

Evaluating the Effectiveness of Remote Behavioral Interventions Facilitated by Health Care Providers at Improving Medication Adherence in Cardiometabolic Conditions: A Systematic Review and Meta-Analysis

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Abstract

Background Although cardiometabolic conditions account for over 32% of all global deaths, nearly half of the patients with cardiometabolic conditions do not take medication as prescribed. Remote behavioral interventions have been shown to potentially improve adherence in these patients and further support cost effective clinical practice.

Purpose To evaluate the effectiveness of remote behavioral interventions at improving treatment adherence and to explore behavioral intervention components associated with it.

Methods We searched MEDLINE, EMBASE, PsycINFO, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Web of Science in April 2021. Random-effects meta-analyses were utilized.

Results In total, 40 studies, including 24,672 participants, were included. The overall quality of evidence, assessed using the *RoB2 tool*, was low. The intervention had a small (odds ratios [OR] = 1.70, 95% CI: 1.47, 1.96, $N = 4823$ $p < .001$) to moderate effect (SMD = 0.57, 95% CI: 0.38, 0.76, $N = 20,271$, $p < .001$) on the dichotomous and continuous outcomes, respectively. Systolic blood pressure (SBP) was reduced by 3.71 mmHg (95% CI: 3.99, 3.43, $N = 6,527$, $p < .001$) and participants receiving the intervention were twice more likely to achieve blood pressure (BP) control (OR = 2.14, 95% CI: 1.61, 2.84, $N = 1,172$, $p < .001$). Generally, HbA1c decreased by 0.25% (95% CI: 0.33, 0.17, $N = 6,734$, $p < .001$), whereas low-density lipoprotein (LDL)-cholesterol dropped by 6.82 mg/dL (95% CI: 8.33, 5.30, $N = 4,550$, $p < .001$) in favor of the intervention. There was a trend suggesting a potential positive effects on reducing visits to emergency department (OR=0.76, 95% CI: 0.57, 1.01, $N = 4,182$) and mortality rates (OR=0.78, 95% CI: 0.42, 1.42, $N = 1,971$), and no risk for hospital readmission (OR=1.00, 95% CI: 0.83, 1.20, $N = 5,402$), favoring the intervention.

Conclusions Despite low quality of evidence, remote consultations are effective at improving medication adherence and clinical indicators, and potentially cost-effective solution for health care services.

Keywords: Interactive remote behavioral interventions · Telemedicine · Remote consultations · Medication adherence · Cardiometabolic conditions

Introduction

Cardiovascular diseases are the leading cause of mortality and morbidity worldwide. According to the World Health Organization (WHO), approximately 17.9 million deaths were attributed to cardiovascular diseases in 2019, representing about 32% of all global deaths and nearly 40% of all premature deaths. Of these, 85% were due to heart attack and stroke [1].

Recently, diabetes and metabolic syndrome have emerged as contending global health challenges. The incidence of diabetes has almost quadrupled, from 108 million in 1980 to 422 million in 2014. An estimated 1.5 million deaths in 2019 were directly caused by diabetes, whereas another 2.2 million were attributable to high blood glucose in 2012. Diabetes is a major cause of heart attacks and strokes. Between 2000 and 2016, there was a 5% increment in premature mortality from diabetes [2]. The

prevalence of obesity, a component of metabolic syndrome, has nearly tripled since 1975. In 2016, close to 650 million people were obese [3]. Common behavioral risk factors (non-adherence to prescribed medication, poor diet, inadequate physical activity, and smoking) and interlinked pathogenesis cluster these diseases into a group known as “cardiometabolic conditions.”

Di Angelantonio et al. found that cardiometabolic multimorbidity is associated with multiplicative increment in the risk of mortality and with significantly reduced life expectancy, compared with single morbidity [4]. Moreover, evidence suggests that cardiometabolic multimorbidity is associated with complications that are higher than each clinical condition alone [5], with increments in health care use, such as visits to the emergency department or readmissions, limitations in physical function and greater disability [6], lower quality of life [7, 8], and

with mental health conditions such as depression and anxiety [9, 10], all of which lead to inefficiency of fragmented health care.

One way to modify the trajectory, and manage the risks associated with cardiometabolic conditions, is to support individual-level health behavior change [11], such as adherence to prescribed pharmacological treatment [12].

Medication adherence refers to the “extent to which patients take their medications as prescribed by, and agreed with, their healthcare providers to produce the therapeutic result [12, 13]. Nonadherence is estimated to be at around 50% in high-income countries and even higher rates were observed in lower- and middle-income countries [14]. Medication nonadherence is linked to poor rates of treatment efficacy and disease control, adverse clinical outcomes, and increased healthcare expenditure and utilization, despite the availability of effective pharmacological treatments [12–14]. For example, poor adherence to therapy contributes to a lack of good blood pressure (BP) control in more than two-thirds of hypertensive patients [15].

Evidence about treatment adherence is based on proxy or self-reported measures of adherence, which limits our knowledge about the magnitude of this problem. The lack of a “gold standard” method to estimate adherence entails trading-off between different methods of measurements depending on the setting and available resources [16], which alarmingly compromises the provision of effective and cost-effective health care. Moreover, there is no evidence about effective and scalable interventions to support medication adherence, and therefore, we do not know how to best support the individual manage the health care risks associated with these long-term health conditions [17, 18].

Remote behavioral interventions are a promising and potentially cost-effective solution to improve medication adherence and achieve related health outcomes [19]. These interventions are facilitated remotely by health care providers, for example, using a telephone, video, or SMS text messages combined with minimal physical contact, and utilize information and communication strategies to impact on individuals’ decision-making and therefore the actions they take regarding their health. These remotely delivered interventions aim to overcome geographical barriers and improve health outcomes and coverage by providing advice and support using technologies that are accessible to the majority of the population [19–22].

With the outbreak of the COVID-19 pandemic, in-person remotely delivered consultations have become vital in providing continuity of care whilst enabling the adoption of health-protective strategies to reduce the spread of the virus. National Health Service England and Improvement guidelines describe remote consultations as “part of the COVID-19 response” and highlight their importance in primary health care service provision. The majority of consultations in primary care have since shifted to mostly remote-based consultations. Thus, evaluation of the effectiveness of remotely delivered intervention in improving adherence and health outcomes is cardinal. This review focuses on studies that employ remote behavioral interventions facilitated by health-care providers to improve treatment adherence [23].

Previous review has evaluated the efficacy of various remotely delivered interventions at improving adherence and clinical outcomes in communicable and noncommunicable diseases; however, they have not evaluated the effectiveness of such interventions at supporting treatment adherence [24,

25]. We have previously evaluated the effect of automated digital interventions in improving treatment adherence in cardiometabolic conditions; however, we have not investigated the impact of the in-person remotely delivered behavioral interventions [26]. To the best of our knowledge, there is no review that has evaluated the impact of behavioral interventions facilitated remotely by health care providers in supporting treatment adherence in patients with cardiometabolic health conditions.

