Integrated probability of coronary heart disease subject to the –308 tumor necrosis factor–α SNP: a Bayesian meta–analysis

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Abstract

We present a meta–analysis of independent studies on the potential implication in the occurrence of coronary heart disease (CHD) of the single–nucleotide polymorphism (SNP) at the –308 position of the tumor necrosis factor alpha (TNF–α) gene. We use Bayesian analysis to integrate independent data sets and to infer statistically robust measurements of correlation. Bayesian hypothesis testing indicates that there is no preference for the hypothesis that the –308 TNF–α SNP is related to the occurrence of CHD, in the Caucasian or in the Asian population, over the null hypothesis. As a measure of correlation, we use the probability of occurrence of CHD conditional on the presence of the SNP, derived as the posterior probability of the Bayesian meta–analysis. The conditional probability indicates that CHD is not more likely to occur when the SNP is present, which suggests that the –308 TNF–α SNP is not implicated in the occurrence of CHD.

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I. INTRODUCTION

Coronary heart disease (CHD) is now widely accepted to consist of a chronic inflationary disease [1]. CHD is a complex disease with multifold etiology, with both genetic and environmental factors contributing to its occurrence and development.

Among the genetic factors potentially implicated in the emergence of CHD, the tumor necrosis factor alpha (TNF–α) has attracted a great interest for its involvement in the inflammatory response of the immune system [2]. There is evidence that TNF-α is implicated in an increased susceptibility to the pathogenesis of a variety of diseases. In particular, high serum levels of TNF–α affect endothelial cell hemostatic function and hence may modify the risk for developing CHD [3]. There is also the suggestion that the TNF–α gene affects the modulation of lipid metabolism, obesity susceptibility and insulin resistance, thus being potentially implicated in the development of CHD (see Ref. [4] and references therein).

Among the several single–nucleotide polymorphisms (SNPs) that have been identified in the human TNF-α, the best documented one is at the position –308 of the TNF–α gene promoter. This SNP involves the substitution of guanine (G) for adenine (A) and the subsequent creation of two alleles (TNF1(A) and TNF2(G)) and three genotypes (GG, GA and AA) [5]. It has been hypothesised that the TNF–α SNP could change the susceptibility to CHD. However, the results on its association with CHD are contradictory, some implying different influence of the two alleles on the prevalence of CHD, others implying no association (see Ref. [6] and references therein).

In order to infer the risk of CHD derived from potential risk factors, it is important to develop a formalism that infers correlations among different intervening factors and combines independent data sets for a consistent inference of the correlations. In Ref. [8] we introduced a formalism based on Bayesian inference to infer the correlation of the occurrence of CHD with two risk factors and tested a simplistic model for the signal pathway on the three–variable data set from Ref. [9]. In this manuscript we extend the formalism to extract information from the combination of data from independent studies and to quantify the combined risk of occurrence of CHD from the –308 TNF–α SNP.

The most exhaustive meta–analysis to date on this correlation is the frequentist analysis in Ref. [6] covering Caucasian, Asian, Indian and African populations. This meta–analysis found a 1.5 fold increased risk of developing CHD when the SNP is present in the Caucasian population, but found no association in the other ethnicities. A more recent meta–analysis, covering the same data sets, found no association in the Caucasian or in the Asian population [7].

In this manuscript we propose a meta–analysis based on Bayesian analysis in an attempt to establish the potential implication of –308 TNF–α SNP in the occurrence of CHD. This manuscript is organized as follows. In Section II we describe the data sets selected. We then perform the Bayesian analysis of the selected data sets, combined by ethnicity and CHD phenotype. In Section III we propose two hypotheses and test which best and most simply

describes the data. In Section IV we infer the conditional probabilities for the occurrence of CHD given the presence of the SNP. In Section V we test the sensitivity of this formalism to low–significance data sets, to data sets with extreme results and to extreme data sets. Finally in Section VI we summarize the results.

II. DATA SELECTION

Our analysis is based on twenty data sets (indexed i) on two CHD phenotypes (indexed j) selected from the studies compiled in Ref. [6], following a well-documented study identification, data acquisition and selection strategy, including also statistical tests (Hardy–Weinberg equilibrium, heterogeneity, publication bias). We include fifteen data sets from studies on Caucasians, where six studies are on the CHD phenotype coronary stenosis (CS) [9–14] and nine studies are on the CHD phenotype myocardial infarction (MI) [15–22]. We also include five data sets from studies on Asians on the CHD phenotype coronary stenosis [23–27]. We selected the studies that reported the genotypes of both CHD patients and non–CHD (control) patients for the two CHD phenotypes separately. Among the rejected data sets are three studies on Caucasians (for not reporting data on non–CHD patients), four studies on Asians (three for not reporting data on non–CHD patients and one for not separating the CHD phenotypes), the study on Indians and the study on African both for not separating the CHD phenotypes).

The data consist of frequencies of occurrence of the –308 TNF–α SNP in randomly selected CHD patients and non–CHD (control) patients, respectively $n_{SNP,CHD}$ and $n_{SNP,\overline{CHD}}$. The data are summarized in Table I (columns 3–6). The errors indicated were computed from error propagation. Assuming that the methods for measuring the presence of the SNP have a success rate of $r_{\rm suc} = 0.88$ [31], and furthermore that the error of a counting result is given by the Poisson approximation $\sqrt{n}$, then the error of a counting result n on the presence of the SNP is given by $(1 - r_{\rm suc})\sqrt{n}/2$.

A. Data heterogeneity

In order to investigate the heterogeneity in the data sets, we compare the size of the effect (defined as a measure of the difference between CHD and non–CHD patients) in each study [28]. As a measure of the size of the effect we use the fraction of SNP in the population of CHD patients and in the population of non–CHD patients, respectively $f_{SNP{\rm in}CHD} = n_{SNP,CHD}/n_{CHD}$ and $f_{SNP{\rm in}\overline{CHD}} = n_{SNP,\overline{CHD}}/n_{\overline{CHD}}$, where $n_{CHD} = n_{SNP,CHD} + n_{\overline{SNP},CHD}$ is the total number of CHD patients and $n_{\overline{CHD}} = n_{SNP,\overline{CHD}} + n_{\overline{SNP},\overline{CHD}}$ is the total number of non–CHD patients. Moreover, the ratio of these two fractions gives an indication of the signal of the correlation. Hence, if $f_{SNP{\rm in}CHD}/f_{SNP{\rm in}\overline{CHD}} > 1$, the SNP is proportionally more frequent in CHD than in non–CHD patients, hence the study favours a positive correlation

