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Assessment of Systematic Effects of Methodological Characteristics on Genetic Associations

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ASSESSMENT OF SYSTEMATIC EFFECTS OF METHODOLOGICAL CHARACTERISTICS ON GENETIC ASSOCIATIONS

BADR ABDULRAHMAN ALJASIR

Thesis submitted to the Faculty of Graduate and Postdoctoral Studies in Partial fulfillment of the requirements for the MSc degree in Epidemiology

Epidemiology and Community Medicine

Faculty of Medicine

University of Ottawa

Your file Votre référence
ISBN: 978-0-494-51633-1
Our file Notre référence
ISBN: 978-0-494-51633-1

Acknowledgments

I would like to express my gratitude to the following institutions and individuals who have helped to make this research project a rewarding experience:

The National Guard Health Affairs, Kingdom of Saudi Arabia, who through scholarship funding gave me the opportunity to pursue specialist education in the field of epidemiology.

The Department of Epidemiology and Community Medicine, University of Ottawa, for giving me the opportunity to join the epidemiology program.

My supervisors and advisors for their friendship, mentoring, and ongoing guidance; they started me on this path and have been with me every step of the way. Without them, this thesis would not have been realized:

- Dr. Julian Little, Ottawa, Canada
- Dr. David Moher, Ottawa, Canada
- Dr. Julian Higgins, Cambridge, England
- Dr. John Ioannidis, Ioannina, Greece.

Dr. Brenda Wilson, for her invaluable help and enlightening insights.

My colleague, Mr. Alex Yurkiewch, for his magnificent contribution during the process of data extraction.

Ms. Anne Marie Todkill, Ms. Diana-Lynn Fox, Ms. Valery L'Heureux, and Ms. Fay Draper for their unstinting support in the preparation of this thesis.

My father, mother, and sisters, who have been wonderfully tolerant and ever-encouraging.

My incredible wife, who is beyond simple acknowledgments. She remains my constant inspiration.

CONTENTS

TABLES

FIGURES

ABSTRACT

Background: The effective use of knowledge related to gene-disease associations relies on the optimal conduct and reporting of research studies. Transparent reporting enables readers to identify the strengths and weaknesses of research studies and subsequently to determine the quality of evidence that they offer.

Objective: To investigate the relation between methodological characteristics and the direction and magnitude of effects observed in case-control studies of gene-disease associations.

Methods: Articles were randomly selected from a database of published studies on genetic associations and other epidemiologic research pertaining to the human genome (the HuGE Literature Finder). The analysis evaluated 511 articles indexed in HuGENet in 2007. Gene-gene interaction studies and gene-environment interaction studies were excluded. Univariate and multivariate meta-regression analyses using a random effects model were used to assess the relationship between methodological characteristics and the direction and magnitude of genetic associations.

Results: The studies included in the analysis had been conducted in a total of 52 countries and were published in 220 journals (median impact factor 5.1). The multivariate meta-regression model of methodological characteristics was able to account for 17.2% of the between-study variance in the magnitude of gene-disease associations. Of the factors included in the multivariate regression model, the following tended to be associated with a smaller magnitude of effect: replication of a previously conducted study; nested case-control study design; individual matching of study participants; and reporting of sample size or of statistical power calculation. Moreover, the magnitude of effect tended to decrease as the number of controls increased. By contrast, studies that did not report the process of selecting control participants or that reported that the genotype distribution departed from Hardy–Weinberg equilibrium tended to be

associated with larger magnitudes of effect. Studies conducted in North America, Europe, and China had similar magnitudes of effect.

Conclusion: Within the constraints of limitations in reporting, a number of methodological features of gene-disease association studies are associated systematically with the magnitude of effect observed. This provides evidence to direct efforts to improve the reporting of research on genetic associations.

CHAPTER ONE

1. Background

The process of generating and testing hypotheses related to gene-disease associations has become more common since the publication of the human gene sequence and as a result of continuing improvements in the laboratory techniques available to genetic researchers. As a result, studies that investigate the association between genetic risk factors (whether multiple genotypes or single-gene mutations) and human disease are being published with increasing frequency. A well-developed body of knowledge about human genetic susceptibility is vital to continuing progress in identifying the causes of diseases influenced by genetic factors, investigating the natural history of these diseases, and developing gene-based therapies and prevention (1–10).

The effective use of knowledge related to gene-disease associations relies on the optimal conduct and reporting of research studies. Transparent reporting enables readers to identify the strengths and weaknesses of research and subsequently to determine the quality of evidence supporting any particular piece of knowledge in the field of gene-disease associations. In view of the increasing application of systematic reviews to genetic studies specifically and observational studies in general, the importance of adequate research reporting is receiving increased attention at the level of both primary studies and systematic reviews (11–18). Issues related to the methodological and analytic processes of conducting primary studies, such as research design, study population, study sample, control characteristics, similarities in methods of processing and handling laboratory samples for cases and controls, quality assurance measures (e.g., blinding of staff conducting the research), statistical methods, and selective outcome reporting may affect the validity of the results, making the strength of the evidence base questionable. Previous research indicates the importance of some of these characteristics for genetic studies (19–22).

Hardy–Weinberg equilibrium is considered an important factor to take into account when assessing the outcomes of gene-disease association studies (23, 24). It is defined by Mayo as follows:

> the state of the genotypic frequency of two alleles of one autosomal gene locus after one discrete generation of random mating in an indefinitely large population: if the alleles are A and a with frequencies p and q (= 1− p), then the equilibrium gene frequencies are simply p and q and the equilibrium genotypic frequencies for AA, Aa and aa are p^2, 2pq and q^2. (25)

According to Hardy–Weinberg equilibrium, in the absence of mutations the distribution of alleles and genotypes in the general population is stable from generation to generation. In general, it is expected that the control-group alleles and genotypes included in the investigation in gene-disease association studies would be in equilibrium and it is assumed that this would also be the situation in the general population (23, 25–28).

However, the extent to which methodological characteristics play a role in gene-disease association studies is still uncertain (11, 12, 19, 20, 29–35).

In an effort to assess the reporting of methodological characteristics and its relation to outcomes, Bogardus and colleagues (23) concluded that a substantial proportion of articles included in their review showed defects in basic research design and reporting despite the fact that they were published in four of the most widely read biomedical journals. Methodological factors such as replicability and objectivity of the findings, characteristics and delimitation of the comparison group, and the use of quantitative measures to present the results were shown to be inadequate, or inadequately reported. Because such deficiencies can lead to flawed conclusions related to molecular genetics and the subsequent application of erroneous information, researchers should be encouraged to disclose these methodological factors in their study reports (23). Such factors were examined by Peters and colleagues (36) with respect to a set of gene-disease association studies; their systematic review and re-analysis of banked genetic materials showed that the quality of the studies was not uniform and that the related

outcomes were infrequently reproducible. The authors emphasized the importance of reporting methodological factors to achieve more reliable gene-disease association outcomes (36). In another assessment of the quality of gene-disease association studies specific to the topic of sepsis, Clark and colleagues (37) found that methodological deficiencies in such studies included features such as inadequate control group selection; failure to provide a statistical power calculation; inadequate blinding; failure to use a quality-control measure to assure validity of the genotyping process; lack of independent replication of the association finding; flawed case definition; and flawed conduct and reporting of the statistical analysis. Clark and colleagues recommended that investigators report on these methodological factors and that peer reviewers and journal editors use a checklist to assess the quality of gene-disease association studies (37).

In a similar effort to assess the reporting of case-control studies in the field of psychiatry, including genetic studies, Lee and colleagues reported that the studies included in their review, which were published during 2001–2002, suffered from selection bias and the poor reporting of other factors related to the recruitment of study participants, blinding of the investigators to the participants' health status, and matching of cases and controls; moreover, these researchers concluded that the quality of reporting was worst in genetic studies (38). They reported that the status of reporting on methodological factors differed according to journal of publication and subspecialty within psychiatry, which may be an indication that the quality of reporting of methodological factors varies according to disease specialty in general (38).

Cancer and pre-cancerous diseases have been shown to be subject to more accurate diagnosis (case definition) in comparison with other diseases and, relative to the investigation of non-cancerous conditions, to use different sampling and genotyping processes (39, 40). Thus, it might be anticipated that gene-disease association studies related to cancer and pre-cancerous diseases could be associated with magnitudes of effect that differ from those found in studies that report on non-cancerous diseases.

In a review of genetic association studies conducted between 2001 and 2006, Yesupriya and colleagues found that reporting on sample size estimation, the use of unrelated study participants, and the replication of study findings had showed improvement during that period (21). Although the results of their review indicated that the quality of reporting in genetic association studies is improving, little is known about the association between individual methodological factors and the relevant study outcomes. An investigation of such associations would provide evidence-based knowledge on the effect that reporting on each methodological factor might produce on gene-disease association findings. Such investigation may, in turn, encourage researchers to improve their reporting process.

International collaborative efforts to improve the reporting of studies are an emerging topic of research. Given the importance of transparent reporting of studies by investigators, and in view of the fact that incomplete reporting can bias results, reporting guidelines have been developed to ensure that certain types of information are included in research reports. An early example of this approach is the CONSORT statement for reporting two-group parallel randomized trials. The CONSORT statement is available in ten languages other than English. It includes a 22-item checklist and a flow diagram to improve the reporting of trials and the assessment of trial progress (41, 42). Numerous guidelines have been developed for the reporting of various types of studies (42–45). Among these is the STROBE (Strengthening the Reporting of OBservational studies in Epidemiology) Statement (45) for improving the reporting of observational epidemiological studies (specifically: cross-sectional, case-control, and cohort studies). Among recently published efforts to improve the conduct and reporting of gene-disease association studies (15, 16, 22, 24, 29, 31, 40, 46–64) is STREGA (STrengthening the REporting of Genetic Associations), which is an extension of the STROBE statement. STREGA provides a 22-item checklist to improve the transparency of reporting in genetic association studies, with the ultimate aim of improving the utilization of the knowledge that results from this research (64).

The aim of improving the research process related to gene-disease association studies is supported by national and international groups. Among these is the Human Genome Epidemiology Network (HuGENet), whose focus is the relation between human health and genetic variants (19, 65). One objective of HuGENet is to improve human genome research and its application at various levels. This includes the large HuGENet literature database, which is built from references extracted from PubMed and contains over 30 000 research studies referencing over 3000 genes and over 1900 health outcomes and diseases as of the end of 2007 (65). This database helps researchers to identify the published literature related to gene-disease associations (65) and was used to identify the sampling frame for the studies included in this thesis.

Given the complex features of gene-disease association studies, detailed investigations of the reporting process are needed to determine the potential associations between specific methodological characteristics and potential bias in results. An association between a particular genetic variant and a disease can be positive, inverse, or absent, and can be masked or augmented by biases or the play of chance. So far, however, only a very small proportion of gene-disease associations has been replicated (12, 32, 66, 67), and the prior probability of any association between the gene and the disease under investigation is very low (68). Further, the magnitude of associations replicated in studies of candidate genes has been modest, with odds ratios in the order of 0.7–1.5 (66). In genome-wide association studies (sometimes considered to be "agnostic" in the sense that no additional weighting is given to putative associations for which there is *a priori* mechanistic evidence), the odds ratios of replicated associations have been around 1.1 (67, 69, 70). Therefore, the *a priori* assumption is made that the major influences on the genetic associations observed will be non-causal. Nevertheless, it has been recognized that true associations may be one source of difference in the magnitude of odds ratios across studies, and this likelihood was kept under consideration through the different stages of this research.

Most studies investigating gene-disease associations use a case-control design (65). Therefore, this thesis focused on case-control studies, including those nested within cohort studies. In an effort to provide evidence based on the latest available studies published within an identified time frame, the sampling process involved only studies indexed in HuGENet in 2007. Articles related exclusively to family-based association studies (which use relatives of cases, such as unaffected siblings, as controls) were not included in the present study in view of aspects of the sampling and analytic process that differ from those of general case-control studies. Family-based association studies represent only a small percentage of case-control articles from the HuGENet database investigating gene-disease associations (50, 65, 71–74).

Genome-wide association studies have become feasible with the latest advances in genotyping laboratory technologies, which enable researchers to investigate the association between hundreds and thousands of genotypes and a specific disease, as opposed to the much lower number of genotypes that can be investigated in classical gene-disease association studies. Although the technology for conducting such studies has become increasingly available, relatively few diseases and conditions (e.g., type II diabetes, gastroenterological illnesses such as inflammatory bowel disease, and psychiatric illnesses) had been investigated in this manner at the time the research for this thesis was being carried out. Furthermore, thus far the methodological and analytic processes associated with genome-wide studies have varied widely from one study to another, raising concerns about the reliability of their outcomes. Adding to this consideration is the fact that these studies still represent only a small proportion of the published studies in comparison with the widely used candidate gene-disease association studies (67, 75–81). Thus, genome-wide association studies were not included in this investigation, with the intention of minimizing heterogeneity in relation to methodologies, analytical processes, and outcomes.

It is anticipated that the findings of this research will assist researchers conducting case-control studies of gene-disease associations as well as those conducting

systematic reviews of such studies to identify methodological factors that influence the outcomes of original studies and of subsequent reviews. It is also hoped that the present analysis will be of help to future researchers in the development of evidence-based quality-assessment criteria for reporting observational studies related to gene-disease associations (82–86).

1.1 Research aim and objectives

1.1.1 Aim

To investigate the relation between methodological characteristics and the direction and magnitude of effects observed in case-control studies of gene-disease associations.

1.1.2 Objectives

1. To identify and verify the feasibility of extracting methodological characteristics and related information from a sample of gene-disease association studies.

2. To conduct meta-epidemiologic analyses using separate analyses for each characteristic in order to investigate the association between methodological characteristics and effect estimates.

3. To conduct a multivariate analysis to determine the association between methodological characteristics and effect estimates.

CHAPTER TWO

2. Methods – Part I

The aim of this investigation was to examine the relation between methodological characteristics and the direction and magnitude of effects observed in case-control studies of gene-disease associations. The primary methodological process originally proposed for the extraction of variables is described in this chapter, along with the originally proposed variable list. The modifications that were undertaken are also described in this chapter, while the complete methodological process is described in full detail in Chapter 3 (under Methods – Part II, 3.1–3.5).

The overall design was tested in a pilot study conducted in stages. This was done in an effort to determine the most suitable method of conducting the study using an independent sample from that used for the main research. The pilot study was used to test the process and feasibility of variable extraction and to determine whether any modifications to the proposed variable list were required. The pilot study also provided training for the assessors in using the data collection instruments and ensured that the data extractors were in agreement in their interpretation of the data extraction process. Additionally, the pilot study worked through any "bugs" in the Systematic Review Software (SRS), an Internet-based software that allows reviewers to conduct independent extraction of the data related to a systematic review project.

- **Search strategy for identification of studies:** The sampling frame comprised studies investigating at least one gene-disease association, indexed in HuGENet in 2007 (further details, section 3.2).

- **Types of gene-disease associations:** All types of gene-disease associations were to be included regardless of genotype or disease type (further details, section 3.1.1).

- **Outcome measure:** The outcome measure was the reported measure of association (e.g., odds ratio) along with the reported uncertainty measure (e.g., 95% confidence interval or *p*-value) of the gene-disease association considered in the primary

analysis. Where multiple primary outcomes were reported, the one reported in the study abstract was selected. If more than one primary analysis was reported in the abstract, one was selected at random. When the measure of association was not reported or unclear, but the data allowed for the calculation of a measure of association, this measure of association along with the uncertainty measure was calculated (further details, section 3.3.3).

- **Selection of studies:** Simple computer-generated random sampling was used to select the citations included in the pilot study. Two reviewers assessed each study independently. The title, abstract, and keywords of every record retrieved were reviewed. The full text of relevant articles was retrieved for more detailed examination to ensure eligibility of the included articles. Disagreements between the reviewers were resolved through consensus and third-party arbitration, as required.

- **Data extraction:** Two reviewers extracted details about the included studies using an electronic data extraction form developed by the investigator. Data extraction was completed independently. Disagreements were resolved through consensus and third-party arbitration, as required. Table 2.1 lists the preliminary data extraction items selected after a review of pertinent literature and the STROBE statement, and taking the opinions of experts in the field of genetic research and systematic reviews into consideration (supervisors and advisors). Further modifications were made after analysis and discussion of the results of the pilot study with experts in the field.

2.1 Pilot study (stage one)

The first stage of the pilot study was conducted using 50 reports (87–136) selected by means of the same sampling process proposed for the main research. Five studies were excluded from the pilot study. Three of these were gene-environment interaction studies (88–90), one was a gene-gene interaction study, (87) and the fifth was a study examining the association between genetic variation and normal physiology (91). Table 2.2 presents the weighted kappa statistic for each question on the data extraction form that used categorical outcomes. After this process, the results of the

pilot study were discussed by the investigator in three meetings with the thesis supervisors and experts in the field of genetic epidemiology and systematic reviews. Table 2.3 shows the list of questions that were proposed as requiring modification or deletion from the preliminary list, while Table 2.4 lists the additional variables that were proposed. The rationale for modifying the variables listed in Table 2.3 was a low kappa score. During the discussion of results, it became apparent that low kappa scores were associated with difficulties and misinterpretation in extracting the information on the variables. For example, the variable relating to individual matching of cases and controls required refinement; thus, this variable was kept but the categories of response were changed from "matched" and "not matched" to "individually matched" (e.g., 1:1 or 1:2 matching), "frequency matched," and "not matched." This variable was tested further in the second stage of the pilot study.

Other variables were difficult to extract as a result of incomplete reporting of the required information in the articles included in the pilot study (n = 45). This was evident, for example, in the frequency of responses to the question of whether the process of genotyping, handling the samples, and transportation and storage was similar for cases and controls ("Yes," "No," "Cannot tell"). Data from the included studies showed incomplete reporting, such that not all of the components of the question could be answered clearly, leading to variability in the responses of the two reviewers.

Another important factor that was discussed after completion of the first pilot study was that independent testing for departure from Hardy–Weinberg equilibrium (HWE) in the control group could not be conducted, since a non-negligible portion of the studies did not provide the information that would have enabled such a calculation (e.g. 2 × 3 tables); adding to this difficulty was the large number of genetic markers tested in each study, which also made such testing unfeasible. To test for the effect of reporting on departure from HWE, other variables were introduced and were subsequently tested in the second stage of the pilot study (Table 2.3).

Other proposed variables (Table 2.4) required more discussion of the process of review as opposed to changes in their content (e.g., whether the association was claimed to be a first report or a replication, or whether this was not reported).

