

# Claims of Sex Differences

## An Empirical Assessment in Genetic Associations

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SEX IS A FACTOR THAT HAS BEEN invoked extensively in the past as a modulator of effects in clinical research. However, empirical data from randomized trials suggest that many claimed subgroup differences based on sex have been spurious and led to serious misconceptions.<sup>1</sup> For example, aspirin was believed to be ineffective in secondary prevention of stroke in women for more than 10 years based on an underpowered subgroup analysis.<sup>2</sup>

In the human genome era, for many common diseases, published research has often considered that some common gene variants may have different effects in men vs women. Many diseases or traits with strong genetic backgrounds have different prevalence in the 2 sexes. For example, autoimmune diseases, endocrinopathies, and longevity are more common in women, while coronary artery disease, ischemic stroke, and high cholesterol levels are more common in men.<sup>3</sup> These observations do not necessarily mean that a specific gene variant should also have a different effect in men vs women. For most phenotypes, many common gene variants are likely to be responsible for determining susceptibility to disease.<sup>4</sup> Among autosomal variants, only some of them, if any, may interact with sex. However, given that sex information is always readily available in such studies, it is easy to test whether it influences genetic effects. Eventually, a large number of claims are made for sex dif-

**Context** Many studies try to probe for differences in risks between men and women, and this is a major challenge in the expanding literature of associations between genetic variants and common diseases or traits.

**Objective** To evaluate whether prominently claimed sex differences for genetic effects have sufficient internal and external validity.

**Data Sources** We searched PubMed through July 6, 2007, for genetic association studies claiming sex-related differences in the articles' titles. Titles and abstracts and, if necessary, the full text of the article were assessed for eligibility.

**Study Selection** Two hundred fifteen articles were retrieved by the search. We considered eligible all retrieved association studies that claimed different genetic effects across sexes of 1 or more gene variants for any human disease or phenotype. We considered both biallelic and multiallelic markers (including haplotypes) and both binary and continuous phenotypes and traits. We excluded non-English-language studies; studies evaluating only 1 sex; studies in which sex was treated only as an independent predictor of disease; studies that did not address any association of the investigated genetic variant with a disease or trait; studies not involving humans; and studies in which the authors did not claim any sex difference.

**Data Extraction** Two evaluators independently extracted data with a third evaluator arbitrating their discrepancies. Data evaluation included whether analyses were stated to have been specified a priori; whether sex effects were evaluated in the whole study or subgroups thereof; and whether the claims were appropriately documented, insufficiently documented, or spurious. For appropriately and insufficiently documented claims we performed the calculations for gene-sex interaction whenever raw data were available. Finally, we compared the sex-difference claims with the best internal validity against the results of other studies addressing the same interaction.

**Results** We appraised 432 sex-difference claims in 77 eligible articles. Authors stated that sex comparisons were decided a priori for 286 claims (66.2%), while the entire sample size was used in 210 (48.6%) claims. Appropriate documentation of gene-sex interaction was recorded in 55 claims (12.7%); documentation was insufficient for 303 claims and spurious for the other 74. Data for reanalysis of claims were available for 188 comparisons. Of these, 83 (44.1%) were nominally statistically significant at a  $P = .05$  threshold, and more than half of them ( $n = 44$ ) had modest  $P$  values between .01 and .05. Of 60 claims with seemingly the best internal validity, only 1 was consistently replicated in at least 2 other studies.

**Conclusion** In this sample of highly prominent claims of sex-related differences in genetic associations, most claims were insufficiently documented or spurious, and claims with documented good internal and external validity were uncommon.

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ferences. However, are these claims justified and valid?

Herein, we describe empirically a large sample of prominently claimed sex differences for genetic effects. We evaluated whether these claims were methodologically robust or were made based on selected and/or suboptimal analyses and with insufficient or spurious documentation. We also examined whether claims that seemingly had optimal internal validity had been corroborated by any additional studies.

## METHODS

### Selection of Studies

We aimed to assemble a sample of studies that claimed sex subgroup differences in gene-disease associations and in which the claim was so prominent that it was mentioned even in the title of the article. Sex subgroup differences are a very common theme in the epidemiological literature. Assembling all of them or even a systematic fraction thereof would be prohibitive. Any electronic search would yield only a modest sample of the thousands of articles evaluating sex subgroup differences, since these are often listed as secondary or tertiary results. Conversely, by focusing on the title, we would favor the selection of most prominent perceived subgroup differences between sexes. These studies are the ones in which the authors (and apparently also the peer reviewers and editors) are most confident of the strength of the observed sex subgroup differences.

We searched PubMed through July 6, 2007. PubMed is considered highly representative and inclusive of genetic epidemiology studies.<sup>5</sup> We used a search strategy that would have high specificity for assembling a convenient sample of eligible studies: *polymorphism\* [ti] AND (gender [ti] OR sex [ti])*. We perused titles and abstracts and, if in doubt, also the full text, for eligibility. We considered eligible all retrieved association studies that claimed different genetic effects across sexes of 1 or more gene variants for any human disease or phenotype. We considered both biallelic and multiallelic

markers (including haplotypes) and both binary and continuous phenotypes and traits.

We excluded non-English-language studies; studies evaluating only 1 sex; studies in which sex was treated only as an independent predictor of disease; studies that did not address any association of the investigated genetic variant with a disease or trait; studies not involving humans; and studies in which the authors did not claim any sex difference. Eligible studies were included regardless of the extent of the quantitative information that they provided to support their claims. Eligibility assessment was performed by 2 independent evaluators (N.A.P. and A.T.). Discrepancies were resolved by consensus.

### Data Extraction

Two evaluators independently extracted data, with a third evaluator arbitrating their discrepancies. We extracted the following data from each eligible study: first author, journal of publication, year, total sample size, percentage of women, gene(s) and variant(s) for which sex differences were claimed, and disease/phenotype(s) thereof.

For each pair of gene variant and phenotype for which the investigators claimed a sex difference, we recorded the exact phrasing of the claim and any allusion that the difference was tested based on a priori plans or as part of post hoc analyses; the type of genetic variant (eg, biallelic, multiallelic single-locus, haplotypes of many variants); and the type of phenotype (ie, binary outcome or continuous trait). Especially for biallelic variants, we recorded if a specific genetic contrast (recessive, dominant, additive, allele-based, model-free, or other/unclear) was used. We also recorded (per sex) the presented effect sizes and measures of uncertainty thereof or raw data that could be used to verify the presence of each claimed sex difference.

For each claim of sex difference, we recorded whether it was based on an analysis of the entire study sample or

a subset thereof. If the latter, we recorded the definition of the subset and whether any a priori justification was provided for the subset selection. We specified whether subsets were defined based on genetic information for the gene variant of interest (eg, comparison of AA vs aa homozygotes without consideration of Aa heterozygotes; comparison of haplotypes 1 vs 4 without consideration of haplotypes 2 and 3), genetic information for some other gene variant (eg, selection of individuals who have some specific genotype for another gene marker), other patient characteristics (eg, age, ethnic or racial descent), other considerations, or combinations of the above.

