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Poor reporting quality and high proportion of missing data in economic evaluations alongside pragmatic trials: a cross-sectional survey

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Abstract

Background Lack of data integrity is a common problem in randomized clinical trials and is more serious in economic evaluations conducted alongside explanatory clinical trials. Despite pragmatic randomized controlled trials (pRCTs) becoming recognized as the best design for economic evaluations, information on the proportion, handling approaches, and reporting quality of missing data in pRCTs-based economic evaluations remains limited. This study aimed to investigate the quantity and reporting quality of missing data in economic evaluations conducted alongside pragmatic clinical trials.

Methods In this cross-sectional survey, data were extracted from PubMed and OVID (Embase, CENTRAL, HTA database, and NHS EED) from January 1, 2010, to April 24, 2022. Economic evaluations conducted alongside pRCTs were included. Two independent reviewer groups identified relevant articles, and data were extracted by three groups comprising two reviewers each. Descriptive analyses were performed to assess the characteristics of the included studies, missingness in the included studies, and handling of missing data.

Results Overall, 715 studies were identified, of which 152 met the inclusion criteria. In total, 113, 119, and 132 articles reported missing data, costs, and effects, respectively. More than 50% (58/113) of the articles reported the proportion or quantity of overall missingness, and 64.71% and 54.55% reported missing costs and effects, respectively. The proportion of missingness of < 5% in the overall group was 3.45%, whereas the proportions of missing costs and effects were both < 10% (5.26% vs. 8.45%, respectively). In terms of the proportion of missing data, the overall missingness rate was 30.22% in 58 studies, whereas the median proportion of missing data was slightly higher than that of missing effects (30.92% vs. 27.78%). Of the included studies, 56 (36.84%) conducted a sensitivity analysis on handling missing data. Of these, 12.50% reported missing mechanisms, and 83.93% examined handling methods.

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Conclusions Insufficient description and reporting of missing data, along with a high proportion of missing data in pRCT-based economic evaluations, could decrease the reliability and extrapolation of conclusions, leading to misleading decision-making.

Keywords Economic evaluations, Pragmatic trials, Missing data, Cross-sectional survey

Background

Missing data, which may lead to selection and information biases and jeopardize the validity, generalizability, and precision of study results, is one of the most frequent problems in clinical trials [1–3]. In trial-based economic evaluations, the rate of data integrity in economic outcomes may be much lower than that in clinical outcomes. As previous trial-based economic evaluations have shown, randomized clinical trials may have data on 80–95% of complete cases of clinical outcomes [4–7], whereas only 50–80% of randomized participants have complete economic data [8–11]. The following reasons could explain why a high proportion of missing values occurs in trial-based economic evaluations. First, economic evaluations tend to collect rich, longitudinal information from individuals, such as their use of healthcare services and health-related quality of life, which usually consists of multiple questions to calculate total cost and health utility [12, 13]. If one component question is missing, the total cost and health utility are also absent [14]. Therefore, missingness is more likely to occur in economic data. Second, economic variables may be considered less important by the researchers responsible for data collection, which could trigger higher rates of missingness [15].

Normally, randomized controlled trials (RCTs) are divided into explanatory and pragmatic. Explanatory RCTs (eRCTs) aim to compare the efficacy of interventions under rigorous conditions, while pragmatic RCTs (pRCTs) focus on assessing the effectiveness of interventions in routine clinical practice. Hence, pRCTs can have high external validity and offer more relevant and applicable evidence to healthcare decision-making than eRCTs [16, 17]. The characteristic features of pRCTs include (1) selecting clinically relevant alternative interventions for comparison, (2) recruiting participants from heterogeneous practice settings, and (3) collecting data on a broad range of health outcomes, including patient-reported, global, and subjective outcomes [17, 18]. Thus, well-conducted pRCT-based economic evaluations are more likely to generalize the results to an extended clinical setting and inform health-related decision-making. As the International Society for Pharmacoeconomics and Outcomes Research proposes, pragmatic effectiveness trials are the best vehicles for economic studies [17]. However, one of the inevitable limitations of pragmatic design is that increasing non-adherence to the trial protocol, and even the use of electronic health records results in inconsistent data collection and missing data [17–19]. Missing data may seriously compromise the credibility of causal inferences from pRCTs [20].

