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ORIGINAL ARTICLE

Identifying compliant participants through data matching improved estimation of intervention efficacy: randomized trials with opt-in/opt-out strategies

Shu Kay Ng*, Joshua Byrnes, Paul Scuffham

School of Medicine and Menzies Health Institute Queensland, Griffith University, Nathan Q4111, Australia

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Abstract

Objectives: We propose a data-matching approach to estimate intervention efficacy for randomized controlled trials (RCTs) when there is noncompliance to the allocated treatment with induced selection bias.

Study Design and Setting: We considered a large RCT to compare health care costs and hospital length of stay 12 months after randomization. Participants allocated to the intervention group were eligible to receive health-coaching and disease-management services. An opt-out approach was adopted for recruitment. Control-group participants received usual care but were allowed to opt-in to receive the intervention. Using ''nearest-neighbor''-matched data, we identified compliant participants in both arms to estimate intervention efficacy. Results were compared with intention-to-treat (ITT), instrumental-variable−adjusted ITT, per-protocol (PP), and as-treated (AT) analyses.

Results: The ITT estimated an intervention effect of a 1.5% reduction in cost, but 56.7% of intervention-group participants did not receive health coaching. The PP and AT found an increase in cost of 9.4% and 17.1%, respectively. The matching method estimated a 12.3% reduction in cost. After adjustment for baseline covariates, the intervention group had lower same-day admission cost (13.6%; 95% CI: 7.3%−20.0%; $P < 0.001$) and shorter hospital stay (11.2%; 95% CI: 2.6%−19.9%; $P = 0.021$).

Conclusion: Opt-in/opt-out strategies in RCTs misled intervention comparisons and the matching approach improved estimation of intervention efficacy.

Keywords: Noncompliance; Selection bias; Randomized controlled trial; Health coaching; Nearest-neighbor matching; Opt-in recruitment strategy; Opt-out recruitment strategy

1. Introduction

Randomized controlled trials (RCTs) are considered the gold standard in clinical research for their potential to reduce bias through randomization such that participants in the study arms have similar characteristics and any difference in outcomes between the study arms can be attributed to the intervention under study [1,2]. However, selection bias can occur when individuals are requested to give consent for participation in a trial and when individuals are assigned to a treatment arm once they have been accepted for a trial [3−8]. The former kind of selection bias may result in an overrepresentation of relatively advantaged participants (such as individuals with higher socioeconomic status) who agree to participate in a trial; it can be reduced by randomization but has impact on interpretation and generalization of findings [9]. Conversely, the second kind of selection bias cannot be reduced by randomization as it occurs after the assignment of treatment arms, inducing a serious impact on estimating intervention effects due to noncompliance with assigned treatments [10]. The situation may be complicated further by ethics approval requirements and new rulings in conducting clinical research [3]. An ''opt-out'' approach (contact was made unless individuals indicated unwillingness to participate) ensures a better response rate by following up nonresponse to an initial invitation [11]. In addition, there may be an ''opt-in'' strategy for giving the participants assigned to the control group

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* Corresponding author: School of Medicine, Griffith University, Room 2.41, N78, 170 Kessels Road, Nathan Q4111, Australia. Tel.: +617 3735 9131; fax: +617 3735 9133.

E-mail address: s.ng@griffith.edu.au (S.K. Ng).

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What is new?

Key findings

- We showed that opt-in and opt-out recruitment strategies in randomized controlled trials (RCTs) inflated selection bias due to noncompliance (as shown in this study, participants with higher health care needs were more likely to engage).
- We considered a conceptual framework with three levels of ''principal compliance'' (Always-takers, Compliant participants, Never-takers) and developed a new approach to identify compliant participants for comparison of intervention efficacy.
- Always-takers (opt-in) had the highest health care needs among the participants in the control group and Never-takers (opt-out) had the lowest health care needs among those allocated to the intervention group.

What this adds to what was known?

- The intention-to-treat (ITT) analysis actually measures intervention effectiveness (as there are opt-in and opt-out participants who do not comply with the assigned treatment); instrumental variable (IV) adjusts the ITT for noncompliance, but the assumption for IV adjustment is not always valid; per-protocol and as-treated analyses measure treatment efficacy, but they are subject to selection bias.

What is the implication and what should change now?

