Intelligent Optimization of Diversified Community Prevention of COVID-19 Using Traditional Chinese Medicine

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Abstract—Traditional Chinese medicine (TCM) has played an important role in the prevention and control of the novel coronavirus pneumonia (COVID-19), and community prevention has become the most essential part in reducing the risk of spread and protecting public health. However, most communities use a unified TCM prevention program for all residents, which violates the "treatment based on syndrome differentiation"

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principle of TCM and limits the effectiveness of prevention. In this paper, we propose an intelligent optimization method to develop diversified TCM prevention programs for community residents. First, we use a fuzzy clustering method to divide the population based on both modern medicine and TCM health characteristics; we then use an interactive optimization method, in which TCM experts develop different TCM prevention programs for different clusters, and a heuristic algorithm is used to optimize the programs under the resource constraints. We demonstrate the computational efficiency of the proposed method, and report the application results of the method in TCM-based prevention of COVID-19 in 12 communities in Zhejiang province, China, during the peak of the pandemic.

Using a "one-size-fits-all" prevention program for all residents is rarely effective, while developing a personalized program for each resident would be too expensive. We prefer to develop a set of diversified prevention programs, each for a group of residents.

I. Introduction

The ongoing outbreak of the novel coronavirus pneumonia (COVID-19), declared by the World Health Organization as a global public health emergency, has been reported in over twenty-two million cases in over 200 countries and territories as of August 21, 2020. Community prevention and control has become the most basic and essential part in reducing the risk of spread and protecting public health during the pandemic [1], [2]. Currently, community prevention is a significant challenge, not only because there is still no effective antiviral or vaccine, but also because of the pressing need to restart economy and restore social life [3], [4].

Although modern medicine offers accurate diagnosis and treatment methods for many diseases, it shows weakness in preventing emerging infectious diseases such as COVID-19 for which there is no vaccine, because epidemic prevention solutions based on modern medicine heavily rely on a clear understanding of the pathogenic mechanism and a number of large case-controlled studies [5], [6], and the misuse of antibiotics can cause severe side effects [7].

Traditional Chinese medicine (TCM) has been developed and used in prevention and treatment of various diseases for thousands of years in Chinese history. TCM is a comprehensive system of treatment of acute and chronic disorders as well as for the prevention of such disorders mainly based on herb medicine [8]. Unlike modern medicine that focuses on killing viruses, TCM pays attention to improving the inherent self-resistance and reducing the likelihood of disease onset by using a unique holistic approach to establish equilibrium in the whole and individual parts of the body [9]. The present principles on prevention of COVID-19 are to tonify body energy to protect the outside body, dispel wind, dissipate heat and dissipate dampness [10]. Facing an emerging infectious disease, TCM prescriptions (formulae) are made by combining existing crude herbs or minerals instead of developing new drugs. That is why TCM has achieved great success in response to recent epidemics such as SARS, H1N1, and Zika [11]–[15], and is playing a vital role in reducing the incidence rate and controlling the spread of COVID-19 [16]–[18].

However, we believe that there is much room for improving community prevention of the pandemic using TCM. For example, since the COVID-19 outbreak in China, many local public health administrations have issued TCM prevention programs for COVID-19, and some communities used a single program or prescription for all residents [19], [20]. Such a "one-size-fits-all" solution violates the "treatment according to three factors (time, place, and people)" and "treatment based on syndrome differentiation" principles of TCM and, therefore, limits the effectiveness of prevention.

According to requirements of local governments to improve community prevention of COVID-19, we propose an intelligent, diversified community prevention method for COVID-19 by combining TCM and modern computational intelligence methods. First, we use a fuzzy clustering method to classify the population based on both modern medicine and TCM health characteristics. According to the health characteristics, TCM experts develop a TCM prevention program for each cluster. The initial program for each cluster aims to maximize the prevention effect on residents in the cluster. Nevertheless, the demands of all initial programs often exceed the available resources. We then use an interactive optimization method to continually evolve the prevention programs until all programs are approved by the TCM experts while all resource demands are satisfied. The proposed method has been practiced in a number of communities in Zhejiang province and extended to many other regions in China. The main contribution of this work is the combination of traditional medicine with computational intelligence methods for diversified prevention of COVID-19; in particular, we propose an improved fuzzy clustering method for residence grouping, and employ bio-inspired optimization to fully utilize available resources to develop diversified programs to improve prevention effects.

II. Fuzzy Clustering of Community Residents

Using a "one-size-fits-all" prevention program for all community residents fails to consider interpersonal differences and is rarely effective. On the contrary, developing a personalized prevention program for each resident would be too expensive due to limited medical resources under the pandemic. We prefer to develop a set of diversified prevention programs, each for a group of residents with similar physical characteristics. The characteristics include both modern medicine characteristics and TCM health characteristics, as summarized in Table I. The data sources include both modern healthcare records and TCM records of the residents. Those characteristics are used as input features for grouping, and the value of each feature is normalized, e.g., real values (such as height and weight) are normalized to [0,1], and exclusive labels (such as sex and illness) are represented by binary variables. In this study, we use a total of 1148 features for grouping. However, for most residents, many features can be absent.

