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Systematic review

Participation in clinical trials improves outcomes in women's health: a systematic review and meta-analysis

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Background Previous reviews examining the effect of participation in trials on outcomes have not consistently shown benefit. Obstetrics and gynaecology is a unique disease area posing challenges for both researchers and patients.

Objectives To determine whether participation in randomised controlled trials (RCTs), compared with non-participation, has a beneficial effect on women's health.

Search strategy Medline, Embase, the Cochrane Library, and PsycInfo were searched up to December 2015.

Selection criteria We selected studies that reported the same clinical outcomes for participants in a women's health RCT and a comparable non-participant cohort.

Data collection and analysis Data were extracted on quality, characteristics and study results. Outcomes were compared using logistic regression.

Main results There were 21 relevant studies (20 160 women, 4759 outcome events). Trial participants, compared with non-participants, had 25% better odds of improved outcomes on average (OR 0.75; 95% CI 0.64–0.87; I^2 = 64.3%). The beneficial effect of participating in a trial was larger in comparisons where: RCTs were of high quality (OR 0.62; 95% CI 0.50–0.76) versus low (OR 0.92; 95% CI 0.74–1.16); and RCT intervention was not available to non-participants (OR 0.57; 95% CI 0.47–0.69) versus when it was (OR 1.13; 95% CI 0.89–1.44). The effect of trial participation was not influenced by effect size within the RCT (P = 0.48), whether funding was received or not (P = 0.13), whether non-participants received any treatment or not (P = 0.49), and the quality of the comparison of RCT participants with non-participants (P = 0.88).

Conclusions Women participating in RCTs on average experienced better outcomes compared with those outside trials.

Keywords Neonate, randomised, systematic review, trial participation, women's health.

Tweetable abstract Participants in obstetric and gynaecology RCTs experience better outcomes compared with non-participants.

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Introduction

Clinical research aims to benefit people in the future, enabling them to live longer, healthier lives, but might it also be of benefit to its subjects? Trial participants receive care under enhanced oversight[1,2] above and beyond usual care, which is ensured by ethics and governance approvals,[3] data and safety monitoring,[4] and protocol compliance. Yet research on the effect of participation in trials versus non-participation has not consistently shown evidence of benefit.[5–8] This may be because the way innovations tested in trials differ from care outside trials[9,10] varies by clinical area, and combining data from a number of specialities into a single synthesis can mask an effect.

Previous reviews[5–8] on effect of participation in trials have not examined speciality subgroups. Research in women's health, which tends to be publicly funded, with industry funding lagging behind,[11] is unique in many

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ways:[12,13] for example, due to the combination of mother and offspring as a single unit, the social and cultural sensitivities in gynaecology, complex disease processes, interventions and outcomes, which may predispose participants to benefit or harm in a manner that cannot be surmised from the broad syntheses previously reported.[5–8]

Therefore, there is good reason to believe that the influence of trial participation in women's health could be distinct from other specialties.[14,15] The objective of this systematic review was to test the hypothesis that there is a benefit of participation in women's health trials, versus non-participation, and to explore reasons for heterogeneity.

Methods

We performed the review in line with current methodological practice with a prospectively registered protocol (PROSPERO registration number: CRD42015025007),[16] and reported it in accordance with the PRISMA statement.[17]

Data sources and study selection

We conducted a comprehensive literature search to identify eligible studies in the specialty of obstetrics and gynaecology[18] adopting well-developed search strategies (Supporting Information Appendix S1).[8] Twenty-four obstetrics and gynaecology RCTs were identified in a previous review searching until 2010.[8] We updated the search from this review until December 2015 and filtered for studies in women's health by screening titles to identify additional studies. We used a combination of keywords and word variants: 'randomised clinical trial', 'non trial', 'refusers', 'decline', 'preference trial' and 'standard care' to interrogate MEDLINE (1966 to December 2015), Embase (1980 to December 2015), Cochrane Central Register of Controlled Trials (CENTRAL; 1960 to last quarter of 2015) and PsycINFO (1880 to December 2015).