- The new method identifies compliant participants in both treatment arms by data matching on the basis of participants with known compliance information; this method is useful for analyzing future RCTs that anticipate strong selection bias.

the opportunity to receive the same active treatment as those in the intervention group. When participants do not adhere to the protocol of the assigned treatment due to selection bias, the estimation of intervention effects and interpretation are not straightforward.

The most widely used approach in estimating intervention effects is intention-to-treat (ITT), where treatment comparisons are based on the assigned treatment arms, regardless of whether the participants complied with the treatment. While ITT analysis preserves the benefits of randomization, it provides valid measures of the intervention ''effectiveness'' rather than the treatment ''efficacy'' (the effectiveness of an intervention when it is in fact taken) about which many researchers want to know. The ITT analysis can be adjusted for noncompliance to estimate intervention efficacy using the randomization indicator as an instrumental variable (IV) [10,12−14]. Alternatively, per-protocol (PP) and as-treated (AT) analyses are simple approaches to estimate treatment efficacy, but they are subject to selection bias [10]. Many studies have identified strong selection bias in RCTs [3,4,7,9]. However, besides the proposal of allocation concealment and masking [15−17], few studies consider an appropriate way to correct for selection bias due to noncompliance in estimating intervention effects. How these methods (ITT with or without IV adjustment, PP, or AT) influence the comparison of treatments remains unclear, especially when noncompliance of assigned treatment protocols and selection bias exist. In this study, we propose a new approach with the use of ''nearest-neighbor'' matched data to identify compliant participants in both arms and hence to estimate intervention efficacy for RCTs with opt-in and/or opt-out recruitment strategies. Novelty lies in the idea of identifying compliant participants in both arms by data matching on the basis of participants with known compliance information, not the matching method itself.

2. Methods

2.1. Setting

The Costs to Australian Private Insurance−Coaching Health (CAPICHe) is a parallel-group RCT of the relative impact of telephonic health-coaching support on health care cost and utilization of participants in a disease-management program in Australia [18,19]. The trial enrolled participants sourced from Bupa Australia health-fund members and received ethical approval from Griffith University Human Research Ethics Committee (Ref.: MED/12/11/HREC). It was registered with the Australian New Zealand Clinical Trials Registry (Ref.: ACTRN12611000580976). The published protocol provides information on prespecified inclusion and exclusion criteria, sample-size calculation, data collection, and follow-up [18].

2.2. Randomization, recruitment, and intervention program

Participants who met the inclusion criteria were randomly selected from Bupa Australia claims database. Independently of Bupa Australia, the samples were then randomized into the intervention or control groups in a 4:1 ratio stratified by five diagnosed chronic conditions [18]. The effectiveness of randomization for each batch of data was checked. The participants allocated to the intervention group were eligible to receive disease-management services provided by Bupa Health Dialog [19]. An opt-out approach (contact was made unless they contacted the intervention provider to signal unwillingness to participate) was adopted for recruitment.

In the control group, the participants received a letter outlining the services from Bupa Health Dialog. These participants received usual care but were given the opportunity, via mail, to opt-in to receive health coaching. Opt-in participants received the same services as that provided to a participant assigned to the intervention group. Health coaches had the same quality of information available about the members and had all the same educational resources at their disposal as they did for the intervention group. Other than participants in the usual-care arm who opted-in to the intervention and received health coaching, the health coaches were blind to whether participants were in the CAPICHe intervention group or were receiving health coaching as part of the usual business for Bupa [19].

Outcome measures are nonmaternity health care costs and hospital length of stay 12 months after randomization, presented as a value and a percentage of difference.

2.3. Methodology and statistical methods

Our approach to addressing selection bias due to noncompliance of assigned treatment involved two data matching on the basis of participants with known compliance information, as indicated by the hollow arrows in Fig. 1. The correction of selection bias was implemented by considering three levels of "principal compliance" corresponding to "Always-takers," "Compliant participants," and "Never-takers" [10]. This approach is in contrast to the inverse-probability-weighting method that has been used in RCTs in which data on compliance are missing [20]. As illustrated in Fig. 1, Always-takers in the control group (cell A) are participants who opted in to receive coaching (n = 153 out of 8,883 randomized to the control group), whereas the participants who did not engage (n = 8,730) were either Compliant participants (cell B) or Never-takers (cell C). As the principal-compliance levels of these 8,730 participants were not observable, the actual numbers of participants in cells B and C were unknown. In the intervention group, engaged participants (n = 15,375) were either Always-takers (cell D) or Compliant participants (cell E), while Never-takers (cell F, n = 20,160) are participants who did not engage in the program. With the same reason above, the actual numbers of participants in cells D and E were unknown. For RCTs that adopt opt-in and/or opt-out recruitment strategies, it is anticipated that there would be selection bias in those participants who engaged in health coaching and likely to be associated with higher costs or longer hospital stay in the follow-up period.