Table 2.1: Variables proposed for inclusion in the analysis before the pilot study was conducted

A. Study type and characteristics

1. Type of case-control study (classical / nested)
2. Whether cases and controls were individually matched (matched, not matched)
3. Country of origin of research study (the category "multi-centre" to be used if more than one country was involved)
4. Journal type
5. Impact factor based on 2006 data
6. Whether the association was claimed to be a first report or a replication (first report / replication / combination or not reported)
7. Disease category (allergy / andrology / breast / cardiology / dentistry / dermatology / ear, nose, and throat / endocrinology / gastroenterology / gynecology and obstetrics / hematology / hepatology / infectious diseases / metabolic disorders / nephrology / neurology / ophthalmology / orthopedics / prostate / psychiatry / respiratory / rheumatology / thyroid / urology / vascular)
8. Whether the study investigated an association of a gene with cancer or a pre-cancerous lesion (yes / no)
9. The gene included in the analysis
10. The single nucleotide polymorphism selected in the study (free-text answer)

B. Characteristics of study population

1. Number of participants in each group of cases and controls
2. Whether the control group was population-based from an identified sample frame; population-based without detail as to the sampling frame; or hospital-based or some other specific group; not clear or cannot tell

C. Methodological characteristics

1. Whether the processes for genotyping, handling the samples, and transportation and storage were similar for cases and controls (yes / no / cannot tell)
2. Whether the process of validation or calibration of genotyping was blinded for cases and controls (yes / no / cannot tell)
3. Whether the genotyping of cases and controls was performed in the same laboratory (yes / no / cannot tell)
4. Whether any method of quality assurance was reported, e.g., blinding (yes / no)

D. Outcomes analysis

1. What was the primary reported measure of association and the corresponding uncertainty measure?
2. Were 2 × 2 or 2 × 3 tables given for the characteristics of genotyping for cases and controls?
3. What genetic model was used with the odds ratio? (dominant / co-dominant [per allele] / recessive / AA versus aa / A versus a / other / unclear)
4. Were the statistical methods for adjustment for covariates specified? (yes / no or not applicable)
5. Did the researchers test for deviation from the Hardy–Weinberg equilibrium in the control group? (yes /no)
6. If the study tested for deviation from the Hardy–Weinberg equilibrium in the control group, what was the result?

Table 2.2: Kappa statistic for questions reporting categorical outcomes in the pilot study (stage I), (n = 45)

Questions that used categorical outcomes in the data extraction form	Kappa statistic (95% CI)
What type of case-control study was used? (classic / nested)	0.71 (0.49–0.94)
Was individual matching used for cases and controls? (matched / not matched)	0.44 (0.18–0.69)
What was the country of origin of the research study (the category "multi-centre" to be used if more than one country was involved)	1.00 —
Was the association claimed to be the first reported or a replication (first reported / replication / combination or not reported)	0.62 (0.41–0.82)
Did the study investigate an association of a gene with cancer or a pre-cancerous lesion? (yes / no)	1.00 —
What was the disease category? (allergy / andrology / breast / cardiology / dentistry / dermatology / ear, nose, and throat / endocrinology / gastroenterology / gynecology and obstetrics / hematology / hepatology / infectious diseases / metabolic disorders / nephrology / neurology / ophthalmology / orthopedics / prostate / psychiatric / respiratory / rheumatology / thyroid / urology / vascular)	0.89 (0.78–1.00)
What was the composition of the control group? (population-based from an identified sample frame / population-based without detail as to the sampling frame / hospital-based or some other specific group / not clear or cannot tell)	0.56 (0.34–0.77)
Was the process of genotyping, handling the samples, transportation and storage similar for cases and controls? (yes / no / cannot tell)	0.59 (0.30–0.88)
Was the process of validation or calibration of genotyping blinded for case and controls? (yes / no / cannot tell)	0.71 (0.48–0.94)
Was the genotyping of cases and controls performed in the same laboratory? (yes / no / cannot tell)	0.62 (0.33–0.92)
Was any method of quality assurance reported? (yes / no)	0.96 (0.76–1.00)
What was the measure of association reported in the abstract of the study? (odds ratio, 2 × 2 table, 2 × 3 table)	0.93 (0.83–1.00)
What genetic model was used with the odds ratio? (dominant / co-dominant [per allele] / recessive / AA versus aa / A versus a / other / unclear)	0.52 (0.32–0.72)
What was the reported measure of uncertainty for the odds ratio? (confidence interval / *p*-value / standard error / variance)	0.65 (0.42–1.00)
Did the study report any testing for deviation from the Hardy–Weinberg equilibrium in the control group? (yes / no)	0.95 (0.83–1.00)
Were the statistical methods for adjustment of the covariates specified? (yes / no or not applicable)	0.90 (0.76–0.97)

CI = confidence interval

Table 2.3: Proposed variables to be modified or deleted from the data extraction form on the basis of the pilot study results and experience gained by the assessors

Which gene was included in the analysis?
Which single nucleotide polymorphism was selected in the study? (free text answer)
Was the process of genotyping, handling the samples, and transportation and storage similar for cases and controls?
Was the process of validating or calibrating the genotyping blinded for cases and controls?
Was genotyping performed in the same laboratory for cases and controls?
What was the result for the Hardy–Weinberg equilibrium in the control group, if reported? (free text answer)

Table 2.4: Proposed variables to be added to the data extraction form on the basis of the pilot study results and experience gained by the assessors

How many genes were included in the analysis?
How many genetic markers were tested?
What was the source of the data used in the study? (primary collection and analysis of the data / building on pre-existing data by collecting more information or blood samples / secondary analysis of pre-existing data / cannot tell)
Was the process of handling the sample and genotyping described? (yes for cases and controls / yes for cases only / yes for controls only / neither / cannot tell)
What was the specific reported number of participants in the case and control groups associated with the extracted outcome?
Did the study report any result of calculating study power or sample size? (yes, no)
Did the study report any relatedness between the case and control groups (blood relation or relatives) for the specific reported outcome? (yes, no, unclear))
If deviation from the Hardy–Weinberg equilibrium was reported in the control group, what was the result? (all included genotypes were in equilibrium / some included genotypes were in equilibrium [including the extracted outcome] / some included genotypes were in equilibrium [not including the extracted outcome] / genotypes were not in equilibrium or not clear / Hardy–Weinberg equilibrium was not reported)
Did the data allow for the calculation of deviation from the Hardy–Weinberg equilibrium for the control group, e.g., by providing a 2×3 table, *p*-value, or inbreeding coefficient for the extracted outcome?

2.2 Pilot study (stage two)

The purpose of the second stage of the pilot study was to test the suggested modifications to the data extraction form. This stage was conducted using 20 reports (137–156) that investigated gene-disease associations selected randomly using the same sampling process that was proposed for the main research and the first pilot study. Two gene-gene interaction association studies (137, 138) and one genome-wide association study (139) were excluded.

Table 2.5 presents the calculated weighted kappa statistic for each question in the data extraction form that used categorical outcomes.

The results of the second stage of the pilot study were also discussed with the supervisors and with experts in the field of genetic epidemiology in the United Kingdom and Greece. In light of these discussions, the extraction process was finalized. One modification that was adopted concerned the extraction process for the measure of association along with its uncertainty level. This was to ensure agreement in the independent blinded extraction of variables by the two reviewers, thus providing a more systematic approach that might lead to more valid inferences regarding associations between outcomes and methodological characteristics.

Taking these objectives into consideration, the extraction of the reported measure of association (e.g., odds ratio [OR]) along with the reported uncertainty measure (e.g., 95% confidence interval [CI] or *p*-value) was changed to the following process:

- For studies that provided more than one measure of association, the reported measure of association with the most extreme reported uncertainty measure (in the study abstract) was extracted.

- The extraction process for the measure of association was directed toward ORs with a reported uncertainty measure (e.g., 95% CI or *p*-value). If the OR was not reported, the extraction was directed toward outcomes from a 2×2 table that represented the number of cases and controls with and without the genetic marker(s) under investigation. For studies that did not report outcomes as ORs or in 2×2 tables, the extraction was directed toward outcomes for cases and controls

presented in the form of 2 × 3 tables; in such cases, for each group were extracted the genotyping sequences AA, Aa, and aa that were associated with different types of uncertainty measure, such as *p*-value, chi-square, and standard errors of the mean.

- The measure of association was to be related to the overall case-control investigation when this was reported in the abstract. When measures of association were presented for subgroups only, the reviewers extracted the one with the most extreme reported uncertainty measure.

- If the paper reported independent analyses for more than one study, then the reviewers extracted the one with the most extreme reported uncertainty measure (e.g., 95% CI or *p*-value).

- If the paper did not report any measure of association in the abstract, then the entire article was reviewed to identify the reported measure of association (e.g., OR) along with the reported uncertainty measure (e.g., 95% CI or *p*-value) according to the same systematic process already described.

- When either the measure of association or the genetic model or both were unclear, but the data allowed for the calculation of a measure of association (e.g., OR), this measure of association along with the uncertainty measure (e.g., 95% CI or *p*-value) was to be calculated.

The data extraction form was modified slightly and finalized. Table 2.6 lists the questions that were deleted from the extraction form.

Table 2.5: Kappa statistic for questions reporting categorical outcomes in the pilot study (stage II), (n = 17)

Question	Kappa statistic (95% CI)	
What type of case-control study was used? (classic / nested)	0.85	(0.70–0.95)
Was matching used for cases and controls? (individually matched [e.g., 1:1 or 1:2] / frequency matched for one or several factors / not matched)	0.75	(0.73–0.90)
What was the country of origin of the research study (the category "multi-centre" to be used if more than one country was involved)	0.92	(0.77–1.00)
Was the association claimed to be a first report, or a replication (first report / replication / combination or not reported)	0.82	(0.71–0.91)
Did the study investigate an association of a gene with cancer or a pre-cancerous lesion? (yes / no)	1.00	—
What was the disease category? (allergy / andrology / breast / cardiology / dentistry / dermatology / ear, nose, and throat / endocrinology / gastroenterology / gynecology and obstetrics / hematology / hepatology / infectious diseases / metabolic disorders / nephrology / neurology / ophthalmology / orthopedics / prostate / psychiatry / respiratory / rheumatology / thyroid / urology / vascular)	0.80	(0.77–0.92)
What was the composition of the control group? (population-based from an identified sample frame / population-based without detail as to the sampling frame / hospital-based or some other specific group / not clear or cannot tell)	0.78	(0.70–0.97)
What was the source of the data used in the study? (primary collection and analysis of the data / building on pre-existing data by collecting more information or blood samples / secondary analysis of a pre-existing data / cannot tell)	0.76	(0.69–0.89)
Was the process of handling the sample and genotyping described? (yes for cases and controls / yes for cases only / yes for controls only / neither / cannot tell)	0.72	(0.65–0.93)
Was any method of quality assurance reported, e.g., blinding? (yes, no)	0.84	(0.51–1.00)
Did the study report any result of calculating study power or sample size? (yes, no)	0.82	(0.49–1.00)
Did the study report any relatedness between the control and cases group (blood relation or relatives) for the specific reported outcome? (yes, no, unclear)	0.73	(0.60–0.96)
Were the statistical methods for adjustment for the covariates specified? (yes / no or not applicable)	0.96	(0.76–1.00)
What was the measure of association reported in the abstract of the study? (odds ratio / 2 × 2 table / 2 × 3 table)	0.65	(0.45–1.00)
What genetic model was used with the odds ratio? (dominant / co-dominant [per allele] / recessive / AA versus aa / A versus a / other / unclear)	0.45	(0.25–0.89)
What was the reported measure of uncertainty for the odds ratio? (confidence interval / *p*-value / standard error / variance)	0.88	(0.58–1.00)
Did the study report any testing for deviation from the Hardy–Weinberg equilibrium in the control group? (yes, no)	1.00	—
If deviation from the Hardy–Weinberg equilibrium was reported in the control group, what was the result? (all included genotypes were in equilibrium / some included genotypes were in equilibrium [including the extracted outcome] / some included genotypes were in equilibrium [not including the extracted outcome] / genotypes were not in equilibrium or not clear / Hardy–Weinberg equilibrium (HWE) was not reported)	1.00	—
Did the data allow for the calculation of deviation from the Hardy–Weinberg equilibrium for the control group, e.g., by providing a 2 × 3 table for the extracted outcome? (yes, no)	1.00	—

CI = confidence interval

Table 2.6: Proposed variables to be deleted from the data extraction form on the basis of the pilot study results and experience gained by the assessors

Outcomes extraction: What model was used with the odds ratio? (dominant / co-dominant [per allele] / recessive / AA versus aa / A versus a / other / unclear)

2.3 Final data extraction form

A. Study design and characteristics

1. What type of case-control study was used? (classic / nested)
2. Was matching used for cases and controls? (individually matched / frequency matched for one or several factors / not matched)
3. What was the country of origin of the research study? (the category "multi-centre" to be used if more than one country was involved)
4. Journal (free text answer)
5. Was the association claimed to be a first report, or a replication? (first report / replication / combination or not reported)
6. How many genes were included in the analysis?
7. How many genetic markers were tested?
8. Did the study investigate an association of a gene with cancer or a pre-cancerous lesion? (yes / no)
9. What was the disease category? (allergy / andrology / breast / cardiology / dentistry / dermatology / ear, nose, and throat / endocrinology / gastroenterology / gynecology and obstetrics / hematology / hepatology / infectious diseases / metabolic disorders / nephrology / neurology / ophthalmology / orthopedics / prostate / psychiatric / respiratory / rheumatology / thyroid / urology / vascular)

B. Population and methodological characteristics

1. What was the final reported number of participants in the case and control groups?
2. What was the composition of the control group? (population-based from an identified sample frame / population-based without detail as to the sampling frame / hospital-based or some other specific group / a combination of population and other specific group / not clear or cannot tell)
3. What was the source of the data used in the study? (primary collection and analysis of the data / building on pre-existing data by collecting more information or blood samples / secondary analysis of pre-existing data / cannot tell)
4. Was the process of handling the sample and genotyping described? (yes for cases and controls / yes for cases only / yes for controls only / neither / cannot tell)
5. Was any method of quality assurance reported, e.g., blinding? (yes / no)
6. Did the study report any result of calculating study power or sample size? (yes / no)
7. Did the study report any relatedness between the control and cases groups (blood relation or relatives) for the specific reported outcome? (yes / no / unclear)

C. Outcomes analysis processes and Hardy–Weinberg equilibrium

1. What was the measure of association reported in the abstract of the study? (e.g., odds ratio, 2 × 2 table, 2 × 3 table)
2. What was the specific reported number of participants in the case and control groups associated with the extracted outcome?

3. If an odds ratio was reported, what was:

    a. The value reported?

    b. The reported measure of uncertainty? Report the numeric measure of uncertainly that was used as well (confidence interval, *p*-value, standard error and variance)

4. If a 2 × 2 table was used, report:

    a. The numbers of cases with and without the genetic exposure and the numbers of controls with and without the genetic exposure.

    b. The reported measure of uncertainty? Report the numeric measure of uncertainly that was used as well (confidence interval, *p*-value, standard error and variance)

5. If a 2 × 3 table was used, report:

    a. The numbers of cases and controls with AA, Aa, and aa.

    b. The reported measure of uncertainty? Report the numeric measure of uncertainly that was used as well (confidence interval, *p*-value, standard error and variance)

    c. The intended association that was investigated (e.g. AA Vs Aa+aa, AA Vs Aa, AA Vs aa, etc)

6. Were the statistical methods for adjustment for the covariates specified? (yes / no or not applicable)

7. Did the study report any testing for deviation from Hardy–Weinberg equilibrium in the control group? (yes / no)

8. If deviation from Hardy–Weinberg equilibrium was reported in the control group, what was the result? (all included genotypes were in equilibrium / some included genotypes were in equilibrium [including the extracted outcome] / some included genotypes were in equilibrium [not including the

extracted outcome] / genotypes were not in equilibrium or not clear / Hardy–Weinberg equilibrium was not reported)

9. Did the data allow for the calculation of deviation from Hardy–Weinberg equilibrium for the control group, e.g., by providing a 2 × 3 table, *p*-value or inbreeding coefficient for the extracted outcome? (yes / no)

D. Variables that were generated from the aforementioned extracted variables

1. Journal impact factor as reported in 2006 (157, 158).
2. Ratio of genetic markers per gene tested (equal to the number of genetic markers tested per gene).
3. Case/control ratio (ratio of the final included number of cases to the final number of included controls).

CHAPTER THREE

3. Methods–Part II

3.1 Selection criteria

3.1.1 Types of studies

The sampling frame comprised studies investigating at least one gene-disease association indexed in HuGENet in 2007. In view of the fact that most studies of gene-disease associations use a case-control design, and in an effort to enhance the homogeneity of the included studies, this research was limited to case-control designs, including nested designs (65). Studies of gene-environment and gene-gene interactions were not included. These studies account for a minority of published studies, (84) which raised concern that the number of studies identified might have been insufficient to detect the influence of their various methodological characteristics on outcomes. This was of particular concern given the potential for explanatory analysis, selective reporting, and considerable variation in analytic approach in gene-environment and gene-gene interaction studies (85). Taking these factors into consideration, and after extensive discussion with experts in the field of systematic reviews and genetic epidemiology, it was decided that articles that reported exclusively family-based analyses and those that reported genome-wide association studies would not be included. This was intended to increase the homogeneity of the included studies and thus enhance the ability to detect the effect of each of the investigated methodological factors on the gene-disease association outcome.

3.1.2 Types of gene-disease associations

All types of gene-disease association were included, regardless of the genotype or disease type.

3.2 Search strategy for the identification of studies

Studies related to gene-disease associations were extracted from the HuGE Literature Finder, a comprehensive database maintained by HuGENet (the Human Genome

Epidemiology Network), which contains over 30 000 research studies, referencing over 3000 genes and over 1900 health outcomes/diseases as of the end of 2007 (65, 82). The database is developed from references extracted from PubMed (which contains all studies indexed in MEDLINE, and hence all those related to gene-disease associations). The database is curated in that a researcher based in the CDC's National Office of Public Health Genomics who is familiar with the eligibility criteria for human genome epidemiology reviews each title and abstract (or in a few cases, the full text), considering the following inclusion criteria:

- Human study population
- Genotype measured or inferred at one or more loci
- Epidemiologic study design: cohort, case-control, case only, clinical trial
- Population-based analysis, e.g. association with disease (other analyses are considered in the database but are not pertinent to this thesis)

It has the following exclusion criteria:

- No human data: e.g., study of gene function in animal model
- No population-based analysis: e.g., linkage study in high-risk family, case report.

The HuGENet database helps researchers locate the published literature related to gene-disease associations, and allows investigators to identify studies broadly, such as by study type, disease category, and year of publication. In an effort to provide evidence based on the latest available data, the process of extraction was limited to studies published in journals indexed in the HuGENet database during 2007 (65).

3.2.1 Language restrictions

Only studies published in English were extracted. Although it is unknown whether such a restriction introduces bias in the estimate of effectiveness of gene-disease association studies, at least two studies have shown that such bias is not present when clinical effectiveness reviews are restricted to English-language

publications (159, 160). A further consideration is that recent data suggest that the possibility cannot be dismissed that there is selective reporting of genetic epidemiology studies originating from Asian countries, mainly China (161). In view of these observations, this study was restricted to those published in English.

3.2.2 Sample size calculation

The sample size calculation was based on a review of published studies investigating the effect of study characteristics on magnitude and direction of the reported effect (e.g., odds ratio) (159, 160). In an investigation of the association between study characteristic and reported effect size, Moher and colleagues (159) found that the reported median effect size was 0.5 (i.e., log odds ratio of −0.7 with a standard deviation of 1.13). In subsequent work, these investigators considered a 25% change in the overall pooled log odds ratio as an indication of effect modification by study characteristic (e.g., language of publication), assuming a random effect, a two-sided t-test, 95% confidence interval, and 80% power (160). Previous meta-analyses of gene-disease associations have indicated more marked contrasts in the results of individual studies (162). In light of this earlier methodological research, for the present study it was calculated that a total sample size of 484 reports would be required to detect a difference of 25% in the effect size exerted on gene-disease associations by a methodological characteristic. On the basis of the pilot study, the sample size was increased by 10% to 533 reports, to allow for the exclusion of ineligible studies after the preliminary determination of eligibility based on a review of the study title and abstract.