Two reviewers (MD and SN) independently reviewed all citations and abstracts to identify those that potentially fulfilled the selection criteria. The final selection of articles was based on independent review of their full texts. Studies were included in the systematic review if an RCT in the specialty of obstetrics and gynaecology reported the same clinical outcomes for participants and their comparable non-participants outside the trial in the same publication. For meta-analysis, studies were retained if it was possible to construct 2 × 2 data tables. Studies were excluded if they lacked a comparable non-participant group, if the subject was outside obstetrics and gynaecology, if the paper was about *in vitro* or animal research, or if the outcome reported was not patient-centred. When duplicate studies existed, we only used the most up-to-date articles. Disagreements that could not be resolved between primary reviewers were referred to an independent third adjudicator (JZ or KK) who was not involved in the initial screening. This involved the adjudicator reviewing the full text against the inclusion and exclusion criteria.

Data extraction and study quality assessment

Data extraction was performed on a piloted form in triplicate (MD, SN and NW/KK) to ensure reliability and accuracy. Disagreements were resolved via consensus (MD, SN, NW and KK) or arbitration (JZ). For the selection of outcomes we adhered to the principles employed by the definition of core sets based on relevance and importance to stakeholders.[19,20] In cases where core sets had not been developed, the most clinically relevant patient-centred outcomes (as judged by obstetrician-gynaecologist reviewers, SN and KK) were identified prior to event rate data extraction for 2 × 2 tables. Extraction of continuous data was complicated by the mixtures of post-intervention and change from baseline results.[21] We preferred post-intervention results, but these were not reported in a manner that allowed inclusion in meta-analysis. We also collected data regarding the care setting, study design, and the intervention and comparator within the trial, and their use among non-participants. We attempted to collect missing data by contacting study authors.

Quality of RCTs was assessed using the Jadad scale[22] (scored 0–5) scrutinising the method of randomisation, blinding and patient withdrawals or dropouts.[22] RCTs with a score of ≥3 were considered to be of high quality.[23] Quality of the comparison between RCT participants and non-participants was assessed using a modified Newcastle Ottawa score (NOS)[24] and focused on three domains (scored using a star rating system) addressing the risk of selection bias (baseline comparability), performance bias (exposure to RCT or not) and ascertainment bias (outcome assessment).[24] Selection bias assessment (maximum 4 stars) examined whether known confounding factors were measured, reported and found comparable. Performance bias assessment (maximum 3 stars) scrutinised clarity of the correct allocation of participants and non-participants to within or outside RCT groups considering rates of switches from RCT to outside group. Ascertainment bias assessment (maximum 5 stars) evaluated whether RCT participants and non-participants had similar methods of outcome assessment, follow up of groups, and completeness of data. Studies with ≥6 stars were considered to be high quality if they scored ≥2 stars per domain.

Data synthesis

We calculated the odds ratio (OR) and 95% confidence interval (CI) for each study using the 2 × 2 data tables for comparison of outcomes amongst RCT participants versus non-participants. We produced a Forest plot to visually inspect variability between studies and computed the

I-squared statistic to quantify its magnitude (assuming 25–75% indicated moderate heterogeneity).[25] We examined funnel asymmetry to test for publication and related biases.[26] We pooled the individual OR estimates across studies using a random effects model.[27]

Multilevel logistic regression models including interaction terms (the product of a covariate and main effect, i.e. participating in a trial or not) were used to explore sources of heterogeneity.[28] Interactions found statistically significant were further explored to produce estimates of the effect of participating in a trial for the different subgroups. We hypothesised that the effect of participating in an RCT versus non-participation would be influenced by factors related to the RCT (effect of intervention versus control within trial, quality of RCT, and funding use) and to being outside it (use of RCT intervention among non-participants, availability of other treatments or observation only among non-participants, and quality of the comparison between participants and non-participants); all six factors were analysed.

Analysis was performed using STATA software (StataCorp. 2014. *Stata Statistical Software: Release 13*. College Station, TX, USA: StataCorp LP).

