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Compliance with telephone-based lifestyle weight loss programs improves low back pain but not knee pain outcomes: complier average causal effects analyses of 2 randomised trials

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Abstract

We conducted a complier average causal effect (CACE) analyses for 2 pragmatic randomised controlled trials. We aimed to assess the effectiveness of telephone-based lifestyle weight loss interventions compared with usual care among compliers. Participants from 2 trials with low back pain (n = 160) and knee osteoarthritis (n = 120) with a body mass index ≥27 kg/m^2 were included. We defined adherence to the telephone-based lifestyle weight loss program as completing 60% (6 from 10) of telephone health coaching calls. The primary outcomes for CACE analyses were pain intensity (0-10 Numerical Rating Scale) and disability (Roland Morris Disability Questionnaire for low back pain and Western Ontario and McMaster Universities Osteoarthritis Index for knee osteoarthritis). Secondary outcomes were weight, physical activity, and diet. We used an instrumental variable approach to estimate CACE in compliers. From the intervention groups of the trials, 29% of those with low back pain (n = 23/80) and 34% of those with knee osteoarthritis (n = 20/60) complied. Complier average causal effect estimates showed potentially clinically meaningful effects, but with low certainty because of wide confidence intervals, for pain intensity (−1.4; 95% confidence interval, −3.1, 0.4) and small but also uncertain effects for disability (−2.1; 95% confidence interval, −8.6, 4.5) among compliers in the low back pain trial intervention compared with control but not in the knee osteoarthritis trial. Our findings showed that compliers of a telephone-based weight loss intervention in the low back pain trial generally had improved outcomes; however, there were inconsistent effects in compliers from the knee osteoarthritis trial. Complier average causal effect estimates were larger than intention-to-treat results but must be considered with caution.

Keywords: Compliance, Musculoskeletal, Telephone, Lifestyle

1. Introduction

Randomised controlled trials (RCTs) are the gold standard method for estimating effects of health interventions. However, interpreting estimates of effect from RCTs is challenging when participants do not fully comply with interventions.[27,32] For example, when an RCT demonstrates no difference in intervention effects, and compliance is poor, it is difficult to know whether the intervention was ineffective or whether it would have been effective had it been complied to.[26–28] Interpreting trials of complex and pragmatic health interventions can be challenging because compliance can be as low as 34%, and treatment effects are typically small.[3,23] It is useful for policy makers to know whether an intervention is effective in those who comply when making decisions for directing health resources, and RCTs do not routinely provide this information.[26]

Poor compliance to treatment is rarely rigorously considered in usual analyses of RCTs. The intention-to-treat (ITT) effect, where all randomised participants are included in analyses (regardless of compliance), gives an unbiased estimate of the effect of allocation to an intervention vs control.[26] However, when compliance

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is poor, the ITT estimate can underestimate the effect of undertaking intervention treatment as prescribed because effects are diluted by those who did not receive the treatment.[9,11,26] Per-protocol (excludes participants who do not fully comply) or as-treated effects (compares participants with the intervention they actually receive) are sometimes estimated to account for poor compliance.[32] However, these methods introduce high risk of bias from unknown sources, selection bias, and possible confounding.[26,28,32]

In a pragmatic RCT with imperfect intervention compliance, estimating the complier-average causal effect (CACE) can be informative. Complier average causal effect provides an estimate of intervention effects between groups taking into account if participants complied to the intervention or would have complied if offered. The benefit of CACE over per-protocol and as-treated analyses is that CACE preserves random assignment.[7,26,28] Therefore, CACE provides more robust estimates of intervention effects when compliance is poor.

