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Research Paper

Health literacy and exercise-focused interventions on clinical measurements in Chinese diabetes patients: A cluster randomized controlled trial

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ABSTRACT

Background: The diabetes patients in China have low health literacy and low levels of physical activities which may result in the poor glycemic control and other clinical outcomes. This study is designed to evaluate the effectiveness of health literacy and exercise-focused interventions on clinical outcomes among Chinese patients with type 2 diabetes (T2DM).

Methods: In this cluster randomized controlled trial, 799 T2DM patients with the most recent A1c $\geq$ 7·5% (58 mmol/mol, or fasting glucose level $\geq$10 mmol/L) were recruited from 35 clinics in 8 communities in Shanghai, China, and randomized into one standard care (control) arm and three intervention arms receiving interventions focused on health literacy, exercise or both. A1c (primary outcome), blood pressure and lipids (secondary outcomes) were measured at baseline, 3-, 6-, 12-months of intervention period and 12-months after completion of the interventions. This trial is registered with the International Standard RCT Number Register, number ISRCTN76130594.

Findings: The three intervention groups had more reductions in A1c than the control group, with 0·90% reduction in the health literacy, 0·83% in the exercise and 0·54% in the comprehensive group at 12-months (p<0·001) and these improvements remained even after a 1-year follow-up period post intervention. The risk of suboptimal A1c ($\geq$7·0% or 53 mmol/mol) was also significantly lower in three intervention groups than control group at each follow-up visit, with adjusted risk ratios (RR) ranging from 0.06 to 0.16. However, the control group has greater reductions in low-density lipoprotein (LDL) than the health literacy group from baseline to 12-months (β=0·55, p<0·0001) and from baseline to 24-months (β=0·62, p<0·0001). A higher risk of abnormal LDL was also observed for the health literacy group at 12-months [adjusted risk ratio (RR): 2·22, 95%CI: 1·11-4·44] and 24-months [adjusted risk ratio (RR): 2·37, 95%CI: 1·16-4·87] compared to the control group. No significant benefits in systolic blood pressure (SBP), diastolic blood pressure (DBP) and low-density lipoprotein (HDL) were observed from the interventions compared to the usual care.

Interpretation: The health literacy and exercise interventions result in significant improvements in A1c. However, no significant benefits in blood pressure and lipids control were observed. These effective interventions may have potential of scaling up in China and other countries to help diabetes patients manage their blood glucose levels.

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1. Introduction

Type 2 diabetes (T2DM) is a chronic condition that requires patients to follow specific evidence-based self-care recommendations. Low health literacy, defined as the extent to which individuals

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Research in context

Evidence before this study

We searched in PubMed for randomized controlled trials and reviews of trials published up to April 9, 2019 to identify effect evaluations of health literacy and exercise interventions in diabetes patients using the terms “diabetes”, “intervention”, “health literacy”, “exercise”, and “clinical outcomes” without language restriction. We found two reviews that included a total of 10 studies with inconsistent results. Five of 10 studies observed decreases in A1c level, two of 7 studies reported significant improvements in SBP and DBP, while one of 3 studies showed improved lipids in patients. All these studies were conducted in the United States. With regard to exercise intervention, aerobic, resistance, combined aerobic and resistance exercise were usually used in diabetes patients. Walking has been suggested the best self-directed aerobic activity to improve A1c, and higher intensity exercise was more effective in improving other metabolic measurements.

Added value of this study

To our knowledge, this is the first trial assessing the impact of a health literacy intervention on diabetes patients in China. The rapid and sustainable beneficial effects of health literacy and exercise-focused interventions on A1c were observed in Chinese diabetes patients. More importantly, the interventions were successfully integrated into routine healthcare services of clinics, making it possible to scale up the interventions.

Implications of all the available evidence

Health literacy and exercise-focused interventions should be implemented in diabetes patients to improve their glycemic control status and clinical outcomes. Further research is required to evaluate the cost-effectiveness of the interventions and determine whether the health services can be implemented on a larger scale in China and other countries.

attain, manage, and understand health information and apply that information in health decision-making [1], is common in Chinese diabetes patients [2]. In the United States (US), low health literacy or numeracy (the ability to understand and use numbers in daily life [3] has been associated with limited adherence to recommendations, poorer glycemic control status and worse clinical outcomes, even after adjusting for potential confounders such as educational level and types of insurance [4].

In China, the provision of diabetes education has been suggested to help achieve better glycemic control [5,6], but only one-fifth of patients have A1c less than 6·5% (48 mmol/mol) [7]. Poor glycemic control may, in part, be due to inadequate approaches to address health literacy. Previous studies have demonstrated that providing low literacy materials or low literacy forms of communication can improve comprehension for patients with both low and high health literacy levels [8,9]. A randomized controlled trial (RCT) demonstrated that health literacy was a significant factor in predicting patients' improvement in A1c from the intervention, and suggested that addressing health literacy could improve patient outcomes [10]. Two RCTs performed in the US found that the health literacy- and numeracy-sensitive diabetes care led to significant improvements in glycemic control, self-efficacy, and other outcomes [11]. In China, however, diabetes management has not specifically addressed health literacy or numeracy issues.

In addition to addressing health literacy, addressing exercise can be another important component to diabetes self-care [12]. Exercise interventions, either aerobic or resistant, may help to bridge the knowledge-attitude-practice (KAP) gap, and thus reduce A1c and decrease the risk of diabetes complications [13,14]. It has been suggested that walking was the best self-directed aerobic activity to improve A1c, and higher intensity exercise was more effective in improving other metabolic measurements [15].

In China, the huge number of diabetes patients, poor glycemic control status and epidemic of diabetes complications suggest that innovative approaches to address barriers in diabetes management are needed. In this study, we specifically designed a health literacy focused intervention, an exercise intervention (i.e. supervised walking) and a comprehensive intervention strategy for Chinese diabetes patients to evaluate their effects through a cluster RCT. We hypothesize that the three interventions will improve glucose, blood pressure and serum lipids in diabetes patients.

2. Methods

2.1. Study design

In this four-arm cluster RCT, we randomized 8 Community Healthcare Centers (CHCs) that included 35 clinic sites in the Minhang and Changning districts of Shanghai, China. The 8 CHCs were selected by convenience from a total of 26 CHCs in this region, with 4 from the Minhang District and 4 from the Changning District. From each CHC, 3–5 clinic sites were selected. All clinic sites met the following criteria: (1) at least 20 patients can be recruited; (2) at least 2–4 physician(s), nurse practitioner(s), or diabetes educator(s) can participate in the interventions as a team; (3) site agrees to participate for a minimum of 2 years; and (4) site agrees to be randomized to any arm of the study [16].

Ethics approval was obtained from the Medical Ethics Committee of Fudan University (IRB00002408 & FWA00002399) before recruiting study participants (registration number: 2013-06-0451). All local medical ethics committees agreed with this approval. This trial was registered with the International Standard RCT Number Register (number: ISRCTN76130594).

This trial was presented in adherence strictly to the Consort guidelines.

2.2. Subjects

During the period of Feb 2015 and March 2016, a total of 800 patients with T2DM were recruited from the 35 selected clinic sites through the Diabetes Management systems [17,18] (Fig. 1). Inclusion criteria at the patient level included: 1) Patient had a clinical diagnosis of T2DM according to the 1999 criteria of the World Health Organization; 2) Age 18–85 years; 3) Most recent A1c $\geq$ 7·5% (58 mmol/mol, or fasting glucose level $\geq$10 mmol/L); and 4) Patient agreed to participate in the study for the full two years duration. Exclusion criteria at the patient level included: 1) Poor visual acuity (vision worse than 0·1/4·0 using the Standard Logarithmic Visual Acuity Chart); 2) Significant dementia, or psychosis (by health provider report or chart review); 3) Terminal illness with anticipated life expectancy $<$2 years; 4) No permission from their physicians. Informed consent was collected from each participant.

