Text message interventions for improving medication adherence in patients with coronary heart disease: a systematic review and individual patient data meta-analysis

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Abstract

Background: Following a primary cardiovascular disease (CVD) event, patients with established Coronary Heart Disease (CHD) remain at high risk for secondary CVD events and related mortality. However, this risk is reduced by secondary prevention therapies (comprising medication and lifestyle approaches), with an absolute reduc-tion in CVD events being directly related to risk factor control. Unfortunately, adherence to secondary pre-vention therapies remains poor. Text Message Interventions (TMIs) using short message service (SMS) may have a role in improving cardiovascular medication adherence, particularly owing to their simplicity, accessi-bility and scalability as compared to other approaches.

Objective: To determine the effect of TMIs on cardiovascular medication among CHD patients, using a pooled analysis of individual patient data (IPD) from randomised clinical trials (RCTs).

Methods: Eligible RCTs were identified via systematic review and their corresponding authors were invited to submit IPD for a pooled analysis. Eligible RCTs included participants diagnosed with CHD prior to the intervention and used TMIs to provide participants with educational information. Control groups comprised standard care. The primary outcome was cardiovascular medication adherence (yes/no), and the secondary outcomes were defined as: LDL < 70mg/dL, blood pressure < 140/90, BMI < 25kg/m2, physical activity guideline met, smoking status (current vs never/previous).

Results: Of 21 eligible RCTs, IPD was available from five studies totalling 3488 trial participants (Table 1). IPD analysis found no statistically significant association between the use of TMIs and medication adherence (odds ratio (OR): 1.17, 95% CI: 0.67-2.07, p=0.576); LDL targets (OR: 1.05, 95% CI: 0.89-1.23, p=0.6); blood pressure targets (OR: 0.92, 95% CI: 0.71-1.2,

p=0.6); and, smoking status (OR: 0.96, 95% CI: 0.73-1.25, p=0.7). However, there was a statistically significant association between the use of TMIs and BMI targets (OR: 1.39, 95% CI: 1.1-1.75, p=0.006), and meeting physical activity guidelines (OR: 1.94, 95% CI: 1.12-3.34, p=0.017). Interaction analysis revealed that TMIs had a greater effect on adherence in men (OR: 1.12, 95% CI: 0.95-1.31) than in women (OR: 0.72, 95% CI: 0.57-0.93, p=0.015). Prediction analysis revealed that fe-male participants (OR: 0.66, 95% CI: 0.49, 0.88) and retired participants (OR:0.41, 95% CI: 0.31, 0.55) were significantly less likely to adhere to the prescribed medication regimen. Having a partner (OR: 1.31, 95% CI: 1.02, 1.68) and being on more medications (OR: 1.44, 95% CI: 1.34, 1.55) were positively associated with medication adherence.

Conclusions: While the statistical significance of TMIs effect on medication adherence remains uncertain, this analysis cor-roborated prior studies findings' on the factors determining adherence, including gender, employment sta-tus, and marital status. Process evaluation with realist approaches might better elucidate the role of these factors. However, heterogeneity in adherence measures between studies was an issue in this and several pri-or metanalyses that should be addressed in future work.

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Original Manuscript

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Conclusion

While the statistical significance of TMIs effect on medication adherence remains uncertain, this analysis corroborated prior studies findings' on the factors determining adherence, including gender, employment status, and marital status. Process evaluation with realist approaches might better elucidate the role of these factors. However, heterogeneity in adherence measures between studies was an issue in this and several prior metanalyses that should be addressed in future work.

Keywords: short message service; SMS; trials; RCTs; risk factor

Manuscript

Introduction

Cardiovascular disease (CVD) remains a leading cause of death worldwide and coronary heart disease (CHD) remains the largest contributor to CVD events.[1] Following a primary CVD event, patients with established CHD remain at particularly high risk for secondary CVD events and related mortality.[2] However, this risk is reduced by the aggressive use of secondary prevention therapies (comprising medication and lifestyle approaches), with an absolute reduction in CVD events being directly related to the control of the corresponding risk factor (Box 1).[3]

Box 1: Guideline recommendations for secondary prevention of CHD	
Medication therapies[3] • Statin therapy to reduce low-density lipoprotein cholesterol (LDL-C) [4] • Antihypertensive therapy to reduce blood pressure[5] • Antiplatelet use for antithrombotic effects[6]	**Lifestyle change** (particularly for high-risk patients)[3] • Dietary modification[7] • Physical activity/exercise[8] • Smoking cessation[9] • Obesity avoidance[10]

Challenges in adherence to secondary prevention therapies

Unfortunately, adherence to secondary prevention therapies remains poor. Systematic reviews and meta-analyses have estimated adherence to secondary prevention pharmacological therapies at between 50% and 66% at 12-24 months following discharge, with 30% of patients discontinuing one or more medications within 90 days of discharge from an index CVD event.[11-14]

A meta-analysis of prevalence attributed nearly a tenth of CVD events to poor medication adherence alone.[15] Recent reviews have identified non-adherence to cardiovascular medication as being due to either disease factors, therapy factors, healthcare (system) factors, social factors, and patient factors,[11, 16] of which 85% are considered modifiable.[1718, 19] However, the uptake of supervised cardiac rehabilitation programs remains poor, with an estimated 25% participation rate.[19] As a result, digital health innovations - particularly mobile health (i.e. mhealth) applications – are being tested for improving CVD medication adherence.

Text messaging interventions (TMIs) for improving medication adherence

Text Message Interventions (TMIs) using short message service (SMS) may have a role in improving cardiovascular medication adherence, particularly owing to their simplicity, accessibility and scalability as compared to other approaches.[20-24] While they have been shown to produce moderate reductions in blood pressure (BP) and Body Mass Index (BMI) among primary prevention populations,[25, 26] their impact on CVD risk factors among secondary prevention populations is less well understood.

