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Heterogeneity in application, design and analysis characteristics was found for controlled before-after (CBA) and interrupted time series (ITS) studies included in Cochrane reviews

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Abstract

Objective

To examine the application, design and analysis characteristics of controlled before-after (CBA) and interrupted time series (ITS) studies and their use in Cochrane reviews.

Study Design and Setting

We searched the Cochrane library for reviews including these study designs from May 2012 - March 2015 and purposively selected, where available, two reviews each across ten pre-specified intervention types. We randomly selected two CBA and two ITS studies from each review. Two researchers independently extracted information from the studies and the respective reviews.

Results

69 reviews considered CBA and ITS studies for inclusion. We analysed 21 CBA and 16 ITS studies from 11 and 8 reviews respectively. Cochrane reviews inconsistently defined and labelled CBA and ITS studies. Many studies did not meet the Cochrane definition or the minimum criteria provided by Cochrane EPOC. The studies present a heterogeneous set of study features and applied a large variety of analyses.

Conclusion

While CBA and ITS studies represent important study designs to evaluate the effects of interventions, especially on a population or organisational level, unclear study design features challenge unequivocal classification and appropriate use. We discuss options for more specific definitions and explicit criteria for CBA and ITS studies.

Key words (index-appropriate): Controlled Before-After Studies, Interrupted Time Series Analysis, review, methods, Public Health

Running title: Analysis of CBA and ITS studies included in Cochrane reviews

Word Count: 197 (max. 200)

What is new?

- CBA and ITS studies are increasingly used but inconsistently labelled and defined in Cochrane reviews.
- Variable definitions and unclear key characteristics challenge their identification and classification as well as distinction from other study designs.
- We detail and explain CBA and ITS study characteristics and propose steps towards a consensus process to define key characteristics of these two study designs

1. Introduction

One key element of evidence-informed healthcare and public health is that treatment and policy decisions are informed by the best available scientific evidence [1]. Decisions are ideally guided by well-conducted systematic reviews that gather evidence from well-conducted primary studies to assess whether an intervention is more effective and preferably also less costly than another intervention.

Interventions in the field of public health, health services, health systems and health policy tend to be more difficult to evaluate than clinical interventions [2-4]. In these fields especially, it may not be possible to conduct randomised controlled trials (RCTs) for reasons of feasibility (e.g. interventions to reduce ambient air pollution [5]), ethical considerations (e.g. home-based palliative care [6]) or lack of political will [7]. Consequently, assessments of effectiveness in such cases often have to rely on nonrandomised studies [8, 9]. Among these, interrupted time series (ITS) and controlled before-after (CBA) studies are the study designs most commonly included in Cochrane reviews [10].

A CBA study is defined in the Cochrane Handbook as a study in which observations are made before and after the implementation of an intervention, both in a group that receives the intervention and in a control group that does not [11]. The Cochrane Effective Practice and Organisation of Care (EPOC) Group, based on a long experience in considering nonrandomised studies, has developed criteria for inclusion of CBA studies in systematic reviews, to ensure a minimum level of methodological rigour [12]. They recommend at least two intervention sites and two control sites [12], as well as contemporaneous data collection [13].

While the methodological literature on CBA studies is limited, there is disagreement as to whether a key characteristic of a CBA study is that the investigator has no control over the intervention allocation [11, 12, 14, 15]. Incoherent use of terminology leads to a lack of differentiation between features of CBA studies and other study designs, such as nonrandomised controlled trials (NRCTS) [8, 10, 15, 16].

An ITS study is defined in the Cochrane Handbook as a study that uses observations at multiple time points before and after an intervention (the 'interruption'). The design attempts to detect whether the intervention has had an effect significantly greater than any underlying trend over time [11, 12]. The study is frequently conducted retrospectively using routine data [17, 18] and usually, there is no investigator control over the allocation of the intervention [11, 12]. Cochrane EPOC specify minimum criteria that ITS studies must use at least three data points before and three after the intervention, and clearly define the point in time when the intervention occurred [12].

Several papers have examined the use of ITS studies in health research with respect to methodological aspects [16, 19-24]. It was noteworthy that ITS studies applied inappropriate methods for statistical analysis, which led to the frequent judgment of statistically non-significant effects as significant [19].

Clarity about CBA and ITS studies in terms of design, data collection and data analysis would be helpful for researchers wishing to conduct a CBA or ITS study and facilitate a common terminology. Likewise, improved knowledge and transparency about these study designs would make it easier to search for and include these study designs in systematic reviews [25]. Ultimately, decision makers will have more certainty to recommend for or against an intervention based on studies that generate valid findings [26].

The objective of this study was therefore to examine the application, design and analysis characteristics of CBA and ITS studies included in Cochrane reviews. We based our analysis on the Cochrane database because it is a generally accepted point of reference for evidence-informed decision-making in health and because it applies relatively homogenous standards in terms of study design terminology.

Primary question:

What are the characteristics of CBA and ITS studies included in Cochrane reviews in terms of design, conduct and analysis?

Secondary questions:

Which types of interventions are assessed by Cochrane reviews that consider and identify CBA and ITS studies? How are CBA and ITS studies defined by review authors? How are CBA and ITS studies (as defined by Cochrane authors) defined and labelled by primary study authors?

