The final version of this paper was published in the *Journal of Clinical Epidemiology*, *2015; 68:525-533.*

Instrumental variable meta-analysis of randomised trials of epidural analgesia in labour to adjust for non-compliance

Melanie Bannister-Tyrrell [a] *, Branko Miladinovic [b], Christine Roberts [a], Jane Ford [a]

a. Clinical and Population Perinatal Health Research, Kolling Institute of Medical Research, Building 52, University of Sydney at Royal North Shore Hospital, St Leonards 2065, New South Wales, Australia

b. Centre for Evidence Based Medicine, Morsani College of Medicine, University of South Florida, 3515 East Fletcher Avenue, MDT 1201 Tampa, Florida 33612

* Corresponding author: Address all correspondence to Melanie Bannister-Tyrrell, Clinical and Population Perinatal Health Research, University Department of Obstetrics and Gynaecology (Building 52), Royal North Shore Hospital, St Leonards, NSW 2065 Australia. melanie.bannister-tyrrell@sydney.edu.au

Abstract

Objective: Intention-to-treat analysis of randomised controlled trials may cause bias towards the null where non-compliance with the allocated intervention occurs. Instrumental variable analysis allows estimation of the causal effect adjusted for non-compliance. The aim of this study is to compare intention-to-treat and instrumental variable meta-analysis of the association between epidural analgesia in labour and caesarean section.

Study design and Setting: The study was restricted to 27 trials in a recent Cochrane Systematic Review. For trials with data on compliance, the association between epidural analgesia in labour and caesarean section was calculated using intention-to-treat analysis and instrumental variable analysis. Fixed-effects meta-analysis was used to calculate pooled risk ratios.

Results: In 18 trials with data on compliance, 23% of women allocated to epidural analgesia did not comply and 27% of women allocated to the control received epidural analgesia. Data on outcomes in non-compliant groups were available for 10 trials. The pooled risk ratio for caesarean section following epidural analgesia in labour was 1.37 (95% CI 1.00-1.89, p=0.049) using instrumental variable analysis compared to 1.19 (95% CI 0.93-1.51, p=0.16) using intention-to-treat analysis.

Conclusion: Intention-to-treat meta-analysis underestimates the effect of receiving epidural analgesia in labour on caesarean section compared to instrumental variable meta-analysis.

Running title: Instrumental variable meta-analysis of randomised controlled trials of epidural analgesia in labour

Manuscript word count: 2802

Key words: Instrumental variables, non-compliance, randomised controlled trials, intention-to-treat, epidural analgesia, caesarean section

What's new?

Key findings

- Randomised controlled trials of epidural analgesia in labour often have high rates of non-compliance. When analysed by intention-to-treat, non-compliance may bias the estimate of towards the null when analysing individual trials and in meta-analysis.
- Instrumental variable analysis estimates the causal effect of treatment assignment adjusted for non-compliance. Using instrumental variables to conduct meta-analysis produced an estimate of the risk ratio for the association between epidural analgesia in labour and caesarean section that was 15% higher than the corresponding intention-to-treat meta-analysis estimate.

What this adds to what is known

- This is the first study to present instrumental variable meta-analysis of randomised controlled trials using aggregate data from published studies and by applying a method that is not sensitive to differences in baseline risk between compliers and non-compliers.

What is the implication, what should change now?

- Investigators conducting randomised controlled trials and meta-analyses should collect and report data on outcomes in compliant and non-compliant groups where non-compliance is substantial.
- Instrumental variable analysis should be conducted in addition to intention-to-treat analysis to reduce bias caused by non-compliance, particularly when the outcome of interest is an adverse event rather than a treatment benefit.

Introduction

Randomised controlled trials (RCTs) analysed by intention-to-treat (ITT) test the effect of assigning an intervention [1]. ITT analysis is considered the primary and least biased analysis of RCTs as it preserves the balance of confounding variables achieved by randomization. However in many RCTs, participants do not receive the intervention that was allocated to them. Non-compliance describes failure to comply with allocated treatment in the intervention arm, and contamination describes uptake of the treatment in the control arm [2, 3]. As non-compliance and contamination increase, any true treatment effect may be biased by attenuation towards no difference in outcomes between treatment and control groups when analysed by ITT [4].

