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Collaborative Chronic Care Models for Mental Health Conditions: Cumulative Meta-Analysis and Meta-Regression to Guide Future Research and Implementation

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Abstract

Objective—Prior meta-analysis indicates that collaborative chronic care models (CCMs) improve mental and physical health outcomes for individuals with mental disorders. This study aimed to investigate the stability of evidence over time and identify patient and intervention factors associated with CCM effects in order to facilitate implementation and sustainability of CCMs in clinical practice.

Method—We reviewed 53 CCM trials that analyzed depression, mental quality of life (QOL), or physical QOL outcomes. Cumulative meta-analysis and meta-regression were supplemented by descriptive investigations across and within trials.

Results—Most trials targeted depression in the primary care setting, and cumulative meta-analysis indicated that effect sizes favoring CCM quickly achieved significance for depression outcomes, and more recently achieved significance for mental and physical QOL. Four of six CCM elements (patient self-management support, clinical information systems, system redesign,

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and provider decision support) were common among reviewed trials, while two elements (healthcare organization support and linkages to community resources) were rare. No single CCM element was statistically associated with the success of the model. Similarly, meta-regression did not identify specific factors associated with CCM effectiveness. Nonetheless, results within individual trials suggest that increased illness severity predicts CCM outcomes.

Conclusions—Significant CCM trials have been derived primarily from four original CCM elements. Nonetheless, implementing and sustaining this established model will require healthcare organization support. While CCMs have typically been tested as population-based interventions, evidence supports stepped care application to more severely ill individuals. Future priorities include developing implementation strategies to support adoption and sustainability of the model in clinical settings while maximizing fit of this multi-component framework to local contextual factors.

Suggested MESH Keywords

Comparative Effectiveness Research; Disease Management; Models; Organizational; Delivery of Health Care; Integrated; Patient-Centered Care

Introduction

There is growing evidence that collaborative chronic care models (CCMs) are effective across a broad range of mental health conditions treated across primary care and specialty mental health settings (1). These models, originally described by Wagner and colleagues (2–7), involved several of a set of four elements: self-management support to help patients take a more active role in their care; clinical information systems, such as provider feedback and electronic registries; delivery system redesign to support prevention-oriented clinical care; and decision support, such as the use of treatment guidelines or expert consultants. Two additional core components were later added: healthcare organization support by local leadership and linkages to community resources (5,6), bringing the total number of CCM elements to six.

Given the strong evidence base for CCMs in mental disorders (1,7–9), the key issue becomes how best to implement and sustain these models in practice (10–13). Several specific questions arise. First, are any of the six elements essential for CCM effects, and are any superfluous? Second, what are the populations and settings most likely to benefit from CCMs? Finally, looking within studies, are there intermediate clinical processes that link the CCM elements to their clinical effects, such as medication prescription indicators?

Existing reviews of CCMs for medical illnesses have been inconclusive regarding which elements are required for CCM effects (4), but have provided some clues regarding key populations or clinical processes. Patients suffering from more severe illness may be more likely to benefit from CCMs (4), and adherence to treatment guidelines by clinicians may be an important intermediary of CCM outcomes (4–6).

There have been no comprehensive reviews of how specific CCM elements, setting/population factors and intermediate clinical processes impact outcomes for mental health conditions. The most germane data come from a meta-analysis focused on primary care depression trials, which indicated that several provider-level factors and process variables may predict CCM effects (9). One descriptive review also investigated CCMs for depression in primary care (14), and found that interventions featuring the first four CCM elements above were generally effective. That study did not explore the role of particular elements in predicting outcomes.

We therefore utilized extensive data obtained in our previous systematic review and meta-analysis (1) to attempt to identify the factors associated with CCM success for mental health conditions. First, we used cumulative meta-analysis to determine to what extent clinical trial effect sizes for CCMs have achieved statistical significance over time for key outcome domains. Second, we used descriptive and bivariate analyses to determine whether individual CCM elements or other trial characteristics (e.g. populations or settings) were related to outcomes; to our knowledge this is the first review to explore the possible relationship between specific CCM elements and clinical outcomes across mental health conditions. We also descriptively reviewed and summarized the role of intermediate clinical processes of care that could be responsible for CCMs' clinical effects. Once again, a unique contribution of this study is its consideration of these factors across mental health CCMs. Third, we used meta-regression to quantitatively determine whether any of these factors are associated with positive clinical outcomes. Fourth, we supplemented these analyses with a descriptive review of determinants of CCM effects identified within individual CCM trials themselves.