This review has two aims. First aim is to evaluate the effectiveness of remote behavioral interventions facilitated by health care providers at improving treatment adherence in people with cardiometabolic health conditions. Specifically, this review evaluates the effect of the remotely delivered behavioral interventions in supporting medication adherence, clinical indicators (e.g. blood pressure, cholesterol), and overall clinical outcomes. The second aim is to evaluate the behavioral components associated with the effectiveness of the interventions in supporting treatment adherence. Overall, this review aims to inform recommendations about the development of behavioral interventions facilitated remotely by health care providers to support treatment adherence in patients prescribed medication for long-term health conditions as an adjunct to usual care consultations.

Methods

A review protocol, registered with PROSPERO [23], adhered to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines [27]. There were no deviations from the protocol.

Study Eligibility

The PICOS framework as outlined in Table 1 was used to define the study question and identify eligible studies.

Table 1. PICOS Framework

Population	Adults 18 years old and elder, on oral pharmacotherapy for cardiometabolic conditions (CHD, CVA, HTN, DM, HF, dyslipidaemias)
Intervention	Behavioral interventions facilitated by health care providers using remote delivery modes like telephone, video, SMS text messages, email, web-based applications, or a combination of these delivery modes, aiming to provide advice and support about medication adherence
Comparator	Usual/standard care, that could consist of in-person face-to-face consultations in health care setting, minimal or no behavioral advice for medication adherence facilitated by any other delivery mode
Outcomes	Primary outcome is changes in medication adherence Secondary outcomes are (a) changes in all or any of the BP, LDL-C, HbA1c (b) changes in all or any of mortality, hospital admissions, emergency department visits (c) behavioral components that are associated with changes in medication adherence
Study Design	Randomized control trials (RCTs)

CHD coronary heart disease; CVA cerebral vascular accident; HTN hypertension; DM diabetes; HF heart failure; RCTs, randomized control trials; BP, blood pressure; LDL-C, low-density lipoprotein cholesterol; HbA1c, glycated hemoglobin; SMS short message service.

The population of interest was adults aged ≥ 18 years, on oral pharmacotherapy (all or $\geq 50\%$ of participants) for long-term cardiometabolic conditions. No restrictions on settings were applied. Eligible interventions were facilitated remotely by a health care provider using any or combination of the following: telephone calls, video, text messaging, emailing, and web-based applications. Health care providers could be a doctor, nurses, pharmacists, healthcare assistants, medical students, or other qualified personnel. The intervention consisted of the provision of behavioral advice to support medication adherence. Multicomponent interventions, in which the intervention was remotely delivered and consisted primarily of behavioral advice for medication adherence, were included.

This review considered only randomized control trials (RCTs). Studies when the control group received usual or standard care, such as in-person face-to-face consultations or minimal remote advice about health care, were included. Eligible studies should have at least reported the primary outcome of medication adherence (e.g. taking at least 80% of prescribed tablets, or having medication dispensed for at least 95% of days of the prescribed period); outcomes for clinical indicators such as blood pressure (BP), low-density lipoprotein (LDL) and glycated hemoglobin (HbA1c) as proxy measures of treatment adherence, and overall clinical outcomes (i.e. mortality, reduction in hospital admissions or visits to the emergency department).

Excluded studies were automated digital interventions, interventions not involving a health care provider and remote communications facilitating study procedures only (e.g. welcome messages, or end of the trial notifications, instruction about procedures such as the use of BP monitor or glucose devices) and did not offer any additional behavioral advice on adherence, or interventions implemented only to collect study data. Studies in which the delivery mode aimed to provide solely enhanced usual care to the intervention group such as medication adjustments or telemonitoring of BP or glucose levels, were excluded.

Search Strategy

The search for relevant articles was conducted on MEDLINE, EMBASE, PsycINFO, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Web of Science between 3rd and 7th April 2021. References of some key articles and eligible trials were also searched. The search strategy was developed using keywords mapped onto the PICOS framework and by inspecting the keywords used by other relevant reviews. The search terms ([Supplementary Table 1](#)) were adapted for use in the respective bibliographic databases. The search terms included terms describing the intervention (remote behavioral interventions, #1), the condition (cardiometabolic, #2), the health problem (medication adherence, #3), and study design (RCT, #4) of interest. Filters for controlled or RCTs were applied. There was no limitation on the period of publication though only articles in English were considered. Gray literature was not searched.

Study Screening

The search results were managed in the web-application Rayyan [28]. After the removal for duplicates, two reviewers (C.I.C. and A.K.) independently screened titles and abstracts and discussed and resolved conflicts between them. A third reviewer, S.S. was involved in case of a tie. Studies eligible for full-text screening were then independently screened against

the inclusion/exclusion criteria and the reasons for exclusion were noted. At the same time, references from eligible studies were screened for additional studies. In some cases, authors of primary studies were contacted to clarify the nature of the intervention, provide missing data, or provide full texts for inaccessible studies. Studies that did not meet the inclusion/exclusion criteria and whose full texts were inaccessible, were excluded. Protocols, feasibility/pilot, and mediation studies were also excluded at this point. A small number of duplicated studies were found and excluded. Eligible studies were then taken forward for data extraction and coding.

Data Extraction and Coding

Outcome data, measured using direct or indirect measures and summarized as continuous (mean and standard deviation), dichotomous (adherent/nonadherent), multi-level (low/less favorable, moderate/favorable, and high/very favorable), and mean values, were extracted into the *Revman 5.4.1* software [29]. Study characteristics were summarized using an Excel data extraction form. Where more than one intervention group was compared in a trial, the most enhanced arm was selected and extracted as the intervention group, and the least enhanced intervention was the comparator group. The intervention components were coded using a theoretical framework. The framework included coding for the following intervention components: “tailored,” when the intervention provided different information to participants based on individual characteristics; “education,” when the intervention provided generic information about the health conditions and the adherence to prescribed treatment; “motivation,” when the intervention aimed to support motivation to adherence; and “reports on behavior,” when the intervention prompted participants to report on medication adherence. This framework was developed based on the literature and previous research recommending effective ways to conceptualize the components and functions of medication behavior change interventions [17, 30].

Baseline and final values closest to the cessation of the intervention were selected for data extraction points, presuming the intervention effect would attenuate further away after its cessation. For studies in which the baseline data or change from baseline were not reported, only final follow-up outcome data were extracted. This was especially relevant in cases where a range of measurement methods was used to measure adherence behaviors. At these occasions, it was decided not to contact the primary authors, but to estimate values based on reported data. The reviewers independently coded all data reported and met to resolve any conflicts. If the reviewers’ estimated values did not align with those reported by the primary authors, then the reviewers’ agreed and estimated data were included in the analysis.