Study	Phenotype	CHD patients		Controls		Bayes factor	
(i)	(j)	GG	GA/AA	GG	GA/AA	$(H_1^{i,j}/H_0^{i,j})$	(H_1^j/H_0^j)
Allen et al. (NA)	Cauc CS	127	53	222	107	0.14 ± 0.05	
Elahi et al. (A)		59	38	41	54	3.54 ± 1.12	0.049 ± 0.014
Georges et al. (A)		613	236	222	92	0.08 ± 0.03	$0.041 \pm 0.016^*$
Sbarsi et al. (A)		175	73	185	56	0.33 ± 0.11	
Szalai et al. (A)		229	89	181	87	0.19 ± 0.07	$0.048 \pm 0.019^{**}$
Vendrell et al. (A)		231	110	159	48	1.33 ± 0.46	
Antonicelli (A)	Cauc MI	224	69	246	64	0.12 ± 0.04	
Bennet et al. (A)		799	368	1037	460	0.05 ± 0.02	
Dedoussis et al. (A)		206	31	227	10	26.14 ± 8.56	0.026 ± 0.011
Herrmann et al.† (NA)		325	120	376	158	0.11 ± 0.04	
Herrmann et al.‡ (NA)		117	79	97	79	0.19 ± 0.06	$0.035 \pm 0.015^*$
Koch et al. (NA)		565	228	244	96	0.07 ± 0.03	$0.030 \pm 0.012^{**}$
Padovani et al. (A)		120	28	114	34	0.17 ± 0.06	
Tobin et al. (A)		365	182	337	168	0.07 ± 0.03	
Tulyakova et al. (NA)		242	64	177	69	0.60 ± 0.21	
Chen et al. (NA)	Asian CS	29	11	21	9	0.27 ± 0.08	0.151 ± 0.057
Hou et al. (NA)		268	32	802	103	0.05 ± 0.02	
Li et al. (NA)		66	8	138	20	0.12 ± 0.04	$0.114 \pm 0.043^*$
Liu et al. (A)		234	52	142	34	0.10 ± 0.03	$0.103 \pm 0.037^{**}$
Shun et al. (A)		54	19	118	20	1.10 ± 0.34	

Table I. **Data sets and results of hypothesis testing.** Column 1: Studies selected for the meta–analysis. The index (A) indicates that a possible association was measured in the original publication; the index (NA) indicates that no association was measured in the original publication. Column 2: The phenotype of the patients in the studies grouped by ethnicity. Columns 3–6: Genotypic frequencies of TNFα–308 in CHD patients and control patients from twenty studies (indexed i) and for two CHD phenotypes (indexed j), namely coronary stenosis (CS) and myocardial infarction (MI). Columns 7–8: The Bayes factors for the hypotheses considered, for each data set $(H_1^{i,j}/H_0^{i,j})$, and for the meta–data set of each CHD phenotype (H_1^j/H_0^j). † French cohort. ‡ Irish cohort. * Excluding Elahi et al., Dedoussis et al. and Chen et al., respectively for each phenotype. ** Excluding Georges et al., Bennet et al. and Hou et al., respectively for each phenotype.

between the presence of the SNP and the occurrence of CHD; if $f_{SNP\text{in}CHD}/f_{SNP\text{in}\overline{CHD}} < 1$, the SNP is proportionally less frequent in CHD than in non–CHD patients, hence the study favours a negative correlation; if $f_{SNP\text{in}CHD}/f_{SNP\text{in}\overline{CHD}} = 1$, the SNP is equally frequent in CHD and in non–CHD patients, hence the study favours no correlation.

We plot this ratio of fractions for each study, grouped by ethnicity and CHD phenotype, in Fig. 1. We also plot the ratio for the combined data sets included in each panel. We

observe that the ratio of the data sets are asymmetrically distributed about the ratio equal to one, showing a predominance of ratios smaller than one. The ratio of the combined data sets included in each panel is slightly smaller than one for the Caucasian studies (for both CHD phenotypes) and larger than one for the Asian studies. This asymmetry indicates heterogeneity in the studies, as also observed in the meta–analysis of Ref. [6].

In Fig. 2 (left panel) we plot this ratio of fractions as a function of the sample size. We observe that smaller data sets are distributed across a wide range of values of this ratio, whereas larger data sets are distributed more closely to one.

III. HYPOTHESES TESTING

First we test the hypothesis H_1 that the presence of TNF–α SNP is related to the occurrence of CHD against the null hypothesis H_0 that the presence of the SNP is unrelated to the occurrence of CHD. By the Bayes theorem, the probability of a hypothesis H_n given the data D_{SNP} is the posterior probability of the corresponding hypothesis

$$P(H_n|D_{SNP}) = \frac{P(D_{SNP}|H_n)P(H_n)}{P(D_{SNP})}, \tag{1}$$

where $P(D_{SNP}|H_n)$ is the evidence, $P(H_n)$ is the prior probability of H_n and $P(D_{SNP}) = \sum_n P(D_{SNP}|H_n)P(H_n)$. The subscript in D_{SNP} reminds us that the random variable is the occurrence of the SNP. In order to infer which hypothesis is more likely in view of the data, we compare the evidence computed for the two hypotheses. The evidence is the integral of the likelihood over the k–dimensional parameter space $p_{n,k}$ of the hypothesisH_n

$$P(D_{SNP}|H_n) = \int d^k p_{n,k}\ P(D_{SNP}|p_{n,k}, H_n)P(p_{k,n}|H_n). \tag{2}$$

Assuming equal prior probabilities for the two hypotheses, then

$$\frac{P(H_1|D_{SNP})}{P(H_0|D_{SNP})} = \frac{P(D_{SNP}|H_1)}{P(D_{SNP}|H_0)}. \tag{3}$$

We compute the evidence of the two hypotheses for each data set separately, as well as for the combined data sets grouped by CHD phenotype. We follow the procedure detailed in Ref [8], which we here summarize for one data set and then generalize for the combined data sets. In all cases, we choose a uniform distribution for the prior of the parameters, which is justified by the absence of an *a priori* bias on the values of the parameters [29].

The evidence of H_0 is computed assuming that the presence of the SNP is described by a binomial distribution with one parameter only, namely the probability p_0 that the SNP occurs in a given population. For n_{SNP} occurrences of the SNP and $n_{\overline{SNP}}$ non–occurrences of the SNP in a sample of size $n = n_{SNP} + n_{\overline{SNP}}$, the likelihood $P(D_{SNP}|p_0, H_0)$ is given by

