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Comparing alternative design options for chronic disease prevention interventions

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Abstract

Background While the randomized clinical trial is considered to provide the highest level of evidence in clinical medicine, its superiority to other study designs in the context of prevention studies is debated. The purpose of this review was (i) to gather evidence about challenges facing both randomized controlled trials and observational designs for the conduct of population-based chronic disease prevention interventions and (ii) to consider the suitability of recently proposed hybrid designs for population-based prevention intervention studies. Methods Rapid review methods were employed for this study. Articles published within 2007-2012, were included if they: (i) discussed challenges or benefits related to any intervention study design, (ii) compared randomized controlled trials (RCT) and observational designs or (iii) introduced a new study design potentially applicable to population-based interventions. After initial screening, papers retained for inclusion were subjected to content analysis and synthesis. Results A total of 35 included articles were reviewed and used for synthesis. Both RCTs and observational studies are subject to multiple challenges, the main being external and internal validity for RCTs and observational designs, respectively. Four new hybrid designs identified. Conclusion Although any high quality design can produce high level of evidence, multiple challenges with prevention intervention RCTs or observational studies identified. New hybrid designs that carry benefits of randomized and observational methods may be the road ahead for to assess the effects of population-based interventions.

Keywords

Cohort studies, intervention studies, prevention, randomized controlled trial, research design

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BSTRACT

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Methods:

Rapid review methods were employed for the current study. Articles published n the last five years were included if they: (i) discussed challenges or benefits related to

any intervention study design; (ii) compared RCT and observational designs; or (iii) introduced a new study design potentially applicable to population-based interventions. After initial screening, papers retained for inclusion were subjected to content analysis and synthesis.

Results:

A total of 35 included articles were reviewed and used for synthesis. Both RCTs and observational studies are subject to multiple challenges, the main being external and internal validity for RCTs and observational designs, respectively. Four new hybrid designs identified.

Conclusion:

Although, usefulness of current study designs for assessment of population based chronic disease prevention interventions is not evidenced, any high quality design, including observational studies, can produce high quality evidence. New hybrid designs that carry benefits of randomized and observational methods may be the road ahead for to assess the effects of population-based interventions.

Key words: Prevention; Intervention studies; Cohort studies; Randomized controlled trial; Research design

Title: Comparing alternative design options for chronic disease prevention interventions

INTRODUCTION

Alternative designs have recently been introduced to overcome the design challenges of traditional randomized controlled trials (RCTs) and observational studies. These alternative design options are of particular interest because of the investments made in cohort studies and increased attention to participant engagement in epidemiological research. The Ontario Health Study [1] was a motivating example for considering this issue because it is a large cohort study with internet-based enrolment and data collection, with considerable attention given to participant engagement. These issues, along with the strengths and limitations of both RCTs and observational studies were discussed in a workshop [2] held under the auspices of the Cancer Care Ontario Population Studies Research Network (PSRN) in January 2013, and this paper is a companion to two other rapid reviews [3,4] that were commissioned for this workshop.

Chronic diseases have overtaken communicable diseases as the primary cause of disease and death in developed countries, and a similar trend is appearing in low- and middle-income countries [5]. Concomitantly a profound change in the understanding of disease etiology is emerging, moving from single cause models to multifactorial models such as the "web of causation" [6]. This has implications for the design of health intervention research, with an evolution from investigation of the effect of single agents on single outcomes in the first clearly documented randomized controlled trials in the 1940s to the development of a framework for the design and evaluation of complex interventions in the first decade of the 21st century [7-9].