A. An Improved Fuzzy c-Means Clustering Method

For such a high-dimension grouping problem with many missing values, classical hard clustering methods such as K-means clustering [22] are not very effective. In this study, we use an improved fuzzy c-means (FCM) clustering method [23]. In brief, FCM groups a set of data points by minimizing the overall fuzzy-membership-weighted distance of the data points from cluster centroids:

$$\min J(U,V) = \frac{1}{cn}\sum_{i=1}^{c}\sum_{j=1}^{n} u_{ij}^{m} d_{ij}^{2} \tag{1}$$

where n is the number of data points, c is the number of clusters, u_{ij} is the membership degree of the jth data point to the ith cluster subject to $\Sigma_i u_{ij} = 1$, d_{ij} is the distance between the jth data point and the ith cluster centroid, m is a control parameter with a default value of 2, $U = (u_{ij})_{c\times n}$ is the weight matrix, and $V = [\mathbf{v}_1, \mathbf{v}_2, \ldots, \mathbf{v}_c]$ is the set of cluster centroid vectors.

Xu and Wu [24] extended the standard FCM to intuitionistic FCM based on new distance measures defined on intuitionistic fuzzy sets (IFS) [25] that capture more uncertainty information. Here, we use Pythagorean fuzzy sets (PFS) [26], which allow for a larger body of membership grades than IFS, to further improve clustering. Formally, let S be an arbitrary non-empty set, a PFS is a mathematical object of the form:

$$P = \{\langle x, \mu_P(x), \nu_P(x) \rangle \mid x \in S\} \tag{2}$$

where $\mu_P(x): S \to [0,1]$ and $\nu_P(x) : S \to [0,1]$ are respectively the membership degree and non-membership degree of the element x to S in P. PFS extends IFS in that the membership degrees satisfy $\mu_P^2(x) + \nu_P^2(x) \le 1$. The hesitant degree of $x \in X$ is expressed as:

$$\pi_P(x) = \sqrt{1 - \mu_P^2(x) - \nu_P^2(x)} \tag{3}$$

In our improved Pythagorean FCM, data points and cluster centroids are represented by Pythagorean fuzzy number (PFN) vectors, where the distance between two PFN $\beta_1 = P(\mu_{\beta_1}, \nu_{\beta_1})$ and $\beta_2 = P(\mu_{\beta_2}, \nu_{\beta_2})$ is calculated as [27]:

$$|\beta_1, \beta_2| = \sqrt{\frac{(\mu_{\beta_1}^2 - \mu_{\beta_2}^2)^2 + (\nu_{\beta_1}^2 - \nu_{\beta_2}^2)^2 + (\pi_{\beta_1}^2 - \pi_{\beta_2}^2)^2}{2}} \tag{4}$$

and the distance d_{ij} in Eq. (1) between a D-dimensional data point $\mathbf{x}_j$ and a cluster centroid $\mathbf{v}_i$ is calculated as:

$$\| \mathbf{x}_j, \mathbf{v}_i \| = \sqrt{\frac{\sum_{d=1}^{D} |x_{jd}, v_{id}|^2}{D}} \tag{5}$$

Algorithm 1 presents the Pythagorean FCM method, which minimizes the objective function $J(U, V)$ by iteratively updating the fuzzy membership weights according to the distances between data points and centroids (Line 11) and updating the centroids according to the membership and

TABLE 1 **Physical characteristics for grouping community residents.**

TYPE	CHARACTERISTICS	NUMBER OF INDICATORS
BASIC HEALTH METRICS	AGE, SEX, OCCUPATION, HEIGHT, WEIGHT, HEART RATE, BLOOD PRESSURE, VITAL CAPACITY, …	121
TCM CONSTITUTIONS	MILD, YANG DEFICIENCY, YIN DEFICIENCY, PHLEGM DAMPNESS, WET & HEAT, QI STAGNATION, QI DEFICIENCY, BLOOD STASIS, SPECIAL	9
TCM SYNDROMES [21]	SHIRE JINYIN, PIXU SHIYUN, XUEXU FENGZAO, SHIRE YUZU, SHIRE SHANGYIN, QIZHI XUEYU, QIXU BUZU, GANSHEN BUZU, …	50
PAST ILLNESSES	DISEASES AND THE CORRESPONDING INDICATORS	484
CURRENT ILLNESSES	DISEASES AND THE CORRESPONDING INDICATORS	484

Algorithm 1 **Pythagorean fuzzy c-means clustering algorithm.**

1 Initialize a $c \times n$ matrix U and a set $V^{(0)}$ of c cluster centroids;
2 Let $k = 0$;
3 **while** $\|V^{(k+1)}, V^{(k)}\| > \epsilon$ **do**
4 **for** $j = 1$ *to* n **do**
5 **if** $\exists i' : 1 \le i' \le c : \|\mathbf{x}_j, \mathbf{v}_{i'}\| = 0$ **then**
6 **for** $i = 1$ *to* c **do**
7 **if** $i = i'$ **then** $u_{ij}^{(k)} \leftarrow 1$;
8 **else** $u_{ij}^{(k)} \leftarrow 0$;
9 **else**
10 **for** $i = 1$ *to* c **do**
11 $u_{ij}^{(k)} \leftarrow \dfrac{1}{\sum_{i'=1}^{c}\left(\dfrac{\|\mathbf{x}_j, \mathbf{v}_i\|}{\|\mathbf{x}_j, \mathbf{v}_{i'}\|}\right)^{\frac{2}{m-1}}}$;
12 **for** $i = 1$ *to* c do
13 $\mathbf{v}_i^{(k)} \leftarrow \left\{\left\langle \beta_d, \dfrac{\sum_{j=1}^{n} u_{ij}^{(k)} \mu_{\beta_d}^2}{\sum_{j=1}^{n} u_{ij}^{(k)}}, \dfrac{\sum_{j=1}^{n} u_{ij}^{(k)} \nu_{\beta_d}^2}{\sum_{j=1}^{n} u_{ij}^{(k)}} \right\rangle \middle| 1 \le d \le D \right\}$;
14 $k \leftarrow k + 1$;
15 **return** (U, V);

non-membership degrees of data points to clusters (Line 13) to apply the derivative of $J(U, V)$ [24].