Results

Of the 17 013 records identified (Figure 1), 21 studies[29–49] (20 160 women, 4759 outcome events) were included [see Supporting Information Table S1 for excluded studies[50–61]]. The number of outcome events for RCT participants included were 1055 and for non-participants 3704. There was good agreement for study selection amongst primary reviewers (weighted $\kappa = 0.82$). Funnel plot analysis exhibited no evidence of publication and related biases with either the Begg's ($P = 0.25$) or the Egger's ($P = 0.56$) test (Figure 2).

Characteristics and quality of included studies

There were 11 obstetric and 10 gynaecological studies, predominately from high-income countries (Supporting Information Table S2). With respect to design, all studies were RCTs, of which eight were partially randomised patient preference trials,[35–37,40,42,44–46] and the others conventional RCTs. Size of studies varied (median 293, range 33–5519) with three papers involving <100 participants [29,32,33] and four involving >2000 participants.[39,43,46,48] All but one of the studies[48] were set in secondary care, defined as services provided by medical specialists based in a hospital or clinic setting. The trial interventions can be arranged into three categories: medical 12, surgical 6, and other 3. Of the 15 studies that received funding,[29,30,33,34,36,37,39,41–44,46–49] three received funding from commercial organisations.[34,43,44] Around half of RCTs were of poor quality mainly due to inadequacies in blinding and in description of withdrawals (Figure 3); lack of transparency of randomisation introduced risk of bias in two studies.[29,31] The quality of comparison between RCT participants and non-participants was high in 18 studies; the remaining three studies had a risk of bias in the selection and performance domains.[29,30,40]

Data synthesis

Overall, when compared with non-participants, RCT participants had 25% better odds of improved outcomes on average (OR 0.75; 95% CI 0.64–0.87; $I^2 = 64.3\%$) (Figure 4). Analysis exploring sources of heterogeneity showed that the beneficial effect of participating in a trial was larger for two subgroups: high quality RCTs (OR 0.62; 95% CI 0.50–0.76) versus low quality RCTs (OR 0.92; 95% CI 0.74–1.16); and when RCT intervention was not available to non-participants (OR 0.57; 95% CI 0.47–0.69) versus when it was (OR 1.13; 95% CI 0.89–1.44). The effect of participating in a RCT was not influenced by the remaining subgroups: effect of intervention within the RCT ($P = 0.48$), whether funding was received or not ($P = 0.13$), whether non-participants received treatment or not ($P = 0.49$), and quality of the comparison of RCT participants with non-participants ($P = 0.88$).

Discussion

Main findings

Our study found that women participating in trials had better health outcomes than those cared for outside trials. Our subgroup analysis demonstrated that the observed effect was enhanced in comparisons involving high quality RCTs and in comparisons where the RCT intervention was not available outside the trial. The benefit accrued by women participating in RCTs was sustained irrespective of whether the RCT intervention was effective or not.

Strengths and limitations

To our knowledge, this is the first systematic review investigating the association between trial participation and outcomes exclusively in women's health. Building on previous works[5–8] that investigated this question more generally, we focused on the obstetrics-gynaecology specialty.[18] This is the first review to report a significant benefit as a result of trial participation. Due to the distinct nature of women's health we focused solely on this disease area and within this subgroup analyses we observed an effect not previously seen in overall syntheses. A retrospective study of a regional cancer centre in the USA found clinical trial participation to improve significantly the survival of women with ovarian cancer compared with non-participants (median 46 versus 25 months, 95% CI 1.03–2.15 months, $P = 0.03$).[62] That paper, though not part of our meta-analysis, reached the same conclusion as ours.

