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Twin Research and Human Genetics, 2018; 21(1):51-56

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11 November 2019

http://hdl.handle.net/2440/111648

Twins as participants in randomised controlled trials: a review of published literature

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Keywords: Twin Research, RCT, randomization, sample size,

Abstract

Monozygotic (MZ) and dizygotic (DZ) twins participate in research to partition variance in health, disease and behavior into genetic and environmental components. However, there are other innovative roles for twins in medical research. One such way is involving MZ and/or DZ twins concordant for a specific phenotype, in a co-twin control designed randomised controlled trial (RCT). This provides the most effective way to control for confounding factors, as one twin from each pair receives the intervention and the other twin acts as their control. To our knowledge, no reviews have been conducted that summarize the involvement of twins in RCTs. Therefore, we conducted a systematic literature search using the USA Clinical Trials Database, NHS electronic databases, MEDLINE, EMBASE, and PsychINFO for RCTs that involved MZ and/or DZ twins as clinical trial participants. From 1598 articles, 50 peer-reviewed English language publications met our pre-defined inclusion criteria. Sample sizes for RCTs ranged from a total number of participants 2 to 1162; however, 32 (64 %) studies had a sample size of 100 or less, and of those 12 (24%) had less than ten.

Both MZ and DZ twins have been recruited to the RCTs. In most instances (33/50) each twin from a pair were assigned to different study arms. Most of those studies (24/33) included MZ twins only.

Despite the methodological advantages, the use of MZ and DZ twins as participants in interventional RCTs appeared limited. We discuss the issue of different ways of randomizing twins and the implications for sample size and power. The use of twin registries and international collaborations is discussed as a way to facilitate larger sample size trials and best practice for the design of RCTs involving twins.

Introduction

Twins studies are best known for using the classical twin design, based on comparisons between the similarity of monozygotic (MZ, identical) and dizygotic (DZ, fraternal) twins to partition the variance in health, disease and behaviour into genetic and environmental components, predominantly using observational study designs (Boomsma et al., 2002, van Dongen et al., 2012)

Studies involving twins have become increasingly relevant due to the continuous work of twin registries and studies that have, collectively, amassed data and biological material on hundreds of thousands of twins, and have provided a valuable resource for studying complex genetic phenotypes and their underlying biology (Hur & Craig, 2013). The availability of longitudinal data through the International Society of Twin Studies and International Network of Twin Registries (INTR) is also proving to be a valuable resource, not only for new studies but also for global collaborations (Buchwald et al., 2014). Data derived from a collaboration of 54 international twin cohort databases participating in the CODATwins Project is a prime example (Jelenkovic et al., 2015, 2016; K. Silventoinen et al., 2015; Karri Silventoinen et al., 2016; Yokoyama et al., 2016).

Within-pair comparisons of phenotypically-discordant MZ and DZ twin pairs through an observational co-twin controlled design can illuminate the non-shared environmental differences influencing human traits. However, such comparisons are arguably more efficient in intervention co-twin control studies using phenotypically-concordant pairs, where one twin is randomly assigned to receive the intervention and the other twin acts as their control. A comparison between the co-twin control design in intervention and non-intervention studies, along with other novel utilities of this design have been discussed in detail previously (Plomin & Haworth, 2010).

The term “intervention” refers broadly to any clinical manoeuvre offered to study participants that may have an effect on their health status (Jadad, A.R, 1998). Randomised

controlled trials (RCTs) are considered the gold standard for testing interventions and 'the most rigorous way of determining whether a cause-effect relationship exists between treatment and outcome and for assessing the cost effectiveness of a treatment' (Sibbald & Roland, 1998). Random allocation provides participants the same chance of being assigned to each of the treatment groups (Altman DG, 1991). The purpose of random allocation is to ensure that the characteristics of participants are as similar as possible across treatment groups prior to the initiation of an intervention (baseline). If randomization is done properly, it reduces the risk of a serious imbalance in known and unknown factors that could influence the clinical course of the participants. Therefore, any significant differences between treatment groups in the outcome of interest can be attributed to the intervention and not to any unidentified factor(s).

However, involving MZ twins in a co-twin control designed RCT has advantages over the traditional RCT involving unrelated individuals. The co-twin control design can provide perfect control for many of the potential confounding factors that could be imbalanced between treatment groups by chance, especially genetic makeup due to matching. Confounding poses a considerable threat to the validity of studies aiming to identify causal mechanisms, creating spurious associations. Confounders can be either measured, and thereby statistically controlled, or unmeasured. The latter introduces the greatest problems for causal inference. Genetic confounding of identified associations is often a very real possibility but is frequently overlooked by researchers. There is also the possibility of unmeasured environmental confounding, occurring when there are one or more contextual factors that affect both the exposure and the outcome. Twin samples allow generalizable assessments of associations and the ability to evaluate the extent of both genetic and environmental confounding; one of the reasons for the increased popularity of twin studies over the past decades (Gjerde et al., 2016).