Methods for evaluating population-based interventions are often considered in the framework of RCTs, including cluster and individual-level trial designs. In the RCT

design, participants are assigned at random to one or more intervention groups to assess the efficacy of the intervention to promote behaviour change and/or improve health outcomes. Carefully designed, conducted and analysed RCTs are considered to provide the highest level of internal validity, relative to other study designs, and to form the cornerstone of evidence-based medicine [10]. On the other hand, RCTs cannot be used to assess the effects of potentially harmful exposures, and their expense has limited the range of potentially beneficial exposures investigated. Moreover, RCTs tend to have been implemented with strict eligibility criteria, limiting generalizability. Whilst the risk of bias of observational studies is greater than for RCTs, they can be used to investigate a wider range of exposures than RCTs and thereby suggest options to prevent disease in a population, potentially can have greater generalizability and tend to be less expensive. Two major types of observational studies are the cohort design and the case-control design. The cohort design can yield information about multiple diseases or outcomes, providing that it is sufficiently large to have adequate statistical power to detect the effects of the exposure (s) under investigation, and the length of follow-up is sufficient to address latency of effect. The case-control study is typically smaller than a cohort study, and can yield information about the effects of multiple exposures on a disease or outcome in a much shorter period of time [10].

RCTs and observational studies have positive attributes as well as limitations. Novel study designs and variations of established designs have been explored to evaluate interventions. Some of these may offer new possibilities for maximizing both internal and external validity, especially in the context of chronic disease prevention research.

A need for a study on the challenges using traditional research designs in the context of population-based prevention interventions was identified by the Cancer Care Ontario PSRN. The objective of the current review is to obtain information about the attributes of RCTs, observational studies and proposed alternative designs that are pertinent to disease prevention studies.

METHODS

This review adopted the approach to rapid reviews outlined by Khangura et al. [11]: (i) needs assessment; (ii) question development and refinement; (iii) proposal development and approval; (iv) systematic literature search; (v) screening and selection of studies; (vi) narrative synthesis of included studies; (vii) report production; and (viii) ongoing follow-up and dialogue with knowledge users.

Search Strategy

We searched Ovid MEDLINE™ In-Process & Other Non-indexed Citations and Ovid MEDLINE™ (1946 to present). In consultation with a professional medical literature research librarian at the University of Ottawa Health Sciences Library, several potential search strategies were designed and tested (by reviewing the first 200 citation titles). Appendix A shows the search strategy that generated the most relevant citations and therefore used in this review. We included two categories of articles - i) systematic reviews and ii) commentaries and editorials - with the expectation that our research question would be best answered by these two types of literature. Because this was a rapid review, we limited the search to articles published in the period of Jan 1, 2007 until September 17, 2012, only in the English language. Note our search was not confined to any particular population. The quality of evidence was not evaluated as it

was not either possible or appropriate given the nature of our approach and given the exploratory nature of the research question (60).

Selection criteria and process

We selected studies according to the following criteria.

Inclusion criteria were that the article:

- was published in English; and
- discussed strengths and limitations of RCTs and/or observational studies in the context of chronic disease prevention interventions: or
- compared RCTs with observational studies; or
- introduced alternative research designs for population-based studies.

Exclusion criteria were that the article was not published in English and did not meet one of the above inclusion criteria.

We uploaded the literature search results to RefWorks software for the study selection process. The search yielded 1305 non-duplicate citations, which were screened for relevance by MG. After this first level screening, 87 articles remained. Next, full-text screening was performed by MG and then reviewed by JL. Disagreements were resolved by consensus. Once completed, 27 articles were retained for analysis and narrative synthesis (Table 1). An additional 15 other articles deemed to be relevant were provided by JL for inclusion, among which 8 articles were deemed suitable for inclusion in the synthesis.

Data extraction and process

Using an extraction table (key elements of which are summarized in Table 1), we synthesized the details regarding the strengths and limitations of RCTs and

observational studies, or the features of the newly introduced population-based research designs and how they compare to the traditional study designs (RCTs and observational studies). Next, we conducted narrative synthesis and prepared an initial report, which was submitted to the PSRN. The key messages were then presented in a Cancer Care Ontario workshop and discussed with the variety of health experts who participated during and after the workshop [2]. Their comments were collected anonymously (with permission) and were also incorporated in the present knowledge synthesis.

RESULTS

This synthesis is organized into four sections: (i) key challenges encountered in RCTs; (ii) key challenges encountered in observational studies; (iii) a comparison of these two designs; and (iv) a review of some recent, innovative research designs and their strengths and limitations.

1. Challenges encountered in RCTs:

A) *Bias:* Five potential sources of bias were identified that may influence the results of RCTs.

