



## Effect of telehealth interventions on major cardiovascular outcomes: a meta-analysis of randomized controlled trials

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### Abstract

**Background** Telehealth interventions (THI) were associated with lower levels of cardiovascular risk factors in adults, whereas the effect of THI on cardiovascular disease (CVD) still remains controversial. A meta-analysis was conducted to summarize the evidence from randomized controlled trials (RCT) which investigated potential impact of THI on the incidence of CVD in patients with or without prior CVD. **Methods** PubMed, EmBase, and the Cochrane Library were searched to identify RCTs to fit our analysis through December 2016. Relative risk (RR) with its 95% confidence interval (CI) was used to measure the effect of THI using a random-effect model. Sensitivity analysis, subgroup analysis, heterogeneity tests, and tests for publication bias were also conducted. **Results** Eight RCTs were included and with a total of 1635 individuals. The summarized results indicated that participants who received THI showed a significant reduction of the CVD incidence as compared with usual care (RR: 0.59; 95% CI: 0.47–0.74;  $P < 0.001$ ). Furthermore, the effect of THI was greater in patients with history of CVD (RR: 0.55; 95% CI: 0.44–0.70;  $P < 0.001$ ) than in patients without history of CVD (RR: 0.99; 95% CI: 0.51–1.94;  $P = 0.977$ ). Sensitivity analysis suggested that the intervention effect persisted and the conclusion was not changed. Subgroup analysis indicated mean age, study quality might play an important role on the risk of CVD. **Conclusions** The findings of this study indicated THI could reduce the recurrence of CVD. Further large-scale trials are needed to verify the effect of THI on CVD in healthy individuals.

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**Keywords:** Cardiovascular disease; Meta-analysis; Telehealth interventions

## 1 Introduction

Cardiovascular diseases (CVD) are the leading cause of death among most of the adults worldwide,<sup>[1]</sup> and accounts for about 40% deaths in China.<sup>[2]</sup> Currently, preventive strategies are perceived as major public health priorities due to the increasing disease burden of CVDs from the past several years. Health education to some extent might affect the cardiovascular risk levels which have been studied previously in patients with different characteristics.<sup>[3–5]</sup> They indicated that participants who received health education could modulate the levels of cholesterol, blood pressure, glycemia, and changed their adverse lifestyle, which in-

cluded smoking, low levels of physical activity, and unhealthy diet. Accompanied with the development of telehealth, the methods of patient consultation, monitoring, and education have also been changed.<sup>[6]</sup> However, the intervention effects of telehealth on CVD have not been shown to be beneficial and adherence of participants might also contribute as an important impact.

Over the past few years, extensive studies have put forward which describe the importance of cardiovascular risk factors as principle outcomes for individuals who received telehealth intervention (THI) rather than the CVD.<sup>[7–9]</sup> Although numerous studies have illustrated the effect of THI on the incidence of CVDs,<sup>[10–17]</sup> controversy still remains due to the shorter follow-up duration which might affect the incidence rates of CVD in patients. Thus, we performed a meta-analysis based on randomized controlled trials (RCT) to compare the incidence of CVD between participants who received THI and those who received usual care.

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## 2 Methods

### 2.1 Data sources, search strategy, and selection criteria

This review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement, issued in 2009.<sup>[18]</sup> We systematically searched three electronic databases including PubMed, EmBase, and the Cochrane library for potentially relevant studies through December 2016, with the following core search terms: telemedicine, web-based strategies, email, mobile phones, mobile applications, text messaging, monitoring sensors, and CVD without any language restrictions. Further to the search, ongoing trials in the meta Register of Controlled Trials were also searched, which include the studies that are completed but not published. Finally, the reference lists of retrieved publications were reviewed for additional potential trials.