For each claim of sex difference, we also recorded whether it was appropriately documented, insufficiently documented, or spurious. For appropriately documented claims, 3 criteria were required. First, the article had to address a genetic effect that was based on the same genetic contrast in both sexes. Second, it did not compare different subsets in the 2 sexes (eg, old men vs young women). Third, it needed to either report a nominally statistically significant (defined as a *P* value threshold of .05) test that examined sex-gene interaction or the interaction had to be very obvious because the presented confidence intervals of effects for each sex were not overlapping. Insufficiently documented claims were those in which only the first 2 criteria were fulfilled. Spurious claims failed either one or both of the first 2 criteria.

Insufficient documentation does not mean that the claim is necessarily inappropriate and wrong. An insufficiently documented claim may be correct (a significant interaction may exist after all) or wrong (a significant interaction may not exist), but this is not clear from the analyses performed or the way the claim is made in the article.

### Reanalysis of Sex Claims

For each sex claim that was not spurious and where suitable information was available, we tried to perform calcula-

tions to test whether there was indeed a nominally statistically significant sex subgroup difference in the effect sizes (sex-gene interaction).

Whenever a dominant, recessive, or allele-based model was implied, we used for each sex the natural logarithm of the odds ratio (binary outcomes) or the absolute difference (continuous outcomes) and their variances. Whenever effect sizes were not reported for both sexes, we tried to estimate them from the presented information on published  $2 \times 2$  tables and means per sex. Whenever variances were not reported, we tried to estimate them from the presented information on confidence intervals, standard deviation, or standard error of the mean and number of observations. We then calculated the  $z$  score as a ratio where the nominator is the difference of normalized effects and the denominator is the square root of the variance of the difference. Whenever an additive model was implied, we fitted trend models for each sex and used the resulting coefficients and respective standard errors to calculate the  $z$  score. Finally, whenever a model-free approach was implied, we used an analysis of variance with a sex-genotype interaction term.

All these analyses were performed using the data that pertain to the same subjects for which the sex subgroup difference was originally claimed by the authors. Thus, if the sex claim had been made for the entire study population, we examined sex-gene interaction in the entire population; if the claim had been made for a subset, we examined sex-gene interaction in that same subset. When both unadjusted and adjusted estimates of effect were available in full detail, we used the unadjusted estimates, except when both unadjusted and adjusted estimates were reported as different claims. In this case, both were used if possible.

### Corroboration of Statistically Significant Sex-Gene Interactions by Other Studies

Even if a sex-gene interaction has been presented with optimal statistical and

analytical support, it is not certain that it truly exists. Genetic effects are subject to an extensive multiplicity of testing and are also susceptible to diverse errors and biases.<sup>6</sup> Therefore, replication by additional independent studies is considered essential for reinforcing the credibility of genetic effects.<sup>7</sup> We examined whether proposed sex-gene interactions in our sample had indeed been evaluated by additional studies and, if so, whether the results of these studies agreed with the proposed interactions.

We focused on claims of sex differences that met all of the following criteria: their analyses were stated to have relied on a priori considerations, raw data were provided, sex-gene interaction was nominally statistically significant at the  $P = .05$  level on our reanalysis of the data, and either the whole study sample had been analyzed or a subset had been selected based on a priori considerations. These claims were the ones that apparently had the best possible internal validity.

We perused in detail each of the articles reporting such claims and recorded whether they had cited any previous studies investigating the same sex-gene interaction. Additionally, we searched the ISI Web of Knowledge for articles that cited the articles meeting the criteria mentioned above. We then retrieved these cited and citing studies and examined whether they had evaluated the same sex-gene interaction and, if so, what was found.

We acknowledge that our search strategy may not have been 100% sensitive to find all studies that tested these interactions. However, there is no documented reliable strategy to retrieve all such articles, and interactions are probably often buried in text or not reported at all, especially if not nominally significant ( $P > .05$ ) and "noteworthy." However, prior supporting studies are very likely to have been cited in these articles when the interactions were the main theme and even were part of the article's title. Similarly, subsequent studies that did find the same interaction would be

likely to cite an article in which the main theme had been that same interaction. Overall, our strategy probably favors the retrieval of studies that agreed rather than disagreed with the proposed interactions.

Analyses were conducted in Intercooled Stata, version 8.2 (Stata Corp, College Station, Texas).  $P$  values are 2-tailed.

## RESULTS

### Eligible Sample of Articles and Sex Subgroup Claims

The electronic search yielded 215 citations; 138 were excluded on close scrutiny: 5 were non-English-language papers, 34 studies evaluated only 1 sex, 11 used sex as an independent predictor, 28 were not association studies, 54 were nonhuman studies, 4 had no claim of sex difference, and we could not find the full articles for 2 citations. Seventy-seven articles<sup>8-84</sup> were eligible and contained a total of 432 distinct claims of sex subgroup differences (median = 4 [interquartile range {IQR}, 2-7] claims per article).

These studies were published between 1994 and 2007 in 63 different peer-reviewed journals with a median impact factor of 3.868 (IQR, 2.826-5.699). The median sample size of these studies was 560 (IQR, 274-921) and the median proportion of women was 49% (IQR, 44%-53%). Sixty-three different genes were implicated across the 432 claims. The claims pertained to a wide variety of diseases and phenotypes, the most common being hepatitis C virus infection ( $n = 32$  claims), high-density lipoprotein cholesterol ( $n = 26$ ), lung cancer ( $n = 21$ ), type 2 diabetes mellitus ( $n = 19$ ), multiple sclerosis ( $n = 18$ ), hypertension ( $n = 14$ ), low-density lipoprotein cholesterol ( $n = 13$ ), Paget disease of bone ( $n = 12$ ), and diabetic nephropathy in type 1 diabetes ( $n = 10$ ) (TABLE 1).