B. A Metaheuristic for Optimizing Clusters

The performance of FCM clustering heavily depends on the quality of initial cluster centroids [28], [29]. Instead of randomly setting initial cluster centroids, we use a metaheuristic algorithm, ecogeography-based optimization (EBO) [30], to optimize initial cluster centroids [29]. The algorithm starts by initializing a population of solutions, each representing a set $V^{(0)}$ of c initial cluster centroids. Let $J(\mathbf{x})$ denote the resulting $J(U, V)$ value obtained by the FCM method from the initial cluster centroids of $\mathbf{x}$; each solution $\mathbf{x}$ is assigned with an emigration rate $E_r(\mathbf{x})$ that is inversely proportional to $J(\mathbf{x})$ and an immigration rate $I_r(\mathbf{x})$ that is proportional to $J(\mathbf{x})$:

$$E_r(\mathbf{x}) = \frac{J_{\max} - J(\mathbf{x}) + \epsilon}{J_{\max} - J_{\min} + \epsilon} \tag{6}$$

$$I_r(\mathbf{x}) = \frac{J(\mathbf{x}) - J_{\min} + \epsilon}{J_{\max} - J_{\min} + \epsilon} \tag{7}$$

where $J_{\max}$ and $J_{\min}$ are the maximum and minimum $J(\cdot)$ values among the population, respectively, and ϵ is a small positive number to avoid division-by-zero. In this way, a better solution has a higher probability of emigrating features to other solutions, while a worse solution has a higher probability of immigrating features from other solutions [31].

The EBO algorithm then continually evolves the solutions using two migration operators: local migration and global migration. Local migration updates a solution $\mathbf{x}$ at each dimension d by migrating the corresponding dimension of a neighboring solution $\mathbf{x}^{\dagger}$ as follows:

$$x'_d = x_d + rand(0,1) \cdot (x^{\dagger}_d - x_d) \tag{8}$$

where $rand(0,1)$ produces a random number uniformly distributed in (0, 1), and $\mathbf{x}^{\dagger}$ is selected from all neighbors of $\mathbf{x}$ with a probability proportional to $E_r(\mathbf{x}^{\dagger})$.

Global migration updates a solution $\mathbf{x}$ at each dimension d by migrating the corresponding dimensions of both a neighboring solution $\mathbf{x}^{\dagger}$ and a non-neighboring solution $\mathbf{x}^{\ddagger}$ as follows:

$$x'_d = \begin{cases} x^{\dagger}_d + rand(0,1) \cdot (x^{\ddagger}_d - x_d), & f(\mathbf{x}^{\ddagger}) \le f(\mathbf{x}^{\dagger}) \\ x^{\ddagger}_d + rand(0,1) \cdot (x^{\dagger}_d - x_d), & f(\mathbf{x}^{\ddagger}) > f(\mathbf{x}^{\dagger}) \end{cases} \tag{9}$$

where $\mathbf{x}^{\dagger}$ is selected from all neighbors of $\mathbf{x}$ and $\mathbf{x}^{\ddagger}$ is selected from all non-neighboring solutions of $\mathbf{x}$; the selection probabilities are proportional to E_r.

EBO uses a parameter η as the probability of performing global migration and, therefore, $(1-\eta)$ as the probability of performing local migration. The value of η dynamically increases from a lower limit $\eta_{\min}$ to an upper limit $\eta_{\max}$ with generation g of the algorithm:

$$\eta = \eta_{\min} + \frac{g}{g_{\max}}(\eta_{\max} - \eta_{\min}) \tag{10}$$

In this study, we use a local random neighborhood structure [32], which randomly assigns k_N neighboring solutions to each solution in the population (where k_N is a parameter set to 3); if the current best solution has not been updated after a number $\hat{g}$ of consecutive generations, the neighborhood structure is randomly reset. Algorithm 2 presents the pseudocode of the EBO algorithm, where Line 4 invokes Algorithm 1 to evaluate the fitness of each solution (initial centroid setting).