$$P(D_{SNP}|p_0, H_0) = p_0^{n_{SNP}}(1-p_0)^{n_{\overline{SNP}}}. \tag{4}$$

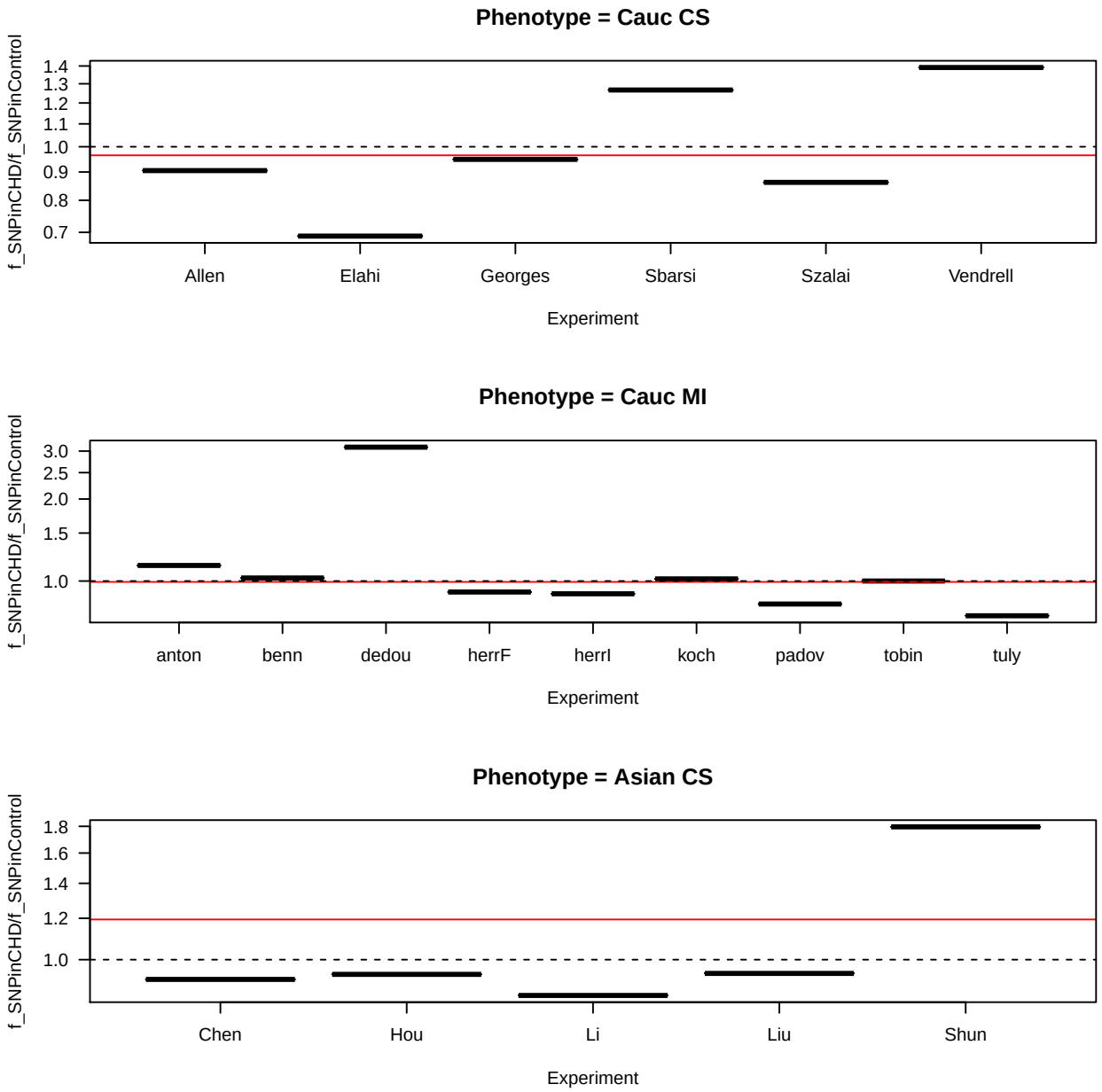

Figure 1. **Funnel plot for the ratio of SNP fractions.** The ratio of the fraction of SNP in the population of CHD patients to the fraction of SNP in the population of non–CHD patients, $f_{SNPinCHD}/f_{SNPinControl}$, for each study, grouped by ethnicity and CHD phenotype. Top panel: Caucasians with coronary stenosis; Middle panel: Caucasians with myocardial infarction; Bottom panel: Asians with coronary stenosis. The solid horizontal line is the ratio of the combined data sets included in each panel. The dashed horizontal line marks the ratio equal to one.

Moreover, assuming a uniform prior distribution for p_0, $P(p_0) = 1$, we find that

$$P(D_{SNP}|H_0) = \int_0^1 dp_0 \; P(D_{SNP}|p_0, H_0)P(p_0|H_0) = \frac{n_{SNP}!\; n_{\overline{SNP}}!}{(n_{SNP} + n_{\overline{SNP}} + 1)!}. \tag{5}$$

The evidence of H_1 is computed assuming that the presence of the SNP is described by a binomial distribution with two parameters, namely the probability $p_{1,CHD}$ that the SNP

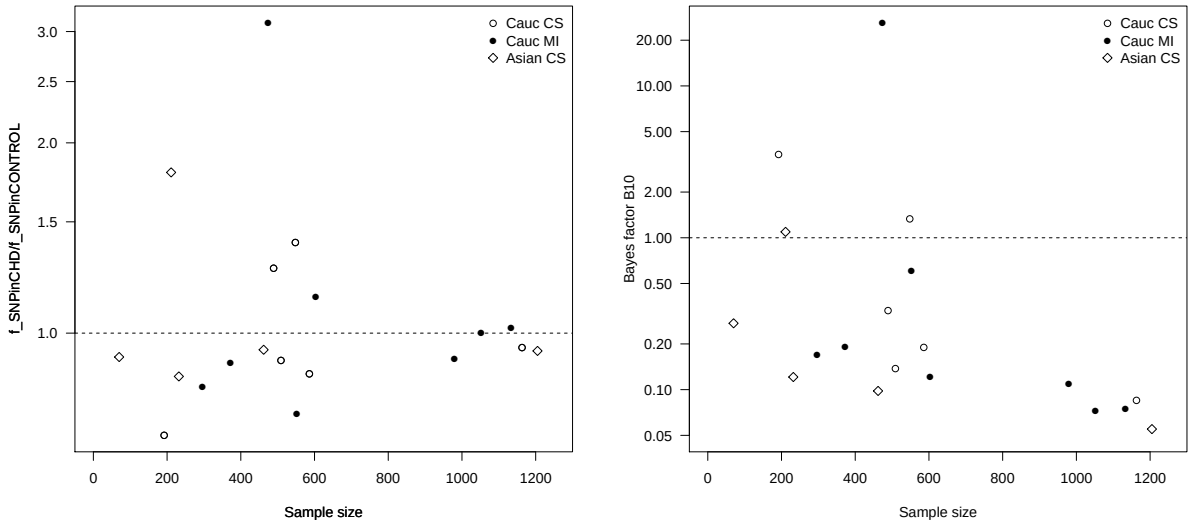

Figure 2. **Scatter plots as a function of the sample size.** Left panel: The ratio of the frequency of SNP in the CHD population to the frequency of SNP in the non–CHD population as a function of the sample size. Right panel: The Bayes factor for the two hypotheses discussed in the text as a function of the sample size.

occurs in the subset of CHD patients and the probability $p_{1,\overline{CHD}}$ that the SNP occurs in the subset of non–CHD patients,

$$P(D_{SNP}|H_1) = \int_0^1 dp_{1,CHD} \int_0^1 dp_{1,\overline{CHD}} \times P(D_{SNP}|p_{1,CHD}, p_{1,\overline{CHD}}, H_1) P(p_{1,CHD}, p_{1,\overline{CHD}}|H_1). \quad (6)$$