The intervention efficacy is estimated on the basis of compliant participants who adhere to the protocol of the allocated treatment (i.e., cell E vs. cell B). Let $\bar{y}_{rp}$ denote the sample means (some are not observable) for the corresponding randomized group (r = 0: control group; r = 1: intervention group) and compliance information (p = A: Always-takers; p = C: Compliant participants; p = N: Never-takers); the proposed data-matching approach provides an estimate of treatment effect as follows:

$$\hat{\delta}_{DM} = \bar{y}_{1C} - \bar{y}_{0C} \quad (1)$$

This new matching approach will provide a better estimation of intervention efficacy, as supported by that cells B and E are the only groups of compliant participants for each treatment arm. The compliant participants were identified using nearest-neighbor data matching (see Supplementary Material for Stata command [21] "teffects nnmatch"). Always-takers in the intervention group (cell D) were matched with reference to the (observed) Always-takers in the control group (cell A), while Never-takers in the control group (cell C) were matched with the observed Never-takers in the intervention group (cell F) (see Fig. 1). The intervention-to-control ratio of 4:1 was assumed to remain in the matching, which is plausible when the randomization is effective (effectiveness of randomization can be verified

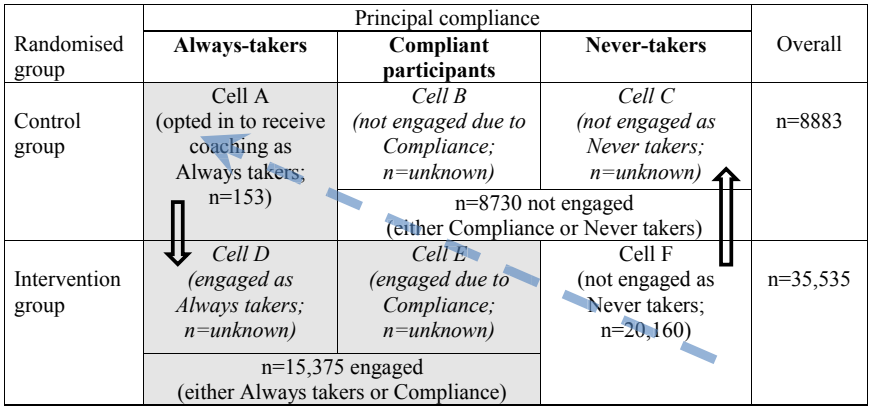

Fig. 1. Classification of participants by treatment group and principal compliance (unobservable principal compliance information was presented in italic; shaded cells correspond to participants who received coaching. Nearest-neighbor data matching for cells C and D with reference to known observed compliance from cells F and A was indicated by the hollow arrows. Strong selection bias anticipated; higher costs for participants with higher engagement levels represented by the semi-transparent and dashed arrow across the three levels of principal compliance). Through data matching, we have n = 5,040 in cell C and hence n = 3,690 in cell B, whereas n = 599 in cell D due to overlapping of 13 matched participants and hence n = 14,776 in cell E.

from the data). For matching cell D from cell A, four nearest-neighbor matches for each participant in cell A were obtained, based on the Mahalanobis distance measure [22] (the covariance-adjusted distance between two points) using age, randomization batch, historical cost and admission rate, and the number of coexisting conditions, whereas exact match was performed for engagement level (three categories: number of coaching sessions 1–2, 3–6, >6; only available for engaged participants), gender, state of residence, and clinical condition. That is, engaged participants in the intervention group (cells D and E) were split into cell D (participants matched from cell A) and cell E (nonmatched remainders). For matching cell C from cell F, the nearest-neighbor match of each participant in cell F was obtained using the same distance measure as mentioned previously except with regards to the engagement level. To keep the 4:1 intervention to control ratio, the best $n = 5{,}040$ (20,160 divided by 4) nearest neighbors based on the Mahalanobis distances were considered as Never-takers in cell C. A comparison study was conducted to compare the crude estimates of intervention effects (without adjustment for baseline covariates) using the data-matching approach, the ITT (with or without adjustment using the randomization indicator as an IV [10,12–14]), PP, and AT methods, where