The literature search, study selection were conducted by 2 authors independently, and any inconsistencies between these 2 authors were settled by group discussion until a consensus was reached. We restricted our study to RCTs, which are less likely than observational studies to be subject to confounding variables or bias. A study was eligible for inclusion in our meta-analysis if the following criteria were met: (1) the study was a RCT; (2) participants were adults and children were excluded; (3) participants who received THI (telemedicine, web-based strategies, email, mobile phones, mobile applications, text messaging, monitoring sensors) and usual care; (4) the trial should report the incidence of CVD measure in the THI and usual care groups.

### 2.2 Data collection and quality assessment

A standard protocol was adopted independently by two authors to extract the data from all included trials, and any differentials between these two authors were resolved for an agreement though a group discussion. The collected data include first author's name, publication year, country, sample size, mean age, percentage male, participant status, intervention, and the duration of follow-up, and the incidence of CVD. Simultaneously, the quality of included trials were evaluated using Jadad score<sup>[19]</sup> which ranged from 0 to 5, and based on the following items such as randomization, concealment of the treatment allocation, blinding, completeness of follow-up, and the use of intention-to-treat analysis. In our analysis, we considered a study with a score of 4 or greater to be of high quality.

### 2.3 Statistical analysis

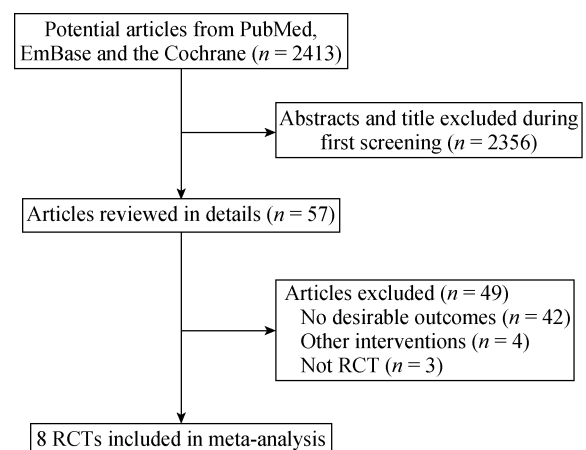
The results of each RCT was assigned as binary data, and events of CVDs, and sample sizes in each group were ex-

tracted from each trial to calculate relative risks (RR) and 95% confidence intervals (CIs). The comparison of summarized RRs between THI and usual care was performed using fixed-effect and random-effects models respectively, and then the results from the random-effects model were presented here.<sup>[20,21]</sup>

The heterogeneity between studies was evaluated by using  $I^2$  statistic and Q statistic, and  $P$  value for Q statistic of less than 0.10 was considered as the existence of statistically significant heterogeneity.<sup>[22,23]</sup> Sensitivity analysis was performed by removing each trial from the overall analysis were performed to evaluate the impact of single study.<sup>[24]</sup>  $P$  value for heterogeneity between subgroups was also calculated by using Chi-square test and meta-regression.<sup>[25]</sup> Subgroup analysis was conducted for CVD incidence based on publication year, sample size, mean age, percentage male, participant status, follow-up duration and study quality. Ratios of RR between subgroups were also calculated.<sup>[26]</sup> Publication bias was evaluated by using funnel plots, Egger, and Begg tests.<sup>[27,28]</sup> All reported  $P$  values were two-sided and  $P < 0.05$  was regarded as statistically significant for all included studies. Statistical analyses were performed using Stata version 10.0 (StataCorp LP, College Station, TX, USA).

## 3 Results

The primary electronic search produced 2,413 articles. Of these, 2356 searched results were excluded after the initial review. Fifty-seven potentially eligible studies were retrieved and reviewed, while 49 RCTs were excluded due to non-reporting of CVD incidence ( $n = 42$ ), participants receiving other interventions ( $n = 4$ ), and other study designs ( $n = 3$ ). Finally, eight trials were selected for the meta-analysis.<sup>[10-17]</sup> The details of study selection process are shown in Figure 1. A manual search of the reference