The TEXTMEDS (Text Messages to Improve Medication Adherence and Secondary Prevention After Acute Coronary Syndrome) trial of 1424 patients with Acute Coronary Syndrome (ACS) found that a post-discharge program of text message reminders had no effect on medication adherence to 5 indicated cardioprotective drugs, but demonstrated small effects on lifestyle risk factors.[27] Several

other studies point to improvements in medication-mediated risk factors (e.g. LDL-C and blood pressure lowering) as a proxy indicator for improved adherence.[28-30] However, recent systematic reviews provide a more promising picture. The 2024 update of the Cochrane review of TMIs for secondary prevention of CVD (i.e. the third update in a decade) found that 10 out of 18 studies (N=8136) demonstrated beneficial effects on medication adherence, but did not perform a meta-analysis owing to study heterogeneity.[31]

Rationale

Recognizing the inherent challenges of pooling aggregates in a traditional meta-analysis, we considered the added utility of an individual patient data (IPD) meta-analysis which would allow for the standardization (and subsequent pooled analyses) of homogenized outcome measures at the IPD level. This approach has been shown to reduce heterogeneity, improve statistical power, and improve the consistency of the analysis.[32] Additionally, individual patient data would allow for interrogation of population subgroups (e.g. by age, gender, and other sociodemographic variables) to determine which patient groups might benefit the most from TMIs for improving medication adherence and CVD risk factors.

This study therefore aimed to conduct a pooled analysis of individual patient data (IPD) to determine the effect of TMIs on cardiovascular medication adherence among established CHD patients and examine the factors that may impact this. Secondly it aimed to determine the effect of TMIs on CVD risk factors in patients who have CHD.

Methods

We performed a systematic review of randomized controlled trials (RCTs) and an analysis of IPD compiled from included studies. Methods have been developed in accordance with the PRISMA-IPD checklist (PROSPERO Registration no.: CRD42022302657).[33]

To be eligible for inclusion, participants must have had a diagnosis of CHD prior to beginning the intervention, the definition of which must have aligned with the universal definition of acute coronary syndrome,[34] which includes: documented prior myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention, symptomatic coronary artery stenosis identified on CT or invasive coronary angiography, symptomatic stable angina, or imaging evidence of coronary artery disease or myocardial ischemia.

We included TMIs using SMS to provide participants with reminders or educational information. Any duration or frequency of intervention was suitable. Studies that used other forms of intervention in the absence of SMS messaging, such as email, letters, phone calls, application-based reminders, other electronic reminders were excluded, though these modalities were permitted in the control group. We included studies in which control groups comprised of either standard of care, with no or very few SMS message reminders (relative to intervention) or education. Alternative (i.e. non-SMS) methods of reminders or education, such as email, letters, phone calls, face-to-face visits, pill box reminders or electronic applications were permitted in the control group.

Outcomes were defined as follows:

1. **Primary outcome**: Adherence to cardiovascular medications (specifically; LDL-C lowering

therapy, antihypertensive therapy, and antiplatelet therapy) after at least 30 days of intervention, with different thresholds for adherence between studies. Outcome measures included Medication Possession Ratios (MPRs) and Adherence Assessment Scales (AASs).

2. **Secondary outcome**: Changes in CVD risk factors after at least 30 days of intervention. We considered risk factors as defined by the Australian CVD risk calculator. [35] Outcome measures & criteria were as follows:
    - LDL-C < 70mg/dL (yes/no);
    - Blood pressure < 140/90 mmHg (yes/no);
    - BMI < 25kg/m^2 (yes/no);
    - Exercising ≥30 min/d (moderate exercise) on 5 or more days per week (yes/no);
    - Smoking status (current smoker vs never/ex-smoker).

Searching was conducted between December 2021 – March 2025, and included a computerized search of MEDLINE, EMBASE, PsycINFO (Ovid), and Web of science, based on a combination of relevant Medical Subject Headings (MeSH) and free text terms with the use of relevant filters for randomised controlled trials. All studies from the year 1990 onwards and published in English were included. Studies from other systematic reviews in the field were included for screening. PROSPERO was searched for other ongoing systematic reviews and meta-analyses prior to this study being performed.

We also searched for ongoing trials in the prior 32 months from the following trial registries:[36] Clinicaltrials.gov (https://clinicaltrials.gov/), World Health Organization's International Clinical Trials Registry Platform (ICTRP) (https://trialsearch.who.int/), Australia and New Zealand Clinical Trials Registry (https://www.anzctr.org.au/). Two reviewers (LW, NG) independently performed the literature search and independently screened potential study abstracts for inclusion. Full-text articles of potentially eligible studies were then screened to ensure they met inclusion criteria. A third reviewer (JB) was involved for resolving discrepancies. Reasons for study exclusion were recorded and reported using a PRISMA flow chart. We contacted the authors of studies that were observed to have incomplete or unpublished information.

Data available for the individual level patient analysis was requested from corresponding authors of each study. Data were extracted from identified sources into a Microsoft excel spreadsheet on both a study level, and an individual level. The data extraction was performed by two independent reviewers (HM & MG) with a third reviewer (SM) to solve disagreements between the two.

Once the IPD was extracted, continuous variables were transformed into dichotomous variables to ensure homogeneity for pooling. Adherence measures were reported as either Medication Possession Ratios (MPR) or as Adherence Assessment Scores (AAS), with differing definitions of what constituted ‘adherent’ between studies. To enable homogeneity for pooling, IPD primary outcome variables were transformed into a dichotomous variable (i.e. adherent /non-adherent) based on the following decision algorithm:

- Where a study provided data for both MPRs and AASs, we opted to use MPR.
- Outcome reported as MPR: Individuals with MPR ≥80% were considered ‘adherent’, and those whose MPR <80% were considered ‘non-adherent’.
- Outcome reported as AAS: Individuals scoring 100% were considered adherent, and those scoring <100% were considered non-adherent.

The difference in adherence standards for the MPRs and AASs were agreed through author consensus, and corroborated by reviews of adherence measures that confirm the widespread use of these conventions in practice.[37, 38 39]

We conducted a one-stage meta-analysis wherein the IPD was pooled, followed by statistical models being run on the combined dataset.[40-42] Continuous outcomes from IPD were analysed using a linear mixed model with the end-of-trial value as the outcome, the treatment arm as a fixed effect, and a random trial intercept and random trial-by-treatment interaction. For dichotomous data, a logistic mixed model was used with the same variables as the continuous outcome model. Similar models were used for primary and secondary outcomes, depending on data type. Forest plots were used to illustrate differences in primary and secondary endpoints.