### Reported A Priori Evaluation of Sex Claims

Of the 432 claims, 286 (66.2%) were reported as being based on a priori stated comparison of the sexes and 68

**Table 1.** Evaluated Articles Making Prominent Claims for Sex Differences in Their Titles

Source	Total Sample, No.	Women, %	No. of Claims	Gene	Variant/Haplotype <sup>a</sup>	Disease/Trait
Méplan et al, <sup>9</sup> 2007	75	56	23	<i>SePP</i>	Ala234Thr	Plasma selenoprotein P Glutathione peroxidase 3 Thioredoxin reductase 1 Erythrocyte thioredoxin reductase 1 Glutathione peroxidase 1 activity Glutathione peroxidase 1 protein Glutathione peroxidase 1 activity/protein ratio Lymphocyte glutathione peroxidase 4
Hayashi et al, <sup>10</sup> 2007	200	58	10	<i>ESR1</i>	30T/C 401T/C	Systolic blood pressure Mean arterial pressure HDL cholesterol Brachial-ankle pulse-wave velocity
Baud et al, <sup>11</sup> 2007	612	58	4	<i>COMT</i>	Val158Met	Anger Anger control
Yang et al, <sup>12</sup> 2007	898		2	<i>CTLA-4</i>	+49A/G	Cord blood IgE levels $\geq 0.5$ kU/L
Glorioso et al, <sup>13</sup> 2007	712	48	8	<i>ATP1A1</i> <i>Dear</i>	SNP1 SNP10 SNP11 SNP12 CC haplotype <i>ATP1A1</i> SNP1-SNP2 TT haplotype TG haplotype	Hypertension Normotension
Gallagher et al, <sup>14</sup> 2007	1095	46	3	<i>UGT2B17</i>	ins/del	Lung cancer Lung adenocarcinoma
Beyens et al, <sup>15</sup> 2007	302 690 992	44 53 50	12	<i>TNFRSF11B</i>	rs1485286 C/T (SNP 11) rs2073617 rs6415470 rs11573869 GA rs2073618 TGGACGC TCGATGC haplotypes distribution	Paget disease of bone
Leung et al, <sup>16</sup> 2007	560	26	2	<i>SLC11A1</i>	SLC6a/b	Tuberculosis
Bolufer et al, <sup>17</sup> 2007	897	47	9	<i>GSTM1</i> <i>NQO1</i> <i>GSTT1</i>	ins/del *2 variant ins/del	Acute myeloblastic leukemia Acute lymphoblastic leukemia
Yamaguchi et al, <sup>18</sup> 2007	4854	45	19	<i>THBS2</i> <i>F3</i> <i>ADIPOQ</i> <i>PON1</i>	T>G (3' UTR) -603A>G G>T (intron 2) A>G (Arg160Gly)	Type 2 diabetes mellitus
Russo et al, <sup>19</sup> 2007	1604	50	4	<i>CYP11B2</i>	-344C/T	Systolic blood pressure Diastolic blood pressure Hypertension
Froehlich et al, <sup>20</sup> 2007	174	49	2	<i>DRD4</i>	7 allele	Rule learning and reversal, total trials adjusted Rule learning and reversal, stages completed
Dedoussis et al, <sup>21</sup> 2007	173	53	8	<i>PPARG2</i>	Pro12Ala	Total triglycerides Total cholesterol HDL cholesterol Apolipoprotein B Total cholesterol/HDL cholesterol ratio Apolipoprotein B/Apolipoprotein A1 ratio
Barnett et al, <sup>22</sup> 2007	8707		6	<i>COMT</i>	Val108/158Met	Selective attention Verbal IQ Total IQ Working memory count Global score Opposite words
Schott et al, <sup>23</sup> 2007	1274	52	11	<i>CTLA-4</i>	318C; 49A A49G	Hepatitis C virus infection
Niemi et al, <sup>24</sup> 2006	32	44	9	<i>SLCO1B1</i>	c.521T>C	Pharmacokinetics of pravastatin

(continued)

**Table 1.** Evaluated Articles Making Prominent Claims for Sex Differences in Their Titles (cont)

Source	Total Sample, No.	Women, %	No. of Claims	Gene	Variant/Haplotype <sup>a</sup>	Disease/Trait
Asselbergs et al, <sup>25</sup> 2006	2527	53	6	<i>PAI</i> <i>AT1R</i> Bradykinin B(2) receptor	4G/5G A1166C 58CT	Plasminogen activator inhibitor I levels Tissue plasminogen activator
Yiannakouris et al, <sup>26</sup> 2003	118	53	2	Leptin	G-2548A	Soluble leptin receptor levels Free leptin index
Seripa et al, <sup>27</sup> 2006	1408	53	3	<i>ApoE</i>	ε4 allele	Age ≥60 y (longevity)
Paladino et al, <sup>28</sup> 2006	495	43	21	<i>IL-10</i>	G-1082A	Hepatitis C virus infection
Korner et al, <sup>29</sup> 2007	943	52	3	<i>FAS</i>	Val1483Ile	Body mass index HDL cholesterol LDL cholesterol/HDL cholesterol ratio
Sundar et al, <sup>30</sup> 2006	1691	64	3	<i>ABCA1</i>	R219K R219K; G-17C	Late-onset Alzheimer disease
Ozawa et al, <sup>31</sup> 2006	992	62	5	<i>KCNQ1</i>	G643S	Heart rate QTf (Fridericia correction) T-wave interval Tpe/Qt ratio
Ben Assayag et al, <sup>32</sup> 2006	545	52	10	Fibrinogen Bb	G455A	Erythrocyte percentage Vacuum radius Erythrocyte sedimentation rate Plasma fibrinogen Correlation between vacuum radius and plasma fibrinogen levels Correlation between erythrocyte percentage and plasma fibrinogen levels
Kates et al, <sup>33</sup> 2006	58	45	3	<i>COMT</i>	Val158Met	Full-scale IQ Dorsal prefrontal volume Orbital prefrontal volume
Mizuno et al, <sup>34</sup> 2006	194	49	2	<i>5-HTTLPR</i>	Long/short	Sensitivity to stress (state) Sensitivity to stress (trait)
Mlynarski et al, <sup>35</sup> 2005	794	48	9	<i>CCR5</i>	A59029G 32 bp ins/del A; Ins haplotype A; Del haplotype G; Ins	Diabetic nephropathy in type 1 diabetes
Derzbach et al, <sup>36</sup> 2005	308	50	4	<i>ESR1</i>	Pvull	Necrotizing enterocolitis Patent ductus arteriosus Period of oxygen supplementation Intraventricular hemorrhage
Gloria-Bottini et al, <sup>37</sup> 2005	337	46	1	<i>ACP1</i>		Birth weight/placental weight ratio
Sjoberg et al, <sup>38</sup> 2006	200	60	5	<i>5-HTTLPR</i>	l/s	Depression self-rating scale
Tan et al, <sup>39</sup> 2005	616	36	5	<i>Nogo</i>	CAA insertion/deletion TATC insertion/deletion CAA+TATC- CAA+TATC+ CAA-TATC-	Schizophrenia
Shi et al, <sup>40</sup> 2005	2192	49	20	<i>MTHFR</i>	C677T A1298C	Lung cancer
Foltnie et al, <sup>41</sup> 2005	291	40	1	<i>BDNF</i>	Val66Met	Planning ability in Parkinson disease
Kajinami K, <sup>42</sup> 2005	338	40	5	<i>ESR1</i> <i>ApoA1</i> <i>ESR1</i> ; <i>APOA1</i>	Pvull-XbaI+ +83 variant Pvull-XbaI+; +83	HDL cholesterol
Kantarci OH, <sup>43</sup> 2005	861	66	13	<i>IFNG</i>	CA12/G haplotype CA13/A D12S313;3'(325)*G>A I1 (761)*CAN; D12S2510 D12S2510; D12S2511 3'(325)*A I1 (761)*CA12 I1 (761)*CA13 3'(325)*G	Multiple sclerosis