III. Interactive Optimization of Prevention Programs

After clustering the community residents into c groups, we invite TCM experts to assess the health characteristics of each cluster (and examine typical residents if possible), and develop diversified prevention programs according to the characteristics. Note that the number p of prevention programs approximates, but does not necessarily equal, the number c of clusters. That is, the TCM experts typically develop a prevention program (including a TCM prescription and other supplementary means such as acupuncture and moxibustion) for a cluster; they

Algorithm 2 **The EBO algorithm for enhancing the fuzzy clustering method.**

1 Randomly initialize a population of solutions (initial set of cluster centroids);
2 **while** *the stopping criterion is not satisfied* **do**
3   **foreach** *solution* $\mathbf{x}$ *in the population* **do**
4   Use Algorithm 1 to produce the clustering results (U, V) from the initial cluster centroids of $\mathbf{x}$;
5   Let $\mathbf{x}^*$ be the best solution in the population;
6   **foreach** *solution* $\mathbf{x}$ *in the population* **do**
7   Compute $E_r(\mathbf{x})$ and $I_r(\mathbf{x})$ according to Eqs. (6) and (7);
8   **foreach** *solution* $\mathbf{x}$ *in the population* **do**
9   **for** $d = 1$ *to* n **do**
10   **if** $rand(0,1) < I_r(\mathbf{x})$ then
11   Select a neighboring $\mathbf{x}^{\dagger}$ with probability proportional to $E_r(\mathbf{x}^{\dagger})$;
12   **if** $rand(0,1) < \eta$ **then**
13   Select a non-neighboring $\mathbf{x}^{\ddagger}$ with probability proportional to $E_r(\mathbf{x}^{\ddagger})$;
14   Do global migration according to Eq. (9);
15   **else**
16   Do local migration according to Eq. (8);
17   **if** *the migrated solution* $\mathbf{x}'$ *is better than* $\mathbf{x}$ then
18       $\mathbf{x} \leftarrow \mathbf{x}'$;
19   Update η according to Eq. (10);
20   **if** $\mathbf{x}^*$ *has not been updated for* $\widehat{g}$ *consecutive generations* **then**
21   Randomly reset the neighborhood structure;
22 **return** the clustering result of the best known solution $\mathbf{x}^*$.

A TCM prescription can have dozens of ingredients, and a drug can have dozens of alternative drugs. Therefore, the solution space of the problem can be very large.

may also develop a prevention program for two similar clusters as they consider appropriate. For a cluster with high-risk residents (with suspected symptoms of COVID-19 or serious underlying illnesses), they can decide to develop one prevention program for each resident.

When developing initial programs, the TCM experts aim to maximize the prevention effect on residents of each cluster without considering the limits of medical resources including herbal medicines, patent medicines, medical devices, pharmacists, and other paramedical personnel. If the demands of the programs exceed the available resources, we use an intelligent optimization algorithm to optimize the programs subject to the resource constraints. However, any prevention program produced by computer algorithms must be checked and, if necessary, modified by the TCM experts before implementation. The above process continues until all prevention programs satisfy the resource constraints and are approved by the TCM experts. Fig. 1 illustrates the interactive optimization process.

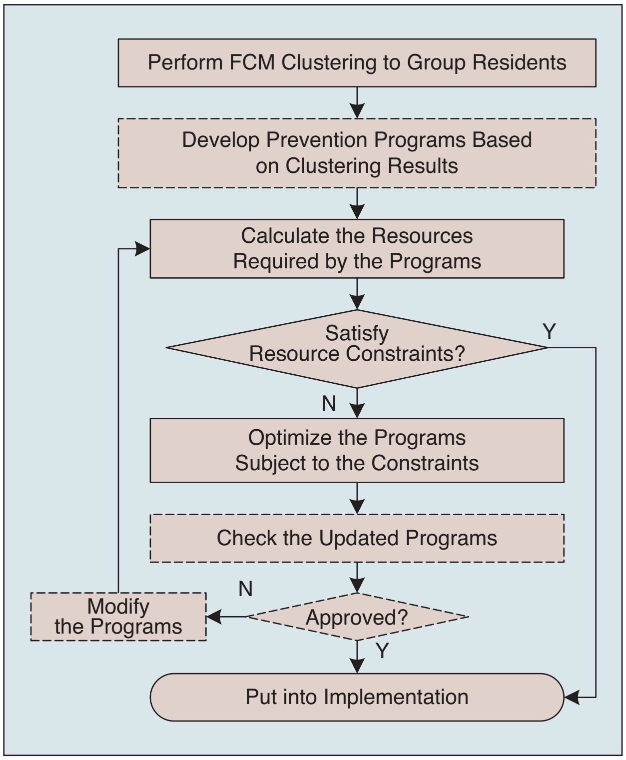

FIGURE 1 Flowchart of the interactive optimization of TCM prevention programs. Rectangles with dash borders are performed by TCM experts, while rectangles with solid borders are performed by computer.

A. Optimization Problem

The prevention program optimization problem is formulated as follows. TCM experts have developed N basic prevention programs, denoted by $\{P_1, P_2, \ldots, P_N\}$, for residents from M communities. The programs involve K types of drugs, K_1 types of other medical resources (such as TCM material and movable devices) that can be shared among the communities, and K_2 types of other medical resources (such as immovable devices and staff belonging to given communities) that cannot be shared among the communities. When there is no confusion, we use k as the index for the above three classes of resources.

The problem is to optimize the distribution of medical resources among the prevention programs for the M communities. In the local region, the total available quantity of each drug k is $\hat{q}_k^{\mathrm{D}}$ $(1 \le k \le K)$, total available quantity of each other sharable resource k is $\hat{q}_k^{\mathrm{G}}$ $(1 \le k \le K_1)$, and available quantity of each non-sharable resource k in community i is $\hat{q}_{ik}^{\mathrm{F}}$ $(1 \le k \le K_2; 1 \le i \le M)$.