DZ twins may also allow for matching due to shared environment as well as some genetic component and age, which can potentially justify the choice for recruiting DZ twins rather than siblings for a study. However, challenges such as teasing out individual factors in the context of complex interacting contributors may arise when using DZ twins in RCTs. It is also believed that the co-twin control RCT approach will have the additional advantage of requiring a relatively smaller sample size without reducing the statistical power (Plomin & Haworth, 2010). However, if twins from the same pair are randomly assigned to the same treatment group or independently of each other, rather than to different treatment groups as in the co-twin control design, the benefits in sample size for an RCT involving twins may be lost (Yelland et al, 2017). Intervention studies involving twins do exist in the literature. One such trial testing the effect of Vitamin C intake on common cold symptoms found that the relative power of this design compared to an unpaired design could be 2 to 14 times stronger, which means an unpaired study design would require much larger sample sizes to detect the same effect (Carr et al., 1981; Martin et al., 1982).

However, in our opinion the full advantages and the rationale for involving twins in RCTs have not been adequately discussed or explored. Therefore, we carried out this review as the first step to identify studies using twins as participants for RCTs. In-depth analyses of the quality of individual studies and methodological issues of these studies or meta-analysis was not an aim of this review. Instead, we aimed to identify all published material including RCTs involving only twins as participants up until 2015 using the selection criteria described below, and to summarise basic trial characteristics including sample size, inclusion criteria, whether trials include only MZ, DZ or both, and randomisation method (i.e., whether same pair twins were randomly assigned to the same treatment group independent of each other, or to different treatment groups in a co-twin control design).

Materials and Methods

A comprehensive search was carried out using the following databases: USA clinical trial (https://clinicaltrials.gov/), MEDLINE (1946 - 2015), EMBASE (1974 - 2015) and PsychINFO (1806 - 2015). We also performed an extensive search using PubMed (all publications until March 2015). Searches were confined to articles in English.

In the NHS library electronic database searches (MEDLINE, EMBASE and PsychINFO), the search term "twins", "randomi*, "control*" "trial*"with Boolean operator AND was used in "title and abstract". Each database was searched individually using the search terms. This allowed for all alternative spelling (randomised and randomized), variations of control (control, controls and controlled) and singular or pleural trial (trial and trials) to be searched simultaneously. The search terms used for the PubMed search also took all of used these variations into account (as per the NHS library search).

Data extraction

Data was extracted by one reviewer (DG), and then checked independently by a second reviewer (AS). All publications identified in the searches were searched for duplicates. Eligibility for inclusion in the review was decided by DG and AS. Full versions of publications selected were obtained and reviewed independently by three authors (AS, DG, and TS). Any discrepancy in judgements was resolved through consensus. Abstracts eligible for inclusion were confined to those reporting on a RCT that had used only twins as study participants but not mothers pregnant with twins. Information was extracted from each of the studies relating to authors, study location, database, twin registry (if any), condition, primary outcome, sample size, eligible age, eligible sex, zygosity, twin assignment (same treatment groups, different treatment groups or independent allocation), masking and control arm.

Results

USA clinical trial database

The initial search using the USA clinical trial database resulted in a total of 90 clinical trials. Of these, 50 studies were registered with twins as study participants, and 40 studies were registered with mothers who were pregnant with twins as study participants. Of the 90 twin studies, there were 29 RCTs. Of these, 23 had used mothers pregnant with twins as the study participants and only six studies had recruited twins as the study participants (Figure 1).

<INSERT Figure 1 here>

Extended search using other databases

After taking into account all duplicates and discounting papers including mothers pregnant with twins, the NHS library searches gave a total of 51 papers on RCTs using twins as study participants; 47 from MEDLINE, and a further 4 papers not found in MEDLINE were found in EMBASE. No additional papers were found in PsychINFO.

PubMed searches gave additional 8 papers using twins as study participants that were not found in either the MEDLINE or EMBASE search. The search term “Twins and Randomized Control Trial” found two papers, the terms “Twins and Randomised Controlled Trial” found five, the term “Twins and Randomised Control Trials” found one. The search terms “Twins and Randomised Controlled Trial” and “Twins and Randomised controlled trials” gave the exact same result when substituting the ‘s’ for a ‘z’ in the word ‘randomised’. The full text of all 59 potentially relevant papers were examined in more detail, and 50 were consistent with the inclusion criteria for this review (Figure 2).