Although several previous studies have revealed that missing data are common in traditional trial-based economic evaluations, and the reporting quality is poor [12, 21, 22], information on the proportion, handling approaches, and reporting quality of missing data in pRCT-based economic evaluations remains limited. Therefore, the aim of this cross-sectional analysis was two-fold: First, to provide a comprehensive qualitative description of the extent of and handling approaches to missing economic outcomes in the included pRCT-based economic evaluations published over the last 10 years. Second, to provide a critical review of reporting and potential methodological issues in handling missing data to provide suggestions on how missing data should be reported for future research and update the methodological guidelines on handling missing data in pRCT-based economic evaluations, in accordance with the CONSORT-Outcome 2022 statement, the framework, and guidelines for the treatment of missing data in economic evaluations [23–25].

Materials and methods

This was a descriptive cross-sectional survey and is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [26] (Appendix Table S1).

Data source and search strategy

A systematic literature search was performed using PubMed, Embase, the Cochrane Central Register of Controlled Trials(CENTRAL), the Health Technology Assessment Database(HTA database), and the National Health Service Economic Evaluation Database (NHS EED). The criteria for including studies were as follows: (1) study design: pragmatic trial or naturalistic trial or practical trial; (2) study related to economic evaluation; and (3) covering the period from January 1, 2010, to December 31, 2021, and a complementary search on 24 April 2022. Studies that met the following criteria were excluded: (1) secondary analyses; (2) abstracts, comments, letters, notes, editorials, protocols, subgroup analyses, pilot and feasibility trials, post-hoc analyses, and reviews; and (3) written in languages other than English. A complementary search was performed based on the inclusion and exclusion criteria; all relevant materials

from the included studies, such as published articles, supplementary materials, online appendices, study protocols or designs, and any accompanying randomized controlled trials (if published separately) were downloaded and carefully evaluated. Table S2 provides the complete search strategy used to find original research articles for inclusion in our systematic review.

Study selection and data extraction

We used the Noteexpress (a citation manager tool to help researchers organize research notes and bibliographic references, generate bibliographies automatically, search and capture bibliographic data from the Internet; https://www.inoteexpress.com/) as a literature management tool as well as for back-to-back literature screening. The titles and abstracts were screened by two sets of two independent reviewers (CW, WL, XZ, and WH). The same reviewers assessed the full texts of the identified studies for eligibility, and the reasons for exclusion were recorded. Discrepancies were resolved by consensus or by WH.

We used the Wenjuanxing platform (an online survey tool; https://www.wjx.cn/) to make the data extraction form, and reviewers accessed the data extraction form through WeChat (a mobile messaging application and social networking platform; https://web.wechat.com/) to collect data from all eligible studies. Two reviewers (YX and RS) pilot-tested the predefined form to confirm its completeness, appropriateness, and applicability. Three teams of reviewers (YX, RS, JH, WL, CW, and LZ) independently collected the data from all eligible studies. Discrepancies were resolved by consensus or by WH.

The following basic information was extracted: sample size, follow-up time, country, journal impact factor quartile, and whether economy-related outcomes were the primary endpoints of each eligible study. Notably, data pertaining to the study's sample size generally cover the expected and reported sample sizes. Information on the occurrence of missing data, proportion of missing data, missing patterns, missing mechanisms, methods of handling missingness, imputation level, and relative information of multiple imputation (MI) were also extracted. Additionally, we obtained information on whether the sensitivity analysis results were consistent with the primary results.

Statistical analysis

Descriptive analysis was conducted for all the variables. For continuous variables, data are presented as mean (standard deviation, SD) if normally distributed and otherwise as median (interquartile range, IQR) or median (range). For categorical variables, data are presented as frequencies divided by the total number and proportion. Descriptive analysis of all the variables was conducted using Microsoft Excel v16.0 (Microsoft, United States).

Results

Selected articles

Using our search strategy, a total of 715 articles were retrieved from the databases. After removing 234 duplicates, 481 studies were left for the first-round screening and 243 studies for full-text screening. Finally, 152 studies were retained based on both met the eligibility and exclusion criteria (Fig. 1).