When RCTs have been affected by high rates of noncompliance and contamination, investigators have often presented per-protocol and/or as-treated analyses to supplement the primary ITT analysis [1]. Per-protocol analysis explores outcomes in allocation-compliant participants only and an as-treated analysis investigates outcomes according to treatment actually received, regardless of allocation. Per-protocol and as-treated analyses aim to provide an estimate of treatment efficacy if one actually receives a treatment, rather than the effect of being assigned to a treatment. This information may be of more interest to individuals and health practitioners interested in the effect of actually taking a treatment rather than the effect of offering treatment. However, per-protocol and as-treated analyses are biased because noncompliance and contamination cannot be assumed to be random with respect to the outcome and therefore confounding by compliance behaviour is introduced.

A Cochrane Systematic Review of RCTs of epidural versus non-epidural or no analgesia in labour [5] found that epidural analgesia in labour was not associated with risk of caesarean section (RR 1.10, 95% CI 0.97-1.25, 27 RCTs, 8417 women). However, many of the RCTs of epidural analgesia in labour are affected by high rates of non-compliance and contamination [6]. Challenges in interpreting the ITT results of individual RCTs extend to difficulties interpreting the results of meta-analyses. When several RCTs in a meta-analysis are

affected by non-compliance and contamination, the ITT pooled effect may be biased towards no treatment difference. It is particularly important to address the risk of noncompliance and contamination causing bias towards the null when the primary outcome (caesarean section) is an adverse event rather than a treatment benefit [7]. Therefore, a true increased risk of caesarean section associated with use of epidural analgesia in labour may not be detected using meta-analysis of ITT results of RCTs affected by noncompliance and contamination.

An alternative analytical approach is to use instrumental variables (IV) to effectively adjust for noncompliance and contamination in RCTs [8]. As depicted in Figure 1, an IV is a variable Z that is strongly correlated with the exposure X but independent of the outcome Y, other than through its association with the exposure. An IV must also be independent of measured (C) and unmeasured (U) confounders. In a RCT, treatment allocation can be considered as an IV [2, 8]. IV analysis estimates the causal effect of treatment allocation adjusted for noncompliance and contamination [9], thus preserving the advantages of the original randomization while providing a more realistic estimate of the true treatment effect [2].

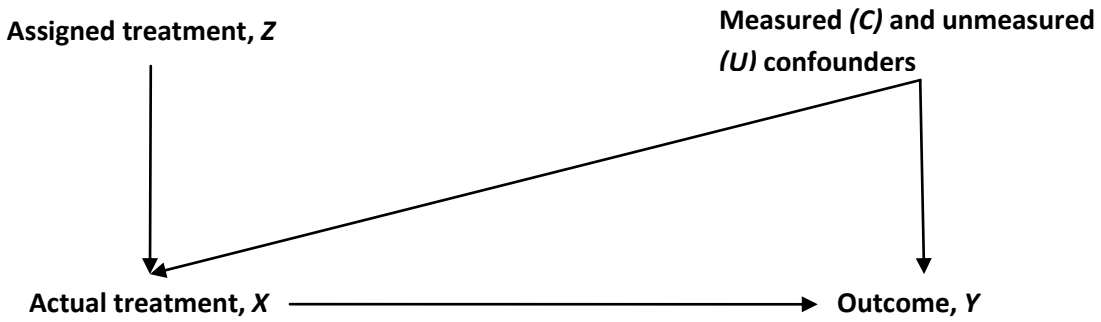

Figure 1: Causal diagram for effect of treatment allocation as an instrumental variable on outcome of a RCT.

The aim of this study is to conduct an exploratory meta-analysis of the association between epidural analgesia in labour and caesarean section using IV analysis and compare to ITT estimates.

Methods

Data sources

The study was restricted to 27 RCTs included in the Cochrane Systematic Review [5] of epidural analgesia compared to no/other analgesia in labour that reported on the outcome of caesarean section (analysis 1.3) [10-36]. The majority of the included RCTs were conducted in the 1990s and 13 were conducted in the USA and Canada, compared to seven in the UK/Europe and seven elsewhere. The RCTs varied in their inclusion criteria, with 16 studies restricted to nulliparous women and four studies that were conducted in women with pregnancy hypertension and/or pre-eclampsia. Studies varied in their labour management strategies, with some institutions adopting aggressive management of labour protocols including liberal use of oxytocin augmentation whereas other institutions followed more conservative approaches. Crossover to alternate analgesia was usually permitted but varied from prohibition [20] or discouragement of crossover [31] to more permissive approaches [22, 29].