**Figure 1. Study selection process.** RCT: randomized controlled trial.

**Table 1. Baseline characteristic of studies included.**

Study	Publication years	Country	Sample size	Mean age, yrs	Percentage male, %	Participants status	THI	Control	Definition of CVD	Follow-up duration, yrs	Jadad score
Scherr <sup>[10]</sup>	2009	Austria	120	66.0	73.1	Acute worsening of heart failure	Telephone, SMS text, data monitoring	Pharmacological treatment	Worsening CHF or cardiac death	0.5	3
Appel <sup>[11]</sup>	2011	USA	415	54.0	36.4	Obese patients with one or more cardiovascular risk factors (hypertension, hypercholesterolemia, or diabetes).	Telephone, a study-specific Web site, and e-mail with or without group and individual sessions	Self-directed	CVD	2.0	4
Dendale <sup>[12]</sup>	2012	Belgium	160	75.8	67.5	CHF	Telephone, Data Monitoring	Usual care	Hospitalizations for heart failure and death	0.5	2
Vernooij <sup>[13]</sup>	2012	Netherlands	330	59.9	74.5	Atherosclerosis in the coronary, cerebral, or peripheral arteries and with at least two treatable risk factors not at goal.	Web-based	Contact their treating physician at the hospital or the general practitioner for risk factor management	CVD, death and hospitalizations for vascular disease	1.0	4
Frederix <sup>[14]</sup>	2015	Belgium	80	60.5	83.0	CAD	Email, SMS text, Data Monitoring	Cardiac rehabilitation	Hospitalizations for CVD	0.4	3
Reid <sup>[15]</sup>	2011	Canada	223	56.4	84.3	ACS	Web-based	Physical activity guidance from their attending cardiologist and an education booklet	CVD	1.0	4
Blasco <sup>[16]</sup>	2012	Spain	203	60.8	80.3	ACS	SMS text, Smart Phon	Usual care	CVD, rehospitalizations or death	1.0	2
Southard <sup>[17]</sup>	2003	USA	104	62.3	75.0	CVD	Web-based	Usual care	CVD	0.5	3

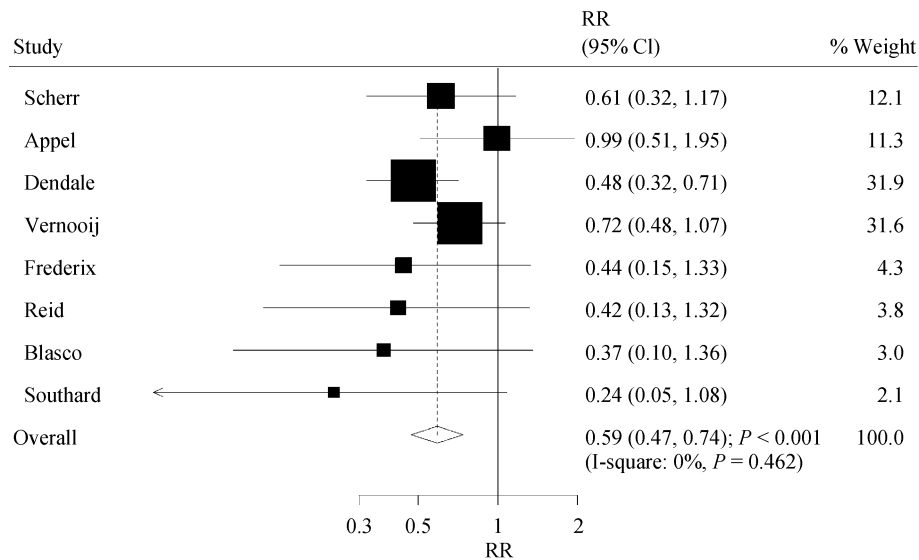
ACS: Acute coronary syndromes; CAD: Coronary artery disease; CHF: Chronic heart failure; CVD: Cardiovascular disease; SMS: short messaging service; THI: Telehealth interventions.

lists of these studies did not yield any new eligible studies. The general characteristics of the included studies are presented in Table 1.