(continued)

**Table 1.** Evaluated Articles Making Prominent Claims for Sex Differences in Their Titles (cont)

Source	Total Sample, No.	Women, %	No. of Claims	Gene	Variant/Haplotype <sup>a</sup>	Disease/Trait
Chang et al, <sup>44</sup> 2004	644	47	2	<i>CTLA-4</i>	G49A	Cord blood IgE levels
Cui et al, <sup>45</sup> 2004	1000	48	1	<i>TSP-4</i>	A389P (29926G>C)	Myocardial infarction
Schrijver et al, <sup>46</sup> 2004	477	52	5	<i>TGFB1</i>	T869C 869T;915G 869C;915C	Multiple sclerosis
Liu et al, <sup>47</sup> 2004	1949	50	4	<i>SOD2</i> <i>SOD2; MPO</i>	Ala16Val Ala16Val; MPO variant	Non-small cell carcinoma
Szczeklik et al, <sup>48</sup> 2004	857	60	1	<i>COX-2</i>	G-765C	Asthma
Corder et al, <sup>49</sup> 2004	5615	44	2	<i>ApoE</i>	Epsilon4	Senile plaque
Chen et al, <sup>50</sup> 2004	745	43	2	<i>XBP1</i>	197C/G	Schizophrenia
Kajinami et al, <sup>51</sup> 2004	344	40	5	<i>MDR1</i>	C3435T G2677T/A; C3435T haplotype GC	HDL cholesterol LDL cholesterol
Yang et al, <sup>52</sup> 2004	1333	50	6	<i>CTLA-4</i>	G49A	IgE levels log IgE levels IgE levels ≥ 100 kU/L Allergic rhinitis
Gong et al, <sup>53</sup> 2004	189	33	2	<i>SP-B</i>	Exon 4 variant	Acute respiratory distress syndrome Direct pulmonary injury
Ko et al, <sup>54</sup> 2004	716	46	4	<i>HL</i>	-514C/T -250G/A	HDL cholesterol
Nakanishi et al, <sup>55</sup> 2004	249	51	5	<i>FABP2</i>	Ala54Thr	Total triglycerides Total cholesterol LDL cholesterol Body mass index
Chen et al, <sup>56</sup> 2004	277	47	1	<i>CCL2</i>	-2518; -2076	Behçet syndrome
Espino-Montoro et al, <sup>57</sup> 2003	104	43	11	<i>ApoC3</i>	S1/S2	Total triglycerides VLDL triglycerides LDL triglycerides HDL triglycerides Total cholesterol VLDL cholesterol LDL cholesterol Triglycerides-VLDL/HDL cholesterol ratio Total apolipoprotein B Basal glucose Basal insulin
Vandenbroeck et al, <sup>58</sup> 2003	449	54	8	IFNG/IL26 region	D12S2510 IFNGCA*13; D12S2510*8; D12S2511*9	Rheumatoid arthritis
Song et al, <sup>59</sup> 2003	271	53	1	<i>CYP11B2</i>	C-344T	Renal survival in IgA nephropathy
Laule et al, <sup>60</sup> 2003	1000	24	3	<i>eNOS</i>	CA repeat	Acute coronary syndrome
Reich et al, <sup>61</sup> 2003	81	42	7	<i>AGT1R</i>	A1166C	Systolic blood pressure Diastolic blood pressure Mean arterial pressure Change in glomerular filtration rate Increase in renal vascular resistance
Watson et al, <sup>62</sup> 2003	559	36	3	<i>ApoE</i>	Exon 4 variant	Colorectal cancer Advanced Dukes stage C and D tumors
Stankovic et al, <sup>63</sup> 2002	385	45	3	<i>ACE</i>	I/D	Hypertension
Gyorffy et al, <sup>64</sup> 2002	210	48	1	<i>VDR</i>	BsmI; ApaI; Tru9I	Type 1 diabetes mellitus
Minihane et al, <sup>65</sup> 2002	135	44	1	<i>APOC3</i>	T2854G	Total triglycerides
Wu et al, <sup>66</sup> 2001	306	45	4	<i>MTHFR</i>	C677T	Ischemic stroke
Lio et al, <sup>67</sup> 2002	450	57	1	IL-10 promoter	G-1082A	Longevity
Liu et al, <sup>68</sup> 2002	417	62	10	<i>ESR1</i>	PvuII; XbaI	Lupus nephritis Hematologic disorder in lupus nephritis Hypertension Glomerular thrombi in lupus nephritis Glomerulosclerosis in lupus nephritis Interstitial vasculitis in lupus nephritis Interstitial injury in lupus nephritis

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**Table 1.** Evaluated Articles Making Prominent Claims for Sex Differences in Their Titles (cont)

Source	Total Sample, No.	Women, %	No. of Claims	Gene	Variant/Haplotype <sup>a</sup>	Disease/Trait
Sciacca et al, <sup>69</sup> 2002	872	56	1	<i>IL-1A</i>	C889T	Age at myasthenia gravis onset
Ordovas et al, <sup>70</sup> 2002	1577	52	7	<i>APOA1</i>	G75A	HDL cholesterol
Oh and Barrett-Connor, <sup>71</sup> 2001	1126	59	7	<i>ApoE</i>	Exon 4 variant	Total cholesterol LDL cholesterol Waist circumference Total cholesterol/HDL cholesterol ratio
Ellsworth et al, <sup>72</sup> 2001	608	48	2	E-selectin	S128R	Coronary artery calcification
Du et al, <sup>73</sup> 2000	186	59	5	<i>5-HTTLPR</i> <i>5-HTT</i>	Long/short VNTR	Conscientiousness Neuroticism
Bullido et al, <sup>74</sup> 2000	371	62	3	<i>LRP</i> <i>ApoE</i>	Exon 3 C>T A491T (-491-427) haplotype	Alzheimer disease
Kark et al, <sup>75</sup> 2000	819	36	3	<i>CETP</i>	TaqI	HDL cholesterol Apolipoprotein A-I HDL cholesterol and triglycerides correlations
Durlach et al, <sup>76</sup> 1999	406	43	5	<i>CETP</i>	TaqI	HDL cholesterol Coronopathy in type II diabetes
Sagnella et al, <sup>77</sup> 1999	1366	54	2	<i>ACE</i>	I/D	Hypertension
Reynolds et al, <sup>78</sup> 1999	288	58	1	<i>MPO</i>	SpN	Alzheimer disease
Freire et al, <sup>79</sup> 1998	242	43	1	<i>AGT</i>	M235T	Nephropathy in type 1 diabetes
Suarez et al, <sup>80</sup> 1997	589		23	<i>VDR</i>	BsmI	Body mass index Length Weight Body surface area
Lehtimäki et al, <sup>81</sup> 1997	58	48	2	<i>ApoE</i>	Epsilon4	LDL cholesterol Total cholesterol
Carter et al, <sup>82</sup> 1997	502	54	4	Fibrinogen Bb	Arg448Lys	Acute stroke Fibrinogen levels at 3 mo
Ferrières et al, <sup>83</sup> 1994	263	56	14	<i>ApoE</i>	Epsilon4	Total cholesterol LDL cholesterol Total apolipoprotein B LDL apolipoprotein B VLDL cholesterol Total triglycerides
von Eckardstein et al, <sup>84</sup> 1994	614	31	4	<i>Apo A-IV</i>	Gln360His	Apolipoprotein A-I Apolipoprotein A-IV Lecithin:cholesterol acyltransferase
Hansen et al, <sup>8</sup> 1994	782	8	3	<i>ApoB</i>	All haplotypes (XbaI and Ins/Del)	Ischemic heart disease