2. Methods

2.1. Identification and analysis of systematic reviews including CBA and ITS studies

Ijaz et al. (2014) documented the use of CBA and ITS studies as well as other nonrandomised studies in Cochrane reviews up to May 2012 [10]. As we expected the conduct of CBA and ITS studies in primary research as well as their inclusion in systematic reviews to have increased in recent years we updated the search by Ijaz et al (2014) replicating their methods. An a priori protocol of our study is available online. Our search sought to identify reviews published between May 2012 and March 2015, whose authors explicitly used the terms “controlled before-after” or CBA and “interrupted time series” or ITS studies (i.e. merely “before-after studies” or “time series” were excluded).

For all reviews including nonrandomised studies, one author (SP) extracted information with cross-checks performed by two further authors (EAR and DP). Information was extracted on (i) type of study designs included and number of studies identified for each type; (ii) responsible Cochrane Group; (iii) definition of CBA and/or ITS study by review authors; (iv) risk of bias/quality appraisal tool and assessment used by review authors (v) level of intervention (i.e. population, organisational and individual level) and (vi) type of health intervention. While descriptions and definitions are often used interchangeably, reviews may state criteria without a clear notion of the features of the study design they refer to. This is why we also specifically examined whether reviews provided definitions.

We pre-specified and defined ten intervention types. We based this on a previous publication, where we had made a first pragmatic attempt towards a classification of public health interventions [4]. These included behavioural/educational, clinical, environmental, health policy, health system, nutrition, occupational, pharmaceutical, screening, and vaccination interventions (see Appendix A for definitions). We examined the labelling and descriptions of CBA and ITS studies as well as their applications to different intervention types across the included reviews.

2.2. Selection and analysis of CBA and ITS studies

As we were interested in obtaining insights regarding the use of CBA and ITS studies across different areas of health, we purposively selected two reviews per intervention type from those reviews that

had included at least two CBA or two ITS studies. A minimum of two studies was considered important to ensure a reasonable applicability of the study designs to a given intervention type and a minimum degree of representativeness in study conduct. For those intervention types, where we had to choose among several options (e.g. health systems), we chose reviews from different Cochrane groups and assessing different interventions. For each selected systematic review, we randomly selected two studies, using an online random choice generator [27]. We undertook the selection process separately for CBA and ITS studies.

For the selected CBA and ITS studies two authors (SP, JB, AF, DP, TM, CR, JPTH, EAR, LMP) independently extracted information onto a data extraction form that was specifically developed for the purposes of this study and pre-tested in five studies. The data extraction form considered (i) publication characteristics (i.e. year of publication, journal, country of study, language of study, funding source, terminology/labelling and definitions); (ii) application characteristics (i.e. study objective, population, intervention, comparison and outcome, type of intervention, level of intervention); and (iii) methodological characteristics covering study design (e.g. setting, control, allocation, temporal design), data collection (e.g. number of measurements, outcome assessments, source of data, timing) and data analysis (e.g. statistical methods, unit of analysis) and reported strengths and weaknesses of study design. Results were compared to achieve consensus, and uncertainties and discrepancies were extensively discussed, if necessary with the whole author team.

Using the extracted data across studies, we assembled information on how CBA and ITS studies were defined by primary study authors and, comparing design and analysis features, attempted to define key characteristics of both study designs.

3. Results

3.1 Identification and analysis of systematic reviews

For the period May 2012 to March 2015 we found 136 Cochrane reviews (4.8% of a total of 2861 Cochrane reviews published in this time period) that considered nonrandomised studies for inclusion (Supplemental Table 1). The 136 reviews included a total of 1956 studies; the most prevalent study designs according to the labels employed by review authors are listed in Table 1. 19 reviews identified no studies for inclusion.

Table 1. Study designs among the 1956 studies included in Cochrane reviews that considered nonrandomised studies according to the labels employed by review authors (May 2012 - March 2015)

Label	Number (percentage)
RCTs	597 (31%)
cohort studies	166 (9%)
CBA	168 (9%)
ITS	143 (7%)
cross-sectional studies	109 (6%)
controlled clinical trials (CCT)	91 (5%)
uncontrolled before-after studies	76 (4%)
observational studies	75 (4%)
Cluster RCT	65 (3%)
Case control	60 (3%)
Retrospective cohort studies	55 (3%)
NRCT	42 (2%)

Prospective controlled cohort studies	26 (1%)
Prospective cohort studies	25 (1%)

Sixty-nine of the reviews explicitly considered CBA and ITS studies for inclusion (see Appendix B for a complete reference list). Among these, 18 reviews identified at least two CBA studies (range: 2-30 CBA studies) and 16 reviews identified at least two ITS studies (range: 2-52 ITS studies). Altogether, twelve reviews identified both CBA and ITS studies. Additionally, five and three reviews identified only one CBA and ITS study, respectively.

3.1.1. Which types of interventions are assessed by Cochrane reviews that consider and identify CBA and ITS studies?

In our sample of 69 reviews, CBA and ITS studies were most widely considered in reviews of health system interventions (n=36), followed by reviews of behavioural (n=8), environmental (n=6), occupational (n=5), clinical (n=5), and health policy (n=4) interventions. They were rarely, or not at all considered in reviews of vaccination, screening, pharmaceutical or nutrition interventions. Among the reviews considering CBA and ITS studies, twelve were targeting the population, 43 the organisational and 14 the individual level. Tables 2 and 3 show how CBA and ITS studies have recently been applied in reviews that actually identified these study designs, suggesting that both study designs are most frequent in reviews of health system interventions directed at an organisational level. We included CBA and ITS studies that derived from the same reviews [28, 29].

