JAMA | Original Investigation

Personalized Patient Data and Behavioral Nudges to Improve Adherence to Chronic Cardiovascular Medications
A Randomized Pragmatic Trial

P. Michael Ho, MD, PhD; Thomas J. Glorioso, MS; Larry A. Allen, MD, MHS; Richard Blankenhorn, MSDA, BSF; Russell E. Glasgow, PhD; Gary K. Grunwald, PhD; Amber Khanna, MD; David J. Magid, MD, MPH; Joel Marrs, PharmD, MPH; Sylvie Novins-Montague, BA; Steven Orlando, PharmD; Pamela Peterson, MD, MSPH; Mary E. Plomondon, PhD; Lisa M. Sandy, MA; Joseph J. Saseen, PharmD; Katy E. Trinkley, PharmD, PhD; Shawni Vaughn, MAS; Joy Waughtal, MPH; Sheana Bull, PhD

IMPORTANCE Poor medication adherence is common. Text messaging is increasingly used to change patient behavior but often not rigorously tested.

OBJECTIVE To compare different types of text messaging strategies with usual care to improve medication refill adherence among patients nonadherent to cardiovascular medications.

DESIGN, SETTING, AND PARTICIPANTS Patient-level randomized pragmatic trial between October 2019 to April 2022 at 3 US health care systems, with last follow-up date of April 11, 2023. Adult (18 to <90 years) patients were eligible based on diagnosis of 1 or more cardiovascular condition(s) and prescribed medication to treat the condition. Patients who did not opt out and had a 7-day refill gap were randomized to 1 of 4 study groups.

INTERVENTION(S) Generic text message refill reminders (generic reminder); behavioral nudge text refill reminders (behavioral nudge); behavioral nudge text refill reminders plus a fixed-message chatbot (behavioral nudge + chatbot); usual care.

MAIN OUTCOMES AND MEASURES Primary outcome was refill adherence based on pharmacy data using proportion of days covered at 12 months. Secondary outcomes were clinical events of emergency department visits, hospitalizations, and mortality.

RESULTS Among 9501 enrolled patients, baseline characteristics across the 4 groups were comparable (mean age, 60 years; 47% female [n = 4351]; 16% Black [n = 1517]; 49% Hispanic [n = 4564]). At 12 months, the mean proportion of days covered was 62.0% for generic reminder, 62.3% for behavioral nudge, 63.0% for behavioral nudge + chatbot, and 60.6% for usual care (P = .06). In adjusted analysis, when compared with usual care, mean proportion of days covered was 2.2 percentage points (95% CI, 0.3-4.2; P = .02) higher for generic reminder, 2.0 percentage points (95% CI, 0.1-3.9; P = .04) higher for behavioral nudge, and 2.3 percentage points (95%, 0.4-4.2; P = .02) higher for behavioral nudge + chatbot, none of which were statistically significant after multiple comparisons correction. There were no differences in clinical events between study groups.

CONCLUSIONS AND RELEVANCE Text message reminders targeting patients who delay refilling their cardiovascular medications did not improve medication adherence based on pharmacy refill data or reduce clinical events at 12 months. Poor medication adherence may be due to multiple factors. Future interventions may need to be designed to address the multiple factors influencing adherence.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03973931

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: P. Michael Ho, MD, PhD, Institute for Health Research, Kaiser Permanente Colorado, 16601 E Centretech Pkwy, Aurora, CO 80011 (p.michael.x-ho@kp.org).

JAMA. 2025;333(1):49-59. doi:10.1001/jama.2024.21739
Published online December 2, 2024.

Mobile health technologies are increasingly used in health care but often not rigorously tested to assess effectiveness. Text messaging is a form of mobile health communication technology shown to improve health care behaviors such as diabetes self-management.[1-4] Text messages can be augmented with chatbots that can facilitate interactive conversations with patients and/or brief behavioral interventions that nudge patients to improve health behaviors.[5-7] However, it is unclear if adding behavioral nudges or chatbots to generic text messages can further enhance the impact.

Poor medication adherence is common among patients with chronic diseases requiring daily medications. Nonadherence to chronic cardiovascular medications has been associated with increased adverse outcomes, including hospitalization and mortality.[8,9] Text messaging adherence interventions have generally used generic messages and reminded patients prior to the medication refill due date. This may lead to message overload, given the ubiquity of texting within and outside of health care settings. It is unknown if reminders targeting patients identified as nonadherent can be more effective.

This was a pragmatic patient-level randomized trial across 3 diverse health care systems to improve refill adherence among patients nonadherent to their chronic cardiovascular medications. The study hypothesis was that generic text message reminders would improve refill adherence compared with usual care and that incorporating behavioral nudges and a chatbot to address common medication adherence barriers would further improve refill adherence. The study assessed the effectiveness of these interventions on refill adherence using pharmacy refill data as well as clinical outcomes of emergency department visits, hospitalizations, and mortality.

Key Points

Question Can test message reminders improve medication adherence and clinical outcomes among patients nonadherent to cardiovascular medications?

Finding In a pragmatic randomized trial of 9501 patients at 3 US health care systems, the 3 text messaging medication refill reminder strategies tested (generic reminders, behavioral nudge reminders, and behavioral nudge reminders plus a fixed-message chatbot) did not increase refill adherence at 12 months or reduce clinical events.

Meaning Additional interventions need to be rigorously tested to try to improve adherence to chronic cardiovascular medications given the growing incidence of cardiovascular conditions.

Methods

Trial Design

This was a patient-level randomized pragmatic trial testing different text messaging strategies to improve refill adherence among patients with poor adherence to prescribed cardiovascular medicines. We conducted the study at 3 health care systems: Denver Health and Hospital Authority, a safety net hospital system in Denver County; Veterans Administration (VA) Eastern Colorado Health Care System, serving veterans in the Rocky Mountain region; and UCHealth's University of Colorado Hospital, an academic medical center. The study protocol is available in Supplement 1 and the statistical analysis plan in Supplement 2.

Participants

Inclusion and Exclusion Criteria

Potential eligible patients aged 18 years to less than 90 years were identified based on the presence of 1 or more cardiovascular condition (hypertension, hyperlipidemia, diabetes, coronary artery disease [CAD], or atrial fibrillation) as defined by diagnosis and procedural codes; they were prescribed 1 or more classes of medications to treat the condition within the prior 100 days.[10] Patients were excluded based on the following using electronic health record (EHR) data: (1) no landline or cell phone listed; (2) enrolled in hospice or palliative care; (3) non-English-speaking or non-Spanish-speaking; (4) home address outside of Colorado or homeless as defined in the EHR; or (5) current pregnancy. Race and ethnicity data were obtained from the EHR as recorded by each health system.