For $n_{SNP,CHD}$ occurrences of the SNP and $n_{\overline{SNP},CHD}$ non–occurrences of the SNP in a subset of CHD patients $n_{CHD} = n_{SNP,CHD} + n_{\overline{SNP},CHD}$, and for $n_{SNP,\overline{CHD}}$ occurrences of the SNP and $n_{\overline{SNP},\overline{CHD}}$ non–occurrences of the SNP in a subset of non–CHD patients, $n_{\overline{CHD}} = n_{SNP,\overline{CHD}} + n_{\overline{SNP},\overline{CHD}}$, the likelihood $P(D_{SNP}|p_{1,CHD}, p_{1,\overline{CHD}}, H_1)$ is separable and given by

$$\begin{aligned} P(D_{SNP}|p_{1,CHD}, p_{1,\overline{CHD}}, H_1) &= p_{1,CHD}^{n_{SNP,CHD}} (1 - p_{1,CHD})^{n_{\overline{SNP},CHD}} \\ &\times p_{1,\overline{CHD}}^{n_{SNP,\overline{CHD}}} (1 - p_{1,\overline{CHD}})^{n_{\overline{SNP},\overline{CHD}}} \\ &\equiv P(D_{SNP}|p_{1,CHD}, H_1) P(D_{SNP}|p_{1,\overline{CHD}}, H_1). \end{aligned} \quad (7)$$

Assuming a uniform probability for $p_{1,CHD}$ and $p_{1,\overline{CHD}}$, $P(p_{1,CHD}, p_{1,\overline{CHD}}|H_1) = 1$ and moreover that the priors on $p_{1,CHD}$ and $p_{1,\overline{CHD}}$ are separable, the posterior distribution will also be separable and given by

$$\begin{aligned} P(D_{SNP}|H_1) = &\int_0^1 dp_{1,CHD}\ P(D_{SNP}|p_{1,CHD}, H_1) P(p_{1,CHD}|H_1) \\ &\times \int_0^1 dp_{1,\overline{CHD}}\ P(D_{SNP}|p_{1,\overline{CHD}}, H_1) P(p_{1,\overline{CHD}}|H_1) \end{aligned}$$

$$= \frac{n_{SNP,CHD}!\; n_{\overline{SNP},CHD}!}{(n_{SNP,CHD} + n_{\overline{SNP},CHD} + 1)!} \frac{n_{SNP,\overline{CHD}}!\; n_{\overline{SNP},\overline{CHD}}!}{(n_{SNP,\overline{CHD}} + n_{\overline{SNP},\overline{CHD}} + 1)!}. \qquad (8)$$

In order to compare the hypotheses, we take the ratio of the corresponding evidences, $B_{10} = P(H_1|D)/P(H_0|D)$, which we present in Table I (columns 7–8). This quantity is known as the Bayes factor and gives empirical levels of significance for the strength of the evidence of the test hypothesis over that of the null hypothesis. It also encapsulates the Occam's factor, which measures the adequacy of a hypothesis to the data over the parameter space of the hypothesis [29]. The levels of significance ascribed to the Bayes factor are calibrated by the Jeffrey's scale [30]. According to this scale, a Bayes factor larger than one indicates that H_1 is favoured over H_0. Otherwise, H_0 is favoured over H_1. For the data sets taken separately, the results from this hypothesis test mostly agree with the corresponding results presented in the meta–analysis by Chu et al. (see Fig. 1 of Ref. [7]).

We plot the Bayes factor for each study, grouped by ethnicity and CHD phenotype, in Fig. 3. For the data sets taken separately, we observe that the Bayes factor is asymmetrically distributed about the Bayes factor equal to one, with most Bayes factors being smaller than one. The exceptions are Elahi et al. [10], Vendrell et al. [9] and Dedoussis et al. [17] for the Caucasian population, and Shun et al. [27] for the Asian population. This asymmetry indicates heterogeneity in the results. For the combined data sets included in each panel, the Bayes factor takes values $0.03 - 0.05$ for the Caucasian population and 0.15 for the Asian population, which indicates that there is no evidence for H_1 over H_0. We also observe that for the Caucasian population the Bayes factor of the combined data sets is outside the range of variability of the Bayes factor of the data sets considered separately. This suggests that the combination of the Caucasian data sets causes a new data pattern to emerge. Conversely the combination of the Asian data sets leads to an approximately average data pattern. Hence we conclude that the data favour H_0 over H_1. Since H_0 yields trivial results, in the subsequent subsections we present the results also for H_1 to illustrate the application of the formalism to a more general setup. It is also instructive to compare the subsequent results using both hypotheses.

In Fig. 2 (right panel) we plot the Bayes factor as a function of the sample size. We observe that smaller data sets are distributed across a wide range of values of the Bayes factor, whereas larger data sets are distributed across values smaller than one.

A. Correlation sign

Comparing Fig. 3 with Fig. 1, we observe that, among the studies with Bayes factor larger than one, Elahi et al. has a ratio $f_{SNP\text{in}CHD}/f_{SNP\text{in}\overline{CHD}} < 1$, i.e. the SNP is proportionally less frequent in CHD than in non–CHD patients, which indicates a negative correlation between the presence SNP and the occurrence of CHD. Another example of comparatively large Bayes factor and low ratio $f_{SNP\text{in}CHD}/f_{SNP\text{in}\overline{CHD}}$ is the study of Tuliakova et al. This