3.3 Methods of the review

3.3.1 Selection of studies

Simple computer-generated random sampling was used to select the 533 citations included in this thesis. The selection process was assessed in the pilot study. If the randomization process had selected an article previously used in the pilot study or it was not available as a full text in English, it was replaced by either the next article in the list of citations or the previously listed one; the next or previous listed article was selected alternately to ensure randomization and reduce selection

bias. Two reviewers assessed each study independently. The title, abstract, and keywords of every record retrieved were reviewed. The full text of relevant articles was retrieved for more detailed examination to ensure eligibility of the included articles. Disagreements between the reviewers were resolved by consensus and discussion with a third party when required. All duplicate citations were removed (see Figure 3.1 for the sampling process). A final list of 511 citations was uploaded to TrialStat: SRS, an Internet-based system for conducting systematic reviews (163). A data extraction form was developed using the system and was used for the review process and data entry.

3.3.2 Data extraction

Two reviewers extracted details regarding the included studies using an electronic data extraction form developed by the investigator after a review of the pertinent literature, taking the opinions of experts in the field of genetics research and systematic reviews into consideration. It had been tested and modified as required during the process of conducting the pilot study. Data extraction was completed independently by the two reviewers. Disagreements were resolved through consensus and third-party arbitration, as required.

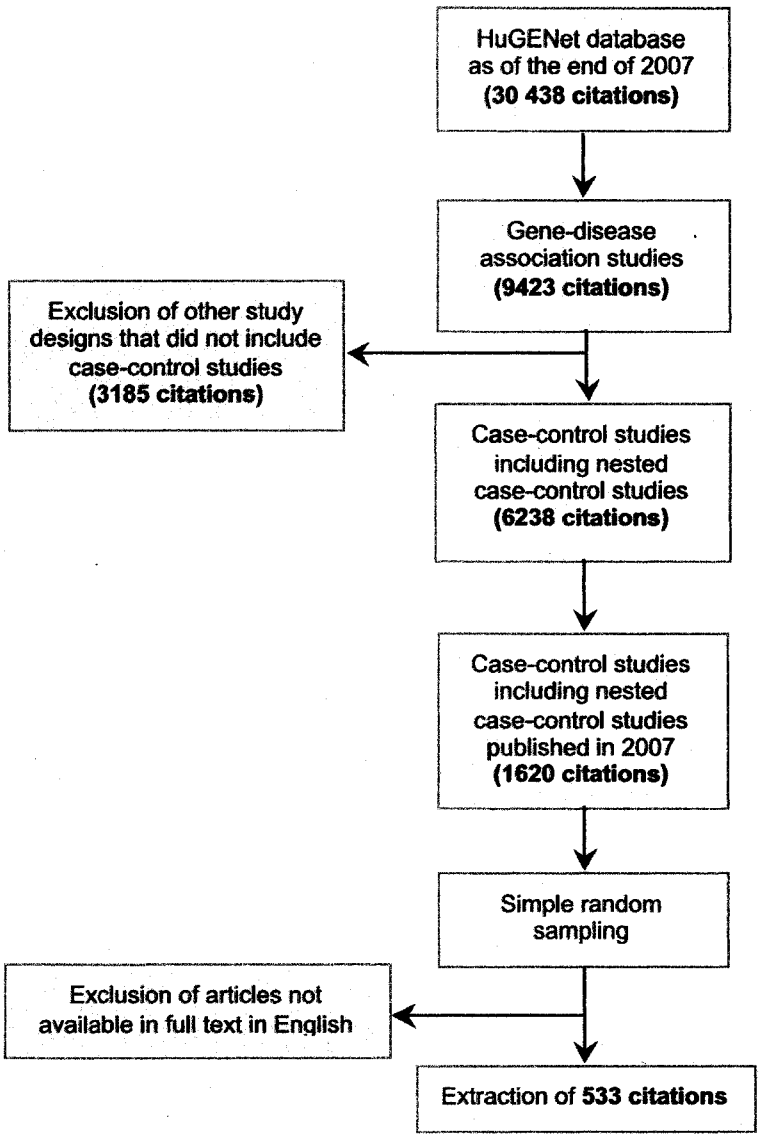

Figure 3.1: Sampling process for the citations included in the meta-analysis

3.3.3 Outcome measure

The outcome measure extracted for this analysis was the reported measure of association (e.g., odds ratio) along with the reported uncertainty measure (e.g., 95% confidence interval or *p*-value) of the genetic model considered in the primary analysis. In light of the experience gained from the pilot study, and after conducting several meetings with experts in the field of systematic reviews and genetic epidemiology, the process of extracting the reported measure of

association (e.g., odds ratio) along with the reported uncertainty measure (e.g., 95% confidence interval or *p*-value) was refined. The intention was to ensure a high level of agreement in the independent blinded extraction of all of the variables by the two reviewers and to provide a more systematic process of extraction that might lead to more valid inferences regarding the influence of methodological variables on outcome. With these objectives in mind, the extraction of the reported measure of association (e.g., odds ratio) along with the reported uncertainty measure (e.g., 95% confidence interval or *p*-value) was changed from depending, in part, on a random process to the following systematic approach:

- When more than one measure of association was given, the one with the most extreme reported uncertainty measure (in the study abstract) was extracted.
- The extraction process was directed toward odds ratios with reported uncertainty measures (e.g., 95% confidence interval or *p*-value). If the odds ratio was not reported, the extraction was directed toward outcomes from a 2×2 table that represented the number of cases and controls with and without the genetic marker or markers under investigation. For studies that did not report any odds ratio or 2×2 table outcomes, the extraction was directed toward outcomes presented in the form of a 2×3 table for cases and controls in which, for each group, the genotyping sequences AA, Aa, and aa that were associated with different types of uncertainty measure (such as *p*-value, chi-square, and standard errors) were extracted.
- The measure of association extracted was the one related to the overall case-control group investigated when this was reported in the abstract. If measures of association were presented for subgroups only, the reviewers extracted the one with the most extreme reported uncertainty measure.

- If the paper reported independent analyses for more than one study, the reviewers extracted the one with the most extreme reported uncertainty measure (e.g., 95% confidence interval or *p*-value).
- If the paper did not report any measure of association in the abstract, then the entire article was reviewed to identify the reported measure of association (e.g., odds ratio) along with any reported uncertainty measure (e.g., 95% confidence interval or *p*-value) according to the systematic process already described.
- When the measure of association and/or the genetic model was unclear, but the data allowed for the calculation of a measure of association (e.g., odds ratio), this measure of association along with the uncertainty measure (e.g., 95% confidence interval or *p*-value) was calculated.

3.3.4 Final data extraction form

The final data extraction form and the derived variables from the included questions are given in Chapter 2 (Methods – Part I, 2.3).

3.4 Data management

The Internet-based Systematic Review Software system (TrialStat: SRS) was used for the review process and data entry (163). After data extraction and review by the two reviewers had taken place and agreement was reached on all of the extracted records, the main investigator transferred the data from TrialStat:SRS to the SAS 9.1 (Statistical Analysis System version 9.1) and Comprehensive Meta Analysis software systems that were used for the analyses. To ensure optimum quality of the transferred data, 10% of the data transferred to both software systems were double-checked with the data extracted originally in TrialStat:SRS.

3.5 Statistical analysis

Descriptive and graphical presentations of the data were used to summarize and investigate the associations between the different variables and the outcomes of interest. To the broad categories of disease given in the final list (see Section 2.3), specific categories for thyroid, breast, and prostate diseases were added, as these are frequently investigated in the gene-disease association literature and pertain to more or less independent organs from the medical point of view.

The extracted outcomes were used to generate a common effect measure (regression coefficient) and measure of uncertainties, allowing further analysis of each study using the meta-regression model. The log odds ratio, as a reflection of the regression coefficient, was preferred to an odds ratio for the presentation of results for three reasons. First, the log odds ratio offers a unified presentation of results when displayed in relation to the different extracted methodological characteristics (both categorical and continuous variables); scatter plots that display the outcomes of a gene-disease association against a continuous methodological characteristic should be displayed in the log format (log odds ratio) (164). Second, because of the large number of included studies, displaying forest plots in the log odds ratio format provides a more meaningful presentation than the odds ratio for results that have a very narrow confidence interval. Third, presenting the results in the log odds ratio format helps to provide detail regarding the actual values used for univariate and multivariate models, which might allow their further use by readers.

The Q-value, a measure of weighted squared deviations, for assessing dispersion between the magnitudes of effects observed between the categories of each methodological characteristic was calculated along with the *p*-value under random effect. A univariate and multivariate meta-regression under a random effects model using an unrestricted maximum likelihood was used for the analysis; it was assumed that the studies were different, that the gene-disease associations investigated in the different studies varied, and that there might be different interpretations for the specific study results. The percentage variation between study variance (tau squared) was calculated for each methodological factor under the random effects model using

an unrestricted maximum likelihood for both the univariate and multivariate analyses (28, 165–171).

The methodological characteristics intended to be included in the univariate meta-regression analysis are characterized in Table 3.1.

Any of the investigated categorical methodological characteristics in the univariate meta-regression analysis that were shown to be associated with a reduction in the residual between-study variance (by $\geq 0.5\%$) or with the presence of statistically significant heterogeneity (significant Q-value), or for which the pooled outcomes (log odds ratio) of gene-disease associations tended to show different levels of significance when grouped according to methodological characteristic, were included in the multivariate model for further evaluation.

Any of the investigated continuous methodological characteristics in the univariate meta-regression analysis that were shown to be associated with a reduction in the residual between-study variance (by $\geq 0.5\%$) or with the presence of statistically significant intercept regression coefficient, were included in the multivariate model for further evaluation.

Forest plots and scatter plots were presented whenever possible for the different analytical models (164, 167, 168). The potential for publication bias was assessed through visual inspection of funnel plots for asymmetry (172) and statistically through the fail-safe N and Egger's regression asymmetry tests (173). The usual aim of investigating publication bias in a systematic review is to determine whether there is a tendency toward selective reporting of outcomes, to detect systematic differences between smaller and larger studies, and to ensure that all studies related to a specific disease or condition have been identified (164). However, the assessment of publication bias was used in this thesis to investigate in general terms (that is, for all diseases and conditions) the trend of outcomes reporting in relation to study size. That being said, because the present systematic review extracted the outcomes with the most extreme reported uncertainty measure, any publication bias could not be considered an indication of the trend of the overall reporting of outcomes related to gene-disease association studies but rather a description of those outcomes with the

most extreme reported uncertainty measure that were included in the analysis. When a continuous variable showed some effect, cumulative meta-analysis was used to provide further graphical representation of the effect of an increase in that variable on the pooled gene-disease association outcomes. This was done by adding each study to the cumulative analysis sequentially according to the increasing value of the continuous variable under investigation. Sensitivity analysis was used, when appropriate, to determine whether combining two classes or more of categorical variables reduced further the residual between-study variance.

Statistical analyses were conducted using SAS 9.1 and Comprehensive Meta Analysis, as mentioned previously (174). Independent testing for departure from Hardy–Weinberg equilibrium could not be conducted in the control group because the results of the pilot study demonstrated that a non-negligible portion of the studies did not provide the required information that would have made such a calculation possible (e.g., a 2 × 3 table). Adding to this difficulty was the large number of genetic markers tested in each study, which also made independent testing for Hardy–Weinberg equilibrium unfeasible. However, several other approaches to assess the association between the characteristics of Hardy–Weinberg equilibrium in the control group, and the reported measure of association, were introduced instead (Table 3.1).

Table 3.1: Classification of variables used in data extraction

Effect of design and other basic study characteristics

Categorical

- Study design
- Matching of cases and controls
- Claim of first report or of replication
- Origin of study (continent level)
- Association with a cancerous or a pre-cancerous disease
- Disease category

Continuous

- Number of reported genes
- Number of reported genetic markers
- Ratio of genetic markers tested to number of genes reported
- Journal impact factor

Population and methodological characteristics

Categorical

- Handling of specimens and genotyping for cases and controls
- Reporting of sample size/study power calculations
- Data source for included studies
- Selection of control participants
- Relation between case and control groups (blood relation)
- Reporting of quality assurance method
- Reporting of statistical adjustment for covariates

Continuous

- Final reported sample size
- Final reported number of cases
- Final reported number of controls
- Ratio of cases to controls

Hardy–Weinberg equilibrium assessment in the control group

Categorical

- Reporting on departure from the Hardy–Weinberg equilibrium
- Results of Hardy-Weinberg assessment
- Data that would allow independent testing for departure from the Hardy–Weinberg equilibrium

Continuous

- None

CHAPTER 4

4. Results

A total of 30 438 citations to genetic research were identified using the HuGENet literature database as of the end of 2007. Of these, 9423 citations were gene-disease association studies. Case-control studies represented 6238 of these citations, of which 1620 were published in 2007. A random sampling of these citations was conducted to reach the predetermined sample size of 533 citations. Twenty-two citations were then excluded after full review of each text, such that 511 citations in total were included in the final study sample (175–685).

4.1 Excluded studies

A list of the excluded studies (686–707) along with the reasons for exclusion is presented in Table 4.1.

Table 4.1: Studies excluded from meta-analysis and reasons for exclusion (n = 22)

Study	Journal of publication	Reason for exclusion
Atz et al.	*Psychiatric Genetics*	Gene-gene interaction
Boesgaard et al.	*Diabetic Medicine*	Cross-sectional study
Corvin et al.	*Neuroscience Letters*	Cross-sectional study
Cox et al.	*Nature Genetics*	Meta-analysis
Gerger et al.	*Breast Cancer Research and Treatment*	Gene-gene interaction
Glatt et al.	*Drug and Alcohol Dependence*	Meta-analysis with family-based association study
Hall et al.	*Carcinogenesis*	Gene-environment interaction
Hui et al.	*Hypertension Research*	Gene-environment interaction
Lee et al.	*Carcinogenesis*	Gene-environment interaction
Lilla et al.	*International Journal of Cancer*	Gene-environment interaction
McCarty et al.	*Environmental Health Perspectives*	Gene-environment interaction
McCaskie et al.	*Human Genetics*	Cross-sectional study
McLaughlin et al.	*Lancet Oncology*	Gene-environment interaction
Nowotny et al.	*American Journal of Medical Genetics*	Cross-sectional study
Scott et al.	*Ophthalmology*	Gene-environment interaction
Shen et al.	*Annals of Human Genetics*	Gene-gene interaction
Shirts et al.	*Schizophrenia Research*	Gene-environment interaction
Sigurdson et al.	*Cancer Epidemiology Biomarkers and Prevention*	Gene-environment interaction
Sziller et al.	*Human Reproduction*	Gene-environment interaction
Yang et al.	*American Journal of Clinical Nutrition*	Cross-sectional study
Zeggini et al.	*Science*	Meta-analysis study
Zuo et al.	*Biological Psychiatry*	Gene-gene interaction

4.2 Characteristics of included studies

4.2.1 Design and other basic study characteristics

The case-control studies selected for analysis (n = 511) were published in 220 journals with a median impact factor (2006) of 5.1. Basic design characteristics are summarized in Table 4.2. Nested case-control studies represented 8.22% of this sample (n = 42). The 511 studies reported a median number of 1 gene, with a maximum number of 135 reported genes. The median number of genetic markers reported was 3, with a minimum number of 1 and a maximum of 1515. The median ratio of genetic markers per gene was 2:1.

Cases were reported to be individually matched to controls in 28 (5.48%) of the studies. First reporting of a gene-disease association was claimed in 275 (53.82%) studies, while replication of previously conducted research was claimed in 199 (38.94%) (Table 4.2).

The 511 studies included in the analysis were conducted in 52 countries; the most frequent country of origin was the United States (18.20%), followed by China (15.10%). Twenty-eight (5.48%) of the studies were multi-centre studies conducted in more than one country. Cancerous or pre-cancerous lesions were investigated in 187 (36.59%) of the studies. Of the disease categories, gastroenterological diseases were the most commonly investigated (10.37%), followed by neurological diseases (8.41%) and vascular diseases (7.83%) (Figure 4.1).

Table 4.2: Reported design and other basic characteristics of case-control studies published in 2007 and randomly selected from the HuGENet literature database (n = 511)

Reported characteristics	Number of studies (%)	
Study design		
Classic case-control	469	(91.78)
Nested case-control	42	(8.22)
Matching of cases and controls		
Individually matched	28	(5.48)
Frequency matched	249	(48.73)
Not-matched	234	(45.79)
First report or replication		
First report	275	(53.82)
Replication	199	(38.94)
Combination or not reported	37	(7.24)
Origin of study		
Africa	16	(3.13)
Asia	155	(30.33)
Australia	14	(2.74)
Europe	180	(35.23)
North America	100	(19.57)
South and Middle America	18	(3.52)
Multi-centre (country level)	28	(5.48)
Investigated gene association with a cancerous or a pre-cancerous disease		
Yes	187	(36.59)
No	324	(63.41)

4.2.2 Population and methodological characteristics

Table 4.3 summarizes the methodological characteristics of the studies included in the analysis. Sample sizes of 500 or fewer participants were reported in 190 (37.18%) of the studies, while 182 (35.62%) reported sample sizes of 1000 participants or more. The median number of participants was 712 (range 43 to 16 612). The mean ratio of cases to controls was 0.96.