Univariable logistic regression analyses were performed to identify factors associated with medication adherence (primary outcome). All variables with p-value ≤ 0.10 were subsequently tested in a multivariable logistic regression analysis, and the Least Absolute Shrinkage and Selection Operator (LASSO) regularisation technique was used to select variables for the final multivariable logistic regression analysis (to avoid overfitting).

An Interaction analysis was conducted to determine differences in treatment effects between groups. A Risk of Bias analysis was conducted for included studies, and ROBVIS was used to illustrate the results.[43] A funnel plot for publication bias was not done as guidelines recommend this only when there at least 10 studies in the analysis, while only 5 were available for analysis.[44]

Findings & Results

We included 5 RCTs (comprising pooled IPD of 3488 trial participants) for inclusion in a one-stage meta-analysis (Fig 1). We outline the data and analysis for primary and secondary outcome below.

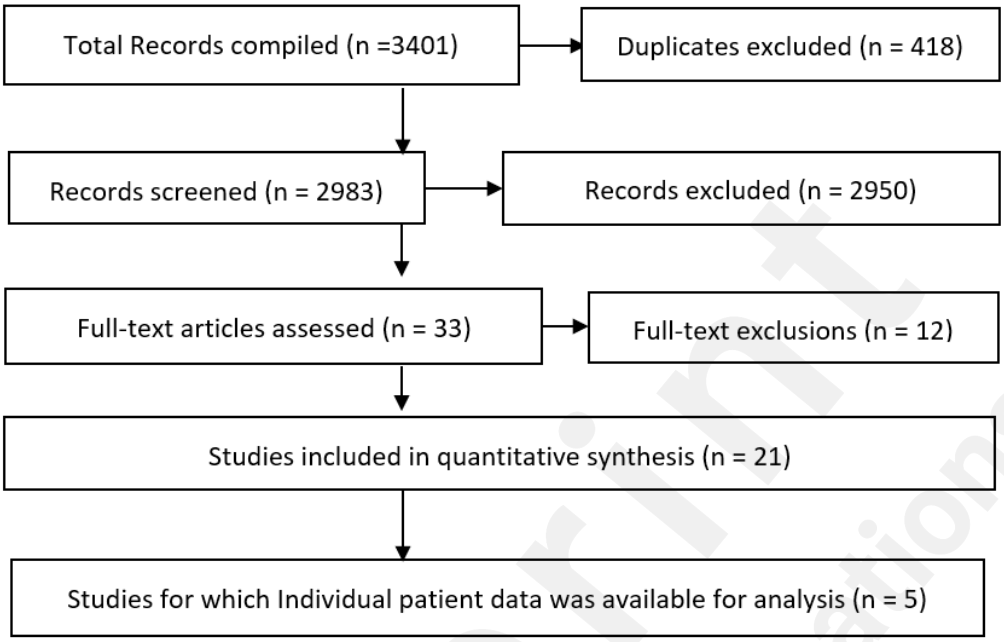

Figure 1. PRISMA Flow chart

Baseline characteristics

Table 1 outlines the baseline characteristics for each included study (Table 1). With regards to study size, the study by Chow and colleagues was the largest contributor to our analysis (N = 1,424), followed by Bermon and colleagues (N = 930), and Bae and colleagues (N = 879). All studies comprised a 1:1 allocation between treatment and control groups. The mean age of participants ranged from 57.2 to 63.5 years. The gender distribution of participants was predominantly male, (range: 73.3% to 83.3% male). Notably, no two studies were conducted in the same country, with one each from (in alphabetical order) Australia, Brazil, Canada, Colombia, and South Korea.

Table 1. Baseline Characteristics by Study

Study		Bermon *et al.* 2021	Passaglia *et al.* 2020	Ross *et al.* 2021	Bae *et al.* *2021*	Chow *et al.* *2022*
No. of Participants		(N = 930)	(N = 180)	(N = 75)	(N = 879)	(N = 1,424)
Treatment Group*	Control Group	414 / 805 (51.4%)	72 / 147 (49.0%)	36 / 68 (52.9%)	352 / 735 (47.9%)	676 / 1,368 (49.4%)
	Intervention Group	391 / 805 (48.6%)	75 / 147 (51.0%)	32 / 68 (47.1%)	383 / 735 (52.1%)	692 / 1,368 (50.6%)
Gender*	Female	165 / 805 (20.5%)	38 / 147 (25.9%)	20 / 68 (29.4%)	123 / 735 (16.7%)	278 / 1,368 (20.3%)
	Male	640 / 805 (79.5%)	109 / 147 (74.1%)	48 / 68 (70.6%)	612 / 735 (83.3%)	1,090 / 1,368 (79.7%)
Age#		63.3 (9.9)	57.4 (10.3)	60.3 (9.3)	60.2 (10.2)	58.0 (10.7)

*n / N (%); #Mean (SD)

Primary outcome

Each of the included studies' adherence measures, time points, and medication groups are outlined in the table below (Table 2). All studies measured adherence across the same four medication groups, except one study which measured three. Durations of the included studies included 60 days (n=1), 6 months (n=2) and 12 months (n=2).

Table 2. Adherence measures, time points, and medication groups for included studies

Study ID	Measure		Time point(s)	Medication groups studied	Adherence at endpoint	
	MPR[a]	AAS[b]			Adherent (%)	95% CI
Bermon et al. 2021	No	MARS-5[c]	0, 12 months	Antiplatelets, statins, β-blockers, and ACE-I /ARBs (n=4)	358 / 885 (40.5%)	36.2 - 43.1%
Passaglia et al. 2020	No	MAT[d]	0, 6 months	Antiplatelets, statins, and β-blockers (n=3)	23 / 147 (15.6%)	10.4 - 22.8%
Ross et al. 2021	No	MMAS-8[e]	0, 60 days	Antiplatelets, statins, β-blockers, and ACE-I /ARBs	26 / 68 (38.2%)	27.0 - 50.9%

			(2 months)	(n=4)		
Bae et al. 2021	Yes[f]	Modified MMAS-6	0, 6 months	Antiplatelets, statins, β-blocker, and ACE-I /ARBs (n=4)	700 / 735 (95.2%)	93.4 - 96.6%
Chow et al. 2022	Yes[g]	No	0, 6, 12 months	Antiplatelets, statins, β-blocker, and ACE-I /ARBs (n=4)	854 / 1,368 (62.4%)	59.8 - 65.0%

