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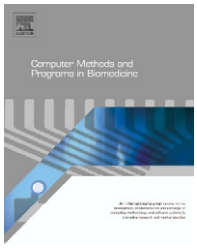

Second-order interactions with the treatment groups in controlled clinical trials

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ABSTRACT

The occurrence of significant second-order interactions for group characteristics was examined using real data in a randomized controlled trial (RCT). The interactions exist in all RCTs; they could be easily overlooked when using the simple randomization or stratification methods, but could become more obvious when minimization methods are used. Using real data from an RCT, the minimization method enabled balancing the distributions of the four selected stratified factors. Analyses for three-way second-order interactions including six additional potential confounding variables (for a total of 10 variables) presented 8 significant second-order interactions with the treatment groups. Interaction effects need to be evaluated when treatment effects are examined to maximize the power of the treatment effects in any RCTs. A stepwise regression method with piecewise linear functions would be useful to select the significant variables with interaction effects affecting the treatment outcomes in RCTs. Additional ways to handle interaction effects in RCTs are presented in this paper.

1. Introduction

The benefits and significance of evidence-based practice (EBP) have been widely acknowledged in the health care professions [1–3]. As research findings are used to advance the standards of care through EBP, reliable evidence from well-designed randomized clinical trials (RCTs) aimed at improved health outcomes is pivotal [2,3]. With the greater emphasis on the quality of RCTs, random allocation methods need to be examined more closely. In addition, as the scientific fields move forward, newly documented confounding variables identified for the population of interests on selected outcomes for the treatment effects need to be controlled by using more efficient random allocation methods. Thus, to advance the quality of RCT designs, the purpose of this paper is to present the real case examples with the confounding variables and their interactions with the treatment effects, using the computerized minimization method.

The random allocation of the research participants using the minimization method, and the occurrence of significant second-order interactions for group characteristics, were examined using real data in an RCT of high-risk mother-baby dyads. One hundred and eighty-eight dyads were randomly allocated into two groups using the minimization method, including four stratified variables selected based on prior studies in the population. Six additional variables (less significant, however, could be additional confounders in the field) were used to examine the frequency of imbalance and magni-

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tude of interactions in combinations. Three-way interactions (2^3 blocks) were computed by using multi-way contingency table analysis. The interactions exist in all RCTs; they could be easily overlooked when using the simple randomization or stratification methods, but could become more obvious when minimization methods are used. Interaction effects need to be evaluated when treatment effects are examined to maximize the power of the treatment effects in any RCTs.

2. Random allocation

Random assignment of research participants into treatment conditions with blinding to the treatment is a significant quality indicator for the objectivity of the treatment effects in RCTs [4–7]. Random allocation is performed with the aim of balancing the distribution of confounding factors (variables) between two or more treatment groups. However, simple randomization cannot assure the balance of heterogeneous characteristics between and among groups, particularly when the sample size is fewer than 1000 [8,9]. With the aid of computer programs, the minimization method not only enhances the objectivity of the random assignment; but also the feasibility of stratifying more than three binary confounding variables. This is the feasibility limit when using the stratified block randomization method [10]. The unbalanced covariates in an RCT would decrease the statistical power when comparing treatment effects. And, without balancing group confounders, erroneous conclusions could be derived [11,12]. Therefore, when additional confounding variables are identified for the outcomes, it is critical to balance and to control the newly documented confounding variables by using a more efficient random allocation method such as the minimization method.

2.1. *Minimization program*

To enhance the quality and objectivity of the randomization, the computer-aided minimization method has been widely used to balance the confounding variables including subject characteristics between treatment groups in RCTs. Pocock and Simon's minimization method and Zelen's balancing method enable the balancing of each confounding factor (variable) between and among treatment sub-groups over the entire duration of the trial [13–17]. The method was used increasingly in the 1990s due to the availability of computer programs [9]. The minimization method is more efficient than the simple random method and the stratified block randomization when measuring treatment effects, needing fewer subjects, by balancing confounding factors between and among treatment groups. Thus, a computer-aided minimization program can be used to not only balance the confounding variables, but to also enhance the objectivity, the efficiency, and the quality of randomization method for RCTs.

2.2. *Three-way or second-order interactions in RCTs*

The minimization method does not guarantee the balanced distribution of interactions of factors between the treatment groups, especially when additional significant confounding factors interacts with the treatment effects for the population of interests. However, the interaction effects can be more clearly presented when using the minimization method, to suggest the needed controls in the analyses and the stratifications for future RCTs. A binary variable such as "race status" includes two marginal cells of "White" and "Non-white", or "multiple birth status" includes two marginal cells of "singleton" and "twins". When these two binary variables are associated, there are 2^2 or 4 cells (blocks). In binary 3-factor interactions, a third binary variable "sex of newborns", with two marginal cells of "boys" and "girls", would yield 2^3 or 8 cells, including interactions between all 3 pairs of variables.

In RCTs, if the interaction of factors is overlooked, it could yield a serious bias in estimating the treatment effects. For example, two medications are examined in an RCT, the new drug (D1) and the standard drug (D2). D1 has a much greater effect on male gender with positive complications than the D2. As the simple random assignment could not achieve balanced groups in the RCT, if the male patients in the D1 group accidentally have more complications at considerable greater effects, the treatment effect of the D1 group would be overestimated with complications. In this case, the distributions of "gender" and "the status of complications" might be completely balanced between D1 and D2 using the minimization method, considering the significant interaction effects for the treatments within the RCTs. In addition, the interactions of treatment effects could be compared using multiple regression models such as a logistic regression model and Cox's proportional hazards model [18]. Although the need to address these interaction effects has been mentioned, and it would become more obvious when using the minimization method [10,18]; to-date, however, limited reports have presented the interaction effects using the minimization method.

3. Methods

Random allocation was performed using a web-based minimization program [19] (Fig. 1) in a study involving high-risk mother-baby dyads. The RCT lasted 5 years at three tertiary care centers located in two metropolitan areas where both high-risk pregnant mothers and newborns could be cared for [20]. A total of 353 mothers agreed and gave their consent to participate in the study, with 388 newborns that included 33 pairs of twins and 1 set of triplets. There were 239 premature births. Mean gestational age at birth was 31 weeks, and birth weight was 1672 g. Mother's mean ages were 25 years. To qualify for the study, high-risk infants without severe congenital defects had to be intubated with an endotracheal tube; needed ventilatory support with respiratory failures, and also umbilical central line catheters to assess oxygenation and supply nutrients. The treatment group had advanced central-line monitoring of body's oxygenation status, and the control group had the routine peripheral only monitoring. The courses of oxygen support and oxygenation complications for the hospital stay were the outcome variables of the study. Some cases that were not included in the trial because of emergency admissions with uncertain prognosis for high-risk of death, or being cared for by the clinicians who were unable to coor-