10P19	chr8_9549092_G_A_b38	rs1458942	9.60E-06	-0.54	Brain - Amygdala
ENSG00000233609.3	RPL10P19	chr8_9549092_G_A_b38	rs1458942	1.10E-05	-0.43	Brain - Cerebellum
ENSG00000173273.15	TNKS	chr8_9549092_G_A_b38	rs1458942	1.90E-05	0.28	Brain - Putamen (basal ganglia)
ENSG00000173273.15	TNKS	chr8_9549092_G_A_b38	rs1458942	1.90E-05	0.11	Nerve - Tibial
ENSG00000272267.2	RP11-375N15.2	chr8_9549092_G_A_b38	rs1458942	4.70E-05	-0.19	Thyroid
ENSG00000233609.3	RPL10P19	chr8_9549092_G_A_b38	rs1458942	6.10E-05	-0.22	Nerve - Tibial
ENSG00000248538.6	RP11-10A14.5	chr8_9549092_G_A_b38	rs1458942	6.60E-05	0.27	Heart - Atrial Appendage
ENSG00000173281.4	PPP1R3B	chr8_9549092_G_A_b38	rs1458942	6.90E-05	-0.096	Artery - Tibial
ENSG00000254340.1	RP11-10A14.3	chr8_9549092_G_A_b38	rs1458942	1.10E-04	-0.24	Esophagus - Muscularis
ENSG00000248538.6	RP11-10A14.5	chr8_9549092_G_A_b38	rs1458942	1.20E-04	0.26	Testis
ENSG00000253958.1	CLDN23	chr8_9549092_G_A_b38	rs1458942	1.40E-04	0.16	Skin - Not Sun Exposed (Suprapubic)
ENSG00000085063.14	CD59	chr11_33708514_A_C_b38	rs11032350	1.50E-07	-0.15	Skin - Sun Exposed (Lower leg)
ENSG00000085063.14	CD59	chr11_33708514_A_C_b38	rs11032350	1.60E-06	-0.12	Skin - Not Sun Exposed (Suprapubic)
ENSG00000110429.13	FBXO3	chr11_33708514_A_C_b38	rs11032350	5.50E-06	0.12	Esophagus - Mucosa
ENSG00000205177.6	C11orf91	chr11_33708514_A_C_b38	rs11032350	6.70E-06	-0.15	Adipose - Visceral (Omentum)
ENSG00000254508.5	FBXO3-AS1	chr11_33708514_A_C_b38	rs11032350	2.20E-05	-0.22	Testis

ENSG00000205177.6	C11orf91	chr11_33708514_A_C_b38	rs11032350	2.30E-05	-0.2	Heart - Left Ventricle
ENSG00000110427.14	KIAA1549L	chr11_33708514_A_C_b38	rs11032350	2.90E-05	-0.2	Muscle - Skeletal
ENSG00000205177.6	C11orf91	chr11_33708514_A_C_b38	rs11032350	4.10E-05	-0.21	Nerve - Tibial
ENSG00000205177.6	C11orf91	chr11_33708514_A_C_b38	rs11032350	5.80E-05	-0.23	Skin - Sun Exposed (Lower leg)
ENSG00000110429.13	FBXO3	chr11_33708514_A_C_b38	rs11032350	6.30E-05	0.14	Testis
ENSG00000205177.6	C11orf91	chr11_33708514_A_C_b38	rs11032350	7.40E-05	-0.22	Skin - Not Sun Exposed (Suprapubic)
ENSG00000205177.6	C11orf91	chr11_33708514_A_C_b38	rs11032350	8.00E-05	-0.18	Esophagus - Mucosa
ENSG00000205177.6	C11orf91	chr11_33708514_A_C_b38	rs11032350	1.30E-04	-0.18	Muscle - Skeletal

*NES: normalized effect size.

Table x5.6 EQTL look-ups for 4 (pairs of) shared risk loci for endometriosis and from multi-trait genetic analysis.

Gencode Id	Gene Symbol	Variant Id	SNP Id	P-Value	NES	Tissue
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.00E-130	-0.59	Whole Blood
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	5.00E-109	-0.57	Adipose - Subcutaneous
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.20E-102	-0.51	Thyroid
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	3.10E-97	-0.45	Nerve - Tibial
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	4.20E-96	-0.49	Esophagus - Mucosa
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.80E-92	-0.47	Artery - Tibial
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	3.00E-86	-0.44	Skin - Sun Exposed (Lower leg)
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.40E-82	-0.5	Esophagus - Muscularis
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	2.10E-78	-0.4	Lung
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.50E-74	-0.5	Cells - Cultured fibroblasts
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	2.10E-72	-0.48	Adipose - Visceral (Omentum)
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.20E-70	-0.5	Heart - Atrial Appendage
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.30E-66	-0.5	Artery - Aorta
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	7.90E-66	-0.42	Skin - Not Sun Exposed (Suprapubic)
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	8.60E-64	-0.56	Breast - Mammary Tissue
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	7.80E-63	-0.6	Colon - Transverse
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.70E-57	-0.4	Muscle - Skeletal
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	2.70E-56	-0.58	Pancreas
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.40E-54	-0.52	Esophagus - Gastroesophageal Junction
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	5.00E-54	-0.46	Heart - Left Ventricle
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	4.30E-49	-0.55	Stomach
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	6.90E-46	-0.42	Testis

ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	5.10E-40	-0.52	Colon - Sigmoid
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	7.50E-39	-0.64	Brain - Cerebellum
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.00E-37	-0.59	Spleen
ENSG00000234667.1	ACTBP13	chr3_49934081_C_A_b38	rs7613875	3.60E-37	-0.41	Skin - Sun Exposed (Lower leg)
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.50E-33	-0.65	Pituitary
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	7.00E-30	-0.55	Brain - Cortex
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.20E-29	-0.5	Prostate
ENSG00000182179.12	UBA7	chr3_49934081_C_A_b38	rs7613875	4.10E-29	-0.2	Whole Blood
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.40E-28	-0.63	Small Intestine - Terminal Ileum
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	8.40E-27	-0.42	Brain - Nucleus accumbens (basal ganglia)
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.20E-25	-0.46	Artery - Coronary
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.70E-23	-0.44	Brain - Cerebellar Hemisphere
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	4.20E-21	-0.38	Brain - Caudate (basal ganglia)
ENSG00000185614.4	FAM212A	chr3_49934081_C_A_b38	rs7613875	7.20E-21	0.27	Esophagus - Mucosa
ENSG00000182179.12	UBA7	chr3_49934081_C_A_b38	rs7613875	3.80E-20	-0.21	Esophagus - Mucosa
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	4.60E-20	-0.39	Brain - Frontal Cortex (BA9)
ENSG00000234667.1	ACTBP13	chr3_49934081_C_A_b38	rs7613875	5.10E-20	-0.37	Skin - Not Sun Exposed (Suprapubic)
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	2.10E-19	-0.33	Adrenal Gland
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	1.20E-17	0.53	Brain - Cerebellum
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	3.00E-17	-0.42	Brain - Putamen (basal ganglia)
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	3.70E-17	0.23	Adipose - Subcutaneous
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	4.20E-17	0.2	Skin - Not Sun Exposed (Suprapubic)
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	2.20E-16	0.26	Nerve - Tibial
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	2.50E-16	-0.43	Liver
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	2.00E-15	-0.33	Ovary
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	2.70E-15	-0.57	Minor Salivary Gland
ENSG00000182179.12	UBA7	chr3_49934081_C_A_b38	rs7613875	4.50E-15	-0.34	Pancreas
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	6.30E-15	-0.33	Brain - Hypothalamus
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	2.00E-14	-0.31	Brain - Hippocampus
ENSG00000182179.12	UBA7	chr3_49934081_C_A_b38	rs7613875	2.60E-14	-0.26	Colon - Transverse
ENSG00000185614.4	FAM212A	chr3_49934081_C_A_b38	rs7613875	4.20E-14	0.48	Brain - Cerebellum
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	8.50E-14	0.17	Skin - Sun Exposed (Lower leg)
ENSG00000182179.12	UBA7	chr3_49934081_C_A_b38	rs7613875	1.30E-13	-0.19	Skin - Not Sun Exposed (Suprapubic)

ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	2.50E-13	-0.47	Brain - Spinal cord (cervical c-1)
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	4.80E-13	-0.43	Vagina
ENSG00000185614.4	FAM212A	chr3_49934081_C_A_b38	rs7613875	6.60E-13	0.16	Skin - Not Sun Exposed (Suprapubic)
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	8.10E-13	0.28	Adipose - Subcutaneous
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	8.40E-13	0.17	Artery - Tibial
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	2.30E-12	-0.47	Brain - Anterior cingulate cortex (BA24)
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	2.40E-12	0.29	Brain - Cerebellum
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	2.40E-12	0.48	Brain - Cerebellar Hemisphere
ENSG00000187492.8	CDHR4	chr3_49934081_C_A_b38	rs7613875	2.90E-12	0.36	Testis
ENSG00000182179.12	UBA7	chr3_49934081_C_A_b38	rs7613875	3.60E-12	-0.18	Artery - Aorta
ENSG00000185614.4	FAM212A	chr3_49934081_C_A_b38	rs7613875	6.60E-12	0.44	Brain - Cerebellar Hemisphere
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	6.90E-12	-0.57	Cells - EBV-transformed lymphocytes
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	1.70E-11	0.29	Nerve - Tibial
ENSG00000164076.16	CAMKV	chr3_49934081_C_A_b38	rs7613875	2.10E-11	0.49	Stomach
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	3.40E-11	0.2	Nerve - Tibial
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	3.80E-11	0.25	Muscle - Skeletal
ENSG00000185614.4	FAM212A	chr3_49934081_C_A_b38	rs7613875	6.00E-11	0.18	Muscle - Skeletal
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	8.50E-11	0.18	Artery - Tibial
ENSG00000182179.12	UBA7	chr3_49934081_C_A_b38	rs7613875	9.80E-11	-0.19	Stomach
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	1.50E-10	0.2	Skin - Sun Exposed (Lower leg)
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	2.40E-10	0.17	Thyroid
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	3.20E-10	0.21	Thyroid
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	3.50E-10	0.43	Brain - Nucleus accumbens (basal ganglia)
ENSG00000182179.12	UBA7	chr3_49934081_C_A_b38	rs7613875	3.60E-10	-0.13	Skin - Sun Exposed (Lower leg)
ENSG00000228008.1	CTD-2330K9.3	chr3_49934081_C_A_b38	rs7613875	4.50E-10	0.4	Artery - Aorta
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	7.70E-10	0.2	Skin - Not Sun Exposed (Suprapubic)
ENSG00000182179.12	UBA7	chr3_49934081_C_A_b38	rs7613875	8.70E-10	-0.096	Nerve - Tibial
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	1.20E-09	0.31	Artery - Tibial
ENSG00000185614.4	FAM212A	chr3_49934081_C_A_b38	rs7613875	1.70E-09	0.12	Skin - Sun Exposed (Lower leg)
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	2.00E-09	0.19	Cells - Cultured fibroblasts
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	2.20E-09	0.24	Brain - Cerebellar Hemisphere
ENSG00000182179.12	UBA7	chr3_49934081_C_A_b38	rs7613875	3.00E-09	-0.27	Spleen

ENSG00000001617.11	SEMA3F	chr3_49934081_C_A_b38	rs7613875	4.90E-09	-0.22	Nerve - Tibial
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	8.60E-09	0.18	Breast - Mammary Tissue
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	1.10E-08	0.23	Heart - Atrial Appendage
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.10E-08	-0.37	Brain - Substantia nigra
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.30E-08	-0.49	Kidney - Cortex
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	2.00E-08	0.17	Artery - Aorta
ENSG00000182179.12	UBA7	chr3_49934081_C_A_b38	rs7613875	2.40E-08	-0.099	Cells - Cultured fibroblasts
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	3.70E-08	0.29	Cells - Cultured fibroblasts
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	4.00E-08	0.099	Thyroid
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	4.60E-08	0.19	Esophagus - Muscularis
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	6.20E-08	0.15	Brain - Cortex
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	6.90E-08	-0.4	Uterus
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	7.90E-08	0.28	Pituitary
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	1.20E-07	0.39	Brain - Cortex
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	1.30E-07	0.17	Artery - Aorta
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	1.30E-07	0.12	Esophagus - Muscularis
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	1.30E-07	0.15	Pancreas
ENSG00000182179.12	UBA7	chr3_49934081_C_A_b38	rs7613875	1.40E-07	-0.088	Artery - Tibial
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	3.30E-07	0.15	Lung
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	3.40E-07	0.11	Colon - Transverse
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	3.70E-07	0.14	Adipose - Visceral (Omentum)
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	4.30E-07	0.14	Brain - Nucleus accumbens (basal ganglia)
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	6.30E-07	0.16	Esophagus - Muscularis
ENSG00000182179.12	UBA7	chr3_49934081_C_A_b38	rs7613875	7.40E-07	-0.095	Lung
ENSG00000164076.16	CAMKV	chr3_49934081_C_A_b38	rs7613875	7.40E-07	0.18	Testis
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	7.70E-07	0.17	Breast - Mammary Tissue
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	8.10E-07	0.15	Colon - Sigmoid
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	8.10E-07	0.23	Esophagus - Gastroesophageal Junction
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	9.70E-07	0.15	Adipose - Visceral (Omentum)
ENSG00000001617.11	SEMA3F	chr3_49934081_C_A_b38	rs7613875	9.90E-07	-0.18	Heart - Atrial Appendage
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	1.10E-06	-0.25	Whole Blood
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	1.10E-06	0.32	Brain - Cerebellar Hemisphere
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	1.20E-06	0.29	Brain - Cerebellum