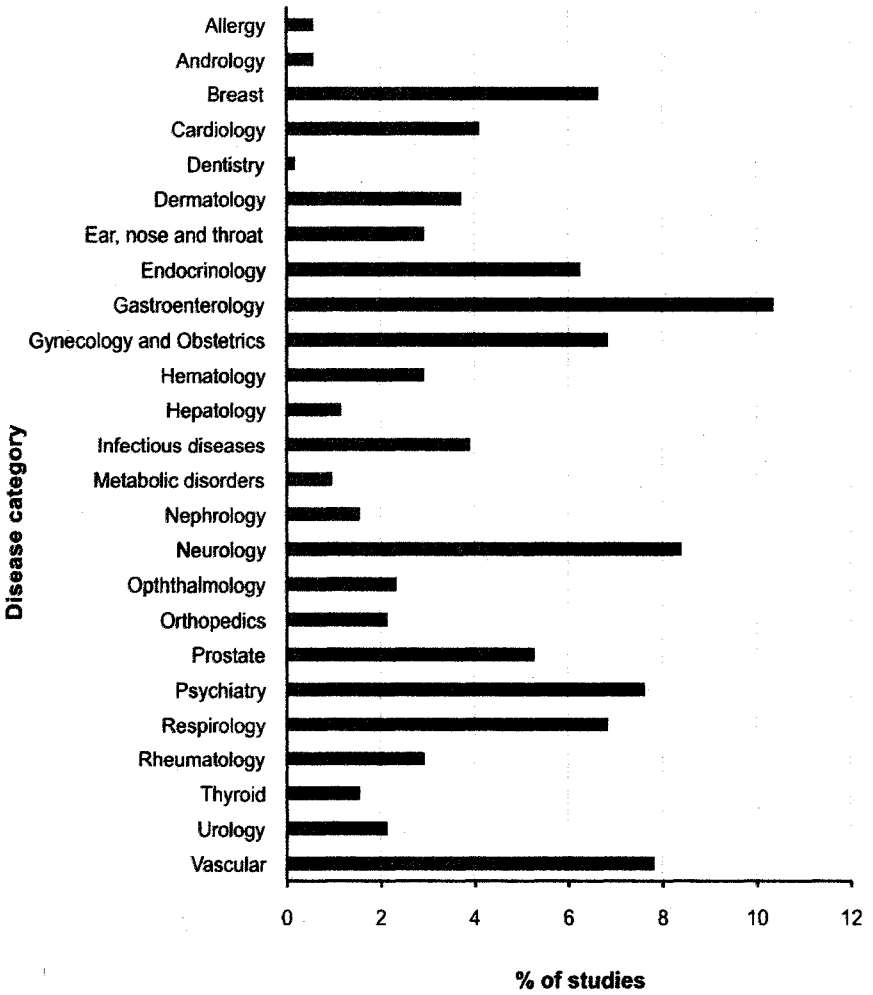

Figure 4.1 Disease-related categories investigated in the studies included in the meta-analysis (n = 511)

Sample sizes or study power calculations were reported in 131 (25.64%) of the included studies. The most commonly reported data source for the studies was primary data collection and analysis (82.58%), followed by building on pre-existing data by collecting more information or blood and other specimens (16.24%) (Table 4.3).

As to the selection of control participants, half of the studies (50.49%) reported that they had drawn upon special groups such as hospital patients, blood-bank

donors, hospital employees, or visitors accompanying patients. The use of population-based controls selected according to a specified sampling frame and process was reported in 106 (20.74%) of the studies.

Table 4.3: Reported population and methodological characteristics of case-control studies published in 2007 and randomly selected from the HuGENet literature database (n = 511)

Reported characteristics	Number of studies (%)
Total number of study participants	
≤ 500	190 (37.18)
501–1000	139 (27.20)
> 1000	182 (35.62)
Sample size or study power calculations	
Yes	131 (25.64)
No	380 (74.36)
Data source for the included studies	
Primary collection and analysis of data	422 (82.58)
Building on pre-existing data	83 (16.24)
Secondary analysis of pre-existing data	6 (1.17)
Selection of control participants	
Special groups (e.g., hospital patients, blood-bank donors)	258 (50.49)
Population-based, with details on the sampling frame	106 (20.74)
Population-based, without details on the sampling frame	51 (9.98)
Combination of special groups and population controls	20 (3.91)
Not reported / unclear	76 (14.87)
Relatedness of cases and controls (blood relationship)	
Yes	6 (1.17)
No	155 (30.33)
Unclear	350 (68.49)
Any method of quality assurance	
Yes	247 (48.34)
No	264 (51.66)
Statistical adjustment for covariates	
Yes	230 (45.01)
No, or not applicable	281 (54.99)

Almost two thirds of the articles did not state whether cases and controls were related by blood. Processes for handling specimens and genotyping were described for cases and controls in 481 (94.13%) of the studies and were unreported or unclear for both cases and controls in 18 studies (3.52%). The high

percentage of studies that reported the process of handling specimens and genotyping precluded analysis of this methodological characteristic, as it would not have provided helpful information in explaining heterogeneity between studies. Almost half of the studies (48.34%) reported some method of quality assurance, such as blinding the genotyping process to the participants' status as cases or controls, using a different method of validation for laboratory diagnosis, and validating the results against an external control. Statistical adjustment for the effect of covariates was reported in 230 (45.01%) of the studies.

4.2.3 Hardy–Weinberg equilibrium assessment

Control-group testing for deviation from Hardy–Weinberg equilibrium (HWE) was reported in 425 (83.17%) of the included studies, and in most of these (79.10%) the distribution of genotypes in the control group did not depart from HWE. Data that would enable independent testing for departure from HWE were reported in three quarters of the included articles (77.69%); such reporting included 2 × 3 tables showing genotype distribution among the controls, *p*-values, and inbreeding coefficients (Table 4.4).

Table 4.4: Reporting of Hardy–Weinberg equilibrium in case-control studies published in 2007 and randomly selected from the HuGENet literature database (n = 511)

Reported characteristics	Number of studies (%)
Testing for departure from Hardy–Weinberg equilibrium (HWE)	
Yes	425 (83.17)
No	86 (16.83)
HWE outcomes	
All included genotypes were in equilibrium	336 (65.75)
Some included genotypes were in equilibrium (including that associated with the extracted outcome)	27 (5.28)
Some included genotypes were in equilibrium (not including that associated with the extracted outcome)	30 (5.87)
Genotypes were not in equilibrium or it was not clear	32 (6.26)
Not reported	86 (16.83)
Data that would allow independent testing for departure from HWE	
Yes	397 (77.69)
No	114 (22.31)

4.2.4 Characteristics of extracted outcomes

A single measure of a gene-disease association along with the corresponding measure of uncertainty was extracted from each included study. The different types of outcome measure that were reported were odds ratios, 2 × 2 tables, and 2 × 3 tables. It was possible to extract odds ratios from 347 (67.91%) of the included studies, while outcomes were extracted from 2 × 2 tables in 132 (25.83%) of the studies and from 2 × 3 tables in 32 (6.26%) of the studies.

The pooled log odds ratio for all of the included studies was 0.21 (95% confidence interval [CI] 0.18–0.25). The pooled log odds ratio was 0.24 (95% CI 0.20–0.29) for studies that presented results as odds ratios, 0.15 (95% CI 0.07–0.22) for studies that reported outcomes in 2 × 2 tables, and 0.18 (95% CI 0.04–0.31) for studies that reported results in 2 × 3 tables. Under the random effects model, the heterogeneity between studies by type of outcome extracted had a Q-value of 4.80 and borderline statistical non-significance ($p = 0.091$). Figure 4.2 depicts the pooled log odds ratio stratified by type of outcome extraction under the random effects model.

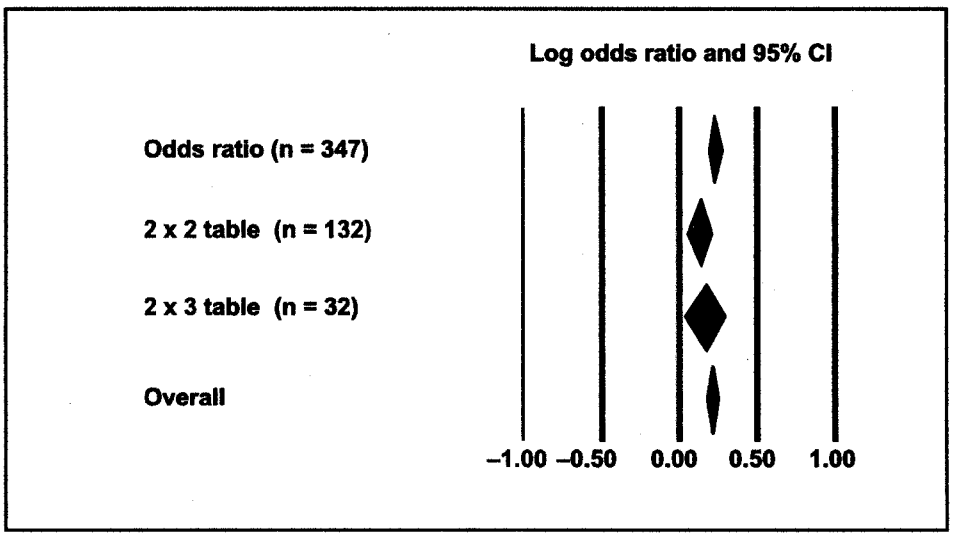

Figure 4.2: Pooled log odds ratio and 95% confidence interval (CI) for all included studies (n = 511), grouped by type of outcomes reporting

Publication bias was assessed both visually in a funnel plot and by means of statistical analyses. The fail-safe N was calculated as 76 811, which means that 76 811 studies with a null effect size would need to be located and included in the study sample for the combined 2-tailed *p*-value to exceed the nominal 5% for statistical significance; that is to say, for the effect to be nullified, 150.3 studies with non-significant results would need to be located for every study included in the present analysis. The result of Egger's test of the intercept (which assesses asymmetry of the funnel plot) was 0.81 (95% CI 0.40–1.20). Figure 4.3 shows a funnel plot of precision in which the studies are distributed approximately symmetrically around the log odds ratio of the effect size.

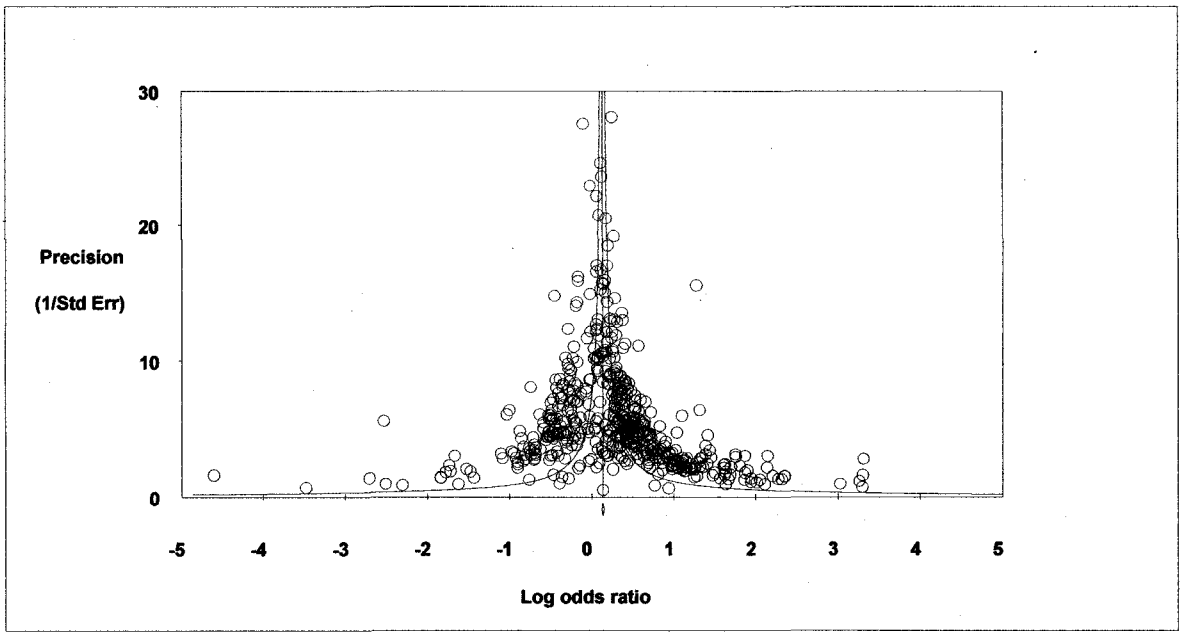

Figure 4.3: Funnel plot of precision by log odds ratio for the assessment of publication bias in gene-disease association studies (n = 511)

4.3 Univariate analysis of methodological characteristics

4.3.1 Effect of design and other basic study characteristics

Adjustment for study design (classic vs. nested case-control studies) in univariate meta-regression analysis reduced the residual between-study variance from 0.3200 to 0.3187. Thus, study design explained 0.41% of the between-study variance in magnitude of effect. The Q-value of dispersion was 2.61 (p-value = 0.106), indicating that the difference in log odds ratio between classical case-control studies and those with a nested design was not statistically significant (Table 4.5; Figure 4.4). However, the magnitude of effect for the nested design was smaller and not statistically significant in comparison with the classic design.

Univariate meta-regression analysis of the effect of case-control matching showed a decrease in the residual between-study variance by 0.88%. The Q-value of dispersion was 5.91 ($p = 0.052$), indicating that individual matching of cases and controls did not produce a statistically significant difference in log odds ratios for gene-disease outcomes in comparison with frequency matching or non-matching of cases and controls. As shown in Figure 4.4, individually matched studies were associated with smaller log odds ratio in comparison with frequency matching or non-matching of cases and controls.

The characteristic of (1) being a first report, (2) a replication of previously conducted research, or (3) a combination or not reporting this characteristic accounted for 1.97% of the residual between-study variance. Further sensitivity analyses that included the third category with either of the other two added no further reduction to the residual between-study variance (results not shown). The Q-value of dispersion was 11.48 ($p = 0.003$), indicating significant dispersion between gene-disease outcomes according to whether the study was claimed to be (1) a first report, (2) a replication, or (3) a combination or did not report this characteristic. The log odds ratio of gene-disease outcomes for first reported case-control studies was larger in comparison with studies that reported replicated findings and with those studies that reported a combination of new and replicated findings or that did not report this characteristic (Figure 4.4).

As mentioned earlier, the studies included in the analysis (n = 511) were conducted in 52 countries. Univariate meta-regression analysis was not conducted at the individual country level: because there were several countries with only 1 study, univariate meta-regression would have resulted in over-fitting of the data. Univariate meta-regression analysis at the continent level resulted in a 3.16% reduction in the residual between-study variance. The Q-value was 19.76 ($p = 0.003$), indicating significant dispersion between gene-disease outcomes when continents were included as a covariate in the meta-regression model (Table 4.5). The log odds ratios of gene-disease outcomes for Asia, Europe, and North America demonstrated closely related values (Figure 4.4).

Table 4.5: Results of univariate meta-regression analysis of effect of reported design and other basic study characteristics on magnitude of effect (log odds ratio) (n = 511)

Reported characteristics	Log odds ratio (95% CI)	
Study design		
Classic case-control	0.25	(0.20–0.31)
Nested case-control	0.01	(−0.09 to 0.29)
Matching of cases and controls		
Individually matched	0.05	(−0.19 to 0.29)
Frequency matched	0.28	(0.20–0.36)
Not matched	0.22	(0.14–0.30)
First report or replication		
First report	0.31	(0.23–0.39)
Replication	0.17	(0.08–0.25)
Combination or not reported	0.16	(−0.04 to 0.36)
Origin of study		
Africa	−0.04	(−0.36 to 0.28)
Asia	0.25	(0.16–0.35)
Australia	0.47	(0.15–0.78)
Europe	0.21	(0.12–0.30)
North America	0.22	(0.10–0.34)
South and Middle America	0.60	(0.29–0.92)
Multi-centre (country level)	0.27	(0.05–0.49)
Investigated gene association with a cancerous or a pre-cancerous disease		
Yes	0.22	(0.13–0.31)
No	0.26	(0.19–0.33)

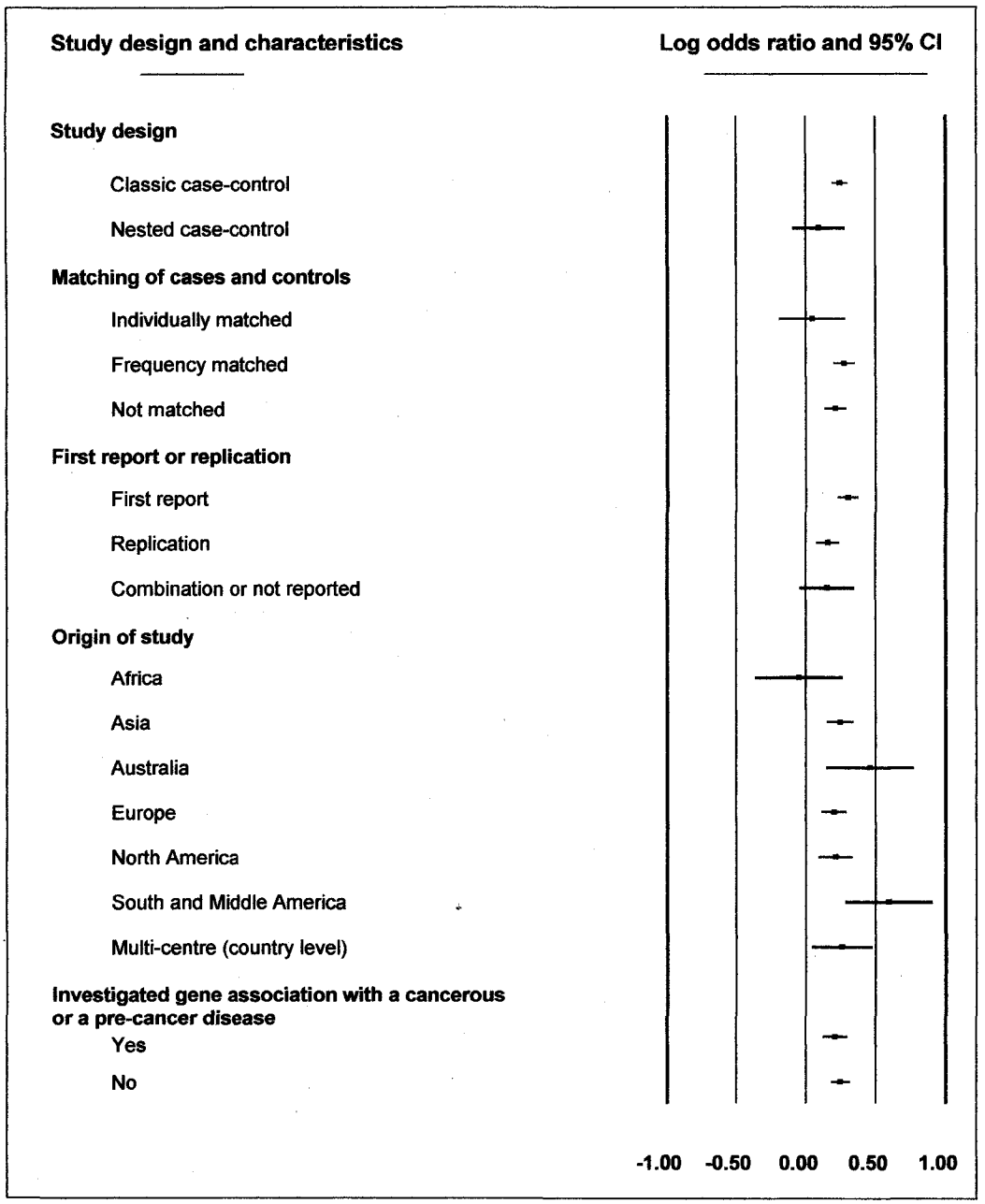

Figure 4.4: Forest plot of results of univariate meta-regression analysis of effect of reported design and other basic study characteristics on magnitude of effect (log odds ratio) (n = 511)

Adjustment for disease category reduced the residual between-study variance by 5.72%, with a Q-value of 36.78 ($p = 0.046$). The marginally significant p-value indicates the presence of dispersion between gene-disease outcomes after adjustment for disease category. When univariate meta-regression analysis examined whether studies that investigated cancer differed from those that investigated non-cancerous diseases, a minimal reduction of the residual between-study variance (< 0.001%) was shown; the Q-value of 0.17 for dispersion ($p = 0.68$) was not significant.