[a]***MPR**: Medication possession ratio;* [b]***AAS**: Adherence Assessment Scoring;* [c]***MARS-5**: Medication Adherence Report Scale – 5-questions (Adherent: MARS-5 score=25);* [d]***MAT**: Medida de Adesão aos Tratamentos (scored out of 7);* [e]***MMAS-8**: Morisky Medication Adherence Scale – 8 questions (Low, medium, or high adherence)*

[f]*: 'Adherent' defined as 25/30 days (83.3%) for 4 medication classes.*

[g]*: 'Adherent' defined as 24/30 days (80%) for 4 medication classes.*

Rates of adherence were notably higher in the studies that used MPR as compared to those using AAS (Table 2). Pooled IPD analysis of the included studies found no statistically significant association between the use of TMIs and changes in medication adherence (Odds Ratio (OR): 1.03, 95% CI: 0.54 - 1.95, p=0.929), as illustrated in Figure 2.

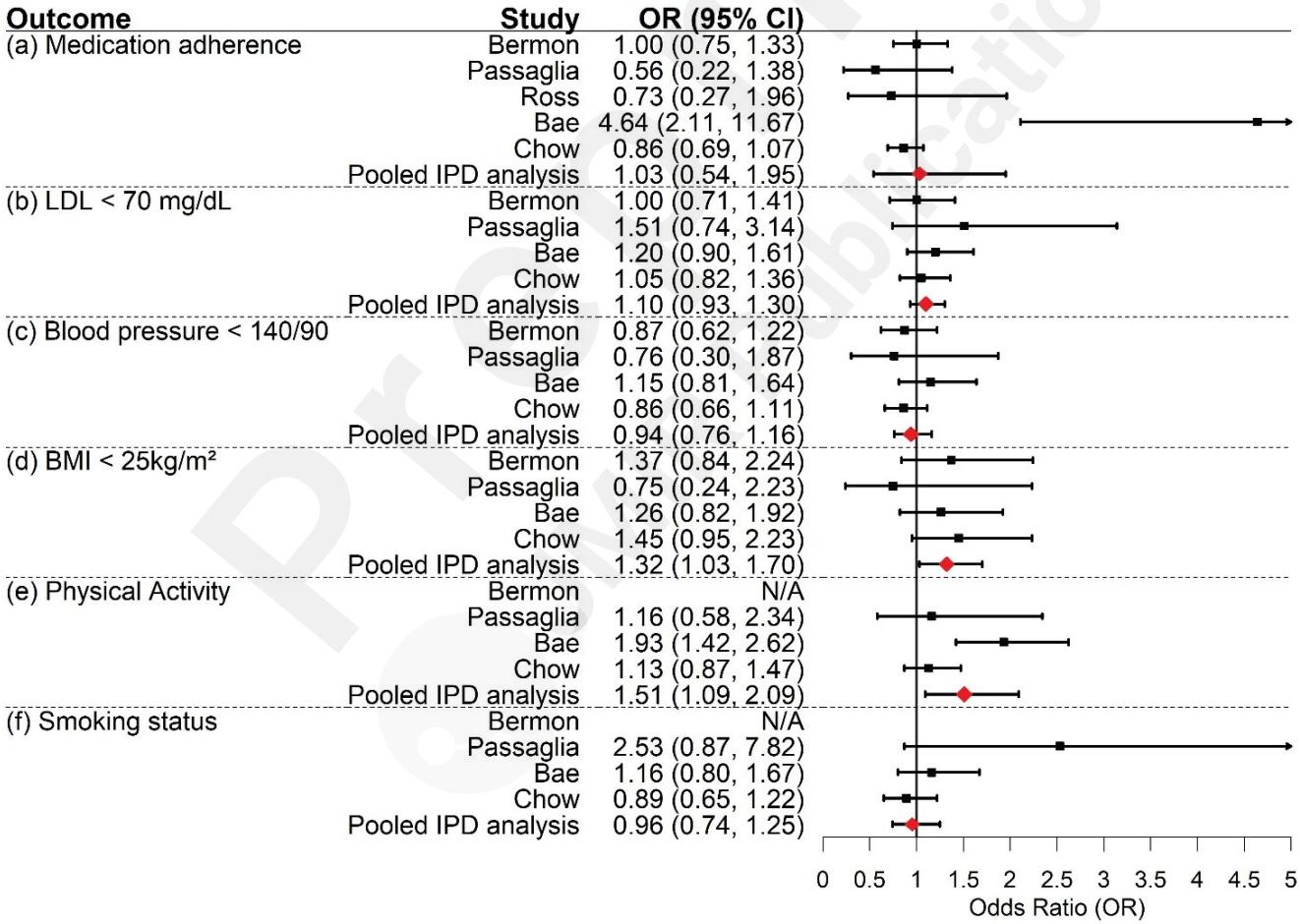

Figure 2: Forest plot depicting association between TMI and (a) medication adherence, (b) LDL-C < 70mg/dL; (c) Blood pressure < 140/90mmHg, (d) BMI < 25kg/m^2, (e) meeting physical activity (f) smoking status

Secondary outcomes

IPD analysis of the included studies found no statistically significant association between the use of

TMIs and the likelihood of LDL-C < 70mg/dL (OR: 1.10, 95% CI: 0.93-1.30, p=0.3, Fig 2b); the likelihood of blood pressure < 140/90mmHg (OR: 0.94, 95% CI: 0.76-1.16, p=0.6, Fig 2c); and, smoking status (OR: 0.96, 95% CI: 0.74-1.25, p=0.8, Fig 2f).
However, the IPD analysis did identify a statistically significant association between the use of TMIs and the likelihood of BMI < 25kg/m^2 (OR: 1.32, 95% CI: 1.03-1.70, p=0.028, Fig 2d), and the likelihood of meeting the physical activity guidelines (OR: 1.51, 95% CI: 1.09-2.09, p=0.013, Fig 2e). Continuous outcomes analyses are reported in the supplementary file.

Interaction analysis

Three interaction terms were tested: age (< 75 vs >=75), BMI (overweight vs not overweight) and sex (female vs male). Interaction analysis revealed no significant interaction in age (p=0.228) and BMI (p=0.758), However, the TMI was found to have a greater effect on adherence in men (OR: 1.12, 95% CI: 0.95-1.31) than in women (OR: 0.72, 95% CI: 0.57-0.93, p=0.015) (Table 3).