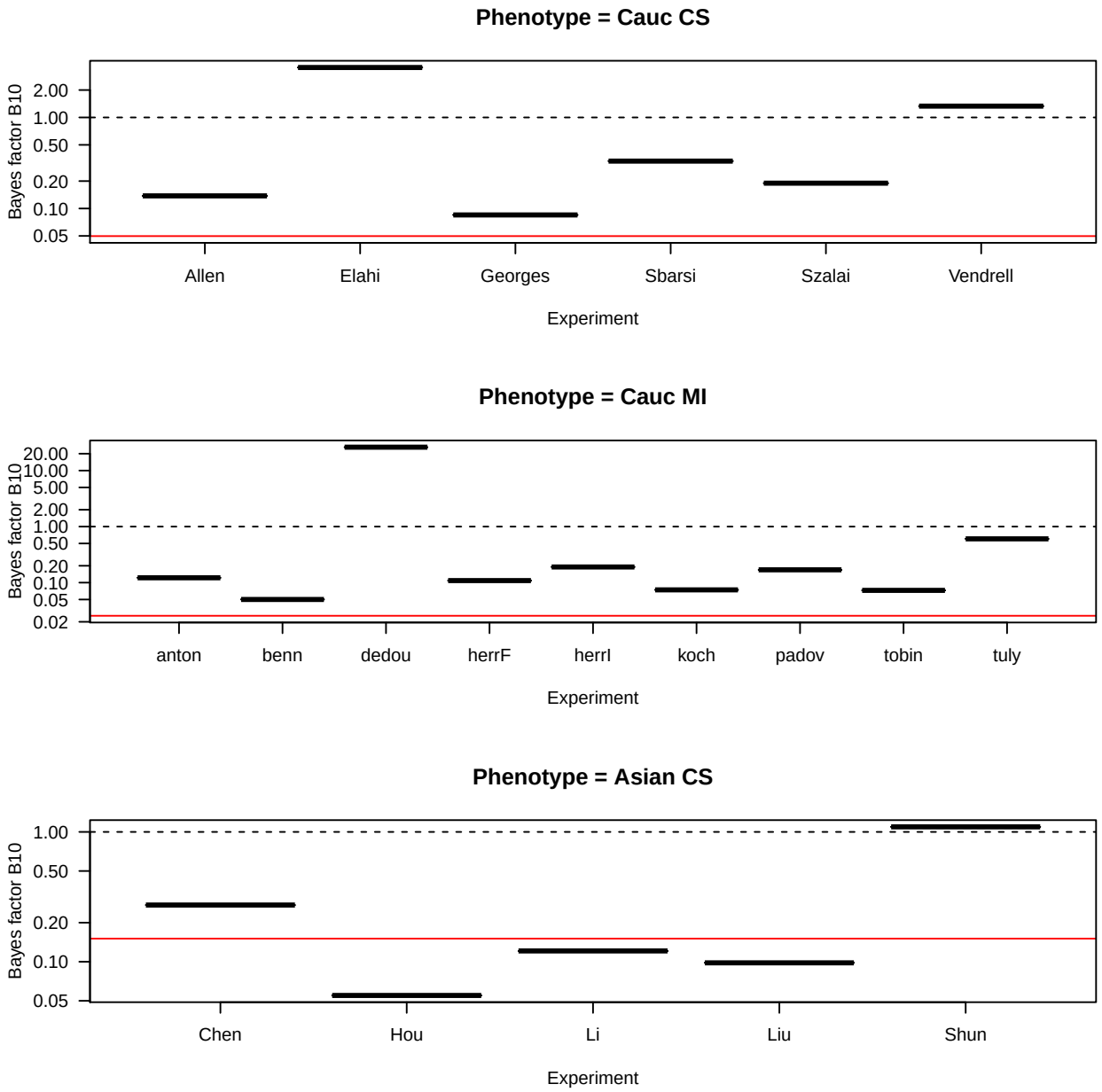

Figure 3. **Funnel plot for the Bayes factor.** The Bayes factor for each study, grouped by ethnicity and CHD phenotype. Top panel: Caucasians with coronary stenosis; Middle panel: Caucasians with myocardial infarction; Bottom panel: Asians with coronary stenosis. The solid horizontal line is the average Bayes factor of the data sets included in each panel. The dashed horizontal line marks the Bayes factor equal to one.

indicates that the hypotheses as formulated do not distinguish the signal of the correlation.

To further explore how the ratio $f_{SNP\text{in}CHD}/f_{SNP\text{in}\overline{CHD}}$ affects the result of the hypothesis testing, we considered several realizations of CHD populations with the same n_{CHD} but with different fractions of SNP. More specifically for each combined data set, we varied $n_{SNP,CHD}$ while varying simultaneously $n_{\overline{SNP},CHD}$ so as to keep n_{CHD} constant. Throughout the different realizations, the control population was kept equal to the com-

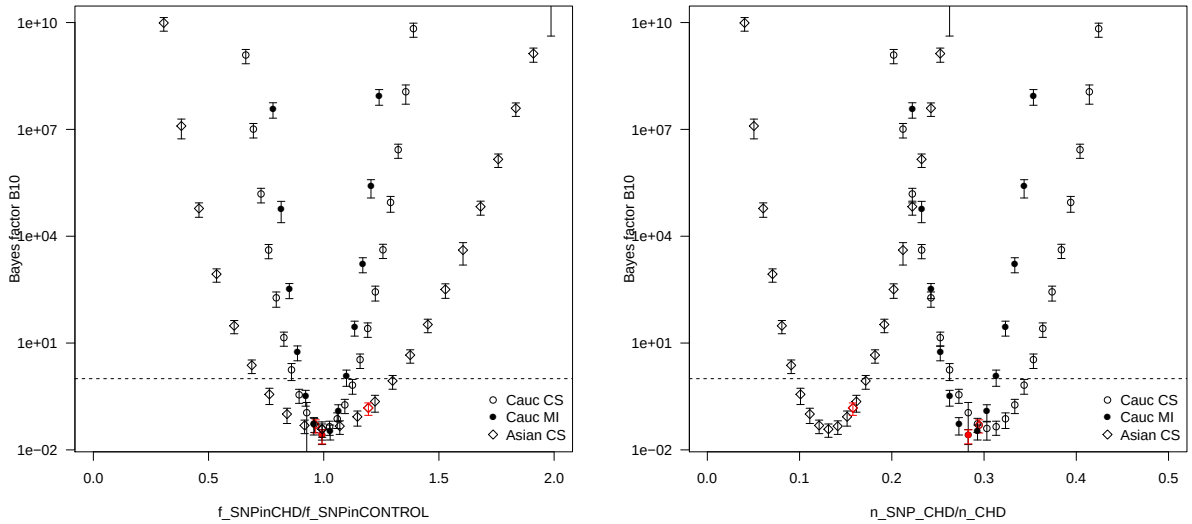

Figure 4. **Bayes factor as a function of the frequency of SNP in the CHD populations.** The Bayes factor for several realizations of CHD populations with the same n_{CHD} but with different fractions of SNP, grouped by ethnicity and CHD phenotype. The realizations that correspond to a real combined data set are marked as red points. The dashed horizontal line marks the Bayes factor equal to one. Left panel: The Bayes factor as a function of $f_{SNP\text{in}CHD}/f_{SNP\text{in}\overline{CHD}}$. Right panel: The Bayes factor as a function of $f_{SNP\text{in}CHD}$.

trol population of the combined data sets grouped by ethnicity and CHD phenotype. For each realization, we computed both $f_{SNP\text{in}CHD}$ (note that $f_{SNP\text{in}Control}$ is by construction kept fixed) and B_{10}, and plotted the results in Fig. 4. The realizations with the $f_{SNP\text{in}CHD}$ of a real combined data set are marked as red points. In the left panel, we plotted B_{10} as a function of $f_{SNP\text{in}CHD}/f_{SNP\text{in}\overline{CHD}}$. In the right panel, we plotted B_{10} as a function of $f_{SNP\text{in}CHD}$ for a better visualization. We observe that B_{10} follows a parabola, taking the minimum value when $f_{SNP\text{in}CHD}/f_{SNP\text{in}\overline{CHD}} = 1$ and increasing in both directions with the increase of $|f_{SNP\text{in}CHD}/f_{SNP\text{in}\overline{CHD}} - 1|$. This confirms that the hypotheses as formulated do not distinguish between a positive correlation of the SNP with CHD ($f_{SNP\text{in}CHD}/f_{SNP\text{in}\overline{CHD}} > 1$) and a negative correlation ($f_{SNP\text{in}CHD}/f_{SNP\text{in}\overline{CHD}} < 1$). Hence, the value of $f_{SNP\text{in}CHD}/f_{SNP\text{in}\overline{CHD}}$ complements the value of B_{10} in the characterization of the correlation.

IV. INFERENCE OF CONDITIONAL PROBABILITIES

A. Posterior probability for the occurrence of CHD

We proceed to compute the probability for the occurrence of CHD, i.e. given the data on the presence of the SNP, we want to determine the probability that a patient has CHD.