Interventions for musculoskeletal conditions are increasingly using telehealth as an important mode of delivery.[17] However, there are mixed results on the effectiveness and compliance to telehealth interventions for musculoskeletal conditions, particularly those targeting weight loss and lifestyle behaviours.[17] We completed 2 RCTs of telephone-based lifestyle weight loss interventions for patients with low back pain (LBP) and knee osteoarthritis (OA).[18,31] The interventions involved up to 1 physiotherapy face-to-face consultation and referral to a telephone-based lifestyle weight loss coaching service.[18,31] The ITT analyses showed no overall effect on the primary outcome of pain; however, only 34% of participants complied with a reasonable dose of the intervention. We therefore aimed to answer the question "Does compliance to a telephone-based lifestyle weight loss intervention improve pain and disability for patients with LBP or knee OA?"

2. Methods

2.1. Design

We conducted CACE analyses on data from 2 pragmatic, 2-arm RCTs completed in January 2016 in the Hunter New England Local Health District, New South Wales (NSW), Australia. Both trials were prospectively registered (Australian New Zealand Clinical Trial Registry ACTRN12615000478516 for the LBP trial and ACTRN12615000490572 for the knee OA trial) and approved by an Institutional Ethics Committee (Hunter New England Research Ethics Committee [approval No. 13/12/11/5·18] and University of Newcastle Human Research Ethics Committee [approval No. H-2015-0043]). Full details, analysis plans, and outcomes of the 2 RCTs are reported elsewhere.[18,20,30,31]

2.2. Participants

The trials were part of a cohort multiple RCT design. Consenting participants in an existing cohort, who had been patients referred for outpatient orthopaedic consultation at a public hospital, were screened for eligibility at the 12-month follow-up point in the cohort. Eligible participants were enrolled in the RCTs based on their main orthopaedic complaint (LBP or knee OA) and randomised to the offer of a new treatment (intervention group) or usual care and remain part of the cohort on orthopaedic surgical waitlists (control group). The RCTs included a total of 280 patients: 160 with chronic LBP and 120 with knee OA. Eligibility criteria included being overweight or obese (body mass index [BMI] between 27 and 40 kg/m^2) and having self-reported LBP or knee pain intensity of ≥3 on a 0 to 10 Numerical Rating Scale (NRS) or pain having a moderate impact on daily activities (adapted from item 8 on Short Form-36). Participants were randomised through 1 central randomisation schedule generated by an independent statistician (using SAS 9.3) a priori in a 1:1 ratio to the intervention or usual care.

2.3. Interventions

Participants in the intervention groups of both RCTs received brief advice over the telephone by trained interviewers about the potential benefits of improving lifestyle risk factors (eg, weight loss and physical activity) for their pain condition. Participants were then referred to a free telephone-based lifestyle weight loss coaching service, the NSW Get Healthy Telephone Coaching and Information Service (GHS). The GHS provides up to 10 individually tailored calls over 6 months aiming to help participants lose weight, improve healthy eating habits, and increase physical activity.[21] Health coaches used motivational interviewing techniques and self-regulation principles of goal setting and overcoming barriers to support participants to make sustainable healthy behaviour changes. Advice for weight loss, dietary change, and physical activity was based on recommendations from the Australian Guide for Healthy Eating and National Physical Activity Guidelines.[2,3]

All GHS coaches were university-qualified allied health professionals and participated in a 2-hour training session provided by the study investigators (C.M.W. and S.J.K.). The training session involved evidence-based information regarding diagnosis and management of the conditions including the role of weight loss and lifestyle in pain management. Training included provision of resources and case studies to help support coaches in tailoring support for participants in chronic pain.

Because weight loss is not a core recommended treatment for LBP, but it is for knee OA, intervention participants in the LBP trial only were offered 1 face-to-face physiotherapy consultation to describe the potential role of weight management for chronic back pain. The consultation also aimed at improving understanding of lifestyle factors that influence their LBP and encouraging engagement with GHS and making healthy lifestyle changes. The usual care group remained on surgical waitlists and could receive any care outside of the study.