Table 3. Interaction analysis between sex and text messaging intervention on adherence

Sex	OR (95% CI)	P-value
Male	1.12 (0.95,1.31)	0.015
Female	0.72 (0.57,0.93)	

Predictors of medication adherence

Analysis of predictors of medication adherence revealed that female participants and retired participants were significantly less likely to adhere to the prescribed medication regimen, whereas having a partner and being on more medications were positively associated with medication adherence (Table 4).

Table 4. Predictors of medication adherence (multivariable model)

Characteristic	OR[1]	95% CI[1]	p-value
Sex			**0.005**
Male	—	—	
Female	0.66	0.49, 0.88	
Employment status			**<0.001**

Characteristic	OR[1]	95% CI[1]	p-value
Employed	—	—	
Unemployed	0.57	0.39, 0.83	
Retired	0.41	0.31, 0.55	
Marital status			**0.036**
Single/Widowed	—	—	
Married/De facto	1.31	1.02, 1.68	
Number of medications	1.44	1.34, 1.55	**<0.001**

Risk of bias

Risk of bias outcomes for the 5 included studies were similar in several assessment domains, i.e. random sequence generation, blinding (participants, personnel and outcome assessment), and selective reporting (Figure 3). All studies reported using random sequence generation to avoid selection bias. Regarding allocation concealment, while three studies were judged to be low risk ,[29, 45, 46] two had an unclear risk of bias (reporting limitations).[47, 48] Whilst blinding of participants was not possible with this intervention, all 5 studies were judged to be low risk in their blinding of outcome assessors.

Regarding incomplete outcome data, four studies were judged to have a higher risk of attrition bias owing to elevated dropout rates. In the study by Bae and colleagues, 15.9% and 10% of participants were lost to follow-up in the control and intervention groups, respectively.[47] The study by Passaglia and colleagues lost 18.3% of participants to follow- up.[48] Both these studies did not perform an intention-to-treat analysis.[47, 48] In the study by Ross and colleagues, 5% and 19% of participants were lost to follow-up in the control and intervention groups, respectively - constituting a difference between allocation groups.[46] The study by Bermon and colleagues also reported imbalanced dropout in the control group (11.5%) and intervention group (15.3%).[29] The study by Chow and colleagues was judged to have a lower risk of attrition bias.

All 5 studies had published trial protocols/registry entries with defined *a priori* outcomes that were reported in the final results and were judged to be at low risk of reporting bias . Two studies were at risk of other sources of bias: the pilot study by Ross and colleagues did not calculate sample size;[46] and 20 participants (26.6%) from the intervention group in Passaglia and colleagues' study did not receive text messages as expected, potentially compromising study power.[49]

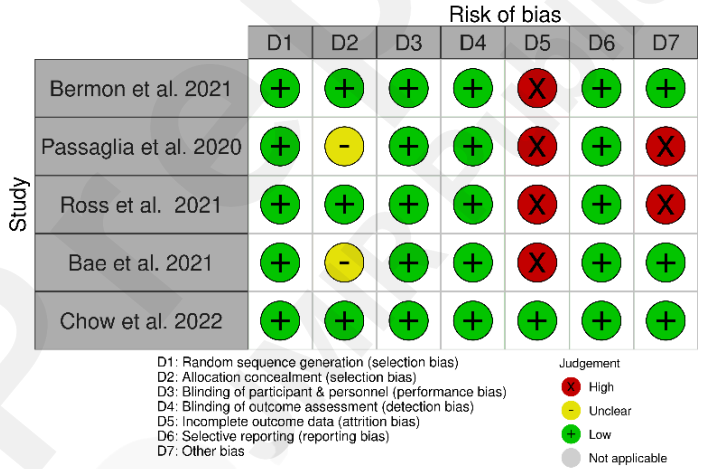

Figure 3: Risk of Bias analysis

Discussion

This pooled IPD analysis found no statistically significant association between the use of TMIs and changes in overall medication adherence among CHD patients. However, improvements in control of some CVD risk factors were noted, with a statistically significant association between the use of TMIs and meeting the physical activity guidelines, as well as having a BMI < 25kg/m^2. Other CVD risk factors (i.e. LDL-C < 70mg/dL, Blood pressure < 140/90 mmHg, and smoking status) showed no significant association with the use of TMIs.

Interaction analysis revealed that TMI was found to have a greater effect on improving medical adherence in men than on women. Regarding predictors of medication adherence, female participants and retired participants were significantly less likely to adhere to the prescribed medication regimen, while having a partner and taking more medications increased the likelihood of medication adherence.

How (and by how much) can medication adherence be improved?

High medication adherence and patient compliance has been shown to significantly improve health outcomes in CHD while also reducing the costs of secondary prevention by 10.1%-17.8%.[50] However, effectively improving medication adherence has been a longstanding challenge, and several different approaches have been implemented, including the provision of patient education, medication reminders, cognitive-behavioural interventions, engaging healthcare team members and improving medication regimen.[51] Many of these have demonstrated improvements in medication adherence: trials of the combination 'polypill' report medication adherence improvements of between 4.2 and 16.7%;[52] cardiac rehabilitation programs have shown a 14% improvement in medication adherence;[53] and 7 of 8 trials of community-pharmacist-led interventions (including but not limited to, adherence counselling, medication reviews and patient education), reported improvements in medication adherence.[54] While TMIs enable a wider reach and better cost-effectiveness than these options, quantifying their effect on medication adherence remains a challenge.

What impact do TMIs have on medication adherence?

Systematic reviews and meta-analyses on the impact of SMS interventions on CVD medication adherence paint an ambivalent picture.[28-30] A 2024 Cochrane review (n=8136) identified 10 studies that showed a beneficial effect, while 8 others showed a reduction or no difference in medication adherence.[55] Notably, the review included all the studies included in this review, and decided against conducting a meta-analysis owing to excessive heterogeneity in outcome measures – ultimately reporting an uncertain effect.[55] A 2024 network meta-analysis of 21 RCTs (N=3,904 patients) that compared the relative medication adherence impacts of several mhealth interventions found that while telephone support, telemonitoring interventions and app-based interventions demonstrated medication adherence outcomes superior to usual care, there was no statistically significant difference when comparing TMIs to usual care.[56] This corroborated the findings of a 2020 meta-analysis of 6 RCTs (N= 1,158 patients) which also found the same.[57] Most recently, a 2025 RCT of 9,501 CHD patients found no statistically significant difference in medication adherence or clinical events at 12 months between those receiving SMS reminders or usual care.[58] Importantly, this RCT comprised a larger sample size than any prior RCT or meta-analyses (including this one). This suggests that the detectable effect size may be smaller than expected, or that – like with many complex interventions – other variables are at play.