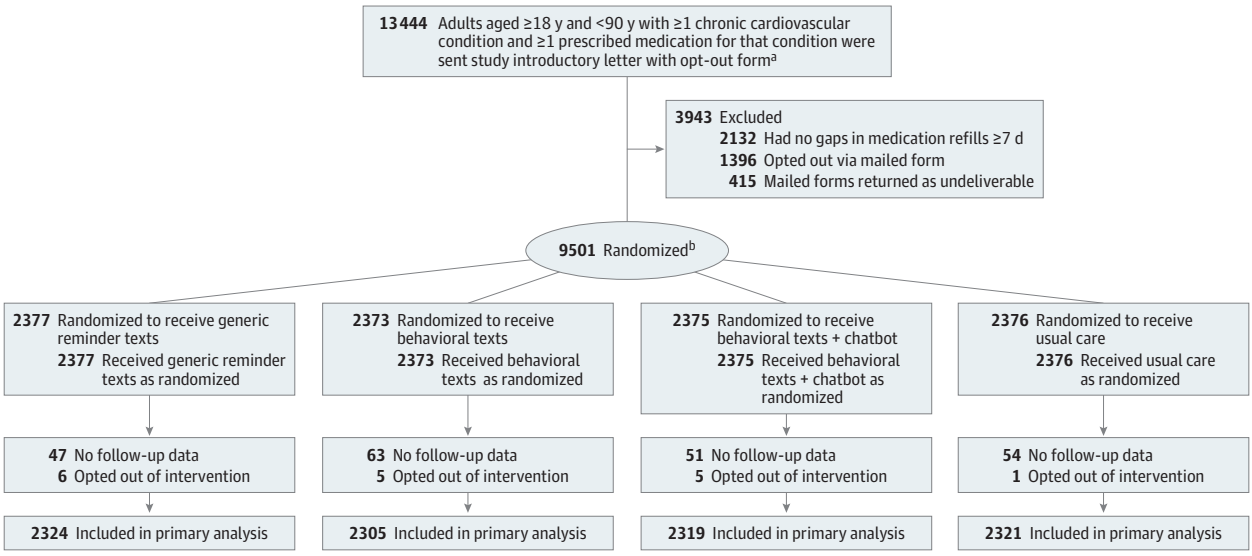
Potential eligible patients were mailed a study introduction letter and an opt-out form if the patient decided not to participate. Patients who did not return the opt-out form were monitored daily for a medication refill gap using pharmacy dispensing data. We determined if medications were available to a patient on a given day for each medication class based on prior fill days, number of days supplied, cancellation dates, and inpatient days in which medication would be supplied. Patients with a refill gap of at least 7 days for any of the cardiovascular medication classes of interest were randomized.

Interventions

Randomization was stratified by health care system and number of baseline medications and occurred in blocks of 4 patients within strata to ensure balance using an automated process. Once randomized, patients remained in the same study group for the entire study whether they had subsequent refill gaps. Patients were not blinded to their study group. The 4 study groups were (1) generic reminder text message (generic reminder; a text message reminder to refill medication with a refill gap); (2) behavioral nudge text (behavioral nudge; a text message reminder incorporating behavioral nudges to refill medication); (3) behavioral nudge text plus a fixed-message chatbot (behavioral nudge + chatbot; text message incorporating behavioral nudges plus a chatbot that engaged patients to assess common barriers to medication adherence using preprogrammed algorithms); and (4) usual care (patients did not receive text messages).[10]

Messages were delivered in either English or Spanish based on patients' language preference in the EHR and only delivered when patients have a refill gap of 7 days or longer, in

Figure 1. Patient Flow in a Study of Message Reminders to Improve Adherence to Chronic Cardiovascular Medications



[a]Study introductory letters were mailed to potentially eligible patients to provide information about the study as well as an opportunity to opt out if they chose not to participate.

[b]Randomization was stratified by health care system and number of baseline medications and occurred in blocks of 4 patients within strata to ensure balance across study groups using an automated process.

contrast to other medication refill reminders that are delivered prior to the refill due date. Patients were provided a secondary opportunity to change their default language via text messaging. Examples of English or Spanish messages are presented in eTable 1 in Supplement 3. Patients could opt out of the study by replying "STOP" to any text message. Refill reminder messages stopped once there was a pharmacy record denoting that the medication was refilled or the patient had replied "DONE." Patients could return the text message reminders with questions. Clinical pharmacists at each health system responded to clinical questions when appropriate.[11] For patients without cell phones (≈9% of patients), interactive voice response automated telephone calls delivered the same messages as texts.

Mobile Messenger (Upland Communications) was used to deliver the text messages. The study was deemed minimal risk, and a waiver of consent was obtained from the Colorado Multiple Institutional Review Board.

Outcomes

The primary outcome was refill adherence defined by proportion of days covered (PDC) in the 365 days following randomization for all medication classes identified with a refill gap at baseline. In secondary analysis, we assessed median gap lengths among enrolled patients for the medications in which the patient had a refill gap by evaluating the time from enrollment (start of initial gap[s]) to the first fill, right-censoring at death or end of follow-up. In a further analysis, all subsequent gaps after enrollment were also considered, treating each individual medication class gap as a unique time-to-event record. PDC describes overall medication availability, while gap length describes more direct effects of the intervention in terms of patients' responses to refill reminders. Secondary outcomes include time to clinical events defined by emergency department visits, hospitalizations, and mortality, measured as time from enrollment to the first event.

Sample Size

We estimated that a total sample size of 476 patients was needed to detect a 10-percentage point difference in PDC, accounting for multiple comparisons across the 4 study groups with 80% power. We enrolled 9501 patients across the 3 health care systems, which was a significantly greater number for several reasons: (1) to have sufficient sample size to detect a smaller difference in overall PDC and within specific subgroups; (2) to test the impact of an opt-out approach on patient enrollment, particularly among patients traditionally underrepresented in clinical trials given the minimal-risk study; (3) the study was funded as part of the National Institutes of Health Pragmatic Trials Collaboratory, where there is interest in implementing cost-effective, large-scale research studies that engage health care systems; and (4) sample size considerations were discussed and approved by our data and safety monitoring board and funder (National Heart, Lung, and Blood Institute).