<INSERT Figure 2 here>

Trial Characteristics

Sample size and allocation of twins

The sample size varied greatly across the RCTs included in the review. Table 1 illustrates that 42% of RCTs had a sample size which fell within 10-100 twin pairs. Twenty four percent of the studies had a sample size smaller than 10 twin pairs as research participants. Therefore, the majority of studies had 100 twin pairs or less as participants.

<INSERT Table 1 here>

Zygosity and twin assignment across the randomised controlled trials

As illustrated in Table 1, 13 RCTs assigned both twin in a pair to the same study arm, 10 of which included both MZ and DZ twins, two included only MZ twins and one included only DZ twins. This is in contrast to 33 RCTs where twin pairs were assigned to different study arms, of which 6 included both MZ and DZ twins, 24 included only MZ twins and 3 included only DZ twins. In most instances (33/50) the pair of twins had been assigned to different study arms, and most of these studies (24/33) had been with MZ twins.

Location of studies

The vast majority of the studies included in this review were conducted in the USA (21). The remaining studies were from Canada (5), Australia (3), UK (3), Finland (2), Germany (2), Greece (2), and one from each of the following countries; Bangladesh, Belgium , Dominican Republic , France , Hawaii , Hong Kong , India , Iran , Norway , Switzerland , Taiwan and Thailand .

A twin registry had been used to support recruitment in 8 of the RCTs. These were the Australian Twin Registry (3), the Twin Research Registry, UK (3), the St Thomas UK Adult Twin Registry (1), and the University of Washington Twin Registry (1). In the remaining 39 studies, there was no evidence of a twin registry being used to support recruitment. RCTs were diverse in nature and areas included preterm birth nutrition, behaviour, dental health, antiviral treatments, and co-bedding of twins (twin infants sleeping together).

Discussion

Randomised controlled trials involving only twins as participants are limited, as shown by this review. Only 50 studies met our inclusion criteria after a comprehensive search in clinical trials and NHS library databases, even across a wide range of disciplines. Out of the 186,027 clinical trials registered in the USA clinical trial register, only 6 RCTs used twins as participants. While it is impossible to determine how many twin RCTs had been reported through PubMed and other data bases, it is clear that it is disproportionate to the number involving singletons. Therefore, it can be concluded that specifically using twins in RCTs is not common compared to using singletons.

Randomisation of twins in a RCT

When twins participate in a clinical trial, they may be randomised to the same treatment group, independent of each other, or to different treatment groups as in the co-twin control design. Our review found that most clinical trials used the co-twin control design with MZ twins. Therefore, it could be concluded that in the majority of studies, MZ twins had been used for perfect control of genetic variation between the treatment groups. Recent work suggests that twins and their parents have a strong preference for assigning both twins to the same treatment group, rather than using the co-twin control design (Bernardo, Nowacki, Martin, Fanaroff, & Hibbs, 2015). This has important implications for future RCTs conducted in twins, since recruitment may be more successful if both twins in a pair will receive the same treatment, although the impact of different methods of randomising twins on the sample size must also be considered.

The impact of twins on sample size and power

The sample size of trials included in our review ranged from 2 to 1162 (table 1) and in the majority of trials (64%), the sample size was 100 or less. Although we did not attempt to assess whether the sample size was adequate for addressing the specific research question of each trial, this does raise the issue of whether small RCTs involving twins are adequately powered to detect meaningful treatment effects. One of the advantages of conducting RCTs in twins is that the sample sizes can be less compared to using non-twin RCTs (Miller et al., 1995; Carr et al., 1981; Martin et al., 1982). However, this will depend on how twins from the same pair are randomised. If the co-twin control design is used, such that one twin from each pair receives the intervention and the other acts as their control, the trial will have more power than a trial in singletons, and hence the sample size can be reduced. In contrast, if both twins are assigned to the same treatment group, the trial will have less power than a trial in singletons, thus requiring a larger sample size. This is due to the fact that comparisons of the intervention and control conditions must be made across twin pairs, rather than within twin pairs as in the co-twin control design. If twins from the same pair are randomised independently (ignoring that they are twins and treating as individuals), the trial will likely have similar power to a trial in singletons. Methods for calculating the sample size for trials involving twins only or a combination of singletons and twins have been discussed elsewhere (Yelland et al, 2017).