Methods

Search Strategy and Study Identification

This study is based on a subset of trials from our initial meta-analysis (1). In that study, relevant randomized controlled trials of CCMs were identified via MEDLINE, PsychINFO, EMBASE, SCOPUS, the Cochrane database, and www.clinicaltrials.gov, along with review of references from identified articles. Medical Subject Heading (MeSH) Search terms included: Case Management, Combined Modality Therapy, Continuity of Patient Care, Cooperative Behavior, Mental Health Services, Primary Health Care/organization & administration, Patient Care Team, Practice Guidelines, Delivery of Health Care/methods. CCMs were defined *a priori* as interventions with at least three of the six elements mentioned above; kappa for inter-rater agreement in identifying CCMs was 1.00, and intra-class correlation for the number of CCM elements present was 0.93 (1). In our initial study, trials with two or fewer CCM elements were excluded (the most common reason for exclusion), as were studies that did not assess our main outcomes (explained below) and those that only compared two CCM conditions without including a non-CCM control group. This study was exempt from human subjects research oversight as it only reviewed published studies.

Data Extraction

We focused on three clinical outcome domains that were reported in at least fifteen trials from our original review, in order to identify domains likely to have sufficient numbers of studies for quantitative analyses. Three domains met this criterion: depression, mental quality of life (QOL), and physical QOL. Data were extracted when reported regardless of the primary diagnosis being targeted, as in the original meta-analysis, and further detail on these domains can be found in the results below.

We identified which of the six CCM elements an intervention included, as well as population, setting, and other trial implementation factors identified by the investigators *a priori* (Table 1). Shared decision-making, defined as the process by which patients and care providers mutually agree to a treatment plan (15–18), was included for exploratory purposes.

Analyses

First, we conducted cumulative meta-analysis (19,20) to estimate the overall cumulative effect size as each study is added to the analysis over time. A cumulative effect size provides

an estimate of how rapidly, and stably, evidence in an outcome domain converges around a particular effect size. We also conducted meta-regression (21,22) to determine whether individual CCM elements, population, setting, or other trial implementation factors, identified *a priori*, predicted outcome effect sizes across studies. For all outcome analyses, effect sizes were calculated using Cohen's *d* (22,23) as in our prior meta-analyses (1).

Only a subset of studies provided sufficient information for meta-analysis (i.e. reported mean, standard deviation, and sample size for both the CCM and control condition). We therefore used chi-squared tests (for categorical variables) and point-biserial correlations (for continuous variables) to determine whether any CCM elements, population, trial, or other implementation factors were associated with trials that resulted in statistically significant results ($p < .05$), among the larger body of studies that reported *p*-values. To further investigate possible predictors of CCM effects, we supplemented quantitative between-study analyses with a descriptive summary review of data relevant to potential CCM mechanisms reported within individual trials.

Results

Fifty-three trials (24–75) published between 1994 and 2010 reported depression, mental QOL, or physical QOL outcomes. Of these, 46 reported results for depressive symptoms, assessed via a variety of measures including the Center for Epidemiological Studies Depression Scale (76), the Beck Depression Inventory (77), the Hamilton Depression scale (78), and the Hopkins Symptom Checklist – 20 item version depression subscale (79). A total of 20 trials reported results for mental QOL, and 18 for physical QOL; nearly all studies assessing QOL relied on either the Short Form Health Survey 36-item (80) or 12-item version (81). Further detail on individual study characteristics can be found in the e-tables.

The most commonly targeted diagnosis among reviewed trials was depression ($n = 39$), followed by bipolar disorder ($n = 4$), anxiety disorders ($n = 3$), and mixed or multiple disorders (in some cases including physical comorbidities; $n = 10$). Several trials contributed outcomes in multiple domains, which were analyzed independently.

Thirteen of these trials included meta-analyzable outcomes for depressive symptoms, and six each for mental and physical QOL. Compared to studies included in the meta-analysis, those excluded were less likely to include the CCM element of clinical information systems, ($p < .001$), and more frequently included healthcare organization support ($p = .04$).