Table 2. Characteristics of reviews including CBA studies according to intervention type, level, responsible Cochrane Group and number of studies identified (May 2012 – March 2015)

Intervention type (number of reviews)	Cochrane Group* (number of reviews)	Population level	Organisational level	Individual level	Number of CBA studies
Health systems (11)	EPOC (6) Injuries (1) OSH (3) PH (1)		11		42
Behavioural (3)	Injuries (1) DA (1) PH (1	2	1		32
Health policy (1)	OSH (1)		1		3
Environmental (2)	PH (1) ARI (1)	1	1		13
Occupational (2)	Injuries (1) OSH (1)		2		20
Clinical (1)	PAPAS (1)			1	2
Nutrition (1)	DPLP (1)			1	11
Screening (1)	PAPAS (1)		1		2
Pharmaceutical, Vaccination (0)	-				-

* ARI = Acute Respiratory Infections, DA = Drugs and Alcohol, DPLP = Developmental, Psychosocial and Learning Problems, EPOC = Effective Practice and Organisation of Care, OSH = Occupational Safety and Health, PH = Public Health, PAPAS = Pain, Palliative and Supportive Care.

Table 3. Characteristics of reviews including ITS studies in terms of intervention type, level, responsible Cochrane Group and number of studies identified (May 2012 – March 2015)

Intervention type (number of reviews)	Cochrane Group* (number of reviews	Population level	Organisational level	Individual level	Number of ITS studies
Health systems (10)	EPOC (8) OSH (1) PH (1)		10		93
Behavioural (3)	DA (1) EPOC (1) TA (1)	3			32
Health policy (4)	DA (1) EPOC (1) OSH (1) PH (1)	2	2		23
Occupational (2)	Injuries (1) OSH (1)		2		14
Clinical, environmental, nutrition, pharmaceutical, screening, vaccination (0)	-	-	-	-	-

* ARI = Acute Respiratory Infections, DA = Drugs and Alcohol, DPLP = Developmental, Psychosocial and Learning Problems, EPOC = Effective Practice and Organisation of Care, OSH = Occupational Safety and Health, PH = Public Health, PAPAS = Pain, Palliative and Supportive Care, TA = Tobacco Addiction.

3.1.2. How are CBA and ITS studies defined by review authors?

About a third of the 69 reviews considering both CBA and ITS studies reported the EPOC criteria of two intervention and two control sites (43%) for CBA studies and three data points before and three after intervention and a clearly defined intervention time point (36%), respectively, for ITS studies (Fig. 1). For CBA studies, many also referred to 'contemporaneous data collection' and/or 'an appropriate choice of control'; the need for 'same time periods before and after the intervention' was also specified repeatedly. For ITS studies, 25% of reviews described one of the two EPOC criteria, mostly omitting a clearly defined intervention time point. Less than a tenth of all reviews (4% for CBA and 7% for ITS studies) referred to EPOC criteria for CBA or ITS studies without stating them.

Among the seven reviews that provide specific definitions for CBA studies, two reported the Cochrane Handbook definition [11] together with the EPOC criteria [30, 31], another two referred to "prospective cohort studies" [32, 33]. Four of the five reviews that provided definitions for ITS studies reported them together with the EPOC criteria. Two reviews explicitly referred to the Cochrane Handbook definition for ITS studies [30, 31].

