Combining Information on Multiple Detection Techniques to Estimate the Effect of Patent Foramen Ovale on Susceptibility to Decompression Illness

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Introduction

The assembly and the maintenance of the International Space Station is expected to require hundreds of extravehicular excursions (EVA's) in the next 10 years. During an EVA, in order to allow movement and bending of limbs, spacesuit pressures are reduced to about 4.3 psi. as compared with about 14.7 psi. for normal atmospheric pressure at sea level. However, the exposure of astronauts to reduced pressures in spacesuits, is conducive to formation and growth of gas bubbles within venous blood or tissues, which could cause decompression illness (DCI), a pathology best known to occur among deep-sea divers when they return to the surface. To reduce the risk of DCI, astronauts adjust to the reduced pressure in stages for a prolonged time known as a "pre-breathe" period prior to their extravehicular activity.

Despite the use of pre-breathe protocols, an increased risk of DCI can arise for about 25% of humans who have a small hole, known as a *patent foramen ovale* (PFO), between two chambers of the heart. The atrial septum's fossa ovalis, an embryological remnant of a flap between the septae primum and secundum allows fetal right atrial blood to pass into the left atrium, and usually closes after birth (Hagen, *et al,. 1984)*. If fusion does not occur, a valve-like opening, the foramen ovale persists between the two atria. It has been suggested that astronauts with PFO's might be at greater risk of stroke or other serious neurological DCI because bubbles from a venous site may traverse a PFO, travel to the aorta and then enter the cerebral circulatory system causing a stroke (Figure 1).

Astronauts are not now screened for PFO's, however consideration is being given to doing so. Here, we study three main methods abbreviated here as "TTE", "TCD" and "TEE", for detecting PFO's in

living subjects. All involve the introduction of bubbles into a vein, immediately after which a sensory probe attempts to detect the bubbles in systemic circulation. Presence of the injected bubbles in the systemic circulation is indicative of a PFO. More detailed descriptions are given after the explanation of PFO;s under Figure 1. Even if a true PFO affects the risk of DCI, there remains a question of how effective screening would be if the detection method has errors of omission and/or commission. Of the three methods studied here, TEE is the "gold standard", matching autopsy results with near-perfect sensitivity and specificity (Schneider, *et al.*, 1996). However TEE is also the most difficult method to implement, requiring an internal esophagal probe, and is therefore not widely used. Currently, the easiest to use and most common PFO detection method is TTE, which uses an external chest probe. This method has a specificity of near 100%, but suffers from a low sensitivity rate (about 30%). More recently, TCD has been developed, which uses ultrasound probes to detect the presence of bubbles in cerebral arteries. Studies indicate that TCD is quite effective, having a sensitivity of about 91% and a specificity of about 93% (Droste, *et al.*, 1999) when applied correctly, however implementation is difficult and requires considerable training.

To date, there has been little published research on the association between real or detected PFO's and risk of cerebral DCI in a reduced-pressure environment (as would be the case with astronauts), however there are available studies on PFO-DCI association for divers. Here, we used a form of meta-analysis of diving studies to estimate the value of screening for PFO's for each of the three procedures even though each study used only one of the three. A key assumption that would allow us to combine the disparate studies was examined. Comparisons of combined results with estimates made separately for each technique were also made.

Statistical Analysis

Objectives. There were two main objectives of our statistical analysis. The first was to estimate the odds ratio for incidence of DCI with respect to whether or not a subject is classified as having a PFO, using a) TTE and b) TCD and c) TEE. The second objective was to estimate how much, if any, beneficial effect