Statistical Methods

PDC was calculated for each month in the 12 months following enrollment among all medication classes identified as gapping at baseline. Patients active on multiple study medication classes had all combinations of follow-up days for all baseline medications counted in the denominator, and days adherent were counted in the numerator. We analyzed this

Table 1. Baseline Characteristics of Study Population

Characteristic	No. (%)			
	Generic reminder texts (n = 2324)	Behavioral nudge texts (n = 2305)	Behavioral nudge + chatbot texts (n = 2319)	Usual care texts (n = 2321)
Health care system				
Denver Health	1786 (77)	1781 (77)	1775 (77)	1785 (77)
UCHealth	239 (10)	225 (10)	240 (10)	235 (10)
VA	299 (13)	299 (13)	304 (13)	301 (13)
Demographics				
Age, mean (SD), y	59.9 (12.5)	60 (12.9)	60.1 (12.7)	60.1 (12.6)
Sex				
Female	1087 (47)	1075 (47)	1101 (47)	1088 (47)
Male	1237 (53)	1230 (53)	1218 (53)	1233 (53)
Race[a]	2056 (88)	2067 (89)	2070 (89)	2066 (89)
American Indian or Alaska Native	22 (1)	27 (1)	23 (1)	35 (2)
Asian	29 (1)	31 (1)	21 (1)	29 (1)
Black or African American	391 (17)	378 (16)	356 (15)	392 (17)
Native Hawaiian/Pacific Islander	3 (<1)	2 (<1)	6 (<1)	3 (<1)
White	1601 (69)	1615 (70)	1646 (71)	1598 (69)
Multiple	10 (<1)	14 (1)	16 (1)	9 (<1)
Ethnicity[a]	2304 (99)	2288 (99)	2302 (99)	2299 (99)
Hispanic	1100 (47)	1147 (50)	1168 (50)	1149 (50)
Non-Hispanic	1204 (52)	1141 (50)	1134 (49)	1150 (50)
Preferred Spanish-language communication	619 (27)	650 (28)	682 (29)	654 (28)
Marital status	2311 (99)	2287 (99)	2302 (99)	2307 (99)
Married	994 (43)	940 (41)	980 (42)	950 (41)
Single	883 (38)	883 (38)	870 (38)	874 (38)
Divorced/widowed	434 (19)	464 (20)	452 (19)	483 (21)
Insurance	2201 (94)	2209 (95)	2189 (94)	2209 (95)
Medicare	853 (37)	878 (38)	860 (37)	889 (38)
Medicaid	659 (28)	632 (27)	629 (27)	665 (29)
Commercial	463 (20)	471 (20)	500 (22)	441 (19)
VA	8 (<1)	7 (<1)	8 (<1)	12 (1)
None	218 (9)	221 (10)	192 (8)	202 (9)
Medical history[b]				
Depression	421 (18)	463 (20)	442 (19)	416 (18)
Chronic kidney disease	191 (8)	202 (9)	203 (9)	189 (8)
Heart failure	160 (7)	199 (9)	163 (7)	171 (7)
Cerebrovascular disease	142 (6)	145 (6)	125 (5)	134 (6)
Posttraumatic stress disorder	118 (5)	114 (5)	102 (4)	108 (5)
Prior myocardial infarction	95 (4)	109 (5)	121 (5)	98 (4)
Substance abuse	89 (4)	101 (4)	116 (5)	88 (4)
Prior coronary revascularization	63 (3)	56 (2)	70 (3)	58 (2)
Qualifying condition(s)[c]				
Hypertension	1837 (79)	1829 (79)	1821 (79)	1864 (80)
Diabetes	1148 (49)	1164 (50)	1162 (50)	1149 (50)
Hyperlipidemia	1072 (46)	1052 (46)	1089 (47)	1054 (45)
Coronary artery disease	305 (13)	325 (14)	352 (15)	328 (14)
Atrial fibrillation	132 (6)	152 (7)	130 (6)	134 (6)
>1 Qualifying condition	1406 (60)	1390 (60)	1410 (61)	1438 (62)

(continued)

Table 1. Baseline Characteristics of Study Population (continued)

Characteristic	No. (%)			
	Generic reminder texts (n = 2324)	Behavioral nudge texts (n = 2305)	Behavioral nudge + chatbot texts (n = 2319)	Usual care texts (n = 2321)
Baseline medication classes[d]				
Active class(es)				
1	597 (26)	564 (24)	567 (24)	557 (24)
2	551 (24)	572 (25)	584 (25)	591 (25)
≥3	1176 (51)	1169 (51)	1168 (50)	1173 (51)
Medication class(es) with refill gap[e]				
1	1626 (70)	1604 (70)	1603 (69)	1635 (70)
2	449 (19)	464 (20)	455 (20)	437 (19)
≥3	249 (11)	237 (10)	261 (11)	249 (11)
Intervention delivery				
Text messages	2126 (91)	2089 (91)	2117 (91)	0
Interactive voice response telephone messages	198 (9)	216 (9)	202 (9)	0

Abbreviation: VA, Veterans Administration.

[a] Race and ethnicity categories were obtained from the electronic health record.

[b] Medical history was based on diagnosis and procedural codes.

[c] Qualifying conditions for patients were defined by specific cardiovascular diagnosis and procedural codes and prescription of 1 or more classes of medications to treat the cardiovascular condition of interest within the prior 100 days.

[d] Patients with eligible cardiovascular conditions were also required to be prescribed at least 1 class of medications to treat the cardiovascular condition (see eTable 5 in Supplement 3 for cardiovascular condition and classes of medications).