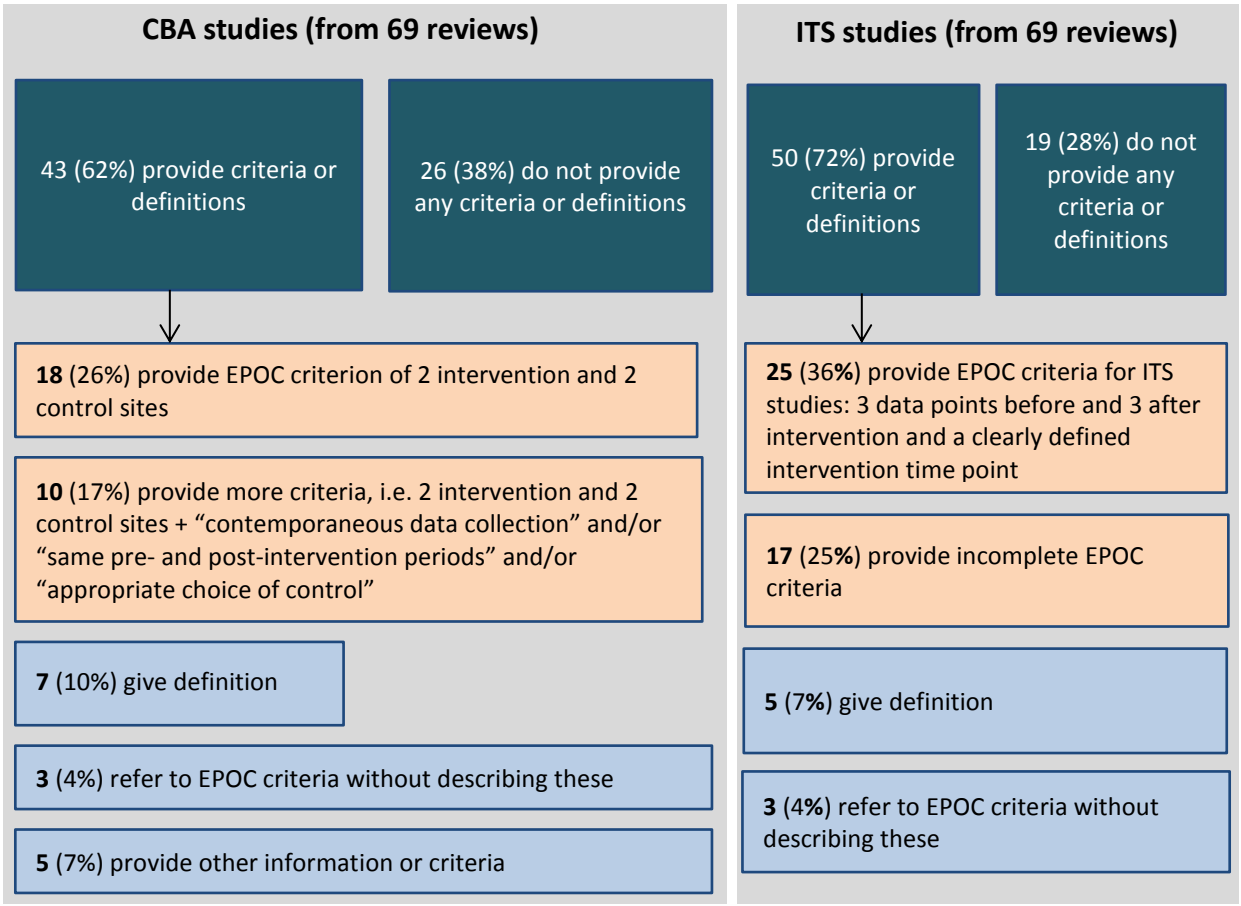

Figure 1. Criteria for CBA and ITS studies as used in Cochrane reviews

3.2. Selection and analysis of primary studies

For the analysis of CBA studies we purposively selected eleven reviews, covering two reviews each for behavioural, environmental, health policy and health system interventions and one review each for nutrition, occupational, and screening interventions. Among the 22 CBA studies we randomly selected from these reviews, one study (from the screening review) was excluded post selection due to an initial misclassification (i.e. it was identified as a CBA study at abstract level but the review authors labelled the study in the risk of bias assessment as a CCT) [34]. For the analysis of ITS studies, we selected eight reviews, two each concerned with behavioural, health policy, health system and occupational interventions. Random selection of two studies from each review yielded 16 ITS studies.

3.2.1. How are CBA and ITS studies labelled or defined by primary study authors?

Primary study authors did not label any study "CBA". The descriptions of CBA labels shown in Table 4 were often mentioned in combination with "before and after the intervention". Primary study authors labelled their study as an "ITS" in only one study. All other studies used various descriptions with "time series" mentioned most often in combination with "analysis" or "design". None of the included studies gave a definition of the study design.

Table 4. Labels of CBA and ITS studies in primary studies

CBA labels	ITS labels
"quasi-experimental" (n=5)	"time series analysis/design" (n=5)
"survey" (n=4)	"observational" (n=3)
"comparative study" (n=3)	"analysis" (n=3)
"observational" (n=2)	"difference-in-difference" (n=2)
"cross-sectional" (n=2)	"retrospective" (n=2)
"natural experimental" (n=2)	"surveys" (n=1)
"case-control" (n=1)	"interrupted time series" (n=1)
"prospective cohort" (n=1)	"natural experimental research" (n=1)
"difference-in-difference" (n=1)	

3.2.2. What are the characteristics of CBA and ITS studies included in Cochrane reviews in terms of design, conduct and analysis?

CBA studies

Among the 21 selected CBA studies, five were not CBA studies according to the Cochrane definition (Fig. 2) because they lacked control sites [35, 36] or measurements before the intervention [37-39]; in one study hospital units were randomised into control and intervention group and we therefore classified it as a cluster-RCT [40]. Of the 16 actual CBA studies, nine fulfilled the EPOC criteria (i.e. two intervention and two control sites, contemporaneous data collection). Compared to the Cochrane Handbook, Cochrane EPOC provides a more specific definition of a CBA study where the investigators do not have control over the intervention allocation. If we adopt this more specific definition, of the selected 16 CBA studies, six complied with both the EPOC definition and criteria.