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

<sup>a</sup>Gene variant nomenclature follows the convention used in each article.

(15.7%) were acknowledged to be post hoc analyses; in the other 78 (18.1%), the analysis plan was unclear.

### Genetic Variants and Phenotypes and Genetic Contrasts Involved

The variant of interest was of a biallelic locus in 328 claims, a multiallelic single locus in 44, multilocus haplotypes in 45, and multiple polymorphisms without haplotype construction in 15. The phenotype was binary in 212 claims, continuous in 218, and categorical in another 2 (cross-tabulations and other supplementary

data are available at [http://www.dhe.med.uoi.gr/sup\\_mat.php](http://www.dhe.med.uoi.gr/sup_mat.php)).

Among the biallelic variants, a specific genetic contrast was used in 227 claims (recessive in 33, dominant in 95, additive in 19, allele-based in 16, and model-free [all 3 genotypes considered separately] in 64). The remaining 101 were based on other, more peculiar genetic contrasts (wild-type homozygous vs variant homozygous, n=30; heterozygous vs variant homozygous, n=8; heterozygous vs wild-type homozygous, n=13; and other considerations, n=50).

### Analyzed Population in Sex Claims

The entire sample size was used in 210 claims (48.6%) and the other 222 used subsets of the study population. The subset selection was based on genetic information for the gene variant of interest in 60 claims, on genetic information for some other gene variant in 2, on other patient characteristics in 101, and on combinations of the above in 59. The selection of the subset was reported to have been determined a priori in 98 claims (44.1%), it was acknowledged to have been done post hoc in 43 claims (19.4%), and the timing

of the selection was unclear in 81 claims (36.5%).

### Documentation of Sex Claims

Appropriate documentation was evident in only 55 claims (12.7%). This includes 49 claims that performed statistical testing for interaction and another 6 for which no formal testing was

shown, but the sex-specific 95% confidence intervals of the genetic effects were readily presented and did not overlap. Forty-four (44/49 [89.8%]) of the provided *P* values were between .01 and .05. The smallest *P* value reported was .00008.

A total of 303 claims had insufficient documentation. In 81 claims, the

investigators said that a statistically significant effect was found in one sex but not in the other, and both effects were in the same direction. In 46 claims, they stated that there was a statistically significant effect in one sex but not in the other, and the point estimates were in opposite directions. In 16 claims, they stated that a larger

**Table 2.** Examples of Insufficiently Documented Claims

Type of Insufficient Documentation	Example <sup>a</sup>	Source
Significant effect in one sex only, effects in the same direction	"... after stratification by sex significantly increased odds of developing ARDS were found in women with a variant SP-B allele (OR, 4.5; 95% CI, 1.1-18.8; <i>P</i> = .03) [Table 4], but not in men." (OR, 1.2; 95% CI, 0.4-3.8)	Gong et al, <sup>53</sup> 2004
Significant effect in one sex only, point estimates in opposite direction	"Analysis of male study subjects provided a statistically significant risk reduction for the ε3/ε3 genotype (OR, 0.53; 95% CI, 0.32-0.89) . . . whereas absolutely no effect was revealed in women (OR, 1.04; 95% CI, 0.52-2.09)."	Watson et al, <sup>62</sup> 2003
Larger or more statistically significant effect in one sex than in the other, significant effects in both	"... in the male group . . . there was a slight and significant ( <i>P</i> < .05) increase in total, VLDL, LDL, and HDL triglycerides and an increase of VLDL cholesterol in carriers of the S1S2 genotype ( <i>P</i> < .05) . . . the women carrying the S1S2 mutation had much more marked differences regarding plasma lipids and lipoprotein composition." Women: <i>P</i> < .001 for total, VLDL, and LDL triglycerides and VLDL cholesterol; <i>P</i> < .05 for HDL triglycerides (data from table)	Espino-Montoro et al, <sup>57</sup> 2003
Significant effect in one sex, no information on direction in the other sex	"Regression analysis showed no association between neonatal morbidity and genotype in girls. However, boys carrying 'p' allele were at lower risk for patent ductus arteriosus (OR [95% CI], 0.24 [0.05-0.971]; <i>P</i> < .05."	Derzbach et al, <sup>96</sup> 2005
Significant effect in one sex only, direction of effects not specified in either sex	"When significance was assessed separately for the two sexes, however, Taq1B polymorphism was found to affect HDL-C significantly in males ( <i>F</i> = 3.640; <i>P</i> = .028) but not in females ( <i>F</i> = 0.947; <i>P</i> = .390)."	Durlach et al, <sup>76</sup> 1999

Abbreviations: ARDS, acute respiratory distress syndrome; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OR, odds ratio; VLDL, very low-density lipoprotein.

<sup>a</sup>Text inside apostrophes indicates verbatim text.

**Table 3.** Examples of Spurious Claims

Type of Spurious Claim	Example <sup>a</sup>	Source
Comparison of male cases directly with female cases, ignoring controls	"Similarly, the frequency of 6/6 homozygotes was significantly higher ( <i>P</i> = .023; EF = 0.24) and that of D12S2510*8 carriers lower ( <i>P</i> = .025; PF = 0.26) in female patients compared with male patients."	Vandenbroeck et al, <sup>58</sup> 2003
Comparison of male vs female cases with a given genotype, ignoring other genotypes	"As a result, the difference in HDL-C between sexes, reconsidered on the basis of Taq1B genotype, was found to be significant at the <i>P</i> < .0001 and <i>P</i> < .0005 levels, respectively, in B1B1 and B1B2 subjects . . ."	Durlach et al, <sup>76</sup> 1999
Comparisons of different genetic groups in male vs female cases	"... females of the AA genotype demonstrated the greatest fall in GFR compared with the other three groups ( <i>P</i> = .01 vs males of the AC/CC genotype)."	Reich et al, <sup>61</sup> 2003
Comparisons of one sex against a subgroup of the other sex	"The distribution of haplotypes differed significantly among subgroups of patients, mainly because of a higher frequency of the Ins/X- and a lower frequency of the Del/X+ haplotypes in female and older male patients than in younger male patients and in reference men."	Hansen et al, <sup>9</sup> 1994
Comparison of different subgroups of gene exposure-defined categories	"For the MTHFR A1298C polymorphisms, the 1298CC genotype showed increased risk of lung cancer in those women who reported ever smoking (adjusted OR, 2.25; 95% CI, 1.19-4.23) . . ." Men: adjusted OR, 0.44; 95% CI, 0.20-0.95 (data for table, but adjustment is not for smoking)	Shi et al, <sup>40</sup> 2005

Abbreviations: CI, confidence interval; EF, etiologic fraction of attributable risk; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; OR, odds ratio; PF, prevented fraction.