Univariate meta-regression analysis of the effect on the log odds ratio of the reported number of genes, genetic markers tested, and the ratio of genetic markers tested to the number of genes examined showed a minimal change in the residual between-study variance (< 0.001%) and in the intercept regression coefficient (Table 4.6). As shown by the scatter plots in Figures 4.5 to 4.7, the regression of different covariates on the log odds ratio of the gene-disease association outcomes did not deviate significantly from the horizontal axis. Univariate meta-regression analysis for journal impact factor showed a reduction of the residual between-study variance of 0.13%. As the impact factor of the journal increased, the log odds ratio decreased, although not significantly (Table 4.6, Figure 4.8). These results were in agreement with the cumulative meta-analysis of the gene-disease studies, in which the cumulative pool of the magnitude of effect (log odds ratio) became smaller with the increase in the journal impact factor (see Appendix I).

Table 4.6: Results of univariate meta-regression analysis of reported number of genes investigated, number of genetic markers, ratio of markers to genes, and journal impact factor on magnitude of effect (log odds ratio) (n = 511)

Reported characteristic	Slope	(95%CI)
Number of genes investigated	0.001	(−0.008 to 0.003)
Number of genetic markers tested	0.000	(−0.001 to 0.007)
Ratio of number of genetic markers tested to number of genes investigated	0.002	(−0.007 to 0.004)
Journal impact factor	−0.004	(−0.012 to 0.005)

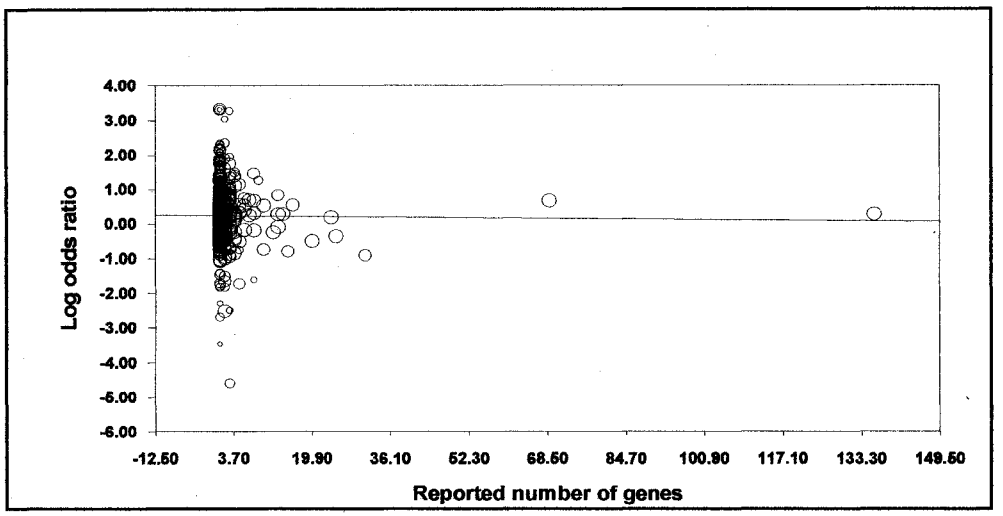

Figure 4.5: Univariate meta-regression analysis scatter plot of effect of reported number of genes on magnitude of effect (n = 511)[1]

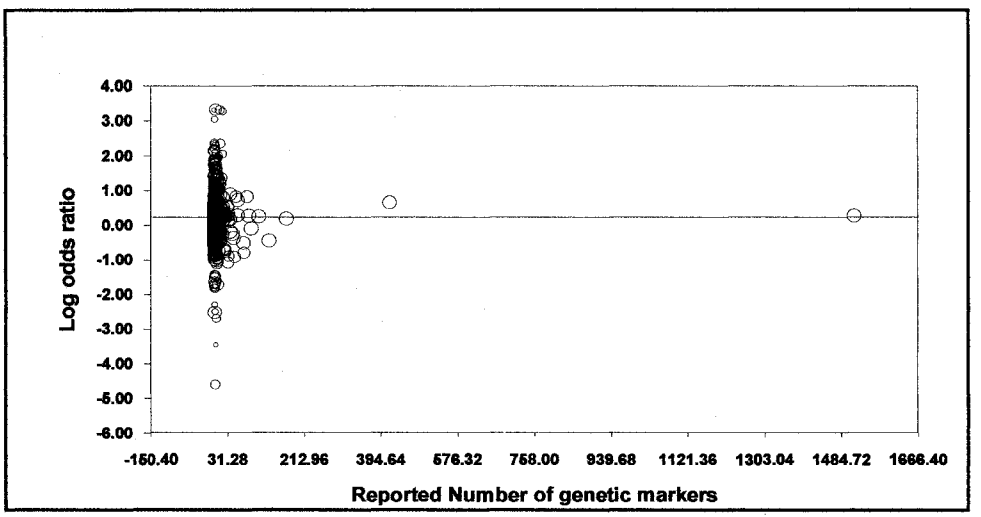

Figure 4.6: Univariate meta-regression analysis scatter plot of effect of reported number of genetic markers on magnitude of effect (n = 511)

[1] In all scatter plots shown in this chapter, the size of each circle corresponds to the inverse variance of the log odds ratio in the gene-disease association study that it represents.

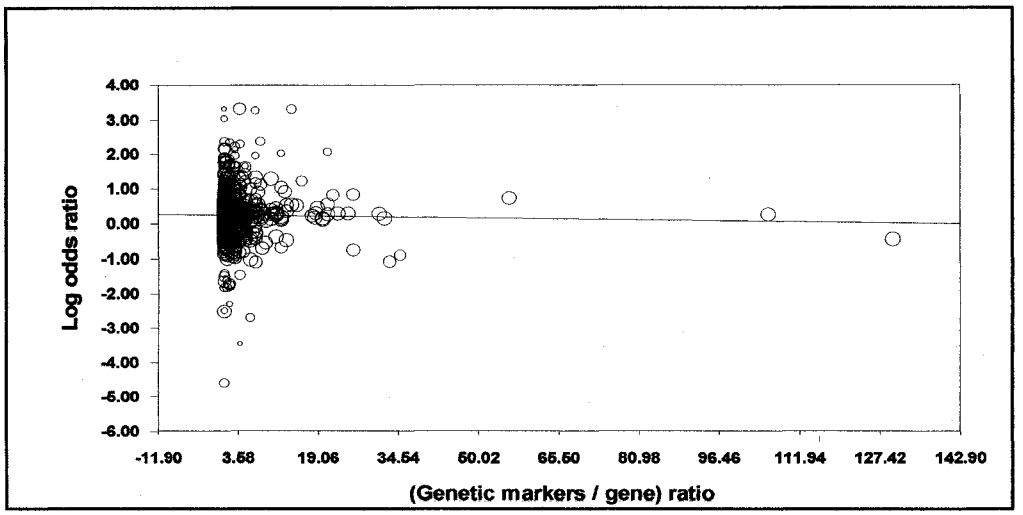

Figure 4.7: Univariate meta-regression analysis scatter plot of effect of ratio of reported number of genetic markers to reported number of genes on magnitude of effect (n = 511)*

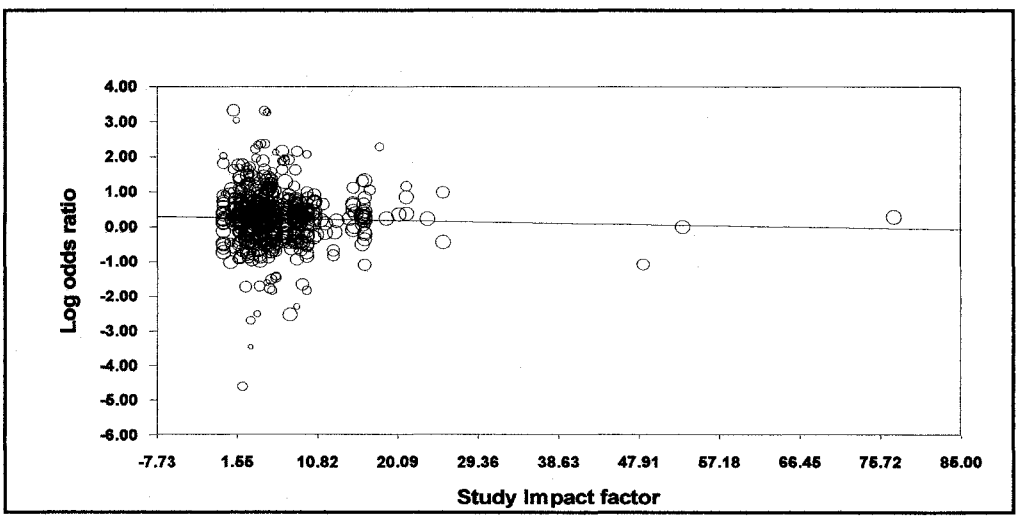

Figure 4.8: Univariate meta-regression analysis scatter plot of effect of journal impact factor on magnitude of effect (n = 511)*

4.3.2 Population and methodological characteristics

4.3.2.1 Factors related to study size and proportion of participants included in the analysis.

Univariate meta-regression analysis of the effect of the final reported sample size showed that an increased sample size was associated with a statistically significant reduction in the magnitude of reported gene-disease association outcomes ($p = 0.034$) and with a 1.00% reduction in the residual between-study variance (Table 4.7, Figure 4.9). These results were in agreement with the cumulative meta-analysis, in which the cumulative pool of the log odds ratio became smaller with the increase in the final reported sample size (see Appendix II).

As the final reported number of cases increased, the log odds ratio of gene-disease association outcomes decreased. The univariate meta-regression analysis was not statistically significant. Adjustment for the final reported number of cases reduced the residual between-study variance by 0.84 % (Figure 4.10). The cumulative pool of the log odds ratio became smaller as the final reported number of cases increased (see Appendix III).

With regard to the final reported number of controls, the log odds ratio of gene-disease association outcomes decreased significantly as the final reported number of controls increased ($p = 0.03$). Adjustment for this variable reduced the residual between-study variance by 1.06% (Figure 4.11). The cumulative pool of the log odds ratio also became smaller with the increase in the final reported number of controls (see Appendix IV).

Investigation of the role of the ratio of cases to controls showed a statistically non-significant effect on the log odds ratio of gene-disease association outcomes ($p = 0.98$); adjustment for this variable reduced the residual between-study variance by < 0.001% (Figure 4.12).

Table 4.7: Results of univariate meta-regression analysis of effect of reported sample size and number of cases and controls on magnitude of effect (log odds ratio) (n = 511)

Reported characteristics	Slope	(95%CI)
Final sample size	−0.00003	(−0.0001 to −0.0000)
Final number of cases	−0.0001	(−0.0001 to 0.000)
Final number of controls	−0.0001	(−2.175 to −0.000)
Ratio of cases / controls	0.001	(−0.108 to 0.110)

CI = confidence interval

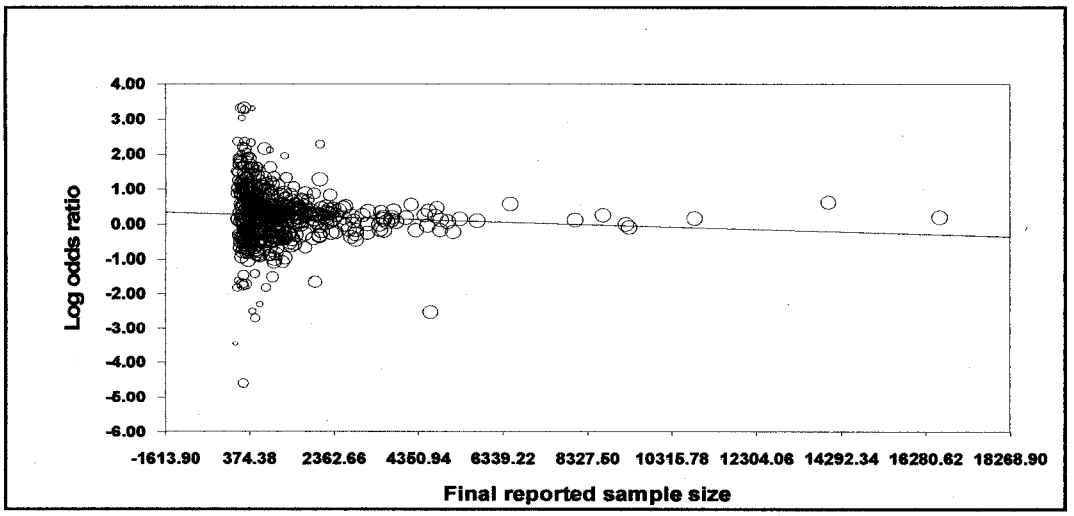

Figure 4.9: Univariate meta-regression analysis scatter plot of effect of final reported sample size on magnitude of effect (n = 511)*

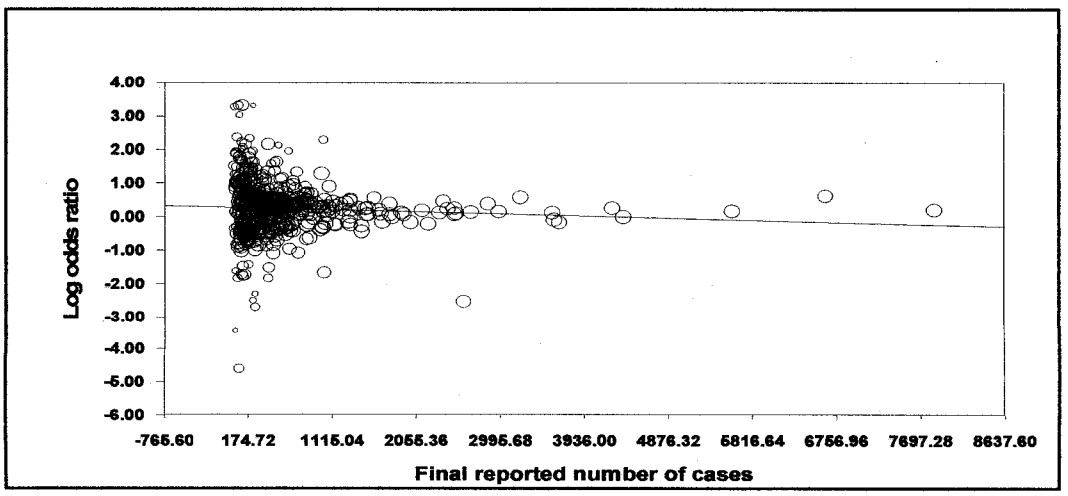

Figure 4.10 Univariate meta-regression analysis scatter plot of effect of final reported number of cases on magnitude of effect (n = 511)

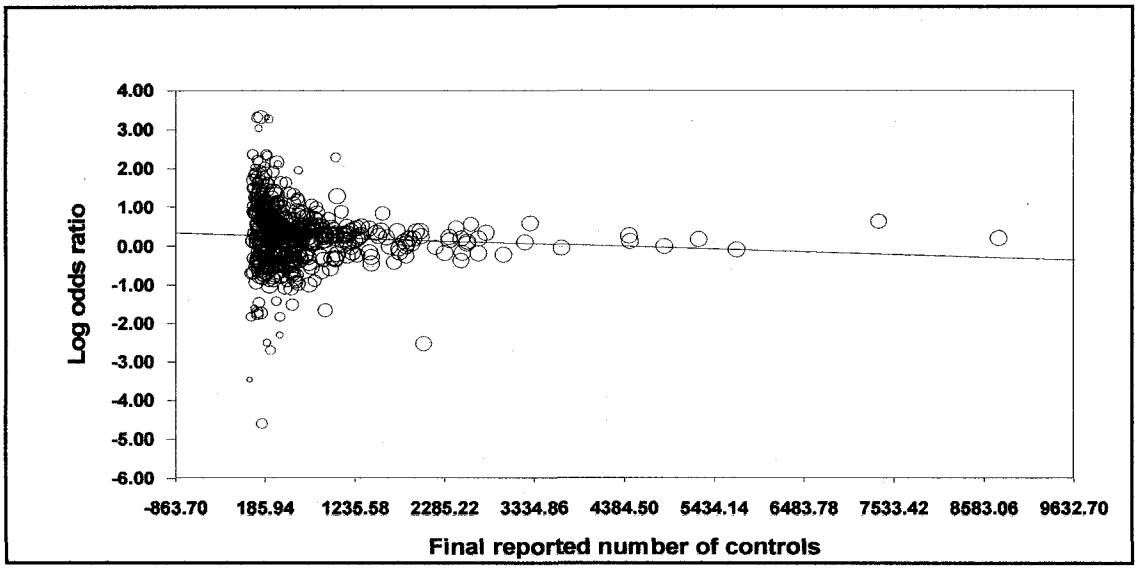

Figure 4.11 Univariate meta-regression analysis scatter plot of effect of final reported number of controls on magnitude of effect (n = 511)

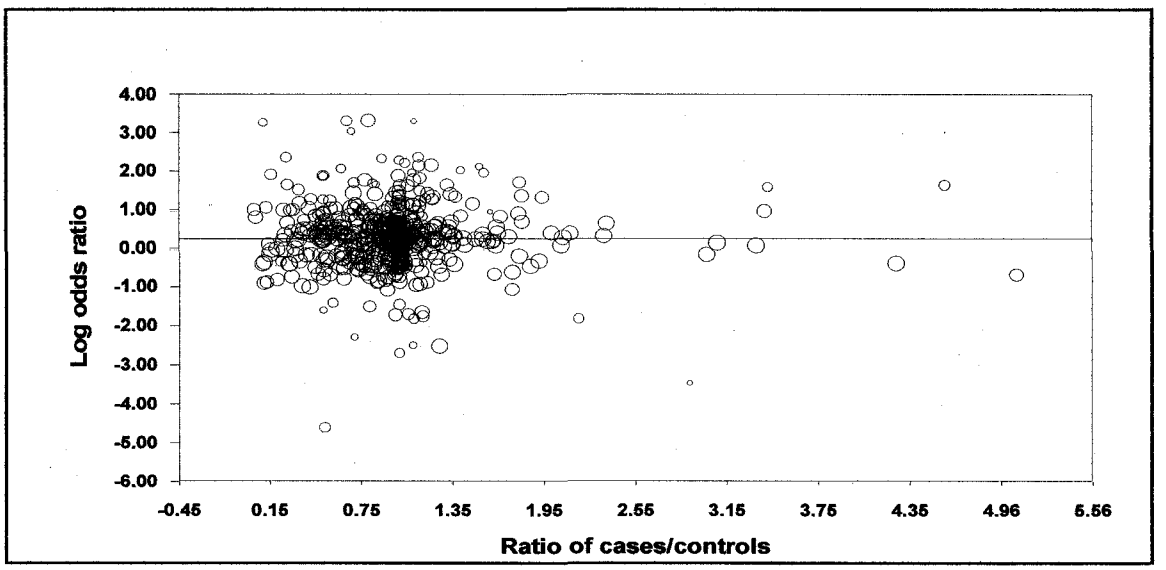

Figure 4.12 Univariate meta-regression analysis scatter plot of effect of ratio of cases to controls on magnitude of effect (n = 511)*

4.3.3 Factors related to selection of study participants and quality assurance

The results of univariate meta-regression analysis of the effect of reported methods of participant selection and of quality assurance on the magnitude of gene-disease association outcomes are shown in Table 4.8. The reporting of sample size or study power calculation reduced the residual between-study variance by 1.41% in comparison with the model without covariate analysis (Figure 4.13). The Q-value of dispersion was 9.06 ($p = 0.003$). As shown in Figure 4.13, studies that reported the sample size or power calculation tended to show smaller log odds ratios for gene-disease association outcomes in comparison with studies that did not report sample size or power calculation.