Data extraction

References for all studies included in the Cochrane meta-analysis were retrieved and data on allocation, compliance and frequency of caesarean section in compliant and non-compliant groups were recorded. In RCTs with an active control treatment such as narcotic analgesia, women allocated to the control group but who refused any analgesia were classified as 'compliant' in this meta-analysis because they did not receive epidural analgesia. Where complete data on non-compliance and contamination was not available in the published study, authors were contacted to request additional information. Current contact details could not be retrieved for the three oldest studies, which were therefore not included [28, 33, 34].

Analysis

For each trial with complete information on compliance, the association between epidural analgesia in labour and caesarean section was calculated using an ITT analysis and an IV analysis. We use the notation

introduced by Cuzick *et al.* [3] to define the IV estimator where non-compliance in the epidural group and contamination in the control group occur:

P_{11}=P(caesarean|randomised to epidural, received epidural) (allocation-compliant treatment group)

P_{10}=P(caesarean|randomised to epidural, did not receive epidural) (non-compliant group)

P_{00}=P(caesarean|randomised to control, did not receive epidural) (allocation-compliant control group)

P_{01}=P(caesarean|randomised to control, received epidural) (contamination group)

α=proportion randomised to epidural who comply

γ=proportion randomised to control who receive epidural

θ=proportion randomised to epidural group

N=total sample size

The unbiased IV estimator of the risk ratio for the effect of epidural analgesia on caesarean section in those who would comply with receiving epidural analgesia if it had been offered to them, $\hat{\beta}$, is estimated as follows:

$$\hat{\beta} = \frac{\alpha\hat{p}_{11} - \gamma\hat{p}_{01}}{(1-\gamma)\hat{p}_{00} - (1-\alpha)\hat{p}_{10}}$$

The asymptotic variance for $\log(\hat{\beta})$ is derived using a Taylor series expansion of $\hat{\beta}$:

$$\alpha Var(log\hat{\beta}) = \frac{1}{N(\alpha p_{11} - \gamma p_{01})^2}(\alpha\theta^{-1}p_{11}(1-p_{11}) + \gamma(1-\theta)^{-1}p_{01}(1-p_{01}) + \hat{\beta}^{\,2}((1-\alpha)\theta^{-1}p_{10}(1-p_{10}) + (1-\gamma)(1-\theta)^{-1}p_{00}(1-p_{00})))$$

Fixed-effects meta-analysis was used to obtain a pooled risk ratio and 95% confidence interval for the association between epidural analgesia in labour and caesarean section, first using the ITT estimate for each RCT, and then using the IV estimate for each RCT. The risk ratio, variance and heterogeneity in the ITT meta-

analysis was compared to the IV meta-analysis. The primary analysis was restricted to RCTs with complete compliance data available and a sensitivity analysis was conducted including additional RCTs for which outcomes in one group were estimated based on the per-protocol analysis presented in the published study. Simple linear regression was used to determine whether non-compliance and contamination were linearly associated with the difference between the IV and ITT estimates. Per-protocol and as-treated meta-analyses were also conducted for comparison to ITT and IV results.

IV analysis of each RCT was conducted in Microsoft Excel, using a spreadsheet designed by one of the authors (BM). Meta-analysis was conducted using the *metan* command in StataIC 13.

Results

Data extraction

In the 27 RCTs included in the Cochrane review, 4459 women were allocated to receive epidural analgesia and 4426 were allocated to receive non-epidural or no analgesia. There were 470 caesarean deliveries in women allocated to epidural analgesia compared to 419 caesarean deliveries in women allocated to non-epidural or no analgesia. The pooled estimate of the risk ratio for association between epidural analgesia in labour and caesarean section in these 27 RCTs is 1.10 (95% CI 0.97-1.25, p=0.12) (Figure 2). Note that for two RCTs, [14, 20] the number of caesarean sections reported in the Cochrane review differed to the number of caesareans reported in the cited reference for these RCTs. For one RCT [29], the Cochrane review presented the per-protocol analysis, which was the main analysis presented in the published study. In the current meta-analysis, outcomes according to randomisation group were derived from additional data in the publication. Inclusion of the corrected results for these three RCTs did not change the pooled risk ratio reported in the Cochrane Systematic Review but decreased heterogeneity from I^2=7% to 0%.