Risk of Bias in Individual Studies

The risk of bias for individual studies was evaluated using the Cochrane Risk of Bias tool Version 2 (RoB2). Using this tool, bias in RCTs was assessed in different aspects of trial design, conduct, and reporting, known as domains of a singular outcome: adherence. “Intention-to-treat” and unadjusted values were used to examine the effect of assignment to the intervention as opposed to the effect of adherence to the intervention (per-protocol effect). Where these were unavailable, the most comparable data were used. “Publication” or “non-reporting bias” was assessed using the funnel plot and Egger’s test using STATA 17.

Meta-Analysis

At the meta-analysis, where both subjective and objective measures were reported, the most objective measurement was selected and included in the analysis to reduce measurement bias. Where more than one outcome measure was provided, the most comparable measure across the studies were included. Due to the observed heterogeneity, the standardized mean difference (SMD) was deemed an appropriate measure for continuous outcome data.

Clinical indicators were summarized using the mean difference (MD). This is an appropriate summary statistic when the outcome measurements in all studies are on the same scale/unit.

Binary outcomes for medication adherence, BP control, and overall clinical outcomes were coded (adherent/totals, achieved BP control/totals, reduced mortality or not, reduced hospitalizations or not, and reduced visits to the emergency department or not) and were summarized using odds ratios (OR). Cohen's *d* classification of effect sizes was used to categorize the effect sizes for continuous outcomes into small, medium, and large sizes. Additionally, continuous and dichotomous outcomes were classified as small, medium, and large effect sizes and compared with each other to enable interpretation and form recommendations for research, practice, and policy making [31].

The random-effects model with inverse-variance was selected as it incorporates an assumption that the different studies are estimating different, yet related, intervention effects. The I^2 statistic was used as a measure of heterogeneity. Values between 0% and 25% are considered not important, 25% and 75% may represent moderate heterogeneity, and 75% and 100% represent considerable heterogeneity. When heterogeneity is high, additional analysis is recommended to explore potential moderators [32].

Subgroup Analysis

Three subgroup analyses to investigate the variables that might explain heterogeneity were conducted: the clinical health condition, the measurement of the behavioral outcome, and the intervention components.

Results

The search identified 5,031 articles. After the removal of duplicates, 4,224 articles remained for the title and abstract screening, during which 3,945 articles were excluded. Out of 279 articles considered for full-text screening, 40 eligible studies were included in the review and quantitative analysis. The reasons for exclusion were noted and are listed in Fig. 1. No additional study was included from searching references of included studies.

All the studies consisted of behavioral interventions that were delivered remotely. In total, 24,672 participants were randomized, 11,876 of whom were in an experimental group and 12,796 in a control group. Fourteen studies were conducted in the USA, four in the UK, three in Denmark, four in Iran, four in China, two in South Korea, two in Netherlands, and one each in Brazil, Spain, Canada, Greece, Vietnam, and Sweden. One study was conducted in multiple countries (Belgium, France, Germany, Italy, Spain, Switzerland, and the UK).

The participants were recruited from primary care practices ($k = 18$), secondary care ($k = 15$), tertiary care ($k = 1$), and pharmacy settings ($k = 6$). There were 36 individually

randomized trials and four cluster RCTs. The targeted health conditions included cardiovascular ($k = 14$), diabetes ($k = 8$), hypertension ($k = 7$), and multiple cardiometabolic conditions ($k = 11$) (Supplementary Table 2). The study duration ranged from 1 to 12 months. Self-report questionnaires were used in 17 studies, whereas more objective measures were in 19 studies. Four studies used both.

Regarding the intervention delivery mode, most interventions were telephone-based (95%), one used SMS and one was web-based. Four studies were multicomponent (remote and face-to-face, with much of the behavioral communication facilitated remotely) and 36 were only remote-based interventions. The most frequently coded intervention component to support treatment adherence in the intervention group was "motivation" in 37 studies; followed by "education" in 24 studies; "tailored" and "report on behavior", each in 18 studies. None was coded in the control group.

Most of the studies reported the frequency of telephone calls ranging from multiple telephone calls per week to two calls per month, with the time duration of an average call ranging from about 5–30 min. One study used interactive text messaging and another web-based video conferencing in a virtual clinic. Health care providers facilitating the intervention included nurses ($k = 14$), pharmacists ($k = 18$), doctors ($k = 1$), medical assistants ($k = 1$), and counselors/advisors ($k = 6$). A detailed description of both the intervention and the comparator groups in each study is provided in Supplementary Table 3.

Risk of Bias Assessment

The Cochrane risk of bias tool 2 was used for quality assessment for parallel group, individually randomized and cluster RCTs, respectively. Although all the included studies were RCTs, their risk of bias varied considerably possibly due to study design, conduct, intervention behavioral components and strategies content, and outcome measurements. Almost half (17/40) of them were judged as having "some concerns." Ten had "high risk" of bias and three had "low risk" (Supplementary Fig. 1). The overall risk of bias is summarized in Fig. 2.

Meta-Analyses

Medication adherence

Meta-analyses for the primary outcome were conducted using continuous and dichotomous outcomes. The continuous data showed that, on average, the intervention had a moderate and significant effect on improving medication adherence (SMD = 0.57, 95% CI: 0.38, 0.76, $N = 20,271$, $p < .001$). Heterogeneity among the studies was high and statistically significant ($\tau^2 = 0.20$, $Chi^2 = 813.19$, $df = 23$, $p < .001$, $I^2 = 97\%$), suggesting that the effect of the intervention varied considerably among the individual studies (Fig. 3). The dichotomous outcome effect size of the odds of improvement in adherence increased by 70% (OR = 1.70, 95% CI: 1.47, 1.96, $N = 4,823$, test for overall effect $Z = 7.21$, $p < .001$) in favor of the intervention. However, using Cohen's *d* equivalency table, this was smaller effect size in comparison to the continuous outcome. Heterogeneity was moderate ($Chi^2 = 49.63$, $df = 16$, $p < .001$, $I^2 = 68\%$), also indicating that the effect of the intervention was different across the studies (Fig. 4). In both cases, there were sufficient number of studies and participants to detect an effect if indeed there was one.