2.4. Outcome measures

The main outcomes for the CACE analyses were self-reported pain intensity and disability over 26 weeks. Pain intensity was measured as the average back or knee pain intensity over the past week on an 11-point NRS ("0" = no pain and "10" = worst possible pain) collected at weeks 2, 6, 10, 14, 18, 22, and 26. Disability was measured using the Roland Morris Disability Questionnaire (RMDQ) for LBP and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for knee OA (higher scores indicate worse disability) collected at baseline and at weeks 6 and 26. We defined a clinically meaningful result based on the literature, as a 1-point decrease in pain on the NRS,[24] a 3-point decrease in disability for LBP on the RMDQ[15], and at least a 5.3-point decrease for knee OA for the WOMAC.[29]

The trials collected data on a comprehensive list of secondary outcomes; however, we only included 3 key secondary outcomes for this CACE analysis, collected at baseline and at weeks 6 and 26: self-reported weight (in kilograms), physical activity levels (minutes of moderate-to-vigorous physical activity [MVPA] through the Active

Australia Survey), and dietary intake (serves of fruit, vegetables, and discretionary choices through a short food frequency questionnaire). The secondary outcomes were chosen because they were the primary lifestyle targets of the intervention and the hypothesised mechanisms of effect on pain and disability.

Participant demographics collected at baseline included age, sex, BMI, pain intensity, pain duration, education level, health insurance, and smoking prevalence.

2.5. Definition of compliance

We defined compliance for CACE analyses as completing minimum 6 of 10 telephone coaching calls (or prior graduation, as deemed by the coach) with the NSW GHS. An additional criterion in the LBP trial was attendance at the physiotherapy consultation. These definitions were based on the median number of completed GHS calls reported to have an effect on health behaviour in the general population.[25] We also conducted a sensitivity analysis of a lower threshold of completing 4 or more calls (plus attending face-to-face consultation for participants with LBP).

2.6. Patient involvement

No patients were involved in setting the research question, outcome measures, or study design. No patients were asked to advise on interpretation or writing of results. There are no plans to disseminate the results to participants.

3. Analysis

We examined demographic and condition-related characteristics in compliers and noncompliers in the intervention group for each trial. Detailed baseline characteristics for intervention and control groups are published elsewhere.[18,31]

3.1. Complier average causal effect analysis

We calculated CACE estimates (mean difference between groups, intervention minus control among compliers) for pain, disability, weight, physical activity, and dietary outcomes. We present between-group differences at week 26 for all outcomes and compare CACE with unadjusted ITT effects.

Common approaches for estimating CACE categorise study participants as "compliers" (intervention group participants who fully participate in the new treatment and control group participants who do not participate in the new treatment), "always-takers" (always participate in the new treatment regardless of randomisation, if they are offered it), "never-takers" (always reject the new treatment regardless of randomisation, if they are offered it), and "defiers" (always do the opposite of their treatment assignment, ie, reject the treatment when in the intervention group and accept the treatment when in the control group).[5,27]

To identify compliers, we used standard assumptions for CACE analyses.[5,6] We assumed, because of random assignment, that each group (intervention and usual care) has an approximately equal proportion of "compliers," "always-takers," and "never-takers."[6] However, we do not learn anything about the interventions effect in "always-takers" and "never-takers" (because there is no variation in treatment received), and we also assumed there are no "defiers" in both the groups.[5,27] We observed compliance in the intervention group, but it could not be observed in the usual care group. Therefore, because of randomisation, we assumed that the proportion of would-be-compliers in the usual care group was the same as the proportion of compliers that were observed in the intervention group.[5,6] We compared outcomes in participants who would have complied with the intervention from the usual care group, if offered (would-be-compliers), with observed compliers from the intervention group to produce a treatment effect among compliers (CACE estimate).

We used an instrumental variable approach to estimate CACE. We assumed that random allocation to the intervention is an instrumental variable that does not directly affect the outcome rather indirectly affect the outcome through participation (*exclusion restriction*), randomisation determines the intervention provided (*relevance*), and randomisation does not share common causes with the outcome (*ignorable treatment assignment*).[14] Analyses include all eligible "compliers" defined as participants who provided follow-up data at 26 weeks.