International collaborations using twin registries

We found that only 11/50 (22%) of the studies used twin registries for recruitment. One option particularly for multi-centre RCTs with a relatively large sample size is international collaboration, as currently utilised in non RCT twin research (Buchwald et al., 2014). CODA Twins project was a classic example initiated in 2013 by identifying all twin projects in the world. It comprises 67 twin projects having data from both monozygotic (MZ) and dizygotic (DZ) twin pairs. The main sources used to identify the projects were a special issue of Twin

Research and Human Genetics (Hur and Craig 2013), and the participants of the International network of twin registries consortium (INTR) (Buchwald et al. 2014, van Dongen et al. 2012). The INTR is a platform for international collaborations, and would be an excellent resource for large scale multi-centre clinical trials.

Implications for future work and directions

To understand the potential benefits of the co-twin control design, it would be useful to compare the sample sizes of twin RCTs and non-twin RCTs required to detect the same effect size. The advantages and disadvantages of inclusion of both MZ and DZ twins in RCTs needs more in-depth discussion and are areas for future methodological research.

Contamination between intervention and control twin participants allocated to different treatment groups (particularly in psychological interventions) especially among twins living together will be an important issue to address.

Limitation of the review

In-depth analyses of the quality of individual fifty studies qualified for the review and methodological issues of these studies were not done. We did not include a meta-analysis for this review.

Conclusion

Both MZ and DZ twins have been used in RCTs. However, on a majority of instances they have been MZ twins randomised to opposite arms of a RCT.

The continuous development and implementation of innovative twin designs in intervention studies, especially RCTs, indicates that twin research can extend beyond the more widely recognised heritability estimates towards the possibility of inference on causation.

Acknowledgements

JMC is supported by grants from the Australian National Health and Medical Research Council (grant number 1079102), the Financial Markets Foundation for Children (grant number 2015-111), the Cerebral Palsy Alliance Research Foundation (grant number PG2316), and by the Victorian Government's Operational Infrastructure Support Program. LNY is supported by an Australian National Health and Medical Research Council Early Career Fellowship (ID 1052388).

Conflict of Interest

None declared by any

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Figure 1: PRISMA diagram to illustrate the literature search process and the resulting number of reviewed articles from USA Clinical Trial database.

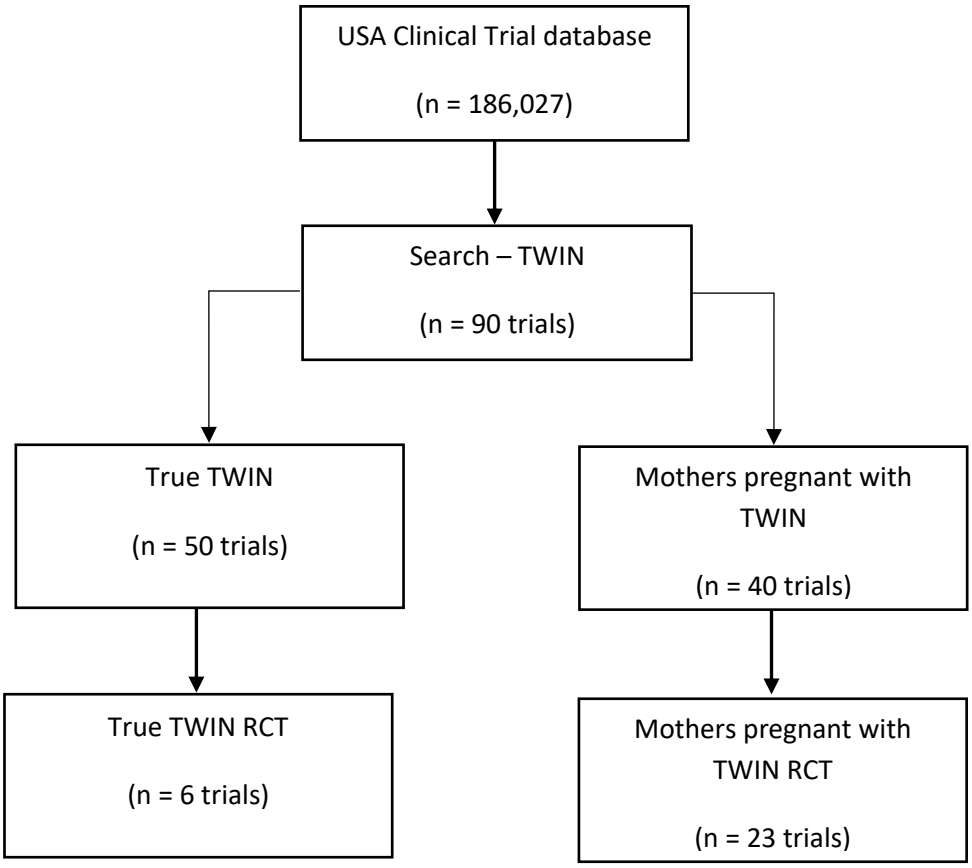

Figure 2: PRISMA diagram to illustrate the literature search process and the resulting number of reviewed articles found in the Medline, Psych INFO and EMBASE databases.