Delving into the reasons for the heterogeneity between studies, the 2024 Cochrane review recognised

that the effect of TMIs on medication adherence was subject to a plethora of contextual factors, and recommended the use of "process evaluation and qualitative studies to… identify the individual and organisational-level factors affecting the implementation, adoption, and effectiveness of interventions."[55] Building on this, the 2025 RCT by Ho and colleagues also called for TMIs to "be designed to address the multiple factors influencing adherence."[58]

As our analysis showed, TMIs improved medication adherence differently between genders, with a greater effect on men than on women. The analysis of predicting factors also found that female participants and retired participants were significantly less likely to adhere to the prescribed medication regimen, while having a partner and taking more medications increased the likelihood of medication adherence. Addressing these factors, or specifically targeting TMIs towards patients with these attributes could produce greater improvements in medication adherence.

Unpacking the determinants of medication adherence: What works, and why?

A 2024 review classified the barriers to cardiovascular medication adherence as: condition/disease-related factors, treatment/therapy-related factors, healthcare (team and system)-related factors, patient-related factors and social/socioeconomic factors.[11, 16] Realist evaluation utilise theory-driven approaches to identify context-dependant explanations for intervention outcomes, based on the aforementioned factors.

For example, a 2018 realist review on chronic diseases in low-resource settings found that TMIs had a greater impact on certain subgroups – specifically, participants with low literacy, stressful life events, and those who were earlier in the disease trajectory.[59] This illustrates the important role of patient factors in intervention effect, and highlights importance of targeting interventions. Personalisation and tailoring of interventions is important in addressing patient-related factors, such as participants' illness experience, their receptiveness to risk/prevention information; and their digital literacy. [60-62] A 2022 realist review of 31 interventions for CVD medication adherence also identified a host of intervention-related factors (i.e. intervention complexity, customisation, and drivers) and system-related factors (i.e. a local champion or 'driver', the technology being used, and stakeholder involvement).[63]

Study duration could be a determining factor too. A 2025 meta-analysis found that educational programmes could significantly improve medication adherence at 2 to 6 months post-intervention, but had no effect in the first month of intervention.[64] Corroborating this, the briefest study in our analysis by Ross and colleagues also had the lowest odds of effect (OR:0.73, 95%CI: 0.27-1.96); suggesting that longer duration trials may demonstrate more robust findings.[46] Extraneous factors may also impact the effectiveness of TMIs; for example, excessive SMS reminders from other sources (e.g. pharmacies' Prescription Reminder Services) which result in participants' text message 'fatigue'.

Methodological challenges in measuring medication adherence

The aforementioned Cochrane meant-analysis opted not to conduct a meta-analysis on the 18 included studies, citing heterogeneity in definitions and metrics of medication adherence.[55] This reflects the methodological challenges that were encountered this IPD analysis, and warrants a closer look at medication adherence measures.

Three main approaches are used to measure medication adherence: Proportion of Days Covered (PDC), Medication possession ratio (MPR), and Adherence Assessment Scoring (AAS) – the latter two of which were seen in this review.[65] However, a variety of approaches exist for calculating each

of these measures too, calling their comparability (and fungibility) into question. Efforts to standardise MPR measurement methods have been unsuccessful, with comparative analyses demonstrating wide and statistically significant differences in adherence estimates between several studies' MPR calculation methods.[37, 66] Reporting the MPR as a range might be one way to address this challenge.[67] Self-reported scoring systems have shown considerable variability in measurement.
A 2023 systematic review which evaluated 27 different medication adherence measurement instruments concluded that while none could be recommended, the MARS-5 and MMAS-8 tools were classed as having 'potential to be recommended for use [i.e. category B]).[68] While this lends credibility to the studies included in our analysis, the need for such a plethora of measurement instruments ought to be questioned, especially when measures are not fungible or comparable.

This review also found that no two included studies used the same adherence measure (i.e. either MPR or AAS); and moreover, no two studies used the same definition for their MPR measure (i.e. 80% vs 83.3%), or the same AAS measure (see legend, Table 2). This heterogeneity necessitated the derivation of a binary variable (i.e. adherent/non-adherent), which very likely reduced the statistical power of the analysis.[69] Recognizing that MPR and AAS would estimate adherence differently, we weighted them accordingly when deriving the binary variable; and subsequently noted that adherence estimates were markedly higher in studies using MPR when compared to those using scoring scales. A 2011 review of 76 studies on cardiovascular medication adherence in resource-limited settings suggested that pill counting (e.g. MPR) tended to result in higher estimations of adherence than self-reported AAS measures, suggesting that may not have been necessary.[13] Future studies could verify this using IPD to inform recommendations for pooling heterogenous adherence measures in future analyses: i.e. determining what constitutes an 'adherent' patient as measured by MPR tools or AAS tools.

Another approach taken by some studies is to eschew adherence measurements altogether, and instead infer adherence changes based on direct measures of risk factor measures: e.g. LDL-C as proxy for statin adherence, heart rate as proxy for Beta-blocker adherence, blood pressure as proxy for ACE-I/ARB adherence, etc. Future work could compare between approaches to assess the reliability and validity of these proxy measures.

Limitations and future work

While pooling IPD conferred greater statistical power to this analysis, the statistically insignificant findings suggest that the detectable effect size may be smaller than expected, or that the required sample size might may be considerably larger - as suggested by a 2025 trial.[58] Of 21 eligible studies, IPD for analysis was available from only 5 trials, and this data unavailability may have introduced bias, as well as contributing to the smaller sample size. The geographical distribution of the included studies offers population diversity that improves the generalisability of the findings, though Asian populations are underrepresented. The population included in each study may also not be representative of people most likely to be non-adherent. Identifying and targeting populations who are more likely to respond to TMIs may be a more definitive way to establish their efficacy in future work.