there would be if potential subjects were screened for PFO using any of the three detection methods. Here, we use the convention that a subject is said to "have" a PFO if and only if the latter is detected using the "gold-standard" method TEE. To meet both objectives, we used results from five retrospective studies of divers who experienced neurological symptoms of DCI. Foramen ovale patency was assessed by TTE in two of the studies (Moon, *et al.,* 1989 ,Wilmshurst *et al.,*1989), by TCD in one study [Louge and Cantais, 1999], and by TEE in the remaining two studies (Germonpre, *et al.,*1998, Schwerzmann *et al.,*2001). In all five studies, PFO status was also assessed on selected groups of divers who did not experience DCI. In addition, we made use of two additional studies (Belkin, *et al.,* 1994, Droste, *et al.,*1999) to obtain estimates of sensitivity and specificity for TTE and TCD respectively. These estimates were incorporated in a combined analysis of data from all three detection methods to produce more efficient estimates of relevant odds ratios for both analysis objectives.

Approach. For a subject examined with the k-th detection method, we define $\hat{X}_k$ to be an indicator of PFO diagnosis; *i.e.* let $\hat{X}_k = 1$ if a PFO is diagnosed; otherwise $\hat{X}_k = 0$. For definiteness, we shall henceforth number the methods in this study as follows: $k = 1, 2, 3$ denotes TTE, TCD and TEE respectively. In a retrospective study involving the k-th method, let $y_{kj} = 1$ if the j-th subject exhibited neurological DCI symptoms; otherwise $y_{kj} = 0$. Also let x_{kj} be the value of $\hat{X}_k$ for the j-th subject. If there is at least one case of DCI and non-DCI in the study, logistic regression can be used to estimate the odds ratio

$$OR_k = \frac{P(DCI \mid \hat{X}_k = 1) / P(no\ DCI \mid \hat{X}_k = 1)}{P(DCI \mid \hat{X}_k = 0 / P(no\ DCI \mid \hat{X}_k = 0)}. \qquad (1)$$

because $\beta_{1k} = \log OR_k$ is the coefficient of x_{kj} in the model

$$\text{logit } P(y_{kj} = 1) = \beta_{0k} + \beta_{1k} x_{kj}. \qquad (2)$$

The coefficient β_{0k} accounts for bias incurred by retrospective inclusion of arbitrary numbers of DCI and non-DCI subjects in the study (Collet , 1999, p. 251). In the case of more than one study, data can be

combined in one logistic regression model with one common value of β_{1k}, but with study-specific values of β_{0k}. Because the risk of neurological DCI is very small, with our without a PFO, OR_k is a very good approximation to the corresponding risk ratio

$$\rho_k = \frac{P(DCI \mid \hat{X}_k = 1)}{P(DCI \mid \hat{X}_k = 0)}. \tag{3}$$

In the second objective of this work, we wish to quantify the effectiveness of each detection method for screening out subjects potentially susceptible to DCI, based on the presence of a suspected PFO. For the k-th procedure, subjects passing the screening test all have $\hat{X}_k = 0$, hence the risk of DCI for such subjects is the denominator of (3). For non-screened subjects, the risk of DCI is simply P(DCI), the unconditional probability of DCI. The ratio $S_k = \frac{P(DCI)}{P(DCI \mid \hat{X}_k = 0)}$ therefore reflects the efficacy of screening, with larger values corresponding to greater reduction in the risk of DCI. In order to calculate estimates of S_k from estimates of ρ_k, it is necessary to know (or at least have an estimate of) θ_k, the proportion of subjects expected to be classified as having a PFO using the k-th method. Since by definition, $\theta_k = P(\hat{X}_k = 1)$, we have $P(\text{DCI}) = \theta_k P(\text{DCI} \mid \hat{X}_k = 1) + (1 - \theta_k) P(\text{DCI} \mid \hat{X}_k = 0)$, hence

$$S_k = \theta_k \rho_k + (1 - \theta_k). \tag{4}$$

In a prospective study of the k-th detection method applied to a random sample of subjects, a good estimate of θ_k is the proportion of subjects classified as having a PFO. Alternatively, θ_k may be expressed as