2.3. Randomization and masking

To limit potential contamination among health care providers and patients, randomization occurred at the level of the CHCs stratified by district. Each CHC was randomized to one of four study arms: 1) health literacy intervention arm; 2) exercise intervention arm; 3) comprehensive intervention (health literacy and exercise together) arm; and 4) standard of care (control) arm.

To achieve the optimal balance by Center site, Center size and population covered, the investigators of the trial employed a group

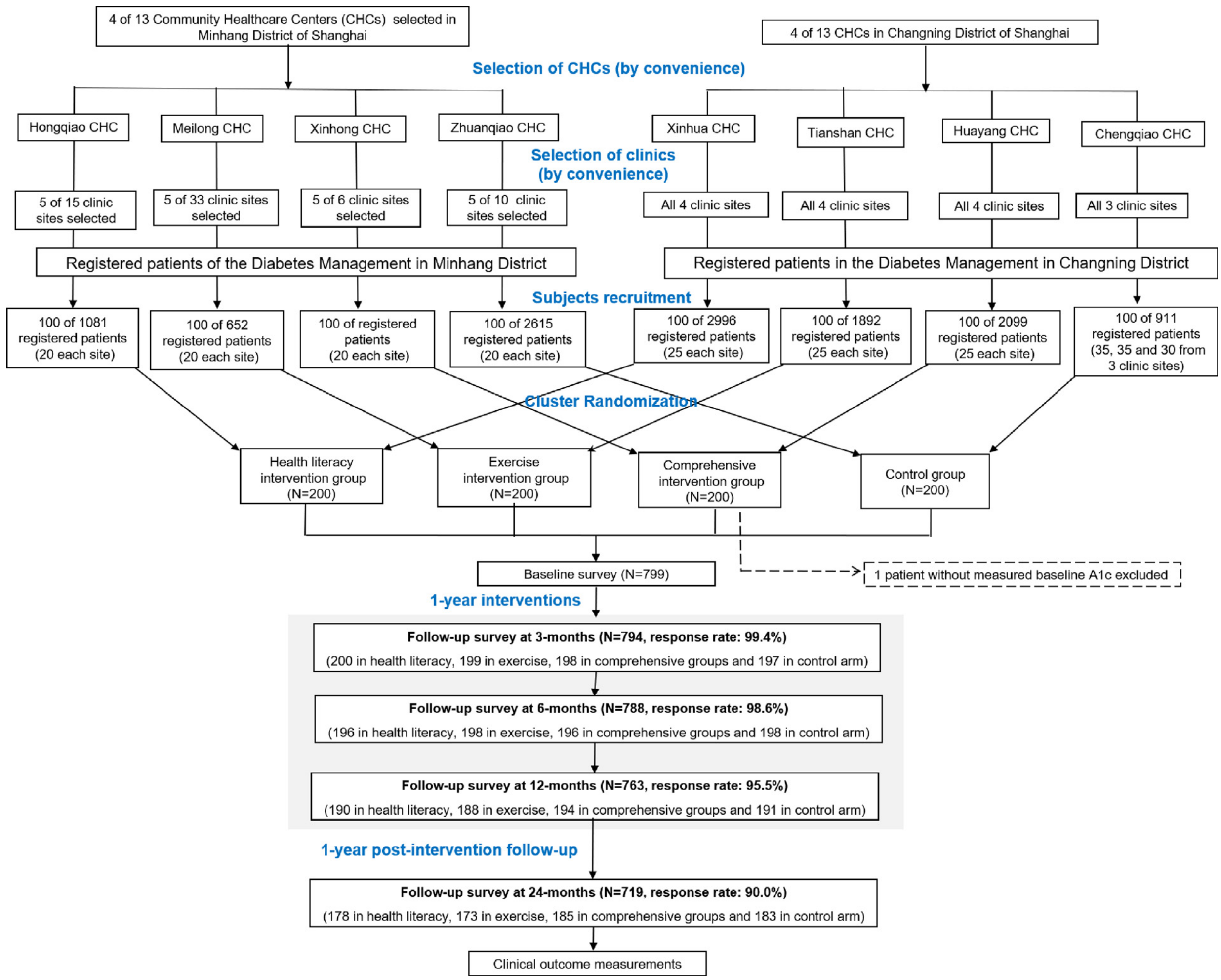

Fig. 1. Patient flow diagram.

matching method. The balance by A1c level and characteristics of recruited patients (including age, sex and insurance status) was reached by recruiting subjects according to the distribution of the variables among eligible patients in the Diabetes Management systems.

Both intervention providers and participants knew which group they were allocated to, but neither knew the hypothesis of the study.

2.4. Interventions

The intervention period lasted for one year. The health literacy intervention included two main components: (1) the Chinese version of Partnership to Improve Diabetes Education (PRIDE)Toolkit, a set of plain-language tools to aid provider-patient communication on diabetes management [19], and (2) a modified Chinese version of Clear Health Communication Curriculum, a structured training program for healthcare providers to improve diabetes-related counseling communication skills, with specific attention to issues of literacy and numeracy.

The PRIDE toolkit consists of 24 educational modules that have been designed specifically to improve understanding and self-management behaviors in patients with lower literacy or numeracy skills. The toolkit includes all components of diabetes self-management including diet, exercise, foot care, glucose monitoring, medication management, and enhanced diabetes log sheets that can be shared with patients to improve their self-management ability. The Toolkit also acts as a disease management intervention at the provider and system level by: 1) acting as a "reminder" system to providers about certain treatment goals, 2) providing a structured approach to addressing self-management goals, and 3) addressing important socioeconomic and community level barriers that can impede diabetes care. Healthcare providers in the intervention Centers were trained for the proper use of the Toolkit materials and used the materials during regular patient-related visits. At each clinic visit, typically occurring 1 or 2 times each month for each patient, physicians spent approximately 5–7 min to share at least two components from the toolkit materials with the patient, and performed and documented at least one goal-setting task with the patient. Nurses or health educators phoned the subjects to supervise after the visit. The healthcare teams in the healthy literacy and the comprehensive groups were required to record the frequency and time of their communications with patients using the toolkit. Paper printouts of toolkit materials were made available in the intervention Centers for easy access.

Healthcare providers in the health literacy intervention arm, either physicians, nurses, or health educators, were also trained to facilitate their use of the Toolkit and heath communication skills. Before the initiation of the intervention, they gathered to obtain 5–6 h of training in the following areas: (1) Diabetes management, (2) Introduction to the PRIDE toolkit, (3) Clear health communication skills including the use of simplified communication with decreased jargon, "teach back", and shared goal setting approaches, and (4) Application of the toolkit using principles of clear health communication.

The patients in the exercise group were required to walk 3 to 5 days a week. In the first 6 months, patients were instructed to walk 30–40 min per day. Then in the following 6 months this increased up to 60−70 min per day. Each daily session could be split in smaller bouts of at least 10 min duration. The intensity of exercise was ideally kept between 12 and 15 in the Borg RPE visual scale. The patients involved were asked to record the time and intensity of each walk in a calendar book which would be checked by their healthcare team members.