This is defined as the posterior probability

$$P(CHD|D_{SNP}, H_n) = \frac{P(D_{SNP}|CHD, H_n)P(CHD)}{P(D_{SNP}|H_n)}. \tag{9}$$

The prior probability $P(CHD)$ is based on the available information on the occurrence of CHD. This probability can be computed by combining all the risk factors per age interval per pathology. According to the European guidelines, less than 4 in 1000 people have CS [32], whereas about 1 in 1000 people have MI [33]. We then use $P(CHD) = 0.004$ for CS and $P(CHD) = 0.001$ for MI.

The evidence $P(D_{SNP}|H_n)$ can be decomposed as

$$P(D_{SNP}|H_n) = P(D_{SNP}|CHD, H_n)P(CHD) + P(D_{SNP}|\overline{CHD}, H_n)P(\overline{CHD}). \tag{10}$$

For the case of H_0,

$$\begin{aligned} P(D_{SNP}|CHD, H_0) &= \binom{n}{n_{SNP}} p_0^{n_{SNP}}(1-p_0)^{n_{\overline{SNP}}} \equiv P(D_{SNP}|H_0) \\ P(D_{SNP}|\overline{CHD}, H_0) &= P(D_{SNP}|H_0), \end{aligned} \tag{11}$$

whereas for the case of H_1,

$$\begin{aligned} P(D_{SNP}|CHD, H_1) &= \binom{n_{CHD}}{n_{SNP,CHD}} p_{1,CHD}^{n_{SNP,CHD}}(1-p_{1,CHD})^{n_{\overline{SNP},CHD}} \\ P(D_{SNP}|\overline{CHD}, H_1) &= \binom{n_{\overline{CHD}}}{n_{SNP,\overline{CHD}}} p_{1,\overline{CHD}}^{n_{SNP,\overline{CHD}}}(1-p_{1,\overline{CHD}})^{n_{\overline{SNP},\overline{CHD}}}. \end{aligned} \tag{12}$$

In the previous section, we computed the evidence by marginalizing the parameters of each hypothesis. Here, assuming a hypothesis H_i and using the Bayes theorem, we compute the posterior probability of each parameter $p_{n,k}$ given the data

$$P(p_{n,k}|D_{SNP}) = \frac{P(D_{SNP}|p_{n,k})P(p_0|H_n)}{P(D_{SNP}|H_n)}, \tag{13}$$

and find for $p_{n,k}$ the value that maximizes the likelihood $P(D_{SNP}|p_{n,k})$. For the case of H_0, $P(D_{SNP}|p_0)$ is given by Eqn. (4), $P(D_{SNP}|H_0)$ is given by Eqn. (5) and $P(p_0|H_0)$ is assumed uniform. Solving for $dP(p_0|D_{SNP})/dp_0 = 0$, we find for the maximum–likelihood value of p_0 the value

$$p_{0(\text{maxL})} = n_{SNP}/(n_{SNP} + n_{\overline{SNP}}). \tag{14}$$

Similarly for the case of H_1, we compute the posterior probability for $p_{1,CHD}$ and $p_{1,\overline{CHD}}$, where $P(D_{SNP}|p_{1,CHD})$ and $P(D_{SNP}|p_{1,\overline{CHD}})$ are given by Eqn. (6), $P(D_{SNP}|H_1)$ is given by Eqn. (8) and both $P(p_{1,CHD}|H_1)$ and $P(p_{1,\overline{CHD}}|H_1)$ are assumed uniform, finding that

$$p_{1,CHD(\text{maxL})} = n_{SNP,CHD}/(n_{SNP,CHD} + n_{\overline{SNP},CHD}), \tag{15}$$

$$p_{1,\overline{CHD}(\text{maxL})} = n_{SNP,\overline{CHD}}/(n_{SNP,\overline{CHD}} + n_{\overline{SNP},\overline{CHD}}). \tag{16}$$

Hypothesis	Probabilities	Phenotype (j)		
		Cauc CS	Cauc MI	Asian CS
H_0	p_0	0.299 ± 0.001	0.284 ± 0.001	0.141 ± 0.001
	$P(CHD\|D_{SNP}, H_0)$	$(4.00 \pm 1.31) \cdot 10^{-3}$	$(1.00 \pm 0.25) \cdot 10^{-3}$	$(4.00 \pm 0.91) \cdot 10^{-3}$
	$P(\text{nextSNP}, CHD\|D_{SNP}, H_0)$	$(1.19 \pm 0.39) \cdot 10^{-3}$	$(0.28 \pm 0.07) \cdot 10^{-3}$	$(0.56 \pm 0.13) \cdot 10^{-3}$
	$P(\text{nextSNP}, \overline{CHD}\|D_{SNP}, H_0)$	0.298 ± 1.093	0.284 ± 1.752	0.141 ± 0.360
	$P(\text{nextSNP}\|D_{SNP}, H_0)$	0.299 ± 1.093	0.284 ± 1.572	0.141 ± 0.360
	$r_{\text{nextSNP,CHD}}$	$(4.00 \pm 14.65) \cdot 10^{-3}$	$(1.00 \pm 5.54) \cdot 10^{-3}$	$(4.00 \pm 10.22) \cdot 10^{-3}$
H_1	$p_{1,CHD}$	0.295 ± 0.001	0.283 ± 0.001	0.158 ± 0.001
	$p_{1,\overline{CHD}}$	0.305 ± 0.001	0.285 ± 0.001	0.132 ± 0.001
	$P(CHD\|D_{SNP}, H_1)$	$(3.42 \pm 7.94) \cdot 10^{-3}$	$(0.98 \pm 3.26) \cdot 10^{-3}$	$(5.00 \pm 7.02) \cdot 10^{-3}$
	$P(\text{nextSNP}, CHD\|D_{SNP}, H_1)$	$(1.00 \pm 2.34) \cdot 10^{-3}$	$(0.28 \pm 0.92) \cdot 10^{-3}$	$(0.79 \pm 1.11) \cdot 10^{-3}$
	$P(\text{nextSNP}, \overline{CHD}\|D_{SNP}, H_1)$	0.304 ± 0.598	0.285 ± 0.926	0.131 ± 0.244
	$P(\text{nextSNP}\|D_{SNP}, H_1)$	0.305 ± 0.598	0.285 ± 0.926	0.132 ± 0.244
	$r_{\text{nextSNP,CHD}}$	$(3.30 \pm 10.02) \cdot 10^{-3}$	$(0.98 \pm 4.54) \cdot 10^{-3}$	$(6.00 \pm 13.84) \cdot 10^{-3}$

Table II. **Probabilities inferred from the combined data sets.** For each hypothesis: a) the parameters given by the maximum–likelihood values, b) the posterior probability for the occurrence of CHD, c) the predicted probabilities for the presence of the SNP, and d) the probability ratio that measures the influence of CHD in the presence of the SNP, $r_{\text{nextSNP,CHD}} \equiv P(\text{nextSNP}, CHD|D_{SNP}, H_i)/P(\text{nextSNP}|D_{SNP}, H_i)$, computed from the combined data of each phenotype.