ENSG00000186792.16	HYAL3	chr3_49934081_C_A_b38	rs7613875	1.20E-06	-0.2	Cells - Cultured fibroblasts
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	1.20E-06	0.17	Heart - Atrial Appendage
ENSG00000001617.11	SEMA3F	chr3_49934081_C_A_b38	rs7613875	1.40E-06	-0.14	Adipose - Subcutaneous
ENSG00000182179.12	UBA7	chr3_49934081_C_A_b38	rs7613875	1.50E-06	-0.17	Small Intestine - Terminal Ileum
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	1.60E-06	0.13	Adipose - Subcutaneous
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	2.10E-06	0.19	Artery - Coronary
ENSG00000182179.12	UBA7	chr3_49934081_C_A_b38	rs7613875	2.20E-06	-0.085	Esophagus - Muscularis
ENSG00000164077.13	MON1A	chr3_49934081_C_A_b38	rs7613875	2.40E-06	-0.16	Testis
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	2.90E-06	0.17	Brain - Hypothalamus
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	6.00E-06	0.13	Colon - Transverse
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	6.90E-06	0.12	Lung
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	7.00E-06	0.13	Esophagus - Gastroesophageal Junction
ENSG00000164077.13	MON1A	chr3_49934081_C_A_b38	rs7613875	8.80E-06	-0.095	Whole Blood
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	1.00E-05	0.11	Stomach
ENSG00000228008.1	CTD-2330K9.3	chr3_49934081_C_A_b38	rs7613875	1.00E-05	0.25	Lung
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	1.10E-05	0.18	Artery - Coronary
ENSG00000186792.16	HYAL3	chr3_49934081_C_A_b38	rs7613875	1.20E-05	-0.31	Pituitary
ENSG00000185614.4	FAM212A	chr3_49934081_C_A_b38	rs7613875	1.30E-05	-0.15	Artery - Aorta
ENSG00000228008.1	CTD-2330K9.3	chr3_49934081_C_A_b38	rs7613875	1.30E-05	0.27	Esophagus - Muscularis
ENSG00000185614.4	FAM212A	chr3_49934081_C_A_b38	rs7613875	1.40E-05	-0.1	Cells - Cultured fibroblasts
ENSG00000176095.11	IP6K1	chr3_49934081_C_A_b38	rs7613875	1.60E-05	0.1	Nerve - Tibial
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	1.70E-05	0.18	Prostate
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	1.80E-05	0.43	Brain - Anterior cingulate cortex (BA24)
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	2.00E-05	0.14	Brain - Anterior cingulate cortex (BA24)
ENSG00000001617.11	SEMA3F	chr3_49934081_C_A_b38	rs7613875	2.30E-05	0.17	Artery - Aorta
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	2.30E-05	0.13	Esophagus - Mucosa
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	2.30E-05	0.11	Esophagus - Mucosa
ENSG00000001617.11	SEMA3F	chr3_49934081_C_A_b38	rs7613875	2.30E-05	-0.15	Adipose - Visceral (Omentum)
ENSG00000003756.16	RBM5	chr3_49934081_C_A_b38	rs7613875	2.50E-05	-0.091	Esophagus - Mucosa
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	2.70E-05	0.19	Colon - Sigmoid
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	2.70E-05	0.13	Muscle - Skeletal
ENSG00000088538.12	DOCK3	chr3_49934081_C_A_b38	rs7613875	3.30E-05	0.14	Skin - Sun Exposed (Lower leg)

ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	3.40E-05	0.32	Brain - Caudate (basal ganglia)
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	3.50E-05	0.097	Adipose - Visceral (Omentum)
ENSG00000001617.11	SEMA3F	chr3_49934081_C_A_b38	rs7613875	4.60E-05	-0.13	Heart - Left Ventricle
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	5.30E-05	0.16	Heart - Left Ventricle
ENSG00000233276.3	GPX1	chr3_49934081_C_A_b38	rs7613875	5.40E-05	-0.19	Adrenal Gland
ENSG00000007402.11	CACNA2D2	chr3_49934081_C_A_b38	rs7613875	5.50E-05	-0.15	Pancreas
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	5.50E-05	0.21	Artery - Aorta
ENSG00000003756.16	RBM5	chr3_49934081_C_A_b38	rs7613875	6.00E-05	-0.061	Nerve - Tibial
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	7.40E-05	0.15	Esophagus - Gastroesophageal Junction
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	7.40E-05	0.091	Skin - Sun Exposed (Lower leg)
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	8.50E-05	0.33	Brain - Hippocampus
ENSG00000004534.14	RBM6	chr3_49934081_C_A_b38	rs7613875	1.30E-04	-0.25	Brain - Amygdala
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	1.30E-04	0.098	Skin - Not Sun Exposed (Suprapubic)
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	1.40E-04	0.17	Testis
ENSG00000187492.8	CDHR4	chr3_49934081_C_A_b38	rs7613875	1.40E-04	0.12	Artery - Tibial
ENSG00000235016.1	SEMA3F-AS1	chr3_49934081_C_A_b38	rs7613875	1.40E-04	0.22	Brain - Cerebellar Hemisphere
ENSG00000228008.1	CTD-2330K9.3	chr3_49934081_C_A_b38	rs7613875	1.40E-04	0.26	Colon - Sigmoid
ENSG00000281691.1	RBM5-AS1	chr3_49934081_C_A_b38	rs7613875	1.60E-04	0.13	Skin - Sun Exposed (Lower leg)
ENSG00000182179.12	UBA7	chr3_49934081_C_A_b38	rs7613875	1.70E-04	-0.16	Liver
ENSG00000228008.1	CTD-2330K9.3	chr3_49934081_C_A_b38	rs7613875	1.80E-04	0.19	Thyroid
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	1.80E-04	0.09	Heart - Left Ventricle
ENSG00000178252.17	WDR6	chr3_49934081_C_A_b38	rs7613875	1.90E-04	-0.15	Skin - Sun Exposed (Lower leg)
ENSG00000001617.11	SEMA3F	chr3_49934081_C_A_b38	rs7613875	2.40E-04	-0.11	Lung
ENSG00000186792.16	HYAL3	chr3_49934081_C_A_b38	rs7613875	2.90E-04	-0.24	Brain - Cerebellum
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	2.90E-04	0.16	Heart - Left Ventricle
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	3.20E-04	0.23	Brain - Cortex
ENSG00000164062.12	APEH	chr3_49934081_C_A_b38	rs7613875	3.20E-04	-0.074	Cells - Cultured fibroblasts
ENSG00000164078.12	MST1R	chr3_49934081_C_A_b38	rs7613875	3.30E-04	0.13	Colon - Sigmoid
ENSG00000185614.4	FAM212A	chr3_49934081_C_A_b38	rs7613875	3.30E-04	-0.096	Artery - Tibial
ENSG00000187492.8	CDHR4	chr3_49934081_C_A_b38	rs7613875	3.40E-04	0.18	Esophagus - Mucosa
ENSG00000164062.12	APEH	chr3_49934081_C_A_b38	rs7613875	3.70E-04	-0.063	Adipose - Subcutaneous
ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	3.80E-04	0.083	Lung

ENSG00000173540.12	GMPPB	chr3_49934081_C_A_b38	rs7613875	4.00E-04	0.072	Colon - Transverse
ENSG00000164068.15	RNF123	chr3_49934081_C_A_b38	rs7613875	4.10E-04	0.077	Heart - Atrial Appendage
ENSG00000233276.3	GPX1	chr3_49934081_C_A_b38	rs7613875	4.10E-04	-0.11	Cells - Cultured fibroblasts
ENSG00000164077.13	MON1A	chr3_49934081_C_A_b38	rs7613875	4.80E-04	-0.083	Esophagus - Muscularis
ENSG00000188338.14	SLC38A3	chr3_49934081_C_A_b38	rs7613875	5.60E-04	-0.13	Thyroid
ENSG00000187492.8	CDHR4	chr3_49934081_C_A_b38	rs7613875	6.00E-04	0.13	Thyroid
ENSG00000001617.11	SEMA3F	chr3_49934081_C_A_b38	rs7613875	6.30E-04	-0.12	Esophagus - Muscularis
ENSG00000067560.10	RHOA	chr3_49934081_C_A_b38	rs7613875	6.60E-04	0.078	Muscle - Skeletal
ENSG00000186792.16	HYAL3	chr3_49934081_C_A_b38	rs7613875	7.60E-04	-0.14	Adipose - Subcutaneous
ENSG00000145020.15	AMT	chr3_49934081_C_A_b38	rs7613875	7.70E-04	-0.073	Esophagus - Mucosa
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	1.00E-115	-0.57	Whole Blood
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	3.70E-111	-0.57	Adipose - Subcutaneous
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	4.00E-104	-0.51	Thyroid
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	6.80E-101	-0.49	Esophagus - Mucosa
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	6.20E-94	-0.44	Nerve - Tibial
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	6.60E-93	-0.47	Artery - Tibial
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	5.80E-90	-0.45	Skin - Sun Exposed (Lower leg)
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	1.10E-81	-0.5	Esophagus - Muscularis
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	7.40E-80	-0.39	Lung
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	2.80E-75	-0.5	Cells - Cultured fibroblasts
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	1.70E-72	-0.48	Adipose - Visceral (Omentum)
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	1.60E-70	-0.43	Skin - Not Sun Exposed (Suprapubic)
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	9.70E-69	-0.51	Heart - Atrial Appendage
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	9.20E-63	-0.6	Colon - Transverse
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	1.20E-62	-0.49	Artery - Aorta
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	7.50E-59	-0.56	Breast - Mammary Tissue
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	8.10E-57	-0.4	Muscle - Skeletal
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	1.20E-56	-0.54	Esophagus - Gastroesophageal Junction
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	1.80E-54	-0.58	Pancreas
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	4.20E-53	-0.46	Heart - Left Ventricle
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	2.60E-49	-0.55	Stomach
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	7.60E-45	-0.41	Testis
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	1.10E-41	-0.54	Colon - Sigmoid

ENSG00000234667.1	ACTBP13	chr3_49902154_G_A_b38	rs3733135	1.10E-38	-0.42	Skin - Sun Exposed (Lower leg)
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	1.00E-37	-0.62	Brain - Cerebellum
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	2.40E-36	-0.57	Spleen
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	5.40E-34	-0.66	Pituitary
ENSG00000182179.12	UBA7	chr3_49902154_G_A_b38	rs3733135	4.40E-33	-0.21	Whole Blood
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	3.80E-31	-0.5	Prostate
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	1.20E-30	-0.54	Brain - Cortex
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	1.50E-28	-0.64	Small Intestine - Terminal Ileum
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	1.00E-25	-0.46	Artery - Coronary
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	1.20E-24	-0.4	Brain - Nucleus accumbens (basal ganglia)
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	2.20E-23	-0.44	Brain - Cerebellar Hemisphere
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	1.70E-22	-0.38	Brain - Caudate (basal ganglia)
ENSG00000185614.4	FAM212A	chr3_49902154_G_A_b38	rs3733135	2.90E-22	0.28	Esophagus - Mucosa
ENSG00000234667.1	ACTBP13	chr3_49902154_G_A_b38	rs3733135	3.30E-22	-0.39	Skin - Not Sun Exposed (Suprapubic)
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	3.00E-21	-0.39	Brain - Frontal Cortex (BA9)
ENSG00000182179.12	UBA7	chr3_49902154_G_A_b38	rs3733135	3.40E-21	-0.22	Esophagus - Mucosa
ENSG00000164078.12	MST1R	chr3_49902154_G_A_b38	rs3733135	5.00E-19	0.54	Brain - Cerebellum
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	7.70E-19	-0.33	Adrenal Gland
ENSG00000164078.12	MST1R	chr3_49902154_G_A_b38	rs3733135	8.70E-19	0.21	Skin - Not Sun Exposed (Suprapubic)
ENSG00000164068.15	RNF123	chr3_49902154_G_A_b38	rs3733135	1.40E-17	0.23	Adipose - Subcutaneous
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	5.20E-17	-0.41	Brain - Putamen (basal ganglia)
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	5.70E-17	-0.42	Liver
ENSG00000164068.15	RNF123	chr3_49902154_G_A_b38	rs3733135	4.00E-16	0.26	Nerve - Tibial
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	5.90E-16	-0.58	Minor Salivary Gland
ENSG00000185614.4	FAM212A	chr3_49902154_G_A_b38	rs3733135	9.60E-16	0.5	Brain - Cerebellum
ENSG00000182179.12	UBA7	chr3_49902154_G_A_b38	rs3733135	1.60E-15	-0.35	Pancreas
ENSG00000182179.12	UBA7	chr3_49902154_G_A_b38	rs3733135	3.40E-15	-0.2	Skin - Not Sun Exposed (Suprapubic)
ENSG00000164078.12	MST1R	chr3_49902154_G_A_b38	rs3733135	1.20E-14	0.18	Skin - Sun Exposed (Lower leg)
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	2.40E-14	-0.32	Brain - Hypothalamus
ENSG00000164068.15	RNF123	chr3_49902154_G_A_b38	rs3733135	2.60E-14	0.19	Artery - Tibial
ENSG00000182179.12	UBA7	chr3_49902154_G_A_b38	rs3733135	4.20E-14	-0.26	Colon - Transverse
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	6.10E-14	-0.45	Vagina
ENSG00000164078.12	MST1R	chr3_49902154_G_A_b38	rs3733135	6.40E-14	0.32	Nerve - Tibial