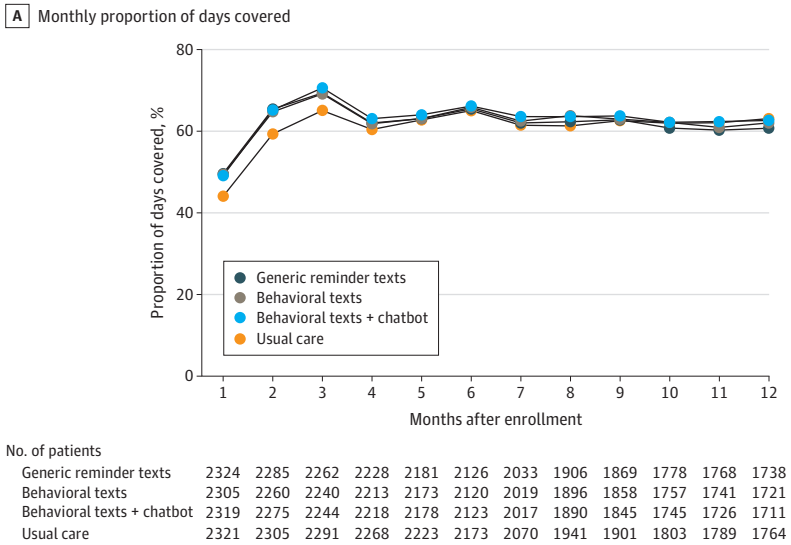
[e] Patients may have more than 1 medication class (eg, anticoagulant, statin, or oral hypoglycemic medications) in which they have a refill gap of 7 days or longer at baseline, which would make them eligible for the study. Patients with refill gaps in more than 1 medication class at baseline were only delivered 1 set of reminder messages to reduce the total number of messages received by the patient.

longitudinal data (up to 12 observations per patient) and estimated absolute differences in PDC between treatment groups and usual care using a generalized estimating equation (GEE) model with an identity link and independence with unequal variances for the covariance structure of the 12 observations, using the *geepack* package in R,[12-14] adjusting for the following variables: health care system; number of medications gapping at baseline; treatment group; follow-up month; patient demographics, including age, gender, race, ethnicity, insurance status, and marital status; and comorbidity variables including hypertension, hyperlipidemia, coronary artery disease, diabetes, atrial fibrillation, chronic heart failure, chronic kidney disease, cerebrovascular disease, prior myocardial infarction, prior revascularization, depression, posttraumatic stress disorder, and substance abuse. To account for potential data missing at random, observation-specific weights specific to each person-period were calculated using logistic regression to estimate the inverse probability that a longitudinal value was observed.[15] Logistic models included the same variables as the GEE models. Weights greater than the 95th percentile were truncated. A multistage gatekeeper approach was used to account for multiple treatment comparisons by comparing each of the 3 treatment groups with the usual care group in stage 1, using corrected thresholds for statistical significance of .05/3; if any test was significant, a significance level of (R/3) × (.05/3) using the Holm method was used for the 3 pairwise comparisons, where R is the number of significant stage 1 tests.[16]

Gap lengths (time to refill) and secondary outcome events were measured as time-to-event outcomes censored at 1 year, time of death, or early termination of follow-up due to opting out or site stoppages. For gap lengths, we first assessed each patient's time from the start of the initial enrollment gap(s) to the first of any medication fill across these classes. If no medication classes were filled, we used the maximum follow-up time across classes. As a secondary analysis, we looked at each gap after the initial enrollment gap(s) individually and assessed time from the start of the gap to a fill, treating each medication class/gap combination as a separate record. We plotted group differences with 1-year Kaplan-Meier curves and from these results summarized percentiles of gap lengths with medians and IQRs. Using 1000 bootstrapped estimates, we also presented the mean difference in median gap lengths between treatment groups and usual care, with 95% confidence intervals.

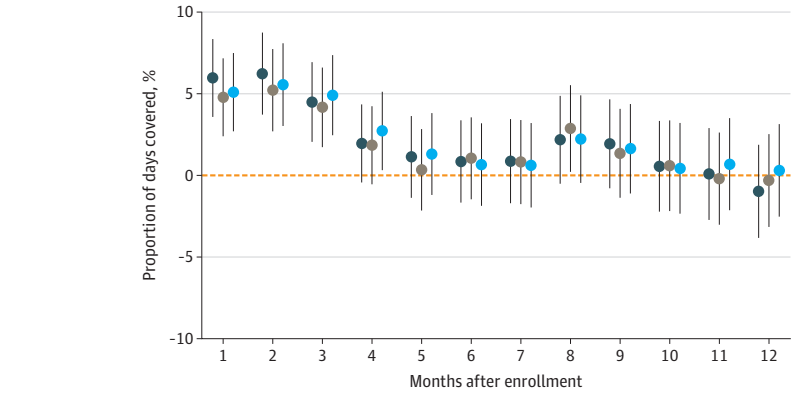
Last, subgroup analyses were performed using the weighted GEE for PDC and gap length approaches described earlier. Subgroups included health care system, qualifying conditions, gender, race, ethnicity, and Spanish as the primary language. For the qualifying condition subgroup analyses, we assessed only study medication classes related to the qualifying condition (eTable 6 in Supplement 3). When assessing patients with Spanish as the primary language, results were

Figure 2. Proportion of Days Covered



No. of patients

Generic reminder texts	2324	2285	2262	2228	2181	2126	2033	1906	1869	1778	1768	1738
Behavioral texts	2305	2260	2240	2213	2173	2120	2019	1896	1858	1757	1741	1721
Behavioral texts + chatbot	2319	2275	2244	2218	2178	2123	2017	1890	1845	1745	1726	1711
Usual care	2321	2305	2291	2268	2223	2173	2070	1941	1901	1803	1789	1764



No. of patients

Generic reminder texts	2324	2285	2262	2228	2181	2126	2033	1906	1869	1778	1768	1738
Behavioral texts	2305	2260	2240	2213	2173	2120	2019	1896	1858	1757	1741	1721
Behavioral texts + chatbot	2319	2275	2244	2218	2178	2123	2017	1890	1845	1745	1726	1711
Usual care	2321	2305	2291	2268	2223	2173	2070	1941	1901	1803	1789	1764

A, Proportion of days covered was calculated using all medication classes identified as gapping at baseline. Patients actively receiving multiple study medications had all combinations of follow-up days for all baseline medications counted in the denominator; days that medications were filled were counted in the numerator. Results were then presented, aggregated by month following enrollment for the initial enrollment gaps and any subsequent gaps. B, Adjusted difference from usual care in proportion of days covered, stratified by follow-up month.

limited to patients at Denver Health and UCHealth since all VA patients were considered English-speaking (a condition required for military service). In subgroup analyses, maximum follow-up at UCHealth was 7 months, due to problems with the pharmacy refill data at that site.

