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A rapid review indicated higher recruitment rates in treatment trials than in prevention trials

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Abstract

Objectives: To test the hypothesis that the percentage of patients screened that randomize differs between prevention and therapy trials.

Study Design and Setting: Rapid review of randomized controlled trials (RCTs) identified through published systematic reviews in August 2013. Individually randomized, parallel group controlled RCTs were eligible if they evaluated metformin monotherapy or exercise for the prevention or treatment of type 2 diabetes. Numbers of patients screened and randomized were extracted by a single reviewer. Percentages were calculated for each study for those randomized: as a function of those approached, screened, and eligible. Percentages (95% confidence intervals) from each individual study were weighted according to the denominator and pooled rates calculated. Statistical heterogeneity was assessed using I^2.

Results: The percentage of those screened who subsequently randomized was 6.2% (6.0%, 6.4%; 3 studies, $I^2 = 100.0\%$) for metformin prevention trials; 50.7% (49.9%, 51.4%; 21 studies, $I^2 = 99.6\%$) for metformin treatment trials; 4.8% (4.7%, 4.8%; 14 studies, $I^2 = 99.9\%$) for exercise prevention trials; and 43.3% (42.6%, 43.9%; 28 studies, $I^2 = 99.8\%$) for exercise treatment trials.

Conclusion: This study provides qualified support for the hypothesis that prevention trials recruit a smaller proportion of those screened than treatment trials. Statistical heterogeneity associated with pooled estimates and other study limitations is discussed.

Keywords: Prevention; Treatment; RCTs; Recruitment rates; Exercise; Screening failures; Consent rates; Eligibility

1. Introduction

It is well documented that inadequate recruitment poses a threat to the successful completion of randomized controlled trials (RCTs) [1]. Excessive optimism about the number of potentially eligible candidates who are available, or will need to be approached for screening, is a key contributory factor; "Lasagna's Law" [2,3] and "Muench's Third Law" [4] state, with tongue partly in cheek, that "in order to be realistic, the number of cases promised in any clinical study must be divided by a factor of at least ten." Some have proposed a corollary to these laws—that the percent yield of those screened or initially contacted is related to the restrictiveness of the research protocol's eligibility criteria and the motivation of patients to enroll [5,6]. It follows that when estimating the availability of participants for a trial, we should apply eligibility criteria carefully to patient records and make cautious estimates for randomization rates, based on previous studies that are analogous in terms of their population, interventions, and research burden [6].

However, the reporting of randomization rates is still variable, meaning data to guide yield estimates are not always readily available [7]. In a widely cited reference text, Spilker and Cramer [5] proposed that we should expect "1 in 5 [20-27%] screened patients to enroll if the trial offers benefit for an active medical problem," and, "1 in 40 [typically 1-6%]… if the trial offers the possibility of disease prevention." Their sample was small and unsystematic, being based on a convenience sample of 10 prevention and 9 treatment trials. A more recent review of 280 highly cited treatment trials published between 2002 and 2010 reported a mean nonenrolment rate of 40.1% (standard deviation:

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What is new?

- The percentage of people randomized from those screened averaged 6% and 5% in prevention studies compared with 51% and 43% in studies evaluating the same interventions for treatment.
- Larger prevention studies are unlikely to achieve randomization rates as high as those that are typical in treatment trials.
- This should be taken into account when planning recruitment rates for future randomized controlled trials.

23.7%) [7]. While encouraging, this proportion may not generalize to other settings, most notably prevention trials, which were not represented in the analysis set. Clearly, there is a need to better establish a realistic recruitment rate for prevention trials because this has profound implications for how we design, cost, and manage such work, given the effort required in screening for eligibility [8,9].

To investigate whether trials investigating disease prevention do indeed recruit smaller percentages of those screened, we undertook a rapid review of published RCTs evaluating metformin monotherapy or exercise (alone or in combination with other lifestyle interventions) for the prevention or treatment of type 2 diabetes (T2D). We chose this sample frame because each intervention can be used for either the prevention or treatment of T2D. We hoped that as a result, any comparison we made would be controlled for the comparative appeal to patients of an intervention and reliably investigate instead the comparative ease of recruitment. As we discuss in the following sections, there are a number of assumptions in this proposition that may be open to question.

2. Methods

2.1. Literature search

Two separate searches were conducted to identify Cochrane and other systematic reviews, which had already selected RCTs evaluating the use of metformin or exercise for the prevention of, or treatment for, T2D. We used ''search all text'' operations in the Cochrane Database of Systematic Reviews with no restrictions on publication date. The first search was conducted on August 16, 2013, and used the terms ''diabetes'' and ''metformin.'' The second was conducted on August 27, 2013, and used the terms ''diabetes'' and ''exercise.'' Titles and abstracts were screened by one researcher. Systematic reviews evaluating the use of either metformin or exercise, for either the prevention of or treatment for T2D, were included. The systematic review articles were obtained, and the trials that they had deemed eligible for inclusion were compiled so as to exclude any duplicates. The original research articles were obtained.

2.2. Study selection

Individually randomized, parallel group controlled trials were eligible for inclusion if they allocated to one arm either metformin monotherapy (insulin and additional dietary advice permitted) or exercise (including physical activity, advice on either exercise or physical activity, behavior change interventions, and supervised exercise). For the analysis of metformin, we excluded studies where metformin was used in combination with other pharmacotherapies. For the analysis of exercise, we excluded any study where the methods described the arms without mention of exercise. The stated reason for the intervention in any eligible trial had to be either prevention of diabetes or the treatment for T2D in adults. Studies that compared metformin monotherapy (as one arm) with exercise (as another arm) were included. We excluded preventive studies in which the intervention focused on the prevention of gestational diabetes and polycystic ovary syndrome (PCOS). We excluded therapeutic studies which recruited the following populations: type 1 diabetes, gestational diabetes, PCOS, or any other population which was not T2D. We excluded pediatric studies. We excluded cluster trials, crossover trials, and nonrandomized controlled studies. We excluded trials that were not published in English.

2.3. Data extraction

Each research article was read by the reviewer, and the data were extracted into a standardized Excel form, including the details about the population and intervention studied, whether a CONSORT diagram was published and the recruitment metrics from the eligibility criteria. The CONSORT statement proposes that researchers report how many people were assessed for eligibility and excluded based on ineligibility or refusal of consent; we recorded whether these variables were reported.

Where a CONSORT diagram was absent, attempts were made to extract data from the text. Where data were absent from the article, but a previous article relating to the study was cited, this article was retrieved and screened for data. Where this was not the case, or failed, authors were contacted to obtain missing data. Where author contact failed, we estimated the absolute numbers from percentages, where provided, rounding up to the nearest whole number.

2.4. Analysis

We defined those ''approached'' as those invited to screen or where screening was undertaken based on records, the number of records to which researchers attempted to