<sup>a</sup>Text inside apostrophes indicates verbatim text.

or more statistically significant sex effect was seen in one sex than in the other, and the effects were nominally statistically significant in both sexes. In 107 claims, a statistically significant effect was shown in one sex, but there was no information on statistical significance in the other sex. Finally, 53 claims reported a statistically significant effect in one sex and no statistically significant effect in the other, but the direction was not specified in either sex. For all of these situations, the way the claim was made cannot

ensure whether sex-gene interaction is nominally statistically significant or not. Illustrative examples are shown in TABLE 2. Among the claims with insufficient documentation, 9 also reported some formal gene-sex interaction testing that was nevertheless not statistically significant at the  $P=.05$  level ( $P$  value range, .088-.983).

A total of 74 claims were spurious. The reasons for spurious claims are shown in TABLE 3. The most common reasons were the comparison of male vs female cases with a selected geno-

type, ignoring other genotypes (ie, no genetic contrast;  $n=28$  claims), and the comparison of male cases directly with female cases, ignoring controls ( $n=8$  claims). A wide variety of other comparisons were also invoked (Table 3).

### Reanalyses of Sex-Difference Claims

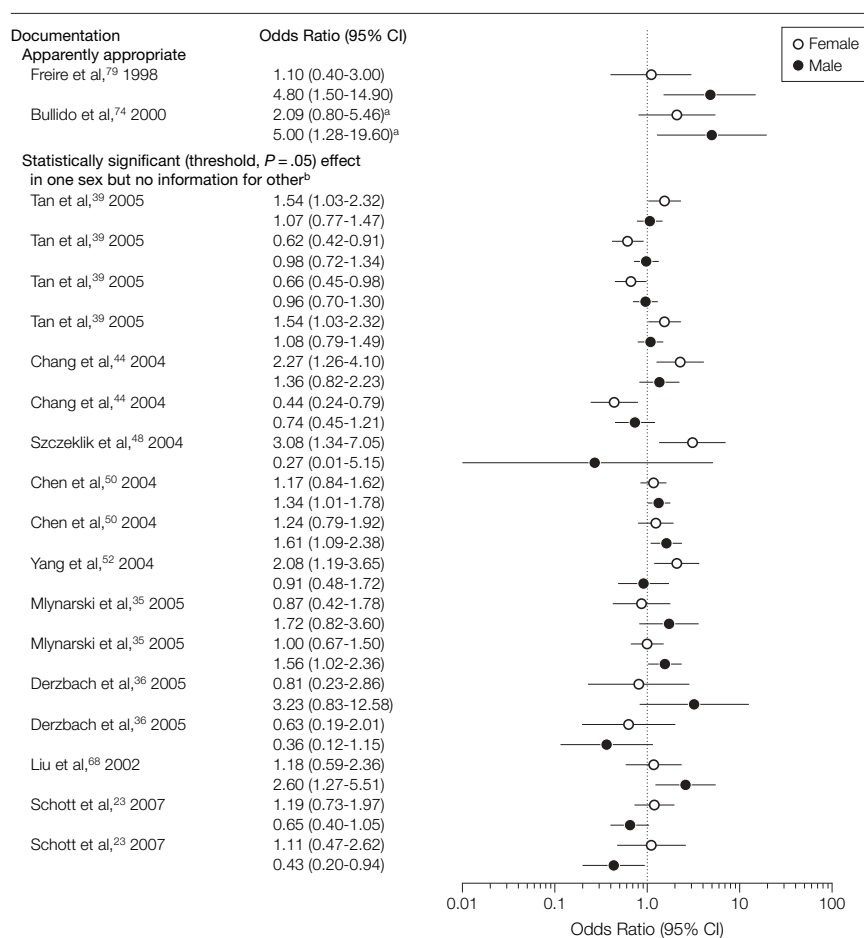
Data were available for the reanalysis of 188 claims (30 appropriately documented and 158 insufficiently documented). Overall, 105 of the 188 claims (55.9%) were not nominally statistically significant based on our calculations. Illustratively, the effect sizes and 95% confidence intervals are shown in pairs for male and female participants for the non-statistically significant claims for which the effect sizes are odds ratios ( $n=44$ ) (FIGURE 1 and FIGURE 2). Eighty-three of the 188 reanalyzed claims were nominally statistically significant, but the majority ( $n=44$ ) had modest  $P$  values between .01 and .05, 25 had  $P$  values between .001 and .01, and only 14 had  $P$  values less than .001 for the interaction.

In 30 claims, the original investigators had provided appropriate statistical documentation and raw data were also available for us to retest gene-sex interaction. Of these, in 23 claims the sex difference was statistically significant in both the reported and calculated  $P$  values, while in the other 7 we could not replicate the alluded statistical significance. Six of these used multivariate analyses, while we could calculate only unadjusted estimates based on given raw data. In the remaining claim, the authors reported to have used a Breslow-Day test of homogeneity with  $P=.05$ . Our reanalysis yielded  $P=.059$ , while our Breslow-Day recalculation gave  $P=.054$ .

### Corroboration of Claims With Best Internal Validity

Of the 432 claims, only 37 claims (in 17 articles) were stated to rely on a priori considerations, had raw data available that documented that they were indeed nominally statistically significant, and had analyses performed on the whole study sample. We found any

**Figure 1.** Effect Sizes for Male and Female Participants in Studies With Apparently Appropriate Sex-Difference Documentation and Those With Statistically Significant Effects in One Sex but No Information for the Other Sex



CI indicates confidence interval. Data are shown for studies in which the effect sizes are odds ratios and in which our reanalysis of the data showed no statistically significant gene-sex interaction. For the 2 claims that seemingly had appropriate documentation with formal interaction testing in the original article, our retesting of the gene-sex interaction showed non-statistically significant results. The full data are available at [http://www.dhe.med.uoi.gr/sup\\_mat.php](http://www.dhe.med.uoi.gr/sup_mat.php).