We carried out several sensitivity analyses for PDC based on different assumptions about medications that were never refilled, patient inclusion criteria, and which medication classes to include; sensitivity analyses for gap length were based on different assumptions about censored observations, as described in the eMethods in Supplement 3. These sensitivity analysis findings were consistent with the primary analysis results. Results are reported according to the CONSORT (Consolidated Standards of Reporting Trials) guideline.

All analyses were performed using R version 4.2.1 (R Foundation).

Results

A total of 9501 patients were enrolled between October 2019 to April 2022, with the last date of follow-up on April 11, 2023. After removing 232 patients without any follow-up data, 9269 patients comprised the analytic cohort and were evenly distributed across the 4 groups (**Figure 1**). Baseline characteristics across the 4 groups were comparable (**Table 1**). In general, the mean age was 60 years, with 47% female, 16% Black, 49% Hispanic, and 28% Spanish-speaking. In terms of the qualifying cardiovascular condition for the study, 79% of patients had hypertension, 46% had hyperlipidemia, 50% had diabetes, 14% had CAD, and 6% had atrial fibrillation. The majority of patients (51%) were prescribed at least 3 cardiovascular medication

Table 2. Differences in Mean Proportion of Days Covered From Usual Care

Primary analysis outcome	Unadjusted proportion of days covered, %[a]				Adjusted absolute difference (from usual care) in percentage points of the proportion of days covered[b]					
	Generic reminder text (n = 2324)	Behavioral nudge text (n = 2305)	Behavioral nudge text + chatbot (n = 2319)	Usual care (n = 2321)	Generic reminder text		Behavioral nudge text		Behavioral nudge text + chatbot	
					Difference (95% CI)	*P* value	Difference (95% CI)	*P* value	Difference (95% CI)	*P* value
3 Mo	61.4	61.1	61.6	56.2	5.6 (3.4-7.8)	<.001[c]	4.8 (2.5-7.0)	<.001[c]	5.2 (3.0-7.4)	<.001[c]
12 Mo	62.0	62.3	63.0	60.6	2.2 (0.3-4.2)	.02	2.0 (0.1-3.9)	.04	2.3 (0.4-4.2)	.02

[a] Unadjusted proportion of days covered was calculated using all medication classes identified as gapping at baseline. Patients active taking multiple study medications had all combinations of follow-up days for all baseline medications counted in the denominator and days that medications were filled counted in the numerator.

[b] Analyses adjusted for health care system, number of medications gapping at baseline, treatment group, follow-up month, patient demographics including age, gender, race, ethnicity, insurance status, marital status as well as comorbidity variables including hypertension, hyperlipidemia, coronary artery disease, diabetes, atrial fibrillation, chronic heart failure, chronic kidney disease, cerebrovascular disease, prior myocardial infarction, prior revascularization, depression, posttraumatic stress disorder, and substance abuse.

[c] Indicates significant result with adjusted level of significance (.05/3).

classes, and 70% of patients had a refill gap for only 1 class. Almost all (93.96%) study text messages were delivered successfully. If a message was returned as "undelivered," the text messaging system would send up to 3 more messages. Among enrolled patients, 38% responded in some way to the messages, with the 2 most common questions related to asking more information about the study and/or asking for the pharmacy refill line.

At 1 year, mean PDC was 62.0% for generic reminder, 62.3% for behavioral nudge, 63.0% for behavioral nudge + chatbot, and 60.6% for usual care (*P* = .06) (**Figure 2**). In adjusted analysis, mean PDC relative to usual care was 2.2 percentage points higher in the generic reminder group (95% CI, 0.3-4.2 [*P* = .02]), 2.0 percentage points higher in the behavioral nudge group (95% CI, 0.1-3.9 [*P* = .04]), and 2. 3 percentage points higher in the behavioral nudge + chatbot group (95% CI, 0.4-4.2; [*P* =.02]) (**Table 2**). Because comparisons were not significant using the adjusted level of significance of .05/3, no pairwise comparisons among intervention groups were performed. There were no differences in time to emergency department visits (log-rank *P* = .70), hospitalizations (log-rank *P* = .56), or death (log-rank *P* = .55) across study groups (**Figure 3**).

Consistent with the primary results, similar trends in treatment effect between the intervention groups relative to usual care were seen in key subgroups, including health systems (Denver Health and VA), qualifying cardiovascular conditions (diabetes, hyperlipidemia, and hypertension), and demographic characteristics (female sex, Hispanic ethnicity, and Spanish-speaking) (eFigure 3 in Supplement 3). In addition, these trends were consistent for cardiovascular conditions and medications generally for primary prevention (eg, hypertension) vs secondary prevention (eg, CAD).

Post Hoc Analysis

Given that most medication refills were 30 or 90 days following the initial delay, we conducted a post hoc analysis of the intervention effect on shorter-term adherence. At 3 months, mean PDC relative to usual care was 5.6 percentage points higher in the generic reminder group (95% CI, 3.4-7.8; *P* < .001), 4.8 percentage points higher in the behavioral nudge group (95% CI, 2.5-7.0; *P* < .001), and 5.2 percentage points higher in the behavioral nudge + chatbot group (95% CI, 3.0-7.4; *P* < .001) (Figure 2B and Table 2). Next, since the intervention targeted refill adherence delays, we also evaluated median gap lengths to assess whether the intervention reduced the number of days patients were without medications. The initial enrollment gaps were 9 days for the generic reminder group, 9 days for the behavioral nudge group, 10 days for the behavioral nudge + chatbot group, and 15 days for the usual care group (**Table 3**). The mean reduction in median initial refill gap length relative to usual care was 5 days for all 3 intervention groups (95% CI, 3-7 [*P* < .001] for generic reminder; 95% CI, 3-7 [*P* < .001] for behavioral nudge; 95% CI, 3-7 [*P* < .001] for behavioral nudge + chatbot). For all subsequent gaps, the median length for individual medication gaps was 20

Figure 3. Kaplan-Meier Rates for Secondary Clinical Outcomes Stratified by Treatment Group