$$\theta_k = (1 - \alpha_k)\lambda + \beta_k(1 - \lambda) \tag{5}$$

where λ is the incidence of true PFO's in the general population, $\alpha_k = P(\hat{X}_k = 0 \mid X = 1)$ and $\beta_k = P(\hat{X}_k = 1 \mid X = 0)$. Here, X is an indicator variable which reflects the actual presence of a PFO. (Since TEE is assumed to be errorless, $X \equiv \hat{X}_3$, however for now we remove the "hat" and the subscript "3" to emphasize true PFO status.) Because we lacked studies of TTE and TCD applied to randomly selected

subjects, we instead used (5) to estimate θ_1 and θ_2. Assuming no errors with TEE, we took θ_3 equal to λ = 263/975 $\doteq$ 0.27, the widely recognized value obtained by Hagen, *et al.*, 1984. For TTE, we estimated α_1 = (1- sensitivity), as 0.71 with combined data from the studies of Schwerzmann *et al.*, 2001. For this detection method, we also assumed the specificity to be unity (Belkin, *et al.*, 2001, 1994), hence we took β_2 = (1 – specificity) = 0. From a study of TCD effectiveness (Droste, *et al.*, 1999), we estimated α_2 = 0.09 (sensitivity = 0.91) and β_2 = *0.07* (specificity = 0.93). Using (5), we then obtained the estimates θ_1 = 0.078 (TTE) and θ_2 = 0.297 (TCD). See Table 6 for a summary of these characteristics.

Combining results. Although results from the study of each detection method can be used independently to estimate the DCI risk ratio *(3)* and the screening benefit ratio *(4)*, it is possible to combine studies of all three methods to produce improved estimates of (3) and (4) provided α_k, β_k and λ are known and the following assumption holds:

> *Assumption A: Given that a subject has a true PFO (i.e. detected by TEE), the risk of DCI during a dive is the same whether or not the PFO is also detected by one of the two imperfect methods (TTE or TCD).*

Some justification of this assumption is provided by Lynch, *et al.*(1984), who demonstrated that the amount of saline contrast material across a PFO was not correlated with the magnitude of the right-to-left shunting (RLS flow) as detected by TTE. For example, a PFO detected only by TEE and missed by TTE or TCD may still allow large amounts of RLS and may therefore lead to paradoxical cerebral embolization. Conversely, there are no published conclusive findings that would enable us to conclude that a PFO detected by TTE, for example, is somehow more "severe" and is therefore associated with an increased risk of paradoxical cerebral embolization.

With the help of *Assumption A*, we proceed to express each of the risk ratios ρ_k in terms pf the risk ratio ρ for a perfect method. Data from all five studies can then be used in a single analysis to estimate each of the ρ_k. For imperfect detection methods, let $P_{1k} = P(DCI \mid \hat{X}_k = 1)$ and $P_{0k} = P(DCI \mid$

$\hat{X}_k = 0)$. Also let the corresponding risks in terms of true PFO status be $P_1 = P(DCI \mid X = 1)$ and $P_0 = P(DCI \mid X = 0)$ with ratio $\rho = P_1/P_0$. By definition, $P_{1k} = P(DCI, \hat{X}_k = 1)/P(\hat{X}_k = 1) = P(DCI, \hat{X}_k = 1)/\theta_k$. The quantity $P(DCI, \hat{X}_k = 1)$ can be decomposed as follows:

$$P(DCI, \hat{X}_k = 1) = P(DCI \mid \hat{X}_k = 1, X = 1)P(\hat{X}_k = 1 \mid X = 1)P(X = 1)$$

$$+ P(DCI \mid \hat{X}_k = 1, X = 0)P(\hat{X}_k = 1 \mid X = 0)P(X = 0) \quad (6)$$