Among the included studies, two were conducted in USA,<sup>[11,17]</sup> two in Belgium,<sup>[12,14]</sup> one in Austria,<sup>[10]</sup> one in the Netherlands,<sup>[13]</sup> one in Canada,<sup>[15]</sup> and one in Spain.<sup>[16]</sup> In addition, these trials involved 1,635 individuals with 80 to 415 in each trial. The mean age ranged from 54.0 to 75.8 years, the percentage of male ranged from 36.4% to 84.3%, and the duration of follow-up ranged from 0.4 to 2.0 years. Seven trials included patients with prior CVD, while the remaining one trial included obese patients with one or more cardiovascular risk factors (such as hypertension, hypercholesterolemia, or diabetes). Study quality was assessed and was listed in Table 1. Three trials had a score of 4,<sup>[11,13,15]</sup> 3 trials had a score of 3,<sup>[10,14,17]</sup> and the remaining 2

trials had a score of 2.<sup>[12,16]</sup>

After pooling of included RCTs, we noted that the participants who received THI showed a significant reduction in the incidence of CVD when compared with usual care (RR: 0.59; 95% CI: 0.47–0.74;  $P < 0.001$ ; Figure 2), and no evidence of heterogeneity was detected. Sensitivity analysis was conducted, and the conclusion was not affected by exclusion of any specific study (Table 2). Meta-regression was conducted based on sample size, mean age, percentage male and follow-up duration. The results of univariate analysis are shown in Figure 3. We noted that sample size and follow-up duration might significantly contribute to the effect of THI and incidence of CVD ( $P < 0.10$ ). Conversely, mean age and percentage male did not contribute to the effect of THI. Subgroup analyses were conducted to evaluate the effect of THI in specific subsets and the results are listed in Table 3.



**Figure 2.** Effect of THI on the incidence of cardiovascular disease. CI: confidence interval; RR: relative risk; THI: telehealth interventions.

**Table 2.** Sensitivity analysis.

Excluding study	RR and 95% CI	<i>P</i> value	Heterogeneity, %	<i>P</i> value for heterogeneity
Scherr	0.58 (0.45–0.76)	< 0.001	10.2	0.351
Appel	0.55 (0.44–0.70)	< 0.001	0.0	0.660
Dendale	0.65 (0.50–0.85)	0.002	0.0	0.523
Vernooij	0.54 (0.41–0.71)	< 0.001	0.0	0.504
Frederix	0.60 (0.47–0.76)	< 0.001	6.3	0.380
Reid	0.60 (0.47–0.76)	< 0.001	5.5	0.385
Blasco	0.60 (0.47–0.76)	< 0.001	3.0	0.403
Southard	0.60 (0.48–0.76)	< 0.001	0.0	0.500

CI: confidence interval; RR: relative risk.

Overall, we noted that THI showed no effect on the incidence of CVD if the trials were published before 2010, mean age of participants of less than 60 years, healthy individuals, and the trials with higher quality. In other subsets, THI played a significant beneficial effect on the risk of CVD. Finally, subgroup analysis was conducted by excluding the Appel, *et al.*<sup>[11]</sup> study as it included patients without prior history of CVD. After this, we noted that THI significantly reduced the risk of CVD in patients with history of CVD in nearly all subsets except the study that is published before 2010.

Funnel plots are used to qualitatively describe potential publication bias and the results are shown in Figure 4. Further, the quantitative results of Egger and Begg tests were also calculated and indicated no evidence of publication bias (*P* value for Egger: 0.292; *P* value for Begg: 0.266).

## 4 Discussion

The goal of prevention of CVD need effective prevention

strategies and risk reduction programs. Although significant improvement in cardiovascular risk factors by individuals who received THI was observed, the effect on the incidence of CVD still remains unclear. Hence, this meta-analysis study was conducted based on RCTs and explored any possible effect of THI on the risk factors of CVD. This comprehensive quantitative analysis included 1635 individuals from 8 trials and suggested THI significantly reduced the risks associated with CVDs. However, the effects of THI on mean age less than 60 years, and in healthy individuals still needs to be verified on large scale trials in future. Furthermore, we observed that the preventive effect was prominent in people with history of CVD than in people without history of CVD.