Patients in the comprehensive intervention group were given both the literacy and exercise interventions. In the control arm, usual diabetes care was provided in all participating clinics according to the current national guidelines and at the individual clinician's discretion.

2.5. Data collection

Information collected at baseline included age at study entry, sex, date of birth, household composition (number of children, marital status, etc.), health insurance status, employment, income level, years of education, smoking status, dietary habits (measured by 3-day 24 h dietary recall), physical activities (evaluated using the Global Physical Activity Questionnaire) (https://www.who.int/ncds/surveillance/steps/GPAQ_CH.pdf), literacy level (as measured by the validated Chinese versions of Health Literacy Management Scale, HeLMS) [20], diabetes related numeracy (as measured by the Chinese version of the DNT5) [21], years of diabetes diagnosis, current diabetes medications, history of diabetes education and glucose monitoring frequency.

All participants were followed-up at 3-, 6-, 12-months (post enrollment) and 24-months (1-year post-intervention). At baseline and each follow-up survey, blood pressure was measured for each participant according to a standard protocol. Systolic (SBP) and diastolic blood pressure (DBP) were measured twice on the right arm using a standard mercury sphygmomanometer after participants had rested for at least 5 min. If the difference between two measurements exceeded the tolerance of <5 mmHg, the third measurement was taken. A1c was assayed using Point-of-Care high-performance liquid chromatography available in each CHC. Serum lipids were measured using Automatic Analyzer for Lipids only at baseline, 12- and 24-months considering less fluctuation in blood lipids than in blood glucose.

2.6. Statistical analysis

An intent-to-treat analysis was taken in this study. The primary outcome of the study was improvement in A1c, and the secondary outcomes were improvements in blood pressure and serum lipids. Comparisons by intervention status were conducted using χ^2 tests (for categorical variables) and Analysis of Variance (ANOVA) or Kruskal-Wallis H tests (for continuous variables). Generalized Estimated Equation (GEE) was used to address the issue of correlated observations and evaluate the effect of interventions at the 3-, 6-, 12-, and 24-months follow-up surveys relative to baseline and to the control arm by dummy coding baseline and the control group as the reference, patient ID as repeated subject and autoregressive as the working correlation matrix type. Potential confounders adjusted in the models included age, sex, income, educational level, smoking, physical activity, duration of diabetes, anti-diabetic agents and insulin use, c-HeLMS score, correct rate of c-DNT-5 and baseline A1C/ SBP/ DBP/ LDL/ HDL. In addition, the function in GEE model was specified with an intercept and four (baseline to 3-months, 3- to 6-months, 6- to 12-months, and 12- to 24-months) or two slopes (baseline to 12-months, and 12- to 24-months). This allowed examination of change in the outcomes during the intervention period and maintenance of that change in the outcomes after cessation of the interventions. All statistical analyses were conducted using SAS version 9·4 (SAS Institute, Cary, NC, USA).

2.7. Analytical power

According to our previous protocol [16], we anticipated a 0.8% improvement in A1c level with a conservative estimate of the SD at 2.0 and the intraclass correlation at 0.002. We performed a simulation study generating follow-up A1c using the following formula: Follow-up A1c = Baseline A1c + β^* Group + Center Effect + Provider Effect + δ. Using PASS software and with four clusters for 8 Centers, 800 participants in four groups yielded analytical power of 99·9% with 2-sided 5% significance level by assuming 0·8% reduction in A1c. If the improvement in A1c was 0.40%, the statistical power would be 80%.

2.8. Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had access to all the data in the study and had final responsibility for the decision to submit for publication.

3. Results

3.1. Participant characteristics

After excluding one patient without measured baseline A1c, a total of 799 eligible patients with T2DM were included. Table 1 presents the baseline information of the participants. The four groups differed significantly in education, income, occupation, physical activities, glucose lowering drugs and insulin use, health literacy level, levels of low density lipoprotein(LDL), high density lipoprotein (HDL), SBP and DBP (p<0·05). The exercise group had higher levels of education, income, health literacy, HDL and SBP, while the control group had higher intensity of physical activities, numeracy skill and LDL level. No significant difference was observed in age, sex, duration of diabetes, body mass index (BMI) and A1c among the four groups.

3.2. Intervention participation rates

Complete data were available for 763 patients at 12-months, and for 719 patients at 24-months. The response rates were 99·4%, 98·6%, 95·5% and 90·0%, respectively, at 3-, 6-, 12- and 24-months (Fig. 1).

3.3. Change in A1c

As shown in Fig. 2a, the exercise group had a significantly lower A1c at each follow-up visit than at baseline (p<0·05). A significantly lower level of A1c was also observed in the health literacy group at 6-, 12- and 24-months and in the comprehensive group at 6-months (p<0·05). In contrast, no significant change in A1c was observed in the control group (p = 0·58).

After adjusting possible confounders, A1c declined by 0·62% between baseline and 12-months and 0·68% between baseline and 24-months (p < 0·0001) in the health literacy arm. The decreases were 0·55% (p = 0·0002) and 0·72% (p< 0·0001), respectively, in the exercise group, and 0·26% (p = 0·01) and 0·03% (p = 0·83), respectively, in the comprehensive arm. In the control arm, on the contrary, A1c increased by 0·28% (p = 0·03) between baseline and 12-months, and by 0·06% (p = 0·66) from baseline to 24-months. A similar but more pronounced change pattern was observed among the participants with suboptimal baseline A1c [≥7·0% (53 mmol/mol), n = 734] (Table 2).

Irrespective of baseline A1c level, the reduction in A1c was significantly greater in the health literacy and exercise groups than in the control arm at each follow-up visit (all p < 0·05), but only at 3- ,6- and 12-months in the comprehensive group than in the control group (p < 0·05). The reduction in A1c at 12-months reached 0·90%

Table 1
Comparison of baseline characteristics of the participants by groups.