Assumption A is equivalent to the conditional independence of $\hat{X}_k$ from the event of DCI, given that X is known; *i.e.*

$$P(DCI \mid \hat{X}_k, X) = P(DCI \mid X). \quad (7)$$

Under this assumption, the expression *(6)* becomes $P_1(1 - \alpha_k)\lambda + P_0\beta_k(1-\lambda)$. Thus

$$P_{1k} = \frac{P_1(1-\alpha_k)\lambda + P_0\beta_k(1-\lambda)}{\theta_k} \quad (8)$$

where θ_k is given by *(5)*. It follows that P_{1k} is a weighted average of P_1 and P_0; *i.e.*

$$P_{1k} = W_{1k}P_1 + (1 - W_{1k})P_0 \quad (9)$$

where $W_{1k} = (1 - \alpha_k)\lambda/\theta_k$. Using a similar approach for P_{0k}, it can be shown that

$$P_{0k} = (1 - W_{0k})P_1 + W_{0k}P_0. \quad (10)$$

where $W_{0k} = (1 - \beta_k)(1 - \lambda)/(1 - \theta_k)$. Finally, we have

$$\rho_k = \frac{W_{1k}\rho + 1 - W_{1k}}{(1 - W_{0k})\rho + W_{0k}} \quad (11)$$

In our case, we had results from five studies, summarized in Tables 1-5. In general, suppose the i-th study used Method k, with y_{ij} denoting the DCI indicator variable for the j-th subject. Then the logistic model *(2)* applied to this data is of the form

$$\text{logit } P(y_{ij} = 1) = \beta_{0i} + \beta_{1i}x_{ij} \quad (12)$$

where $x_{ij} = \hat{X}_k$ for the j-th subject and $\beta_{1j} = \log OR_k$. However, since $OR_k \doteq \rho_k$. we may express β_{1i} in terms of ρ:

$$\text{logit } P(y_{ij} = 1) = \beta_{0i} + \log\left[\frac{W_{1k}\rho + 1 - W_{1k}}{(1 - W_{0k})\rho + W_{0k}}\right] x_{ij} \qquad (13)$$

With α_k, β_k and λ known, W_{1k} and W_{0k} also become known. From the logistic model (13), we then estimated the parameters ρ and $\beta_{01}, .., \beta_{05}$ by maximum likelihood using the statistical software Stata (references). We then estimated ρ_k by

$$\hat{\rho}_k = \frac{W_{1k}\hat{\rho} + 1 - W_{1k}}{(1 - W_{0k})\hat{\rho} + W_{0k}} \qquad (14)$$

where $\hat{\rho}$ is the maximum likelihood estimate of ρ. Confidence limits for ρ and the $\hat{\rho}_k$ were obtained from the standard error matrix and are shown in Table TBD2. Finally, point estimates and confidence intervals for ρ_k were substituted into (4) to obtain confidence limits for the screening benefit ratio for each procedure.

Results

Tables 1-5 show raw tabulations of PFO and DCI outcomes obtained from the five retrospective studies used in the various analyses. Using only the data pertaining to each procedure, estimates of odds ratios and log odds ratios quantifying the effect of PFO status on DCI risk are shown along with 95% confidence limits in Table 7. Since the overall risk of neurological DCI is very small, odds ratios are considered equivalent to risk ratios. All logs are natural. Note that because of limited amounts of data, the confidence intervals are quite wide. Nevertheless, all three lower 95% confidence limits exceeded one, indicating a significant role for diagnosed PFO status (by any of the three methods) as a predictor of the risk of DCI. Improved estimates obtained from combining the studies under Assumption A are shown in the first part of Table 8. Plots of point estimates and corresponding 95% confidence intervals for the log risk ratio with both the separate and combined data are shown in Figure 2. Note how the addition of the accurate TEE and relatively accurate TCD data dramatically improved the precision of the log risk ratio estimate for TTE. On the other hand, including less accurate TTE and TCD data did not substantially reduce the width of the confidence interval for the TEE log risk ratio. The width of the corresponding

confidence interval for TCD was somewhat reduced, suggesting that use of the TEE data improved precision for TCD, but that the TTE data did not substantially help.