Analogously we define

$$P(\overline{CHD}|D_{SNP}, H_n) = \frac{P(D_{SNP}|\overline{CHD}, H_n)P(\overline{CHD})}{P(D_{SNP}|H_n)}. \tag{17}$$

Finally, using the maximum–likelihood value of $p_{n,k}$, we compute $P(CHD|D_{SNP}, H_n)$ for the data sets combined, which we present in Table II.

For the case of H_0, no information is added to the prior probability and hence the posterior probability equals the prior. Conversely for the case of H_1, information is added to the prior probability, resulting in a posterior probability different from the prior albeit compatible with the prior.

B. Prediction of the presence of the SNP

We now proceed to compute the probability for the presence of the SNP, i.e. given the data we want to determine the probability that a randomly selected patient (with or without CHD) has the SNP. This is defined as

$$P(\text{nextSNP}|D_{SNP}, H_i) = P(\text{nextSNP}|D_{SNP}, CHD)P(CHD|D_{SNP}, H_i)$$

$$+ P(\text{nextSNP}|D_{SNP}, \overline{CHD})P(\overline{CHD}|D_{SNP}, H_i)$$
$$\equiv P(\text{nextSNP}, CHD|D_{SNP}, H_i) + P(\text{nextSNP}, \overline{CHD}|D_{SNP}, H_i). \quad (18)$$

For the case of H_0,

$$P(\text{nextSNP}|D_{SNP}, CHD) = P(\text{nextSNP}|D_{SNP}, \overline{CHD}) = p_0, \quad (19)$$

whereas for the case of H_1,

$$P(\text{nextSNP}|D_{SNP}, CHD) = p_{1,CHD},$$
$$P(\text{nextSNP}|D_{SNP}, \overline{CHD}) = p_{1,\overline{CHD}}. \quad (20)$$

Using the maximum–likelihood values of $p_{n,k}$ and the posterior probability $P(CHD|D_{SNP}, H_i)$ computed above, we compute $P(\text{nextSNP}|D_{SNP}, H_i)$, which we present in Table II.

For completion we invert this probability to find the probability that CHD will occur given that the SNP is present in a randomly selected patient

$$P(CHD|\text{nextSNP}, H_i) = \frac{P(\text{nextSNP}|D_{SNP}, CHD)P(CHD|D_{SNP}, H_i)}{P(\text{nextSNP}|D_{SNP}, H_i)}. \quad (21)$$

Analogously we find the probability $P(\overline{CHD}|\text{nextSNP}, H_i)$.

In order to quantify the influence of CHD in the presence of the SNP, we compute the ratio of $P(\text{nextSNP}, CHD|D_{SNP})$ to $P(\text{nextSNP}|D_{SNP}, H_i)$, which gives an estimate of how much the occurrence of CHD indicates the presence of the SNP. This is also the probability in Eqn. (21). For the case of H_0, this ratio equals the posterior probability of occurrence of CHD. Conversely for the case of H_1, this ratio is different from the posterior probability of occurrence of CHD albeit compatible with it. The occurrence of CHD indicates the presence of the SNP in a few 0.1% of patients ($0.1 - 0.4\%$ in the case of H_0, $0.1 - 0.6\%$ in the case of H_1), which suggests that occurrence of CHD is not a good marker for the presence of the SNP.

In order to quantify the influence of the SNP in the occurrence of CHD, we compute the ratio of $P(CHD|\text{next } SNP, H_i)$ to $P(CHD|D_{SNP}, H_i)$, which gives an estimate of how much the presence of the SNP indicates the occurrence of CHD. This is also the probability in Eqns. (19, 20). The presence of SNP indicates the occurrence of CHD in a few 0.1% of patients ($0.141 - 0.299.\%$ in the case of H_0, $0.158 - 0.295\%$ in the case of H_1), which suggests that the presence of the SNP is not a risk factor for the emergence of CHD.

V. SENSITIVITY OF THE RESULTS

To test the robustness of this meta–analysis, we conceived two tests of the sensitivity of the results, namely to low–significance data sets, to data sets with extreme results and to extreme data sets.

To test the sensitivity of the results to low–significance data sets, we excluded the data sets with comparatively small sample sizes for the same CHD phenotype, namely the study by Elanhi et al. [10] and the study by Chen et al. [23], from the combination. We also excluded the studies with extreme results (i.e., the studies with the largest Bayes factor), namely the study in Dedoussis et al. [17]. We recomputed both the Bayes factors (Table I) and the probabilities of CHD (Table III). We observe that the Bayes factor in the new combination changes by 18%, −38% and 24%, respectively for the CS Caucasian, the MI Caucasian and the CS Asian population. The inferred parameters and probabilities vary by −6 to 6%, −5 to 2%, and −1 to 4%, respectively for the CS Caucasian, the MI Caucasian and the CS Asian population. The largest difference is observed for the CS Caucasian population due to the exclusion of the study by Elanhi et al. [10]. The exclusion of the study by Dedoussis et al. [17] from the MI Caucasian population causes predominantly negative differences.

To test the sensitivity of the results to extreme data sets, we excluded the data sets with comparatively large samples sizes for the same CHD phenotype, namely the study by Georges et al. [12], the study by Bennet el al. [16] and the study by Hou et al. [24], from the combination. These are also the studies with the smallest Bayes factor for each CHD phenotype. We recomputed both the Bayes factors (Table I) and the probabilities of CHD (Table IV). We observe that the Bayes factor in the new combination changes by 3%, −19% and 32%, respectively for the CS Caucasian, the MI Caucasian and the CS Asian population. The inferred parameters and probabilities vary by −20 to −1%, 5 to 11%, and −26 to 25%, respectively for the CS Caucasian, the MI Caucasian and the CS Asian population. The largest difference is observed for the CS Asian population due to the exclusion of the study by Hou et al. [24]. The exclusion of the study by Georges e tal. [12] from the CS Caucasian population causes predominantly negative differences.

In both tests, the differences in the Bayes factor leave the result of the hypothesis testings unchanged, while the differences in the inferred parameters and probabilities also leave the conclusions unchanged. We thus infer that the sensitivity of this formalism to a) low–significante data sets combined with data with extreme results, and to b) extreme data sets renders this formalism significantly robust.

VI. SUMMARY

In this manuscript we investigate the correlation between the occurrence of CHD with the presence of the –308 TNF–α SNP from fifteen independent data sets on Caucasians for two CHD phenotypes and from five independent data sets on Asian for one CHD phenotype. We show how to combine independent data sets and to infer correlations using Bayesian analysis.