Data on compliance with allocated mode of labour analgesia were available from published articles for 18 of the 27 studies (Table 1). There were 888 (23%) women who were allocated to the epidural group who did

not receive epidural analgesia (non-compliance) and 999 (27%) women allocated to the control group who ultimately received epidural analgesia in labour (contamination).

Complete data on the number of caesarean sections in compliant and non-compliant groups were available in the published literature for eight studies [10, 11, 20, 26, 27, 29, 30, 36] and were provided by the authors for two studies [17, 35]. Thus there were 10 RCTs with complete data available on the number of caesarean sections in compliant and non-compliant participants to conduct an IV analysis. In these 10 RCTs, 1684 women were allocated to epidural analgesia and 1732 were allocated to non-epidural or other analgesia. There were 130 caesarean deliveries in women allocated to epidural analgesia and 116 caesarean deliveries in women allocated to the control group. Data on the number of caesarean sections in compliant and non-compliant participants for the epidural group only were available for two studies [15, 31]. For these two studies the number of caesarean sections in the compliant-control and contamination groups were estimated (Supplementary Information) and included in sensitivity analysis.

ITT and IV meta-analysis

The ITT meta-analysis of the 10 RCTs with complete compliance data gives a risk ratio of 1.19 (95% CI 0.93-1.51, p=0.16) for caesarean section following epidural analgesia in labour (Figure 3). The IV meta-analysis of these 10 RCTs gives a risk ratio of 1.37 (95% CI 1.00-1.89, p=0.049) for caesarean section following epidural analgesia in labour (Figure 4). There is no heterogeneity detected in either the ITT or IV result (I^2=0.0). By comparison, meta-analysis when RCTs are analysed per-protocol gives a risk ratio of 1.56 (95% CI 1.19 – 2.05, p=0.001) and when RCTs are analysed as-treated, the risk ratio is 1.72 (95% CI 1.32 – 2.22). There is increased heterogeneity in as-treated (I^2=32%) meta-analysis compared to the IV and ITT estimates.

There was no difference between the ITT and IV estimates for four RCTs with close to full compliance with allocated mode of analgesia [17, 26, 30, 35]. For two RCTs that reported non-significant protective associations between epidural analgesia in labour and caesarean section using ITT analysis [11, 36], the IV point estimate of the risk ratio decreased by 0.07 to a slightly more protective association. For the remaining

three RCTs that reported risk ratios associated with epidural analgesia in labour exceeding one [10, 20, 29], the IV estimate exceeded the ITT estimate by 0.26 to 0.44. There was some evidence for a correlation between percent non-compliance and a positive difference between IV and ITT risk ratio point estimates (β=0.017, 95% CI 0.001-0.034, p=0.04) but no evidence for an association with contamination (p=0.79).

In a sensitivity analysis, including the additional two RCTs with estimated data for the control group resulted in lower effect estimates compared to the primary analysis (ITT risk ratio 1.13, 95% CI 0.92-1.38, p=0.23; IV risk ratio 1.28, 95% CI 0.95-1.72, p=0.10).

Discussion

This study aimed to compare IV meta-analysis of RCTs of epidural analgesia in labour to ITT meta-analysis to estimate the influence of non-compliance and contamination on estimates of the association between epidural analgesia in labour and caesarean section. In RCTs of epidural for labour analgesia with data on non-compliance and contamination, five of 16 RCTs had non-compliance with allocated epidural analgesia exceeding 25% and seven of 16 RCTs had contamination from the control arm to the epidural arm exceeding 25%, including three studies in which contamination exceeded 50%. The IV estimate of the risk ratio for the association between epidural analgesia in labour and caesarean section was 15% higher than the corresponding ITT estimate, demonstrating that non-compliance and contamination bias the ITT estimate of the effect of epidural analgesia on caesarean section towards the null.