Clinical Indicators

Blood pressure

The analysis of systolic blood pressure (SBP) measurements revealed that overall, the intervention led to a significant mean change in SBP by -3.71 mmHg (95% CI: $-3.99, -3.43$, $Z = 25.71$, $p < .001$) in the intervention group as compared

with the control group on the continuous outcome (Fig. 5). Heterogeneity in the continuous outcome was high ($I^2 = 99\%$). On the dichotomous outcome, participants who received the intervention were twice as likely (OR = 2.14, 95% CI: 1.61, 2.84, $Z = 5.23$, $p < .001$) to achieve BP control compared with those that did not (Fig. 6). Even though no heterogeneity was

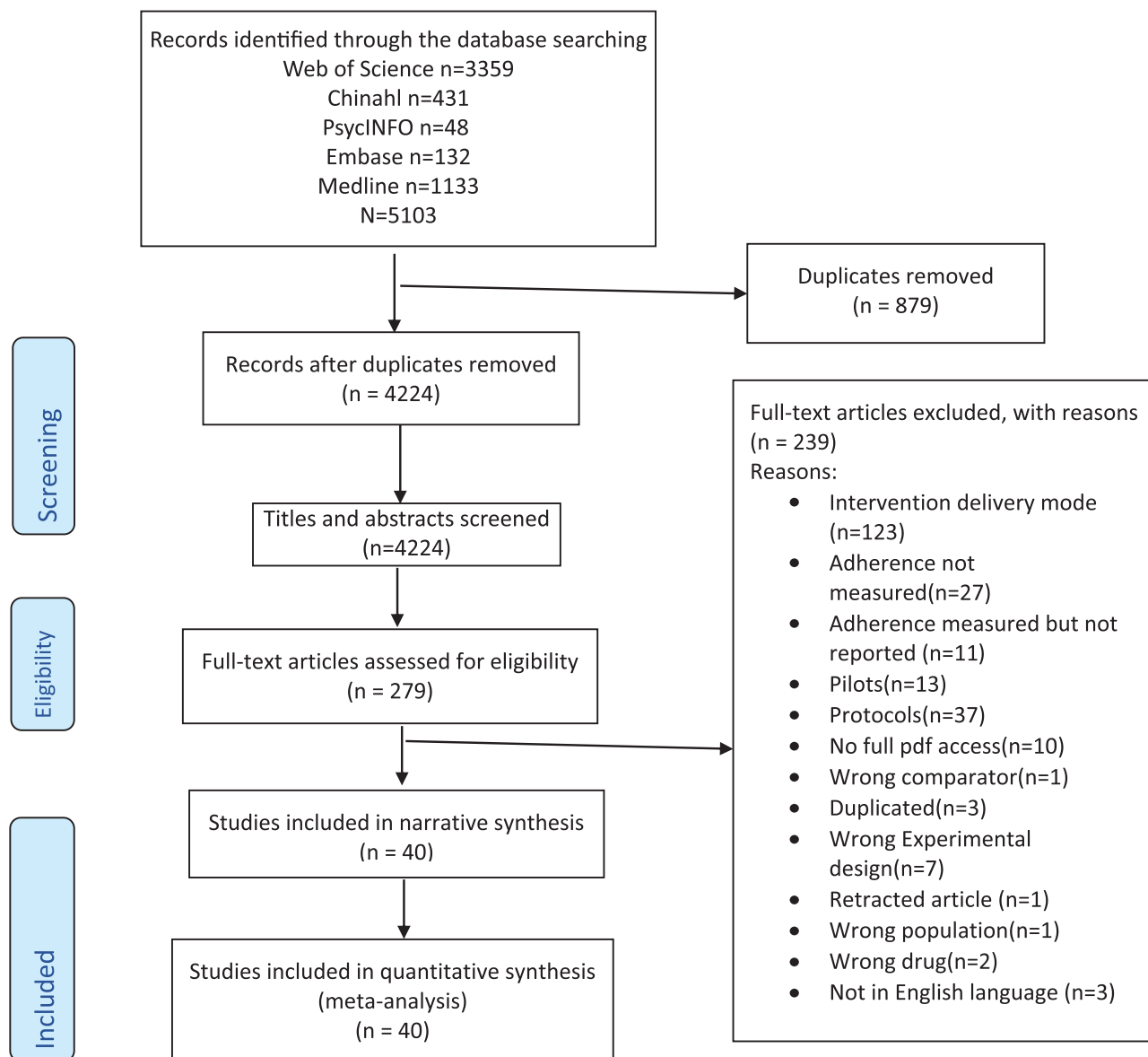


Fig. 1. PRISMA flow diagram of systematic search, inclusion, and exclusion of studies.

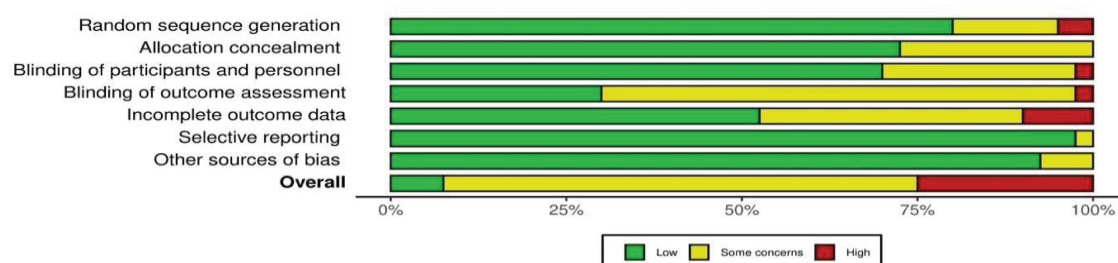


Fig. 2. Summary of the risk of bias assessment for each domain and overall, as a percentage of included studies.