First, a **systematic overestimation of the intervention effect size** can occur in the design of RCTs. As a result, a RCT can be subject to type 1 statistical error, which indicates efficacy when it does not exist [12]. In a review of 38 RCTs published in five high impact journals, only five studies had published a justification for the predicted effect size. In addition, only in two of 38 trials did the observed effect size surpass the predicted effect size. In prevention intervention studies in particular, one way to

estimate the effect size accurately is to look for populations with adequate rate of event of interest. This can be challenging in the studies in the elderly population, where the event of interest can be "trumped" by other events. As an example, since stroke is less common than cardiovascular disease, a trial focusing on cardiovascular disease may not have sufficient power to detect an effect for stroke [13]. Consideration of statistical power is particularly relevant to small-sized RCTs (see below).

Second, **spin or selective reporting** is a twist in the interpretation of findings in which non-statistically significant differences in major endpoints are downplayed and instead the article concentrates on selected significant secondary endpoints [14]. For example, industry funding has been consistently associated with biased conclusions [15]. In a review of 72 papers reporting RCTs with statistically non-significant primary endpoints spin was identified in at least one section of 68% of the abstracts and 61% of the main texts [16].

Third, **withdrawal bias,** which occurs when participants in RCTs withdraw from studies prematurely; because those who withdraw from the studies may be systematically different from those who do not and therefore the results can be distorted. It is very difficult to address this bias during data analysis [17]. Loss to follow-up is especially challenging for non-blinded studies due to participant preference; for example, when participants in the control group lose interest in the trial and withdraw, participants in the intervention group may be more likely to remain in the trial because they perceive the interventions to be novel and potentially life-changing [18].

Fourth, the **crossover phenomenon** occurs when a participant is randomly assigned to one trial arm, but receives some or all of the intervention components that have been offered to the other arm. Moreover, awareness of the other intervention, as distinct from receiving it, can cause changes in outcome [19], and this has been reported earlier in the context of prevention studies [20]. The crossover phenomenon has been reported to be almost 50 percent in control groups in some clinical studies [19], and can also occur in community interventions by contamination between intervention and control communities. For example, in a community nutritional intervention study, a crossover rate of 15.6 to 53.7 percent in the control communities, and 1.4 to 11.7 percent in the intervention communities, was observed [21].

Fifth is the concern of **imbalance**. The validity of a RCT can be compromised when randomization does not balance etiologic factors between study groups (if etiology has a substantial impact on outcome) [22]. This potential problem can be addressed by stratification or blocked randomization.

B) *Generalizability*. **Generalizability (external validity)**, that is the ability to generalize conclusions drawn from studies, can be limited for the RCT design both at individual and community level [23]. The strict inclusion criteria typical of RCTs make it difficult to generalize the results to a general (much broader) population [24]. Other factors that negatively impact generalizability include difficulty in recruiting sufficient numbers of participants and the complexity of including ethnic minorities and geographically remote clusters [25]. Finally, due to heterogeneity in reference populations, it is hard to predict how each individual would response to the same intervention [26]. Community level interventions in particular face the extra challenges

of reaching all the sectors of communities due to logistical, organizational and political obstacles [27]. Additionally, some specific variants of RCTs such as Enriched Enrolment Randomized Withdrawal [EERW] designs, which exclude non-respondent participants, have more issues with external validity [28].

C) *Small-sized RCTs:* **RCTs with comparatively small sample sizes** can lead to erroneous conclusions and unstable estimates of efficacy [29]. The problem is most often small RCTs produce misleadingly large and unstable estimates of benefits and later, larger trials cannot replicate these results. Small RCTs can also produce false negative results, where the results that are potentially beneficial are not detected. With regards to community level interventions in particular, logistical, political and financial issues limit the number of communities to be included in a given study, which lowers the statistical power [30].