The ITT point estimate of the risk ratio in the 10 RCTs (1.19) is slightly higher than the risk ratio of 1.10 (95% CI 0.97-1.25) obtained by ITT analysis of all 27 RCTs. Therefore, the IV estimate of the risk ratio (1.37) may also be higher than the theoretical IV estimate if data on non-compliance and contamination were available for all RCTs included in the Cochrane Systematic Review. In sensitivity analysis, including estimates from two additional RCTs reduced the estimates but the magnitude of difference between ITT and IV results was similar. As compliance data were unavailable for several large RCTs, the risk ratios and p-values in this study may not accurately estimate the results of a systematic IV meta-analysis, if that were possible to conduct.

Nonetheless, IV meta-analysis suggests that the magnitude of the association between epidural analgesia in labour and caesarean section may be underestimated when analysed by ITT. Our study therefore offers a timely perspective on the controversial issue of whether epidural analgesia in labour increases the risk of caesarean section. In contrast to the Cochrane Systematic Review, several cohort studies report that epidural analgesia in labour is associated with caesarean section [37-40] but it has been argued that these studies may be affected by unmeasured confounding, especially by severity of labour pain [41-43]. Our IV meta-analysis presents an additional explanation, which is that estimates of the risk of caesarean section following epidural analgesia in labour in RCTs may be biased towards the null due to non-compliance and contamination.

To the best of our knowledge, this is the first study to present IV meta-analysis of RCTs using aggregate data from published studies and by applying a method that is not sensitive to differences in baseline risk between compliers and non-compliers [3]. IV analysis using this method has previously been applied to an individual patient data meta-analysis of non-experimental data using centre prescribing preference as an IV [44]. The latter study also demonstrated that IV meta-analysis can be used to correct for bias due to non-compliance and produce effect estimates that lead to different conclusions about the efficacy of an intervention compared to ITT analysis.

The limitations of the IV approach include considerable loss of precision in some IV estimates compared to ITT estimates for individual RCTs. To some extent, the loss of precision reflects the uncertainty about the treatment effect in RCTs with non-compliance and contamination and wider confidence intervals are more appropriate than those produced by ITT analysis. Loss of precision also arises when the IV is not strongly associated with the exposure of interest due to poor compliance, as a trade-off arises between low bias and high variance when the IV is weak [45]. The loss of precision relative to the ITT estimate may be considered undesirable despite the reduced bias because large variance reduces confidence in the effect estimate [45]. However in our study the precision of the pooled IV estimate is adequate and better reflects the uncertainty due to non-compliance and contamination than the ITT estimate. Further limitations include that IV analysis

relies on the monotonicity assumption, that is, there are no participants who are 'defiers' that would use epidural analgesia if allocated to the control, but use the control if allocated to epidural. This assumption is considered reasonable when using treatment allocation in a RCT as an IV [9]. IV analysis also requires the exclusion restriction to hold true, that is, that treatment assignment has no effect on the outcome other than through receipt of treatment. This too is generally reasonable in the context of a RCT, though for 'treatment encouragement' designs, the exclusion restriction may be violated if participants take actions other than receive the experimental treatment in response to encouragement [46].

Future RCTs in obstetrics and other fields that could be affected by poor compliance should report outcomes in compliant and non-compliant groups and consider presenting an IV analysis in addition to the ITT analysis. While investigators may make efforts to reduce the rate of non-compliance and crossover, it is unethical to deny labouring women their preferred mode of labour pain analgesia and similar scenarios frequently arise with other interventions. Investigators conducting meta-analyses should aim to collect data on outcomes in compliant and non-compliant groups where non-compliance is substantial and likely inevitable given the nature of the intervention. Future meta-analyses contrasting ITT and IV approaches should also explore whether IV estimates reduce statistical heterogeneity, as although heterogeneity was not detected in this study, non-compliance and contamination may contribute to heterogeneity and there is increasing recognition of the need to adequately explore heterogeneity in meta-analyses [47].

In conclusion, we have found that ITT meta- analysis underestimates the effect of receiving epidural analgesia in labour on caesarean section compared IV meta-analysis because ITT analyses do not adjust for compliance behaviour. IV analysis suggests that it is plausible that epidural analgesia in labour increases the risk of caesarean section. Given ongoing concerns about rising caesarean rates worldwide, the outcomes associated with epidural analgesia in labour should continue to be explored.