The univariate meta-regression analysis of the effect of the source of the data used in the different studies on the log odds ratio of the gene-disease association outcomes was not able to account for the residual between-study variance (< 0.001%). Sensitivity analysis did not show any further reduction in the residual between-study variance (results not shown). The Q-value of dispersion was 3.069 ($p = 0.381$), indicating the absence of statistically significant heterogeneity between the groups. The magnitudes of effects were closely similar whether researchers collected the data primarily by themselves, building on pre-existing data or conducted a secondary analysis of data. However secondary analysis of pre-existing data was associated with a non-statistically significant wider confidence interval (Figure 4.13).

On the other hand, the process of control selection accounted for 3.59% of the residual between-study variance (Q-value= 23.67; $p < 0.001$). As shown in Figure 4.13, not reporting the process of control selection was associated with larger log odds ratios, while the selection of controls from the general population tended to be associated with smaller gene-disease outcomes. Sensitivity analysis of the effect of source of control participants did not show any further reduction in the residual between-study variance (results not shown).

Reporting on whether cases and controls were related reduced the residual between-study variance by 0.66%. The Q-value of 6.00 for dispersion was not statistically significant (p = 0.050). Univariate meta-regression analysis showed that reporting any method of quality assurance reduced the residual between-study variance by < 0.001%; here, the Q-value was 1.356 ($p = 0.244$).

Univariate meta-regression analysis of the effect of statistical adjustment for covariates showed that this variable produced only a minimal reduction in the residual between-study variance (< 0.001). The Q-value for heterogeneity was 2.69; ($p = 0.101$) (Figure 4.13).

Table 4.8: Results of univariate meta-regression analysis of reported participant selection and quality assurance method on magnitude of effect (log odds ratio) (n = 511)

Reported characteristics	Log odds ratio (95% CI)	
Sample size / study power calculations		
Yes	0.12	(0.05–0.19)
No	0.25	(0.21–0.29)
Data source for included studies		
Primary collection and analysis of data	0.24	(0.18–0.31)
Building on pre-existing data	0.22	(0.09–0.35)
Secondary analysis of pre-existing data	0.30	(−0.21 to 0.81)
Selection of control participants		
Special groups (e.g., hospital-based, blood-bank donors)	0.23	(0.15–0.31)
Population based, with details on sampling frame	0.14	(0.02–0.25)
Population based, without details on sampling frame	0.26	(0.09–0.43)
Combination of special groups and population controls	0.09	(−0.17 to 0.35)
Not reported / unclear	0.48	(0.33–0.62)
Relatedness of cases and controls (blood relationship)		
Yes	0.65	(0.13–1.18)
No	0.31	(0.21–0.41)
Unclear	0.21	(0.14–0.27)
Any method of quality assurance		
Yes	0.21	(0.13–0.28)
No	0.28	(0.20–0.35)
Statistical adjustment for covariates		
Yes	0.23	(0.15–0.31)
No / not applicable	0.25	(0.17–0.32)

CI = confidence interval

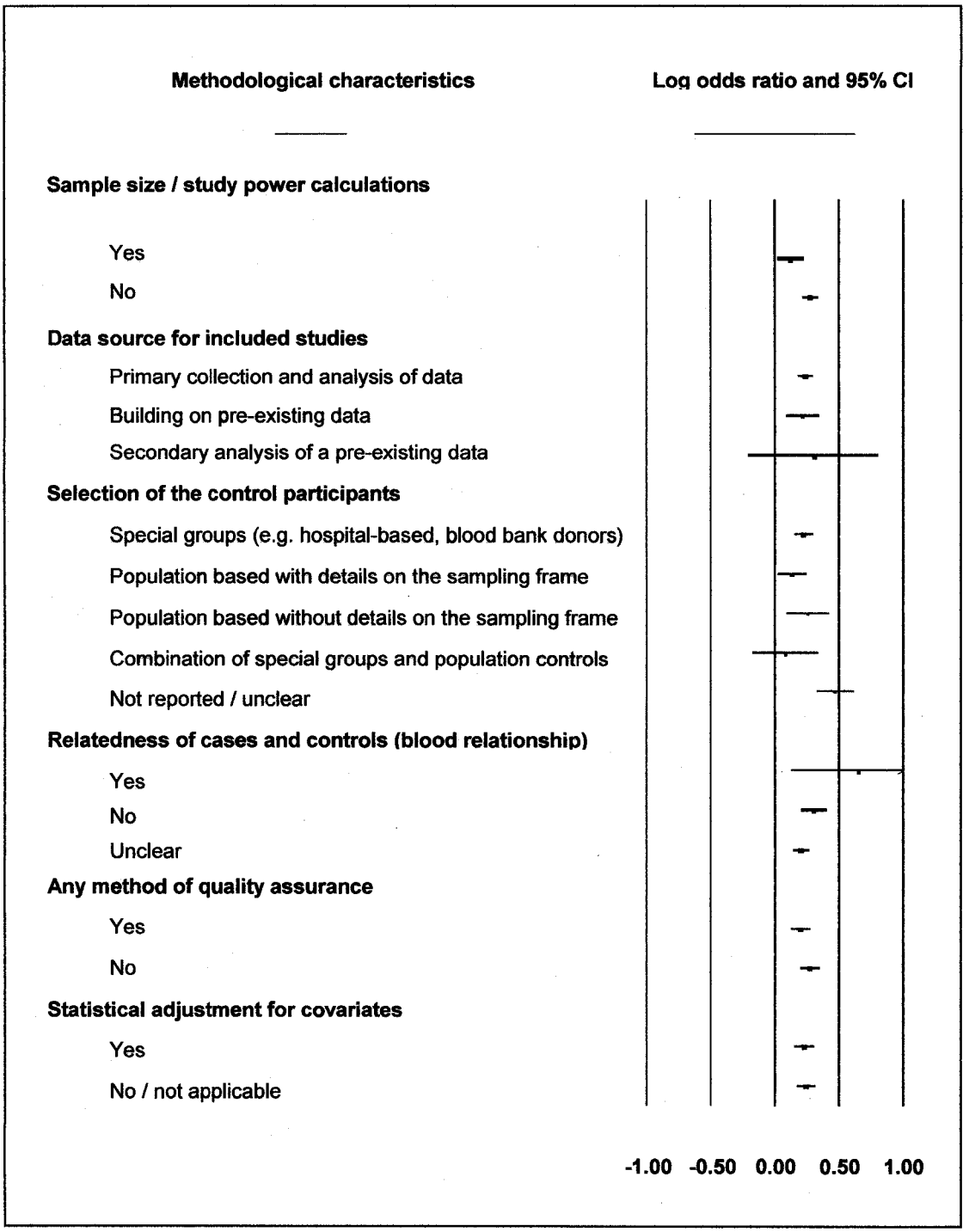

Figure 4.13: Forest plot of results of univariate meta-regression analysis of study participant selection and quality assurance methods on magnitude of effect (n = 511)

4.3.4 Hardy–Weinberg equilibrium assessment

Univariate meta-regression analysis for reporting or not reporting testing for deviation from Hardy–Weinberg equilibrium in the control group produced a 1.75% reduction in the residual between-study variance (Table 4.9). The Q-value of heterogeneity was equal to 13.16 ($p < 0.001$). Including more details regarding HWE results in the meta-regression model resulted in a greater reduction of the residual between-study variance (2.16%), with a Q-value of heterogeneity of 19.70 ($p < 0.001$). Reporting results that would allow for calculation of HWE reduced the residual between-study variance by (0.44%), with a Q-value of 3.40 ($p = 0.065$). Results of the univariate analysis are also represented in Figure 4.14.

Table 4.9: Results of univariate meta-regression analysis of reported factors related to assessment of Hardy–Weinberg equilibrium on magnitude of effect (n = 511)

Reported characteristics	Log odds ratio (95% CI)
Departure from Hardy–Weinberg equilibrium (HWE) assessed	
Yes	0.21 (0.15–0.26)
No	0.44 (0.30–0.59)
Results of testing for departure from HWE	
All included genotypes were in equilibrium	0.18 (0.11–0.24)
Some included genotypes were in equilibrium (including that associated with the extracted outcome)	0.23 (0.01–0.46)
Some included genotypes were in equilibrium (not including that associated with the extracted outcome)	0.37 (0.14–0.59)
Genotypes were not in equilibrium / unclear	0.34 (0.12–0.57)
Hardy–Weinberg equilibrium (HWE) was not reported	0.44 (0.30–0.59)
Data that would enable independent testing for departure from HWE	
Yes	0.22 (0.16–0.28)
No	0.32 (0.20–0.44)

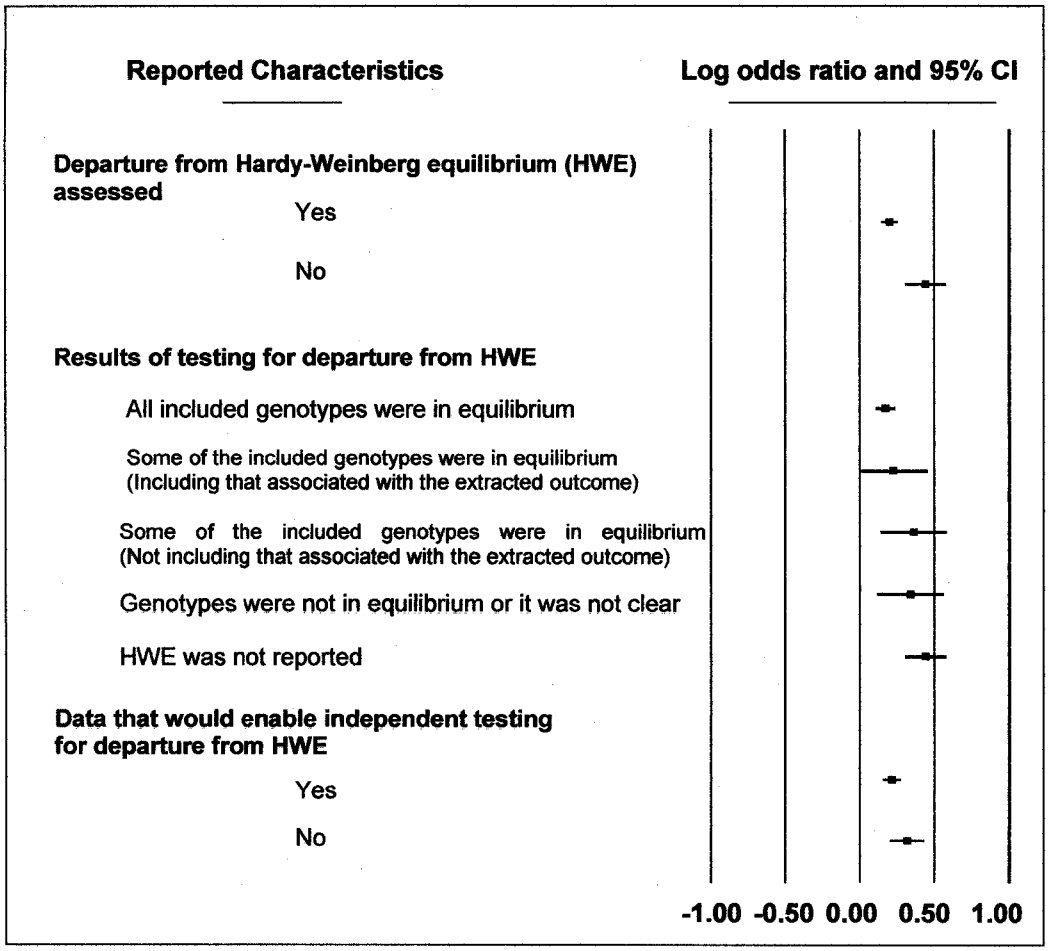

Figure 4.14: Forest plot of results of univariate meta-regression analysis of effect of analysis of Hardy–Weinberg equilibrium on magnitude of effect (n = 511)

4.4 Multivariate meta-regression analysis

Results from the univariate analyses were used for the multivariate meta-regression analysis. The percentage reduction in the residual between-study variance was calculated using the random effects model with an unrestricted maximum likelihood. The percentage reduction in the residual between-study variance shown by univariate and multivariate meta-regression analysis of the methodological characteristics of the included studies is shown in Table 4.10. Multivariate meta-regression analysis showed that when either the final reported sample size or the final reported number of controls was included in the model, the other variable did not explain any further reduction in the residual between-

study variance. The same was true when the final reported number of cases was added to the model with either the final reported sample size or the final reported number of controls. Since the final reported sample size was associated with an increase in the number of controls (Pearson correlation = 0.98), and the final number of reported cases was associated with an increase in the number of controls (Pearson correlation = 0.90), and since the reduction of residual between-study variance was higher when the final number of controls or the final sample size was reported, the final reported number of controls was kept in the model, while the final reported sample size and the final number of reported cases were excluded.

Table 4.10: Results of univariate and multivariate meta-regression analysis of reduction in the residual between-study variance by gene-disease covariates

Reported characteristics	Reduction in residual between-study variance (%)	
	Univariate	Multivariate
Study design	0.41	0.03
Matching of cases and controls	0.88	0.94
First report versus replication of study findings	1.97	1.81
Location of study (continent)	3.16	2.97
Disease category	5.72	6.34
Overall sample size	1.00	0.66
Overall number of cases	0.84	0.59
Overall number of controls	1.06	0.66
Sample size / study power calculations	1.41	0.97
Data source for included studies	< 0.001	0.00
Selection of control participants	3.59	2.38
Blood relationship between cases and controls	0.66	0.00
Testing for deviation from HWE (simple)	1.75	0.75
HWE results (detailed)	2.16	1.09

HWE = Hardy–Weinberg equilibrium

Although reporting the source of data for the included studies was able to account for only very minimal variation between outcomes in the univariate model (< 0.001%), it was included in the multivariate model on the grounds that, since the categories of this methodological characteristic showed different levels of significance, its further evaluation in the multivariate model was warranted. However, because reporting on the source of data did not show any further effect in the multivariate analysis, it was excluded from the final model.

Reporting the relationship between cases and controls was able to explain 0.66% of the between-study variation in outcomes in the univariate model, it was not able to show any effect in the multivariate analysis and therefore was excluded from the final model.

As shown in Table 4.10, reporting detailed results of testing for deviation from HWE reduced the residual between-study variance more than simple reporting of whether HWE testing was conducted. Adding the simple reporting of HWE in the model did not result in any further reduction in the residual between-study variance when detailed reported of HWE was also retained in the model. For this reason, detailed reporting of HWE was kept in the model and simple reporting was excluded.

Thus the multivariate meta-regression analysis using the random effects model with an unrestricted maximum likelihood explained 17.19% of the residual between-study variance. In another words, this model was able to explain 17.19% of the differences between gene-disease association outcomes. As shown in Table 4.10, disease category accounted for the largest proportion of the residual between-study variance (6.34%), followed by the continent in which the study was conducted (2.97%), and reporting on the method of selection of control participants (2.38%).

A multivariate meta-regression model was constructed to determine the effect of each class of the included reported characteristics on the direction of results in the log odds ratio of gene-disease outcomes. The regression coefficient for the

intercept was 0.498 (standard error [SE] = 0.132). The regression coefficient for the final reported number of controls was −0.00005 (SE = 0.000032). Thus, in this model the log odds ratio of gene-disease outcomes is estimated to decrease by 0.00005 per subject increase in the control group.

In addition to the final reported number of controls, Figure 4.15 shows the rest of the factors included in the final multivariate model. Figure 4.15 shows reference classes used in the model and the direction of effect that each individual class had on the multivariate model. The nested case-control study design tended to show smaller log odds ratio in the case-control outcomes in comparison with the reference model. As reported also in the univariate analysis, individually matched case-control studies tended to have smaller log odds ratios in comparison with the reference model. The tendency of studies that were reported to be a replication was to show a smaller magnitude of effect (log odds ratio) compared with studies that claimed to be a first report. With respect to the place of origin of studies, those conducted in North America or Asia showed log odds ratios similar to those of studies conducted in Europe.

Studies that reported a sample size or power calculation tended to have smaller log odds ratios in comparison with the reference model. With regard to the selection of controls, studies that selected controls from hospital populations and other specific groups and those that selected controls from the general population using an identified sampling frame showed similar effect sizes in gene-disease association outcomes, while studies that did not report the source of controls tended to have larger log odds ratios in comparison with the reference model.

As shown in Figure 4.15, reported agreement with HWE was associated with smaller log odds ratios in comparison with no reporting on the results of HWE assessment (reference model), while studies that reported a departure from HWE tended to have larger log odds ratios.

Table 4.11 shows the variables included and those excluded from the final multivariate meta-regression analysis model.

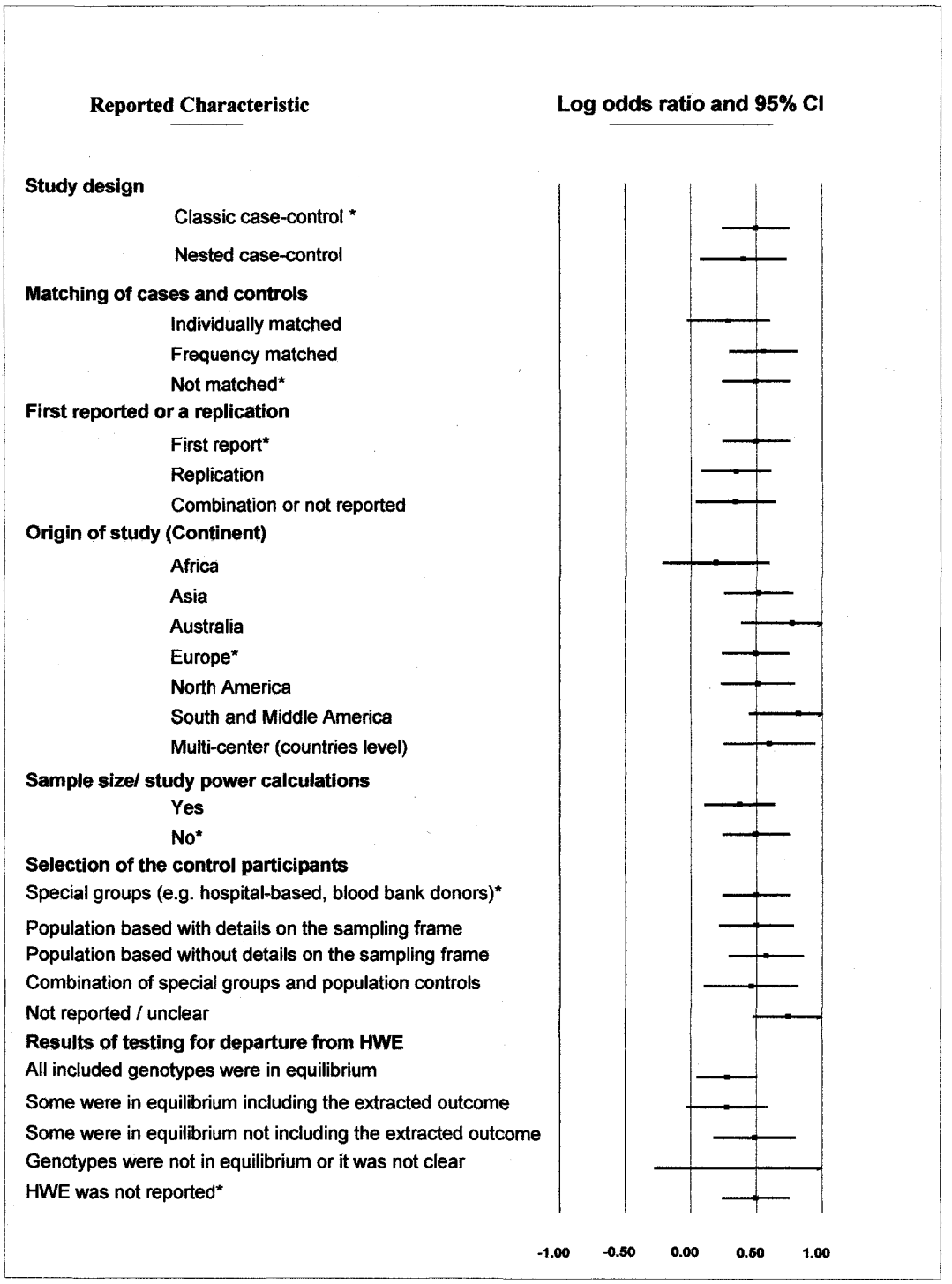

Figure 4.15: Forest plot of results of multivariate meta-regression analysis of covariate effects on the direction of the log odds ratio (n = 511). (*Covariate used as references in the multivariate regression model).