Each prevention program P_j has the following attributes $(1 \le j \le N)$:

- ❏ The number n_j of residents using the program;
- ❏ The set Θ_j of communities that have residents using the program; for each community $i \in \Theta_j$, the number of residents using the program is n_{ij};
- ❏ The set Φ_j of drugs used by the program; for each drug $k \in \Phi_j$, the quantity used per prescription is q_{jk}^{D};
- ❏ The set Ψ_j of other sharable resources used by the program; for each resource $k \in \Psi_j$, the quantity used per prescription is q_{jk}^{G};
- ❏ The set Ω_j of other non-sharable resources used by the program; for each resource $k \in \Omega_j$, the quantity used per prescription is q_{jk}^{F};

In a TCM prescription, many ingredients have alternatives. We use $\Phi'_j \subset \Phi_j$ to denote the subset of drugs that have alternatives in P_j; for each drug $k \in \Phi'_j$, we use a list Λ_k to store its alternative drugs in decreasing order of priority, which are determined by TCM drug properties and effects to the disease (COVID-19 belongs to pulmonary disease in TCM). We consider two types of updates on a TCM prescription:

- ❏ Replacing an auxiliary drug $k \in \Phi'_j$ with an alternative drug $k' \in \Lambda_k$, for example, replacing coix seed with winter melon seed;
- ❏ Replacing a main drug $k \in \Phi'_j$ with an alternative drug $k' \in \Lambda_k$; however, according to compatibility of TCM, a main drug is related to one or more auxiliary drugs, and the corresponding auxiliary drugs should also be reapplied; an example is replacing "astragalus membranaceus (main) + cinnamon (auxiliary)" with "codonopsis pilosula (main) + yam (auxiliary)."

To prevent the updated prescriptions from deviating too much from the original prescriptions developed by TCM experts, for each prevention program, we allow at most one drug (except auxiliary drugs related to a main updated drug) to be updated each time. For either of the two types of updates above, we use $P_j(x_j, x'_j)$ to denote the updated program, where x_j denotes the original drug in the prescription, and x'_j denotes the alternative drug in Λ_{x_j}. Therefore, for the set of original prevention programs $\{P_1, P_2, \ldots, P_N\}$, each solution to the problem can be represented by a $(2N)$-dimensional integer vector $\mathbf{x} = \{x_1, x'_1, x_2, x'_2, \ldots, x_N, x'_N\}$, which indicates that the x_j-th drug in P_j is to be replaced by its x'_j-th alternative $(1 \le j \le N)$; without loss of generality, $x_j = x'_j$ denotes that P_j is unchanged.

Based on the efficacy of the original and alternative drugs, we can determine the quantity of an alternative drug k' used to replace an original drug k in the prescription. Based on the change of the prescription, we can then determine the changes of other medical resources, such as the types and quantities of material and the working hours for processing the drugs. Consequently, we obtain the following attributes of the updated prevention program $P_j(x_j, x'_j)$:

- ❏ The set $\Phi_j(x_j, x'_j)$ of drugs; for each drug $k \in \Phi_j(x_j, x'_j)$, the quantity used per prescription is $q^{\mathrm{D}}_{jk}(x_j, x'_j)$;
- ❏ The set $\Psi_j(x_j, x'_j)$ of other sharable resources used by the program; for each resource $k \in \Psi_j(x_j, x'_j)$, the quantity used per prescription is $q^{\mathrm{G}}_{jk}(x_j, x'_j)$;
- ❏ The set $\Omega_j(x_j, x'_j)$ of other non-sharable resources used by the program; for each resource $k \in \Omega_j(x_j, x'_j)$, the quantity used per prescription is $q^{\mathrm{F}}_{jk}(x_j, x'_j)$.

The objective of the problem is to maximize the overall effects of the updated prevention programs, provided that the resources used by the programs do not exceed the available resources. The effect of each updated program $P_j(x_j, x'_j)$ is evaluated based on its deviation from the original program P_j; the larger the deviation, the smaller the effect is, as we should trust the ability of TCM experts who develop the original program. The deviation of $P_j(x_j, x'_j)$ from P_j is assessed in two aspects:

- ❏ The importance of drug x_j in the original P_j, which is measured by a weight w_{jx_j}; a larger priority indicates a larger deviation;
- ❏ The priority of drug x'_j in the alternative set Λ_{x_j}; a higher priority indicates a smaller deviation.

Here, we calculate the deviation as follows:

$$\Delta P_j(x_j, x'_j) = w_{jx_j} I(\Lambda_{x_j}, x'_j) \tag{11}$$

where $I(\Lambda_{x_j}, x'_j)$ is the index of x'_j in Λ_{x_j} (without loss of generality, we set $\Delta P_j(x_j, x_j) = 0$).