Screening benefit ratios S_k, calculated from *(4)* are also shown in Table 8. Although the benefit of using TTE to screen is statistically significant (lower confidence limit > 1.0), there appears to be little practical benefit for screening with TTE. On the other hand, even with the fairly large uncertainty in the estimate, we could conclude that screening with TCD or TEE would considerably reduce the risk of DCI.

Discussion

A method has been given that allows one to combine the results of studies with disparate diagnostic procedures, to obtain more efficient estimates of screening effectiveness for an outcome (in this case DCI) whose risk is presumably affected by the condition being diagnosed (in this case PFO) by the diagnostic procedures. In order for the method to work, the risk of the outcome must be low enough, with or without the condition, so that odds ratios are essentially equivalent to risk ratios. In addition, a key assumption (*Assumption A)* that allows the combination method to work, is that the risk of the outcome is unchanged by diagnosis of the condition using an imperfect procedure, given that the condition actually does or does not hold. This would not be the case, for example, if TTE misses "small" PFO's that do not contribute to increased risk of DCI, but finds "large" PFO's which do increase the risk of DCI.

How valid is this assumption for TTE? For notational simplicity, let $\hat{X} \equiv \hat{X}_1$, $\alpha \equiv \alpha_1$ and $\beta \equiv \beta_1$. Applying *Assumption A* to *(6)* yields

$$P(\hat{X}=1, DCI) = P_1(1-\alpha)\lambda + P_0\beta(1-\lambda) \qquad (15)$$

where $P_1 = P(DCI \mid X = 1)$ and $P_0 = P(DCI \mid X = 0)$. Thus

$$P(\hat{X}=1 \mid DCI) = \frac{P_1(1-\alpha)\lambda + P_0\beta(1-\lambda)}{\lambda P_1 + (1-\lambda)P_0} \qquad (16)$$

For TTE, $\beta = 0$, hence *(16)* becomes

$$P(\hat{X}=1 \mid DCI) = \frac{P_1(1-\alpha)\lambda}{\lambda P_1 + (1-\lambda)P_0} < \frac{P_1(1-\alpha)\lambda}{\lambda P_1} = 1-\alpha \doteq 0.29 \qquad (17)$$

Equation *(17)* states that the proportion of DCI subjects diagnosed by TTE as having PFO's cannot exceed 0.29, even if every one of these subjects actually had a PFO. In view of *(17)* it is extremely unlikely that as many as 11 of 18 DCI subjects in Study 1 could have been diagnosed with PFO's by TTE *($P < .005$)* or that at least 19 of 29 DCI subjects in Study 2 could have been so diagnosed *($P < .0001$)* even if all such subjects actually had PFO's. The conclusion is that either *Assumption A* is not true for TTE, or the sensitivity of TTE in Studies 1 and 2 was considerably higher than *0.29*. A possible explanation for the latter scenario is that a sensitivity of *0.29* applies to standard clinical application, whereas experimenters in Studies 1 and 2 were especially meticulous about implementing TTE, perhaps with multiple trials if no PFO was detected. If this scenario is true, the effectiveness of TTE as a screening procedure against DCI may actually be higher than previously thought, provided the procedure is applied with the same care as in Studies 1 and 2. For example, a conservative estimate of the sensitivity of TTE using data from Studies 1 and 2, would be to assume every DCI patient in these studies had a PFO. In this case 30 of 47 PFO's would have been detected, (sensitivity = 30/47 = 0.64). Applying (5) yields $\theta_1 = 0.17$. Using the separately obtained odds ratio of 8.6 for TTE (Table 7), with $\theta_1 = 0.17$, yields a screening benefit ratio (4) of $S_1 = 2.3$, considerably higher than the value of 1.24 obtained in Table 8, using the combined data with a sensitivity of 0.29.