Cumulative Meta-Analysis

Cumulative meta-analysis of depression outcomes indicated an early effect of CCM that remained significant throughout subsequent studies (Figure 1). Cumulative effect sizes favoring CCM for mental and physical QOL achieved statistical significance more recently, in 2010 and 2008, respectively.

Cross-Study Descriptive Analyses

CCM Elements—Trial interventions contained 3.75 ± 0.65 elements (range 3–6; Table 1). The four original CCM elements (2) (self-management support, clinical information systems, delivery system redesign, and decision support) were present in at least 75% of trials. The two later elements (5,6), healthcare organization support and linkages to community resources, were each present in only 8% of trials. The modal CCM trial (51%) featured the first four elements but not the last two. Shared decision-making was explicitly mentioned in 30% of the trials.

The relative ubiquity of the first four CCM elements, combined with the relative rarity of the latter two, makes quantitative analysis of particular elements on clinical outcomes difficult. Consistent with this, chi-squared and point-biserial correlations indicated that no individual CCM element or shared decision-making was significantly associated with statistically significant outcomes among the reviewed trials. That is, studies that contained any particular CCM element did not demonstrate statistically greater improvements over control than did studies not containing that element.

Population, Setting, and Trial Implementation Factors—As with the CCM elements, chi-squared and point-biserial correlations revealed no statistically significant effects on outcomes for individual population/setting factors including system setting, clinic setting, disorder/diagnosis, age, gender, or minority status. Thus, although CCMs led to statistically significant improvement compared to control conditions overall, no specific populations, settings, or trial characteristics were associated with larger differences from control. Likewise, trial implementation factors (type of control condition, U.S. versus non-U.S. location, and trial length) were not associated with greater CCM success over control.

Meta-Regression Results

Initially, our meta-regression was conducted in a multivariate manner, with each of the over a dozen predictor variables entered simultaneously. This resulted in no statistically significant findings, and so we instead ran the meta-regression as a series of bivariate analyses. Consistent with the multivariate meta-regression, and with the cross-study descriptive analyses presented above, the bivariate meta-regression analyses (Table 2) did not reveal any CCM element or explicit mention of shared decision-making to be uniquely associated with better clinical outcomes. None of the population/setting or trial implementation factors achieved statistical significance via meta-regression.

Descriptive Review of Findings Within Studies

To further investigate possible predictors of CCM effects, we supplemented quantitative between-study analyses with a review of data reported within individual trials and follow-up studies.

CCM Elements—Some studies in our sample included comparisons between multiple CCM interventions. One study (25) used a cluster-randomized design, and concluded that both patient self-management support and the more system-based CCM elements (clinical information systems, delivery system redesign, and clinical decision support) were both important in leading to improved outcomes. Another study (42) found that a relatively more intensive CCM intervention (featuring both patient self-management support and delivery system redesign) outperformed a less intensive intervention.

Population, Setting, and Trial Implementation Factors—Five studies (34,50,65,68,82) found CCM to be more likely to outperform the control condition for patients with more severe symptoms when compared to those with less severe symptoms. Two studies (45,83) found CCM to be equally effective for more and less severe patient groups, and two others (33,84) found that CCM did not outperform control regardless of initial depression severity.

Regarding comorbidities, one study (85) found that patients with bipolar disorder and comorbid psychosis derived more benefit from the CCM relative to the control condition than did those without psychosis, while those with comorbid cardiovascular conditions derived less benefit than those without cardiovascular conditions, and those with substance or anxiety disorders showed no difference. Another study reported a trend for CCM to be

more effective at reducing mortality for patients with depression and comorbid diabetes than depression alone (86).

Regarding race/ethnicity, one study found no difference in CCM compared to control based on minority status (55); another found that the CCM had greater effects among racial or ethnic minorities than whites (87). Several studies featuring exclusively minority samples found that CCM outperformed the control condition (46,47,60,61), while others found no difference from control (37,62). Only one study explicitly investigated gender, finding CCM to be superior to control for men but not women (26).

Intermediate Clinical Processes—Fourteen trials found CCM to be associated with higher rates of prescriptions or dosages of antidepressants (29,35,36,45,47,50,55,61,66,67,69,70,72,73), although others found no such association (30,31,53,56,63,82). Other studies indicated that CCMs are associated with superior guideline adherence by clinicians (54,58,59,68). Only one study investigated formal mediation (88,89), finding that the CCM intervention was associated with improved clinician guideline adherence, which was in turn associated with improved outcomes in the CCM group (54).