2. Challenges encountered in observational studies:

A) *Bias.* Observational studies are subject to **selection bias** and conventional attempts to correct this type of bias have proved inadequate [22, 31, 32]. Another source of bias in observational studies is insufficient attention to **socio-economic factors**. Socio-economic factors have been shown to be highly correlated with health behaviors and health outcomes. For example, socio-economic status influences access to health care facilities; so that rich and educated individuals have more access to health care facilities that sometimes can explain the discrepancy between the results of RCTs and observational studies [31, 32]. As an example, while observational studies consistently found that hormone replacement therapy (HRT) was protective for coronary heart disease (CHD), a slight increase of CHD among those on HRT was found

in RCTs [33]. More recently, an analysis of 4,286 women aged 60 to 79 years showed that lifetime socioeconomic status is inversely associated with HRT [34]. The article concluded that previous observational studies did not adequately adjust for socio-economic status across the life course.

B) *Protecting vulnerable subjects:* Concerns about **adequately protecting vulnerable patients** in longitudinal observational studies have been raised. Multiple strategies to protect vulnerable populations should be built into the research design to make sure access to evidence-based, efficacious interventions will not be withheld. These protective strategies should be reported adequately to help readers understand whether the results of the study apply to the target population under consideration [35]. For example, in an observational study assessing the association between maternal depression and child growth [36], it was unclear whether women with depression received any intervention while being observed throughout the study [35].

C) *Causal effect:* If causal inferences by observational studies are to provide meaningful guidance for prevention interventions, the subgroups defined by the exposure that is relevant for intervention need to be comparable. To create comparable subgroups and to ensure the objectivity of the study, only information relevant to exposure and potential confounders should be used, without access to any outcome data at the time of defining the subgroups as if there had been random assignment to the subgroups [37].

D) Confounding by indication: Another major challenge with observational designs is **confounding by indication,** whereby a participant's allocation to an

intervention is affected by the risk for the condition that is targeted to be affected by the intervention under study. For example, a reduced risk of [CHD] in people allocated to use HRT was observed because HRT was not prescribed to people at risk of CHD [44].

3. Comparing RCTs and observational studies:

The most important source of concern with observational studies is the issue of **internal validity** [38]. However, RCTs have a very high internal validity and as a result, are widely considered capable of establishing a **causal relationship**. RCTs cannot be used to investigate the effects of potentially harmful exposures. It is also recognized that the potential harms of interventions may not be reliably assessed within RCTs, because of considerations of statistical power, coverage of the scope of patient-centered outcomes, and the typically restrictive eligibility criteria already mentioned; in this situation, evidence from non-randomized studies is needed [39]. Further, as exemplified by the highly respected International Agency for Research on Cancer's classification of carcinogenic agents, causal relationships relevant to disease prevention can be inferred from the results of high quality observational studies [40, 41].

It is widely recognized that, in contrast to RCTs, a major potential source of bias in observational studies is **confounding** by unmeasured (unknown) or poorly measured factors [10]**.** In a review of 14 papers in which 38 comparisons of the effect size derived from randomized and non-randomized (quasi-experimental and observational) studies could be made, it was observed that both types of non-randomized studies produced valid estimate of effectiveness provided that there was adequate control for major confounding factors [42].

In **estimating effect size**, RCTs are typically considered superior to observational studies and quasi-experimental trials (collectively non-RCTs); however, evidence is accumulating that high quality non-RCTs and high quality RCTs can produce similar estimates of effect size. In a comparison of the effect size of 48 pairs of single randomized and non-randomized intervention studies, studying similar populations, interventions and outcomes for low back pain treatment, it was observed that the direction and magnitude of association was similar between pairs of studies that had similar settings, population, interventions, and outcomes [38]. In an assessment of 34 interventions with homogeneous populations, no association between study quality and effect size was detected in either non-RCTs or RCTs [42]. In an investigation of the relationship between study design and the level of evidence, 844 research articles from four high-impact medical journals, published in 2009, were evaluated [34]. Of these studies, 35.7% were RCTs, 9.4% were systematic reviews and meta-analysis and 54.9% were other types of studies. For prevention, 68.1% of the studies used the RCT design, a proportion very similar to studies on treatment (70.6%). The authors concluded that RCTs and systematic reviews were not the only methods that can produce high-level evidence. In fact, each type of study has the capacity to generate high quality evidence.