$$\widehat{\delta}_{ITT} = \overline{y}_{1(A+C+N)} - \overline{y}_{0(A+C+N)} \tag{2}$$

$$\widehat{\delta}_{IV} = \widehat{\delta}_{ITT}/(1 - \widehat{\pi}_{0A} - \widehat{\pi}_{1N}) \tag{3}$$

$$\widehat{\delta}_{PP} = \overline{y}_{1(A+C)} - \overline{y}_{0(C+N)} \tag{4}$$

$$\widehat{\delta}_{AT} = \widehat{\delta}_{PP} + \overline{y}_{0A} - \overline{y}_{1N}, \tag{5}$$

and where $\widehat{\pi}_{rp}$ denotes the proportion of samples with principal compliance (p) in the randomized group (r). From (1) and (4), it can be seen that the data-matching approach estimates treatment efficacy by restricting analysis to participants who comply with the assigned allocation (like PP analysis) and simultaneously correcting for selection bias from Always- and Never-takers due to noncompliance (cell D and cell C in Fig. 1).

To adjust for baseline covariates, zero-inflated regression models [19,23,24] were adopted to estimate the intervention efficacy on health care costs and hospital length-of-stay between compliant participants (cells B and E) identified using the data-matching approach. Regression covariates were historical costs and admission counts, age, gender, state of residence, randomization batch, as well as the diagnosed chronic condition, the count of chronic conditions, and the proportion of admissions due to surgical treatment within the follow-up period. Outcome measures with incomplete follow-up were adjusted in the analyses using the observed days of follow-up as exposure risk [19]. Covariates with a P-value greater than 0.05 were removed from the models. Analyses were undertaken in Stata IC 13.1 (StataCorp, College Station, TX).

3. Results

The study enrolled a total of 44,418 participants, of which 35,535 participants (80%) were allocated to the CAPICHe intervention group and 8,883 participants (20%) were allocated to the usual-care control group. The randomization of treatment groups was effective, as there were no major differences in baseline characteristics (including age group, gender, state of residence, historical health care cost, and frequency of admissions for the prior 12 months to randomization) between the two groups; detailed baseline characteristics of participants are reported elsewhere [19].

Table 1 presents the dose-response relationship. Strong selection bias was observed in that participants with higher engagement levels in health coaching were also associated with significantly higher costs or longer hospital length of stay within 12 months after randomization.

The average health care costs 12 months after randomization for the three levels of principal compliance after data matching were presented in Fig. 2. The trend of increasing costs for Never-takers, Compliant participants, and Always-takers confirmed the existence of strong selection bias. It can be observed that Always-takers in the control group had higher costs compared to those in the intervention group, while Never-takers in the intervention group had higher costs compared to those in the control group.

The crude estimation of intervention efficacy on the health care cost was summarized in Table 2. The ITT compares the outcomes of participants between the intervention group ($4,840) vs. the control group ($4,914), regardless of whether they complied with the treatment allocation (a cost saving of $74, or 1.5%). With adjustment for noncompliance using the IV method [10,12], the adjusted ITT estimate for intervention efficacy is a saving of $178 (i.e., $74/(1-153/8,883-20,160/35,535), or 3.6%). The PP analysis restricts the comparison to participants who comply with the assigned treatment (cells D and E in the intervention group [$5,338] vs. cells B and C in the control group [$4,881]; an additional cost of $457, or 9.4%), whereas the AT analysis compares participant's outcomes according to the treatment actually received (participant received the intervention [cells A, D, E; $5,351] vs. those who did not [cells B, C, F; $4,571]; an additional cost of $780, or 17.1%). In the presence of selection bias, biased estimation of intervention efficacy was obtained with the PP and AT analyses because it involved comparisons across the three levels of principal compliance (see shaded cells in Fig. 1). Comparing compliant participants between cells B and E, the intervention efficacy was $5,332 vs. $6,080 (a saving of $748, or 12.3%).