Table 5 presents a selection of further study design and analysis characteristics (see Supplemental Table 2 for an extended version). There was approximately equal use of CBA studies undertaken in a prospective or retrospective manner. We defined retrospective as a study, in which outcome data collected prior to the study period are used. In contrast, prospective studies collect outcome data during the study period. Defining studies as retrospective or prospective was, however, quite challenging [8] and judgments may vary. For about half of the selected studies, allocation of the intervention was not controlled by the investigators. The median number of sites among studies classified as EPOC CBA studies according to design was 7.5 (range: 3-748) for intervention and 5 (range: 3-8301) for control sites. In some cases the definition of "sites" was unclear and appeared to be synonymous with individuals (e.g. [41]). Study authors used a variety of mostly inappropriate or inefficient statistical analysis methods. Many studies applied simple statistical analysis methods, such as simple t-tests and did not take clustering into account, leading to unit of analysis errors and imprecision of confidence intervals. Studies performed, for example, a simple before and after comparison in the intervention group only or compared post-means of individually aggregated data into intervention and control group.

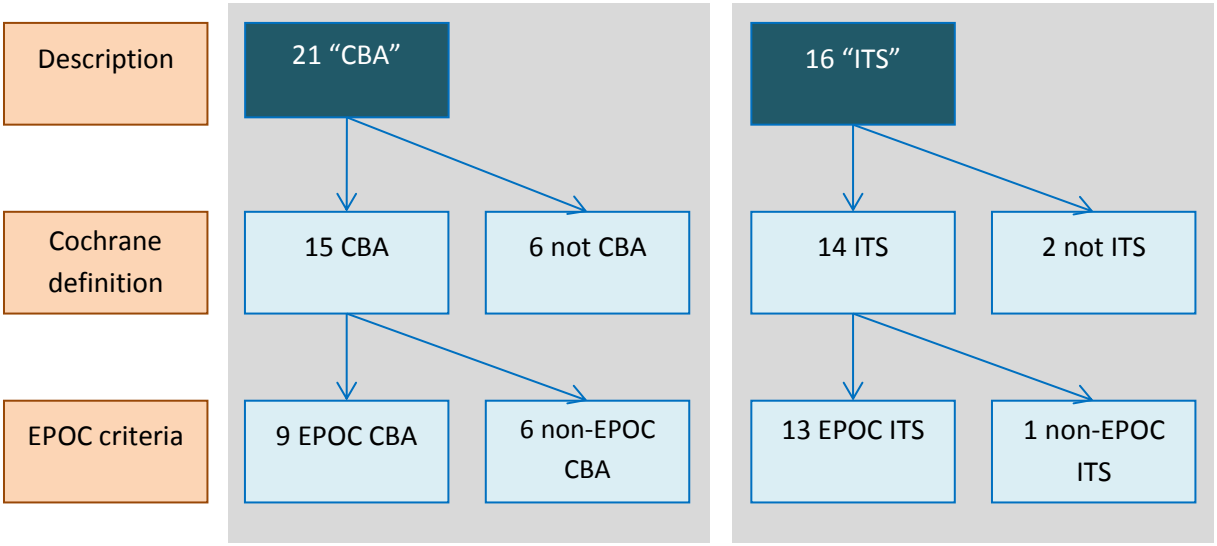

Figure 2. EPOC criteria assessment for CBA and ITS studies

ITS studies

Of the 16 selected ITS studies, two did not meet the Cochrane definition, as they did not include any data before the intervention [42, 43] (Fig. 2). Of the 14 actual ITS studies, one did not comply with the EPOC criteria (i.e. at least three data points before and after the interruption and a clearly defined intervention time point), due to an insufficient number of data points before the intervention. Of the 13 ITS studies complying with EPOC design criteria, five did not perform a statistical analysis and merely displayed the results graphically or reported means before and after the intervention. We identified one study, where the intervention was under control of the investigators [44]. This study was, however, different in many ways, as the review authors lumped together several "meth studies" [35, 44] and included them as a single ITS study [28].

As shown in Table 6 (see Supplemental Table 3 for an extended version), one study applied autoregressive integrated moving average (ARIMA) and at least two studies applied segmented regression analysis, although bad reporting impeded a clear identification. A majority of studies conducted some form of regression analysis and some adjusted or tested for auto-correlation (n=6) and/or reported to adjust for secular trend (n=6). Eight ITS studies [43, 45-52] from five reviews were re-analysed by review authors as recommended by EPOC in case of an inappropriate analysis. For ITS studies adhering to EPOC design criteria the median number of data points was 12 (range: 3-46) before and 12 (range: 3-86) after the intervention. Three studies had a control group and we therefore classified them as controlled ITS studies [52-54]. All studies were conducted retrospectively.

Table 5 CBA study characteristics

Study ID				Study conduct				
	Intervention assessed	Contemp. data collection	Appropriate control	Temporality	Intervention allocation outside of researcher control	No. of int. sites	No. of control sites	Unit of allocation
Georgia Meth 2011	Awareness campaign against drug use	Na	Na	Retr.	Yes	1	0	State
Miller 2000	Alcohol and Drug Abuse Prevention Program	Probably yes	Probably no	Prosp.	No	1	1	School
Pasco 2012	Gatekeeper training program for suicide prevention	Unclear	Probably no	Prosp.	No	1	0	Individual
Tompkins 2009	Gatekeeper training program on suicide prevention	Probably no	Probably yes	Prosp.	No	2 or 3 (unclear)	3	School
Butala 2010	Slum upgrading intervention	Probably yes	Probably yes	Retr.	Yes	14	NR	Community
Taylor 1987	Shelter upgrading for the urban poor	Probably yes	Probably no	Retr	Yes	NR but likely >2	NR but likely >2	Community
Meklin 2005b	Moisture and mould renovations	No	No	Prosp.	No	2	2	School
Shortt 2007	Housing intervention (energy efficiency measures)	Unclear	No	Prosp.	No	54	46	Household
Levine 2012	Safety inspections in hospital on injuries and job loss	Unclear	Unclear	Retr	Yes	409	409	Company
Nelson 1997	Inspections and citation for violating fall prevention rules	Yes	Unclear	Retr	Yes	784	8301	Company
Tucker 2006	Classroom sexual health education and drop-in clinics	Yes	Probably yes	Prosp.	Yes	10	5	School
Hultberg 2005	Co-financed collaboration model of primary care	Probably yes	Probably yes	Prosp.	Yes	3	4	Other: city area
Kaushal 2008	Unit-based clinical pharmacists to reduce medication errors	Yes	Probably yes	Prosp.	No	3	3	Hospital unit
Morriss 2009	A barcode scanning system for	Probably yes	Probably yes	Prosp.	No	1	1	NICU section