Table 4.11: Variables included / excluded from the final multivariate meta-regression analysis model.

Variables included in the final multivariate meta-regression model

Effect of design and other basic study characteristics

- Study design
- Matching of cases and controls
- Claim of first report or of replication
- Origin of study (continent level)
- Disease category

Population and methodological characteristics

- Reporting of sample size/study power calculations
- Selection of control participants
- Final reported number of controls

Hardy–Weinberg equilibrium assessment in the control group

- Results of Hardy-Weinberg assessment (detailed)

Variables excluded from the final multivariate meta-regression model

Effect of design and other basic study characteristics

- Association with a cancerous or a pre-cancerous disease
- Number of reported genes
- Number of reported genetic markers
- Ratio of genetic markers tested to number of genes reported
- Journal impact factor

Population and methodological characteristics

- Handling of specimens and genotyping for cases and controls
- Data source for included studies
- Relation between case and control groups (blood relation)
- Reporting of quality assurance method
- Reporting of statistical adjustment for covariates
- Final reported sample size
- Final reported number of cases
- Ratio of cases to controls

Hardy–Weinberg equilibrium assessment in the control group

- Reporting on departure from the Hardy–Weinberg equilibrium (simple)
- Data that would allow independent testing for departure from the Hardy–Weinberg equilibrium

CHAPTER FIVE

5. Discussion and conclusion

5.1 Discussion

Several investigators have noted a lack of adequate reporting in gene-disease association studies and have suggested that methodological factors may result in biased estimates of effect (21, 23, 36, 37). Such biases can have a negative impact on the evidence base, and in turn interventions based on flawed evidence can adversely affect related health applications (708).

This investigation evaluated the association between the reported methodological characteristics of gene-disease association studies and the outcomes of those studies in order to identify methodological factors that have the potential to influence outcomes; by implication, the identification of such factors can encourage proper methodological reporting. A blinded systematic electronic process of data extraction was conducted by two reviewers on 511 studies published in English; subsequent univariate and multivariate meta-regression analyses under a random effects model using an unrestricted maximum likelihood were designed to be as conservative as possible in discerning and interpreting the effect of any of the extracted methodological characteristics on the magnitude of gene-disease association outcomes. This appears to be the first research to use these methods to investigate the effect of methodological characteristics on the magnitude of outcomes in gene-disease association studies.

This work has benefited from the cooperation of and numerous consultations with experts in the field of genetic epidemiology and systematic reviews in Canada, the United States, the United Kingdom, Greece, and the Netherlands, who assisted the investigator in designing a methodologically sound strategy for data extraction and analysis that would yield conservative and legitimate results. For example, although the purpose of this thesis was to investigate the effect of methodological characteristics on the magnitude of gene-disease associations, in order to ensure that the results of the analyses were not skewed by disease category or medical specialty,

this variable was included in the analyses and in the final multivariate model. Thus, in the multivariate analysis, disease category was associated with the single biggest reduction in between study variance. Several sensitivity analyses were conducted and verified that the associations between the different methodological characteristics included in the final multivariate model and the magnitude of gene-disease association were substantially unchanged when each disease category was excluded in turn.

The sample of studies included in this thesis represents the largest to date that has investigated the possible influence of methodological characteristics on the effect size observed in gene-disease association studies; this large sample was used in an effort to enhance the generalizability and future application of this work (21, 161). By the same token, the included studies covered a larger number of journals than has been used in previously published research and covered a wide range of diseases, extending to almost all medical specialties. The sample included studies conducted in 52 countries, the United States and China being the largest contributors. These two countries are the source of a large proportion of the published gene-disease association studies worldwide (65).

Almost every study included in the sample reported multiple associations. However, in order to better isolate the influence of the methodological variables on the magnitude of outcomes, the systematic process of data extraction that was devised was based on extracting from each study the outcome with the most extreme uncertainty measure (e.g., *p*-value or confidence interval). The extraction process was directed toward odds ratios; if this was not reported, the extraction was directed toward outcomes from a 2×2 table; and if such information was not available the extraction was directed toward outcomes presented in the form of a 2×3 table. The heterogeneity showed borderline statistical non-significance ($p = 0.091$) with respect to the manner of presentation by design, which allowed the pooling of outcomes from the different sources. The fact that the outcomes extracted were deviated to the right (positive log odds ratio) could be attributed to the method used for extraction rather than generalized to an assumption about the outcomes of gene-disease association

studies. It is acknowledged that this approach may have exaggerated the effects of reported methodological characteristics on the magnitude of of gene-disease associations. However, this method of extraction of the outcome reflects the processes whereby researchers select of the results reported in the abstract of articles reporting genetic associations; these results tend to receive greater attention by knowledge users than the rest of the findings reported in the body of the article. The assessment of publication bias indicated that the studies included in the sample had an approximately symmetrical distribution and included a wide range of studies with different sample sizes and outcome measures.

With regard to study design, nested case-control studies tended have smaller magnitudes of effect in comparison with classic case-control studies, although its should be taken into consideration that nested case-control studies represented only 8.2% of the study sample. One explanation for this finding is that because the source of cases and controls is the same, this study design is less prone to selection bias and to bias arising from population stratification, whereas in other case-control studies, there is less confidence that the source population for cases is the same as that for controls. In most nested case-control studies, participants had been followed for a period of time and were subject to similar processes and criteria for data collection, sample collection, processing and analysis and diagnosis of presence or absence of disease. For these reasons, some investigators prefer nested case-control designs to classic case-control designs in molecular and medical research (709–713).

Analysis of the matching of cases and controls showed that studies in which individual matching was reported tended to find smaller magnitudes of effects than studies that used frequency matching or no matching. Studies that used frequency matching for one or several factors tended to show gene-disease associations with a larger magnitude of effect (log odds ratio) than those whose participants were not matched at all. Such differences tended to be smaller within the multivariate model analyses. Judging from the experience gained from the process of data extraction, matching was performed to adjust for many factors, the most common of which were age, sex, ethnicity, and geographical location. Epidemiological studies tend to match

for such factors to overcome confounding in an effort to obtain more precise, unbiased outcomes. Although in genetic association studies it may be important to match for ethnicity and location as a reflection of population stratification, in the current sample the rationale for matching for the selected factors was frequently not addressed, thus raising the concern that over-matching was in fact a feature of individual matching. These findings with respect to matching are consistent with concerns that have been raised that over-matching in case-control studies in an effort to overcome confounding may in fact lead to negative confounding, bringing the outcomes (odds ratios) to null if the effect of this matching is not factored into the statistical analysis. Such practice was observed during the process of data extraction in the present study; frequently, the matching of cases and controls was not accompanied by the appropriate statistical analysis, such as computing the conditional maximum likelihood or the Mantel–Haenszel estimate. The implications of over-matching in gene-disease association studies may require further evaluation in the future (712–715). The findings of this investigation show the need to provide detailed reporting of the process of matching, along with justification for the need to match for the chosen factors and a demonstration that these factors would otherwise result in confounding. Further, these findings point to the need for clear reporting in case-control studies as to whether matching was accompanied by suitable statistical analysis.

The impact of the replication of reported outcomes was also investigated. Studies that reported a replicated finding tended to report smaller magnitudes of effect than studies that claimed to present a first report. Ioannidis and colleagues have drawn the same conclusion from their research; their evaluation of the outcomes of studies included in 36 meta-analyses suggests that replicated findings tend to have smaller magnitudes of effect than first reports (12). This finding supports the suggestion by several researchers that the replication of findings is an important step in ensuring the validity of outcomes of gene-disease association studies (22, 24, 29, 31, 32, 48, 53, 54, 62, 63, 716). Thus, to make more reliable knowledge inferences from gene-disease association studies, users are encouraged to take into consideration whether

the findings were replicated, whether as a part of the same study (using different samples or different stages) or in other research.

The magnitudes of effect reported in European, North American, and Asian studies were similar (bearing in mind, however, that all studies were published in English). Although some analyses have found that the inclusion or exclusion of studies conducted in Asian countries such as China did not alter the overall point estimates, other studies have suggested that the results of gene-disease association studies published in Asia differed systematically from the results of studies published elsewhere (159–161). A possible explanation for this discrepancy is that the sample used in the present study represents studies that were published recently and indexed in HuGENet in 2007, whereas previous analyses were based on studies published between 1991 and 2004. It is possible that changes have occurred recently in publication policies and in the methodological practice of genetic research in Asia (12, 717, 718). Another possible reason for the similarity of results is that the sample used in the present study included a large number of studies from a wider range of countries in Asia than the samples used in earlier methodological analyses, which concentrated mainly on China; this factor might have had the effect of making the magnitude of effects smaller, thus increasing the similarity of effects among the three continents. These findings might reassure researchers conducting systematic reviews of gene-disease association research that studies from Asia in general are frequently recognized to have magnitude of effects similar to those reported in North America and Europe.

To the best of the present investigator's knowledge, this is the first research that has included and compared gene-disease association studies conducted in Africa, Australia, and South and Middle America together with research originating from North America, Europe, and Asia. Studies in the sample that were conducted in Africa, Australia, and South and Middle America tended to have noticeable deviation from unity in comparison with those published elsewhere. (However, studies reported in Africa did find interesting inverse associations between genes and diseases, perhaps pointing to protective effects that may be relevant to the search for preventive

measures to combat prevalent illnesses, e.g., infectious diseases). One explanation for this deviation from the null in studies from Africa, Australia, and South and Central America in comparison with those from North America, Europe, and Asia could be the low number of included studies from the former group, which also had small sample sizes; specifically, in the African and South and Central American studies the median sample size was 247 and 260, respectively, in comparison with a median sample size of 700 and above in studies from other regions. This observation is consistent with the finding reported by Ioannidis and colleagues that large studies tend to have more conservative results in comparison with smaller studies (716). The aggregated magnitude of effects reported in studies from Africa, Australia, and South and Central America also showed wider confidence intervals, which may be attributed again to the low number of included studies from each of these continents and the large variation between magnitudes of effect. The homogeneity of these effect sizes is likely to improve with time and with improvements in the process of conducting and reporting gene-disease association studies (12, 718, 719).

Studies that reported on the calculation of sample size or statistical power tended to produce smaller magnitudes of effect than studies that did not report on these characteristics. In some cases, this reporting reflected good methodological practice; in others, where the researchers were unable to find a significant association between a gene and the putative corresponding disease, it appeared to support a claim that a larger sample size would have provided sufficient statistical power to detect such an association. The consistent reporting of sample size or power calculations will help to resolve doubt about uncertain associations. Thus, investigators of gene-disease association studies are encouraged on carry out sample size or power calculations before conducting their research, rather than performing these calculations post hoc or after the fact; this practice would help to avoid the misinterpretation of findings, and is in agreement with the view of Goodman and colleagues that post hoc power calculation is an inappropriate methodological practice (720).

With respect to the source of the included controls, similar gene-disease association outcomes were obtained whether the controls were selected from specific groups such

as hospital patients or blood-bank donors, or from the general population with detailed reporting on the sampling frame, or, to some extent, from the general population but without a full description of the sampling frame. This reassuring finding is consistent with the finding of Garte and colleagues that the use of hospital controls was not associated with biased outcomes related to genotype frequencies in comparison with the use of controls from the general population (721). The same was also reported by the Wellcome Trust Case Control Consortium, who found that the minimal differences between blood-donor/specific-group controls and population-based controls did not preclude pooling of the two groups for the purpose of investigating a number of genetic disease associations in a genome-wide association study (722).

Interestingly, when control groups were derived from a combination of special groups and the general population, outcomes tended to be of a smaller magnitude. One explanation for this might be the inclusion of a comparatively high number of controls in this mixed group—that is, a median of over 800 participants, as opposed to 300–500 in the other groups. The effect of this on the gene-disease association outcomes was reduced when the number of controls was included in the multivariate analysis, indicating a need for more detailed investigation of such findings in the future.

A major finding drawn from the analysis of the effect of reporting the source of controls was that an absence of this reporting (14.87 %) was associated with larger gene-disease association outcomes in comparison with studies that used population-based or special-group controls. This finding raises questions about the validity of findings in gene-disease association studies in which the source of controls is unreported.

Multivariate analysis demonstrated that, as the final number of reported control participants increased, the magnitude of the gene-disease association outcome decreased. This association was statistically significant, accounting for some of the heterogeneity between study outcomes: the pooled odds ratio of gene-disease

outcomes was lowered by 0.01 for every 100-participant increase in the control group.

In addition, the experience gained during the process of data extraction revealed that the reporting of those who were eligible and those who were actually included was inconsistent and vague (e.g., the abstract of some studies reported the eligible participants as if they were the final reported sample).

On the basis of these points, providing detailed information on the source of study controls along with information on eligible, excluded and included study participants in general, and on controls in particular, along with the reasons for exclusion, might lend more credibility to reported outcomes and enable the future investigation of the influence of these factors on gene-disease association outcomes.

Analysis of reporting on deviation from Hardy–Weinberg equilibrium (HWE) showed that detailed reporting on HWE resulted in a better explanation of the between-studies outcome variations in comparison with simple reporting or no reporting on HWE. This analysis found that studies that reported that genotypes were not in equilibrium, or in which HWE was unclear, produced outcomes with large values, and with very wide confidence intervals, in comparison with studies that reported other results for HWE. As shown in the multivariate model, the important factor was whether in fact the genotype under investigation was associated with the gene-disease outcome, regardless of whether the rest of the genotypes tested were in equilibrium among the control participants. The analysis showed that not reporting on HWE was associated with larger gene-disease outcomes, supporting previous observations that studies that reported disagreement with HWE showed significantly larger outcomes in comparison with other studies included in the meta-analysis. These results suggest that testing for HWE provides an indicator of the validity of gene-disease association outcomes and supports previous descriptions of the importance of such testing in the control group (23, 24, 37, 723, 724).

Two reassuring "negative" findings were that (1) there were no statistically significant difference between studies that investigated cancerous diseases and those

that did not and (2) the number of genes or genetic markers tested in the association made no difference to the magnitude of outcomes. These findings may to some extent give knowledge users confidence in taking into account the outcomes of gene-disease association studies regardless of the number of genes or genetic markers that were tested and included in the analysis.

With respect to the effect of journal impact factor, the present analysis produced a non-significant finding that studies published in journals with lower impact factors tended to have larger magnitudes of effect than studies published in journals with high impact factors. This non-significant finding may support previous reports of the phenomenon whereby journals with lower impact factors tend to publish case-control studies with larger outcomes and exhibit a publication bias, whereby publication depends on the strength and the direction of findings; this finding may also be in line with what has been called a "reverse tower of Babel bias," by which local journals tend to publish more spuriously significant results in comparison with international journals (161, 162, 717).

With respect to the effect of the data source on the reported outcomes of gene-disease association studies, it appeared that reported outcomes were closely similar regardless of whether researchers collected the data primarily by themselves, building on pre-existing data or conducted a secondary analysis of data. The fact that secondary analysis of pre-existing data showed wider confidence intervals might be attributed to the low number of studies included in this category (1.17%). This finding is important in view of the fact that over 17% of the studies included in the sample relied on data collected from previous studies.

With respect to the investigation of the effect of relatedness (i.e., blood relationship) between cases and controls on the magnitude and direction of gene-disease association outcomes, despite the fact that univariate analysis of reporting of blood relationship was able to account for some of the variation between study outcomes, this effect disappeared after adjustment for the other factors in the multivariate analyses. On the other hand, in 68.49% of the studies examined, the relatedness between cases and controls was unclear. Although similar gene-disease association

outcomes were obtained whether relatedness was absent or unclear, those studies that reported the presence of relatedness showed larger outcomes with wider confidence intervals; this finding might be attributed to the low number of studies included in this category (1.17%). Judging from the available evidence, it appears that a definitive assessment of the role of relatedness reporting for cases and controls cannot be determined at the present time. There is a need for more transparent reporting on relatedness to help in the future assessment of the effect of this variable on gene-disease association outcomes.

It has been suggested that reporting on the conduct of measures of quality assurance can influence gene-disease association outcomes, and that failing to carry out such measures might lead to biased outcomes (725). However, the sample of studies included in the present analysis did not produce evidence of this effect, although it demonstrated that studies that reported quality assurance measures had smaller gene-disease association outcomes in comparison with those that did not report any such measure. One possible reason for this effect is that the type of quality assurance reported in each study should be investigated in more detail (e.g., studies that reported blinded genotyping versus studies that did not report blinded genotyping). Nevertheless, such stratification would have required considerable time and effort for data extraction and analysis and would not have been feasible within the time frame of this thesis. Nevertheless, good reporting of the quality-control measures used in gene-association studies is needed to facilitate the future investigation of the influence of quality assurance measures on gene-disease outcomes.

Statistical adjustment for the covariates did not yield sufficient evidence to explain between-study outcomes in comparison with those that did not perform such analyses or for which such analyses were not applicable. It became apparent from the data extraction of the included studies that the use of statistical methods such as logistic regression was associated in the majority of the studies with larger rather than smaller magnitudes of effect. To enable the further investigation of such effects in the future, the conduct and subsequent reporting of statistical adjustments for the covariate will

be needed when applicable, regardless of the statistical significance of the outcome reported.

5.2 Conclusion

The transparent reporting of the methodological characteristics of gene-disease association studies allows readers to better assess the validity of the information derived from these studies and enables the more effective implementation of that information in practice and policy-making in the field of population and public health. In this investigation the association between methodological characteristics and gene-disease association outcomes reported in case-control studies indexed in HuGENet in 2007 was investigated in one of the largest samples of research studies analyzed to date. The purpose of this research was to build an evidence-based evaluation of the influence of methodological factors on outcomes, to test previously suggested hypotheses, and to support an evidence-based understanding of such influences. It should be borne in mind that the studies included in this review were all derived from the literature indexed in PubMed and were all published in English.