A previous meta-analysis study suggested that there were no clear evidences of reduced overall cardiovascular risks, systolic blood pressure, total cholesterol, high-density lipoprotein, and smoking rates in individuals who received THI.<sup>[29]</sup> The study illustrated that study quality, intervention

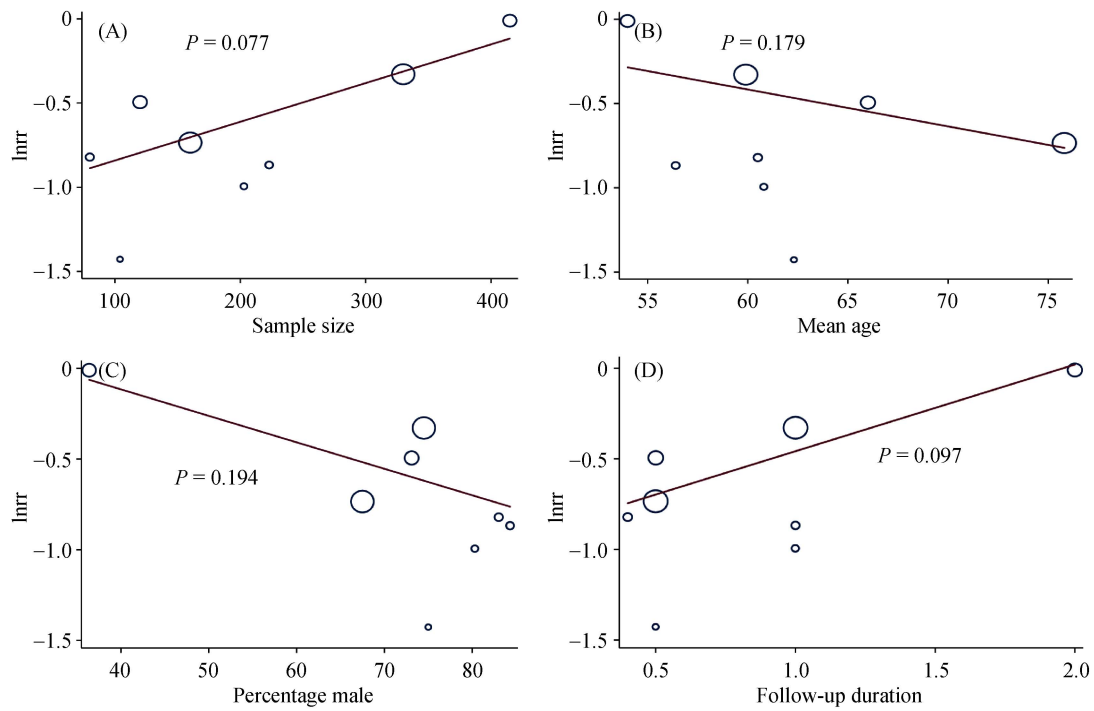
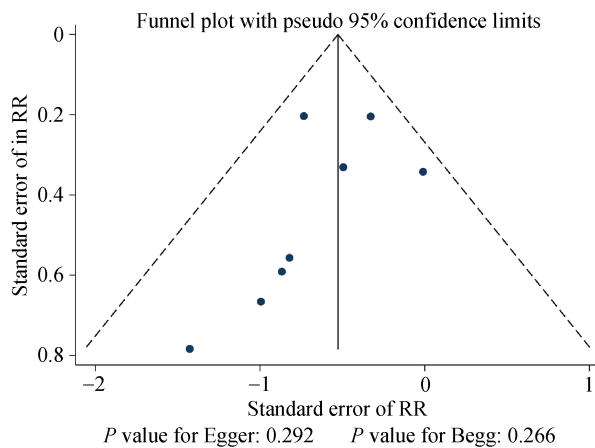


Figure 3. Meta-regression based on sample size, mean age, percentage male, and follow-up duration.