Baseline information	Control group ($n = 200$)	Health literacy group ($n = 200$)	Exercise group ($n = 200$)	Comprehensive group ($n = 199$)	*p* values
Demographic characteristics					
Age (years)	65 (59, 69)	67 (60,71)	66 (60,72)	66 (59,72)	*0·06*
Sex, men (%)	43·0	44·5	48·0	45·2	*0·79*
Educational level (%)					*<0·001*
Primary school or below	18·5	19·6	16·0	32·7	
Junior high school	40·5	39·2	33·5	39·7	
Senior high school	25·0	29·1	30·5	20·1	
College or above	16·0	12·1	20·0	7·5	
Monthly income *per capita* (USD,%)				*<0·001*	
<308	14·6	16·6	6·1	21·1	
308∼769	59·6	58·3	54·5	59·8	
≥770	25·8	25·1	39·4	19·1	
Occupation (%)					*<0·001*
Professional	40·2	30·5	36·0	21·6	
Clerks	32·2	31·0	39·0	32·2	
Manual workers	24·1	31·0	23·0	39·2	
Others	3·5	7·5	2·0	7·0	
Health literacy					
c-HeLMS score	116 (113,120)	116 (104,120)	119 (110,120)	113 (97,120)	*<0·0001*
Correct rate of DNT-5	100 (80,100)	80 (80,100)	80 (80,100)	80 (60,100)	*0·0004*
Status of diabetes					
Years of being diagnosed	9·5 (5·2,14·6)	10·4 (6·0,16·1)	9·5 (4·8,15·9)	9·6 (5·1,14·6)	*0·31*
Treatment regimen (%)					*0·005*
Diabetes pills only	61·5	71·2	64·2	58·6	
Insulin shot only	12·8	5·8	6·9	8·7	
Both	21·6	17·8	18·7	28·6	
Neither	4·1	5·2	10·2	4·1	
Previous diabetes education (%)	76·9	90·2	86·7	82·8	*0·003*
Lifestyle factors					
Current smoking (%)					
Men	45·4	32·6	22·1	34·8	*0·01*
Women	0	0	2·9	1·0	*0·09*
Regular exercise (%)	54·0	44·5	55·0	43·7	*0·03*
Physical activities (Mets, h/week)	72 (53,108)	56 (30,84)	51 (34,81)	50 (28,90)	*<0.0001*
Clinical measurements					
A1C (%)	8·2 (7·5,9·1)	8·1 (7·5,9·3)	8·0 (7·5,9·1)	8·1 (7·7,9·0)	*0·69*
LDL (mmol/L)	3·38 (2·73,4·11)	2·79 (2·22,3·43)	2·87 (2·32, 3·50)	2·81 (2·32,3·51)	*<0·0001*
HDL (mmol/L)					
Men	1·13 (0·94,1·33)	1·22 (1·09,1·42)	1·31 (1·11,1·54)	1·07 (0·90,1·33)	*<0·0001*
Women	1·38 (1·16,1·62)	1·36 (1·20,1·60)	1·41 (1·19,1·64)	1·24 (1·06,1·49)	*0·005*
SBP (mmHg)	131 (125,137)	131 (127,137)	134 (130,139)	130 (127,136)	*<0·0001*
DBP (mmHg)	80 (75,82)	79 (74,81)	80 (76,83)	80 (74,82)	*0·03*
BMI (kg/m^2)	25·1 (23·2,27·0)	25·3 (23·1,27·2)	24·9 (22·9, 26·9)	24·9 (23·3,27·0)	*0·83*

*Median and IQR presented for continuous variables and n (%) presented for categorical variables.

in the health literacy group comparing to the control arm, and was 0·83% in the exercise and 0·54% in the comprehensive group among all participants (Table 2).

3.4. Change in blood pressure

As presented in Table 2 and Fig. 2b and 2c, there were no significant changes between baseline and 3-, 6-, 12- or 24-months for SBP or DBP in the health literacy group and the comprehensive group. However, a significant decreased SBP was observed in the exercise group at 6-months ($\beta = -2{\cdot}47$, $p = 0{\cdot}0008$), while a reduced DBP was observed in the control arm at 3-months ($\beta = -1{\cdot}58$, $p = 0{\cdot}002$). Among 449 participants with SBP >130 mmHg at baseline, there was a significant reduction in SBP from baseline to 3-, 6-, 12- or 24 months in the four arms. Similarly, a significant reduction in DBP was observed among 286 participants with DBP>80 mmHg. The improvements in SBP and DBP in the three intervention groups, however, were not significantly higher than those in the control arm (Table 2).

3.5. Changes in serum lipids

The average LDL was higher at 12-months than at baseline in the health literacy and the exercise groups ($p < 0{\cdot}05$), while it was lower at 24-months than at baseline in the control group ($p = 0{\cdot}003$) (Fig. 2d). After adjusting for potential confounders, a significant increase in LDL was observed in the health literacy group at 12- ($\beta = 0{\cdot}55$, $p < 0{\cdot}0001$) and 24-months ($\beta = 0{\cdot}28$, $p = 0{\cdot}01$) and a significant decrease was found in the control arm at 24-months ($\beta = -0{\cdot}34$, $p = 0{\cdot}0001$) (Table 2). The reduction in LDL was significantly higher in the control group than in the health literacy group from baseline to 12-months ($\beta = 0{\cdot}55$, $p < 0{\cdot}0001$) and from baseline to 24-months ($\beta = 0{\cdot}62$, $p < 0{\cdot}0001$).

Among 516 patients with abnormal LDL (>2·6 mmol/L), serum LDL increased by 0·37 mmol/L ($p = 0{\cdot}008$) in the health literacy group from baseline to 12-months and then decreased, but decreased significantly in the control, the exercise and the comprehensive groups until at 24-months ($p < 0{\cdot}0001$). The reduction was significantly higher in the control group than in the health literacy group, with β being 0·53 ($p = 0{\cdot}002$) from baseline to 12-months and 0·41 ($p = 0{\cdot}006$) from baseline to 24-months (Table 2).

The average levels of HDL remained unchanged during the follow-up period in the four groups (Fig. 2e). After adjusting for potential confounders, however, HDL was observed to increase, but reached significant only in the health literacy group from baseline to 12-months ($\beta = 0{\cdot}08$, $p = 0{\cdot}01$) and in the comprehensive group from baseline to 24-months ($\beta = 0{\cdot}07$, $p = 0{\cdot}01$). The increase in the control group was significantly higher than that in the exercise group, with the differences being $-0{\cdot}12$ mmol/L ($p = 0{\cdot}01$) from baseline to 12-months and $-0{\cdot}10$ mmol/L ($p = 0{\cdot}02$) from baseline to 24-months.