Conclusion

TMIs are seeing increasingly greater utilisation in the secondary prevention of CHD by improving risk factor control.[28-30] While the statistical significance of their effect on medication adherence remains in question, their clinical significance as important tools for improving post-discharge care among patients with CHD is broadly recognised.

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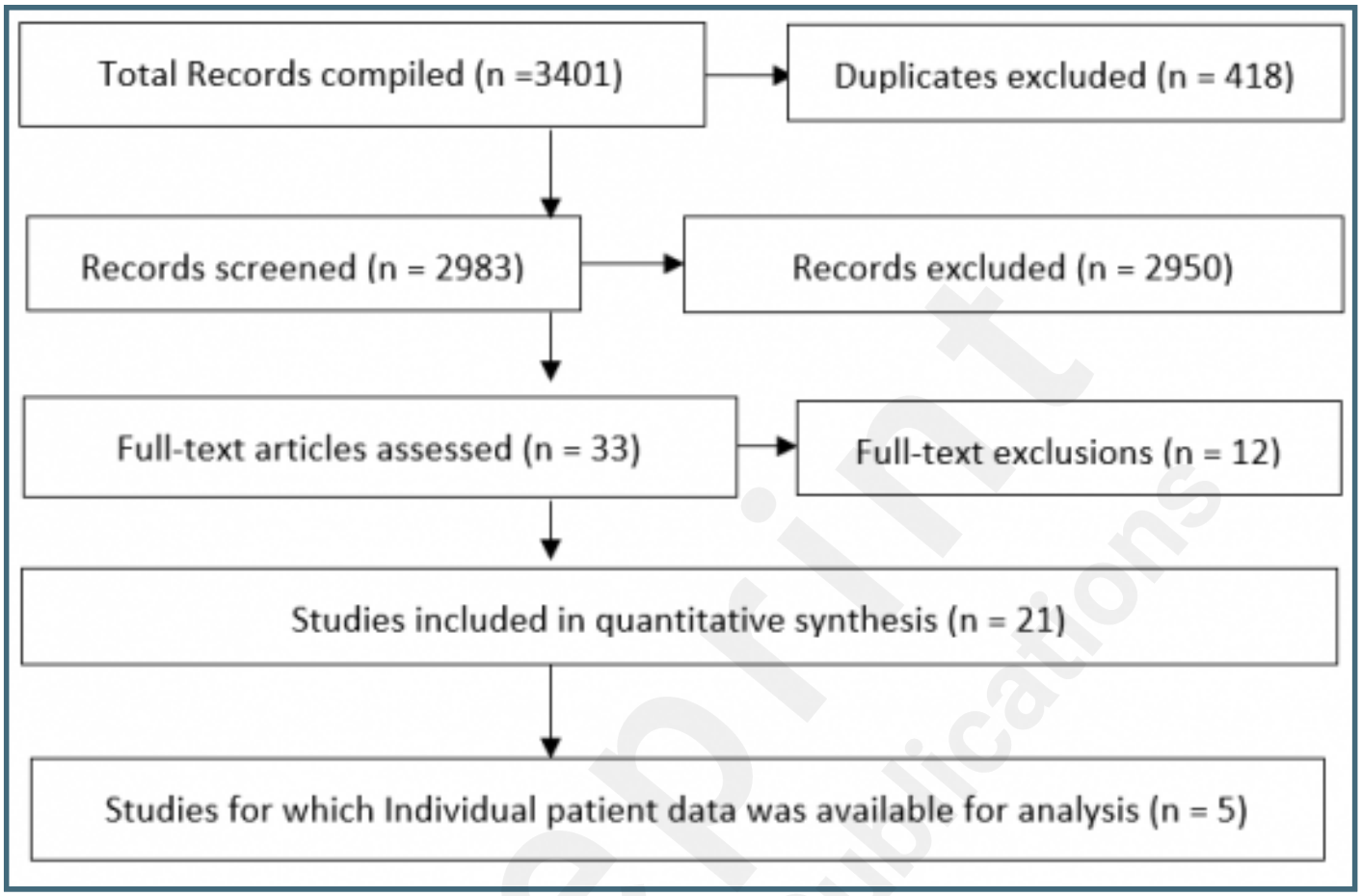
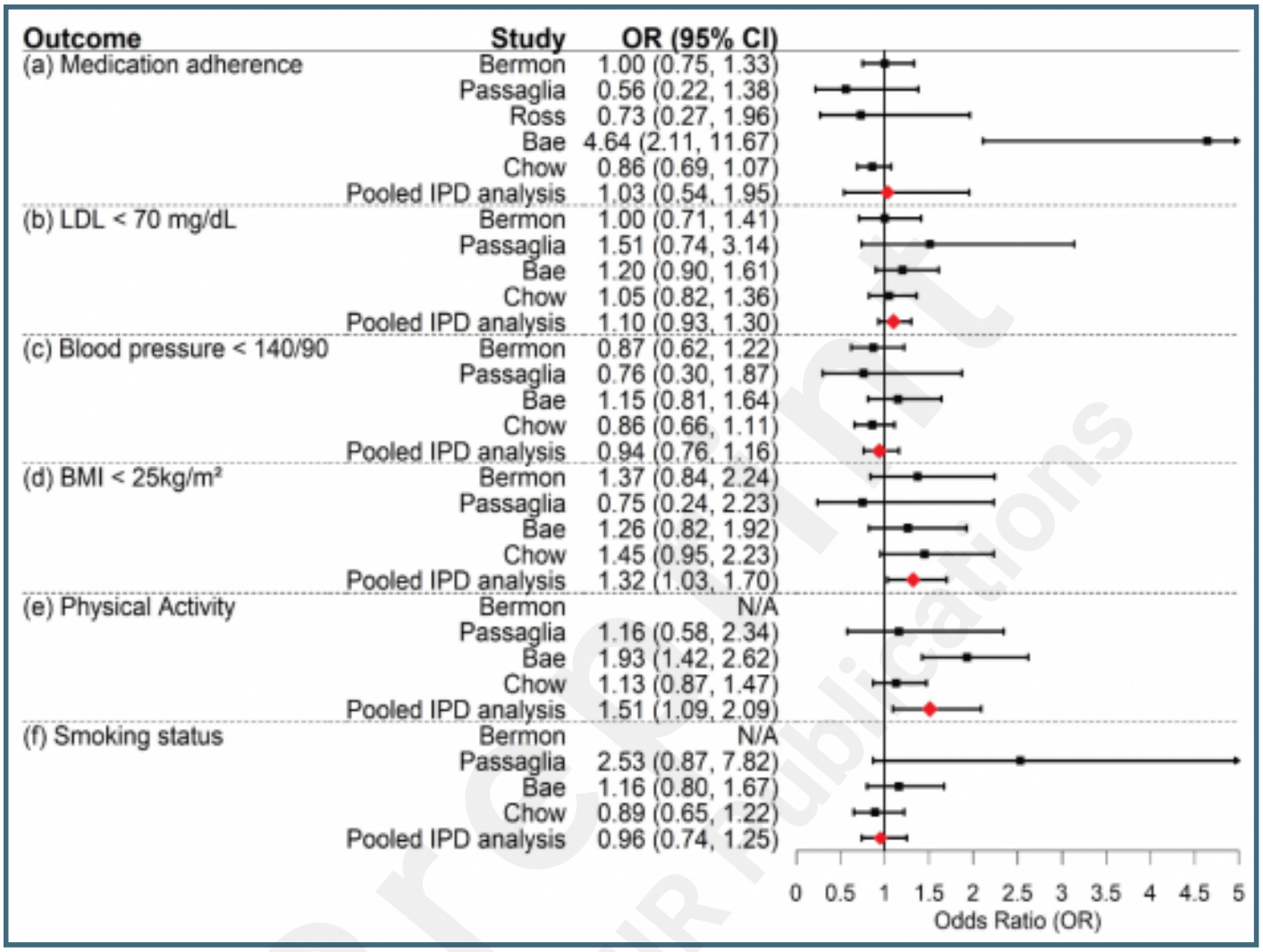
Supplementary Files