	administrating medication							
Coyne 1980	Preschool meals at schools (food programme)	Yes	Probably yes	Prosp.	Yes	5	5	Community
Santos 2005	Food supplementation programme (Milk Program)	Yes	Probably yes	Prosp.	Yes	10	10	Community
Maizlish 1995	Targeted and active surveillance model for health care providers	Unclear	Unclear	Prosp.	Yes	10	NR	Hospital
Smits 2008	In-company workshop on the reporting of occupational diseases	Probably yes	Probably yes	Prosp.	No	NR but likely > 2	NR but likely > 2	Individual
Meyer 1993	Detailed follow-up (DFU) audiometric examinations on air force employees	Na	Na	Retr	Yes	1	1 (same)	Patient
Nilsson 1980	Employees wearing ear muffs	Na	Na	Retr	Yes	1	1 (same)	Individual
Jordan 2003	Application of the nursing nutritional screening tool	Yes	Probably yes	Prosp.	No	1	1	Hospital unit

Abbreviations: retr.=retrospective, prosp.=prospective, NR=not reported, Na=not applicable

Table 6 ITS study characteristics

Study ID		Study conduct					Study analysis according to primary study authors	
	Intervention assessed	Clear intervention time point	Data points before	Data points after	Time period data point	Control group	Analysis characteristics included	Reported analysis method
Grootendorst 2005	Reference pricing of nonsteroidal anti-inflammatory drugs	Yes	13 (for intervention #231)	86 (for int. #268)	Monthly	No	Trend, autocor-relation	Linear regression
Puig 2007	Reference pricing for generics	Yes (but differing between sites & drugs)	16 (varies depending on site & drug)	30(varies depending on site & drug)	Monthly	No	Trend, autocorr-elation	Generalised Least-Squares regression
Smart 1976	Ban on alcohol advertisements	Yes	> 12	>12	Monthly	Yes	Trend	Calculation of geometric mean consumption, t-test for comparison
Makowksy 1991	Lifting of an advertising ban on alcohol	Yes	32	46	Monthly	Yes	Trend, autocor-relation	ARIMA (Box and Jenkins method)
Khan 2003	Change in antibiotic policy and use of antibiotics	Yes (diff. time points for 2 separate interv.)	6 (1st intervention)	12 (1st intervention)	Quarterly	No	-	No statistical analysis
Mercer 1999	Antibiotic control policy	Yes	12	12	Monthly	No	-	No statistical analysis
Goldwater 1989	Introduction of recapping device for needles	Yes	9	36	Monthly	No	-	No statistical analysis
Sossai 2010	Sharps awareness campaign and needlestick prevention devices	Yes (year)	0	5	Yearly	No	-	No statistical analysis
Carpenter 2011	Anti-drug media campaign	Yes	0	3	Na	No		Multivariate logistic regression of post-intervention time
Idaho Meth 2011	Messaging campaign on drug use	Yes	1	3	Yearly	No	-	No statistical analysis
Jackevicius 2001	Publication of scientific evidence on medical practice	Yes	32	28	Monthly	No	Trend, autocor-relation	Segmented regression analysis, linear regression
Lam 2009	Publishing of large RCT about statins in nephrology	Yes	33	7	Other	No	Autocor-relation	Linear regression to estimate annual increase in statin use and subsequent F-test to assess slope difference
Beal 2007	Regulation on architectural design for construction sites	Yes	14	10	Yearly	No	-	No statistical analysis
Lipscomb 2003	Washington State fall standard for the construction industry	Yes	8	31	Quarterly	No	Trend	Poisson regression
Joy 2007	Permissible exposure level (PEL) for noise exposure in coal mining	Yes	12	5	Yearly	No	-	Linear regression
Rabinowitz 2011	Mandatory hearing protection programme	Yes (year)	5	4	Yearly	Yes	-	Difference-in differences analysis based on individual-specific regression coefficients before and after the intervention

4. Discussion

4.1. Key findings

In relation to our primary research question, we found a heterogeneous set of different study designs under the label 'CBA' and 'ITS' studies. Not all studies fitted the Cochrane definition of a CBA and ITS study. We found, for example, CBA studies without control sites as well as ITS studies without an intervention ('the interruption') included in Cochrane reviews. Some CBA studies did not comply with the EPOC criteria, e.g. because of an insufficient number of intervention and control sites; one ITS study had insufficient data points. Researchers were involved in the intervention allocation in almost half of all included CBA studies. According to EPOC-guidance, such studies should be classified as NRCTs. It is also noteworthy that there is a stark discrepancy between methods employed for data collection versus data analysis, where researchers often do not fully exploit the strength of the collected data in their analysis. Bad reporting, however, often precluded clear identification of the analysis methods.