Discussion

Major Findings in Context

This paper extends previous work by describing the cumulative estimate of effect of CCM interventions over time in domains of depression, mental QOL, and physical QOL, and exploring the relationship of individual CCM elements, population/setting/trial factors, and intermediate clinical processes to CCM effects on key mental health outcomes. Such data are essential for optimizing the development and implementation CCMs for mental health conditions in clinical practice.

Cumulative meta-analysis indicates that CCM effect sizes for depression and mental and physical quality of life have achieved statistical significance, although QOL outcomes attained this status more recently than depression outcomes. The majority of trials have utilized the four original CCM elements (patient self-management support, clinical information systems, delivery system redesign, and provider decision support), while the two later elements were utilized in only 8% of trials. Thus the modal trials featured all four elements but not the two elements added to the model later. The first four elements were frequently included in clinical trials by embedding care managers (itself a form of delivery system redesign) who provide self-management support to patients, clinical information systems in the form of registry tracking, and decision support by communicating with mental health specialists. Healthcare organization support and leadership are crucial, however, in moving from the controlled trial environment to implementation (10,12,90,91) and sustainability (13,92) in clinical practice.

Meta-regression did not reveal association of specific CCM elements or shared decision-making with CCM effects, possibly due to skewed distribution of individual elements across CCMs. Thus, there is insufficient evidence at this time to conclude that any single element is essential, or superfluous, to the model. These results mirror previous qualitative reviews of CCMs applied to physical health conditions in primary care (4). Recent meta-regressions of elements of CCMs for heart failure have also been heterogeneous, with one identifying involvement of multiple disciplines as predictive of better outcomes (93), but another finding no relationship between the number of CCM elements and outcomes (94).

Population, Setting, and Trial Implementation Factors—Although meta-regression analyses did not identify specific population, setting, or trial implementation factors associated with better or worse CCM performance, review of individual studies provided some insights. Most notably, a majority of relevant studies (34,50,65,68,82) indicated that those with moderate to severe symptoms may benefit more than those with milder symptoms. Similarly, one study in bipolar disorder indicated that psychotic features (associated with more severe illness) predicted better outcomes, while substance and anxiety disorder comorbidity did not diminish effects (85). This suggests the potential usefulness of stepped care, i.e., gradations of care intensity for different severities of illness or comorbidities (95).

With the exception of illness severity, we could not identify other factors associated with greater CCM effect. That is, although CCM generally outperformed control across the reviewed trials, we could not identify other populations or settings in which the gap between CCM and control was significantly larger. One interpretation of these findings is that CCMs are robust across different settings, disorders, and populations. Alternatively, meta-regression may have been underpowered to detect significant effects.

Intermediate Clinical Processes—No intermediate clinical processes were reported in a sufficient number of trials to conduct between-study quantitative analyses. While only one study (57) performed a mediator analysis linking greater guideline concordance to improved outcome, descriptive intra-study results suggest that medication prescriptions or adherence, as well as guideline concordance by clinicians, were higher for CCM than control subjects across relevant studies. While it makes intuitive sense that improved pharmacological care and guideline concordance could be pathways through which CCMs exert clinical effects, the general lack of explicit mediator analyses within trials (88) makes reaching concrete conclusions difficult.

Future Directions

First, given that cumulative meta-analysis revealed stable effects for CCMs across disorders in the domains of depression, mental QOL, and physical QOL, a critical next step is identifying factors supporting implementation (10,96) and sustainability (13,92) of the model.

Second, given the strength of the evidence base for CCMs targeting depression (1,7–9), additional RCTs for patients with depression in primary care are unlikely to appreciably expand our understanding of the model. Intervention development work is still needed, however, to optimally apply CCMs to evolving needs of other populations and settings (1,97). For instance, the first CCM trial in bipolar disorder demonstrated improved outcome in mental health measures, but not physical QOL (48,49); subsequent model development more explicitly addressed physical health outcomes and demonstrated improvements in this outcome as well (71,98).