In this study the impact of methodological characteristics was investigated in case-control studies exclusively. Further analyses addressing other research designs (e.g., cross-sectional and cohort studies) are needed to obtain a complete assessment of the major methodologies used to investigate gene-disease association studies. Also, other genetic association types should be investigated, such as gene-environment interactions, gene-gene interactions, genome-wide associations and family-based associations. Such research would provide a comprehensive assessment of the impact of methodological characteristics on almost all of the designs used to investigate the relationship between genes and diseases. Also, this will help in assessing the differences in the impact that each methodological characteristic has across all of the aforementioned designs and types.

Among the major points that merit further investigation is the impact of detailed reporting on the use of various quality assurance measures on gene-disease

association outcomes, the effect of statistical adjustment for covariates, and relatedness of cases and controls. Detailed reporting of these factors should be incorporated into the methodological practice of gene-disease association studies to support the credibility of the knowledge derived from such research and to enable the future assessment of the role that these factors play in the effect sizes reported in gene-disease association research.

Accordingly, and to facilitate the practical application of the findings of this research, Table 5.1 summarizes its most important findings. While it is acknowledged that the findings of this research may need further confirmation, researchers and investigators involved in case-control studies of gene-disease associations are encouraged to apply and subsequently report on the methodological items listed in the table. By the same token, peer reviewers and journal editors are encouraged to support reporting on these methodological characteristics in the research they scrutinize and publish. Providing such knowledge will help to improve the validity of gene-disease association outcomes and their subsequent application.

Table 5.1: Main conclusions and recommendations

Items	Comments
Study design	Gene-disease association outcomes tend to be more conservative in nested study designs in comparison with classic case-control studies.
Matching of cases and controls	Detailed reporting of the process of matching and a justification of the factors matched for (i.e., a demonstration that they would otherwise result in confounding) should be provided. Matching should be accompanied by a suitable statistical analysis.
Replication of findings	Knowledge users are encouraged to take into consideration whether the findings were replicated, either as part of the same research or in a different setting.
Origin of studies	Studies conducted in North America, Europe, and Asia report similar magnitudes of outcome. This pattern was not observed in studies from the rest of the world.
Sample size / power	A sample size or power calculation should be conducted before the research study is conducted.
Source of control participants	The source of the control group should be described; the absence of reporting on this variable was associated with larger gene-disease association outcomes. Gene-disease association outcomes show a similar magnitude whether the source of controls is a specific group (e.g. hospital-based) or population based.
Size of control group	The size of the control group should be adequate and justifiable, since gene-disease association outcomes tend to decrease as the number of controls increases. Researchers are encouraged to report the reasons for the exclusion of controls from the study
Hardy–Weinberg equilibrium	Researchers are encouraged to test and report on departure from the Hardy–Weinberg equilibrium in the control group. To support stronger knowledge inferences related to gene-disease associations, the investigated genotype associated with the outcome of interest should be in equilibrium regardless of whether the rest of the genotypes included in the study are in equilibrium.
Number of genes or genetic markers	The magnitude of gene-disease association outcomes is similar regardless of the number of genes or of genetic markers tested. Knowledge users can trust these research findings regardless of the number of genes or genetic markers tested.
Journal impact factor	Different journals can be used for the purpose of knowledge utilization, while taking into consideration the non-significant finding that results tend to be of a slightly larger magnitude in journals with a low impact factor.
Data source	Knowledge related to gene-disease outcomes is closely similar whether researchers used pre-existing data or collected the data primarily by themselves. Knowledge users can trust the research findings from these different sources.

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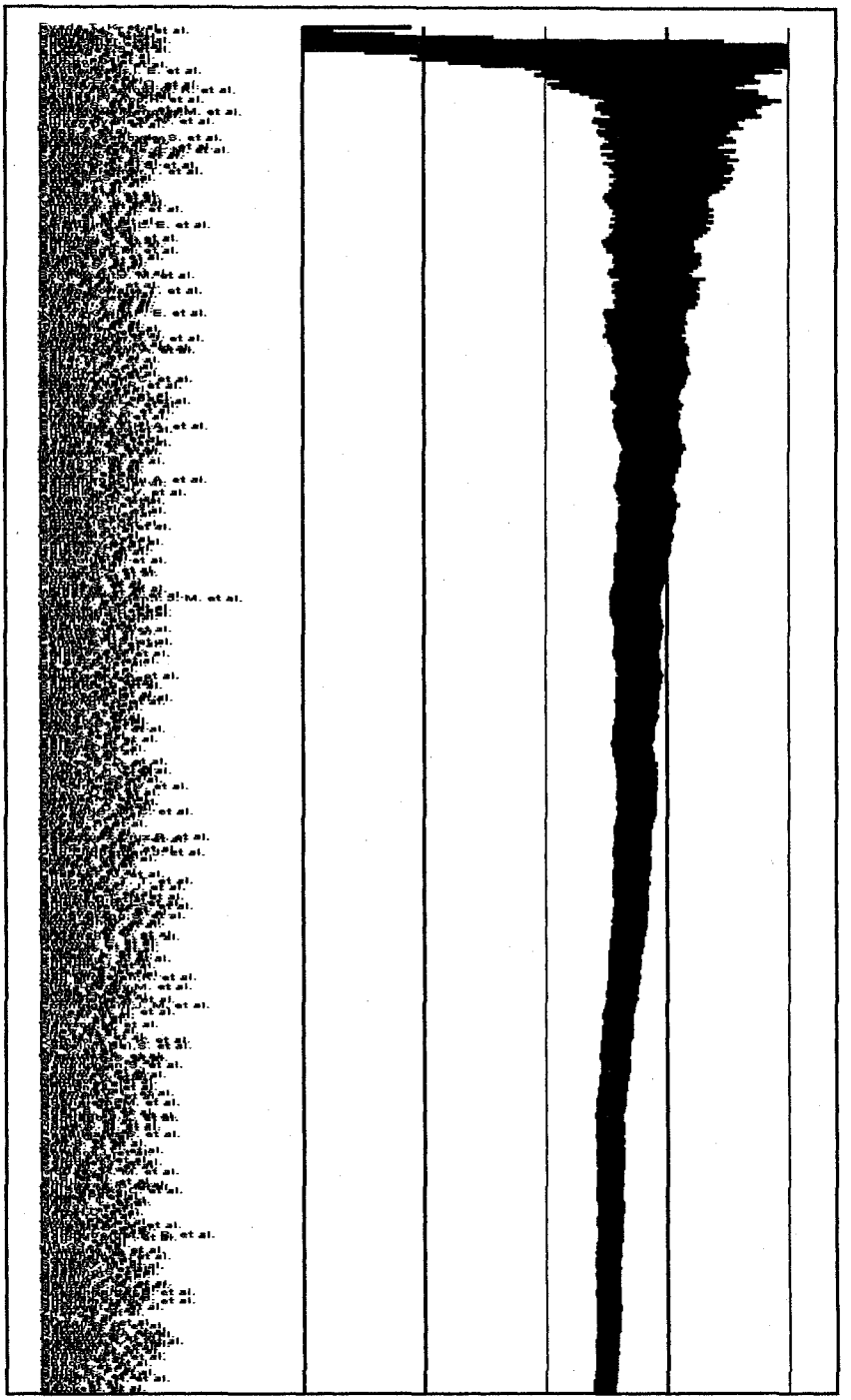
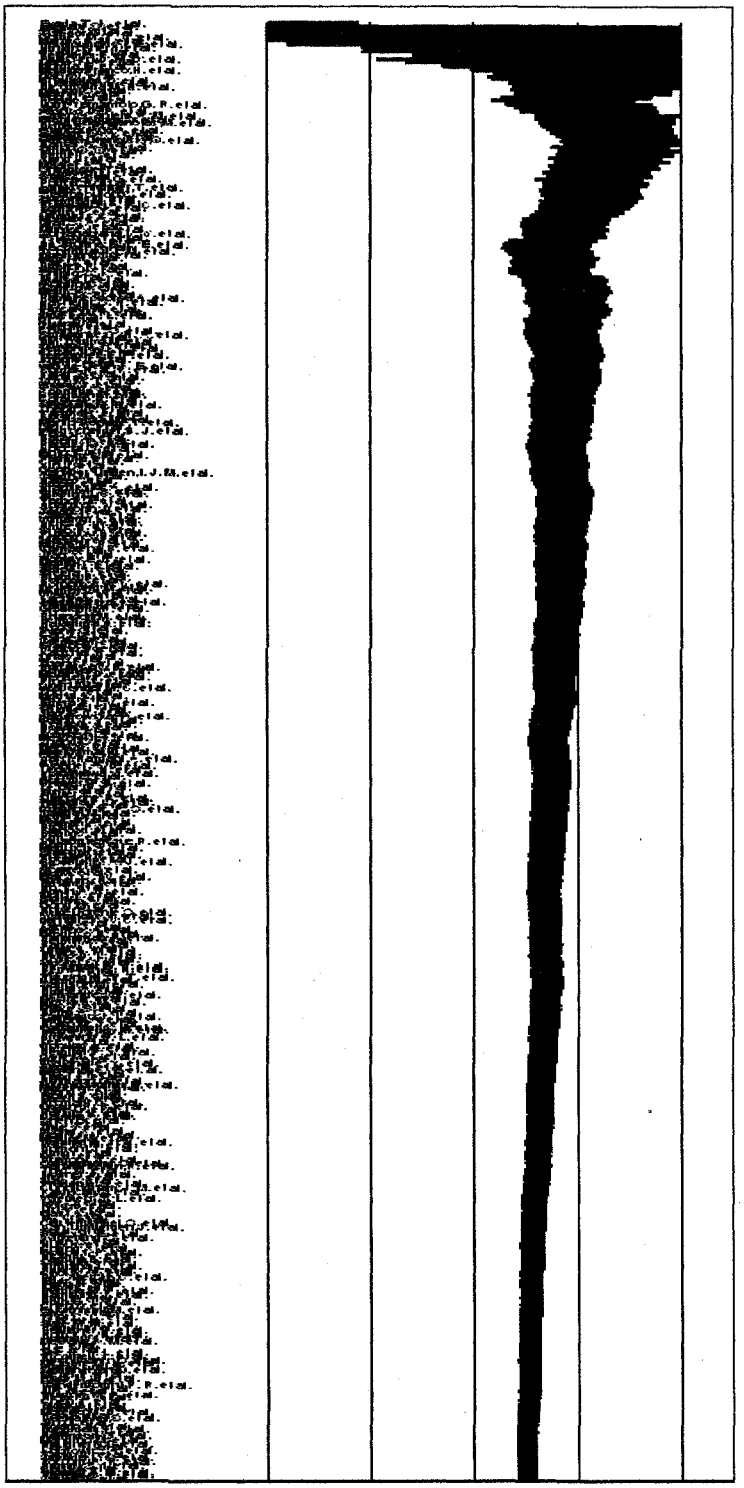
Appendices

Appendix I



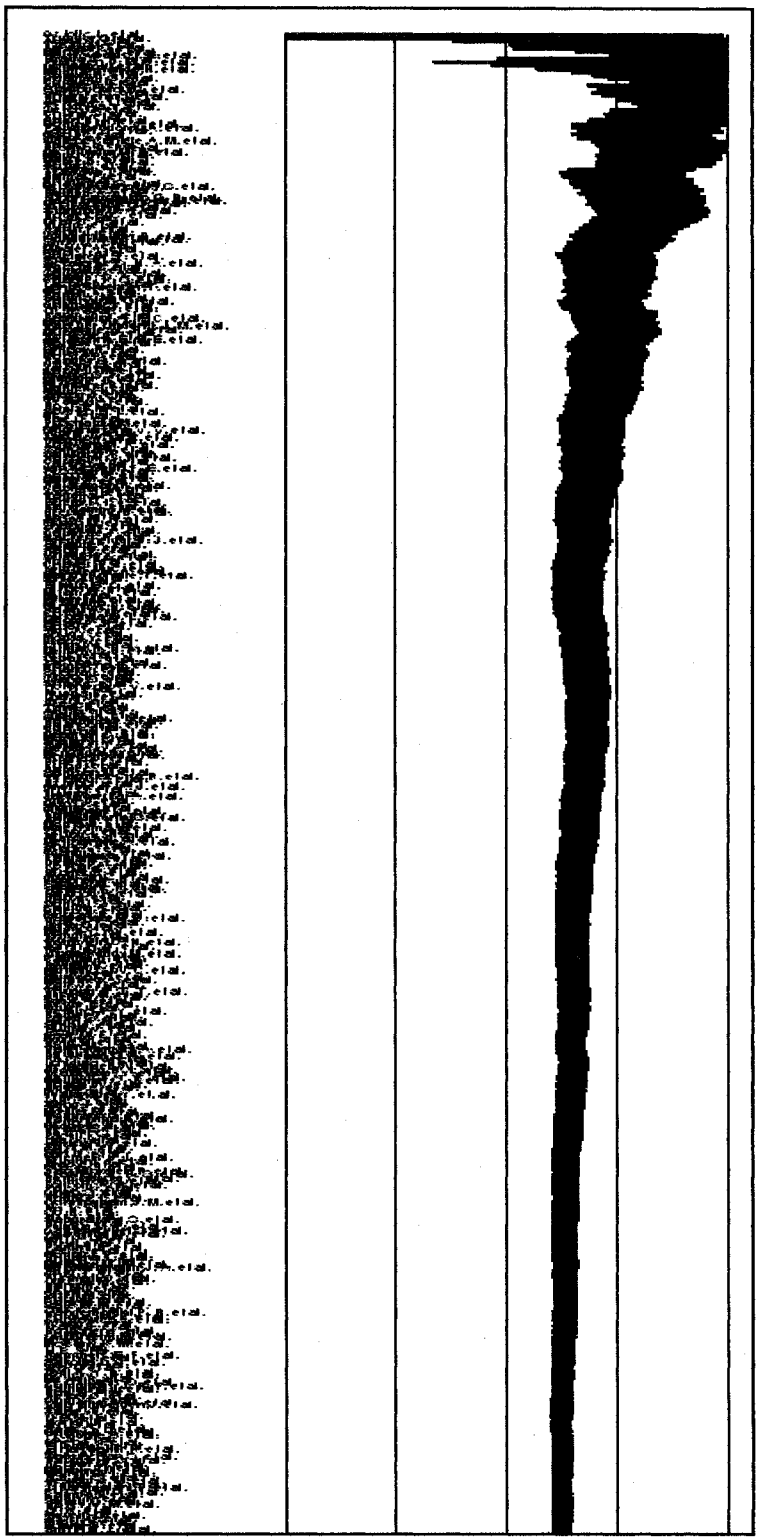
Appendix I: Cumulative meta-analysis of log odds ratio of gene-disease association studies with downward increase in the journal impact factor in each study.

Appendix II



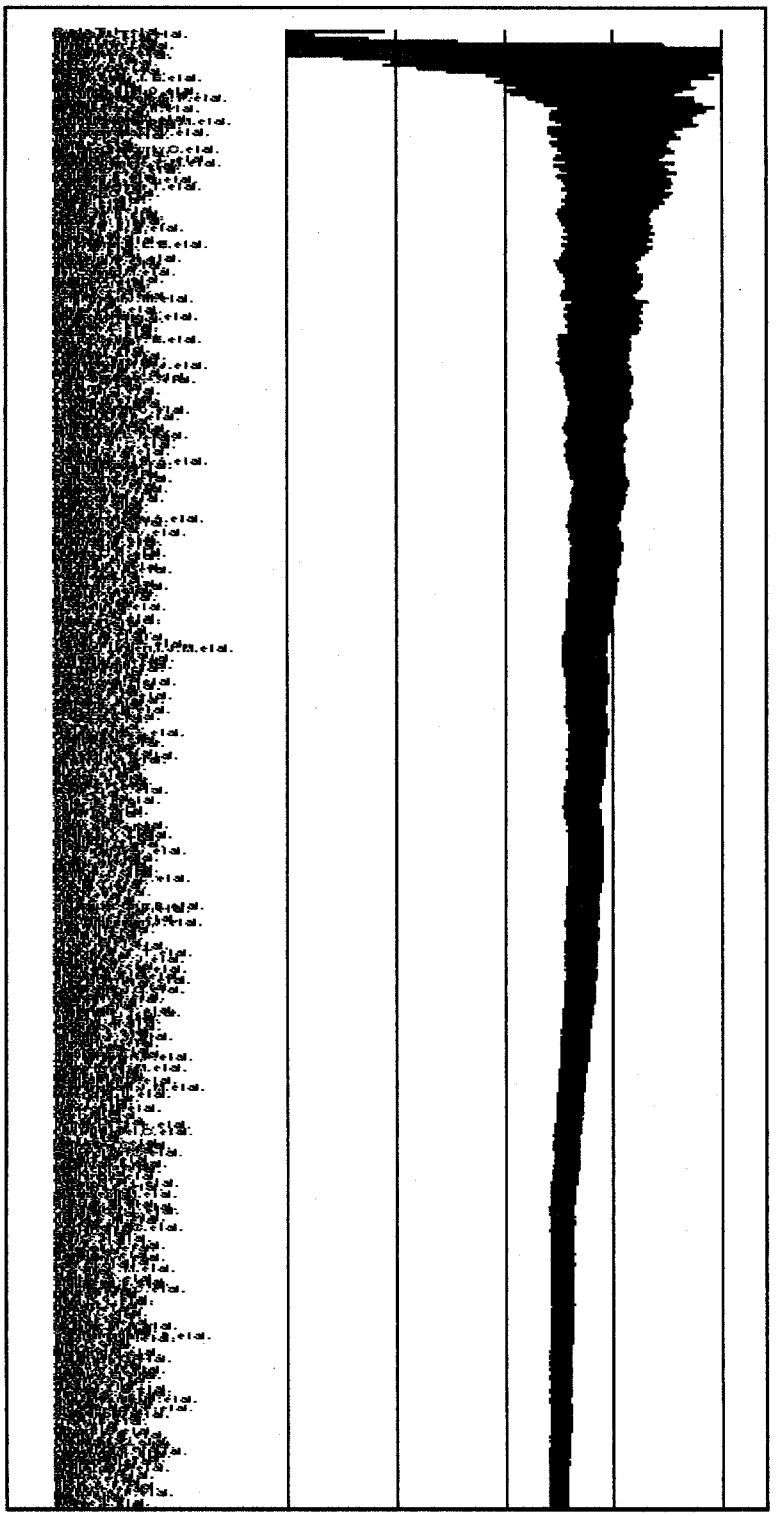
Appendix II: Cumulative meta-analysis of log odds ratio of gene-disease association studies with downward increase in the study sample size in each study.

Appendix III



Appendix III: Cumulative meta-analysis of log odds ratio of gene-disease association studies with downward increase in the study final reported number of cases in each study.

Appendix IV



Appendix IV: Cumulative meta-analysis of log odds ratio of gene-disease association studies with downward increase in the study final reported number of controls in each study.