In relation to our secondary research questions, most Cochrane reviews that included CBA and ITS studies were concerned with interventions on an organisational level; few addressed interventions on a population level and, as expected, very few took place on an individual level. We did not find many reviews of typical public health interventions, for example environmental, vaccination or screening interventions, which would lend themselves to the use of CBA and ITS studies.

There are striking differences among Cochrane reviews with respect to labelling and defining CBA and ITS studies. One third of the included reviews did not provide any criteria for the study designs. These findings were all the more surprising, given that our sample was drawn from the relatively homogeneous and strongly methodologically influenced Cochrane community. Our analysis thus confirms that the inconsistent use of terminology leads to confusion among systematic reviewers regarding what can be classified as an ITS or CBA study [8, 21, 71, 72].

On the primary study level the labels "CBA" and "ITS" appear infrequently; instead a large variety of terms is used. This suggests that CBA and ITS study labels and the study design characteristics associated with them are hardly used or known among primary study authors.

4.2. Towards clearer CBA and ITS study definitions and criteria

Considering the challenges we faced trying to categorize the CBA and ITS studies included in this analysis and considering the limited use of the study design labels in primary research, we explain in detail study characteristics and potentially problematic features.

This discussion is intended to help review authors identify these study designs in the screening process; from our experience the definitions and criteria provided by Cochrane and Cochrane EPOC, while helpful, still leave much space for interpretation, a lack of clarity that is partially responsible for the heterogeneous findings of this study and previous studies [10, 15, 16, 19, 20]. This discussion is also intended to offer input towards consensual definitions and features of these study designs, which would eventually be helpful for both review authors and primary researchers.

4.2.1. CBA studies

Key characteristics

According to EPOC and with some additional elaboration, a high quality CBA study (i) uses at least two intervention and two appropriate control sites, and (ii) employs contemporaneous data collection, whether carried out specifically for this purpose or using existing datasets, at relevant pre- and post-intervention time points at all sites. CBA studies may be prospective or retrospective in nature. The intervention effects can be analysed at cluster or individual level but the analysis should compare the difference in pre-post changes between intervention and control groups.

Explanations

Using two intervention and two control sites may be advantageous because study validity increases with more sites being used. With only one site per group, any difference in observed effect between the intervention and control group may simply be due to underlying differences in the characteristics of the two sites, where these characteristics may be measured, known but not measured or unknown. In circumstances, when more than two levels are involved, e.g. individuals or classes nested within schools and cities, it may be challenging to decide what constitutes the site [73]. Furthermore, should sites be actual locations (e.g. villages, schools) or can other clusters or groups of people (e.g. family members in a household or employees in a given company) form a site? This may, however, be irrelevant as long as the analysis takes the groups into account. The sites should have similar baseline characteristics, by choice or through matching; in case of baseline differences, an appropriate method of statistical adjustment should be applied.

Whereas Cochrane EPOC [12] and Hartling et al. [15] acknowledge CBA studies as natural experiments, in the Cochrane handbook investigator control to some extent is not ruled out [11]. Deeks et al. [14] suggest that a CBA "can also be considered an experimental design if the investigator has control over, or can deliberately manipulate the introduction of the intervention".

The analysis should take into account the presence of a control group. A simple t-test comparing post changes between the groups may not suffice to show an intervention effect, particularly where baseline differences between the groups exist. The analysis should adjust for potential clustering effects where unit of observation and unit of analysis differ. More advanced methods, such as difference-in-differences analysis, adjusting for differences between the different sites, may better reflect the design. Such analysis methods have been widely applied in other disciplines, such as economics [74], and it would be beneficial to take on board lessons learnt.

Differences and similarities in relation to other study designs

CBA studies partially overlap with other study designs with implications for how these studies are searched for, described and appraised as well as synthesised in systematic reviews. The main difficulty lies in differentiating between cluster-NRCTs and CBA studies. One possibility is to use active intervention allocation by the investigator as the distinguishing feature between cluster-NRCTs (present) and CBA studies (absent; natural experiment); this approach has been adopted by Cochrane EPOC [12]. There are, however, cases where such a differentiation is difficult due to poor reporting and various interpretations of what to consider a natural experiment. Interestingly,

Shadish, Cook and Campbell [75] do not distinguish between specific study design labels when describing "quasi-experimental designs that use both control groups and pretests". Acknowledging CBA studies and cluster-NRCTs as part of a broader study design group without the necessity to identify the design more specifically may be another way forward. Differences in study design features could thus be articulated as part of the risk of bias assessment rather than as part of the study classification.

4.1.1. ITS studies

Key characteristics

ITS studies are usually designed as natural experiments. They may be prospective or retrospective in nature and may include a control group (controlled ITS) [8, 15, 22]. As mentioned by Cochrane EPOC ITS studies should (i) use at least three data points before and three after the intervention, and (ii) clearly define the point in time, when the intervention occurred. An appropriate statistical analysis includes adjustment for secular trend.