Third, the development of more efficient CCM models may be especially important for spreading CCM interventions to smaller, less resource-rich practices in which the majority of psychiatrists and mental health practitioners work (99). Future studies might use dismantling designs to compare two active CCM conditions differing by one or two different CCM elements. For example, two studies included in this review (25,42) indicated that patient self-management support may add value above and beyond other CCM elements. Such designs will likely require larger samples than was typically seen in the studies we reviewed, as differences between two active CCM interventions may be expected to be smaller than differences between a CCM and control condition. Such studies could incorporate more detailed measures of the CCM elements (such as recording the number of

care management contacts or attendance of therapy groups) to allow consideration of the CCM elements in a continuous rather than dichotomous (present versus absent) manner. Many studies in this review included such measures, but without enough consistency to allow comprehensive cross-study comparisons.

Some, however, have argued that CCMs are in fact synergistic programs and that attempting to disaggregate elements in the service of efficiency “foster[s] the misconception that a single best type of programme can and does exist” (100) (page 1272). They recommend instead focusing on implementation factors such as local context that will lead to the development of complex—but implementable and sustainable—CCMs.

Finally, our review revealed surprisingly few data on intermediate clinical processes that might explain CCMs’ effects on clinical outcomes. To further explore this domain would not require substantial changes to data collection or study design; rather, studies should explicitly report links among CCM interventions, potential mediators, and outcomes.

Limitations

Our characterization of CCM elements and design factors was limited by information provided in peer-reviewed articles; however, we were nonetheless able to demonstrate high reliability in extracting data. Second, our analytic plan assumed that study characteristics were conceptually distinct and described in sufficient detail for extraction from empirical articles. This may not be the case (100) since, for example, effective use of clinical information systems may depend on system redesign. Third, meta-regression has relatively low power, particularly when the distribution of independent variables are not evenly split, which was the case for the six CCM elements (Table 1). Therefore, we supplemented meta-regression with qualitative analyses, chi-squared tests, and point-biserial correlations. Fourth, these latter strategies used study significance (based on reported *p*-values) as an outcome. While such a “vote-counting” approach has important limitations (101), it was the only way to quantify data from studies that could not be included in the meta-regression. Fourth, despite our broad inclusion criteria, the majority of included studies targeted depression in primary care (and nearly all targeted mood or anxiety disorders). Nonetheless, this review represents the first attempt to systematically include **mental** health conditions other than depression. Fifth, nearly all studies that reported QOL results relied on the Short Form Health Survey (80,81), which may be limited in mental health conditions by a statistically imposed negative correlation between its mental and physical component scores (102). It was, however, the only measure used consistently among the reviewed studies. Finally, while we are aware that our population/setting/trial factors and intermediate clinical processes are similar to the constructs of moderators and mediators, respectively, we avoided using these terms because such analyses typically require within-study data (88,89), and our analyses relied on predominantly cross-study analyses.

Conclusions

Cumulative meta-analysis has revealed significant CCM effects across study populations for depression and, more recently, mental and physical QOL outcomes. No single CCM element, or subset of CCM elements, appears essential to the model, although the four original CCM elements appear sufficient for effects in RCTs. Priorities moving forward include the development of implementation strategies that will support adoption and sustainability of the model in clinical practice. Additional supporting work is also needed in intervention development trials for specific subpopulations and settings. To the degree that CCM elements are in fact separable, dismantling studies can inform efficient model development, particularly investigating patient- versus system- or provider-level elements.

Paramount in all these endeavors is supporting the fit of such multi-component interventions to local context in sustainable fashion.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conventional and Cumulative Meta-Analyses of Outcomes

Figure 1.
Traditional and cumulative meta-analysis of outcomes

TABLE 1

Sample characteristics and operationalization for quantitative analyses (N = 53 trials).