Figures

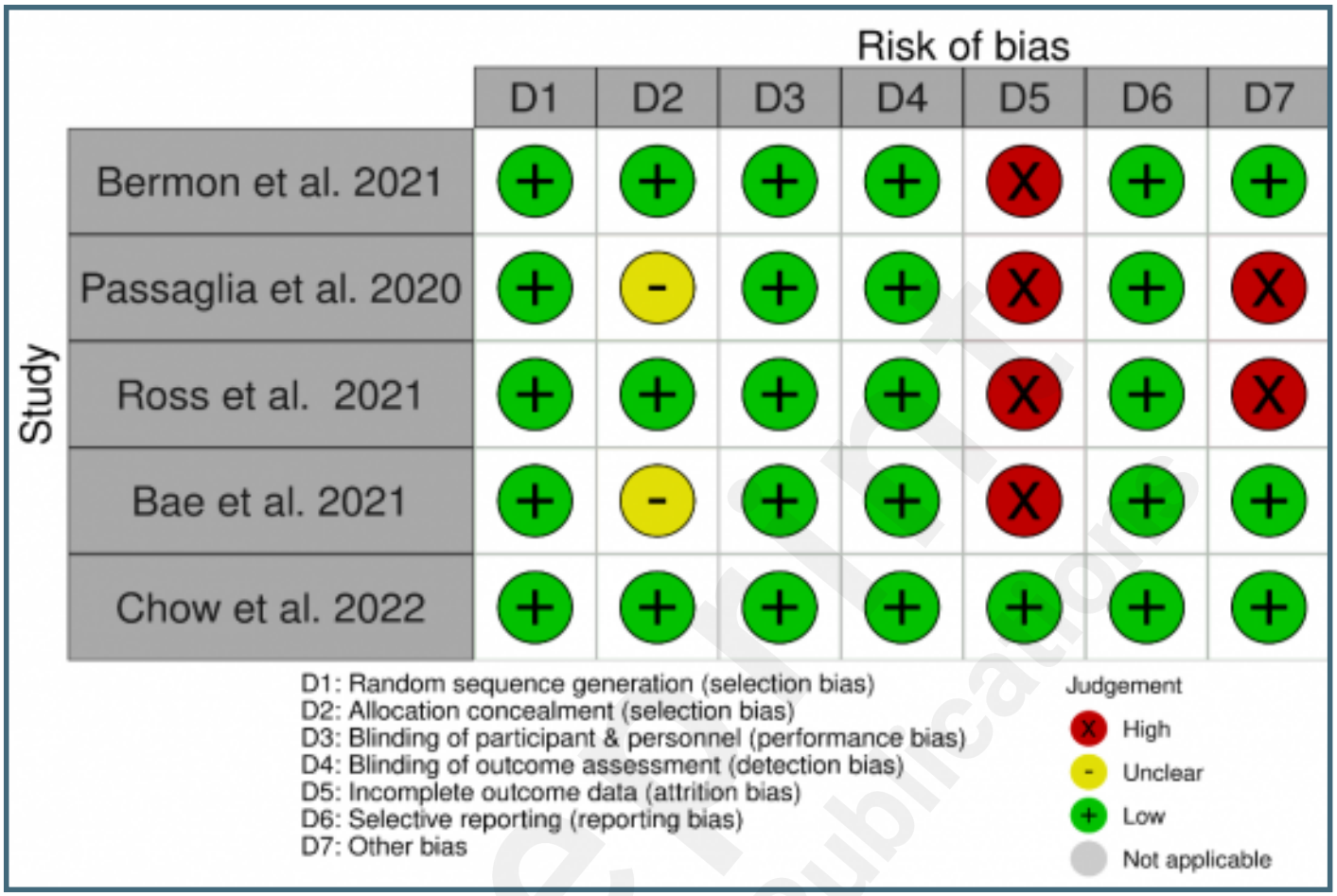
PRISMA Flow chart.



Forest plot depicting association between TMI and (a) medication adherence, (b) LDL-C < 70mg/dL; (c) Blood pressure < 140/90mmHg, (d) BMI < 25kg/m2, (e) meeting physical activity (f) smoking status.



Risk of Bias analysis.



Multimedia Appendixes

Supplementary File.
URL: http://asset.jmir.pub/assets/e284f7a7bc2e1f1ad73e536a2a85c3e1.docx