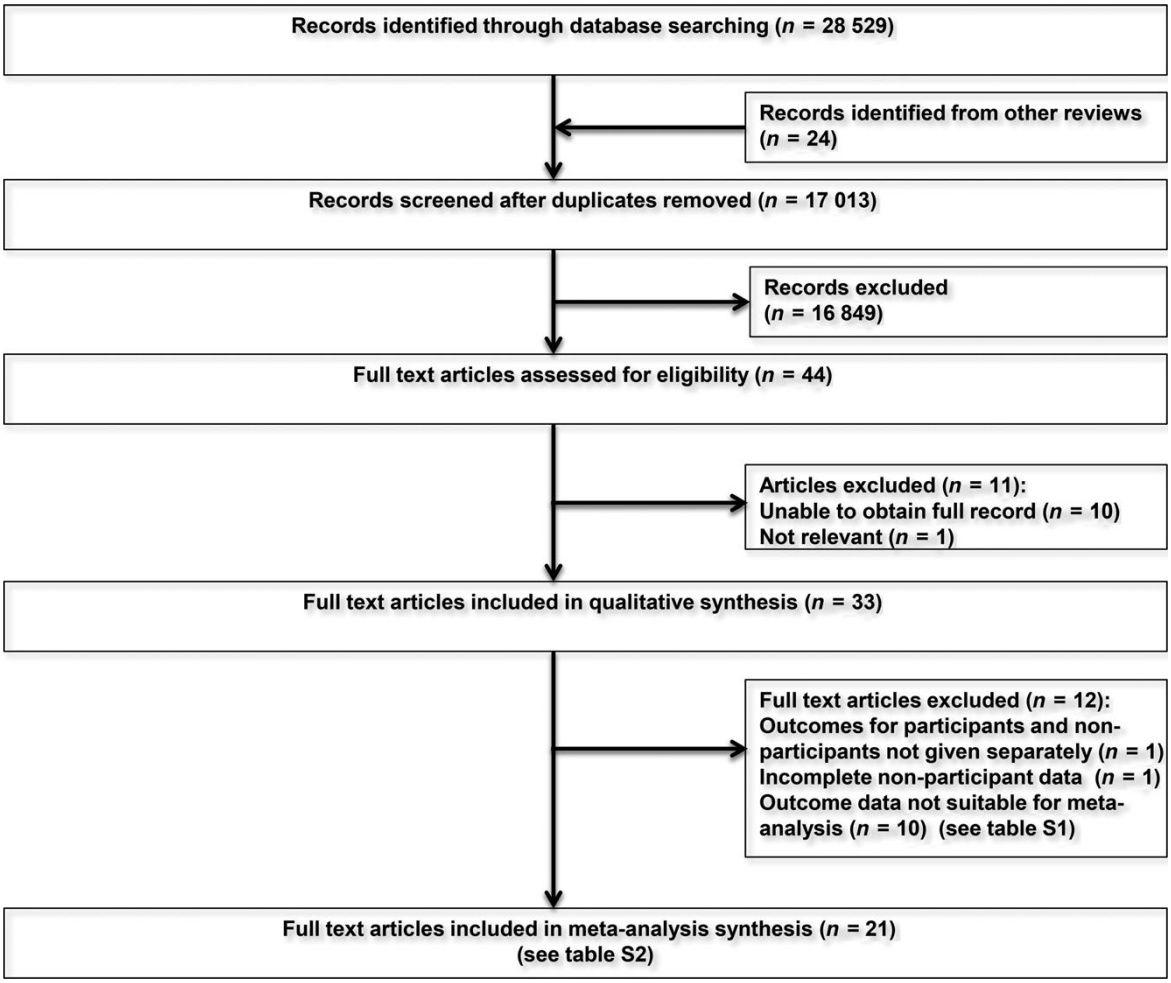

Figure 1. Study selection process for the review on effect of participation in randomised controlled trials (RCTs) versus non-participation in women's health.

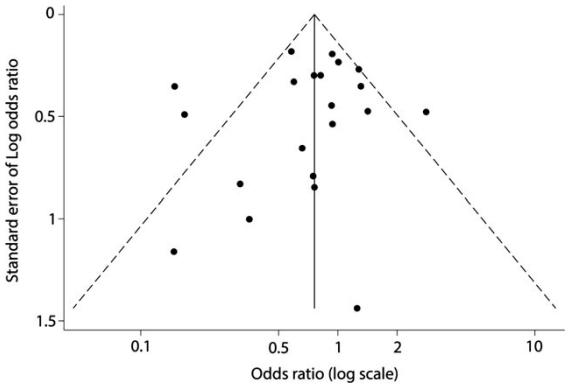

Figure 2. Funnel plot for publication and related biases.