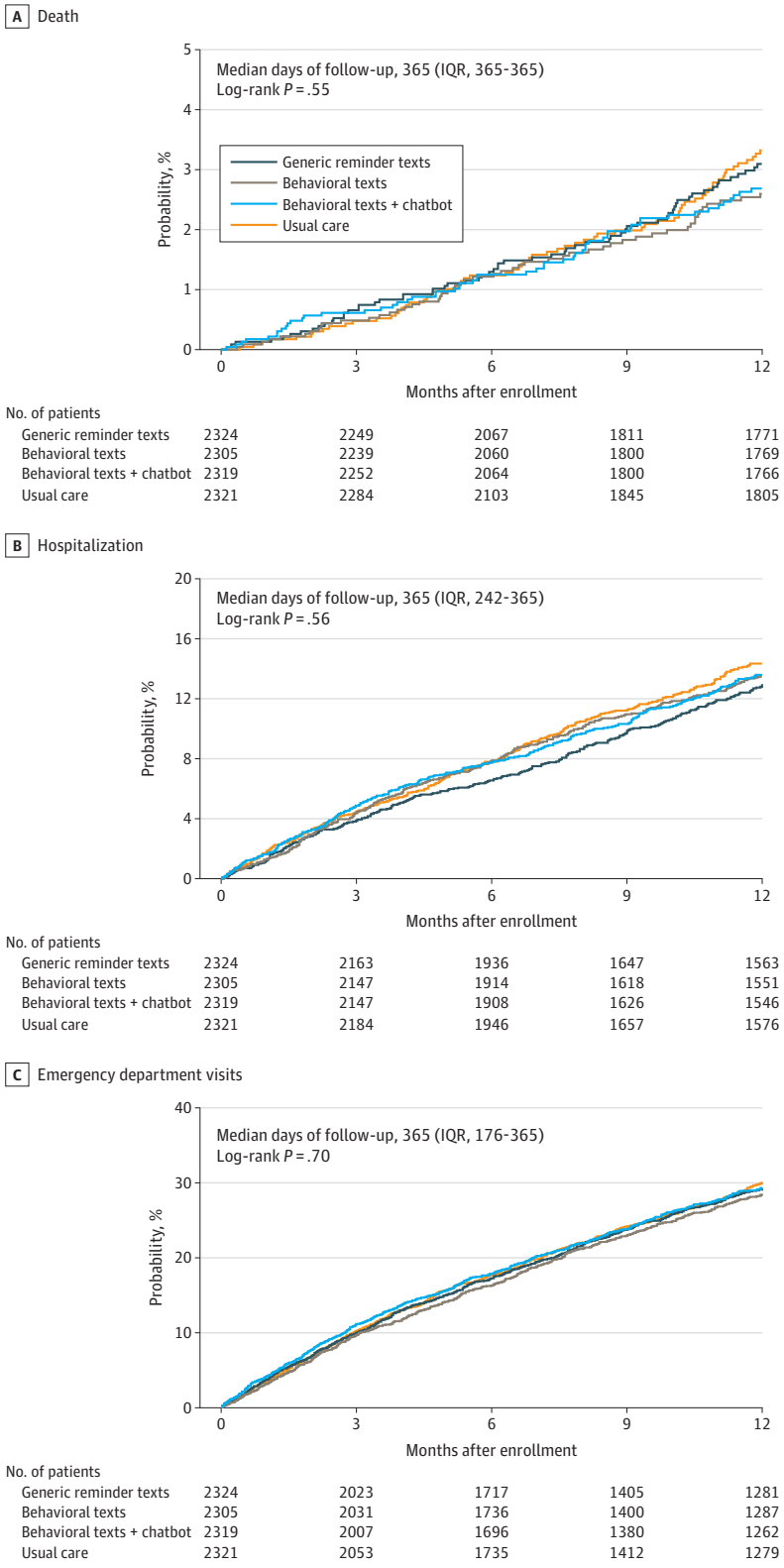


Table 3. Mean Difference in Median Gap Lengths in Days From Usual Care

Secondary analysis	Gap length, median (IQR), d				Mean difference (from usual care) in medians					
	Generic reminder text (n = 2324)	Behavioral nudge text (n = 2305)	Behavioral nudge text + chatbot (n = 2319)	Usual care (n = 2321)	Generic reminder text		Behavioral nudge text		Behavioral nudge text + chatbot	
					Difference (95% CI)	*P* value	Difference (95% CI)	*P* value	Difference (95% CI)	*P* value
Initial gap[a]	9 (1-55)	9 (1-62)	10 (1-59)	15 (1-85)	5 (3-7)	<.001[b]	5 (3-7)	<.001[b]	5 (3-7)	<.001[b]
All subsequent gap(s)[c]	16 (6-56)	17 (6-59)	15 (6-56)	20 (8-58)	4 (1-6)	.01[b]	3 (0-6)	.06	4 (2-7)	.01[b]

[a] Refers to required gap for study inclusion.

[b] Indicates significant result with adjusted level of significance (.05/3).

[c] All gaps following the initial enrollment gap were tracked individually and assessed time from the start of the gap to a fill. Subsequent gaps exclude the initial gap.

days for the usual care group, 16 days for the generic reminder group, 17 days for the behavioral nudge group, and 15 days for the behavioral nudge + chatbot group (Table 3). Additional details regarding the intervention and sensitivity analyses are reported in eFigures 1-4 and eTables 1-7 in Supplement 3.

Discussion

The objective of this study was to assess the effectiveness of different text message reminders to improve medication refill adherence. In a pragmatic trial with high patient enrollment including patients traditionally underrepresented in clinical trials (eg, ≈49% Hispanic) and few patients opting out, overall rates of medication adherence were low (≈60%). Text message reminders were not effective in improving refill adherence at 12 months, regardless of the type of message, generic reminders, behavioral nudges, or behavioral nudges + chatbot. There were no differences in clinical events across the study groups.

In post hoc exploratory analysis focused on the first 3 months, we found refill adherence was 5 percentage points higher and median length of initial gaps was reduced by approximately 5 days for all 3 intervention groups compared with usual care. Although this study did not improve adherence at 12 months, other similar research offers contrasting evidence that text messaging may be an effective approach.[17-19] Differences in message design, frequency, and intensity may explain the differential outcomes. In this trial, up to 5 messages over a 10-day period were sent to remind patients to refill and only when they delayed refilling their cardiovascular medications. In the study by Horne et al,[17] messages were generally sent weekly for a longer duration than in the current study, suggesting that periodic brief reminders over time can be effective. Additionally, the messages in the current study were unidirectional, limiting patient opportunities to engage with messages. Newer technologies, including artificial intelligence–enabled chatbots, may facilitate tailored conversations that meet specific patient needs.[20,21]

In this study, there was no difference between generic reminders and behavioral nudge text messages with or without a chatbot. Prior text messaging studies have typically assessed tailoring or personalization of messages over a short period (eg, 30-90 days) and have not evaluated intervention decay effects over time.[22-25] This study followed up patients for up to 365 days and found that most patients refilled their medications within 30 days of the reminder message (eFigure 2 in Supplement 3). The lack of benefit beyond 30 days may be related to the typical intervention decay observed for other interventions. Furthermore, the intervention was delivered only when patients delayed filling their prescriptions and did not address other aspects of medication-taking behaviors, such as daily reminders. Last, the outcome measure of 12-month refill adherence may not have been a sensitive enough measure to assess the impact of the intervention.