Moreover, we use a weight w_j to denote the susceptibility of residents covered by program P_j to the infectious disease, and use a weight w'_i to denote the importance of each community i (which is related to the openness and population density of the community). The objective of the problem is defined as:

$$\min f(\mathbf{x}) = \sum_{j=1}^{N} \sum_{i \in \Theta_j} w_j w'_i \Delta P_j(x_j, x'_j) \tag{12}$$

The constraints of the problem are the quantities of each drug, other sharable resource, and other non-sharable resource used by the programs cannot exceed available quantities:

$$\sum_{j=1}^{N} n_j q^{\mathrm{D}}_{jk}(x_j, x'_j) \le \hat{q}^{\mathrm{D}}_k, \quad 1 \le k \le K \tag{13}$$

$$\sum_{j=1}^{N} n_j q^{\mathrm{G}}_{jk}(x_j, x'_j) \le \hat{q}^{\mathrm{G}}_k, \quad 1 \le k \le K_1 \tag{14}$$

$$\sum_{j=1}^{N} n_{ij} q^{\mathrm{F}}_{jk}(x_j, x'_j) \le \hat{q}^{\mathrm{F}}_{jk}, \quad 1 \le i \le M; 1 \le k \le K_2 \tag{15}$$

It should be noted that, in Eqs. (13)–(15), we uniformly use the operator Σ for notational simplicity; however, it may not always necessarily be summation. Typically, for drugs and material, Σ denotes summation; for other resources such as devices and personnel, Σ can be other corresponding aggregation operators. For example, supposing that a decocting machine can process 50 doses of a prescription, the operator will add 1 per 50 doses, and will also add 1 if the number of remaining doses is less than 50.

B. Optimization Algorithm

A TCM prescription can have dozens of ingredients, and a drug can have dozens of alternative drugs. Therefore, when the number N of prevention programs is relatively large, the solution space of the problem can be very large, for which exact optimization algorithms are often inefficient.

We use a metaheuristic optimization algorithm, water wave optimization (WWO) [33], to efficiently solve the problem. The algorithm starts by initializing a population of N_P solutions. To evaluate the fitness of each solution $\mathbf{x}$, we employ three penalty functions $v_D(\mathbf{x})$, $v_G(\mathbf{x})$, and $v_F(\mathbf{x})$ to calculate the violations of constraints (13), (14), and (15) as follows:

$$v_D(\mathbf{x}) = \sum_{k=1}^{K} \max\left(0, \sum_{j=1}^{N} n_j n^{\mathrm{D}}_{jk}(x_j, x'_j) - \hat{n}^{\mathrm{D}}_k\right) \tag{16}$$

$$v_G(\mathbf{x}) = \sum_{k=1}^{K_1} \max\left(0, \sum_{j=1}^{N} n_j n^{\mathrm{G}}_{jk}(x_j, x'_j) - \hat{n}^{\mathrm{G}}_k\right) \tag{17}$$

$$v_F(\mathbf{x}) = \sum_{i=1}^{M} \sum_{k=1}^{K_2} \max\left(0, \sum_{j=1}^{N} n_{ij} n^{\mathrm{F}}_{jk}(x_j, x'_j) - \hat{n}^{\mathrm{F}}_{ik}\right) \tag{18}$$

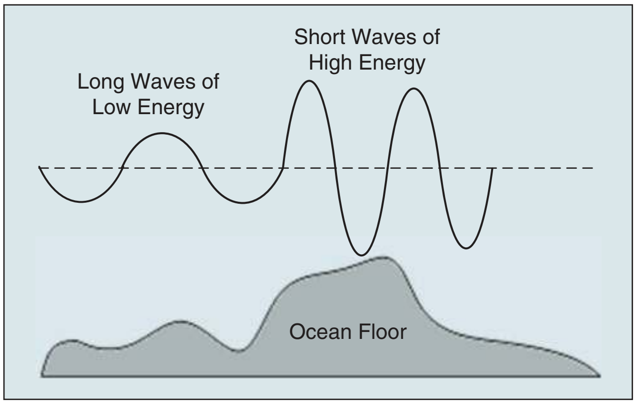

FIGURE 2 Wave lengths of high-fitness and low-fitness waves (solutions).

And the fitness $fit(\mathbf{x})$ is calculated as:

$$fit(\mathbf{x}) = 1/\left(f(\mathbf{x}) + \nu_D(\mathbf{x}) + \nu_G(\mathbf{x}) + \nu_F(\mathbf{x})\right) \tag{19}$$

We sort all N_P solutions in the population in decreasing order of the fitness value. Let $o(\mathbf{x})$ be the index of solution $\mathbf{x}$ in the sorted population; according to the principles of adapting WWO for combinatorial optimization [34], we calculate a wavelength $\lambda(\mathbf{x})$ for each $\mathbf{x}$ as an integer between 1 and N as follows:

$$\lambda(\mathbf{x}) = N - \left\lceil \frac{N_P - o(\mathbf{x})}{N_P - 1}(N-1) \right\rceil \tag{20}$$

where $\lceil \cdot \rceil$ denotes rounding up to the nearest integer.

The WWO iteratively evolves the solutions using three operators including propagation, refraction, and breaking. The propagation operator is based on two neighborhood structures. Given a solution $\mathbf{x}$ to the problem, its neighboring solutions can be obtained using one of the following two approaches:

- Randomly selecting a prescription P_j, changing x'_j to a random drug in Λ_{x_j}; this indicates modifying the alternative drug used in $P_j(x_j, x'_j)$;
- Randomly selecting a prescription P_j, changing x_j to another drug k in Φ_j, and then changing x'_j to a random drug in Λ_k; this indicates modifying both the drug to be replaced in P_j and the alternative drug used in $P_j(x_j, x'_j)$.