Analyses were conducted using STATA v16. For CACE estimates, we used 2-stage least-squares linear regression modelling[27] and an alpha level of 0.05 to calculate 95% confidence intervals. For continuous outcomes, we used *ivregress* (outcome at single time point) or *xtivreg* (outcome over multiple time points). For categorical outcomes, we used *ivprobit* using Newey's efficient two-step estimator to obtain coefficient estimates. We transformed regression estimates from the *probit* model into an approximate of the logistic coefficient[1,22] by multiplying by 1.6, which in turn was exponentiated to obtain the odds ratio.

Regression occurred in 2 stages. First, we estimated the predicted treatment participation for each participant based on group assignment. Second, we regressed the predicted participation rate on the outcome. Standard errors are adjusted in the second stage modelling to account for the lack of heterogeneity in the estimated participation rate. Outcomes measured over multiple time points were modelled using mixed modelling, including a random intercept for participants, and without a fixed effect for time (average outcome). Covariates were not included under assumptions that treatment groups should be balanced about confounders because of randomisation.

Single imputation was conducted for pain over 26 weeks (because of inaccuracies in the estimated rate of participation when using over-time data with missing data) using the participant's mean score over time to fill in their missing data. Two participants (1 in each data set) had no pain measurements; these participants were not included in regression modelling. We dichotomised data for vegetable consumption into <5 serves/day or ≥ 5 serves/day.

3.2. Post hoc analyses

We conducted additional post hoc exploratory analyses, adding baseline weight as a covariate to the CACE and original unadjusted ITT models. The author team decided that baseline weight was considerably different between compliers and noncompliers and the control group (based on a weight difference of $>5\%$). We also considered inclusion of baseline disability and physical activity as covariates.

4. Results

4.1. Compliance

A total of 280 participants were included in analyses (n = 160 LBP trial and n = 120 knee OA trial). Of the 140 participants randomised to the intervention groups (n = 80 back pain and n = 60 knee OA), 29% (n = 23) in the LBP trial participated in 6 or more coaching phone calls and the physiotherapy consultation and 34% (n = 20) in the knee OA trial participated in 6 or more calls (**Table 1**).

4.2. Characteristics of compliers

Compliers of the LBP trial had higher baseline body weight (97.7 vs 89.5 kg), had pain for a longer duration (17.7 vs 11.0 years), higher physical activity levels (162.0 vs 37.7 minutes MVPA/week), and fewer smoked (4% vs 29%) than noncompliers (**Table 2**). Compliers in the knee OA group also had higher baseline body weight and BMI (97.3 vs 91.3 kg and 34.5 vs 32.8 kg/m^2, respectively) but lower physical activity levels (19.0 vs 163.7 minutes MVPA/week) than noncompliers (**Table 2**). All other variables were comparable (**Table 2**).

4.3. Pain intensity and disability

Complier average causal effect estimates in the LBP trial for pain intensity (−1.4; 95% confidence interval [CI], −3.1, 0.40) and disability (−2.1; 95% CI, −8.6, 4.5) favoured the intervention compared with usual care, with low certainty because of wide confidence intervals. In the knee OA trial, there was no effect observed from CACE estimates for pain intensity (−0.4; 95% CI, −2.3, 1.4) and effects favoured usual care for disability (8.8; 95% CI, −12.4, 29.9), with low certainty. CACE estimates for pain intensity and disability were consistently larger in a positive direction compared with ITT effects in the LBP trial but not in the knee OA trial (**Table 3**).

4.4. Secondary outcomes

There was no effect of treatment observed in the CACE estimates for weight in the LBP trial (0.35; 95% CI, −17.1, 17.8) and effects favoured usual care in the knee OA trial (8.0; 95% CI, −6.1, 22.1), with low certainty because of wide confidence intervals (**Table 4**).