Limitations

This study has some limitations. First, the study was conducted in 2 health systems (Denver Health and VA) where a majority of patients filled their prescriptions using health system pharmacies. In 2 of the health systems (Denver Health and UCHealth), patients filling prescriptions outside of health system pharmacies were included; however, not all prescriptions filled at outside pharmacies may have been captured (eg, due to use of prescription discount cards), despite use of national pharmacy claims data (eg, SureScripts). Second, the study demonstrated a modest improvement in refill adherence in post hoc analysis at 3 months. The intervention was not integrated within the health system pharmacy, and co-interventions such as retail pharmacy text message reminders may have limited its effectiveness. However, the use of text messaging may still be a cost-effective strategy for health systems relative to other technologies such as standalone apps or more time-intensive interventions such as motivational interviewing to deploy as a first-line strategy among a series of strategies to improve medication adherence. Future studies could use an adaptive design whereby patients are randomized to more intensive adherence interventions if the initial ones are not effective. Third, text messaging may not have been available to all patients. However, the majority of patients (≈91%) in the intervention groups selected text messages rather than telephone. Text message interventions may be more generalizable than app-based interventions.

Conclusions

Text message reminders did not improve medication refill adherence at 12 months. Given overall low rates of adherence at 12-month follow-up, additional interventions need to be rigorously tested to try to improve adherence to chronic cardiovascular medications, given the growing incidence of chronic cardiovascular conditions.

ARTICLE INFORMATION

Accepted for Publication: September 23, 2024.

Published Online: December 2, 2024. doi:10.1001/jama.2024.21739

Author Affiliations: Rocky Mountain Regional Veteran Affairs Medical Center, Aurora, Colorado (Ho, Blankenhorn, Grunwald, Orlando); Division of Cardiology, University of Colorado School of Medicine, Aurora (Ho, Allen, Khanna, Magid, Peterson); Institute for Health Research, Kaiser Permanente Colorado, Aurora (Ho); Colorado Permanente Medical Group, Denver (Ho); Clinical Assessment, Reporting, and Tracking Program, Office of Quality and Patient Safety, Veterans Health Administration, Washington, DC (Glorioso); Department of Family Medicine, University of Colorado School of Medicine, Aurora (Glasgow, Saseen, Trinkley); Adult and Child Center for Outcomes Research and Delivery Science (ACCORDS), University of Colorado School of Medicine, Aurora (Glasgow, Novins-Montague, Sandy, Trinkley, Waughtal); Department of Biostatistics and Informatics, Colorado School of Public Health, Aurora (Grunwald); Department of Clinical Pharmacy and Translational Science, University of Tennessee Health Science Center, Memphis (Marrs); Department of Pediatrics, University of Colorado School of Medicine, Aurora (Marrs); Denver Health and Hospitals, Denver, Colorado (Peterson); Colorado Clinical and Translational Science Institute, University of Colorado Denver–Anschutz Medical Campus, Aurora (Plomondon, Vaughn); Department of Clinical Pharmacy, University of Colorado Anschutz Skaggs School of Pharmacy and Pharmaceutical Sciences, Aurora (Saseen, Trinkley); Colorado School of Public Health, Aurora (Bull).

Author Contributions: Dr Ho and Mr Glorioso had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Ho, Glorioso, Allen, Glasgow, Khanna, Magid, Peterson, Trinkley, Waughtal, Bull.
Acquisition, analysis, or interpretation of data: Ho, Glorioso, Allen, Blankenhorn, Glasgow, Grunwald, Marrs, Novins-Montague, Orlando, Peterson, Plomondon, Sandy, Saseen, Trinkley, Vaughn, Waughtal, Bull.
Drafting of the manuscript: Ho, Novins-Montague, Orlando, Saseen, Vaughn, Waughtal, Bull.
Critical review of the manuscript for important intellectual content: Glorioso, Allen, Blankenhorn, Glasgow, Grunwald, Khanna, Magid, Marrs, Peterson, Plomondon, Sandy, Saseen, Trinkley, Waughtal, Bull.
Statistical analysis: Glorioso, Grunwald, Plomondon.
Obtained funding: Ho, Magid, Peterson, Bull.
Administrative, technical, or material support: Glasgow, Khanna, Marrs, Novins-Montague, Orlando, Plomondon, Sandy, Trinkley, Waughtal, Bull.
Supervision: Allen, Plomondon, Bull.

Conflict of Interest Disclosures: Dr Allen reported receiving personal fees from ACI Clinical/WCG, Novartis, Quidel, and UpToDate and receiving grants from the National Institutes of Health and the Patient-Centered Outcomes Research Institute. Dr Peterson reported receiving grants from the National Heart, Lung, and Blood Institute (NHLBI). Dr Saseen reported serving on the Amgen lipid monitoring board for 2 large cardiovascular outcome trials. No other disclosures were reported.

Funding/Support: This work was supported within the National Institutes of Health (NIH) Pragmatic Trials Collaboratory by cooperative agreement UG3HL144163 from the NHLBI. This work also received logistical and technical support from the NIH Pragmatic Trials Collaboratory Coordinating Center through cooperative agreement U24AT009676 from the National Center for Complementary and Integrative Health (NCCIH), National Institute of Allergy and Infectious Diseases (NIAID), National Cancer Institute (NCI), National Institute on Aging (NIA), NHLBI, National Institute of Nursing Research (NINR), National Institute of Minority Health and Health Disparities (NIMHD), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), NIH Office of Behavioral and Social Sciences Research (OBSSR), and NIH Office of Disease Prevention (ODP).

Role of the Funder/Sponsor: The study funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the NHLBI or the NCCIH, NIAID, NCI, NIA, NINR, NIMHD, NIAMS, OBSSR, ODP, or NIH.