Study characteristics of the included studies

Among the 152 included studies, the median sample size for economic evaluation was 343 (IQR, 202.5–696), which was slightly smaller than 360 (IQR, 230–750) sprcified in the protocol. The median follow-up period was 12 months (IQR, 6–12). Studies in the UK ($n=90$, 59.21%) conducted the majority of the economic evaluations, followed by those in the Netherlands ($n=24$, 15.79%). More than 60% of the studies ($n=98$, 64.47%) were published in journals with an impact factor in the top quartile. Approximately half of the studies ($n=75$, 49.34%) used economy-related outcomes as primary endpoints (Table 1).

Basic information on missing data

Of the 152 studies, approximately 75% missed cost and effect data simultaneously, whereas 25.66% did not report overall missingness. More specifically, missing effects were more common than missing costs (86.84% vs. 78.29%); however, the number of studies that did not mention missing costs was almost twice that of studies that did not mention missing effects (21.05% vs. 12.50%). More than 50% (58/113) of the studies reported the proportion or quantity of overall missingness, and 64.71% and 54.55% of the studies reported missing costs and effects, respectively. The proportion of missingness of $<5\%$ in the overall group was 3.45%, whereas the proportions of missing costs and effects were both lower than 10% (5.26% vs. 8.45%). In terms of the proportion of missing data, the overall missingness rate was 30.22% in 58 studies, whereas the median proportion of missing data was slightly higher than that of missing effects (30.92% vs. 27.78%). According to the different lengths of follow-up periods, the median proportion of missing data in the>1-year group was higher than that in the ≤ 1-year group, particularly in the overall group (42.20 vs. 29.50%) (Table 2).

Details on dealing with missing data in the primary analyses

Among the studies with missing data, approximately one-quarter reported missing mechanisms, and only a