CCM ELEMENTS	Number of Trials or Mean	Percent or SD	How variable is included in chi-squared, point-biserial correlation, and meta-regression ^a
1: Self-Management Support	50	94%	Yes vs. No
2: Clinical Information Systems	40	75%	Either vs. No
Computer:	23	43%	
Non-computer:	17	32%	
3: Delivery System Redesign	51	98%	Yes vs. No
4: Decision Support	46	87%	Either vs. No
Consultant:	10	19%	
Guidelines:	20	38%	
Both:	16	30%	
5: Healthcare Organization Support	4	8%	Yes vs. No
6: Linkage to Community Resources	4	8%	Yes vs. No
Total number of CCM elements	3.75	0.65	Continuous variable
Shared Decision-Making	16	30%	Yes vs. No
POPULATION/SETTING FACTORS			
System setting			VA or staff model HMO vs. other
Integrated (VA or Staff Model HMO)	25	47%	
Other/multiple	28	53%	
Clinic setting			Primary care vs. other
Primary Care	37	70%	
All other	16	30%	
Disorder/diagnosis			Depression vs. other
Depression	39	74%	
All other diagnoses	14	26%	
Age of participants ^b	51	10	Continuous variable
Percent female ^b	62	28	Continuous variable
Percent minority ^b	42	34	Continuous variable
OTHER TRIAL CHARACTERISTICS			
Type of control condition			Usual care vs. enhanced/other
Usual care	30	57%	
Enhanced usual care	23	43%	
Country			US vs. other
US	48	91%	
All other	5	9%	
Length of intervention (months)	10.34	6.00	Continuous variable
Intervention 6 months	19	36%	

CCM ELEMENTS	Number of Trials or Mean	Percent or SD	How variable is included in chi- squared, point-biserial correlation, and meta-regression ^a
Intervention > 6 months	34	64%	

^aMeta-regression results are summarized in Table 2. Chi-squared and point-biserial correlation results were nonsignificant for all analyses investigating effect of these characteristics on outcomes for depression, mental quality of life, or physical quality of life (see text for details).

^bData are presented as unweighted averages of study percentages (not at the level of the individual patient).

TABLE 2

Meta-regression results.

Variable	Depression (N = 13 studies, 2,007 participants)	Mental Quality of Life (N = 6 studies, 629 participants)		Physical Quality of Life (N = 6 studies, 541 participants)		
	95% CI ^a		95% CI ^a		95% CI ^a	
CCM Elements						
1. Self-Management Support	NA ^b	NA ^b	NA ^b	NA ^b	NA ^b	
2. Clinical Information Systems	0.04	-0.35—0.43	0.10	-0.45—0.64	-0.18	-0.68—0.32
3. Delivery System Redesign	NA ^b		NA ^b		NA ^b	
4. Decision Support	0.22	-0.27—0.71	0.11	-0.43—0.66	-0.42	-0.57—0.49
5. Health Care Organization Support	NA ^b		NA ^b		NA ^b	
6. Linkage to Community Resources	-0.22	-0.67—0.24	-0.24	-0.64—0.15	0.38	-0.20—0.95
Total Number of CCM Elements	-0.01	-0.33—0.31	0.10	-0.25—0.44	-0.19	-0.68—0.31
Shared Decision-Making	0.02	-0.40—0.45	-0.40	-0.98—0.18	0.38	-0.20—0.95
Population/Setting Factors						
System: VA or HMO ^c	-0.06	-0.45—0.33	-0.19	-0.75—0.36	0.23	-0.28—0.75
Setting: Primary Care ^d	0.25	-0.19—0.68	-0.04	-0.55—0.48	-0.03	-0.55—0.48
Disorder/Diagnosis: Depression ^e	0.09	-0.32—0.51	-0.04	-0.55—0.48	-0.03	-0.55—0.48
Average Age of Subjects	0.01	-0.01—0.02	0.00	-0.02—0.02	-0.00	-0.06—0.05
Percentage of Women	-0.00	-0.01—0.00	0.00	-0.01—0.01	-0.00	-0.01—0.01
Percentage of Minorities	0.00	-0.01—0.01	0.00	-0.01—0.01	-0.01	-0.02—0.01
Trial Implementation Characteristics						
Control Condition: Enhanced Usual Care ^f	0.08	-0.29—0.45	-0.04	-0.60—0.52	0.33	-0.45—1.10
Country: non-U.S. ^g	-0.12	-0.91—0.68	0.22	-0.61—1.05	-0.33	-1.10—0.45
Length of Trial (months)	0.01	-0.03—0.05	-0.01	-0.09—0.06	0.03	-0.04—0.09

^aNone of the variables included in the model was individually significantly associated with CCM success (all $p > .10$)

- b Not enough variation to estimate
- c Reference category: other or non-integrated setting
- d Reference category: non-primary care setting
- e Reference category: non-depression diagnoses
- f Reference category: usual care
- g Reference category: U.S. location