ENSG00000185614.4	FAM212A	chr3_49902154_G_A_b38	rs3733135	6.50E-14	0.16	Skin - Not Sun Exposed (Suprapubic)
ENSG00000164078.12	MST1R	chr3_49902154_G_A_b38	rs3733135	6.90E-14	0.29	Adipose - Subcutaneous
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	8.70E-14	-0.32	Ovary
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	8.80E-14	-0.46	Brain - Anterior cingulate cortex (BA24)
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	1.40E-13	-0.31	Brain - Hippocampus
ENSG00000164078.12	MST1R	chr3_49902154_G_A_b38	rs3733135	2.30E-13	0.49	Brain - Cerebellar Hemisphere
ENSG00000164068.15	RNF123	chr3_49902154_G_A_b38	rs3733135	2.50E-13	0.29	Brain - Cerebellum
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	3.70E-13	-0.46	Brain - Spinal cord (cervical c-1)
ENSG00000164078.12	MST1R	chr3_49902154_G_A_b38	rs3733135	4.60E-13	0.27	Muscle - Skeletal
ENSG00000185614.4	FAM212A	chr3_49902154_G_A_b38	rs3733135	8.50E-13	0.45	Brain - Cerebellar Hemisphere
ENSG00000185614.4	FAM212A	chr3_49902154_G_A_b38	rs3733135	1.90E-12	0.19	Muscle - Skeletal
ENSG00000164076.16	CAMKV	chr3_49902154_G_A_b38	rs3733135	2.00E-12	0.51	Stomach
ENSG00000164078.12	MST1R	chr3_49902154_G_A_b38	rs3733135	3.60E-12	0.23	Thyroid
ENSG00000173540.12	GMPPB	chr3_49902154_G_A_b38	rs3733135	4.70E-12	0.21	Skin - Sun Exposed (Lower leg)
ENSG00000173540.12	GMPPB	chr3_49902154_G_A_b38	rs3733135	6.90E-12	0.23	Skin - Not Sun Exposed (Suprapubic)
ENSG00000182179.12	UBA7	chr3_49902154_G_A_b38	rs3733135	7.90E-12	-0.14	Skin - Sun Exposed (Lower leg)
ENSG00000185614.4	FAM212A	chr3_49902154_G_A_b38	rs3733135	1.30E-11	0.13	Skin - Sun Exposed (Lower leg)
ENSG00000182179.12	UBA7	chr3_49902154_G_A_b38	rs3733135	2.10E-11	-0.1	Nerve - Tibial
ENSG00000182179.12	UBA7	chr3_49902154_G_A_b38	rs3733135	2.20E-11	-0.17	Artery - Aorta
ENSG00000173540.12	GMPPB	chr3_49902154_G_A_b38	rs3733135	4.20E-11	0.19	Artery - Tibial
ENSG00000164068.15	RNF123	chr3_49902154_G_A_b38	rs3733135	4.50E-11	0.18	Thyroid
ENSG00000182179.12	UBA7	chr3_49902154_G_A_b38	rs3733135	5.80E-11	-0.19	Stomach
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	7.20E-11	-0.54	Cells - EBV-transformed lymphocytes
ENSG00000187492.8	CDHR4	chr3_49902154_G_A_b38	rs3733135	7.50E-11	0.34	Testis
ENSG00000173540.12	GMPPB	chr3_49902154_G_A_b38	rs3733135	1.10E-10	0.2	Nerve - Tibial
ENSG00000164078.12	MST1R	chr3_49902154_G_A_b38	rs3733135	1.30E-10	0.32	Artery - Tibial
ENSG00000164078.12	MST1R	chr3_49902154_G_A_b38	rs3733135	3.70E-10	0.26	Heart - Atrial Appendage
ENSG00000164068.15	RNF123	chr3_49902154_G_A_b38	rs3733135	5.40E-10	0.2	Cells - Cultured fibroblasts
ENSG00000182179.12	UBA7	chr3_49902154_G_A_b38	rs3733135	5.50E-10	-0.11	Cells - Cultured fibroblasts
ENSG00000164078.12	MST1R	chr3_49902154_G_A_b38	rs3733135	5.70E-10	0.18	Lung
ENSG00000173540.12	GMPPB	chr3_49902154_G_A_b38	rs3733135	6.10E-10	0.11	Thyroid
ENSG00000173540.12	GMPPB	chr3_49902154_G_A_b38	rs3733135	7.70E-10	0.18	Artery - Aorta

ENSG00000228008.1	CTD-2330K9.3	chr3_49902154_G_A_b38	rs3733135	1.30E-09	0.39	Artery - Aorta
ENSG00000164068.15	RNF123	chr3_49902154_G_A_b38	rs3733135	1.30E-09	0.24	Brain - Cerebellar Hemisphere
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	1.40E-09	-0.38	Brain - Substantia nigra
ENSG00000182179.12	UBA7	chr3_49902154_G_A_b38	rs3733135	1.90E-09	-0.26	Spleen
ENSG00000164078.12	MST1R	chr3_49902154_G_A_b38	rs3733135	2.50E-09	0.4	Brain - Nucleus accumbens (basal ganglia)
ENSG00000182179.12	UBA7	chr3_49902154_G_A_b38	rs3733135	3.10E-09	-0.099	Artery - Tibial
ENSG00000164078.12	MST1R	chr3_49902154_G_A_b38	rs3733135	5.40E-09	0.31	Cells - Cultured fibroblasts
ENSG00000173540.12	GMPPB	chr3_49902154_G_A_b38	rs3733135	8.60E-09	0.19	Breast - Mammary Tissue
ENSG00000173540.12	GMPPB	chr3_49902154_G_A_b38	rs3733135	1.10E-08	0.2	Esophagus - Muscularis
ENSG00000164078.12	MST1R	chr3_49902154_G_A_b38	rs3733135	1.10E-08	0.42	Brain - Cortex
ENSG00000173540.12	GMPPB	chr3_49902154_G_A_b38	rs3733135	1.30E-08	0.17	Adipose - Visceral (Omentum)
ENSG00000164068.15	RNF123	chr3_49902154_G_A_b38	rs3733135	1.40E-08	0.13	Esophagus - Muscularis
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	2.20E-08	-0.44	Uterus
ENSG00000164068.15	RNF123	chr3_49902154_G_A_b38	rs3733135	2.60E-08	0.15	Adipose - Visceral (Omentum)
ENSG00000164068.15	RNF123	chr3_49902154_G_A_b38	rs3733135	2.90E-08	0.29	Pituitary
ENSG00000004534.14	RBM6	chr3_49902154_G_A_b38	rs3733135	3.20E-08	-0.5	Kidney - Cortex
ENSG00000173540.12	GMPPB	chr3_49902154_G_A_b38	rs3733135	3.40E-08	0.26	Esophagus - Gastroesophageal Junction
ENSG00000173540.12	GMPPB	chr3_49902154_G_A_b38	rs3733135	3.50E-08	0.16	Pancreas
ENSG00000164068.15	RNF123	chr3_49902154_G_A_b38	rs3733135	4.80E-08	0.15	Brain - Cortex
ENSG00000164068.15	RNF123	chr3_49902154_G_A_b38	rs3733135	7.60E-08	0.18	Artery - Aorta
ENSG00000164068.15	RNF123	chr3_49902154_G_A_b38	rs3733135	1.00E-07	0.16	Colon - Sigmoid
ENSG00000173540.12	GMPPB	chr3_49902154_G_A_b38	rs3733135	1.40E-07	0.19	Heart - Atrial Appendage
ENSG00000164068.15	RNF123	chr3_49902154_G_A_b38	rs3733135	1.50E-07	0.14	Brain - Nucleus accumbens (basal ganglia)
ENSG00000164068.15	RNF123	chr3_49902154_G_A_b38	rs3733135	1.60E-07	0.18	Breast - Mammary Tissue
ENSG00000001617.11	SEMA3F	chr3_49902154_G_A_b38	rs3733135	1.90E-07	-0.2	Nerve - Tibial
ENSG00000164078.12	MST1R	chr3_49902154_G_A_b38	rs3733135	2.10E-07	0.17	Esophagus - Muscularis
ENSG00000182179.12	UBA7	chr3_49902154_G_A_b38	rs3733135	3.40E-07	-0.18	Small Intestine - Terminal Ileum
ENSG00000164078.12	MST1R	chr3_49902154_G_A_b38	rs3733135	3.60E-07	0.11	Colon - Transverse
ENSG00000173540.12	GMPPB	chr3_49902154_G_A_b38	rs3733135	5.00E-07	0.12	Stomach
ENSG00000164068.15	RNF123	chr3_49902154_G_A_b38	rs3733135	5.10E-07	0.13	Lung
ENSG00000173540.12	GMPPB	chr3_49902154_G_A_b38	rs3733135	5.70E-07	0.13	Adipose - Subcutaneous
ENSG00000173540.12	GMPPB	chr3_49902154_G_A_b38	rs3733135	6.00E-07	0.32	Brain - Cerebellar Hemisphere
ENSG00000164076.16	CAMKV	chr3_49902154_G_A_b38	rs3733135	6.00E-07	0.18	Testis

ENSG00000182179.12	UBA7	chr3_49902154_G_A_b38	rs3733135	7.00E-07	-0.094	Lung
ENSG00000173540.12	GMPPB	chr3_49902154_G_A_b38	rs3733135	8.60E-07	0.2	Prostate
ENSG00000001617.11	SEMA3F	chr3_49902154_G_A_b38	rs3733135	8.90E-07	-0.18	Heart - Atrial Appendage
ENSG00000173540.12	GMPPB	chr3_49902154_G_A_b38	rs3733135	9.20E-07	0.28	Brain - Cerebellum
ENSG00000164078.12	MST1R	chr3_49902154_G_A_b38	rs3733135	9.20E-07	0.26	Artery - Aorta
ENSG00000088538.12	DOCK3	chr3_49902154_G_A_b38	rs3733135	9.80E-07	0.17	Skin - Sun Exposed (Lower leg)
ENSG00000186792.16	HYAL3	chr3_49902154_G_A_b38	rs3733135	1.00E-06	-0.2	Cells - Cultured fibroblasts
ENSG00000178252.17	WDR6	chr3_49902154_G_A_b38	rs3733135	1.00E-06	-0.2	Skin - Sun Exposed (Lower leg)
ENSG00000164068.15	RNF123	chr3_49902154_G_A_b38	rs3733135	1.20E-06	0.17	Brain - Hypothalamus
ENSG00000173540.12	GMPPB	chr3_49902154_G_A_b38	rs3733135	1.80E-06	0.19	Heart - Left Ventricle
ENSG00000164077.13	MON1A	chr3_49902154_G_A_b38	rs3733135	2.10E-06	-0.16	Testis
ENSG00000164068.15	RNF123	chr3_49902154_G_A_b38	rs3733135	2.30E-06	0.13	Colon - Transverse
ENSG00000182179.12	UBA7	chr3_49902154_G_A_b38	rs3733135	2.40E-06	-0.086	Esophagus - Muscularis
ENSG00000164068.15	RNF123	chr3_49902154_G_A_b38	rs3733135	2.70E-06	0.11	Skin - Sun Exposed (Lower leg)
ENSG00000228008.1	CTD-2330K9.3	chr3_49902154_G_A_b38	rs3733135	3.10E-06	0.29	Esophagus - Muscularis
ENSG00000164068.15	RNF123	chr3_49902154_G_A_b38	rs3733135	3.40E-06	0.15	Brain - Anterior cingulate cortex (BA24)
ENSG00000173540.12	GMPPB	chr3_49902154_G_A_b38	rs3733135	4.00E-06	0.11	Esophagus - Mucosa
ENSG00000164077.13	MON1A	chr3_49902154_G_A_b38	rs3733135	5.20E-06	-0.098	Whole Blood
ENSG00000164068.15	RNF123	chr3_49902154_G_A_b38	rs3733135	5.20E-06	0.14	Esophagus - Gastroesophageal Junction
ENSG00000173540.12	GMPPB	chr3_49902154_G_A_b38	rs3733135	5.40E-06	0.19	Artery - Coronary
ENSG00000164078.12	MST1R	chr3_49902154_G_A_b38	rs3733135	5.70E-06	0.34	Brain - Caudate (basal ganglia)
ENSG00000185614.4	FAM212A	chr3_49902154_G_A_b38	rs3733135	6.00E-06	-0.15	Artery - Aorta
ENSG00000176095.11	IP6K1	chr3_49902154_G_A_b38	rs3733135	7.40E-06	0.11	Nerve - Tibial
ENSG00000173540.12	GMPPB	chr3_49902154_G_A_b38	rs3733135	1.00E-05	0.28	Brain - Cortex
ENSG00000164078.12	MST1R	chr3_49902154_G_A_b38	rs3733135	1.00E-05	-0.23	Whole Blood
ENSG00000001617.11	SEMA3F	chr3_49902154_G_A_b38	rs3733135	1.10E-05	0.18	Artery - Aorta
ENSG00000164068.15	RNF123	chr3_49902154_G_A_b38	rs3733135	1.20E-05	0.11	Skin - Not Sun Exposed (Suprapubic)
ENSG00000173540.12	GMPPB	chr3_49902154_G_A_b38	rs3733135	1.20E-05	0.2	Colon - Sigmoid
ENSG00000001617.11	SEMA3F	chr3_49902154_G_A_b38	rs3733135	1.20E-05	-0.14	Heart - Left Ventricle
ENSG00000164078.12	MST1R	chr3_49902154_G_A_b38	rs3733135	1.20E-05	0.16	Esophagus - Gastroesophageal Junction
ENSG00000001617.11	SEMA3F	chr3_49902154_G_A_b38	rs3733135	1.30E-05	-0.13	Adipose - Subcutaneous
ENSG00000185614.4	FAM212A	chr3_49902154_G_A_b38	rs3733135	1.30E-05	-0.1	Cells - Cultured fibroblasts