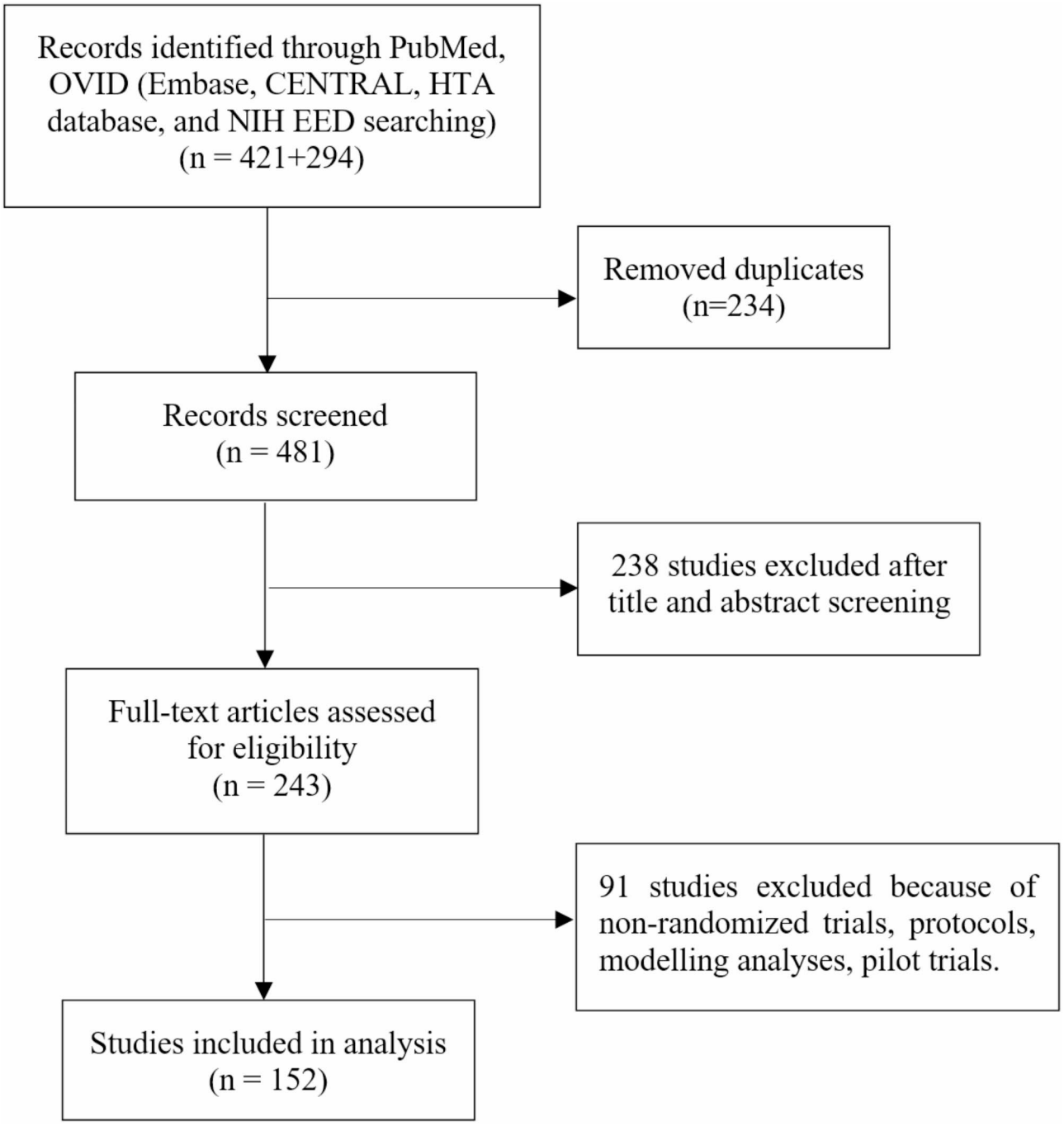

Fig. 1 Flow chart of study selection

few studies further reported the reasons for the missing mechanisms. Missing at random (MAR) was the most popular assumption of missingness, with a proportion of approximately 90%. Regarding specific methods for handling missing data, 27.43% of the studies simultaneously reported methods for handling missing costs and effects; however, the percentage of studies that separately reported the methods of dealing with costs or effects was approximately 80%. More specifically, MI was the most frequently used method (66.32% vs. 70.30%), followed by single imputation (20.62% vs. 16.83%) and deletion (19.59% vs. 12.87%) (Table 3).

Details on dealing with missing data in the sensitivity analyses

Fifty-six (36.84%) studies conducted sensitivity analyses to address missing data. Of these studies, 12.50% reported missing mechanisms, and 83.93% reported

Table 1 Study characteristics of 152 included studies

Characteristics	Included studies (*N* = 152)
Expected sample size for the protocol (median [IQR])	**360[230–750]**
Reported sample size for economic evaluation (median [IQR])	**343[202.5–696]**
Follow-up (month) (median [IQR])	**12 (6–12)**
Country (Top 5), n (%)	
UK	90 (59.21)
Netherlands	24 (15.79)
USA	7 (4.61)
Australia	7 (4.61)
Sweden	4 (2.63)
South Africa	4 (2.63)
France	3 (1.97)
Canada	3 (1.97)
JIFQ, n (%)*	
Q1	98 (64.47)
Q2	37 (24.34)
Q3	13 (8.55)
Q4	2 (1.32)
Unknown	2 (1.32)
Whether the economic-related outcomes were primary endpoints, n (%)	
Yes	75 (49.34)
No	73 (48.03)
Not reported	4 (2.63)

* JIFQ: Journal Impact Factor Quartile. Reuters divides all journals into four equal categories based on their impact factors. The journals in Q1 were the highest ranked (top 25%) in a category, and the journals in Q4 were the lowest

Table 2 Basic information on missing data

Basic information	Number of studies, *n*/*N* (%)		
	Overall*	Cost	Effects
1. The occurrence of missing data			
Missingness	113/152 (74.34)	119/152 (78.29)	132/152 (86.84)
None missingness	0/152 (0)	1/152 (0.66)	1/152 (0.66)
Not reported	39/152 (25.66)	32/152 (21.05)	19/152 (12.50)
2. Reporting the quantity of missing data	**58/113 (51.33)**	**77/119 (64.71)**	**72/132 (54.55)**
2.1 The proportion of missingness < 5%	**2/58 (3.45)**	**4/76 (5.26%)**	**6/71 (8.45%)**
2.2 The proportion of missing data in the follow-up period (median [IQR], %)&	**30.22[20.59–4.67]**	**30.92[15.68–46.43]**	**27.78[14.49–39.80]**
Follow-up ≤ 1 year	29.50[19.95–2.08]	30.93[14.58–46.51]	25.12[14.28–9.96]
Follow-up>1 year	42.20[31.53–1.96]	31.72[19.71–45.76]	34.48[15.37–67.43]

* Overall, both cost and effect data are missing

& The follow-up periods were the time points for calculating the incremental cost-effectiveness ratios

handling methods. In contrast to the primary analyses, complete case analysis was the most popular method for dealing with missing data in the sensitivity analyses. The results of the sensitivity analysis were consistent with those of the primary analyses in 94.64% of the studies (Table 4).