For physical activity, CACE estimates in the LBP trial (192.6; 95% CI, −328.8, 713.9) favoured the intervention group and CACE estimates in the knee OA trial favoured usual care (−14.7; 95% CI, −412.6, 383.1) with low certainty (**Table 4**).

Complier average causal effect estimates in the LBP trial for fruit consumption (OR 1.5; 95% CI, 0.2, 9.8) and fruit and vegetable consumption in the knee OA trial (OR 2.0; 95% CI, 0.2, 20.6 and OR 4.4; 95% CI, 0.2, 79.9, respectively) favoured the intervention (**Table 4**). Complier average causal effect estimates for vegetable consumption in the LBP trial (OR 0.13; 95% CI, 0.01, 2.0) favoured usual care (**Table 4**). For intake of discretionary foods, CACE estimates in the LBP trial (OR 1.2; 95% CI, 0.1, 12) favoured the usual care group, but CACE estimates favoured the intervention group in the knee OA trial (OR 0.1; 95% CI, 0.01, 2.8) (**Table 4**). The dietary outcome results are uncertain because of wide confidence intervals.

Complier average causal effect estimates were inconsistently larger in a positive direction compared with ITT effects for all secondary outcomes across both trials.

Table 1

Treatment assignment and participation in low back pain and knee osteoarthritis trials.

Treatment compliance	≥6 calls (+physiotherapy*)	≥4 calls (+physiotherapy*)
LBP, n (%)	23 (29)	26 (33)
Knee OA, n (%)	20 (34)	25 (42)

* Physiotherapy consultation applies only to patients with low back pain.
OA, osteoarthritis; LBP, low back pain.

4.5. Post hoc analyses

For the LBP trial, post hoc analyses showed similar estimates as the primary analyses for pain and increased effects in the intervention group (decreased disability, weight loss, and increased fruit consumption) when adjusted for baseline weight (Appendix A Table 1, available at http://links.lww.com/PAIN/B518). Complier average causal effect estimates remained larger and in a positive direction compared with ITT effects for all outcomes except for vegetable and discretionary choice intake.

For the knee OA trial, post hoc analyses showed similar estimates as the primary analysis for pain, disability, physical activity, and diet outcomes when adjusted for baseline weight; however, the between-group difference in weight reduced (Appendix A Table 1, available at http://links.lww.com/PAIN/B518). Complier average causal effect estimates remained larger and in a positive direction compared with ITT effects for all outcomes except disability and physical activity.

Inclusion of other baseline covariates (disability and physical activity) did not alter results relative to the primary analysis.

5. Discussion

5.1. Principle findings

In our CACE analysis, we observed decreased pain intensity and disability among compliers with LBP, favouring the telephone-based lifestyle weight loss intervention compared with usual care. Complier average causal effect estimates reached the lower end of a clinically meaningful effect for pain intensity of LBP. However, the size and precision of effects are uncertain because of wide confidence intervals and should be interpreted with caution. Our analysis revealed no change in pain intensity among compliers with knee OA, and disability improvements favoured the usual care group. Wide confidence intervals indicated uncertainty in these estimates. In both trials, CACE estimates showed larger effects in a positive direction compared with ITT effects for most outcomes, except for vegetable and discretionary choice intake in the LBP trial and disability, weight, and physical activity in the knee OA trial.

5.2. Strengths and limitations

No other study has utilised CACE analysis to assess estimates of a healthy lifestyle intervention or telephone-based services for musculoskeletal conditions. Our study used data from 2 high-quality pragmatic trials, which mimicked real-world conditions for treatment allocation.[18,31] A limitation of our study was we did not have a standard definition of a compliance threshold for participating in telephone health coaching. Our definition of compliance "completing 6 or more calls" may have been too conservative. One previous systematic review of telephone-based diet and physical activity interventions indicated that at least 12 calls produce the highest effects in the general population.[8] Another limitation is our analyses are likely to be underpowered because this current analysis was not considered in the original design of the trials.[27] Consequently, precision of our estimates was poor and should be considered when interpretating our results. Finally, although many participants in our study did not require surgery, the generalisability of findings may be limited to patients who had been referred for orthopaedic surgical consultation.