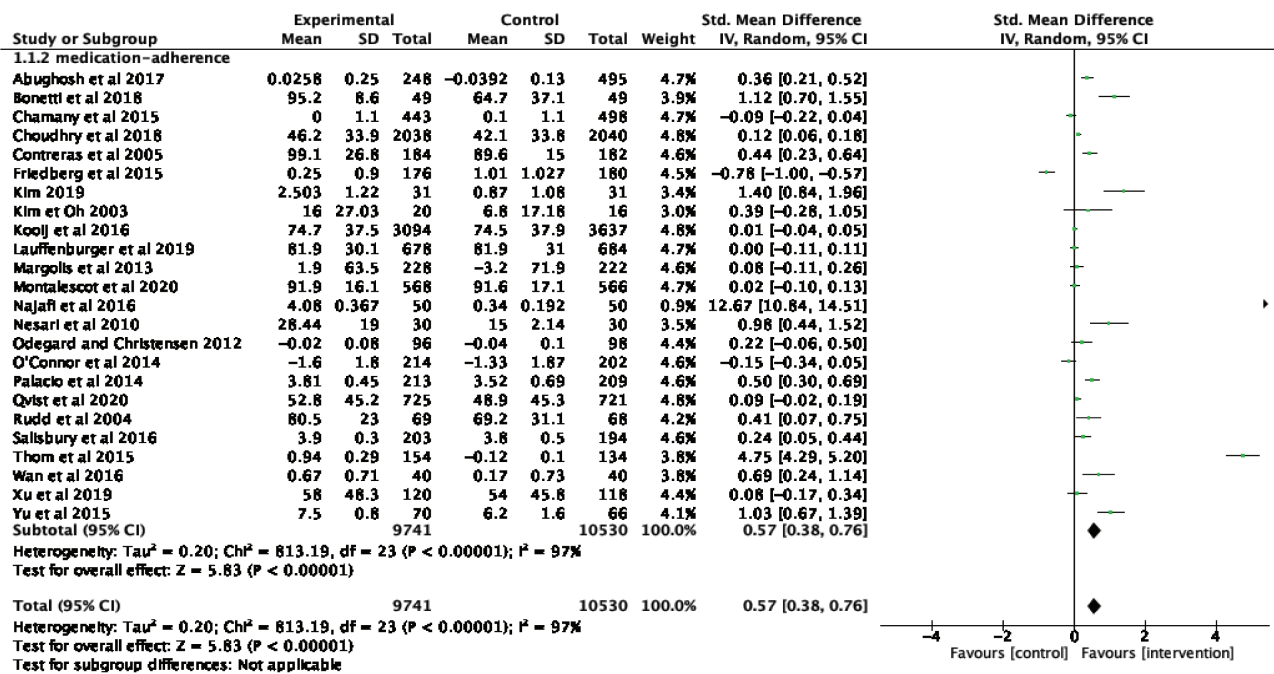


Fig. 3. Meta-analysis of intervention effect on medication adherence (continuous outcomes).

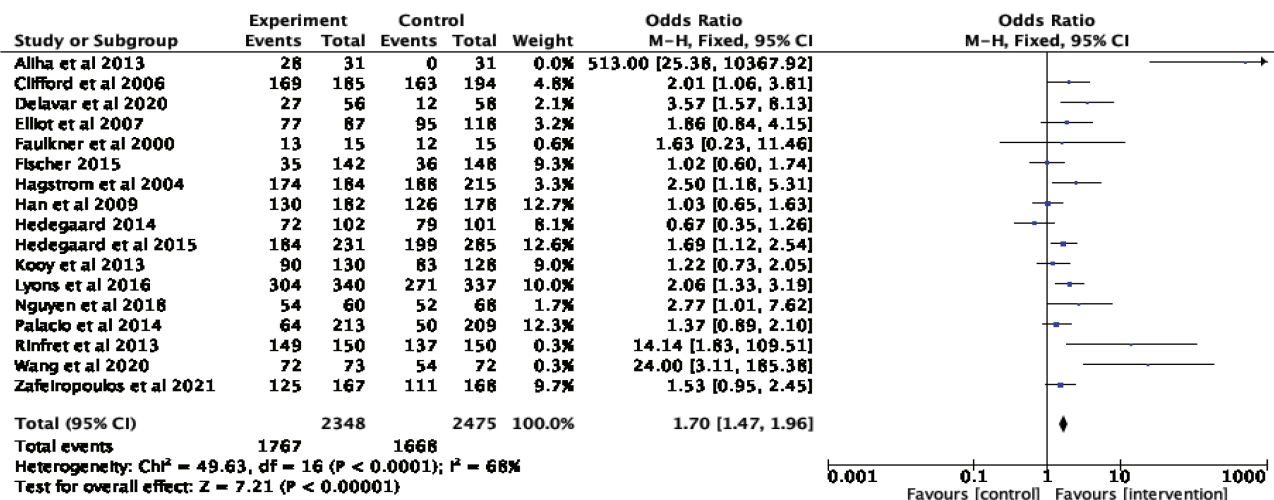


Fig. 4. Meta-analysis of intervention effect on medication adherence (dichotomous outcomes).

noted in the dichotomous outcome, the analysis included only four studies and 1,172 participants.

HbA1c

Overall, there was a small but statistically significant mean change in the HbA1c of -0.25% (95% CI: $-0.33, -0.17$, $Z = 6.04$, $p < .001$) in favor of the intervention on the continuous outcome analysis. Heterogeneity was high ($I^2 = 86\%$), suggesting that the mean reduction in HbA1c was dissimilar among the studies. The analysis was sufficiently powered to detect an effect of the intervention (Fig. 7).

LDL

LDL-cholesterol changed by a mean of -6.82 mg/dL (95% CI: $-8.33, -5.30$) in the meta-analysis of four included studies. This was a significant reduction ($Z = 8.82$, $p < .001$) found

in a few studies with a rather sufficient sample size of participants ($N > 4000$). In this case, too, heterogeneity was moderate, with I^2 -statistic of 70% (Fig. 8).

Overall Clinical Outcomes

Mortality

This review found that participants who received the intervention had a 22% (OR = 0.78, 95% CI: 0.42, 1.42) lower risk of death compared to those who did not receive the intervention (Fig. 9). However, this reduction was not statistically significant ($Z = 0.82$, $p = .41$). No heterogeneity was noted in this outcome.

Readmissions

Generally, there was no statistically significant difference in the odds of readmission between the experimental and

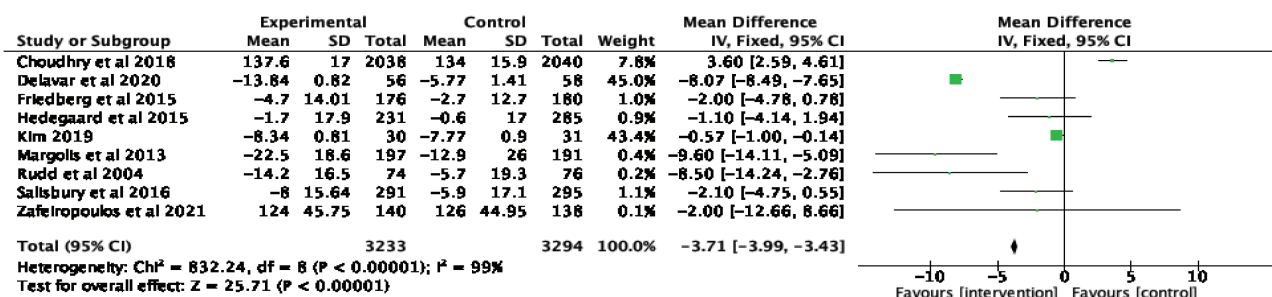


Fig. 5. Meta-analysis of intervention effect on blood pressure (continuous outcomes).

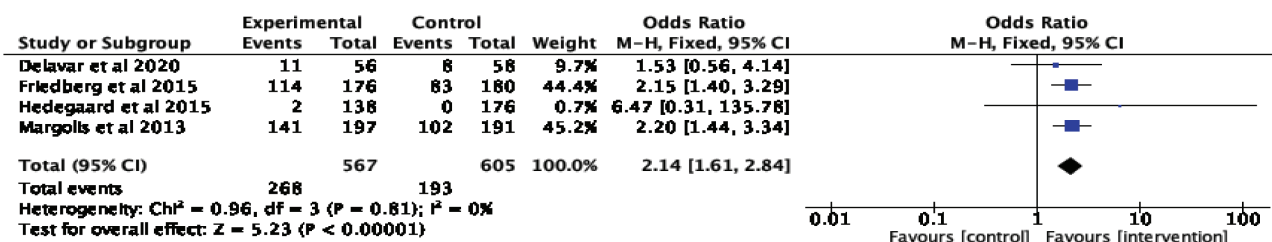


Fig. 6. Meta-analysis of intervention effect on blood pressure control (dichotomous outcomes).