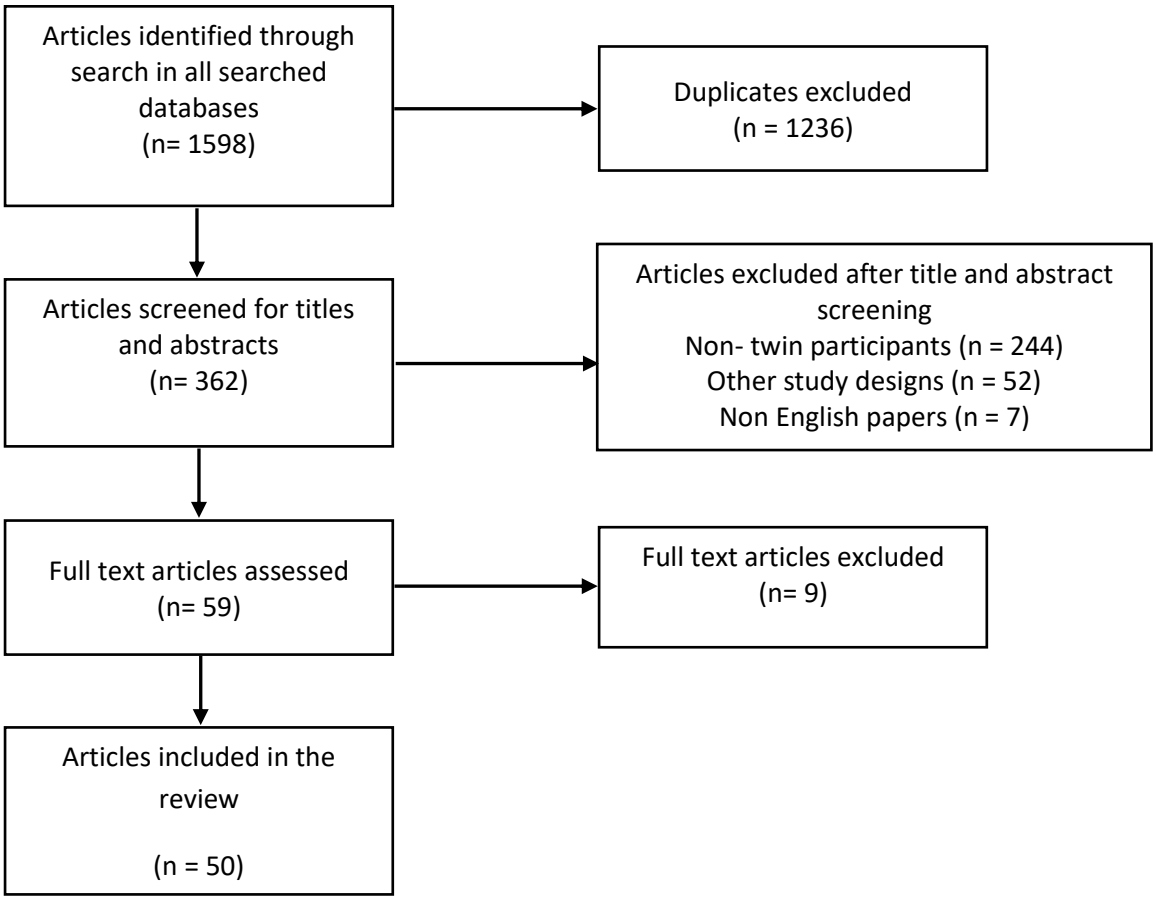

Table 1: Characteristics of randomised controlled trials with twin participants.

Characteristic	Number (Percentage) of Trials (n=50)
Number of participants recruited	
<10	12 (24)
10-100	21 (42)
101-250	14 (28)
>250	3 (6)
Sex	
Males only	7
Females only	9
Males and females	34
Zygosity	
MZ only	27 (54)
DZ only	4 (8)
MZ and DZ	19 (38)
Twin assignment	
Same treatment groups	13 (26)
Different treatment groups	33 (66)
Independent allocation	3 (6)
Unclear	1 (2)
Location	
United States	21 (42)
Canada	5 (10)
Europe	10 (20)
LMIC	2 (4)
Other	12 (24)
Twin recruitment method	
Twin registry	8 (16)
Other	42 (84%)