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Figure legends

Figure 1: Causal diagram for treatment allocation as an instrumental variable for association between treatment and outcome in a randomised controlled trial

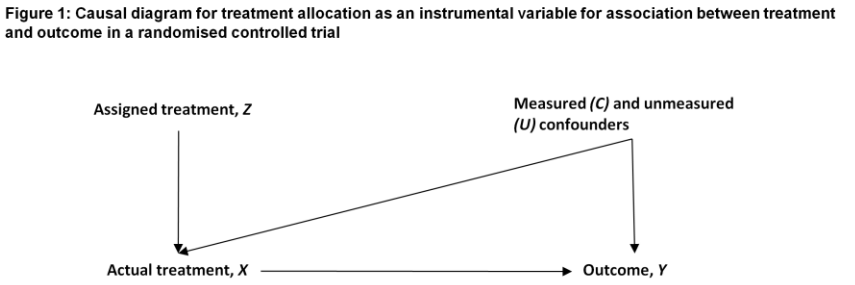

Figure 1 legend: An instrumental variable is a variable (Z) that is strongly correlated with the exposure (X) but independent of the outcome (Y), other than through its association with the exposure. An instrumental variable must also be independent of measured (C) and unmeasured (U) confounders.

Figure 2: Intention to treat meta-analysis of the 27 trials included in Cochrane Systematic Review investigating the association between epidural analgesia in labour compared to other or no analgesia in labour and caesarean section