Discussion

Principal findings

We conducted a cross-sectional analysis of the reporting quality and quantity of missing data in pRCT-based economic evaluations published from 2010 to 2022 and found that the reporting quality of missing data in pRCT-based economic evaluations was insufficient. Although most studies claimed missing values, studies reporting a specific quantity of missing data accounted for approximately 60% of the total sample. Additionally, this percentage was lower in studies with missing costs and effects. In terms of methods for handling missing data, the reporting quality in the primary analyses was higher than that in the sensitivity analyses.

Furthermore, missing data were serious in pragmatic trial-based economic evaluations; almost 90% of studies acknowledged missing data regardless of missing costs

Table 3 Detailed information on handling missing data in primary analyses

Characteristics	Number of studies, *n*/*N* (%)		
	Overall	Cost	Effects
1. Reporting missing mechanism*	31/113 (27.43)	25/119 (21.01)	31/132 (23.48)
MAR	27/31 (87.10)	23/25 (92.00)	28/31 (90.32)
MCAR	3/31 (9.68)	1/25 (4.00)	2/31 (6.45)
MNAR	1/31 (3.23)	1/25 (4.00)	1/31 (3.23)
2. Reporting reasons for missing mechanism selection	**5/31 (16.13)**	**5/25 (20.00)**	**5/31 (16.13)**
3. Reporting methods of handling missingness	**31/113 (27.43)**	**97/119 (81.51)**	**101/132 (76.52)**
MI		**63/97 (66.32)**	**71/101 (70.30)**
Single imputation		**20/97 (20.62)**	**17/101 (16.83)**
Mean imputation		14/20 (70.00)	10/17 (58.82)
LOCF		2/20 (10.00)	4/17 (23.53)
Regression imputation		2/20 (10.00)	2/17 (11.76)
Deletion		**19/97 (19.59)**	**13/101 (12.87)**
CCA		18/19 (94.74)	12/13 (92.31)
ACA		1/19 (5.26)	1/13 (7.69)

MAR (Missing at Random): predictive distribution of missing values given the observed values for each unit is independent of the pattern; MCAR (Missing Completely at Random): the observed units are a random subsample of all the units; MNAR (Missing Not at Random): the probability that a covariate is missing depends on the values of missing covariates; MI, (Multiple Imputation): creating multiple data sets with different sets of draws imputed; LOCF (Last Observation Carried Forward): missing values imputed by the last recorded value for that unit; CCA (Complete Case Analysis): analysis of a set of units with no missing values and modifications and extensions; ACA (Available Case Analysis): analysis includes all units where that variable is present

* One study assumed different mechanisms for the missing costs and effects

Table 4 Detailed information on sensitivity analysis for missing data

Characteristics	Number of studies, *n*/*N* (%)
1. Conducting sensitivity analysis	56/152 (36.84)
2. Reporting missing mechanism	7/56 (12.50)
MNAR	5/7 (71.43)
MCAR	0 (0)
MAR	2/7 (28.57)
3. Handling methods of missing data	**47/56 (83.93)**
CCA	28/47
MI	16/47
Single imputation	7/47
4. Whether the results of the sensitivity analysis were consistent with the primary results*	
Yes	53/56 (94.64)
No	1/56 (1.79)
Not reported	2/56 (3.57)

MAR, missing at random; MCAR, missing completely at random; MNAR, missing not at random; CCA, complete case analysis; MI, multiple imputations

* Note that 'consistency' indicates the direction of results for primary and sensitivity analysis is consistent

or effects, and less than 4% of studies had a missingness proportion of < 5%. The median percentage of missing data was approximately 30%, and the third quartile was 67.43%. Moreover, the longer the follow-up period, the higher the proportion of missing data, particularly in studies with missing costs and effects.