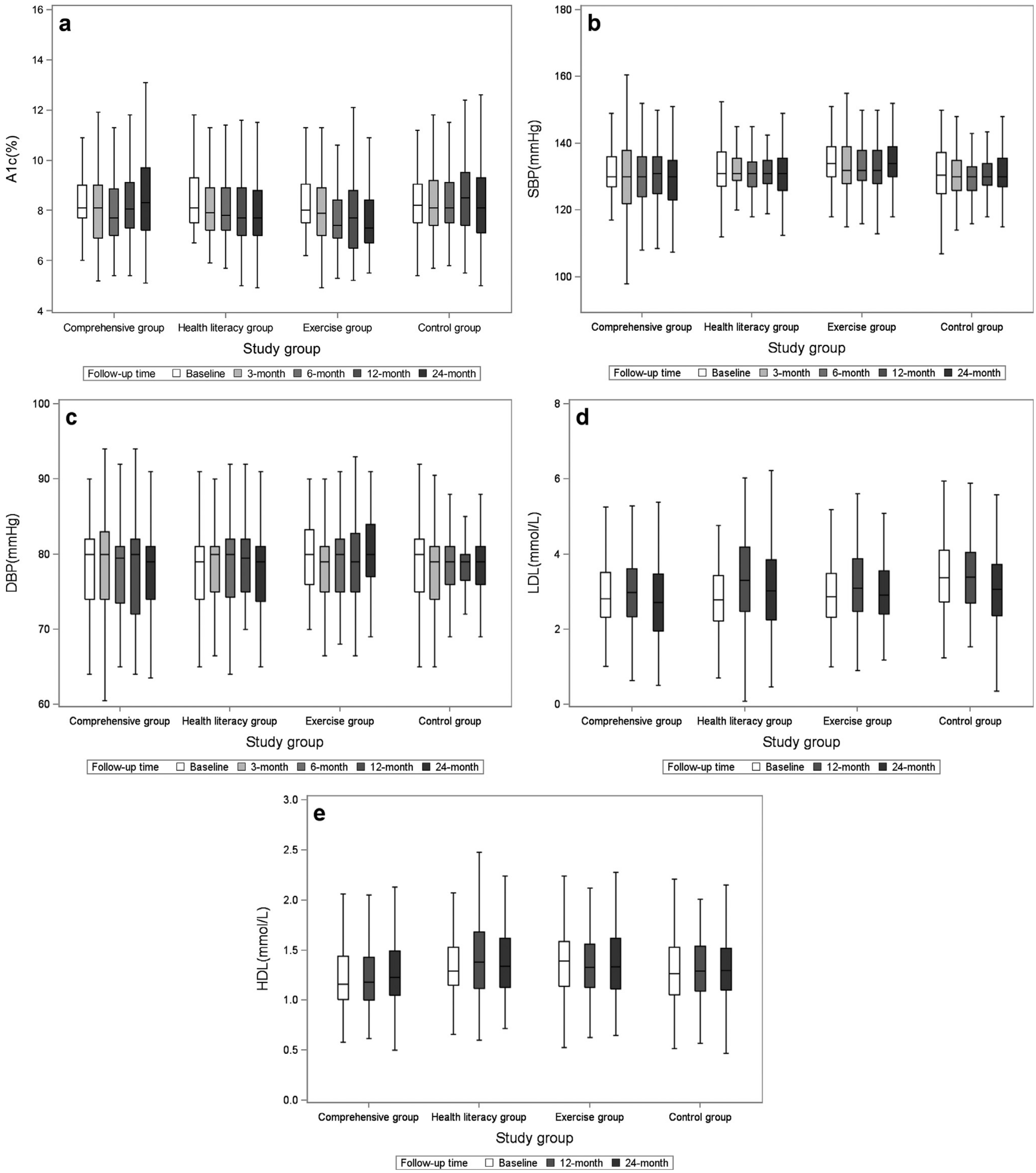

Fig. 2. Average levels of clinical measurements at baseline and follow-up at 3-, 6-, 12- or 24-months (a: A1C; b: SBP; c: DBP; d: LDL; and e: HDL)
The endpoint of upper/ lower whisker is maximum/ minimum;
The upper edge/ center horizontal line/ lower edge of box is 75th/ 50th/ 25th percentile.

Among 277 participants with suboptimal values of HDL (<1.04 mmol/L in men or <1.30 mmol/L in women), increased HDL were observed in all the four groups, but the increases did not significantly differ across the groups (Table 2).

3.6. *Change and maintenance of intervention effects based on GEE model*

Fig. 3a presents the change in A1c from GEE models in participants with A1c≥7·0% (53 mmol/mol). The three intervention groups had significant reductions in A1c at the 3-months survey ($p < 0{\cdot}05$). The downward trend continued in the exercise group ($p = 0{\cdot}005$) and the comprehensive group ($p = 0{\cdot}38$) between 3- and 6-months survey, and in the healthy literacy group to the end of follow-up ($p > 0{\cdot}05$). The control group did not show any obvious change in A1c over the period.

SBP decreased from baseline to 6-months in the four groups, and increased from 6- to 12-months, and decreased again from 12- to 24-months, as shown in Fig. 3b. The changes were significant in the

Table 2
Changes in clinical measurements from baseline to 3-, 6-, 12-, or 24-months of follow-up within the four groups and between the intervention and the control arms.

	All participants				Participants with suboptimal clinical measurements			
	Control group	Health literacy group	Exercise group	Comprehensive group	Control group	Health literacy group	Exercise group	Comprehensive group
A1C					A1C ≥7·0% (53 mmol/mol)			
3-months	0·10 (0·11)	−0·36 (0·09)‡	−0·33 (0·13)*	−0·36 (0·10)‡	−0·02 (0·12)	−0·38 (0·09)‡	−0·40 (0·14)†	−0·38 (0·10)‡
	0 (ref.)	−0·46 (0·13)‡	−0·43 (0·16)†	−0·46 (0·14)‡	0 (ref.)	−0·36 (0·14)†	−0·38 (0·17) *	−0·36 (0·15) *
6-months	0·10 (0·12)	−0·45 (0·12)‡	−0·73 (0·13)‡	−0·45 (0·10)‡	−0·04 (0·14)	−0·51 (0·11)‡	−0·81 (0·14)‡	−0·47 (0·10)‡
	0 (ref.)	−0·55 (0·16)‡	−0·83 (0·17)‡	−0·55 (0·15)‡	0 (ref.)	−0·47 (0·17)†	−0·77 (0·18)‡	−0·43 (0·16)†
12-months	0·28 (0·13)*	−0·62 (0·13)‡	−0·55 (0·15)‡	−0·26 (0·10)*	0·14 (0·15)	−0·67 (0·13)‡	−0·60 (0·16)‡	−0·28 (0·11)†
	0 (ref.)	−0·90 (0·17)‡	−0·83 (0·19)‡	−0·54 (0·15)‡	0 (ref.)	−0·81 (0·18)‡	−0·74 (0·20)‡	−0·42 (0·17)*
24-months	0·06 (0·13)	−0·68 (0·15)‡	−0·72 (0·14)‡	−0·03 (0·15)	−0·08 (0·15)	−0·73 (0·15)‡	−0·82 (0·14)‡	−0·07 (0·15)
	0 (ref.)	−0·74 (0·19)‡	−0·78 (0·18)‡	−0·09 (0·19)	0 (ref.)	−0·65 (0·20)‡	−0·74 (0·19)‡	0·01 (0·20)
SBP					SBP>130 mmHg			
3-months	−0·78 (0·79)	−0·10 (0·84)	−0·98 (0·81)	0·59 (1·16)	−4·52 (1·11)‡	−5·15 (0·95)‡	−3·89 (0·88)‡	−2·36 (1·71)
	0 (ref.)	0·68 (1·18)	−0·20 (1·16)	1·37 (1·43)	0 (ref.)	−0·63 (1·48)	0·63 (1·44)	2·16 (2·06)
6-months	−1·16 (0·87)	−1·52 (0·89)	−2·47 (0·74)‡	−0·65 (0·88)	−7·29 (1·23)‡	−6·28 (1·10)‡	−5·33 (0·87)‡	−5·17 (1·26)‡
	0 (ref.)	−0·36 (1·21)	−1·31 (1·11)	0·51 (1·20)	0 (ref.)	1·01 (1·49)	1·96 (1·33)	2·12 (1·62)
12-months	0·11 (0·90)	−0·48 (0·84)	−1·59 (0·83)	0·14 (0·87)	−6·04 (1·26)‡	−4·33 (0·92)‡	−3·85 (1·03)‡	−4·58 (1·16)‡
	0 (ref.)	−0·59 (1·21)	−1·70 (1·21)	0·03 (1·24)	0 (ref.)	1·71 (1·54)	2·19 (1·62)	1·46 (1·70)
24-months	0·02 (0·91)	−1·74 (0·94)	−0·21 (0·91)	−0·32 (0·84)	−6·56 (1·27)‡	−6·15 (1·13)‡	−3·99 (1·00)‡	−5·32 (1·09)‡
	0 (ref.)	−1·76 (1·32)	−0·23 (1·30)	−0·34 (1·25)	0 (ref.)	0·41 (1·64)	2·57 (1·56)	1·24 (1·61)
DBP					DBP>80 mmHg			
3-months	−1·58 (0·50)†	0·57 (0·47)	−1·05 (0·56)	−0·24 (0·67)	−4·67 (0·80)‡	−3·11 (0·77)‡	−5·08 (0·81)‡	−3·30 (0·94)‡
	0 (ref.)	2·15 (0·69)†	0·53 (0·75)	1·34 (0·84)	0 (ref.)	1·56 (1·14)	−0·41 (1·17)	1·37 (1·26)
6-months	−0·33 (0·56)	0·69 (0·52)	−0·76 (0·58)	−0·39 (0·56)	−5·64 (0·88)‡	−4·09 (0·86)‡	−5·55 (0·75)‡	−4·47 (0·86)‡
	0 (ref.)	1·02 (0·75)	−0·43 (0·79)	−0·06 (0·78)	0 (ref.)	1·55 (1·12)	0·09 (1·04)	1·17 (1·12)
12-months	−0·48 (0·58)	0·74 (0·57)	−1·11 (0·60)	−0·36 (0·57)	−5·64 (0·91)‡	−4·29 (0·99)‡	−5·96 (0·77)‡	−5·22 (0·96)‡
	0 (ref.)	1·22 (0·80)	−0·63 (0·81)	0·12 (0·79)	0 (ref.)	1·35 (1·26)	−0·32 (1·09)	0·42 (1·24)
24-months	−0·30 (0·58)	0·09 (0·52)	0·02 (0·59)	−0·93 (0·53)	−5·59 (0·92)‡	−4·32 (0·78)‡	−4·91 (0·87)‡	−4·53 (0·89)‡
	0 (ref.)	0·39 (0·80)	0·32 (0·85)	−0·63 (0·80)	0 (ref.)	1·27 (1·10)	0·68 (1·17)	1·06 (1·19)
LDL					LDL>2·6 mmol/L			
12-months	−0·002 (0·08)	0·55 (0·10)‡	0·16 (0·08)	0·06 (0·07)	−0·16 (0·08)	0·37 (0·14)†	−0·13 (0·10)	−0·16 (0·08) *
	0 (ref.)	0·55 (0·13)‡	0·16 (0·11)	0·06 (0·11)	0 (ref.)	0·53 (0·17)†	0·03 (0·13)	0·006 (0·12)
24-months	−0·34 (0·09)‡	0·28 (0·11)*	−0·05 (0·09)	−0·14 (0·09)	−0·50 (0·09)‡	−0·09 (0·11)	−0·46 (0·11)‡	−0·43 (0·10)‡
	0 (ref.)	0·62 (0·14)‡	0·29 (0·12) *	0·20 (0·13)	0 (ref.)	0·41 (0·15)†	0·04 (0·15)	0·07 (0·14)
HDL					HDL<1·04 (men) or <1·30 mmol/L (women)			
12-months	0·06 (0·03)	0·08 (0·03)*	−0·06 (0·03)	0·02 (0·02)	0·18 (0·04)‡	0·10 (0·04)†	0·21 (0·06)‡	0·12 (0·03)‡
	0 (ref.)	0·02 (0·05)	−0·12 (0·05) *	−0·04 (0·04)	0 (ref.)	−0·08 (0·07)	0·03 (0·08)	−0·06 (0·06)
24-months	0·05 (0·04)	0·12 (0·07)	−0·05 (0·04)	0·07 (0·03)*	0·14 (0·04)†	0·14 (0·05)†	0·24 (0·06)‡	0·20 (0·03)‡
	0 (ref.)	0·07 (0·07)	−0·10 (0·04) *	0·02 (0·04)	0 (ref.)	−0·002 (0·06)	0·10 (0·07)	0·06 (0·05)