<sup>a</sup>Based on our recalculations.

<sup>b</sup>We recalculated all estimates in this section.

kind of corroboration history for only 3 of them. One sex difference had already been described (same trend) in 2 previous studies. For another claim, a previous study had found no effect while a subsequent one replicated the interaction. The third claim had already been described in a previous study but in the opposite direction; however, 2 previous studies reported no effect (TABLE 4).

Another 23 claims (in 12 articles) were stated to rely on a priori consideration, had raw data documenting a nominally statistically significant sex-gene interaction, and had analyses performed on a sample subset that was also justified a priori. Of these, 2 claims were made in an article that had at least 1 referenced study showing no statistically significant results for the respective sex-gene claim, and 1 had at least 1 reference that had shown results in the opposite direction. We found no subsequent articles replicating any of these 3 claims (Table 4).

## COMMENT

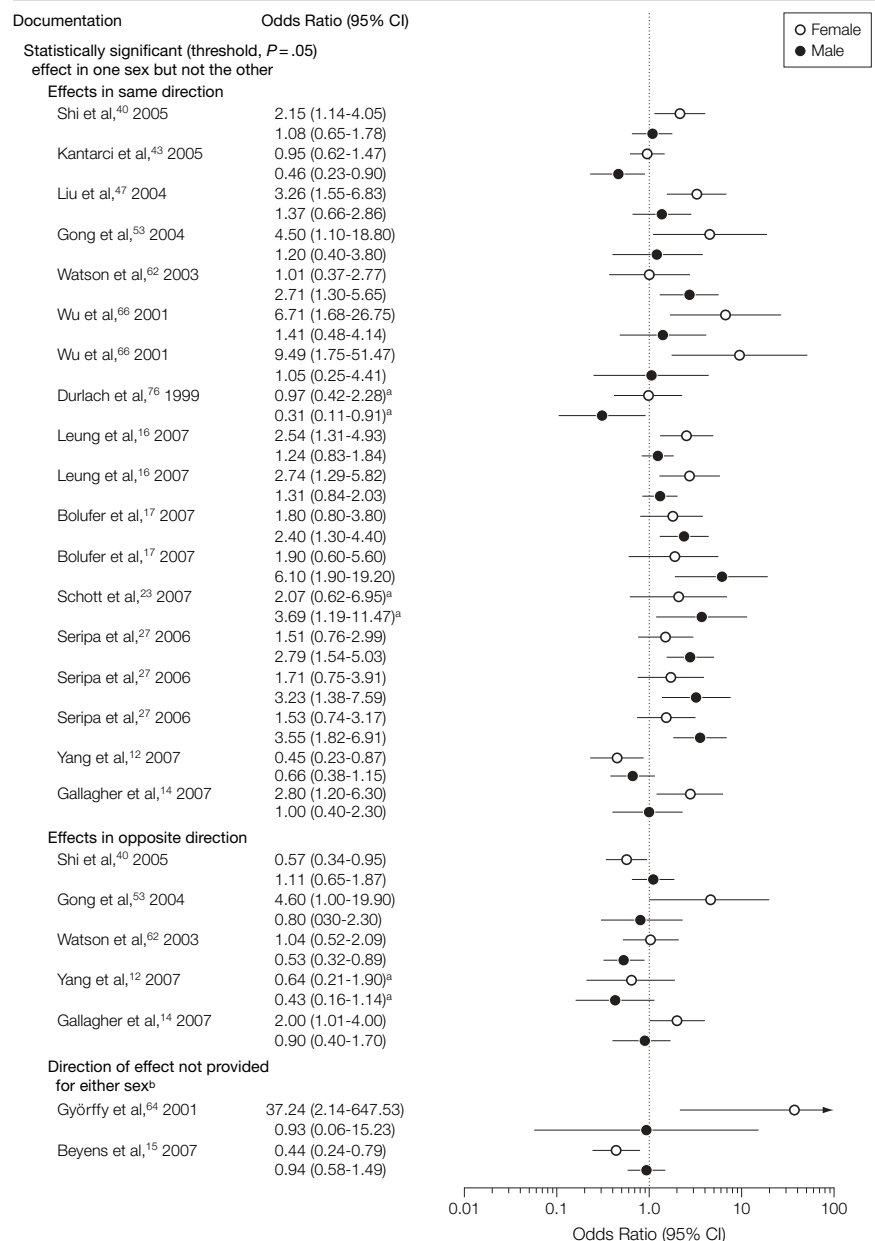
We have empirically evaluated observational studies claiming to have found sex-related differences in genetic effects for common diseases and traits. Claims covered a variety of genes and outcomes. Most authors stated that these analyses had been conceived a priori. Nevertheless, the majority of these claims were insufficiently documented or spurious, and reporting of statistical interaction tests was rare. When we reanalyzed the available data, more than half of the tested gene-sex interactions failed to reach nominal statistical significance at the  $P = .05$  level, and most of those that did reach significance had very modest  $P$  values. Even among the claims that seemingly had the best internal validity, corroboration in other studies was very rare.

Subgroup comparisons have been evaluated previously, mostly in the clinical trials literature.<sup>93-95</sup> To our knowledge, no such assessment exists for genetic epidemiology, although genetic determinants of common traits

represent an exploding clinical research literature.<sup>5</sup> In the clinical trials literature, subgroup analyses with sex or other variables have been a common strategy used to find and report statistically significant results. Some au-

thors have argued for the need to perform and transparently report subgroup analyses, in particular those related to sex.<sup>96</sup> However, the vast majority of claimed subgroup differences are likely to be chance findings.<sup>97,98</sup> No-

**Figure 2.** Effect Sizes for Male and Female Participants in Studies With Statistically Significant Effects in One Sex but Not in the Other Sex



CI indicates confidence interval. Data are shown for studies in which the effect sizes are odds ratios and in which our reanalysis of the data showed no statistically significant gene-sex interaction. The full data are available at [http://www.dhe.med.uoi.gr/sup\\_mat.php](http://www.dhe.med.uoi.gr/sup_mat.php).

<sup>a</sup>Based on our recalculations.

<sup>b</sup>We recalculated all estimates in this section.

torious chance findings were illustrated years ago in the analysis of the ISIS-2 results based on the signs of the zodiac,<sup>99</sup> and the principle has been further elaborated recently in simulations of subgroup analyses that highlight the major threat of false-positive results in such endeavors.<sup>100-102</sup> In the analysis of sex-specific effects in genetic associations, investigators very often seem to fall into classic traps. The most typical error is to claim nominal statistical significance for 1 of the 2 sexes when the difference in the effects between the 2 sexes is not beyond chance. Simulations show that a significant effect in 1 subgroup only may be a very common occurrence even in studies of modest sample size, occurring in 7% to 64% of analyses in 1 simulation study.<sup>100,101</sup> The majority of such claims are expected to be false-positive results.