The baseline characteristics of compliant participants in cells B and E are different, providing further support of the hypothesis that there would be selection bias in those participants who choose to opt-in or opt-out (see Supplementary Table 1). Table 3 presents comparisons of

Table 1. Mean (95% CI) costs and length of hospital stay by the number of coaching sessions

Trial outcomes[a]	1–2 coaching sessions (n = 8,152)	3–6 coaching sessions (n = 6,003)	7+ coaching sessions (n = 1,373)
Nonmaternity cost[b]	$5,046 (4,638 to 5,454)	$5,479 (5,150 to 5,808)	$6,547 (5,827 to 7,268)
Overnight nonmaternity cost[b]	$4,420 (4,149 to 4,692)	$4,905 (4,588 to 5,222)	$5,894 (5,193 to 6,594)
Same-day nonmaternity cost[b]	$456 (422 to 490)	$562 (508 to 615)	$642 (516 to 767)
Hospital length of stay[b]	3.639 (3.371 to 3.907)	4.039 (3.737 to 4.341)	4.535 (3.873 to 5.197)

Abbreviation: CI, confidence interval.
[a] All trial outcomes were obtained in 1 year after randomization.
[b] Testing differences across coaching session groups using ANOVA (all significant with $P < 0.05$).

treatment efficacy for the data-matching method on the basis of compliant participants with adjustment for baseline covariates. Adjusted estimates of health care costs were lower for the intervention group compared to the control group, especially the cost due to same-day admissions (intervention group: $516; 95% CI: $493–$539; control group: $597; 95% CI: $554–$641; reduced cost: $81; 95% CI: $38–$125; $P < 0.001$). The intervention group had a shorter adjusted estimate of hospital stay (4.164 days; 95% CI: 3.967–4.361) compared to the control group (4.691 days; 95% CI: 4.275–5.107) with reduced hospital stay of 0.527 days (95% CI: 0.081–0.974; $P = 0.021$).

4. Discussion

For RCTs, the widely used ITT analysis preserves the benefits of randomization by comparing intervention effects according to the assigned treatments and provides a valid measure of treatment effectiveness, such as a reduction in cost of 1.5% ($74) in this health-coaching trial. This is important information to policy makers and health planners, by knowing the benefit from offering the intervention program to individuals (who may not adhere to treatment protocols). In this trial, 56.7% of participants assigned to the intervention group did not engage in any health coaching. Many researchers thus also want to know the efficacy of the treatment effect when it is in fact taken. While the ITT analysis can be adjusted for noncompliance using the IV method to estimate intervention efficacy, the IV method requires the "exclusion restriction" assumption that means effects (health care costs in this example) are the same between the intervention and control groups for Always-takers (cells A and D) as well as Never-takers (cells C and F) [10,12]. According to our findings displayed in Fig. 2, these assumptions, however, are not valid. The PP and AT analyses were also inappropriate as they suffered from selection bias by comparing participants across different compliance levels. In addition, it is expected that the PP analysis tends to give, on average, higher estimates of intervention effect than the ITT analysis, especially in RCTs with dropouts [25–28]. But the findings obtained in this trial indicated the opposite because of the strong selection bias due to noncompliance (see Table 2). We proposed the matching approach to correct for selection bias due to noncompliance by identifying compliant participants in the intervention and control groups, with whom the intervention efficacy was estimated. We found that, after adjustment for baseline covariates, the total health care costs in the intervention group were $107 (95% CI: −$241 to