Results from the Generalized Estimated Equation (baseline to 3-months, baseline to 6-months, baseline to 12-months and baseline to 24-months) adjusted for age, sex, income, educational level, smoking, physical activities, duration of diabetes, anti-diabetic agents and insulin use, c-HeLMS score, correct rate of c-DNT-5 and baseline A1C/ SBP/ DBP/ LDL/ HDL, respectively· Data presented as β coefficient (SE) within each group compared to baseline levels (the first lines) and β coefficient (SE) of each intervention group compared to the control arm (the second lines)· *$p<0·05$; †$p<0·01$; ‡$p<0·001$.

health literacy group from baseline to 3-months and from 6- to 24-months, in the exercise group from baseline to 3-months, and in the control group from baseline to 6-months ($p < 0·05$). Regarding DBP, all the four groups had distinct declines from baseline to 3-months ($p < 0·001$), but no significant changes there after (Fig. 3c).

Fig. 3d shows a non-significant reduction in LDL in the exercise and the control groups from baseline to 12-months, which was followed by a significant reduction from 12- to 24-months ($p < 0·01$). Significant decreased LDL were observed in the comprehensive group from baseline to 24-months ($p<0·05$). In the health literacy group, on the other hand, LDL increased during the period of intervention ($p = 0·008$), but also decreased subsequently ($p = 0·0002$). The three intervention groups had improved HDL from baseline to 12-months ($p < 0·01$), and were sustained to 24-months with only comprehensive group increased significantly ($p = 0·006$). An increased HDL was also observed in the control group from baseline to 12-months ($p < 0·0001$), but then slightly decreased from 12- to 24-months ($p = 0·46$) (Fig. 3e).

3.7. *Effect of interventions on suboptimal clinical outcomes*

As shown in Table 3, the risk of suboptimal A1c (≥7·0% or 53 mmol/mol) was significantly lower at each follow-up visit than at baseline in three intervention groups, while the risk remained unchanged during the period in the control group. Compared to the control arm, the risk was significantly lower in three intervention groups, with adjusted risk ratios (RR) ranging from 0.06 to 0·16 at each follow-up visit.

The exercise group was more likely to achieve a goal SBP level (≤130 mmHg) at 12-months (RR: 0·65, 95%CI: 0·43-0·99) relative to baseline, while the control group tended to have a goal DBP level (≤ 80 mmHg) at 3-months (RR: 0·58, 95%CI: 0·37-0·90) and 12-months (RR: 0·50, 95%CI: 0·31-0·82). When comparing with the control group, the risk of suboptimal DBP was significantly higher in health literacy group at 12-months [adjusted risk ratio (RR): 2·39, 95%CI: 1·24-4·62] and in comprehensive group at 3-months [adjusted risk ratio (RR): 2·14, 95%CI: 1·17-3·93] and 12 months [adjusted risk ratio (RR): 2·14, 95%CI: 1·09-4·20].

For serum lipids, the risk of abnormal LDL increased 86% (95%CI: 1·12-3·07) in the health literacy group at 12-months relative to at baseline, whereas the risk decreased in the control group at 24-months (RR: 0·46, 95%CI: 0·26-0·80). Compared with the control arm, a higher risk of abnormal LDL was observed for the health literacy group at 12-months [adjusted risk ratio (RR): 2·22, 95%CI: 1·11-4·44] and 24-months [adjusted risk ratio (RR): 2·37, 95%CI: 1·16-4·87].

The risk of abnormal HDL did not change in the four groups over the two year period of follow-up.