The propagation updates each solution $\mathbf{x}$ by performing $\lambda(\mathbf{x})$ steps of neighborhood search, i.e., propagates $\mathbf{x}$ to a $\lambda(\mathbf{x})$-step neighboring solution. In this way, a solution with higher fitness (and therefore smaller wavelength) exploits a smaller area, while a solution with lower fitness explores a larger area, as illustrated in Fig. 2 [33]. If the resulting $\lambda(\mathbf{x})$-step neighbor is better than $\mathbf{x}$, it replaces $\mathbf{x}$ in the population.

The refraction updates a stagnant solution $\mathbf{x}$ that has not been improved for $\hat{g}$ consecutive generations (where $\hat{g}$ is a control parameter) by making it learn from the current best solution $\mathbf{x}^*$. At each dimension j, the pair of components (x_j, x'_j) has a probability of 0.5 of being replaced by the corresponding components $(x^*_j, x^{*\prime}_j)$ of $\mathbf{x}^*$.

The breaking of a newly found best solution $\mathbf{x}^*$ generates at most N one-step neighboring solutions, each being obtained by trying to replace x'_j with a better alternative drug in Λ_{x_j} $(1 \le j \le N)$; if the best neighbor is better than $\mathbf{x}^*$, it replaces $\mathbf{x}^*$ in the population.

Algorithm 3 presents the pseudocode of the WWO algorithm for the prevention program optimization problem.

Algorithm 3 **The WWO algorithm for the prevention program optimization problem.**

Randomly initialize a population of solutions to the problem;
while *the stopping criterion is not satisfied* **do**
  Sort all solutions in increasing order of fitness;
  Let $\mathbf{x}^*$ be the best solution in the population;
  foreach *solution* $\mathbf{x}$ *in the population* **do**
    Calculate $\lambda(\mathbf{x})$ according to Eq. (20);
    `//propagation`
    Let $\mathbf{x}_\lambda = \mathbf{x}$;
    for $k = 1$ *to* $\lambda(\mathbf{x})$ **do**
      Set $\mathbf{x}_\lambda$ to an immediate neighbor of $\mathbf{x}_\lambda$;
    if $fit(\mathbf{x}_\lambda) > fit(\mathbf{x})$ **then**
      $\mathbf{x} \leftarrow \mathbf{x}'_\lambda$;
      if $fit(\mathbf{x}) > fit(\mathbf{x}^*)$ **then**
        `//breaking`
        $\mathbf{x}^* \leftarrow \mathbf{x}$;
        for $j = 1$ *to* N **do**
          if $x'_j > 1$ **then**
            $x'_j \leftarrow rand(1, x_j - 1)$;
            if $fit(\mathbf{x}) > fit(\mathbf{x}^*)$ **then**
              $\mathbf{x}^* \leftarrow \mathbf{x}$;
    else
      if $\mathbf{x}$ *has not been improved for* $\widehat{g}$ *generations* **then**
        Refract $\mathbf{x}$ by learning from $\mathbf{x}^*$;
return the best known solution $\mathbf{x}^*$.

IV. Computational Results

During February and March, 2020, we applied the proposed method to TCM prevention of COVID-19 in two regions in Zhejiang Province, China:

- 39,720 residents in eight communities in Hangzhou city;
- 9,812 residents in four communities in Shaoxing city.

The following subsections report the results of resident clustering and prevention program optimization and implementation.

A. Results of Resident Clustering

Based on the analysis of TCM experts on local populations and TCM symptoms of COVID-19, the number C of clusters is set to 16. We compare the clustering results of K-means [22], DBSCAN [35], standard FCM, intuitionistic FCM (IFCM), Pythagorean FCM (PFCM), PFCM enhanced by EBO, and PFCM enhanced by five other popular metaheuristic algorithms including the genetic algorithm (GA) [36], differential evolution (DE) [37], comprehensive learning particle swarm optimization (CLPSO) [38], and hybrid biogeography-based optimization (HBBO) [39]. The experiments are conducted on a computer with Intel Xeon 3430 CPU and GTX 1080Ti GPU.

Each algorithm runs 30 times with different random seeds (K-means and four basic FCM methods use random initial cluster centroids, DBSCAN uses random order of data, and PFCM with different metaheuristics use randomly initial populations). As we do not know the ground truth class assignments, we use the Davies-Bouldin index [40], which is a function of the ratio of intra-cluster scatter to inter-cluster separation, as the performance metric (lower is better):

$$db = \frac{1}{c}\sum_{i=1}^{c} \max_{1 \le j \le c \wedge i \ne j} \left(\frac{s_i + s_j}{d_{ij}}\right) \tag{21}$$

where s_i is the average distance between each point and the centroid of cluster i, and d_{ij} is the distance between the centroids of clusters i and j.

Fig. 3(a) and (b) compare the performance of the ten clustering algorithms in Hangzhou and Shaoxing, respectively. On both instances, K-means exhibits the worst performance, because it aims to minimize the within-cluster sum-of-squares, but this criterion responds poorly to manifolds with irregular and uncertain shapes which often exist in population health data. FCM achieves significant performance advantage over K-means by incorporating fuzzy logic to effectively deal with uncertainties [24]. DBSCAN shows similar performance as FCM, and the standard deviation of DBSCAN over the 30 runs is smaller. IFCM achieves better results than the standard FCM, and PFCM achieves better results than IFCM, which shows that using extended fuzzy sets can improve the fuzzy clustering by capturing uncertainty information more effectively. Compared to the three basic FCM methods using random initial cluster centroids, PFCM enhanced by metaheuristic optimization to find optimal/sub-optimal initial centroids achieve significant performance advantages, because the quality of initial centroids heavily affects the clustering results. Among the five metaheuristic algorithms, the proposed PFCM-EBO exhibits the best performance, which demonstrates the efficiency of the EBO algorithm in optimizing initial centroids for clustering residents using health data.