Table 3. Subgroup analysis.

Factors	Group	Subsets	RR and 95% CI	P value	I <sup>2</sup> , %	P value for heterogeneity	Ratio of RR between subgroups	P value between Subgroups
Publication years	Overall	2010 or after	0.60 (0.46–0.78)	< 0.001	6.4	0.375	1.20 (0.55–2.64)	0.650
		Before 2010	0.50 (0.24–1.06)	0.069	16.8	0.273		
	Excluding Appel's study	2010 or after	0.56 (0.43–0.72)	< 0.001	0.0	0.575	1.12 (0.51–2.46)	0.778
		Before 2010	0.50 (0.24–1.06)	0.069	16.8	0.273		
Sample size	Overall	≥ 200	0.71 (0.52–0.98)	0.039	0.0	0.441	1.45 (0.93–2.26)	0.101
		< 200	0.49 (0.36–0.67)	< 0.001	0.0	0.725		
	Excluding Appel's study	≥ 200	0.65 (0.45–0.93)	0.020	0.0	0.470	1.33 (0.82–2.14)	0.246
		< 200	0.49 (0.36–0.67)	< 0.001	0.0	0.725		
Mean age, yrs	Overall	≥ 60	0.48 (0.35–0.66)	< 0.001	0.0	0.830	0.65 (0.41–1.02)	0.063
		< 60	0.74 (0.54–1.04)	0.079	0.0	0.437		
	Excluding Appel's study	≥ 60	0.48 (0.35–0.66)	< 0.001	0.0	0.830	0.71 (0.43–1.15)	0.163
		< 60	0.68 (0.47–0.99)	0.046	0.0	0.389		
Percentage male, %	Overall	≥ 80	0.41 (0.21–0.81)	0.011	0.0	0.980	0.66 (0.32–1.38)	0.273
		< 80	0.62 (0.46–0.84)	0.002	26.7	0.244		
	Excluding Appel's study	≥ 80	0.41 (0.21–0.81)	0.011	0.0	0.980	0.72 (0.35–1.49)	0.375
		< 80	0.57 (0.44–0.76)	< 0.001	8.3	0.352		
Participants' status	Overall	Healthy	0.99 (0.51–1.94)	0.977	–	–	1.80 (0.89–3.65)	0.103
		CVD	0.55 (0.44–0.70)	< 0.001	0.0	0.660		
Follow-up duration, yrs	Overall	1 or 2	0.71 (0.52–0.98)	0.039	0.0	0.441	1.45 (0.93–2.26)	0.101
		< 1	0.49 (0.36–0.67)	< 0.001	0.0	0.725		
	Excluding Appel's study	1 or 2	0.65 (0.45–0.93)	0.020	0.0	0.470	1.33 (0.82–2.14)	0.246
		< 1	0.49 (0.36–0.67)	< 0.001	0.0	0.725		
Study quality	Overall	4	0.74 (0.54–1.04)	0.079	0.0	0.437	0.65 (0.41–1.02)	0.063
		< 4	0.48 (0.35–0.66)	< 0.001	0.0	0.830		
	Excluding Appel's study	4	0.68 (0.47–0.99)	0.046	0.0	0.389	1.42 (0.87–2.31)	0.163
		< 4	0.48 (0.35–0.66)	< 0.001	0.0	0.830		

\*CI: confidence interval; CVD: cardiovascular disease; RR: relative risk.