Gathering data for our meta-analysis was challenging, as few researchers conducting RCTs include concurrent non-randomised populations in their studies. Our search emphasised looking for comparisons within the same publications to seek studies where our question could be addressed directly. However, if the RCT and the non-randomised cohort were published separately and there was no cross referencing in the published papers, there is a possibility of missing such studies. For example, Cooper et al.[63] reported an RCT without reference to their patient preference cohort. Although our search picked up the Cooper et al. RCT, in the absence of any identifiable information within it about the non-randomised cohort, we could not include this comparison in our review. To fully take into account the impact of such omissions, a full further review

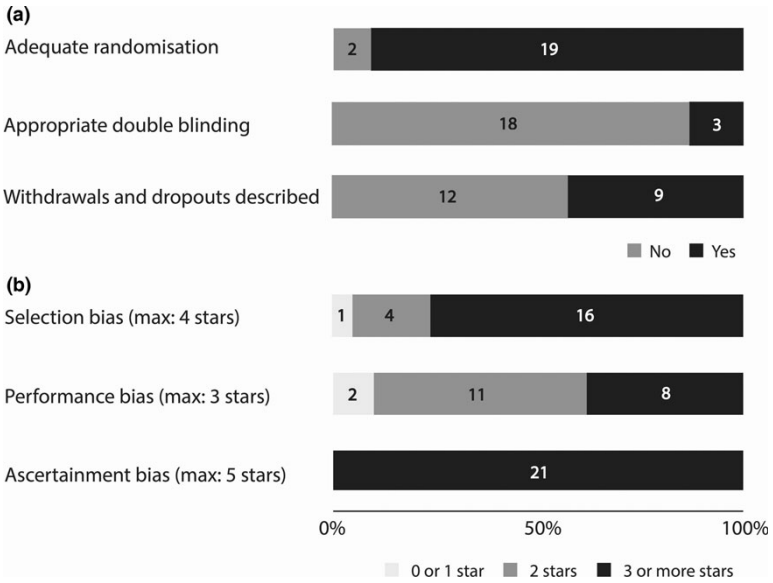

Figure 3. Assessment of (a) randomised controlled trials (RCTs) quality and (b) quality of the comparison between RCT participants and non-participants (numbers within the bars represent the number of studies).

would be needed, including study quality assessments and re-analyses. However, using the author-reported primary outcome (success of treatment at 6 months) it is possible to see that in this individual comparison there was no significant difference between participants (76%, 334/439) and non-participants (82%, 276/338) ($P = 0.06$).[64] Thus our overall conclusion would not necessarily be invalidated.

Given the broad nature of women's health we were aware that there would not be a sufficient number of studies to conduct a meta-analysis of a specific disease area; therefore we had to pool all studies found, leading to moderate heterogeneity given the varieties of settings, methodologies, outcomes and interventions. In some cases, for obstetric studies we selected outcomes related to the health of the fetus (five studies) or neonate (three studies) and not the woman, as fetal and neonatal outcomes are proportional to the health of the mother and are influenced by maternal interventions. To be pragmatic, we had to adapt our protocol by reducing the number of variables such that each subgroup could have sufficient number of studies for a reliable analysis. A random effects model was appropriate in light of the moderately high I–squared statistic. In a previous review,[8] 24 obstetrics-gynaecology RCTs were identified but not all had data available for our planned analysis. In Table S1 we detail potentially eligible studies that we excluded for transparency. Our results were not affected by funnel asymmetry.