Data Sharing Statement: See Supplement 4.

Additional Contributions: We thank all patients and their families, all investigators, and the personnel at the study sites for participating in the study. We also extend our thanks to Catia Chavez, MPH (University of Colorado School of Medicine), who worked on recruiting, conducting participant interviews, and ensuring accurate Spanish translations throughout the duration of the study. Ms Chavez received no compensation for her contributions.

REFERENCES

1. Smith DM, Duque L, Huffman JC, Healy BC, Celano CM. Text message interventions for physical activity: a systematic review and meta-analysis. *Am J Prev Med*. 2020;58(1):142-151. doi:10.1016/j.amepre.2019.08.014

2. Shariful Islam SM, Farmer AJ, Bobrow K, et al. Mobile phone text-messaging interventions aimed to prevent cardiovascular diseases (Text2PreventCVD): systematic review and individual patient data meta-analysis. *Open Heart*. 2019;6(2):e001017. doi:10.1136/openhrt-2019-001017

3. Siopis G, Chey T, Allman-Farinelli M. A systematic review and meta-analysis of interventions for weight management using text messaging. *J Hum Nutr Diet*. 2015;28(suppl 2):1-15. doi:10.1111/jhn.12207

4. Sahin C, Courtney KL, Naylor PJ, E Rhodes R. Tailored mobile text messaging interventions targeting type 2 diabetes self-management: a systematic review and a meta-analysis. *Digit Health*.

2019;5:2055207619845279. doi:10.1177/2055207619845279

5. Tversky A, Kahneman D. The framing of decisions and the psychology of choice. *Science*. 1981;211(4481):453-458. doi:10.1126/science.7455683

6. Volpp KG, Loewenstein G, Troxel AB, et al. A test of financial incentives to improve warfarin adherence. *BMC Health Serv Res*. 2008;8(1):272. doi:10.1186/1472-6963-8-272

7. Thaler RH, Sunstein CR. *Nudge: Improving Decisions about Health, Wealth, and Happiness*. Rev exp ed. Penguin Books; 2009.

8. Rasmussen JN, Chong A, Alter DA. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. *JAMA*. 2007;297(2):177-186. doi:10.1001/jama.297.2.177

9. Wei L, Wang J, Thompson P, Wong S, Struthers AD, MacDonald TM. Adherence to statin treatment and readmission of patients after myocardial infarction: a six year follow up study. *Heart*. 2002;88(3):229-233. doi:10.1136/heart.88.3.229

10. Glasgow RE, Knoepke CE, Magid D, et al. The NUDGE trial pragmatic trial to enhance cardiovascular medication adherence: study protocol for a randomized controlled trial. *Trials*. 2021;22(1):528. doi:10.1186/s13063-021-05453-9

11. Marrs JC, Orlando ST, Saseen JJ, et al. Description of patient questions received by clinical pharmacists in the Nudge study. *Am J Health Syst Pharm*. 2023;80(18):1247-1254. doi:10.1093/ajhp/zxad139

12. Højsgaard S, Halekoh U, Yan J. The R package *geepack* for generalized estimating equations. *J Stat Softw*. 2006;15:1-11. doi:10.18637/jss.v015.i02

13. Yan J, Fine J. Estimating equations for association structures. *Stat Med*. 2004;23(6):859-874. doi:10.1002/sim.1650

14. Yan J. *Geepack*: yet another package for generalized estimating equations. *R News*. 2002;2(3):12-14.

15. Preisser JS, Lohman KK, Rathouz PJ. Performance of weighted estimating equations for longitudinal binary data with drop-outs missing at random. *Stat Med*. 2002;21(20):3035-3054. doi:10.1002/sim.1241

16. Dmitrienko A, Tamhane AC, Wiens BL. General multistage gatekeeping procedures. *Biom J*. 2008;50(5):667-677. doi:10.1002/bimj.200710464

17. Horne BD, Muhlestein JB, Lappé DL, et al. Behavioral nudges as patient decision support for medication adherence: the ENCOURAGE randomized controlled trial. *Am Heart J*. 2022;244:125-134. doi:10.1016/j.ahj.2021.11.001

18. Choudhry NK, Avorn J, Glynn RJ, et al; Post-Myocardial Infarction Free Rx Event and Economic Evaluation (MI FREEE) Trial. Full coverage for preventive medications after myocardial infarction. *N Engl J Med*. 2011;365(22):2088-2097. doi:10.1056/NEJMsa1107913

19. Ho PM, O'Donnell CI, McCreight M, et al. Multifaceted intervention to improve P2Y12 inhibitor adherence after percutaneous coronary intervention: a stepped wedge trial. *J Am Heart Assoc*. 2022;11(13):e024342. doi:10.1161/JAHA.121.024342

20. Zhou S, Silvasstar J, Clark C, Salyers AJ, Chavez C, Bull SS. An artificially intelligent, natural language processing chatbot designed to promote COVID-19 vaccination: a proof-of-concept pilot study. *Digit Health*. 2023;9:20552076231155679. doi:10.1177/20552076231155679

21. Aggarwal A, Tam CC, Wu D, Li X, Qiao S. Artificial intelligence-based chatbots for promoting health behavioral changes: systematic review. *J Med Internet Res*. 2023;25:e40789. doi:10.2196/40789

22. Scott-Sheldon LAJ, Lantini R, Jennings EG, et al. Text messaging–based interventions for smoking cessation: a systematic review and meta-analysis. *JMIR Mhealth Uhealth*. 2016;4(2):e49. doi:10.2196/mhealth.5436

23. Armanasco AA, Miller YD, Fjeldsoe BS, Marshall AL. Preventive health behavior change text message interventions: a meta-analysis. *Am J Prev Med*. 2017;52(3):391-402. doi:10.1016/j.amepre.2016.10.042

24. Orr JA, King RJ. Mobile phone SMS messages can enhance healthy behaviour: a meta-analysis of randomised controlled trials. *Health Psychol Rev*. 2015;9(4):397-416. doi:10.1080/17437199.2015.1022847

25. Mertens S, Herberz M, Hahnel UJJ, Brosch T. The effectiveness of nudging: a meta-analysis of choice architecture interventions across behavioral domains. *Proc Natl Acad Sci U S A*. 2022;119(1):e2107346118. doi:10.1073/pnas.2107346118