Table 2

Characteristics of compliers and noncompliers in the intervention group and study control groups as a reference.

Variable	Condition	Response	Compliers (LBP = 23, kOA = 20)	Noncompliers (LBP = 56, kOA = 39)	Control group (LBP = 80, kOA = 60)
Age (y)	LBP	Mean (SD)	59.7 (12.4)	54.4 (13.5)	57.4 (13.6)
	Knee OA		64.6 (10.3)	62.1 (11.5)	60.2 (13.9)
Sex (female)	LBP	n (%)	11 (48)	37 (66)	46 (57)
	Knee OA		13 (65)	26 (67)	35 (62)
Pain duration (y)	LBP	Mean (SD)	17.7 (15.2)	11.0 (9.8)	18.5 (15.7)
	Knee OA		9.7 (8.9)	9.6 (11.5)	6.7 (8.5)
Country of origin (Australia)	LBP	n (%)	20 (87)	49 (88)	68 (85)
	Knee OA		18 (90)	36 (92)	51 (85)
Education (high school or below)	LBP	n (%)	16 (70)	36 (64)	49 (61)
	Knee OA		17 (85)	31 (79)	43 (72)
Employed	LBP	n (%)	5 (22)	11 (20)	17 (21)
	Knee OA		3 (15)	9 (23)	14 (23)
Private health insurance (none)	LBP	n (%)	21 (91)	52 (93)	71 (89)
	Knee OA		19 (95)	39 (100)	55 (92)
Pain intensity (0-10)	LBP	Mean (SD)	6.7 (1.4)	6.7 (2.0)	6.8 (1.6)
	Knee OA		7.2 (2.2)	6.7 (1.6)	6.8 (2.0)
Disability*	LBP	Mean (SD)	16 (3.7)	14.1 (5.7)	15.8 (5.1)
	Knee OA		48.0 (19.8)	47.9 (16.4)	48.6 (16.5)
Weight (kg)	LBP	Mean (SD)	97.7 (17.5)	89.5 (15.6)	90.8 (14.6)
	Knee OA		97.3 (13)	91.3 (12.5)	89.5 (13.5)
BMI (kg/m^2)	LBP	Mean (SD)	32.9 (3.8)	32.2 (3.4)	32.1 (3.6)
	Knee OA		34.5 (3.5)	32.8 (3.3)	32.1 (3.1)
Physical activity (mins of MVPA/wk)	LBP	Mean (SD)	162 (352.5)	37.7 (117.9)	146.7 (504.0)
	Knee OA		19.0 (37.4)	163.7 (436.9)	100.5 (235.0)
Smoker (yes)	LBP	n (%)	1 (4)	16 (29)	21 (26)
	Knee OA		2 (10)	5 (13)	8 (13)
Alcohol risk score†	LBP	Mean (SD)	2 (2.0)	2 (3.0)	2.2 (2.6)
	Knee OA		4 (4.0)	3 (3.0)	3 (2.8)

The control group data are presented as a reference only.

* Disability was measured using the Roland Morris Disability Questionnaire for those with LBP (0-24) and Western Ontario and McMaster Universities Osteoarthritis Index for knee osteoarthritis (0-96).

† Assessed through Alcohol Use Disorders Identification Test (AUDIT C).

BMI, body mass index; Compliers, 6 or more completed calls for knee OA plus the consultation for the low back pain group; Noncompliers, <6 calls for knee OA, +/− the consultation for the low back pain group alone; LBP, participants with low back pain; kOA, participants with knee OA; MVPA, minutes of moderate-to-vigorous physical activity.