The majority of the comparisons between trial participants and non-participants were of high quality. Several studies included in our meta-analysis were partially randomised patient preference trials,[35–37,40,42,44–46] an approach that allows capture of a concurrent non-participant cohort with the same eligibility criteria as those within the RCT, a feature preferred over historical comparisons.[65,66] However, this design may allow for selection bias, as trial participants that are given a choice of intervention may have inherent psychological differences. For example, there may be different levels of motivation and compliance in participants given a choice of treatment versus trial participants where choice was not offered. To minimise the risk of bias we captured objective clinically important outcomes not influenced by the subjectivity of preference. The quality assessments (Figure 3) reassure us about the low risk of inherent biases and improve the trustworthiness of our finding in the context of observational comparisons.

Interpretation

The public, and even doctors, nurses and allied health professionals, may regard research as an 'experiment', i.e. something 'dangerous' relative to usual care. Our findings challenge this concept, showing conversely that outcomes are worse outside clinical trials, even if the RCT intervention is not effective. Practitioners frequently provide new care without the safeguards typically used to protect trial participants.[67] In this situation, the 'dangerous' experiment is usual care outside a trial. As our result has shown an overall benefit statistically, careful dissemination of this information to potential participants is required. It does

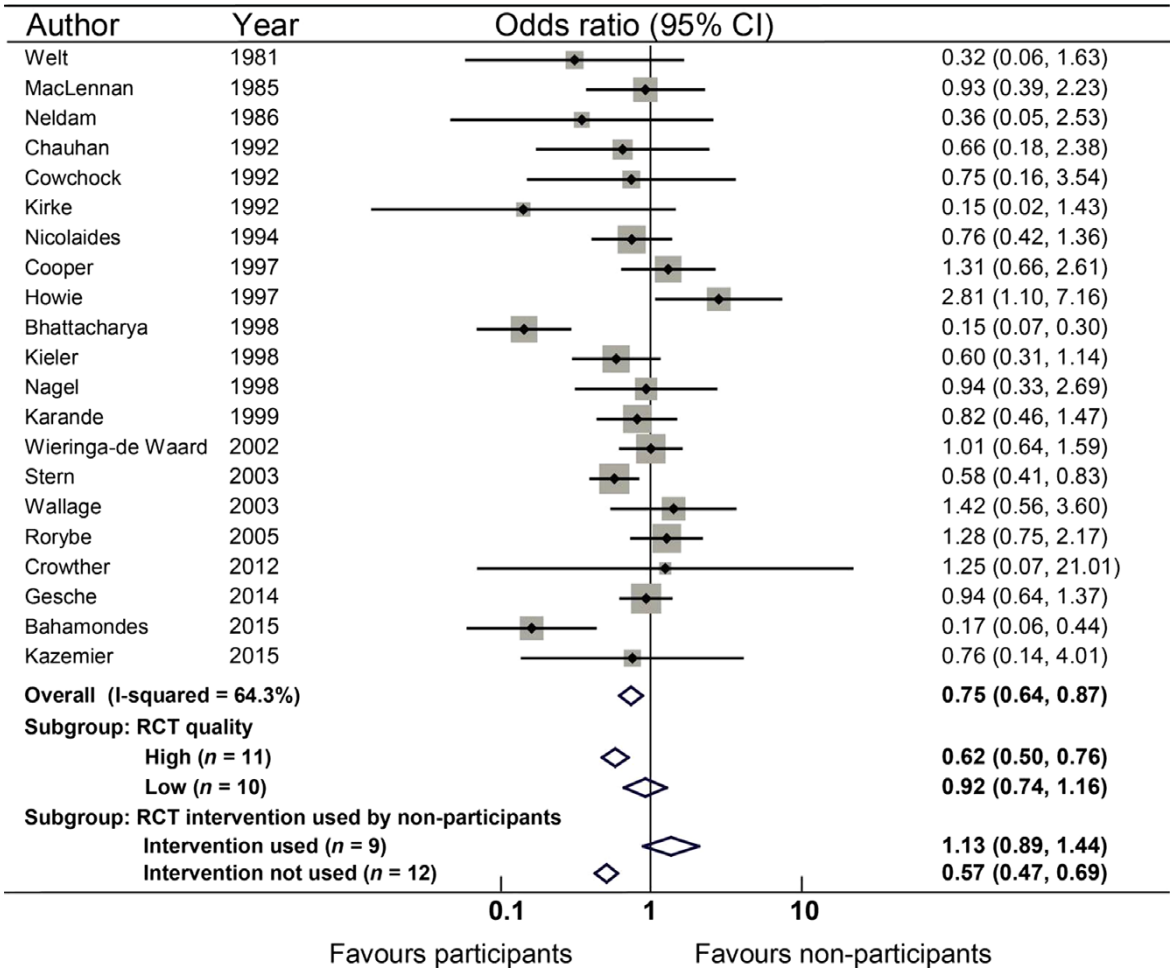

Figure 4. Forest plot of the effect of participation in randomised controlled trials (RCTs) versus non-participation in women's health.

not pose a conflict with the ethical principle of the Helsinki declaration that non-participation does not intentionally affect standard care,[68] but it does offer a new view for consideration by ethicists: is it really ethical to offer care disengaged from research?

Obstetric-gynaecological research poses social and ethical challenges[15] including safety of the fetus, limited observation time period (e.g. gestational duration), women's lifestyle including childcare responsibilities, sensitivity with respect to relationships, and menopause. Further, women are often excluded from clinical trials if they are of childbearing age, pregnant or breast-feeding, when they may still be treated in routine care, thus making it hard to extrapolate results to this subgroup of women who may benefit from the intervention.[12] There has also been political, scientific, and public concern over the lack of representation of women in clinical research in recent decades.[14,69] Thus, there is a need for further research on the health benefits specifically to women participating in RCTs in other fields.