Hypothesis testing on the combined data sets indicates that there is no evidence for a cor-

Hypothesis	Probabilities	Phenotype (j)		
		Cauc CS	Cauc MI	Asian CS
H_0	p_0	0.288 ± 0.001	0.296 ± 0.001	0.136 ± 0.001
	$P(CHD\|D_{SNP}, H_0)$	$(4.00 \pm 1.26) \cdot 10^{-3}$	$(1.00 \pm 0.24) \cdot 10^{-3}$	$(4.00 \pm 0.89) \cdot 10^{-3}$
	$P(\text{nextSNP}, CHD\|D_{SNP}, H_0)$	$(1.15 \pm 0.36) \cdot 10^{-3}$	$(0.30 \pm 0.07) \cdot 10^{-3}$	$(0.55 \pm 0.12) \cdot 10^{-3}$
	$P(\text{nextSNP}, \overline{CHD}\|D_{SNP}, H_0)$	0.287 ± 1.018	0.296 ± 1.605	0.136 ± 0.340
	$P(\text{nextSNP}\|D_{SNP}, H_0)$	0.289 ± 1.018	0.296 ± 1.605	0.136 ± 0.340
	$r_{\text{nextSNP,CHD}}$	$(4.00 \pm 14.16) \cdot 10^{-3}$	$(1.00 \pm 5.54) \cdot 10^{-3}$	$(4.00 \pm 10.00) \cdot 10^{-3}$
H_1	$p_{1,CHD}$	0.290 ± 0.001	0.292 ± 0.001	0.151 ± 0.001
	$p_{1,\overline{CHD}}$	0.287 ± 0.001	0.300 ± 0.001	0.128 ± 0.001
	$P(CHD\|D_{SNP}, H_1)$	$(3.34 \pm 7.57) \cdot 10^{-3}$	$(0.99 \pm 3.18) \cdot 10^{-3}$	$(5.11 \pm 6.96) \cdot 10^{-3}$
	$P(\text{nextSNP}, CHD\|D_{SNP}, H_1)$	$(0.97 \pm 2.19) \cdot 10^{-3}$	$(0.29 \pm 0.93) \cdot 10^{-3}$	$(0.77 \pm 1.05) \cdot 10^{-3}$
	$P(\text{nextSNP}, \overline{CHD}\|D_{SNP}, H_1)$	0.286 ± 0.542	0.300 ± 0.947	0.128 ± 0.234
	$P(\text{nextSNP}\|D_{SNP}, H_1)$	0.287 ± 0.543	0.300 ± 0.947	0.129 ± 0.234
	$r_{\text{nextSNP,CHD}}$	$(3.38 \pm 9.96) \cdot 10^{-3}$	$(0.96 \pm 4.34) \cdot 10^{-3}$	$(6.02 \pm 13.67) \cdot 10^{-3}$

Table III. **Probabilities inferred from the combined data sets excluding the low–significance data sets and the data sets with extreme results.** Excluded: Elanhi et al. [10], Dedoussis et al. [17] and Chen et al. [23]. For each hypothesis: a) the parameters given by the maximum–likelihood values, b) the posterior probability for the occurrence of CHD, c) the predicted probabilities for the presence of the SNP, and d) the probability ratio that measures the influence of CHD in the presence of the SNP, $r_{\text{nextSNP,CHD}} \equiv P(\text{nextSNP}, CHD|D_{SNP}, H_i)/P(\text{nextSNP}|D_{SNP}, H_i)$, computed from the combined data of each phenotype.

relation between the occurrence of CHD and the presence of the SNP, either on Caucasians or on Asians. This result agrees with the previous meta–analyses [6, 7]. As a measure of an eventual correlation, we computed the conditional probability of CHD given the SNP, normalized to the probability that CHD occurs, finding that the presence of the SNP indicates the occurrence of CHD in of order a few 0.1% of patients, i.e. in of order a few 0.1% of the occurrence of CHD is concomitant with the presence of SNP. We also tested the sensitivity of the results by excluding selected data sets from the meta–analysis. We found changes of order a few 10%, leaving the results unchanged and thus establishing this formalism as significantly robust.

An interesting extension of this work for the sake of completion is the inclusion of studies refereeing to Asians, Africans and Indians which are currently too few to extract convincing results.

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Hypothesis	Probabilities	Phenotype (j)		
		Cauc CS	Cauc MI	Asian CS
H_0	p_0	0.308 ± 0.001	0.271 ± 0.001	0.177 ± 0.001
	$P(CHD\|D_{SNP}, H_0)$	$(4.00 \pm 1.08) \cdot 10^{-3}$	$(1.00 \pm 0.20) \cdot 10^{-3}$	$(4.00 \pm 0.63) \cdot 10^{-3}$
	$P(\text{nextSNP}, CHD\|D_{SNP}, H_0)$	$(1.12 \pm 0.33) \cdot 10^{-3}$	$(0.27 \pm 0.05) \cdot 10^{-3}$	$(0.71 \pm 0.11) \cdot 10^{-3}$
	$P(\text{nextSNP}, \overline{CHD}\|D_{SNP}, H_0)$	0.306 ± 0.923	0.270 ± 1.220	0.177 ± 0.314
	$P(\text{nextSNP}\|D_{SNP}, H_0)$	0.308 ± 0.923	0.271 ± 1.220	0.177 ± 0.314
	$r_{\text{nextSNP, CHD}}$	$(4.00 \pm 12.05) \cdot 10^{-3}$	$(1.00 \pm 4.51) \cdot 10^{-3}$	$(4.00 \pm 7.11) \cdot 10^{-3}$
H_1	$p_{1,CHD}$	0.306 ± 0.001	0.270 ± 0.001	0.190 ± 0.001
	$p_{1,\overline{CHD}}$	0.309 ± 0.001	0.271 ± 0.001	0.165 ± 0.001
	$P(CHD\|D_{SNP}, H_1)$	$(3.93 \pm 6.97) \cdot 10^{-3}$	$(0.92 \pm 2.58) \cdot 10^{-3}$	$(3.90 \pm 4.35) \cdot 10^{-3}$
	$P(\text{nextSNP}, CHD\|D_{SNP}, H_1)$	$(1.20 \pm 2.14) \cdot 10^{-3}$	$(0.25 \pm 0.70) \cdot 10^{-3}$	$(0.74 \pm 0.828) \cdot 10^{-3}$
	$P(\text{nextSNP}, \overline{CHD}\|D_{SNP}, H_1)$	0.308 ± 0.535	0.271 ± 0.698	0.165 ± 0.187
	$P(\text{nextSNP}\|D_{SNP}, H_1)$	0.309 ± 0.535	0.271 ± 0.698	0.165 ± 0.187
	$r_{\text{nextSNP, CHD}}$	$(3.90 \pm 9.68) \cdot 10^{-3}$	$(0.91 \pm 3.48) \cdot 10^{-3}$	$(4.48 \pm 7.13) \cdot 10^{-3}$

Table IV. **Probabilities inferred from the combined data sets excluding the extreme data sets.** Excluded: Georges e tal. [12], Bennet el al. [16] and Hou et al. [24]. For each hypothesis: a) the parameters given by the maximum–likelihood values, b) the posterior probability for the occurrence of CHD, c) the predicted probabilities for the presence of the SNP, and d) the probability ratio that measures the influence of CHD in the presence of the SNP, $r_{\text{nextSNP, CHD}} \equiv P(\text{nextSNP}, CHD|D_{SNP}, H_i)/P(\text{nextSNP}|D_{SNP}, H_i)$, computed from the combined data of each phenotype.

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