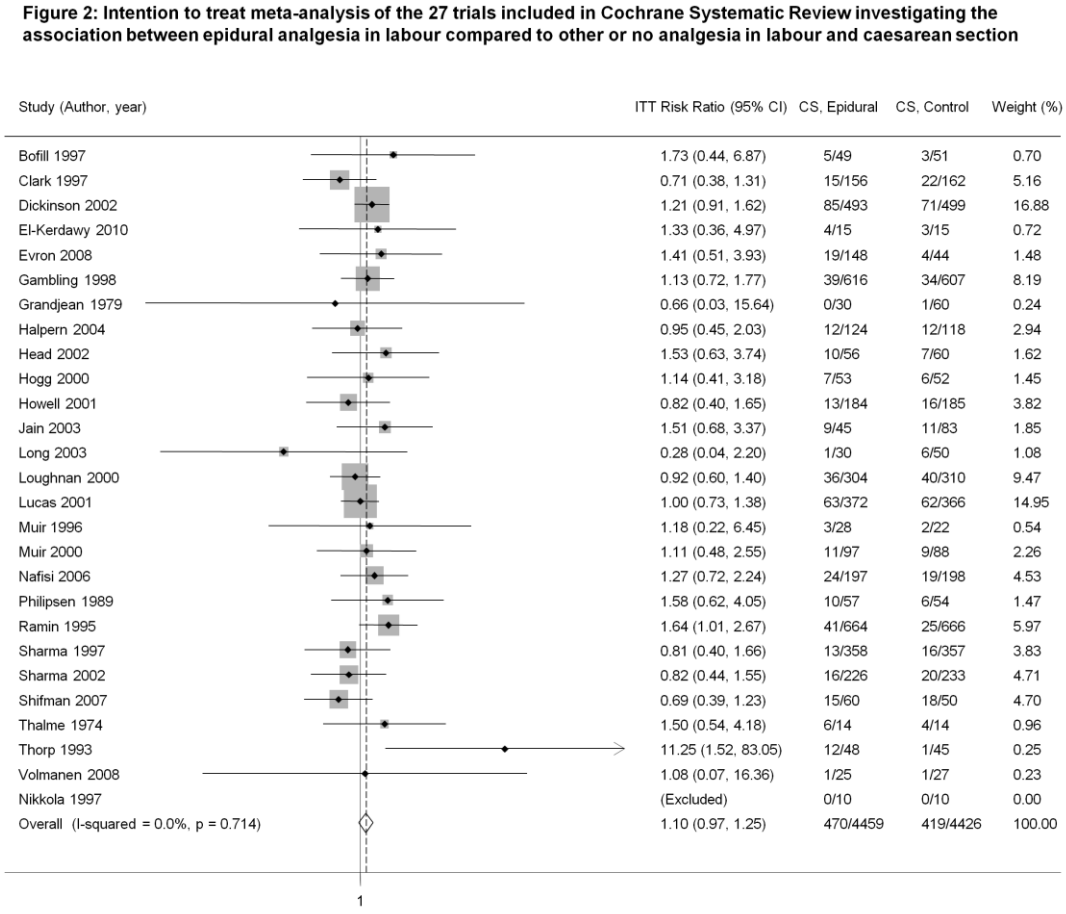

Figure 2 legend: Data for Nikkola 1997 is excluded because there were no caesarean sections and therefore data from this RCT does not contribute to the estimate of the risk ratio. Black markers indicate point estimate of risk ratio for each RCT calculated using intention-to-treat, width of black line indicates 95% confidence interval. Grey squares are proportional to weight of RCT in meta-analysis. Dotted line indicates summary estimate of risk ratio, width of diamond indicates 95% confidence interval for summary estimate.

Figure 3: Studies with complete data on non-compliance: Fixed effects intention to treat meta-analysis of randomised controlled trials of epidural versus non-epidural or no analgesia in labour and caesarean section

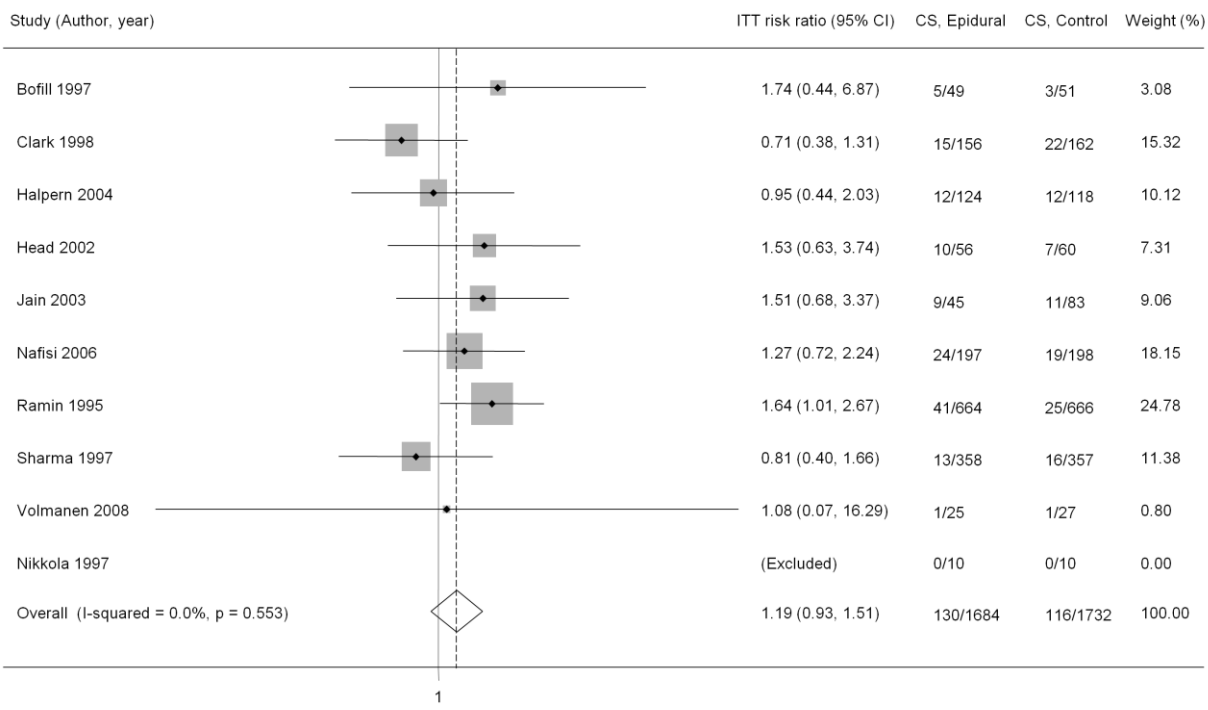

Figure 3 legend: Data for Nikkola 1997 is excluded because there were no caesarean sections and therefore data from this RCT does not contribute to the estimate of the risk ratio. Black markers indicate point estimate of risk ratio for each RCT calculated using intention-to-treat, width of black line indicates 95% confidence interval. Grey squares are proportional to weight of RCT in meta-analysis. Dotted line indicates summary estimate of risk ratio, width of diamond indicates 95% confidence interval for summary estimate.