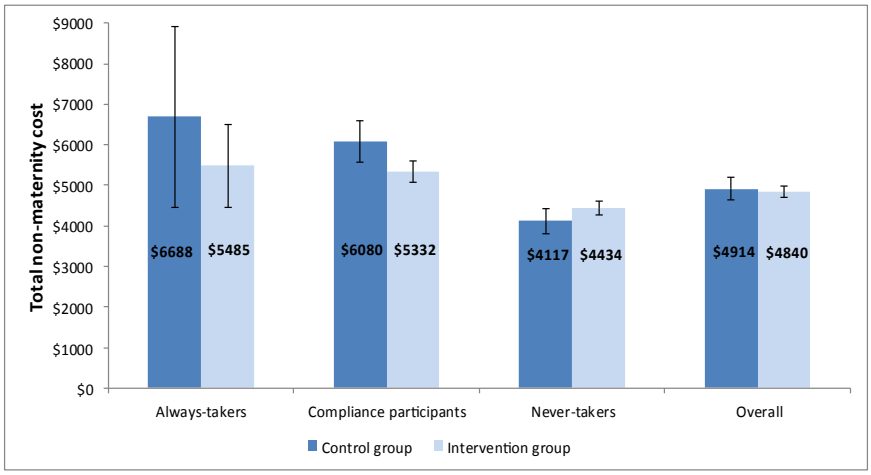

Fig. 2. Mean nonmaternity costs 12 months after randomization by treatment group and principal compliance (the numbers of participants in the control group, n_c, and the intervention group, n_i are: Always-takers, n_c = 153, n_i = 599; Compliance participants, n_c = 3,690, n_i = 14,776; Never-takers, n_c = 5,040, n_i = 20,160; overall, n_c = 8,883, n_i = 35,535). The percentage of opt-in in the control group = 1.7% (153/8,883) and the percentage of opt-out in the intervention group = 56.7% (20,160/35,535).

Table 2. Crude estimation of intervention efficacy on total nonmaternity cost (means and 95% CI)

Comparison method	CAPICHe intervention group	Usual care control group	Intervention effect	Remark
Intention-to-treat (ITT)	Cells D, E, F: $4,840 (4,692 to 4,989)	Cells A, B, C: $4,914 (4,641 to 5,187)	$74 (−238 to 384)	ITT actually measures intervention effectiveness, as participants in cell F (56.7% allocated to the intervention group) did not receive coaching
ITT with IV adjustment	Cells D, E, F: $4,840 (4,692 to 4,989)	Cells A, B, C: $4,914 (4,641 to 5,187)	$178 (−573 to 924)	IV adjusts the ITT estimate for noncompliance, but the assumptions of equal means (cells A and D; cells C and F) are not valid
Per-protocol (PP)	Cells D, E: $5,338 (5,080 to 5,595)	Cells B, C: $4,881 (4,606 to 5,156)	−$457 (−833 to −80)	PP measures intervention efficacy, but it suffers from selection bias due to inclusion of cells C and D in the comparison
As-treated (AT)	Cells A, D, E: $5,351 (5,095 to 5,607)	Cells B, C, F: $4,571 (4,427 to 4,716)	−$780 (−1,074 to −486)	AT measures intervention efficacy, but it suffers from selection bias due to inclusion of cells A and D vs. cells C and F in the comparison
Data matching	Cell E: $5,332 (5,066 to 5,597)	Cell B: $6,080 (5,474 to 6,465)	$748 (167 to 1,329)	Data matching method measures intervention efficacy with adjustment for selection bias due to noncompliance, by comparing compliant participants between cells B and E

Abbreviation: CI, confidence interval.

$455) lower than the control group, representing a 2.0% ($107 of $5,440) reduction in cost ($P = 0.546$). Moreover, the total cost due to same-day admissions was lower ($81 or 13.6%; 95% CI: $38–$125 or 7.3–20.0%; $P < 0.001$) and the hospital length of stay was shorter (0.527 days or 11.2%; 95% CI: 0.081–0.974 or 2.6–19.9%; $P = 0.021$) in the intervention group compared to the control group.

Estimation of intervention efficacy in RCTs by correcting for selection bias due to noncompliance is vital for the scientific rigor of medical and health research to establish evidence-based practices. Although well-planned trial designs with proper allocation concealment and masking certainly help to minimize selection bias [15–17], it is still required in the analysis to correct for selection bias due to different compliance levels of participants, as selection bias may not be fully removed by adjustment for covariates [10]. Our findings demonstrated strong selection bias in compliance with reference to assigned treatment arms when opt-in and opt-out methods were in place. As illustrated by this health-coaching trial, there is a tendency for participants with higher engagement levels to be associated with higher health care costs in the follow-up period (differences across: engagement levels, Table 1; compliance levels, Fig. 2). Always-takers in the control group who opted in to receive coaching had the highest health care costs among the participants in the control group, whereas Never-takers in the intervention group who opted out of coaching engagement had the lowest health care costs relative to other participants in the intervention group (Fig. 2). Differences within compliance levels were also found: Always-takers in the control group had higher health care costs compared to those in the intervention group, whereas

