

ENDGAMES

STATISTICAL QUESTION

What is number needed to treat (NNT)?

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Researchers tested the effectiveness of supplements during pregnancy on pre-eclampsia in a high risk population. A three arm, randomised, blinded, placebo controlled trial design was used. Intervention was two medical food bars a day containing the supplements L-arginine and antioxidant vitamins, antioxidant vitamins alone, or placebo.¹

Participants were pregnant women with a previous pregnancy complicated by pre-eclampsia, or pre-eclampsia in a first degree relative, and deemed to be at increased risk of recurrence of the disease. Women were studied from week 14-32 of gestation and followed until delivery. In total, 228 women were allocated to L-arginine and antioxidant vitamins, 222 to antioxidant vitamins alone, and 222 to placebo.

The primary outcome was development of pre-eclampsia or eclampsia. Antioxidant vitamins alone showed an observed benefit, but this effect was not significant compared with placebo. The proportion of women with pre-eclampsia or eclampsia was reduced significantly in the L-arginine plus antioxidant vitamins treatment group compared with placebo (absolute risk reduction 0.17 (95% confidence interval 0.12 to 0.21)). The number needed to treat (NNT) was 5.73 (4.0 to 10.0). The researchers concluded that supplementation during pregnancy with a medical food containing L-arginine and antioxidant vitamins reduced the incidence of pre-eclampsia and eclampsia in a population at high risk of the condition.

Which of the following statements, if any, are true?

- The number needed to treat is a measure of benefit of the supplements compared with placebo in preventing pre-eclampsia or eclampsia.
- It is estimated that on average, for every 5.73 women given supplements one would not develop pre-eclampsia or eclampsia
- Number needed to treat depends only on the absolute difference in risks of pre-eclampsia or eclampsia between treatment groups
- The larger the value of number needed to treat, the greater the benefit of supplements compared with placebo

Answers

Statements *a* and *c* are true, whereas *b* and *d* are false.

The aim of the trial was to test the effectiveness of supplements during pregnancy in reducing the incidence of pre-eclampsia and eclampsia in a high risk population. Interventions included two medical food bars a day during pregnancy, containing the supplements L-arginine and antioxidant vitamins, antioxidant vitamins alone, or placebo. Antioxidant vitamins alone did not show a significant benefit when compared with placebo. Medical bars supplemented with L-arginine and antioxidant vitamins, when compared with placebo, reduced significantly the proportion of women with pre-eclampsia or eclampsia (absolute risk reduction 0.17 (95% confidence interval 0.12 to 0.21)). The number needed to treat (NNT) was 5.73 and represents a measure of the benefit of intervention with supplements when compared with placebo (*a* is true). Number needed to treat is sometimes referred to as number needed to treat to benefit (NNTB).

Of the 222 women allocated to placebo, 67 (30.18%) experienced pre-eclampsia or eclampsia, compared with 29 (12.72%) of 228 women allocated to the supplement group (L-arginine and antioxidant vitamins). This represented a reduction in risk for supplements compared with placebo of 0.1746 (that is, 0.3018–0.1272). The number needed to treat was calculated as the reciprocal of the risk reduction between treatments; $1 \div 0.1746$ (that is, 5.73). The number needed to treat is the number of participants who needed to be treated with supplements for one less women to experience pre-eclampsia than if those same women had been treated with placebo. On average, if 5.73 women were treated with supplements (L-arginine and antioxidant vitamins) then 0.73 (12.72%) of them would be expected to develop pre-eclampsia or eclampsia, whereas if those same women were treated with placebo then 1.73 (30.18%) of them would develop the outcome. To have direct clinical relevance, the derived number needed to treat would be rounded to six women.

Statement *b* is a common misinterpretation of number needed to treat—that, on average, for every 5.73 women given supplements (L-arginine and antioxidant vitamins), one would

not develop pre-eclampsia or eclampsia (b is false). The statement is indicative that, on average, for every 5.73 women treated with supplements, one would not develop pre-eclampsia or eclampsia whereas the remaining 4.73 would. As a measure of the therapeutic benefit of treatment, number needed to treat compares the effectiveness of treatment with supplements to placebo.

As described, the value of the number needed to treat depended on the difference in risk of pre-eclampsia or eclampsia between treatment groups. The number needed to treat of 5.73 would have been obtained regardless of the absolute risk in each group experiencing pre-eclampsia and eclampsia, but so long as the risk difference was 0.1746 (c is true). However, a number needed to treat of 5.73 may have different clinical implications if the absolute risks were different to those observed.

The importance of the magnitude of the number needed to treat is one that must be made on clinical grounds. None the less, the larger the treatment effect of supplements (L-arginine and antioxidant vitamins) compared with placebo in reducing the incidence of pre-eclampsia and eclampsia, the smaller the number needed to treat (d is false). The ideal value for number needed to treat is one, in which case every woman would not experience pre-eclampsia or eclampsia if treated with supplements and all would experience the outcome with placebo. If there was no treatment effect (that is, no difference between supplements and placebo) the absolute risk difference would be zero and the number needed to treat would therefore approach infinity.

As with other estimates, it is important the uncertainty in the number needed to treat is assessed by a confidence interval. In the example above, the 95% confidence interval is from 4.0 to 10.0. The 95% confidence limits for number needed to treat are

derived in a similar way to the statistic itself. The limits for the 95% confidence interval of the absolute risk difference are obtained; the reciprocal of these are obtained and then reversed, giving the limits of the 95% confidence interval for number needed to treat. The interpretation of the 95% confidence interval is that, with probability of 0.95, the true population parameter of number needed to treat will be contained within the interval—that is, the number of women who need to be treated may be as few as four or as many as 10 in order for one additional woman to benefit compared with if they had been treated with placebo. The challenge is how this degree of uncertainty can be incorporated into clinical decision making. Presumably the intervention is easy enough to implement, and any benefit whatever the uncertainty is acceptable given that it may prevent pre-eclampsia and eclampsia.

Number needed to treat has become popular in therapeutic decision making. This is no doubt because it is easier to interpret information regarding the benefits of treatment when given as a number, instead of probabilities or ratios such as odds ratios and relative risks. However, in addition to number needed to treat, it is important that absolute risks, relative risks, odds ratios, and hazard ratios (where appropriate) are also provided so as to enable the effects of treatment to be fully assessed.

Competing interests: None declared.

- 1 Vellido-Ortega F, Perichart-Perera O, Espino S, Avila-Vergara MA, Ibarra I, Ahued R, et al. Effect of supplementation during pregnancy with L-arginine and antioxidant vitamins in medical food on pre-eclampsia in high risk population: randomised controlled trial. *BMJ* 2011;342:d2901.

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