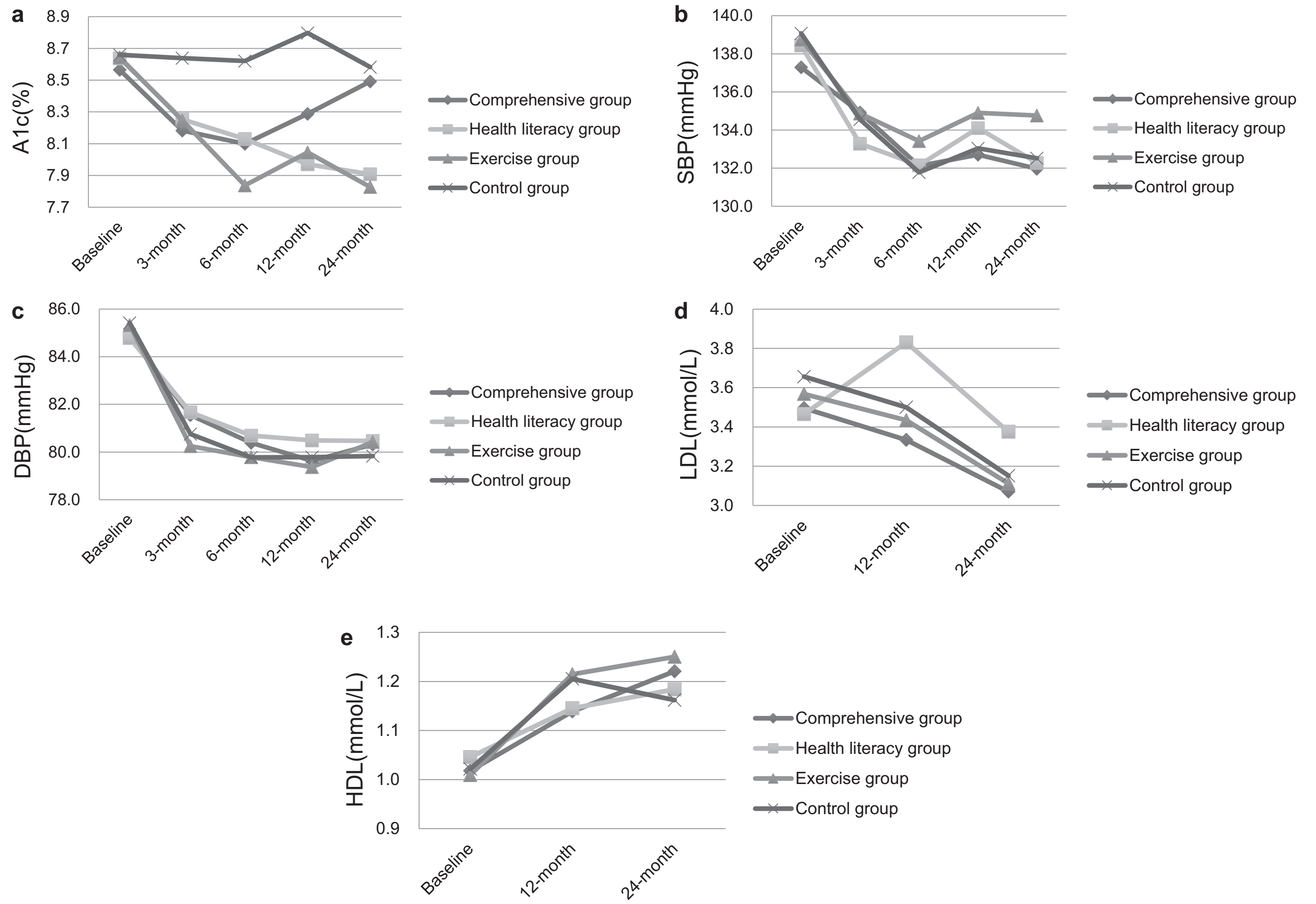

Fig. 3. Changes in A1C (a), SBP (b), DBP (c), LDL (d), and HDL (e) in patients with suboptimal clinical measurements at baseline based on GEE models

Each line was derived from a GEE model with intervention arm dummy coded as a predictor and adjusting for age, sex, income, educational level, smoking, duration of diabetes, antidiabetic drug and insulin use, baseline A1C, c-HeLMS score, correct rate of c-DNT-5. The model consists of an intercept and two (baseline to 12-months and 12- to 24-months) or four slopes (baseline to 3-months, 3- to 6-months, 6- to 12-months, and 12- to 24-months).

4. Discussion

In this study, both health literacy and exercise-focused interventions decreased A1c in diabetes patients in China. The significant improvements in A1c relative to the control arm remained even after a 1 year follow-up period post intervention.

Several previous studies in the US have suggested that interventions addressing literacy could improve patient outcomes, but did not find significant long-term improvements. Among patients with most recent A1c ≥7·0% (53 mmol/mol), Cavanaugh et al. [11] found that the intervention group using the Diabetes Literacy and Numeracy Education Toolkit had a significant higher decrease in A1c at 3-months, but the decrease was comparable to the control group at 6-months. Rosal et al. [22] observed a significant difference in A1c change between the intervention and the control arms at 4-months, but the difference was narrowed and no more significant at 12-months. Our study results were also consistent with previous studies demonstrating that regular exercise not only lowers glucose level and improves insulin resistance, but also has positive impacts on cardiovascular complications [23,24]. In Church's report [25], a combination of aerobic and resistance training was observed to significantly improve A1c compared with the non-exercise control group.

In the comprehensive group, A1c tended to return towards baseline at 24-months, whereas the improvement in A1c persisted over time in other intervention groups. While one might have expected the comprehensive intervention would have had greater improvements in A1c than either intervention alone, it is possible that trying to address both conditions at one time was too overwhelming for providers and patients, and actually resulted in less adherence.

The health literacy and exercise interventions also showed positive effects on blood pressure which is a risk factor for cardiovascular disease in diabetes patients. However, we also observed an improvement in blood pressure in the control arm, without any additional benefits from the interventions. This finding is somewhat consistent with three previous RCTs in which the control groups showed comparable improvements in blood pressure with those in the behavioral intervention groups possibly due to healthcare initiatives [26–28].

Diabetes patients typically have abnormal serum lipids and elevated risk of cardiovascular complications [29]. Previous studies have observed inconsistent effects of diabetes interventions on serum lipids [30–32]. A meta-analysis found that after 12 months of aerobic and resistance training HDL was remarkable higher in the intervention group than in the control group, but the LDL level did not change significantly [33]. In this study, we observed a striking increase in HDL in the health literacy and the exercise groups, but the improvements were also equally observed in the control arm. Interestingly, while LDL decreased in the control, the exercise and the comprehensive groups, it increased in the health literacy group. It is possible that diet module in the PRIDE toolkit used in the health literacy group may increase dietary fat intake in patients who may have over-controlled their diet previously. According to the dietary data collected in this study, energy intake remained unchanged in the health literacy group, but dietary fat intake increased from 78·1 at baseline to 84·0 g/d at 12-months ($p = 0·03$). In the exercise group, both

Table 3
Risk of suboptimal clinical outcomes at 3-, 6-, 12-, and/or 24-months relative to baseline and compared with the control arm.