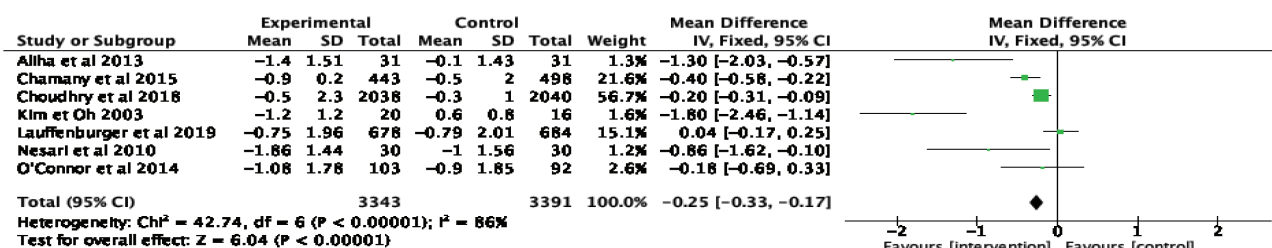


Fig. 7. Meta-analysis of intervention effect on HbA1c (continuous outcomes).

control groups (OR = 1.00, 95% CI: 0.83, 1.20, $Z = 0.03$, $p = .98$) on the dichotomous outcome (Fig. 10) suggesting similar risk of readmission in both intervention and control group. Although heterogeneity was low among the six studies with 5,402 participants ($I^2 = 32\%$), nearly two-thirds of the weight was contributed by one study [45]. Small quantities of events could have underpowered the ability to detect a true effect in this case.

Visits to Emergency Department

In two studies that recorded visits to the Emergency Department, a marginal statistically nonsignificant reduction in the risk of a visit to the emergency department by 24% (OR = 0.76, 95% CI: 0.57, 1.01, $Z = 1.90$, $p = .06$) was observed (Fig. 11) suggesting a potential effect of the intervention at reducing the use of health care resources. Of note is that the study by Choudhry et al. [45] contributed 96% of the overall weight. Between the two studies, heterogeneity was low and nonsignificant.

Publication Bias

Publication bias and small study effect were assessed using the funnel plot and Egger's regression test for both continuous and dichotomous outcome data in STATA 17. In both cases, the plots were asymmetrical, suggestive of potential publication bias and/or small study effects. However, most studies were within the nonsignificant zone (within the funnel). Also, most

small studies with large standard deviations reported an average effect size above the mean rather than below. The larger studies with smaller standard deviations were clustered at the top of the funnel plots and appeared to be roughly symmetrical. Egger's regression test was significant in both cases ($p = .005$ for continuous data, $p = .004$ for dichotomous data). Therefore, the funnel plots suggest that there is evidence of potential publication bias and more so, of small study effects as the smaller studies are more unequally distributed compared with the larger studies (Supplementary Figs. 2 and 3).

Subgroup and Sensitivity Analyses

In summary, between-group analyses show that cardiovascular conditions had the largest effect size of all the subsets for the continuous outcome analysis, whereas there was no effect detected for the dichotomous subgroup analysis. The effect of the treatment prescribed for a specific health condition at explaining intervention effectiveness was unclear. Heterogeneity was high both within each subset and between them. Self-reported measures had a larger effect than objective measures. High and moderate heterogeneity was noted within and between the subsets on the continuous and dichotomous outcomes, respectively. With regard to intervention influences, the within-group analysis shows that tailored advice had a larger and statistically significant effect on improving medication adherence compared to non-tailored interventions; "reporting on medication adherence

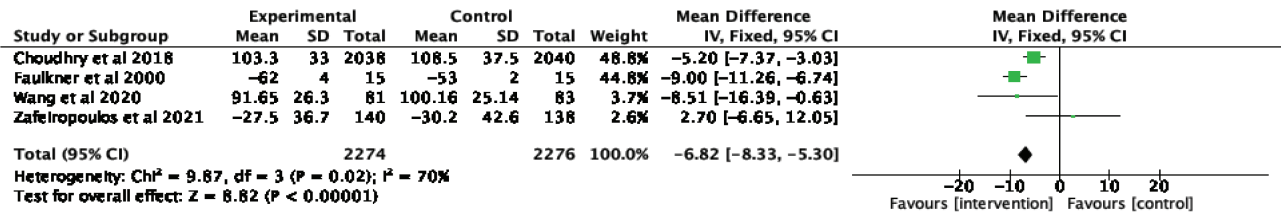


Fig. 8. Meta-analysis of intervention effect on LDL-cholesterol (continuous outcomes).

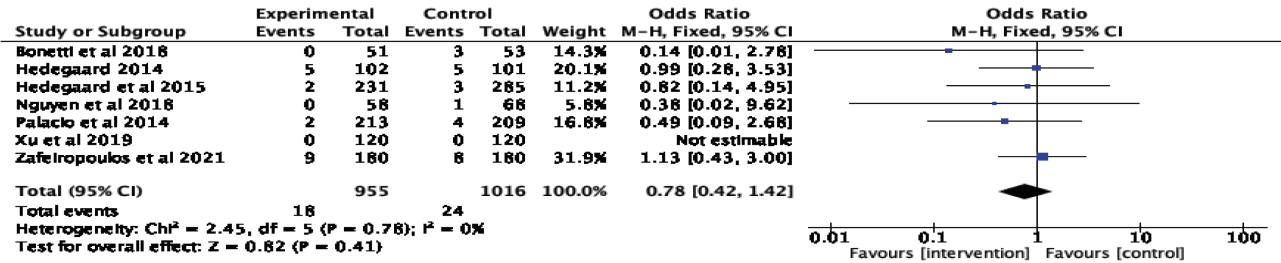


Fig. 9. Meta-analysis of intervention effect on mortality (dichotomous outcomes).