ENSG00000164068.15	RNF123	chr3_49902154_G_A_b38	rs3733135	1.40E-05	0.18	Artery - Coronary
ENSG00000173540.12	GMPPB	chr3_49902154_G_A_b38	rs3733135	1.70E-05	0.36	Brain - Hippocampus
ENSG00000186792.16	HYAL3	chr3_49902154_G_A_b38	rs3733135	1.90E-05	-0.31	Pituitary
ENSG00000164078.12	MST1R	chr3_49902154_G_A_b38	rs3733135	2.30E-05	0.39	Brain - Anterior cingulate cortex (BA24)
ENSG00000164062.12	APEH	chr3_49902154_G_A_b38	rs3733135	2.50E-05	-0.086	Cells - Cultured fibroblasts
ENSG00000164078.12	MST1R	chr3_49902154_G_A_b38	rs3733135	2.50E-05	0.47	Brain - Spinal cord (cervical c-1)
ENSG00000003756.16	RBM5	chr3_49902154_G_A_b38	rs3733135	2.60E-05	-0.091	Esophagus - Mucosa
ENSG00000178252.17	WDR6	chr3_49902154_G_A_b38	rs3733135	3.30E-05	-0.18	Esophagus - Mucosa
ENSG00000187492.8	CDHR4	chr3_49902154_G_A_b38	rs3733135	3.60E-05	0.13	Artery - Tibial
ENSG00000173540.12	GMPPB	chr3_49902154_G_A_b38	rs3733135	3.70E-05	0.095	Lung
ENSG00000007402.11	CACNA2D2	chr3_49902154_G_A_b38	rs3733135	4.80E-05	-0.15	Pancreas
ENSG00000164068.15	RNF123	chr3_49902154_G_A_b38	rs3733135	5.10E-05	0.21	Ovary
ENSG00000164078.12	MST1R	chr3_49902154_G_A_b38	rs3733135	5.80E-05	0.18	Heart - Left Ventricle
ENSG00000001617.11	SEMA3F	chr3_49902154_G_A_b38	rs3733135	5.80E-05	-0.15	Adipose - Visceral (Omentum)
ENSG00000145020.15	AMT	chr3_49902154_G_A_b38	rs3733135	5.80E-05	-0.088	Esophagus - Mucosa
ENSG00000233276.3	GPX1	chr3_49902154_G_A_b38	rs3733135	6.00E-05	-0.19	Adrenal Gland
ENSG00000228008.1	CTD-2330K9.3	chr3_49902154_G_A_b38	rs3733135	6.00E-05	0.23	Lung
ENSG00000173540.12	GMPPB	chr3_49902154_G_A_b38	rs3733135	6.30E-05	0.12	Muscle - Skeletal
ENSG00000164078.12	MST1R	chr3_49902154_G_A_b38	rs3733135	7.40E-05	0.13	Esophagus - Mucosa
ENSG00000145029.13	NICN1	chr3_49902154_G_A_b38	rs3733135	8.40E-05	-0.11	Artery - Aorta
ENSG00000235016.1	SEMA3F-AS1	chr3_49902154_G_A_b38	rs3733135	9.20E-05	0.23	Brain - Cerebellar Hemisphere
ENSG00000164068.15	RNF123	chr3_49902154_G_A_b38	rs3733135	9.50E-05	0.087	Heart - Atrial Appendage
ENSG00000281691.1	RBM5-AS1	chr3_49902154_G_A_b38	rs3733135	9.50E-05	0.14	Skin - Sun Exposed (Lower leg)
ENSG00000173540.12	GMPPB	chr3_49902154_G_A_b38	rs3733135	9.50E-05	0.24	Brain - Caudate (basal ganglia)
ENSG00000178252.17	WDR6	chr3_49902154_G_A_b38	rs3733135	1.20E-04	-0.16	Skin - Not Sun Exposed (Suprapubic)
ENSG00000164078.12	MST1R	chr3_49902154_G_A_b38	rs3733135	1.20E-04	0.09	Adipose - Visceral (Omentum)
ENSG00000187492.8	CDHR4	chr3_49902154_G_A_b38	rs3733135	1.20E-04	0.19	Esophagus - Mucosa
ENSG00000145020.15	AMT	chr3_49902154_G_A_b38	rs3733135	1.40E-04	-0.098	Lung
ENSG00000001617.11	SEMA3F	chr3_49902154_G_A_b38	rs3733135	1.40E-04	-0.11	Lung
ENSG00000114378.16	HYAL1	chr3_49902154_G_A_b38	rs3733135	1.40E-04	0.21	Adrenal Gland
ENSG00000173540.12	GMPPB	chr3_49902154_G_A_b38	rs3733135	1.50E-04	0.14	Liver
ENSG00000173540.12	GMPPB	chr3_49902154_G_A_b38	rs3733135	1.80E-04	0.076	Colon - Transverse

ENSG00000164068.15	RNF123	chr3_49902154_G_A_b38	rs3733135	1.90E-04	0.16	Testis
ENSG00000182179.12	UBA7	chr3_49902154_G_A_b38	rs3733135	2.10E-04	-0.07	Thyroid
ENSG00000067560.10	RHOA	chr3_49902154_G_A_b38	rs3733135	2.20E-04	0.084	Muscle - Skeletal
ENSG00000145029.13	NICN1	chr3_49902154_G_A_b38	rs3733135	2.20E-04	-0.083	Artery - Tibial
ENSG00000088538.12	DOCK3	chr3_49902154_G_A_b38	rs3733135	2.40E-04	0.14	Skin - Not Sun Exposed (Suprapubic)
ENSG00000228008.1	CTD-2330K9.3	chr3_49902154_G_A_b38	rs3733135	2.60E-04	0.19	Thyroid
ENSG00000003756.16	RBM5	chr3_49902154_G_A_b38	rs3733135	2.70E-04	-0.056	Nerve - Tibial
ENSG00000176095.11	IP6K1	chr3_49902154_G_A_b38	rs3733135	2.70E-04	0.078	Artery - Tibial
ENSG00000185614.4	FAM212A	chr3_49902154_G_A_b38	rs3733135	2.80E-04	-0.097	Artery - Tibial
ENSG00000164062.12	APEH	chr3_49902154_G_A_b38	rs3733135	2.80E-04	-0.065	Adipose - Subcutaneous
ENSG00000173540.12	GMPPB	chr3_49902154_G_A_b38	rs3733135	3.10E-04	0.089	Whole Blood
ENSG00000186792.16	HYAL3	chr3_49902154_G_A_b38	rs3733135	3.30E-04	-0.15	Adipose - Subcutaneous
ENSG00000188338.14	SLC38A3	chr3_49902154_G_A_b38	rs3733135	3.50E-04	-0.13	Thyroid
ENSG00000001617.11	SEMA3F	chr3_49902154_G_A_b38	rs3733135	3.50E-04	-0.16	Spleen
ENSG00000114738.10	MAPKAPK3	chr3_49902154_G_A_b38	rs3733135	3.70E-04	-0.076	Muscle - Skeletal
ENSG00000164077.13	MON1A	chr3_49902154_G_A_b38	rs3733135	4.60E-04	0.072	Thyroid
ENSG00000003756.16	RBM5	chr3_49902154_G_A_b38	rs3733135	4.60E-04	-0.065	Adipose - Visceral (Omentum)
ENSG00000186792.16	HYAL3	chr3_49902154_G_A_b38	rs3733135	4.80E-04	-0.15	Lung
ENSG00000068028.17	RASSF1	chr3_49902154_G_A_b38	rs3733135	5.50E-04	0.11	Adipose - Subcutaneous
ENSG00000233276.3	GPX1	chr3_49902154_G_A_b38	rs3733135	5.70E-04	-0.069	Skin - Sun Exposed (Lower leg)
ENSG00000173531.15	MST1	chr3_49902154_G_A_b38	rs3733135	6.10E-04	-0.1	Thyroid
ENSG00000233276.3	GPX1	chr3_49902154_G_A_b38	rs3733135	6.50E-04	-0.11	Cells - Cultured fibroblasts
ENSG00000164062.12	APEH	chr3_49902154_G_A_b38	rs3733135	6.60E-04	-0.083	Skin - Not Sun Exposed (Suprapubic)
ENSG00000188338.14	SLC38A3	chr3_49902154_G_A_b38	rs3733135	7.50E-04	0.14	Skin - Sun Exposed (Lower leg)
ENSG00000173531.15	MST1	chr3_49902154_G_A_b38	rs3733135	8.40E-04	-0.075	Skin - Sun Exposed (Lower leg)
ENSG00000183763.8	TRAIP	chr3_49902154_G_A_b38	rs3733135	9.10E-04	0.097	Skin - Not Sun Exposed (Suprapubic)
ENSG00000178252.17	WDR6	chr3_49902154_G_A_b38	rs3733135	9.50E-04	-0.07	Thyroid
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	4.50E-88	0.87	Cells - Cultured fibroblasts
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	7.60E-71	0.83	Esophagus - Mucosa
ENSG00000253981.5	ALG1L13P	chr8_8278888_C_T_b38	rs1401390	9.30E-52	0.77	Cells - Cultured fibroblasts
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	1.30E-46	-1	Testis
ENSG00000275342.4	PRAG1	chr8_8278888_C_T_b38	rs1401390	2.00E-42	-0.48	Thyroid

ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	1.70E-35	0.63	Adipose - Visceral (Omentum)
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	2.70E-34	-0.71	Nerve - Tibial
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	5.20E-34	0.54	Skin - Not Sun Exposed (Suprapubic)
ENSG00000104626.14	ERI1	chr8_8278888_C_T_b38	rs1401390	3.40E-32	-0.27	Cells - Cultured fibroblasts
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	9.30E-32	-0.91	Pituitary
ENSG00000249188.1	ENPP7P1	chr8_8278888_C_T_b38	rs1401390	5.90E-30	-0.82	Testis
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	4.60E-29	-0.9	Brain - Cortex
ENSG00000254153.1	CTA-398F10.2	chr8_8278888_C_T_b38	rs1401390	1.60E-28	0.45	Skin - Sun Exposed (Lower leg)
ENSG00000254153.1	CTA-398F10.2	chr8_8278888_C_T_b38	rs1401390	3.80E-27	0.49	Skin - Not Sun Exposed (Suprapubic)
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	1.30E-26	-0.9	Brain - Cerebellum
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	1.70E-26	0.61	Colon - Transverse
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	3.00E-26	-0.62	Artery - Tibial
ENSG00000253981.5	ALG1L13P	chr8_8278888_C_T_b38	rs1401390	2.60E-25	0.6	Esophagus - Mucosa
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	1.40E-24	-0.91	Brain - Anterior cingulate cortex (BA24)
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	1.00E-23	-0.83	Brain - Nucleus accumbens (basal ganglia)
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	1.60E-23	-0.7	Brain - Cerebellar Hemisphere
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	1.80E-23	-0.54	Thyroid
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	3.30E-23	-0.6	Brain - Cerebellum
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	4.30E-23	-0.84	Brain - Frontal Cortex (BA9)
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	1.20E-21	0.63	Pancreas
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	2.30E-21	-0.73	Brain - Cortex
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	2.80E-21	-0.81	Brain - Caudate (basal ganglia)
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	2.80E-20	-0.89	Brain - Cerebellar Hemisphere
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	7.30E-20	0.36	Skin - Sun Exposed (Lower leg)
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	2.10E-19	-0.71	Brain - Frontal Cortex (BA9)
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	4.10E-19	-0.86	Brain - Hypothalamus
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	8.90E-19	-0.88	Brain - Hippocampus
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	1.50E-18	0.28	Breast - Mammary Tissue
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	2.40E-18	0.36	Lung
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	4.90E-18	-0.84	Brain - Putamen (basal ganglia)
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	4.40E-17	-0.53	Lung
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	1.20E-16	-0.87	Brain - Amygdala

ENSG00000233609.3	RPL10P19	chr8_8278888_C_T_b38	rs1401390	2.20E-16	0.36	Thyroid
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	2.90E-16	-0.91	Brain - Substantia nigra
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	9.30E-16	-0.96	Brain - Spinal cord (cervical c-1)
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	1.40E-15	-0.68	Brain - Anterior cingulate cortex (BA24)
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	1.70E-15	-0.93	Uterus
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	2.00E-15	0.33	Adipose - Subcutaneous
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	4.80E-15	0.42	Heart - Left Ventricle
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	1.40E-14	-0.52	Artery - Aorta
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	1.90E-14	0.42	Colon - Sigmoid
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	2.80E-14	0.75	Vagina
ENSG00000249188.1	ENPP7P1	chr8_8278888_C_T_b38	rs1401390	1.20E-13	-0.68	Brain - Cerebellum
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	1.40E-13	-0.75	Ovary
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	1.50E-13	-0.6	Esophagus - Gastroesophageal Junction
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	2.20E-12	-0.46	Breast - Mammary Tissue
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	3.80E-12	-0.39	Adipose - Subcutaneous
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	5.10E-12	0.24	Thyroid
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	6.80E-12	-0.44	Pituitary
ENSG00000233609.3	RPL10P19	chr8_8278888_C_T_b38	rs1401390	2.90E-11	0.26	Lung
ENSG00000253981.5	ALG1L13P	chr8_8278888_C_T_b38	rs1401390	4.00E-11	0.38	Skin - Not Sun Exposed (Suprapubic)
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	4.20E-10	0.25	Esophagus - Muscularis
ENSG00000253981.5	ALG1L13P	chr8_8278888_C_T_b38	rs1401390	6.40E-10	0.44	Colon - Transverse
ENSG00000248538.6	RP11-10A14.5	chr8_8278888_C_T_b38	rs1401390	7.50E-10	-0.42	Testis
ENSG00000104626.14	ERI1	chr8_8278888_C_T_b38	rs1401390	2.00E-09	0.26	Testis
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	2.10E-09	0.77	Kidney - Cortex
ENSG00000254153.1	CTA-398F10.2	chr8_8278888_C_T_b38	rs1401390	2.10E-09	0.3	Esophagus - Mucosa
ENSG00000248538.6	RP11-10A14.5	chr8_8278888_C_T_b38	rs1401390	2.20E-09	0.3	Whole Blood
ENSG00000253981.5	ALG1L13P	chr8_8278888_C_T_b38	rs1401390	2.70E-09	0.33	Adipose - Subcutaneous
ENSG00000147324.10	MFHAS1	chr8_8278888_C_T_b38	rs1401390	3.00E-09	0.2	Muscle - Skeletal
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	3.90E-09	0.36	Stomach
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	4.20E-09	-0.64	Cells - EBV-transformed lymphocytes
ENSG00000254153.1	CTA-398F10.2	chr8_8278888_C_T_b38	rs1401390	4.90E-09	-0.25	Thyroid
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	1.00E-08	-0.4	Brain - Hippocampus
ENSG00000233609.3	RPL10P19	chr8_8278888_C_T_b38	rs1401390	1.60E-08	0.52	Brain - Cortex

ENSG00000233609.3	RPL10P19	chr8_8278888_C_T_b38	rs1401390	1.90E-08	0.28	Adipose - Visceral (Omentum)
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	1.90E-08	-0.38	Esophagus - Muscularis
ENSG00000249188.1	ENPP7P1	chr8_8278888_C_T_b38	rs1401390	2.10E-08	-0.47	Pituitary
ENSG00000253981.5	ALG1L13P	chr8_8278888_C_T_b38	rs1401390	4.20E-08	0.43	Pancreas
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	4.70E-08	0.27	Heart - Atrial Appendage
ENSG00000147324.10	MFHAS1	chr8_8278888_C_T_b38	rs1401390	5.50E-08	0.26	Heart - Atrial Appendage
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	6.10E-08	0.24	Nerve - Tibial
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	6.20E-08	-0.44	Colon - Sigmoid
ENSG00000253958.1	CLDN23	chr8_8278888_C_T_b38	rs1401390	7.00E-08	-0.22	Skin - Sun Exposed (Lower leg)
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	7.00E-08	0.2	Muscle - Skeletal
ENSG00000275342.4	PRAG1	chr8_8278888_C_T_b38	rs1401390	8.30E-08	-0.3	Testis
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	8.40E-08	-0.47	Liver
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	9.40E-08	-0.37	Adipose - Visceral (Omentum)
ENSG00000253981.5	ALG1L13P	chr8_8278888_C_T_b38	rs1401390	1.50E-07	-0.45	Brain - Cerebellar Hemisphere
ENSG00000253981.5	ALG1L13P	chr8_8278888_C_T_b38	rs1401390	2.90E-07	0.72	Kidney - Cortex
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	4.10E-07	-0.52	Spleen
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	5.30E-07	0.46	Minor Salivary Gland
ENSG00000253981.5	ALG1L13P	chr8_8278888_C_T_b38	rs1401390	5.30E-07	0.55	Vagina
ENSG00000233609.3	RPL10P19	chr8_8278888_C_T_b38	rs1401390	5.70E-07	0.34	Pancreas
ENSG00000253981.5	ALG1L13P	chr8_8278888_C_T_b38	rs1401390	5.70E-07	-0.37	Brain - Cerebellum
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	5.80E-07	-0.29	Skin - Sun Exposed (Lower leg)
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	5.90E-07	-0.3	Cells - Cultured fibroblasts
ENSG00000233609.3	RPL10P19	chr8_8278888_C_T_b38	rs1401390	1.40E-06	0.13	Whole Blood
ENSG00000233609.3	RPL10P19	chr8_8278888_C_T_b38	rs1401390	1.40E-06	0.45	Brain - Hippocampus
ENSG00000173295.7	FAM86B3P	chr8_8278888_C_T_b38	rs1401390	1.50E-06	0.26	Esophagus - Gastroesophageal Junction
ENSG00000254153.1	CTA-398F10.2	chr8_8278888_C_T_b38	rs1401390	1.50E-06	0.28	Stomach
ENSG00000253981.5	ALG1L13P	chr8_8278888_C_T_b38	rs1401390	1.50E-06	0.12	Whole Blood
ENSG00000253981.5	ALG1L13P	chr8_8278888_C_T_b38	rs1401390	1.80E-06	0.23	Thyroid
ENSG00000253130.1	CTD-3023L14.2	chr8_8278888_C_T_b38	rs1401390	1.90E-06	-0.25	Thyroid
ENSG00000249188.1	ENPP7P1	chr8_8278888_C_T_b38	rs1401390	2.00E-06	-0.52	Brain - Cerebellar Hemisphere
ENSG00000248538.6	RP11-10A14.5	chr8_8278888_C_T_b38	rs1401390	2.10E-06	-0.26	Nerve - Tibial
ENSG00000104626.14	ERI1	chr8_8278888_C_T_b38	rs1401390	2.20E-06	-0.16	Artery - Aorta

ENSG00000253981.5	ALG1L13P	chr8_8278888_C_T_b38	rs1401390	2.30E-06	0.29	Adipose - Visceral (Omentum)
ENSG00000254153.1	CTA-398F10.2	chr8_8278888_C_T_b38	rs1401390	2.30E-06	0.46	Minor Salivary Gland
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	2.50E-06	-0.57	Minor Salivary Gland
ENSG00000254597.1	FAM90A10P	chr8_8278888_C_T_b38	rs1401390	2.50E-06	-0.35	Testis
ENSG00000233609.3	RPL10P19	chr8_8278888_C_T_b38	rs1401390	2.60E-06	0.47	Brain - Anterior cingulate cortex (BA24)
ENSG00000253981.5	ALG1L13P	chr8_8278888_C_T_b38	rs1401390	2.70E-06	0.37	Stomach
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	3.40E-06	-0.3	Skin - Not Sun Exposed (Suprapubic)
ENSG00000173281.4	PPP1R3B	chr8_8278888_C_T_b38	rs1401390	4.30E-06	0.12	Artery - Tibial
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	4.60E-06	-0.46	Artery - Coronary
ENSG00000233609.3	RPL10P19	chr8_8278888_C_T_b38	rs1401390	5.90E-06	0.39	Brain - Caudate (basal ganglia)
ENSG00000233609.3	RPL10P19	chr8_8278888_C_T_b38	rs1401390	6.00E-06	0.45	Brain - Putamen (basal ganglia)
ENSG00000253981.5	ALG1L13P	chr8_8278888_C_T_b38	rs1401390	6.50E-06	0.32	Colon - Sigmoid
ENSG00000233609.3	RPL10P19	chr8_8278888_C_T_b38	rs1401390	8.00E-06	0.19	Adipose - Subcutaneous
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	1.20E-05	-0.35	Stomach
ENSG00000233609.3	RPL10P19	chr8_8278888_C_T_b38	rs1401390	1.50E-05	0.24	Breast - Mammary Tissue
ENSG00000253958.1	CLDN23	chr8_8278888_C_T_b38	rs1401390	1.60E-05	-0.18	Skin - Not Sun Exposed (Suprapubic)
ENSG00000253981.5	ALG1L13P	chr8_8278888_C_T_b38	rs1401390	1.80E-05	-0.41	Brain - Cortex
ENSG00000253981.5	ALG1L13P	chr8_8278888_C_T_b38	rs1401390	2.20E-05	0.38	Liver
ENSG00000275342.4	PRAG1	chr8_8278888_C_T_b38	rs1401390	2.50E-05	-0.14	Adipose - Visceral (Omentum)
ENSG00000233609.3	RPL10P19	chr8_8278888_C_T_b38	rs1401390	2.50E-05	0.23	Colon - Transverse
ENSG00000147324.10	MFHAS1	chr8_8278888_C_T_b38	rs1401390	3.20E-05	-0.13	Esophagus - Gastroesophageal Junction
ENSG00000253893.2	FAM85B	chr8_8278888_C_T_b38	rs1401390	3.60E-05	-0.32	Colon - Transverse
ENSG00000275342.4	PRAG1	chr8_8278888_C_T_b38	rs1401390	5.50E-05	-0.16	Artery - Aorta
ENSG00000233609.3	RPL10P19	chr8_8278888_C_T_b38	rs1401390	5.60E-05	0.22	Heart - Left Ventricle
ENSG00000233609.3	RPL10P19	chr8_8278888_C_T_b38	rs1401390	6.70E-05	0.22	Nerve - Tibial
ENSG00000233609.3	RPL10P19	chr8_8278888_C_T_b38	rs1401390	1.10E-04	0.22	Esophagus - Mucosa
ENSG00000173295.7	FAM86B3P	chr8_8240327_C_T_b38	rs2948308	1.30E-111	0.97	Cells - Cultured fibroblasts
ENSG00000173295.7	FAM86B3P	chr8_8240327_C_T_b38	rs2948308	1.70E-68	0.85	Esophagus - Mucosa
ENSG00000253981.5	ALG1L13P	chr8_8240327_C_T_b38	rs2948308	2.20E-59	0.84	Cells - Cultured fibroblasts
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	1.00E-50	-1.1	Testis
ENSG00000275342.4	PRAG1	chr8_8240327_C_T_b38	rs2948308	4.00E-45	-0.5	Thyroid
ENSG00000173295.7	FAM86B3P	chr8_8240327_C_T_b38	rs2948308	2.90E-39	0.66	Adipose - Visceral (Omentum)
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	3.60E-34	-0.73	Nerve - Tibial