Table 3. Comparison of treatment efficacy for the data-matching method on the basis of compliant participants with adjustment for baseline covariates

Trial outcomes[a]	CAPICHe intervention group ($n = 14,776$)	Usual care control group ($n = 3,690$)	Intervention effect[b] (95% CI)
Total nonmaternity cost	$5,333 (5,154 to 5,512)	$5,440 (5,116 to 5,765)	$107 (−241 to 455)
Total overnight nonmaternity cost	$4,686 (4,516 to 4,857)	$4,960 (4,648 to 5,273)	$274 (−51 to 598)
Total same-day nonmaternity cost	$516 (493 to 539)	$597 (554 to 641)	$81 (38 to 125)
Hospital length of stay	4.164 (3.967 to 4.361)	4.691 (4.275 to 5.107)	0.527 (0.081 to 0.974)

Abbreviation: CI, confidence interval.

Data are adjusted estimates of mean (95% CI) for each outcome using zero-inflated negative binomial distribution with a logit model for characterizing excess zeros.

[a] All trial outcomes were obtained in 1 year after randomization.

[b] Reduction in health care costs or hospital length of stay for the intervention group vs. the control group.

Never-takers in the intervention group had higher health care costs relative to those in the control group. These findings will have great impact on the choice of analysis methods for estimating intervention efficacy in RCTs with strong selection bias due to noncompliance.

4.1. Strengths and limitations

This is a large RCT for health coaching in chronic-disease management, with 44,418 participants in five preselected diagnosed chronic conditions. Previous trials either had relatively smaller sample sizes or focused only on one specific condition [29−31]. With large sample sizes, our trial had sufficient power to detect true differences between the treatment arms if present. Detailed evaluation of the effectiveness of this disease-management program on health care cost and utilization of participants using the ITT analysis with adjustment for baseline covariates was reported elsewhere [19], which provides important information to policy makers and health planners regarding the intervention effectiveness of CAPICHe. The present trial had a number of limitations including a small number of contacts conducted per participant (median: 2; interquartile range: 2−4) and that clinical, surrogate, or summary health outcomes were not measured.

The capability of this new approach for correcting selection bias due to noncompliance has been illustrated in Table 2. Unlike the exclusion restriction assumption for the IV method regarding zero intervention effects for Always- and Never-takers (which are invalid in this health-coaching trial), the proposed data-matching approach needs only effective randomization of participants and the availability of key determinants of the outcome under study (as covariates) for matching participants with known compliance information. The former requirement is a typical assumption for treatment comparisons in RCTs. Other distance measures may be used in data matching, such as propensity scores [32]. An advantage of the nearest-neighbor approach is that it allows performing exact matches for selected covariates, such as engagement level, gender, state of residence, and clinical condition in the present trial. This feature offers a more robust matching of participants. It is worth mentioning that the two data matching did not have equal ‘‘precision.’’ The matching of cell D from cell A may not be sufficiently close because four nearest-neighbor matches for each participant in cell A were considered as Always-takers in cell D. For RCTs without an opt-in strategy for the control group (empty cell A), matching of cell C from cell F is still possible to identify compliant participants in the control group (cell B). Subsequently, through the matching from cell B, compliant participants in the intervention group (cell E) can be found. However, further sensitivity analyses are required to study the impact of the uncertainty in compliance information within this latter matching process on treatment comparisons for these more general RCTs.

4.2. Implications

In conducting RCTs, the selection bias arising from the opt-in and/or opt-out recruitment strategies cannot be reduced by the means of randomization and must be corrected for in the analysis to obtain a bias-corrected estimate of intervention effects. Our method is able to identify nearest-neighbor participants from participants in the other treatment arm with observed compliance levels, thus enabling the estimation of intervention efficacy by comparing outcomes of participants who adhere to the protocol of the allocated treatment in both arms. Our findings are useful for the analysis of future RCTs, where strong selection bias due to noncompliance is anticipated.

CRediT authorship contribution statement

Shu Kay Ng: Conceptualization, Methodology, Software, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Joshua Byrnes:** Conceptualization, Resources, Data curation, Writing - review & editing, Visualization, Project administration. **Paul Scuffham:** Conceptualization, Resources, Writing - review & editing, Visualization, Project administration, Funding acquisition.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jclinepi.2019.07.013.

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