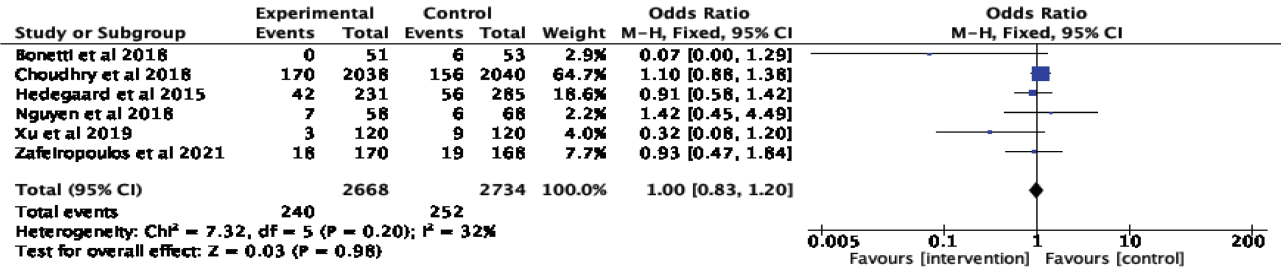


Fig. 10. Meta-analysis of intervention effect on hospital readmissions (dichotomous outcomes).

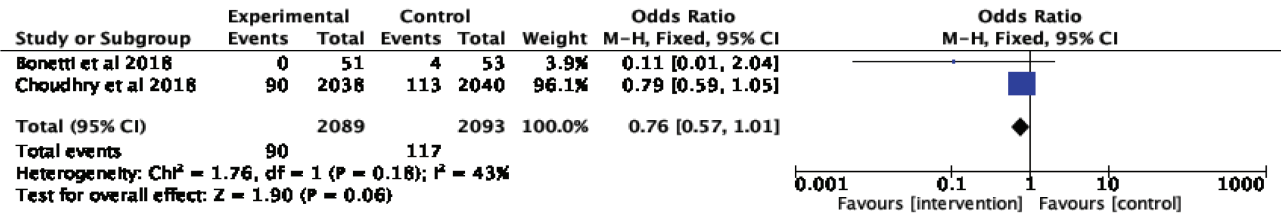


Fig. 11. Meta-analysis of intervention effect on visits to the Emergency Department (dichotomous outcomes).

behavior” had a larger and statistically significant effect on medication adherence compared with interventions that did not prompt reports on behavior; interventions that provided education and advice about the health condition and/or adherence had the larger and statistically significant effect on medication adherence compared to interventions that did not. There was no difference between the interventions that aimed to support motivation to adherence, primarily because most of the studies provided such support. Interventions that consisted of all behavioral components had larger effect at supporting medication adherence compared to intervention with motivational elements only. Findings were supported by both the continuous and dichotomous analyses. (Supplementary Figs. 4–9).

The sensitivity analysis suggested that the effect size was largest in smaller studies although non significantly different compared with medium and larger sample size studies. Larger

studies had small, however statistically significant effect. (detailed results in Supplementary Figs. 10 and 11).

Discussion

Principal Findings

This systematic review with meta-analysis included 40 RCTs ($N = 24,672$). Overall, the intervention had a small to moderate effect on improving medication adherence in cardiometabolic conditions. BP, HbA1c, and LDL improved significantly at a short-term follow-up. There was a tendency favoring the intervention suggesting a positive effect in reducing the use of emergency departments and mortality rates, and no effect in changing hospital readmissions. The sensitivity analysis revealed that study size might have accounted for some of the differences in the magnitude and direction of effect. However, larger studies supported the observed positive effects of the

remote behavioral interventions in supporting medication adherence and clinical indicators.

Between- and within-group analyses further explored heterogeneity and suggested that the interventions were more effective when tailored to the individual, prompted reports on adherence, and provided generic information and advice about the condition and adherence. An observed larger effect of self-reports in comparison to objective measurements suggests that findings must be treated cautiously due to bias. Moving forward, studies should use objective measures to ascertain the effect and the underpinning of the remotely delivered interventions in supporting treatment adherence in patients with cardiometabolic health conditions.

Implications of the Findings: Possible Mechanisms and Significance for Clinicians and Policymakers

At a short-term follow-up, we found a moderate intervention effect at improving medication adherence outcome. Data loss during log transformation of OR might explain the smaller effect size detected at the dichotomous analysis. Continuous outcomes, in contrast, require no such transformations and cover a wider range of values. These meta-analyses show that remote consultations are effective at supporting medication adherence. This result concurs with a previous systematic review of automated telecommunication interventions to improve adherence in cardiometabolic conditions, which found a small but significant effect size in favor of the automated digital interventions [26]. Our paper builds on the evidence that suggested that interactive communication could further support enhance adherence. The surprisingly small effect size in both these papers could be attributed to the Hawthorne effect (leading to a smaller difference between the comparison groups) [33]. Thus, these findings should be treated with caution when translated to real-world practice. Nevertheless, our review had greater power than the previous one and suggests that remote consultations can potentially improve adherence as an adjunct to clinical practice, though the context in which they are most effective needs to be further investigated.

BP, HbA1c, and LDL-C generally showed significant improvement at the end of the intervention. Specifically, systolic BP decreased on average by 3.7 mmHg and the odds of achieving BP control were twice the odds in the intervention group compared with the control. HbA1c was reduced by approximately 0.25% and LDL by 6.82 mg/dL in the experimental group compared to the control. This finding suggests that remote behavioral interventions could potentially have an impact on mitigating important risk factors for morbidity and mortality associated with long term health conditions. An umbrella review on the effectiveness of telemedicine in diabetes, dyslipidemia, and hypertension by Timpel et al. found similar results [34]. However, they did not investigate changes in medication adherence; thus, its effects cannot be attributed to improvements in medication adherence behavior. Even though clinical indicators saw significant improvements in both reviews, these improvements do not necessarily map into clinical guidelines regarding set clinical targets. For example, most hypertension and diabetes clinical guidelines focus on achieving disease control (i.e. BP < 140/80 mmHg, HbA1c < 7%, and LDL < 130 mg/dL) rather than absolute reductions (drop in SBP by 3.7mmHg, or HbA1c by 0.25%, or LDL by 6.82 mg/dL) [35–37]. To address this challenge, our review synthesized evidence

measuring and operationalizing clinical effectiveness in a variety of ways. Our generated evidence-based thresholds add to previous knowledge and could directly inform clinical guidelines about the effects of remote behavioral interventions in managing cardiometabolic conditions. Future research could seek to harmonize the operationalization of intervention effects with clinical guidelines to ensure the results are more relevant for clinical practice and interpretable for policymaking.

No significant effect was found for hospital readmissions, whereas a tendency towards the intervention reducing visits and use of the emergency department and mortality rates was found. However, these analyses were underpowered and a single study [38] contributed the most weight to the analyses. A report, evaluating the overall clinical outcomes and cost-effectiveness of telemedicine, found that mortality and hospital readmissions decreased in heart failure patients. Despite the low quality of evidence, the study showed that remote interventions could potentially benefit heart failure patients to improve overall clinical outcomes at least in the short term [26]. The evidence generated by our review could not provide an answer to this question primarily due to the lack of primary data and the limited power in the analyses. Nevertheless, these are promising results and suggest that remote treatment adherence interventions might be beneficial in monitoring and improving overall outcomes despite the scarcity of evidence. More rigorous data obtained over longer durations are needed to ascertain the effect of remote interventions on overall clinical outcomes and to inform service provision and health policymaking.