Comparison with similar studies

Over the past decade, missing data in piggyback economic evaluations have raised widespread concerns. A piggyback economic evaluation refers to an economic analysis conducted alongside clinical trials, where specific data on resources use and outcome are collected from the individual participants [17, 27]. Our results are generally consistent with and extend the research scope of previous studies on the extent of missing data as well as those on handling methods in trial-based economic evaluations. First, missing data was an issue in most pRCTs-based economic evaluations, with approximately 90% of studies claiming missing costs or effects, and of the studies that reported the quantity of missing data, only two (3.45%) had < 5% of participants with missing data. These results are similar to those of Leurent et al. (2018) who, based on trial cost-effectiveness studies, found only five studies (10%) with > 95% of complete cases [12]. Second, although missing data were common in economic evaluations of pRCTs, < 60% of studies reported the quantity of missing data. The proportion of

trial-based studies reporting the quantity of missing cost or efficacy was 34.1–90.4% [12, 14]. Third, the missing mechanism is linked to the imputation method, as a key concept to address missingness. However, among nearly 90% of studies with missing data, only a quarter reported the missing mechanism, and approximately 20% of these studies reported the reasons for the missing mechanism, which is consistent with the results to Gabrio et al. (2017) study [25]. Fourth, although methodological guidelines recommend conducting sensitivity analyses on departures from the MAR assumption, considering alternative, plausible MNAR mechanisms [28], our study found that only approximately one-third of the studies used different missing data-handling methods for sensitivity analysis, which is consistent with the results of 25% RCT by Noble et al. [14] and approximately 25% by Gabrio et al. [25]

Implications for future research

The findings of this study have important implications for the future economic evaluation of piggybacks. First, an analysis of the comparative costs of alternative treatments or healthcare programs is common to all forms of economic evaluation. Once the important and relevant costs are identified, they must be measured in appropriate physical and natural units [29]. However, our study found a high proportion of important and relevant costs missing from the included articles, which was strongly related to the manner in which costs were collected. Although various cost collection methods exist, a bottom-up method is usually used for individual-level economic evaluation [30]. When this method was used to calculate costs, one missing cost component led to missing total costs [31]. Second, less than 40% of the studies in this review performed sensitivity analyses for the treatment of missing data, although almost all the included studies had missing data. In reality, there will always be some uncertainty in the case of missing data, and it is difficult to have complete confidence in the results that rely on unobserved information [32]. Therefore, sensitivity analysis is particularly important as it can be a valuable tool to deal with the uncertainty caused by missingness and explore the impact of plausible alternative missing data assumptions on the economic evaluation [25]. Owing to the ubiquity of missing data and because the mechanisms of missing data are often not rigorously examined, sensitivity analyses are needed in future studies to compare the results under different hypotheses about the causes for the missing data and different measurement processes to demonstrate the robustness of the results [33, 34]. Finally, the results of this study showed that the reported sample size of economic evaluation was generally smaller than that of clinical trials. However, previous studies indicated that the sample size required to detect significant differences in piggyback evaluations may be greater than that required to demonstrate effects [35–37].Considering the missing data in the pRCT-based economic evaluation, the overall statistical power of the economic evaluation may be insufficient. Therefore, future economic evaluations of piggybacks should increase their sample size by fully considering the potential proportions of missing data. Further information on the sample size and statistical power of the pRCT-based economic evaluation are reported elsewhere [38].

Strengths and limitations

Few studies provide a comprehensive assessment of reporting and the extent of missing data in pRCT-based economic evaluations, and our study enriches the field; however, this study has several limitations. First, despite using comprehensive retrieval strategies in this study, the CONSORT Statement Extension checklist does not require adding the word "pragmatic" to the title or abstract [39], potentially leading to missed eligible trials, thus introducing a possible selection bias and affecting the results. Second, since our study focused on the reporting quality, the methodological quality of handling missing data was neither assessed nor guaranteed. Thus, the scientific rigor and appropriateness of handling methods of missing data, including the quality of MI models, require further research. Finally, this study only included studies published in English, potentially limiting the scope of our findings and introducing a language bias.

Conclusions

The current descriptions and reporting of missing data in most studies are insufficient, and the high proportion of missing data in pRCT-based economic evaluations should be given more attention. There is room to enhance the complete economic outcomes of such studies and improve the reliability of economic results.

Abbreviations

RCTs	Randomized controlled trials
eRCTs	Explanatory RCTs
pRCTs	Pragmatic RCTs
MAR	Missing at random
MCAR	Missing Completely at Random
MNAR	Missing Not at Random
MI	Multiple imputation
LOCF	Last Observation Carried Forward
CCA	Complete Case Analysis
ACA	Available Case Analysis
NHS EED	National Health Service Economic Evaluation Database
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology

Supplementary Information

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Supplementary Material 1

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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