Table 1. Tabulated Results from Study 1. Method: TTE

PFO Status	DCI	No DCI	Total
Yes ($\hat{X} = 1$)	11	0	11
No ($\hat{X} = 0$)	7	12	19
Total	18	12	30

Table 2. Tabulated Results from Study 2. Method: TTE

PFO Status	DCI	No DCI	Total
Yes ($\hat{X} = 1$)	19	15	34
No ($\hat{X} = 0$)	10	48	58
Total	29	63	92

Table 3. Tabulated Results from Study 3. Method: TCD

PFO Status	DCI	No DCI	Total
Yes ($\hat{X} = 1$)	27	13	40
No ($\hat{X} = 0$)	6	51	57
Total	33	64	97

Table 4. Tabulated Results from Study 4. Method: TEE

PFO Status	DCI	No DCI	Total
Yes ($\hat{X} = 1$)	16	5	21
No ($\hat{X} = 0$)	4	15	19
Total	20	20	40

Table 5. Tabulated Results from Study 5. Method: TEE

PFO Status	DCI	No DCI	Total
Yes ($\hat{X} = 1$)	4	9	13
No ($\hat{X} = 0$)	2	37	39
Total	6	46	52

Table 6. Characteristics of Diagnosis Methods (λ = overall incidence of PFO = 0.270)

k	*Method (k)*	*Sensitivity*	*Specificity*	α_k	β_k	θ_k
1	TTE	0.29	1.00	0.71	0.00	0.078
2	TCD	0.91	0.93	0.01	0.07	0.297
3	TEE	1.00	1.00	0.00	0.00	0.270

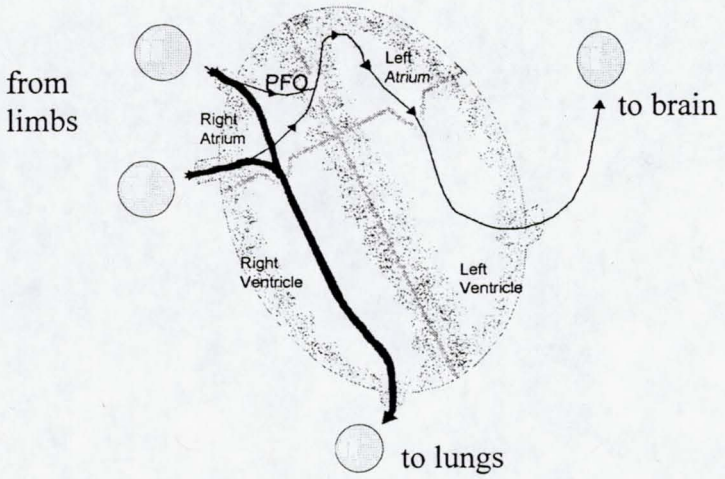
Table 7. Estimated DCI Odds Ratios (estimated separately)

	TTE	TCD	TEE
Odds Ratio (OR_k)	8.6	17.6	10.4
95% Conf. Limits	(3.5, 21.0)	(6.0, 51.7)	(3.3, 33.2)

Table 8. Estimated DCI Risk and Screening Benefit Ratios (from combined data)

	TTE	TCD	TEE
DCI Risk (ρ_k)	4.1	10.3	20.6
95% Conf. Limits	(3.5, 4.7)	(6.1, 17.2)	(8.3, 50.9)
Screening Benefit (S_k)	1.24	3.75	6.28
95% Conf. Limits	(1.20, 1.30)	(2.52, 5.79)	(2.97, 14.47)

Figure 1. Patent Foramen Ovale (PFO)



Explanation of the figure.
Venous bubbles from the limbs travel through the superior and inferior vena cava into the right atrium, then into the right ventricle. Then, those venous bubbles are normally filtered and eliminated in the lungs. If a patent foramen ovale is present, venous bubbles may crossover directly into the left atrium, left ventricle, aorta and finally into the arterial systemic circulation, shunting the lung filter. Bubbles into the carotids may embolize in the brain causing cerebral accidents.