4. Novel Designs:

Ioannidis and Adami proposed the Multi-LIFE design, in which RCTs of lifestyle interventions are nested in large cohort studies and associated biobanks [45]. The main objective of this design is to merge the strengths of RCTs and observational studies. Thus, it was proposed to nest RCTs of lifestyle interventions within large cohorts. These cohorts would then be linked to valid outcome registries, e.g. health administrative databases with validated algorithms to identify outcomes. Participants would be offered

a menu of a large number of potential randomizations. This would enable a factorial design in which joint effects could be assessed. As yet, there are no published examples of this approach. However, the approach is very attractive as it could reduce the opportunity cost of undertaking prevention trials, leveraging the investment made in the cohort study. Also, the infrastructure established for the cohort would help address challenges of statistical power and limited length of follow-up that have bedeviled *ad hoc* prevention trials.

Relton and colleagues introduced a new research design in an effort to challenge some of the problems associated with pragmatic trial designs, notably **recruitment**. The proposed "cohort multiple randomized control trial" (cmRCT) has several innovative features [18]. This design involves recruiting and observing a large cohort of patients with the condition of interest. Then, multiple clinical trials can be conducted using this population. By using random selections of participants, multiple RCTs can be conducted. The outcomes of these randomly selected participants are compared to those of other eligible patients who were not randomly selected and received usual care. This design is most appropriate for open trials comparing an intervention with treatment as usual, for trials that aim to inform health care decision makers in everyday practice, and for trials that answer simply measured or collected outcomes. The population of interest in this design should be stable and easily identifiable. The design is particularly amenable to conditions for which many trials need to be carried out, and so has some conceptual overlap with the Multi-LIFE design (45). The authors identified obesity prevention as an exemplar condition, and have implemented a trial in the UK (46). The design is also potentially valuable for the conditions for which previous trials have struggled to recruit adequate numbers of participants, e.g. scleroderma, for which this design is now

being employed [47]. This design is also suitable for interventions that are highly desired by participants, and so may be of value in participatory action research [48, 49].

Vickers et al [43] introduced another novel RCT design "clinically-integrated randomized trials." This is specific to scenarios in which participants are already seeking interventions from health providers and in which there is equipoise as to which treatment should be administered and can be randomized. Therefore, it could be applicable to disease prevention interventions in the framework of encounters with health care providers. The primary motive is to reduce **the costs** of conducting large trials. Its key feature is that the health-related experience of the participant and the provider is virtually indistinguishable whether or not the participant is randomized, mainly because information is extracted from routine data or concise web-based questionnaires. The integration of RCTs into usual health care provider practice demands more flexible eligibility criteria than in conventional RCTs to enable almost every participant to be randomized. Additionally, since the health-related experience of the participants in the study resembles that of those out of the study, the marginal cost of adding a new participant to the trial is negligible. This design is only possible if participants, providers and payers have no preference as to which intervention be administered to the patients.

Finally, Hakama and colleagues introduced the "randomized health services studies" (RHS) primarily intended for addressing questions in routine health care [50], which appears to be applicable to the evaluation of preventive interventions in the framework of health and social services. In this design, observations occur in everyday health care services with randomization at individual, group or process levels. RCT and

RHS methods have a key difference—the data in a RCT is derived from an *ad hoc* intervention study, whereas in a RHS, data is obtained in the course of routine implementation of health services. The RHS design was applied for the evaluation of cervical and breast cancer screening programs [51, 52].

DISCUSSION

Most of the articles and commentaries discussed the challenges associated with conducting RCTs. These included the overestimation of intervention effect size, selective reporting (spin), withdrawal bias, cross-over phenomenon, generalizability (external validity), randomization problems, small RCT issues, recruitment problems and participant preference. Moreover, it appears uncertain if RCTs provide a true estimate of the effectiveness of interventions in the everyday life of people in the target population outside of the settings of *ad hoc* trials. Nevertheless, some RCTs in the context of prevention have had important impact on disease prevention initiatives. For instance, the Women's Health Initiative trial led to significant drop in the incidence of breast cancer in 2003 [56, 57].