**Figure 4. Funnel plot for cardiovascular disease.** RR: relative risk

methods, and duration of follow-up might bias the treatment effects, which in turn affected their ability to detect a true difference. However, Widmer *et al.* demonstrated that THI can reduce the incidence of CVD, reduction in weight, body mass index, and Framingham 10 year risk percentage, but has no effect on blood pressure.<sup>[30]</sup> The inherent limitations of the previous meta-analysis studies include: (1) the incidence of CVD was not summarized or any potential confounders were not stratified; (2) different intervention methods might bias the effect on CVDs due to intervention effects, which might be associated with the degree of participants achieved; and (3) the duration of follow-up was shorter than expected which caused the incidence of CVD in each group lower than were needed to show a clinical benefit. We therefore conducted a meta-analysis of RCTs to evaluate any possible intervention effect of THI on the incidence of CVD.

The finding of this study was consistent with a recently published trial conducted in Belgium,<sup>[12]</sup> the study involved 160 patients with severe heart failure and found that individuals received telephone, and data monitoring interventions which reduced the mortality and number of days lost to hospitalization, death, or dialysis. However, other studies reported inconsistent results. Scherr, *et al.*<sup>[10]</sup> indicated that intervention using mobile phones has the potential to reduce frequency and duration of heart failure hospitalizations, but the results were not statistically significant. Appel, *et al.*<sup>[11]</sup> suggested no significant differences between telephone, a study-specific website, or e-mail and usual care for the incidence of CVD. Vernooij, *et al.*<sup>[13]</sup> demonstrated that patients with vascular disease received an internet based programme which showed a small effect on the vascular risk. Frederix, *et al.*<sup>[14]</sup> illustrated that patients with coronary artery disease received telemonitoring intervention and showed

a significant increase in the level of oxygen uptake capacity, whereas little effect on CVD. Reid, *et al.*<sup>[15]</sup> suggested that patients with coronary heart disease using an internet-based activity prescription with online coaching were more physically active, whereas the effect on CVD was not associated with significant improvement. Blasco, *et al.*<sup>[16]</sup> study demonstrated that patients with acute coronary syndrome received mobile phone message intervention, which significantly reduced the cardiovascular risk factors, especially in overweight patients. Southard, *et al.*<sup>[17]</sup> study demonstrated that patients with CVD received Internet-based intervention were associated with more weight loss, but no significant effect on other risk profiles. We noted that all these trials reported THI was associated with non-significant reduction of CVD in patients with prior CVD, and the reason could be due to the smaller sample size, shorter follow-up duration, and most of the trials were designed to evaluate the effect of THI on cardiovascular risk factors as primary end point. Therefore, clinically significant differences between THI and usual care in CVDs cannot be detected in individual trial, and hence the summary results should be evaluated. The current study suggested that THI significantly reduced the recurrence of CVD, while it has no significant effect in preventing the onset of CVD. The possible reason for this could be that participants who received THI were associated with lower total cholesterol, systolic blood pressure, smoking rates, and body mass index, and higher high density lipoprotein levels. These factors played an important role in the progression of CVD, especially for patients with history of CVD.<sup>[31]</sup>

The findings of subgroup analysis suggested that THI has significantly related to the reduction of CVD risk in multiple subsets. For example, THI might play a significant effect on CVD in older individuals and in men. The possible reason could be that older patients with higher incidence of CVD and risk profile were more severe than younger patients. Further, greater risk factors in men might affect the incidence of CVD, and THI was associated with lower levels of these risk factors, which included smoking status, and alcohol consumption.<sup>[32–34]</sup> Finally, THI might play a significant role in people with history of CVD as it could modulate the levels of cardiovascular risk factors and the incidence of CVD was higher in patients with history of CVD than in patients without history of CVD.

The study has few limitations which should be highlighted: (1) the duration of follow-up periods were shorter than expected, the follow-up duration for several trials was less than 1.0 year, which might affect the strength of summary results; (2) several important cardiovascular risk factors at baseline were not available, and these factors might

contribute in the progression of CVD; (3) publication bias was inevitably a problem in any meta-analysis; and (4) individual data was not available, which restricted in conducting a more detailed analysis of the study.

The findings of this study indicated that THI could reduce the incidence of CVD. The intervention effects at different subsets, such as participant status, mean age, and men or women needed to be further explored with large scale RCTs in future.

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