Suboptimal clinical outcomes	Adjusted risk ratios (95%CI) relative to baseline				Adjusted risk ratios (95%CI) versus the control group		
	Control group	Health literacy group	Exercise group	Comprehensive group	Health literacy group	Exercise group	Comprehensive group
A1C ≥7·0% (53 mmol/mol)							
3-months	1·63 (0·94,2·85)	0·12 (0·04,0·31)	0·20 (0·10,0·38)	0·10 (0·05,0·23)	0·07 (0·02,0·21)	0·12 (0·05,0·27)	0·06 (0·02,0·16)
6-months	1·25 (0·70,2·24)	0·13 (0·05,0·38)	0·19 (0·10,0·37)	0·13 (0·05,0·29)	0·11 (0·04,0·33)	0·15 (0·07,0·34)	0·10 (0·04,0·26)
12-months	1·40 (0·76,2·58)	0·08 (0·03,0·22)	0·12 (0·06,0·23)	0·17 (0·08,0·37)	0·06 (0·02,0·18)	0·08 (0·04,0·19)	0·12 (0·05,0·31)
24-months	0·78 (0·44,1·37)	0·07 (0·03,0·20)	0·12 (0·06,0·25)	0·12 (0·05,0·29)	0·10 (0·03,0·29)	0·16 (0·07,0·36)	0·16 (0·06,0·42)
SBP>130 mmHg							
3-months	0·99 (0·67,1·48)	1·08 (0·72,1·62)	0·67 (0·44,1·01)	0·95 (0·63,1·44)	1·09 (0·62,1·91)	0·67 (0·38,1·19)	0·95 (0·54,1·69)
6-months	0·88 (0·57,1·36)	0·79 (0·53,1·19)	0·70 (0·45,1·10)	0·67 (0·44,1·04)	0·90 (0·50,1·64)	0·80 (0·42,1·49)	0·77 (0·41,1·42)
12-months	0·89 (0·57,1·39)	0·95 (0·65,1·37)	0·65 (0·43,0·99)	1·03 (0·67,1·57)	1·06 (0·60,1·90)	0·73 (0·40,1·35)	1·16 (0·63,2·14)
24-months	1·06 (0·68,1·67)	0·71 (0·46,1·10)	1·04 (0·64,1·68)	0·84 (0·55,1·29)	0·67 (0·36,1·25)	0·97 (0·50,1·88)	0·79 (0·43,1·47)
DBP>80 mmHg							
3-months	0·58 (0·37,0·90)	1·03 (0·68,1·56)	0·72 (0·46,1·13)	1·24 (0·80,1·91)	1·78 (0·99,3·22)	1·25 (0·67,2·31)	2·14 (1·17,3·93)
6-months	0·76 (0·48,1·20)	1·39 (0·90,2·16)	0·73 (0·45,1·17)	1·02 (0·64,1·62)	1·84 (0·96,3·53)	0·96 (0·49,1·89)	1·34 (0·68,2·63)
12-months	0·50 (0·31,0·82)	1·20 (0·76,1·88)	0·71 (0·44,1·15)	1·07 (0·67,1·73)	2·39 (1·24,4·62)	1·42 (0·72,2·79)	2·14 (1·09,4·20)
24-months	0·85 (0·53,1·36)	1·10 (0·69,1·76)	0·94 (0·60,1·49)	0·79 (0·49,1·27)	1·30 (0·67,2·51)	1·11 (0·58,2·14)	0·93 (0·48,1·80)
LDL>2·6 mmol/L							
12-months	0·84 (0·49,1·43)	1·86 (1·12,3·07)	1·62 (0·96,2·73)	0·88 (0·55,1·40)	2·22 (1·11,4·44)	1·93 (0·95,3·92)	1·05 (0·54,2·04)
24-months	0·46 (0·26,0·80)	1·09 (0·66,1·78)	0·93 (0·52,1·66)	0·64 (0·38,1·06)	2·37 (1·16,4·87)	2·03 (0·93,4·44)	1·40 (0·67,2.91)
HDL<1·04 (men) or <1·30 (women) mmol/L							
12-months	0·92 (0·59,1·46)	1·11 (0·66,1·87)	1·65 (0·88,3·12)	0·95 (0·56,1·63)	1·20 (0·60,2·40)	1·79 (0·82,3·91)	1·03 (0·51,2·08)
24-months	0·71 (0·44,1·14)	1·31 (0·79,2·19)	1·34 (0·66,2·72)	0·53 (0·27,1·02)	1·85 (0·92,3·70)	1·89 (0·81,4·42)	0·75 (0·33,1·67)

Results from the Generalized Estimated Equation (Risk at 3-, 6-, 12- and/or 24-months compared to that at baseline within the four groups and between the intervention groups and the control arm), adjusting for age, sex, income, educational level, smoking, physical activities, duration of diabetes, anti-diabetic agents and insulin use, c-HeLMS score, correct rate of c-DNT-5 and baseline A1C/ SBP/ DBP/ LDL/ HDL.

energy (from 1494 to 1592 kcal, $p = 0{\cdot}03$) and dietary fat intake (from 74·3 to 82·3 g/d, $p = 0{\cdot}005$) increased during the intervention period, whereas intakes of the two nutrients remained unchanged in the comprehensive and the control groups (data not shown in the tables). The potential negative influence of the health literacy intervention needs to be further assessed and addressed.

A1c is a surrogate marker for long term outcomes of diabetes. It is suggested that reducing A1c by 1·0% can reduce risk of CHD by 18%, stroke by 19%, heart failure by 13%, nephropathy by 22% and retinopathy by 24% in Asian patients [34,35]. Achieving target A1c level (<7·0% or 53 mmol/mol) has also been associated with 13% reduced risk of CHD, 13% of stroke, 16% of heart failure, 35% of nephropathy and 53% of retinopathy relative to suboptimal A1c level (≥7·0% or 53 mmol/mol) [36-38]. Therefore, scaling-up of the health literacy intervention at the national level in China may prevent about 691,354 diabetes complications each year, equivalent to about $574 million savings in health-care costs per year assuming 30% loss in effect. For exercise intervention, the number of diabetes complications avoided each year was about 766,687, equivalent to about $557 million savings in health-care costs (*Supplementary appendix*).

There are several strengths in this study. First, a 4-arm clustered randomization design was employed at the clinic level, avoiding potential contamination at the patient or provider level, and providing a "real world" pragmatic design for generalizability. Second, the considerable large sample of 800 patients and less than 10% attrition even at 24 months ensured statistical power to make estimations. Moreover, the subjects had a wide age range, including those over 65 years who were rarely included in most previous studies. Third, an evidence-based intervention approach, particularly the PRIDE, a valid health literacy intervention tool, was used in this study and successful integrated in diabetes clinics, engaging clinicians in delivering the intervention. Finally, the exercise-focus intervention was designed as supervised walking with gradually increased intensity, which is simpler and easier to follow than commonly used aerobic or resistance training [25]. These new approaches, once proved effective in Chinese diabetes patients, has great potential of scaling up in the larger patient population.

Several limitations should be noted when interpreting the results. First, the baseline characteristics of patients at the individual level were incomparable across the four arms due to the limitation of cluster randomization, which may have introduced residual confounding effects in our results. To minimize this potential bias, group matching method for randomization and multivariable models were used to adjust for baseline covariates. Second, given that Shanghai is one of the most economically developed big cities in China whose residents have higher health literacy levels [39], the results may not be generalizable to more rural communities in China. It is possible that the effect of the health literacy intervention could be more impactful in rural communities with lower levels of health literacy and numeracy. Moreover, the control group improved in several parameters with respect to baseline, suggesting effects of usual care or possible regression to the mean in the trial. With the launch of the health-care reform plan in China [40], blood pressure control has become a national public health priority in China. Furthermore, the exercise intensity was self-reported instead of being measured objectively, which may have questionable sensitivity and validity. However, considering that the elder patients might not manage digital devices, it may be feasible to collect information using the IPAQ and ask all subjects to record time and intensity of walking each day. Finally, while our study showed improvements in A1c, blood pressure and lipids, we were unable to adequately analyze process measures such as health care team-led medication changes, patient medication adherence, and other patient self-care activities. We did find significant changes in self-reported exercise and dietary habits, suggesting that our intervention was successful in improving communication to patients to promote behavior change.

To our knowledge, this is the first trial assessing the impact of a health literacy intervention on diabetes patients in China. Using a cluster randomization design, an evidence-based intervention approach, a large sample size with a wide age range and little attrition, we found that subjects who received health literacy and/or exercise interventions had significant improvement in glycemic control. The rapid and sustainable beneficial effects of health literacy and exercise-focused interventions on A1c in Chinese diabetes patients, as well as our successful integration of these interventions into many clinics, provide evidence for potential scaling up of these interventions in China and possibly in other countries.

Declaration of Competing Interest

We declare that we have no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2019.11.004.

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