ENSG00000173295.7	FAM86B3P	chr8_8240327_C_T_b38	rs2948308	2.90E-33	0.55	Skin - Not Sun Exposed (Suprapubic)
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	1.50E-32	-0.7	Artery - Tibial
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	6.60E-30	-0.93	Brain - Cortex
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	7.30E-29	-0.9	Pituitary
ENSG00000254153.1	CTA-398F10.2	chr8_8240327_C_T_b38	rs2948308	8.50E-29	0.51	Skin - Not Sun Exposed (Suprapubic)
ENSG00000104626.14	ERI1	chr8_8240327_C_T_b38	rs2948308	1.10E-28	-0.27	Cells - Cultured fibroblasts
ENSG00000249188.1	ENPP7P1	chr8_8240327_C_T_b38	rs2948308	1.20E-27	-0.82	Testis
ENSG00000253981.5	ALG1L13P	chr8_8240327_C_T_b38	rs2948308	3.00E-27	0.65	Esophagus - Mucosa
ENSG00000173295.7	FAM86B3P	chr8_8240327_C_T_b38	rs2948308	3.40E-27	0.61	Colon - Transverse
ENSG00000254153.1	CTA-398F10.2	chr8_8240327_C_T_b38	rs2948308	3.70E-27	0.44	Skin - Sun Exposed (Lower leg)
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	3.20E-26	-0.58	Thyroid
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	9.20E-26	-0.93	Brain - Cerebellum
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	1.60E-24	-0.93	Brain - Anterior cingulate cortex (BA24)
ENSG00000173295.7	FAM86B3P	chr8_8240327_C_T_b38	rs2948308	2.00E-24	0.4	Skin - Sun Exposed (Lower leg)
ENSG00000173295.7	FAM86B3P	chr8_8240327_C_T_b38	rs2948308	1.60E-23	-0.78	Brain - Cortex
ENSG00000173295.7	FAM86B3P	chr8_8240327_C_T_b38	rs2948308	2.50E-22	-0.71	Brain - Cerebellar Hemisphere
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	3.30E-22	-0.85	Brain - Nucleus accumbens (basal ganglia)
ENSG00000173295.7	FAM86B3P	chr8_8240327_C_T_b38	rs2948308	3.00E-21	0.62	Pancreas
ENSG00000173295.7	FAM86B3P	chr8_8240327_C_T_b38	rs2948308	4.70E-21	-0.6	Brain - Cerebellum
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	4.70E-21	-0.88	Brain - Frontal Cortex (BA9)
ENSG00000173295.7	FAM86B3P	chr8_8240327_C_T_b38	rs2948308	1.60E-20	0.3	Breast - Mammary Tissue
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	5.60E-20	-0.83	Brain - Caudate (basal ganglia)
ENSG00000173295.7	FAM86B3P	chr8_8240327_C_T_b38	rs2948308	5.40E-19	0.48	Heart - Left Ventricle
ENSG00000173295.7	FAM86B3P	chr8_8240327_C_T_b38	rs2948308	1.50E-18	-0.76	Brain - Frontal Cortex (BA9)
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	3.50E-18	-0.9	Brain - Hippocampus
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	3.90E-18	-0.89	Brain - Cerebellar Hemisphere
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	6.90E-18	-0.96	Brain - Amygdala
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	5.20E-17	-0.87	Brain - Hypothalamus
ENSG00000233609.3	RPL10P19	chr8_8240327_C_T_b38	rs2948308	6.30E-17	0.38	Thyroid
ENSG00000173295.7	FAM86B3P	chr8_8240327_C_T_b38	rs2948308	6.60E-17	0.36	Lung
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	7.10E-17	-0.87	Brain - Putamen (basal ganglia)
ENSG00000173295.7	FAM86B3P	chr8_8240327_C_T_b38	rs2948308	1.40E-16	0.36	Adipose - Subcutaneous
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	6.80E-16	-0.85	Ovary

ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	8.40E-16	-0.99	Brain - Spinal cord (cervical c-1)
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	9.30E-16	-0.92	Uterus
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	2.60E-15	-0.52	Lung
ENSG00000173295.7	FAM86B3P	chr8_8240327_C_T_b38	rs2948308	1.70E-14	-0.49	Pituitary
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	8.80E-14	-0.88	Brain - Substantia nigra
ENSG00000173295.7	FAM86B3P	chr8_8240327_C_T_b38	rs2948308	3.30E-13	0.71	Vagina
ENSG00000173295.7	FAM86B3P	chr8_8240327_C_T_b38	rs2948308	5.00E-13	0.41	Colon - Sigmoid
ENSG00000173295.7	FAM86B3P	chr8_8240327_C_T_b38	rs2948308	5.50E-13	-0.64	Brain - Anterior cingulate cortex (BA24)
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	6.30E-13	-0.48	Breast - Mammary Tissue
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	7.30E-13	-0.49	Artery - Aorta
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	2.00E-12	-0.56	Esophagus - Gastroesophageal Junction
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	2.10E-11	-0.75	Cells - EBV-transformed lymphocytes
ENSG00000173295.7	FAM86B3P	chr8_8240327_C_T_b38	rs2948308	2.40E-11	0.42	Stomach
ENSG00000253981.5	ALG1L13P	chr8_8240327_C_T_b38	rs2948308	3.20E-11	0.47	Colon - Transverse
ENSG00000249188.1	ENPP7P1	chr8_8240327_C_T_b38	rs2948308	3.40E-11	-0.65	Brain - Cerebellum
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	4.30E-11	-0.39	Adipose - Subcutaneous
ENSG00000173295.7	FAM86B3P	chr8_8240327_C_T_b38	rs2948308	6.10E-11	0.27	Esophagus - Muscularis
ENSG00000254153.1	CTA-398F10.2	chr8_8240327_C_T_b38	rs2948308	1.80E-10	0.33	Esophagus - Mucosa
ENSG00000253981.5	ALG1L13P	chr8_8240327_C_T_b38	rs2948308	2.10E-10	0.37	Adipose - Subcutaneous
ENSG00000173295.7	FAM86B3P	chr8_8240327_C_T_b38	rs2948308	2.40E-10	0.22	Thyroid
ENSG00000233609.3	RPL10P19	chr8_8240327_C_T_b38	rs2948308	4.30E-10	0.25	Lung
ENSG00000173295.7	FAM86B3P	chr8_8240327_C_T_b38	rs2948308	7.40E-10	0.32	Heart - Atrial Appendage
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	9.20E-10	-0.41	Esophagus - Muscularis
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	2.20E-09	-0.49	Colon - Sigmoid
ENSG00000173295.7	FAM86B3P	chr8_8240327_C_T_b38	rs2948308	2.50E-09	0.23	Muscle - Skeletal
ENSG00000249188.1	ENPP7P1	chr8_8240327_C_T_b38	rs2948308	3.00E-09	-0.51	Pituitary
ENSG00000253981.5	ALG1L13P	chr8_8240327_C_T_b38	rs2948308	4.80E-09	0.35	Skin - Not Sun Exposed (Suprapubic)
ENSG00000248538.6	RP11-10A14.5	chr8_8240327_C_T_b38	rs2948308	1.30E-08	0.29	Whole Blood
ENSG00000173295.7	FAM86B3P	chr8_8240327_C_T_b38	rs2948308	1.70E-08	0.26	Nerve - Tibial
ENSG00000254153.1	CTA-398F10.2	chr8_8240327_C_T_b38	rs2948308	3.70E-08	-0.24	Thyroid
ENSG00000147324.10	MFHAS1	chr8_8240327_C_T_b38	rs2948308	4.40E-08	0.19	Muscle - Skeletal
ENSG00000253981.5	ALG1L13P	chr8_8240327_C_T_b38	rs2948308	4.50E-08	0.43	Pancreas
ENSG00000233609.3	RPL10P19	chr8_8240327_C_T_b38	rs2948308	4.60E-08	0.3	Colon - Transverse

ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	5.20E-08	-0.47	Liver
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	5.90E-08	-0.38	Adipose - Visceral (Omentum)
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	6.00E-08	-0.32	Skin - Sun Exposed (Lower leg)
ENSG00000233609.3	RPL10P19	chr8_8240327_C_T_b38	rs2948308	7.50E-08	0.51	Brain - Cortex
ENSG00000173295.7	FAM86B3P	chr8_8240327_C_T_b38	rs2948308	8.30E-08	0.29	Esophagus - Gastroesophageal Junction
ENSG00000104626.14	ERI1	chr8_8240327_C_T_b38	rs2948308	9.50E-08	0.24	Testis
ENSG00000253958.1	CLDN23	chr8_8240327_C_T_b38	rs2948308	9.60E-08	-0.22	Skin - Sun Exposed (Lower leg)
ENSG00000253981.5	ALG1L13P	chr8_8240327_C_T_b38	rs2948308	1.20E-07	0.13	Whole Blood
ENSG00000173295.7	FAM86B3P	chr8_8240327_C_T_b38	rs2948308	1.30E-07	-0.38	Brain - Hippocampus
ENSG00000275342.4	PRAG1	chr8_8240327_C_T_b38	rs2948308	1.50E-07	-0.3	Testis
ENSG00000173295.7	FAM86B3P	chr8_8240327_C_T_b38	rs2948308	1.60E-07	0.7	Kidney - Cortex
ENSG00000253981.5	ALG1L13P	chr8_8240327_C_T_b38	rs2948308	1.80E-07	0.38	Colon - Sigmoid
ENSG00000253981.5	ALG1L13P	chr8_8240327_C_T_b38	rs2948308	1.90E-07	0.32	Adipose - Visceral (Omentum)
ENSG00000233609.3	RPL10P19	chr8_8240327_C_T_b38	rs2948308	2.50E-07	0.27	Adipose - Visceral (Omentum)
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	3.20E-07	-0.62	Minor Salivary Gland
ENSG00000248538.6	RP11-10A14.5	chr8_8240327_C_T_b38	rs2948308	3.20E-07	-0.36	Testis
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	4.20E-07	-0.52	Spleen
ENSG00000254153.1	CTA-398F10.2	chr8_8240327_C_T_b38	rs2948308	5.10E-07	0.49	Minor Salivary Gland
ENSG00000104626.14	ERI1	chr8_8240327_C_T_b38	rs2948308	5.30E-07	-0.18	Artery - Aorta
ENSG00000253981.5	ALG1L13P	chr8_8240327_C_T_b38	rs2948308	7.00E-07	0.54	Vagina
ENSG00000173295.7	FAM86B3P	chr8_8240327_C_T_b38	rs2948308	8.70E-07	0.45	Minor Salivary Gland
ENSG00000233609.3	RPL10P19	chr8_8240327_C_T_b38	rs2948308	9.10E-07	0.34	Pancreas
ENSG00000253981.5	ALG1L13P	chr8_8240327_C_T_b38	rs2948308	1.00E-06	-0.44	Brain - Cerebellar Hemisphere
ENSG00000233609.3	RPL10P19	chr8_8240327_C_T_b38	rs2948308	1.30E-06	0.46	Brain - Hippocampus
ENSG00000253981.5	ALG1L13P	chr8_8240327_C_T_b38	rs2948308	1.90E-06	0.39	Stomach
ENSG00000147324.10	MFHAS1	chr8_8240327_C_T_b38	rs2948308	2.00E-06	0.23	Heart - Atrial Appendage
ENSG00000275342.4	PRAG1	chr8_8240327_C_T_b38	rs2948308	2.10E-06	-0.16	Adipose - Visceral (Omentum)
ENSG00000253958.1	CLDN23	chr8_8240327_C_T_b38	rs2948308	2.80E-06	-0.2	Skin - Not Sun Exposed (Suprapubic)
ENSG00000233609.3	RPL10P19	chr8_8240327_C_T_b38	rs2948308	3.10E-06	0.26	Breast - Mammary Tissue
ENSG00000253981.5	ALG1L13P	chr8_8240327_C_T_b38	rs2948308	3.30E-06	0.23	Thyroid
ENSG00000254597.1	FAM90A10P	chr8_8240327_C_T_b38	rs2948308	3.40E-06	-0.35	Testis
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	3.50E-06	-0.38	Stomach