Figure 4: Studies with complete data on non-compliance: Fixed effects instrumental variable meta-analysis of randomised controlled trials of epidural versus non-epidural or no analgesia in labour and caesarean section.

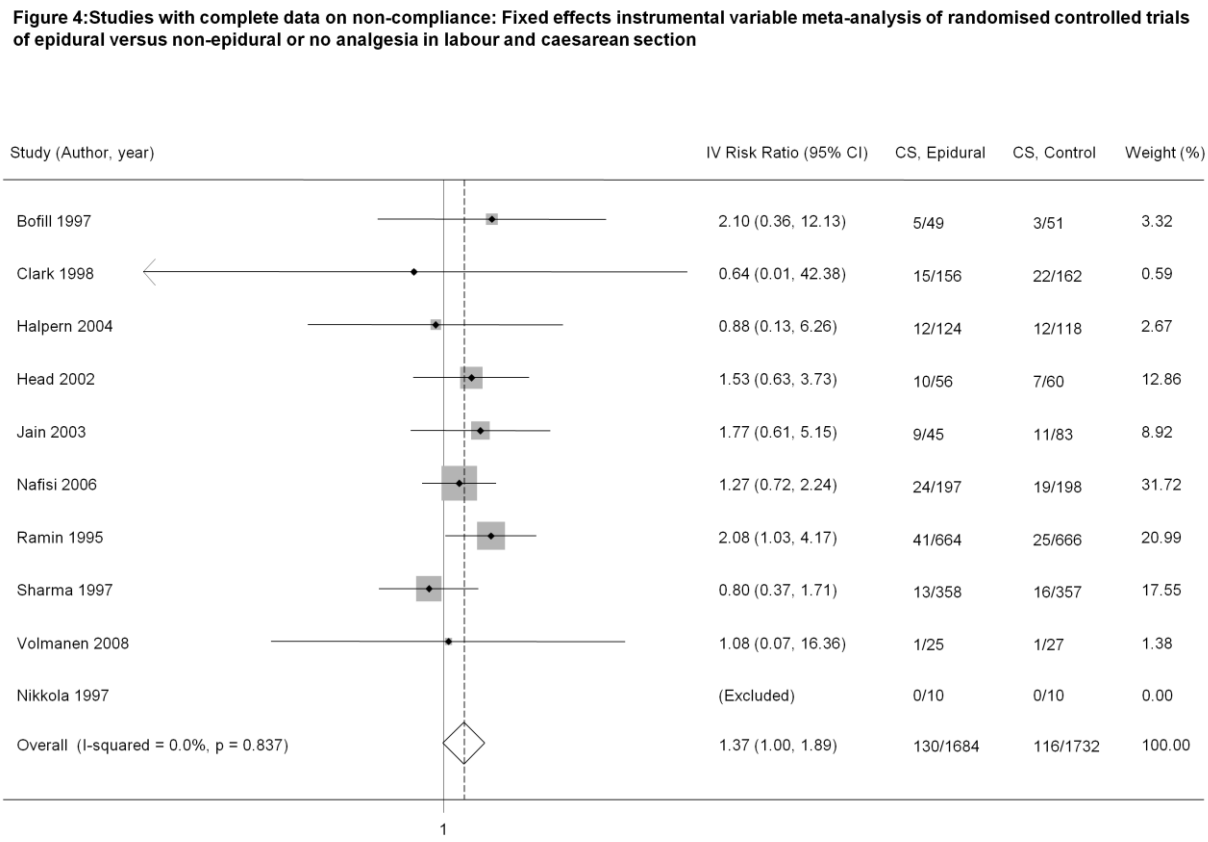

Figure 4 legend: Data for Nikkola 1997 is not shown because there were no caesarean sections and therefore data from this RCT does not contribute to the estimate of the risk ratio. Black markers indicate point estimate of risk ratio for each RCT calculated using instrumental variables estimator, width of black line indicates 95% confidence interval. Grey squares are proportional to weight of RCT in meta-analysis. Dotted line indicates summary estimate of risk ratio, width of diamond indicates 95% confidence interval for summary estimate.