Three methods of PFO detection.
After the injection of an echo contrast agent, contrast-enhanced transthoracic echocardiography (c-TTE) is performed by placing a probe on the chest. However, there are failures to detect the PFO because remote views of the heart from the chest are not ideal. (specificity = 100%)

After the injection of an echo contrast agent, contrast-enhanced transesophageal echocardiography (c-TEE) is performed by placing an endoscopic probe into the oesophagus. This is the gold standard because the close location from the heart provides an excellent view of the heart. (sensitivity = 100%, specificity = 100%)

After the injection of an echo contrast agent, contrast-enhanced transcranial Doppler ultrasonography (c-TCD) is performed by placing a probe on the temporal bone of the skull and detecting bubbles directly in the cerebral arteries. Standardized procedures allow a good sensitivity. (sensitivity > 90%, specificity ≈ 100%)

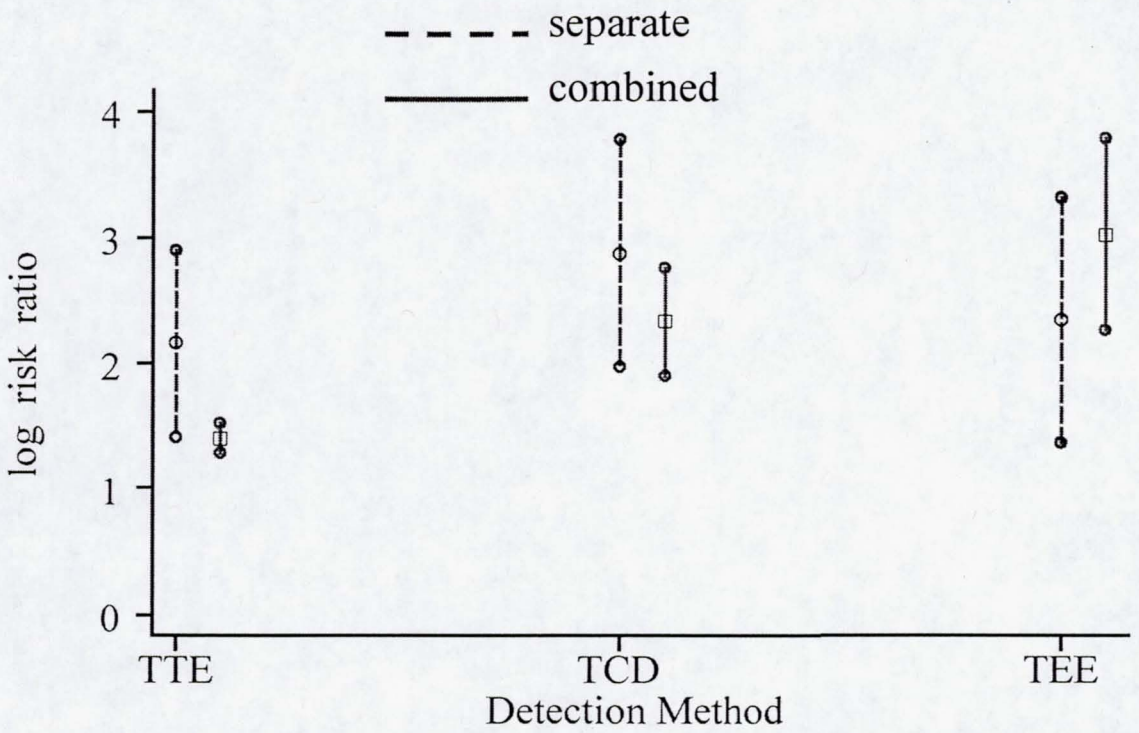


Figure 2. Point estimates and 95% confidence Limits for log risk ratios. Results calculated separately are shown as circles (point estimates) and dashed lines (confidence limits). Results calculated from combined data are shown as squares (point estimates) and solid lines (confidence limits).

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