5.3. Implications for practice and policy

Health policy and practice gain immense value in understanding whether interventions are effective when used.[26] We previously found no effect in ITT analyses of the telephone health coaching as a treatment for LBP and knee OA, suggesting it was unlikely to benefit this population group.[18,31] Our current results suggest

Table 3

Complier average causal effect estimates for pain and disability for low back pain and knee osteoarthritis.

Condition	Outcome	Treatment compliance	N*	Modelled compliance†	Mean difference between groups at 26 wk (95% CI)‡
LBP	Pain	≥6 calls + consult	158	29.5%	−1.4 (−3.1, 0.40)
		≥4 calls + consult	158	33.3%	−1.2 (−2.8, 0.3)
		ITT	158		−0.41 (−0.9, 0.1)
	Disability	≥6 calls + consult	93	39.5%	−2.1 (−8.6, 4.5)
		≥4 calls + consult	93	39.5%	−2.1 (−8.6, 4.5)
		ITT	93		−0.81 (−3.4, 1.8)
Knee OA	Pain	≥6 calls	118	34.5%	−0.4 (−2.3, 1.4)
		≥4 calls	118	43.1%	−0.3 (−1.8, 1.2)
		ITT	118		−0.14 (−0.8, 0.5)
	Disability	≥6 calls	88	37.8%	8.8 (−12.4, 29.9)
		≥4 calls	88	48.6%	6.8 (−9.6, 23.3)
		ITT	88		3.3 (−4.8, 11.5)

* N is the number of participants with data available for analysis in intervention and control groups.

† Compliance is estimated from modelling.

‡ Point estimate is the difference between groups, ie, the results from the proportion of people who participated (4-6 calls + 1 consultation) in the treatment group minus proportion with participation in the control group.

CI, confidence interval; LBP, low back pain; OA, osteoarthritis; ITT, intention-to-treat.

Table 4

Complier average causal effect results for secondary outcomes at 26 weeks.

Outcome	Model	N*	Modelled compliance†	Difference between groups at 26 wk‡
LBP				**Mean difference (95% CI)**
Weight (kg)	≥6 calls + consult	117	35.2%	0.35 (−17.1, 17.8)
	≥4 calls + consult		37%	0.34 (−16.2, 16.9)
	ITT			0.12 (−6.1, 6.4)
Physical activity (mins MVPA/d)	≥6 calls + consult	104	41.9%	192.6 (−328.8, 713.9)
	≥4 calls + consult		41.9%	192.6 (−328.8, 713.9)
	ITT			80.6 (−145.9, 307.1)
		N*	**Modelled compliance†**	**Odds ratio (95% CI)**
Diet (fruit) (≥2 serves/d)	≥6 calls + consult	104	41.9%	1.5 (0.2, 9.8)
	≥4 calls + consult		41.9%	1.5 (0.2, 9.8)
	ITT			1.2 (0.5, 2.6)
Diet (veg) (≥5 serves/d)	≥6 calls + consult	104	42.9%	0.13 (0.01, 2.0)
	≥4 calls + consult		42.9%	0.13 (0.01, 2.0)
	ITT			0.5 (0.2, 1.3)
Diet (DC) (>1 serve/wk)	≥6 calls + consult	104	41.9%	1.2 (0.1, 12.0)
	≥4 calls + consult		41.9%	1.2 (0.1, 12.0)
	ITT			1.06 (0.4, 2.8)
Knee OA				**Mean difference (95% CI)**
Weight (kg)	≥6 calls	96	40%	8.0 (−6.1, 22.1)
	≥4 calls		51.1%	6.3 (−5, 17.5)
	ITT			3.2 (−2.7, 9.1)
Physical activity (MVPA/d)	≥6 calls	89	37.8%	−14.7 (−412.6, 383.1)
	≥4 calls		48.6%	−11.5 (−320.6, 297.7)
	ITT			−5.6 (−159.7, 148.5)
				Odds ratio (95% CI)
Diet (fruit) (≥2 serves/d)	≥6 calls	89	37.8%	2.0 (0.2, 20.6)
	≥4 calls		48.6%	1.7 (0.3, 9.9)
	ITT			1.3 (0.5, 2.9)
Diet (veg) (≥5 serves/d)	≥6 calls	89	36.1%	4.4 (0.2, 79.9)
	≥4 calls		47.2%	3.0 (0.3, 27.8)
	ITT			1.7 (0.6, 4.8)
Diet (DC) (>1 serve/week)	≥6 calls	89	37.8%	0.1 (0.01, 2.8)
	≥4 calls		48.6%	0.2 (0.01, 1.9)
	ITT			0.4 (0.1, 1.3)