Explanations

Although ITS studies are usually defined as natural experiments [12, 15], ITS studies can be used to assess interventions allocated by the investigators [76]. The EPOC threshold of three data points before and after the intervention is based on the reasoning that drawing a line through any fewer than three data points would estimate trend in a very unreliable way. Indeed, several recent studies suggest that sufficient statistical power is only achieved when at least eight data points are included; even more may be required when using ARIMA or segmented regression analysis [22, 24, 77]. Generally speaking, the precision of ITS studies increases with the number of data points. An unequivocal distinction between pre- and post-intervention and implementation time periods is critical; this also refers to multiple interventions implemented sequentially or staggered implementation of a given intervention in different groups, institutions or geographical areas [22]. Adding a control group further enhances the study's validity and minimizes risk of bias [78]: Whereas an ITS study compares the post-intervention trend with a counterfactual (i.e. the prediction of what would have happened in case the intervention had not taken place estimated from pre-intervention trends), a controlled ITS study compares pre- and post-intervention time trends between an intervention and control group. Visualisation of data can help the reader interpret the study results [22, 23, 79] but can also be misleading and should therefore not be used routinely as a means of identifying or measuring an effect [80].

The discrepancies between data collection and analysis in the included ITS studies highlight the importance of a statistical analysis that adjusts for secular trend [17, 19, 22, 24]. ARIMA or segmented regression models, which recognise secular trend as well as auto-correlation, are considered highly appropriate for analysing ITS data [19, 24, 79, 81]; other regression analyses may also be appropriate. Studies whose statistical analysis does not explicitly acknowledge secular trend (e.g. comparison of pre- and post- intervention means) or that merely display results graphically in fact miss the most important strength of the ITS design. EPOC allows ITS studies with inappropriate analysis to be included in systematic reviews, provided the data are re-analysed. This relies, however, partly on primary study authors providing their original data and is a time-consuming and resource-intensive process.

Differences and similarities in relation to other study designs

ITS studies are sometimes interchangeably listed as 'time series'. However, a time series merely investigates an ordered sequence of values of a variable at equally spaced time intervals [82], whereas an ITS study is characterised by an interruption. ITS studies are also closely related to repeated measures studies, where measurements are made in the same individuals at each time point [12]. A further related study design is the regression discontinuity (RD) design, where different temporal occasions can be assigned to different treatment conditions [83].

Especially with respect to controlled ITS studies, it may be hard for systematic reviewers to label these as an ITS study versus a CBA study. As mentioned above, the essential feature of an ITS study is the statistical analysis, which must reflect multiple measurements over time and adjust for important secular trends. If this is not the case, a controlled ITS, with multiple measurements before and after the intervention, may be considered a CBA study.

4.3. Strengths and weaknesses of this study

We analysed a sample of CBA and ITS studies included in recent Cochrane reviews with respect to application and specific methodological characteristics. The sample was intended to be somewhat representative of the pre-specified types of interventions. Representativeness of findings is, however, limited, as we only selected two reviews per intervention type (where available) and two included studies from the selected reviews.

At the primary study level, data extraction was done in duplicate and difficulties were extensively discussed among the data extractors and, where necessary, with the whole author team. As we did not re-analyse the studies, our insights reflect CBA and ITS studies as originally conducted, analysed and reported rather than according to their potential. In fact, we did not contact study authors for missing study details. Finally, the generalizability of our findings is probably limited to Cochrane reviews; we would expect to find even more variation in methodological characteristics of CBA and ITS studies outside of Cochrane.

4.4. Recommendations for research and practice

CBA and ITS studies are increasingly being recognised as important study designs that, if conducted and analysed well, can provide reliable effect estimates of the impacts of interventions, where randomisation is not feasible. Importantly, there is a need to further the understanding of the definitions and key characteristics of these study designs among primary researchers and systematic reviewers, including through textbooks of epidemiology and epidemiological curricula and beyond the field of epidemiology. Recently published research provides the first detailed guidance on how to conduct ITS studies [84]. However, CBA studies in particular almost appear to be "artificial study designs", with the label created by systematic reviewers but little used in the primary research world. More specific definitions and key characteristics would be beneficial for systematic review authors in and outside of Cochrane to facilitate greater clarity with respect to including or excluding study designs. Further discussions should clarify when to include a CBA or ITS study according to EPOC criteria and when to include a study not meeting EPOC criteria but downgrade for risk of bias. This would minimise confusion and improve consistency within Cochrane and beyond.

While we have summarized and explained important features and characteristics of CBA and ITS studies and initiated a discussion about key characteristics, key study design and analysis

characteristics should be clarified and their definitions updated through a consensus process, such as a Delphi procedure. There are direct implications for risk of bias assessment for these study designs that will be developed as the ROBINS-I tool [85] is advanced for different study designs. The development of a new reporting guideline, for example, an extension of the Transparent Reporting of Evaluations with Nonrandomized Designs (TREND) statement [86] could be an important second step. Taken together, this could greatly advance methodological practice at primary study as well as systematic review level and ensure that CBA and ITS studies are put to the best use possible in evaluating the impacts of interventions.

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