ENSG00000253981.5	ALG1L13P	chr8_8240327_C_T_b38	rs2948308	4.30E-06	-0.45	Brain - Cortex
ENSG00000233609.3	RPL10P19	chr8_8240327_C_T_b38	rs2948308	5.30E-06	0.27	Esophagus - Mucosa
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	5.30E-06	-0.35	Colon - Transverse
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	8.60E-06	-0.28	Cells - Cultured fibroblasts
ENSG00000233609.3	RPL10P19	chr8_8240327_C_T_b38	rs2948308	9.30E-06	0.39	Brain - Nucleus accumbens (basal ganglia)
ENSG00000275342.4	PRAG1	chr8_8240327_C_T_b38	rs2948308	1.10E-05	-0.18	Artery - Aorta
ENSG00000253981.5	ALG1L13P	chr8_8240327_C_T_b38	rs2948308	1.20E-05	0.39	Liver
ENSG00000233609.3	RPL10P19	chr8_8240327_C_T_b38	rs2948308	1.30E-05	0.45	Brain - Anterior cingulate cortex (BA24)
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	1.40E-05	-0.5	Vagina
ENSG00000253893.2	FAM85B	chr8_8240327_C_T_b38	rs2948308	1.50E-05	-0.29	Skin - Not Sun Exposed (Suprapubic)
ENSG00000173281.4	PPP1R3B	chr8_8240327_C_T_b38	rs2948308	1.60E-05	0.11	Artery - Tibial
ENSG00000249188.1	ENPP7P1	chr8_8240327_C_T_b38	rs2948308	1.80E-05	-0.49	Brain - Cerebellar Hemisphere
ENSG00000233609.3	RPL10P19	chr8_8240327_C_T_b38	rs2948308	1.80E-05	0.25	Nerve - Tibial
ENSG00000254153.1	CTA-398F10.2	chr8_8240327_C_T_b38	rs2948308	2.00E-05	0.26	Stomach
ENSG00000233609.3	RPL10P19	chr8_8240327_C_T_b38	rs2948308	2.20E-05	0.19	Adipose - Subcutaneous
ENSG00000253130.1	CTD-3023L14.2	chr8_8240327_C_T_b38	rs2948308	2.80E-05	-0.22	Thyroid
ENSG00000233609.3	RPL10P19	chr8_8240327_C_T_b38	rs2948308	3.10E-05	0.23	Esophagus - Muscularis
ENSG00000248538.6	RP11-10A14.5	chr8_8240327_C_T_b38	rs2948308	3.60E-05	-0.24	Nerve - Tibial
ENSG00000253981.5	ALG1L13P	chr8_8240327_C_T_b38	rs2948308	3.70E-05	-0.4	Brain - Frontal Cortex (BA9)
ENSG00000253981.5	ALG1L13P	chr8_8240327_C_T_b38	rs2948308	4.30E-05	-0.32	Brain - Cerebellum
ENSG00000233609.3	RPL10P19	chr8_8240327_C_T_b38	rs2948308	8.50E-05	0.1	Whole Blood
ENSG00000248538.6	RP11-10A14.5	chr8_8240327_C_T_b38	rs2948308	9.30E-05	-0.27	Heart - Atrial Appendage
ENSG00000253981.5	ALG1L13P	chr8_8240327_C_T_b38	rs2948308	1.00E-04	0.21	Skin - Sun Exposed (Lower leg)
ENSG00000233609.3	RPL10P19	chr8_8240327_C_T_b38	rs2948308	1.50E-04	0.2	Artery - Tibial
ENSG00000255310.2	AF131215.2	chr8_10904075_G_A_b38	rs6985109	1.70E-25	-0.35	Skin - Sun Exposed (Lower leg)
ENSG00000269918.1	AF131215.9	chr8_10904075_G_A_b38	rs6985109	3.60E-24	-0.3	Skin - Sun Exposed (Lower leg)
ENSG00000269918.1	AF131215.9	chr8_10904075_G_A_b38	rs6985109	5.80E-23	-0.3	Skin - Not Sun Exposed (Suprapubic)
ENSG00000269918.1	AF131215.9	chr8_10904075_G_A_b38	rs6985109	2.20E-22	-0.28	Esophagus - Mucosa
ENSG00000269954.1	RP11-148O21.6	chr8_10904075_G_A_b38	rs6985109	5.50E-22	0.42	Cells - Cultured fibroblasts
ENSG00000269918.1	AF131215.9	chr8_10904075_G_A_b38	rs6985109	1.90E-21	-0.32	Thyroid
ENSG00000255310.2	AF131215.2	chr8_10904075_G_A_b38	rs6985109	2.30E-21	-0.32	Skin - Not Sun Exposed (Suprapubic)
ENSG00000255310.2	AF131215.2	chr8_10904075_G_A_b38	rs6985109	1.00E-20	-0.39	Nerve - Tibial

ENSG00000255518.1	RP11-148O21.4	chr8_10904075_G_A_b38	rs6985109	1.40E-20	0.44	Cells - Cultured fibroblasts
ENSG00000255310.2	AF131215.2	chr8_10904075_G_A_b38	rs6985109	4.60E-20	-0.35	Thyroid
ENSG00000255310.2	AF131215.2	chr8_10904075_G_A_b38	rs6985109	1.20E-19	-0.52	Heart - Atrial Appendage
ENSG00000254774.1	RP11-148O21.3	chr8_10904075_G_A_b38	rs6985109	1.50E-19	0.43	Cells - Cultured fibroblasts
ENSG00000269918.1	AF131215.9	chr8_10904075_G_A_b38	rs6985109	1.60E-18	-0.46	Heart - Atrial Appendage
ENSG00000255310.2	AF131215.2	chr8_10904075_G_A_b38	rs6985109	1.00E-17	-0.35	Esophagus - Mucosa
ENSG00000269918.1	AF131215.9	chr8_10904075_G_A_b38	rs6985109	2.00E-17	-0.33	Lung
ENSG00000269918.1	AF131215.9	chr8_10904075_G_A_b38	rs6985109	3.20E-17	-0.31	Nerve - Tibial
ENSG00000255310.2	AF131215.2	chr8_10904075_G_A_b38	rs6985109	4.00E-17	-0.4	Lung
ENSG00000255354.1	RP11-148O21.2	chr8_10904075_G_A_b38	rs6985109	1.10E-16	0.37	Cells - Cultured fibroblasts
ENSG00000269918.1	AF131215.9	chr8_10904075_G_A_b38	rs6985109	1.00E-15	-0.31	Esophagus - Muscularis
ENSG00000136573.12	BLK	chr8_10904075_G_A_b38	rs6985109	7.30E-15	0.34	Cells - Cultured fibroblasts
ENSG00000255310.2	AF131215.2	chr8_10904075_G_A_b38	rs6985109	7.90E-15	-0.42	Artery - Aorta
ENSG00000269918.1	AF131215.9	chr8_10904075_G_A_b38	rs6985109	1.80E-14	-0.38	Pancreas
ENSG00000255310.2	AF131215.2	chr8_10904075_G_A_b38	rs6985109	2.10E-14	-0.28	Testis
ENSG00000255310.2	AF131215.2	chr8_10904075_G_A_b38	rs6985109	8.90E-14	-0.47	Pancreas
ENSG00000154319.14	FAM167A	chr8_10904075_G_A_b38	rs6985109	2.30E-12	-0.31	Whole Blood
ENSG00000255310.2	AF131215.2	chr8_10904075_G_A_b38	rs6985109	4.30E-12	-0.22	Breast - Mammary Tissue
ENSG00000079459.12	FDFT1	chr8_10904075_G_A_b38	rs6985109	4.90E-12	-0.23	Artery - Tibial
ENSG00000255310.2	AF131215.2	chr8_10904075_G_A_b38	rs6985109	7.50E-12	-0.33	Artery - Tibial
ENSG00000154316.16	TDH	chr8_10904075_G_A_b38	rs6985109	1.00E-11	0.24	Thyroid
ENSG00000255310.2	AF131215.2	chr8_10904075_G_A_b38	rs6985109	1.50E-11	-0.32	Adipose - Visceral (Omentum)
ENSG00000269918.1	AF131215.9	chr8_10904075_G_A_b38	rs6985109	1.50E-11	-0.27	Stomach
ENSG00000255310.2	AF131215.2	chr8_10904075_G_A_b38	rs6985109	4.20E-11	-0.31	Stomach
ENSG00000269918.1	AF131215.9	chr8_10904075_G_A_b38	rs6985109	6.60E-11	-0.28	Adipose - Subcutaneous
ENSG00000269918.1	AF131215.9	chr8_10904075_G_A_b38	rs6985109	8.00E-11	-0.27	Adipose - Visceral (Omentum)
ENSG00000269918.1	AF131215.9	chr8_10904075_G_A_b38	rs6985109	1.00E-10	-0.3	Artery - Tibial
ENSG00000255020.1	AF131216.5	chr8_10904075_G_A_b38	rs6985109	1.20E-10	-0.31	Stomach
ENSG00000269918.1	AF131215.9	chr8_10904075_G_A_b38	rs6985109	1.60E-10	-0.2	Whole Blood
ENSG00000269918.1	AF131215.9	chr8_10904075_G_A_b38	rs6985109	1.90E-10	-0.22	Breast - Mammary Tissue
ENSG00000269918.1	AF131215.9	chr8_10904075_G_A_b38	rs6985109	5.30E-10	-0.33	Artery - Aorta
ENSG00000255310.2	AF131215.2	chr8_10904075_G_A_b38	rs6985109	6.80E-10	-0.24	Muscle - Skeletal
ENSG00000255310.2	AF131215.2	chr8_10904075_G_A_b38	rs6985109	7.50E-10	-0.26	Adipose - Subcutaneous
ENSG00000154319.14	FAM167A	chr8_10904075_G_A_b38	rs6985109	1.20E-09	0.2	Skin - Sun Exposed (Lower leg)

ENSG00000269918.1	AF131215.9	chr8_10904075_G_A_b38	rs6985109	2.70E-09	-0.23	Testis
ENSG00000255020.1	AF131216.5	chr8_10904075_G_A_b38	rs6985109	3.30E-09	-0.37	Pancreas
ENSG00000255310.2	AF131215.2	chr8_10904075_G_A_b38	rs6985109	3.60E-09	-0.36	Esophagus - Gastroesophageal Junction
ENSG00000255020.1	AF131216.5	chr8_10904075_G_A_b38	rs6985109	4.30E-09	-0.31	Brain - Cerebellum
ENSG00000255310.2	AF131215.2	chr8_10904075_G_A_b38	rs6985109	4.30E-09	-0.17	Whole Blood
ENSG00000269918.1	AF131215.9	chr8_10904075_G_A_b38	rs6985109	4.30E-09	-0.26	Colon - Sigmoid
ENSG00000280273.2	AF131216.7	chr8_10904075_G_A_b38	rs6985109	5.00E-09	0.34	Brain - Nucleus accumbens (basal ganglia)
ENSG00000269918.1	AF131215.9	chr8_10904075_G_A_b38	rs6985109	6.00E-09	-0.26	Colon - Transverse
ENSG00000255310.2	AF131215.2	chr8_10904075_G_A_b38	rs6985109	6.60E-09	-0.3	Colon - Sigmoid
ENSG00000255310.2	AF131215.2	chr8_10904075_G_A_b38	rs6985109	1.00E-08	-0.31	Esophagus - Muscularis
ENSG00000269918.1	AF131215.9	chr8_10904075_G_A_b38	rs6985109	1.60E-08	-0.29	Spleen
ENSG00000104643.9	MTMR9	chr8_10904075_G_A_b38	rs6985109	1.70E-08	-0.2	Colon - Sigmoid
ENSG00000104643.9	MTMR9	chr8_10904075_G_A_b38	rs6985109	3.00E-08	-0.15	Nerve - Tibial
ENSG00000269918.1	AF131215.9	chr8_10904075_G_A_b38	rs6985109	3.80E-08	-0.27	Heart - Left Ventricle
ENSG00000175806.14	MSRA	chr8_10904075_G_A_b38	rs6985109	5.00E-08	0.18	Skin - Sun Exposed (Lower leg)
ENSG00000255310.2	AF131215.2	chr8_10904075_G_A_b38	rs6985109	7.80E-08	-0.22	Brain - Cerebellar Hemisphere
ENSG00000254774.1	RP11-148O21.3	chr8_10904075_G_A_b38	rs6985109	1.20E-07	0.23	Thyroid
ENSG00000255310.2	AF131215.2	chr8_10904075_G_A_b38	rs6985109	1.20E-07	-0.32	Spleen
ENSG00000269918.1	AF131215.9	chr8_10904075_G_A_b38	rs6985109	1.20E-07	-0.24	Esophagus - Gastroesophageal Junction
ENSG00000255310.2	AF131215.2	chr8_10904075_G_A_b38	rs6985109	1.30E-07	-0.28	Brain - Cerebellum
ENSG00000154319.14	FAM167A	chr8_10904075_G_A_b38	rs6985109	1.40E-07	-0.14	Cells - Cultured fibroblasts
ENSG00000255020.1	AF131216.5	chr8_10904075_G_A_b38	rs6985109	1.40E-07	-0.38	Brain - Cortex
ENSG00000269918.1	AF131215.9	chr8_10904075_G_A_b38	rs6985109	1.70E-07	-0.33	Minor Salivary Gland
ENSG00000154328.15	NEIL2	chr8_10904075_G_A_b38	rs6985109	2.20E-07	-0.18	Heart - Atrial Appendage
ENSG00000154316.16	TDH	chr8_10904075_G_A_b38	rs6985109	2.30E-07	0.37	Brain - Nucleus accumbens (basal ganglia)
ENSG00000177710.5	SLC35G5	chr8_10904075_G_A_b38	rs6985109	3.10E-07	0.23	Esophagus - Mucosa
ENSG00000269954.1	RP11-148O21.6	chr8_10904075_G_A_b38	rs6985109	3.60E-07	0.2	Thyroid
ENSG00000175806.14	MSRA	chr8_10904075_G_A_b38	rs6985109	3.90E-07	0.18	Testis
ENSG00000255310.2	AF131215.2	chr8_10904075_G_A_b38	rs6985109	5.60E-07	-0.23	Colon - Transverse
ENSG00000255310.2	AF131215.2	chr8_10904075_G_A_b38	rs6985109	7.10E-07	-0.27	Prostate
ENSG00000164733.20	CTSB	chr8_10904075_G_A_b38	rs6985109	9.20E-07	0.14	Artery - Tibial
ENSG00000154328.15	NEIL2	chr8_10904075_G_A_b38	rs6985109	1.10E-06	-0.25	Pituitary
ENSG00000272505.1	RP11-981G7.6	chr8_10904075_G_A_b38	rs6985109	1.40E-06	-0.29	Brain - Hippocampus