* N is the number of participants with data available for analysis in intervention and control groups.
† Compliance is estimated from modelling.
‡ The point estimate is the difference between groups, ie, the results from the proportion of people who participated (4-6 calls + 1 consultation) in the treatment group minus proportion with participation in the control group.
CI, confidence interval; discretionary choice; ITT, intention-to-treat; LBP, low back pain; OA, osteoarthritis; DC, MVPA, minutes of moderate-to-vigorous physical activity.

that there may be worthwhile benefits of such services for participants with LBP who engage in 4 to 6 calls after a face-to-face clinical appointment. Focusing the provision of such services to likely compliers may yield superior population health outcomes while preserving health resources. This may be achieved by development and validation of clinical prediction tools to support judgement about likely compliance.

Our results show that compliers in the knee OA trial did not benefit from treatment and may have had worse outcomes. Although there are other trials investigating telephone-based interventions, none other consider CACE analyses. A recent systematic review found inconsistent results for trials of primarily telephone-based interventions for OA using mixed-delivery interventions (ie, face-to-face and telephone) and mixed content (not lifestyle alone) and had varied intervention compliance.[17] Another recent Australian study[10] found improvements in function (mean difference WOMAC 4.7; 95% CI, 1.0-8.4) but not pain for people with knee OA after participating in a 6-month telephone-only intervention of physiotherapist-led exercise and helpline advice compared with helpline advice alone. In this trial, the proportion of patients with 5 or more calls was much higher than in our RCTs (87%, compared with <35%). It is likely that the non–disease-specific nature of our intervention led to poorer compliance.[18,31] Our findings from CACE analysis suggest that a general population, that is, non–disease-specific telephone-based health coaching, is not a suitable treatment option for supporting people with knee OA.

5.4. Future research

Although our results, and others,[4,13,28] suggest that compliance is important in healthcare delivery, it remains unknown whether increasing compliance in people who are not likely to comply leads to increased benefit. Complier average causal effect analysis assumes compliance is a prerandomisation characteristic, meaning larger effects could be attributed to characteristics of compliers rather than increases in compliance to an intervention. To support clinical processes, future research needs to test if the best action is to target those who are likely to comply or aim to increase compliance of all participants in need of the treatment (ie, irrespective of their predicted compliance). Determining practical and accurate prediction models of compliance seems to be the most feasible undertaking to assist healthcare professionals in tailoring treatments plans for individuals.

Complier average causal effect analyses are usually not considered in the design of primary trials. Consequently, many important design elements for robust CACE analyses are overlooked. For example, RCTs rarely consider the sample size for CACE analyses or covariates needed to model compliance, which in turn affects the precision of CACE estimates.[12] Where compliance is an important consideration for policy and practice, researchers can provide more useful results from CACE analyses if they are prespecified in RCT protocols to include appropriate sample sizes and covariates needed to model compliance and precise CACE effects.

6. Conclusion

We found small effects of a telephone-based lifestyle intervention for pain and disability for people with LBP, who comply with treatment compared with usual care but not for those with knee OA. Wide mean estimates of confidence intervals are imprecise and should be considered with caution. Our results suggest that future trials of musculoskeletal care should consider the effects of treatment in compliers through CACE because these are likely to be different to treatment effect based on intention-to-treat analysis and provide useful information for clinical decision-making.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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The complier average causal effect analyses were not preregistered in an analysis plan.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/B518.

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