Observational studies are widely considered to be at greater risk of bias than RCTs, and therefore, are usually ranked lower in the hierarchy of evidence. Selection bias and inability to deal with unmeasured confounders result in lower internal validity; for this reason, observational studies may not be the best option for lifestyle intervention studies with subtle effects, as it may be difficult to distinguish between genuine effects and biases. Other issues related to the conduct of observational studies include protecting vulnerable populations, creating comparable study groups and often a lack of consideration of socio-economic factors and other health determinants.

Nevertheless, a number of articles suggested that observational studies can produce a similar level of evidence to RCTs when design issues are adequately addressed. For example, Yang et al [34] emphasized that each type of study design has a unique way of producing high-level evidence.

Many of the risk factors for chronic diseases are affected by societal forces, and therefore, societal-level interventions might be expected to have a greater impact than individual-level interventions [53, 54]. However, the approach to prevention solely based on the manipulation at societal level may not be adequate to reduce the burden of preventable diseases [55], and therefore the development and implementation of new research designs that could address above concerns would have tremendous value. Additionally, the multiple challenges associated with each design approach discussed earlier have created an opportunity for scientists to introduce new research designs to be implemented for population based prevention interventions.

The novel study designs considered in this review were based on incorporating the strengths of both RCTs and observational studies and minimizing the deficiencies associated with each design. These designs included “nested randomized trials in large cohorts” (the Multi-LIFE design), “cohort multiple randomized controlled trials”, “clinically integrated randomized trials” and “randomized health services studies”.

These designs, which combine characteristics of randomized trials and observational studies, are considered efficient ways to address the effects of lifestyle interventions and enable the number of questions that can be answered by randomization to be expanded. They also tackle some of the problems associated with

pragmatic trial designs, such as recruitment. In these methods, the marginal cost of including an additional participant in a trial is negligible. Therefore, there is great interest in combining RCTs and observational studies to design new workable and useful methods in order to inform health care decision makers within usual practice and apply the methods in population based prevention studies to achieve both internal and external validity.

This is an area of ongoing development, as exemplified by a design proposed since the period of our rapid review, the randomized registry trial design and has some similarities to the cohort multiple randomized controlled trials design (58, 59).

When comparing RCTs with observational studies as applied to population-based prevention interventions, both have strengths and limitations. There has been accumulating criticism about the conduct and reporting of RCTs (12, 13, 14, 16, 17, 18, 19, 22, 23, 26, 28, 29, 30), and substantial attention given to the positive aspects of observational studies (31, 34, 35, 37, 38, 40, 41, 43, 44). However, the overall quality of the evidence, as assessed in this rapid review, appears uncertain and imprecise and largely could not be assessed for consistency. The body of evidence is also limited considering the few studies included and the heterogeneity in the included literature.

Strengths and Limitations: This is the first literature review to our knowledge that has systematically reviewed literature to comprehensively describe the challenges associated with the conduct of RCTs and observational studies in the context of prevention intervention studies. Considering the time constraints and research question, the rapid review approach was deemed appropriate by the Cancer Care

Ontario PSRN workshop participants (2). This rapid review, covering articles published over a five-year period as identified by searching one widely used database, identified limited evidence on the challenges applying traditional research designs for population-based chronic disease prevention interventions, and four novel designs.

Knowledge Gaps: Few studies have assessed the strengths and limitations of RCTs and observational studies as applied to population-based prevention interventions. In addition, insufficient experience of the newly proposed hybrid designs has accrued to fully understand the extent to which they add to the strengths and decrease the limitations associated with the traditional designs. We believe this literature gap is genuine but we acknowledge the limitations of our approach, which future studies can address.

Research Implications: Since this rapid review only included studies published between 2007 and 2012, updating this review or expanding the literature search will be important. Given the heterogeneity of the characteristics of the articles that were the basis of the evidence included in this review, additional refinements of design are likely to be developed and implemented in future studies. We propose that future knowledge syntheses on methodological aspects of study designs relevant to prevention interventions more clearly classify the literature as to whether it focused on quantitative analysis of the effects of reported methodological features of the studies considered or was descriptive as the first step in their synthesis. As we anticipate that recently introduced hybrid designs will be implemented in the future studies, we propose that the strengths and limitations of these novel designs be investigated.