It is important to remember that research can be associated with risk. The Women's Health Initiative trial was a large RCT that demonstrated that participation in a trial may result in excess personal risk to participants and it was prematurely terminated due to safety concerns.[70] It is the duty of researchers and clinicians to inform patients of the potential risk and benefit of engagement in research. The beneficial effect generated by trial participation should galvanise clinicians and women into taking part in research, increasing the value of funding and stimulating rapid accrual to women's health RCTs.

Implications for clinical policy and practice

The relative improvement in outcomes we observed within RCTs versus outside trials merits consideration.

Participation in research should not be perceived as an optional extra to practice. One of the major challenges facing research is recruitment failure.[71] The positive effect on health outcomes among women who participate in trials, compared with non-participants, should encourage and engage funding bodies (<1% of UK health research and development funding is granted to maternal and perinatal health[11]), policy makers, researchers, clinicians, women themselves and their consumer groups.

As women's rights are incorporated into global health agenda through UN sustainable development goals,[72] which aim to achieve gender equality and empower women, the opportunity to engage in research should be made integral to service provision to recognise the role trials play in improving outcomes of current patients, not just those in the future. Governments, health insurers, and women's health systems should prioritise research activity including women as a benchmark for service quality. As the saying goes: a day without randomisation is a day without progress.

Conclusion

Women participating in RCTs on average experienced better outcomes compared with those outside trials. Active participation in trials should be employed as a quality benchmark for women's health services. Further research into the factors that have led to the observed benefit is needed.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

MD and SN designed the protocol, data extraction form, literature search and selected eligible texts. MD, SN and NW extracted and cleaned data. MD and SN analysed the data, drafted and revised the paper. NC advised on protocol design, search strategy and revised the paper. JZ and KK wrote the statistical analysis plan, and drafted and revised the paper. JZ and KK resolved the discrepancies between reviewers on data extraction.

Details of ethics approval

Ethical approval was not required for this project.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Characteristics of studies not included in the review of the effect of participation in randomised controlled trials (RCTs) versus non-participation in women's health.

Table S2. Characteristics of studies included in systematic review of the effect of participation in randomised controlled trials (RCTs) versus non-participation in women's health. *Outcomes studied are those used in logistic regression analysis.

Appendix S1. MEDLINE search strategy (adapted for use in other databases and registries).■

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