Regarding publication bias and small study effects, funnel asymmetry plus significant results from Egger's regression test for both continuous and dichotomous outcome data analyses suggest the likelihood of small study effects and publication bias in this field. This was evidenced by the unequal distribution of small studies in the funnel plot, whereas the larger studies appeared more symmetrical. Despite indications of potential bias as shown by Egger's test, it does not provide evidence regarding the nature of the true cause of publication bias.

Three subgroup analyses explored heterogeneity based on the health condition, method of measurements, and intervention components, respectively. Conclusions from these subgroup analyses should be treated cautiously because of decreased power and the lack of information provided in some of the primary studies. In the first subgroup analysis, there was no clear evidence, as to whether or not, the intervention had different effects on improving adherence across populations prescribed treatment for a specific health condition. There was however some promising results suggesting the intervention effective at supporting adherent to those with multimorbidity; patients in this subset might have potentially been more receptive and adherent to the intervention. This is also suggested by another study in which patients with comorbidities, were more likely to adhere to the intervention at a short-term follow-up [39].

In the second subgroup analysis, self-reported measures had a larger effect size as compared to objective measures. This could be attributed to subjective and over reporting bias because participants were aware of both the allocation group and the measured effect [16, 33].

With more objective measures, namely, repeat prescription data and pill counts, bias could have been introduced by

unblinded outcome assessors. One such example is the study by Yu et al. in which both the participants and assessors were unblinded. Future studies could employ objective measurements of adherence, like urinalysis, to provide evidence and inform practice and policymaking.

In the third subgroup analysis, we explored within-study effects. The subsets were based on whether the intervention provided tailored advice (tailored), prompted participants to report on their medication-taking behavior (report behavior), provided education and advice about the health conditions and/or prescribed medication (education), or provided motivational support (motivation). Interventions consisting of the first three components were on average significantly more effective at supporting adherence than those that did not. As for motivational support, comparability within studies was challenging as only a few interventions did not include this component. Furthermore, analysis suggested that the first three behavioral components had a significantly larger effect size above and beyond motivational support alone. These findings are similar to a previous systematic review in which tailored interventions that provided education, information, and prompts/cues to monitor behavior were effective components to explain improvements in adherence [26]. This signifies that tailored behavioral interventions that prompt participants to report on medication-taking behavior and provide advice about the health condition and/or adherence could inform the evidence about effective, replicable, and scalable behavioral interventions to support medication-taking behavior as an adjunct to usual clinical care. Other variables that could have contributed to heterogeneity were not explored, to minimize the possibility of obtaining false-positive results as a result of multiple testing.

Strengths and Limitations of This Review

We carried out a rigorous search of the literature in multiple databases following a preregistered protocol. In addition, the references of included studies were searched to identify eligible trials that might have been missed initially. Furthermore, some authors were contacted to clarify the intervention or provide outcome data when the intervention was not clear, or outcome data were missing. The analysis of 40 eligible studies provided sufficient power to respond to the aims of the review and explore the effect of the intervention in different subgroups. This is important for the external validity of the results. This review is the first to analyze all the available evidence on remote consultations and provide the evidence base to inform future research, clinical practice, and health policy.

One of the disadvantages of this review is that no gray literature was searched. Also, lack of outcome data or incomparable data was a cause for exclusion, which could have potentially biased the results of the review. However, these excluded studies did not differ in the overall effect compared to the included studies and so, the risk of bias from this decision could have been attenuated. Another limitation of this review is that the overall effect was weighted considerably on self-reported outcomes. Due to this overreporting bias, the conclusions about the true effect are to be interpreted cautiously. Finally, the meta-analyses of the clinical indicators, overall clinical outcomes, and subgroup analyses were generally underpowered. This implies that the results from these analyses are to be treated with caution. This entails that less reliable conclusions on clinical indicators could be less conclusive for clinical practice [17].

Strengths and Limitations of the Included Studies

A major strength of the included studies was the RCT study design, which minimizes possible known and unknown selection biases and confounding common in other observational studies. Therefore, the evidence generated by this review should be largely unbiased. The pragmatic design of included studies means that the evidence synthesized from these studies can be used to directly inform clinical practice, research, and policy about the use of remote intervention to improve treatment adherence.

An important limitation of the individual studies was the unexplained heterogeneity, which might have been due to clinical, behavioral, or methodological causes and/or a combination of both. Clinical heterogeneity was in the form of differences in diseases, as well as their definition and measurement. For instance, some studies included hypertensive patients with systolic BP >140/80 mmHg, whereas others included patients with complicated hypertension with BP >160/110 mm Hg. Intervention components, duration, and dosage also varied among the studies. In some trials, interventions were complex with different combinations of behavioral components, duration, and dosage from just one telephone to as many as 16. Methodological heterogeneity was illustrated by different tools used to measure adherence: self-reported or objective measures. Objective measures included pill counts, pharmacy records, prescription, and refill data, and electronic monitoring devices.

Most of the studies had a “some concerns” overall risk of bias judgment which implies the evidence contributed by the studies was not of the highest quality. Future studies should endeavor to provide more rigorous evidence about intervention effectiveness.

Conclusion

This systematic review found that remote consultations are effective at improving medication adherence and clinical indicators, and have the potential to reduce use of health care resources, and morbidity and mortality, and thus to be a cost-effective solution for health care. However, caution in applying these conclusions is vital due to the low quality of evidence. Future studies, therefore, need more rigorous study designs with larger sample sizes and better methodological approaches to further inform evidence for practice.

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Compliance with Ethical Standards

Authors' Statement of Conflict of Interest and Adherence to Ethical Standards The authors declare no conflicts of interest to disclose.

Authors' Contributions C.I.C. contributed into project administration, data acquisition, and data curation, visualization, analysis and writing up. A.K. contributed into leading the project conceptualization, data curation, formal analysis,

investigation, methodology, project administration, resources, validation, visualization and writing, and editing this manuscript. A.K. was the primary supervisor for C.I.C., and provided him with expert advice during all stages of the project. S.S. contributed into funding acquisition and resources.

Transparency Statements

Study registration The study was preregistered at PROSPERO https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021253365

Analytic plan pre-registration The analysis plan was registered prior to beginning data collection at https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021253365

Data availability De-identified data from this study are not available in an a public archive De-identified data from this study will be made available (as allowable according to institutional IRB standards) by emailing the corresponding author.

Analytic code availability There is not analytic code associated with this study.

Material availability Materials used to conduct the study are not publically available.

Supplementary Material

Supplementary material is available at *Annals of Behavioral Medicine* online.

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