Another major problem is the lack of power to detect interactions of effects with sex in these studies. Brookes et al have estimated that a study with 80% power for the overall effect has

only 29% power to detect an interaction effect of the same magnitude.<sup>101</sup> Meaningful pursuit of interactions may require almost a 10-fold increase in the sample size compared with the samples needed to document main effects.<sup>100,103,104</sup> At the same time, these genetic association studies are already more than 10-fold smaller than what would be required to pursue even main effects, based on what is known of the plausible size of effects for common genetic variants.<sup>105</sup> Most of the main effects proposed in the last decade have not been replicated.<sup>106</sup> Under these circumstances, a nominally statistically significant interaction test at the  $P = .05$  threshold probably has very low positive predictive value for the presence of a true interaction.

Some limitations should be addressed. We used a sampling strategy that was systematic but was also heavily driven by convenience. The sampling tends to select more prominently claimed sex differences, and one may assume that these are likely to have better-than-average internal validity and

better-than-average chances of external corroboration. However, this cannot be formally proven. Sex is a patient characteristic available in virtually all genetic association studies, so our sample of articles is probably only the "tip of the iceberg." It is impractical to find and evaluate all sex comparisons, even in a circumscribed sample of the literature. Selective reporting of subgroup and secondary analyses is an increasingly recognized bias that may lead to a preponderance of "positive" findings in the published literature.<sup>107-109</sup> At a minimum, the studies that we evaluated are probably among the ones in which authors were most certain about some, if not all, of the sex claims that they presented in their results; otherwise, they would not have drawn attention to the claims in the titles of their articles.

We should also acknowledge that for some claims, especially the ones that were first made most recently, corroboration may not yet have been performed but may be performed in the future. However, genetic epidemiology is

**Table 4.** Corroboration History for the Gene-Sex Interaction Claims With the Seemingly Best Internal Validity

Source	Gene	Phenotype	Study Sample	Male Point Estimate (95% CI)	Female Point Estimate (95% CI)	Corroboration Studies		Source
						Male Point Estimate (95% CI)	Female Point Estimate (95% CI)	
Stankovic et al, <sup>63</sup> 2002	ACE I/D	Hypertension	Total	2.05 (1.07 to 3.91)	0.72 (0.33 to 1.6)	2.40 (1.30 to 4.50)	1.40 (0.72 to 2.69)	Previous study (Higaki et al, <sup>85</sup> 2000): same trend Previous study (O'Donnell et al, <sup>86</sup> 1998): same trend
						1.36 (1.09 to 1.71)	1.07 (0.87 to 1.32)	
Bullido et al, <sup>74</sup> 2000	LRP A491T	Alzheimer disease	Total	4.30 (1.80 to 10.20) <sup>a</sup>	1.50 (0.80 to 2.70) <sup>a</sup>	2.38 (0.81 to 7.00)	2.35 (0.52 to 9.41)	Previous study (Ahmed et al, <sup>87</sup> 1999): no interaction Subsequent study (Parra-Bonilla et al, <sup>88</sup> 2003): interaction
						6.14 (1.60 to 23.50)	1.20 (0.53 to 2.72)	
Ordovas et al, <sup>70</sup> 2002 <sup>b</sup>	APOA1 G75A	HDL cholesterol	Total	0.00 (-0.02 to 0.03)	0.05 (0.02 to 0.07)	0.27 (0.08 to 0.46)	0.01 (-0.18 to 0.20)	Previous study (Meng et al, <sup>89</sup> 1997): opposite trend Previous study (Mata et al, <sup>90</sup> 1998): no interaction Previous study (Xu et al, <sup>91</sup> 1993): no interaction
						0.07 (-0.19 to 0.33)	-0.07 (-0.28 to 0.14)	
Sagnella et al, <sup>77</sup> 1999	ACE I/D	Hypertension	African	0.79 (0.36 to 1.72)	2.54 (1.38 to 4.65)	1.36 (1.09 to 1.71)	1.07 (0.87 to 1.32)	Previous study (O'Donnell et al, <sup>86</sup> 1998): opposite trend
Ferrieres et al, <sup>83</sup> 1994	apoE e4	LDL cholesterol	e3/2 vs e3/3	0.31 (-0.30 to 0.92)	1.73 (1.15 to 2.31)	NE	NE	Previous study (Kotze et al, <sup>92</sup> 1993): no interaction
Ferrieres et al, <sup>83</sup> 1994	apoE e4	Total cholesterol	e3/2 vs e3/3	-0.05 (-0.72 to 0.62)	1.75 (1.30 to 2.20)	NE	NE	Previous study (Kotze et al, <sup>92</sup> 1993): no interaction

Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NE, no estimate presented.

<sup>a</sup>Based on our recalculations of the raw data; the original study had claimed an odds ratio of 3.2 (95% CI, 1.2-8.6) for male cases and did not report an odds ratio for female cases.

<sup>b</sup>Ordovas et al reported a gene  $\times$  sex  $\times$  polyunsaturated fatty acids intake interaction. Data from Meng et al and Mata et al are based on a low-fat diet, whereas data from Xu et al are based on baseline data.

a quickly moving field, and replication efforts are currently typically performed very rapidly.

The issues addressed herein focus on gene-sex interaction, but their implications probably extend to any kind of subgroup analysis in genetics. Genetic epidemiology is a field that often invites subgroup analyses, not only by sex, but also by age, racial/ethnic descent, other polymorphisms, diet, lifestyle, and other exposures.<sup>110,111</sup> Similar caution may be needed in the analysis, reporting, and interpretation of all of these postulated effect modifications.

We hope that our empirical evaluation will help sensitize clinicians, geneticists, epidemiologists, and statisticians who are pursuing subgroup analyses by sex or other subgroups on genetic associations. The pursuit of gene-sex interactions should not be necessarily abandoned. Ideally, sex differences should be based on a priori, clearly defined, and adequately powered subgroups. Post hoc, discovery-based analyses are also of interest, but their post hoc character should be clearly stated in the manuscript. Both a priori and post hoc claims should be documented by interaction tests and proper consideration of the multiplicity of comparisons involved. Even then, results should be explained with caution and should be replicated by several other studies before being accepted as likely modifications of genetic or other risks.

**Author Contributions:** Dr Ioannidis had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Patsopoulos, Tatsioni, Ioannidis.

**Acquisition of data:** Patsopoulos, Tatsioni.

**Analysis and interpretation of data:** Patsopoulos, Tatsioni, Ioannidis.

**Drafting of the manuscript:** Patsopoulos, Ioannidis.

**Critical revision of the manuscript for important intellectual content:** Patsopoulos, Tatsioni, Ioannidis.

**Statistical analysis:** Patsopoulos, Tatsioni, Ioannidis.

**Obtained funding:** Ioannidis.

**Study supervision:** Ioannidis.

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