Practice Implications: Despite the limitations of the rapid review approach already acknowledged, we believe this review can increase awareness among investigators about design options for prevention intervention studies, especially in the context of increasing public engagement in research [2,3]. This review also pinpoints the importance of developing high quality studies in order to produce high quality evidence, irrespective of the overall design used (34,38).

CONCLUSION

This paper reports the results of a rapid review on the challenges associated with using RCTs and observational designs for chronic disease prevention research. A number of challenges for both designs were identified in the literature review. Also, four new study designs were identified, all of which assigned participants to different intervention arms using randomization, i.e. variants of the RCT design. Each of the new design attempted to utilize easily accessible large longitudinal data sources, e.g. routine health services data and/or biobank data. The integration of RCTs within routinely collected datasets may go some way towards addressing some of the challenges faced by standard RCTs and observational studies. What is required now is a real world investigation of the performance of the new designs in relation to the issues that were identified with RCTs and observational studies.

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Appendix A

Intervention design option Search Strategies employed on September 17, 2012 in MEDLINE

Search strategy for "systematic reviews"

1 Cohort Studies/

2 exp Clinical Trials as Topic/

3 exp Longitudinal Studies/

4 intervention studies/

5 Randomized Controlled Trials as Topic/

6 [natural adj3 experiment].tw.

1 or 2 or 3 or 4 or 5 or 6

Research Design/

7 and 8

0 limit 9 to yr="2007 - 2012"

1 "Review Literature as Topic"/

2 10 and 11

3 limit 10 to [comment or editorial]

Articles identified from systematic literature search						
	Author, Year	Publication type	Summary			
			RCT strengths	RCT limitations	Observational studies: strengths	Observational studies: limitations
1	Aberegg et al., 2010 [12];	Systematic review		systematic overestimation of the intervention effect size (source of bias)		
2	Gorelick, 2009 [13]	Systematic review		Challenges designing primary prevention trials (source of bias)		
3	Ekroth et al., 2011 [14]	Editorial		spin or selective reporting (source of bias)		
4	Boutron et al., 2010 [16]	Systematic review		spin or selective reporting in 61-68% of articles with nonsignificant primary end point (source of bias)		
5	Ye et al., 2011 [17]	Editorial/		Attrition bias, difficult to address during data analysis (source of bias)		
6	Relton et al., 2010 [18]	Commentary, leading to rationale for novel design		Attrition bias due to participant preference (source of bias)		
7	Buckley et al., 2010 [19]	Commentary		Crossover phenomenon (source of bias)		
8	Hayes, 2009 [22]	Commentary		Imbalance randomization based on etiologic factors (source of bias)		
9	Bloomgarden et al., 2009 [23]	Editorial		Limited external validity (generalizability)		
10	Herbert et al., 2007 [26]	Editorial		Difficulty predicting response to treatment due to heterogeneity in the reference population		
11	McGrath, 2011 [28]	Commentary		Enriched Enrolment Randomized Withdrawal		
12	Redman et al., 2007 [29]	Commentary and Editorial		Erroneous conclusions with unstable effect size in Small RCTs		
13	Berger et al., 2012 [30]	Systematic review		over and under-estimation of efficacy and low power in small RCTs		
14	Rosen et al., 2009 [31]	Commentary				Selection bias due to ignorance of socioeconomic factors
15	Yang et al., 2009 [34]	Systematic review with descriptive analysis			each type of study has the capacity to generate high quality evidence	socioeconomic factors need to be considered in observational studies
16	Ross, 2011 [35]	Commentary				Concerns about adequately protecting vulnerable patients
17	Rubin, 2007 [37]	Commentary				causal inferences achieved if study groups are comparable as if subjects are randomized
18	Furlan et al., 2008 [38]	Meta-Analysis Review	Very high internal validity; can produce causal relationship;	Not able to investigate harmful exposures,	high quality non-RCTs and high quality RCTs can produce similar estimates of effect size	Biggest concern: internal validity;