ENSG00000164733.20	CTSB	chr8_10904075_G_A_b38	rs6985109	1.40E-06	0.12	Nerve - Tibial
ENSG00000255310.2	AF131215.2	chr8_10904075_G_A_b38	rs6985109	1.60E-06	-0.29	Brain - Cortex
ENSG00000154316.16	TDH	chr8_10904075_G_A_b38	rs6985109	1.60E-06	0.36	Pituitary
ENSG00000227203.3	SUB1P1	chr8_10904075_G_A_b38	rs6985109	1.70E-06	0.24	Skin - Not Sun Exposed (Suprapubic)
ENSG00000183638.5	RP1L1	chr8_10904075_G_A_b38	rs6985109	1.90E-06	-0.19	Nerve - Tibial
ENSG00000079459.12	FDFT1	chr8_10904075_G_A_b38	rs6985109	1.90E-06	-0.14	Cells - Cultured fibroblasts
ENSG00000280273.2	AF131216.7	chr8_10904075_G_A_b38	rs6985109	2.20E-06	0.31	Brain - Hippocampus
ENSG00000154316.16	TDH	chr8_10904075_G_A_b38	rs6985109	2.50E-06	-0.31	Pancreas
ENSG00000170983.3	LINC00208	chr8_10904075_G_A_b38	rs6985109	2.60E-06	0.16	Testis
ENSG00000280273.2	AF131216.7	chr8_10904075_G_A_b38	rs6985109	2.60E-06	0.27	Brain - Putamen (basal ganglia)
ENSG00000104643.9	MTMR9	chr8_10904075_G_A_b38	rs6985109	2.70E-06	-0.11	Muscle - Skeletal
ENSG00000280294.1	RP11-177H2.1	chr8_10904075_G_A_b38	rs6985109	2.90E-06	-0.2	Skin - Sun Exposed (Lower leg)
ENSG00000183638.5	RP1L1	chr8_10904075_G_A_b38	rs6985109	3.10E-06	-0.2	Adipose - Subcutaneous
ENSG00000255020.1	AF131216.5	chr8_10904075_G_A_b38	rs6985109	3.20E-06	-0.37	Brain - Hippocampus
ENSG00000154319.14	FAM167A	chr8_10904075_G_A_b38	rs6985109	3.20E-06	-0.49	Cells - EBV-transformed lymphocytes
ENSG00000154319.14	FAM167A	chr8_10904075_G_A_b38	rs6985109	3.70E-06	0.19	Skin - Not Sun Exposed (Suprapubic)
ENSG00000255310.2	AF131215.2	chr8_10904075_G_A_b38	rs6985109	3.70E-06	-0.31	Minor Salivary Gland
ENSG00000154316.16	TDH	chr8_10904075_G_A_b38	rs6985109	3.90E-06	0.28	Brain - Cerebellum
ENSG00000269918.1	AF131215.9	chr8_10904075_G_A_b38	rs6985109	3.90E-06	-0.18	Muscle - Skeletal
ENSG00000154328.15	NEIL2	chr8_10904075_G_A_b38	rs6985109	4.70E-06	-0.16	Whole Blood
ENSG00000164733.20	CTSB	chr8_10904075_G_A_b38	rs6985109	5.30E-06	0.12	Esophagus - Muscularis
ENSG00000177710.5	SLC35G5	chr8_10904075_G_A_b38	rs6985109	5.50E-06	0.17	Lung
ENSG00000272505.1	RP11-981G7.6	chr8_10904075_G_A_b38	rs6985109	5.60E-06	-0.43	Brain - Spinal cord (cervical c-1)
ENSG00000255020.1	AF131216.5	chr8_10904075_G_A_b38	rs6985109	5.70E-06	-0.26	Brain - Cerebellar Hemisphere
ENSG00000269918.1	AF131215.9	chr8_10904075_G_A_b38	rs6985109	6.30E-06	-0.38	Vagina
ENSG00000255310.2	AF131215.2	chr8_10904075_G_A_b38	rs6985109	6.70E-06	-0.18	Small Intestine - Terminal Ileum
ENSG00000253641.5	LINCR-0001	chr8_10904075_G_A_b38	rs6985109	7.10E-06	-0.41	Brain - Hippocampus
ENSG00000255310.2	AF131215.2	chr8_10904075_G_A_b38	rs6985109	7.30E-06	-0.26	Pituitary
ENSG00000272505.1	RP11-981G7.6	chr8_10904075_G_A_b38	rs6985109	7.30E-06	-0.19	Thyroid
ENSG00000269918.1	AF131215.9	chr8_10904075_G_A_b38	rs6985109	7.90E-06	-0.21	Pituitary
ENSG00000255310.2	AF131215.2	chr8_10904075_G_A_b38	rs6985109	8.10E-06	-0.28	Heart - Left Ventricle
ENSG00000154319.14	FAM167A	chr8_10904075_G_A_b38	rs6985109	8.70E-06	-0.18	Esophagus - Mucosa
ENSG00000280273.2	AF131216.7	chr8_10904075_G_A_b38	rs6985109	9.00E-06	0.27	Brain - Caudate (basal ganglia)

ENSG00000079459.12	FDFT1	chr8_10904075_G_A_b38	rs6985109	1.10E-05	-0.13	Whole Blood
ENSG00000255310.2	AF131215.2	chr8_10904075_G_A_b38	rs6985109	1.30E-05	-0.22	Cells - Cultured fibroblasts
ENSG00000255310.2	AF131215.2	chr8_10904075_G_A_b38	rs6985109	1.50E-05	-0.29	Brain - Caudate (basal ganglia)
ENSG00000079459.12	FDFT1	chr8_10904075_G_A_b38	rs6985109	1.50E-05	-0.23	Pituitary
ENSG00000255310.2	AF131215.2	chr8_10904075_G_A_b38	rs6985109	1.60E-05	-0.38	Cells - EBV-transformed lymphocytes
ENSG00000269918.1	AF131215.9	chr8_10904075_G_A_b38	rs6985109	1.60E-05	-0.18	Brain - Cerebellar Hemisphere
ENSG00000164733.20	CTSB	chr8_10904075_G_A_b38	rs6985109	1.70E-05	0.14	Stomach
ENSG00000136573.12	BLK	chr8_10904075_G_A_b38	rs6985109	1.70E-05	0.085	Whole Blood
ENSG00000255310.2	AF131215.2	chr8_10904075_G_A_b38	rs6985109	2.10E-05	-0.23	Brain - Nucleus accumbens (basal ganglia)
ENSG00000154319.14	FAM167A	chr8_10904075_G_A_b38	rs6985109	2.10E-05	0.21	Brain - Putamen (basal ganglia)
ENSG00000154316.16	TDH	chr8_10904075_G_A_b38	rs6985109	2.20E-05	0.15	Muscle - Skeletal
ENSG00000280273.2	AF131216.7	chr8_10904075_G_A_b38	rs6985109	2.70E-05	0.36	Brain - Frontal Cortex (BA9)
ENSG00000164733.20	CTSB	chr8_10904075_G_A_b38	rs6985109	2.70E-05	0.18	Cells - Cultured fibroblasts
ENSG00000269918.1	AF131215.9	chr8_10904075_G_A_b38	rs6985109	3.00E-05	-0.18	Prostate
ENSG00000255020.1	AF131216.5	chr8_10904075_G_A_b38	rs6985109	3.40E-05	-0.31	Brain - Anterior cingulate cortex (BA24)
ENSG00000255020.1	AF131216.5	chr8_10904075_G_A_b38	rs6985109	4.00E-05	-0.31	Brain - Frontal Cortex (BA9)
ENSG00000269918.1	AF131215.9	chr8_10904075_G_A_b38	rs6985109	5.60E-05	-0.19	Brain - Cerebellum
ENSG00000154316.16	TDH	chr8_10904075_G_A_b38	rs6985109	5.80E-05	-0.21	Stomach
ENSG00000255518.1	RP11-148O21.4	chr8_10904075_G_A_b38	rs6985109	6.00E-05	0.17	Thyroid
ENSG00000164733.20	CTSB	chr8_10904075_G_A_b38	rs6985109	6.50E-05	0.11	Skin - Sun Exposed (Lower leg)
ENSG00000183638.5	RP1L1	chr8_10904075_G_A_b38	rs6985109	6.70E-05	-0.15	Skin - Sun Exposed (Lower leg)
ENSG00000154328.15	NEIL2	chr8_10904075_G_A_b38	rs6985109	7.00E-05	-0.13	Artery - Tibial
ENSG00000255046.1	RP11-297N6.4	chr8_10904075_G_A_b38	rs6985109	7.30E-05	0.2	Whole Blood
ENSG00000253641.5	LINCR-0001	chr8_10904075_G_A_b38	rs6985109	8.00E-05	-0.2	Lung
ENSG00000177710.5	SLC35G5	chr8_10904075_G_A_b38	rs6985109	8.80E-05	0.17	Whole Blood
ENSG00000171056.7	SOX7	chr8_10904075_G_A_b38	rs6985109	9.60E-05	-0.14	Thyroid
ENSG00000175806.14	MSRA	chr8_10904075_G_A_b38	rs6985109	1.00E-04	0.13	Cells - Cultured fibroblasts
ENSG00000154328.15	NEIL2	chr8_10904075_G_A_b38	rs6985109	1.10E-04	-0.11	Thyroid
ENSG00000177710.5	SLC35G5	chr8_10904075_G_A_b38	rs6985109	1.10E-04	0.19	Thyroid
ENSG00000154328.15	NEIL2	chr8_10904075_G_A_b38	rs6985109	1.20E-04	-0.14	Nerve - Tibial
ENSG00000227203.3	SUB1P1	chr8_10904075_G_A_b38	rs6985109	1.20E-04	0.18	Skin - Sun Exposed (Lower leg)
ENSG00000254556.1	AF131215.4	chr8_10904075_G_A_b38	rs6985109	1.70E-04	-0.17	Skin - Sun Exposed (Lower leg)

ENSG00000204682.5	CASC10	chr10_21541175_A_G_b38	rs11012732	2.50E-06	0.15	Skin - Sun Exposed (Lower leg)
ENSG00000204682.5	CASC10	chr10_21541175_A_G_b38	rs11012732	2.70E-06	0.17	Artery - Aorta
ENSG00000204682.5	CASC10	chr10_21541175_A_G_b38	rs11012732	4.40E-06	0.15	Artery - Tibial
ENSG00000078403.16	MLLT10	chr10_21541175_A_G_b38	rs11012732	2.80E-05	-0.098	Skin - Sun Exposed (Lower leg)
ENSG00000078114.18	NEBL	chr10_21541175_A_G_b38	rs11012732	3.10E-05	-0.2	Whole Blood
ENSG00000204682.5	CASC10	chr10_21541175_A_G_b38	rs11012732	5.30E-05	0.26	Brain - Cerebellum
ENSG00000204682.5	CASC10	chr10_21541175_A_G_b38	rs11012732	1.00E-04	0.16	Esophagus - Muscularis
ENSG00000204682.5	CASC10	chr10_21508343_T_C_b38	rs11012726	1.40E-07	0.17	Skin - Sun Exposed (Lower leg)
ENSG00000078403.16	MLLT10	chr10_21508343_T_C_b38	rs11012726	1.70E-05	-0.11	Skin - Sun Exposed (Lower leg)
ENSG00000204682.5	CASC10	chr10_21508343_T_C_b38	rs11012726	3.00E-05	0.28	Brain - Cerebellum
ENSG00000204682.5	CASC10	chr10_21508343_T_C_b38	rs11012726	5.50E-05	0.17	Esophagus - Muscularis
ENSG00000204682.5	CASC10	chr10_21508343_T_C_b38	rs11012726	1.10E-04	0.13	Artery - Tibial

*NES: normalized effect size.