B. Results of Prevention Program Optimization

The TCM experts develop 15 prevention programs for the 16 clusters of residents (two clusters are very similar and share one program). Among the 39,720 residents in Hangzhou, 4,625 residents agree to adopt the prevention programs, but medical resources required to implement the programs significantly exceed the available resource. Therefore, we use the proposed WWO algorithm to optimize the programs. Among the 15 updated programs, 13 programs are approved by the experts, and the remaining two programs are slightly modified by the experts. The updated programs do not violate the resource constraints and, therefore, are put into implementation. However, during one week of implementation, many resources have been consumed, and the available resources are not sufficient to implement the 15 updated programs. Therefore, we perform a second round of program optimization. Among the 15 programs updated in the second round, 12 programs are approved, and the remaining three programs are modified by the experts. However, the resources required by the programs again exceed the available resources. Therefore, we perform a third round of program optimization, the results of which are approved and put into implementation.

Among the 9,812 residents in Shaoxing, 1,227 agree to adopt the prevention programs. In Shaoxing, we perform two rounds of program optimization, the results of which are put into implementation successively.

In summary, we use the proposed algorithm to solve five instances of the prevention program optimization problem. For comparison, we also implement the following five popular metaheuristic optimization algorithms on these five instances:

- The GA for constrained optimization [41];
- The biogeography-based optimization (BBO) for constrained optimization [42];
- The DE algorithm for constrained optimization [43];
- The cuckoo search (CS) algorithm for integer programming [44];
- The grey wolf optimization (GWO) algorithm for integer programming [45].

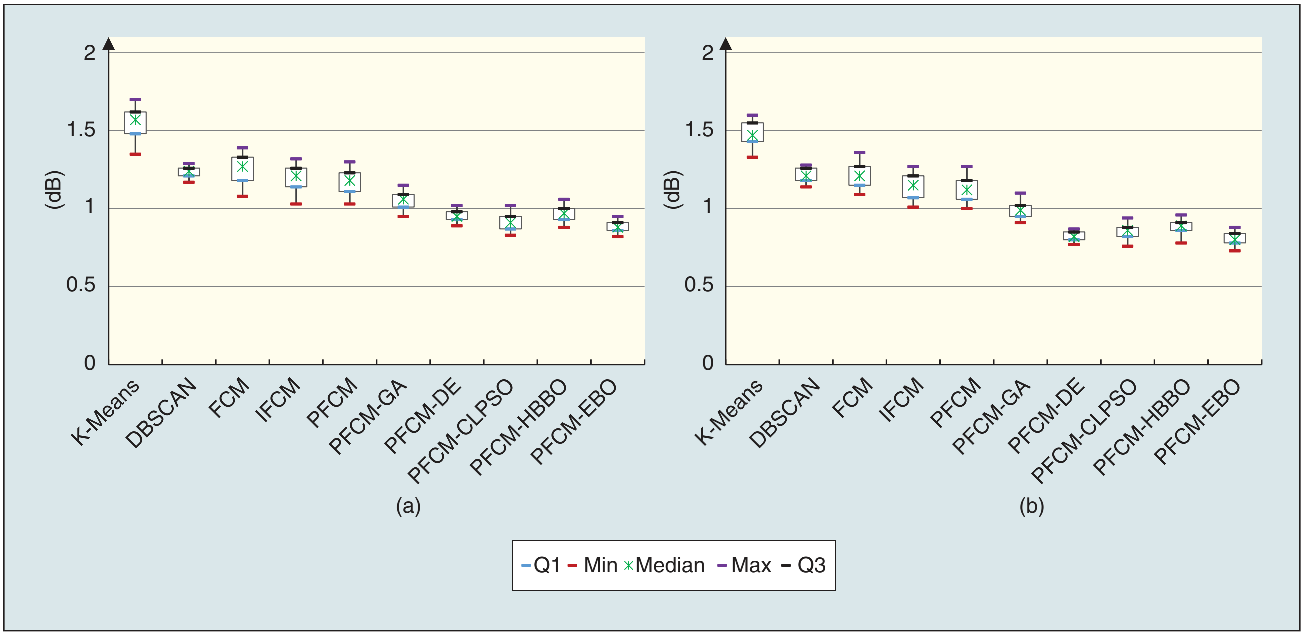

FIGURE 3 Comparison of the ten algorithms for clustering residents in (a) Hangzhou, and (b) Shaoxing. Each box plot shows the maximum, minimum, median, first quartile (Q1), and third quartile (Q3) of the resulting Davies-Bouldin index values over the 30 runs of an algorithm.

Each algorithm runs 30 times with different random seeds. Fig. 4 presents the resulting objective function values obtained by the six algorithms over the 30 runs. As the weights in the objective function (12) are normalized, the objective function value represents the average index of drugs selected from the alternative sets. On the three instances in Hangzhou, the median objective function values of the WWO algorithm are 1.83, 2.71, and 0.39, respectively,

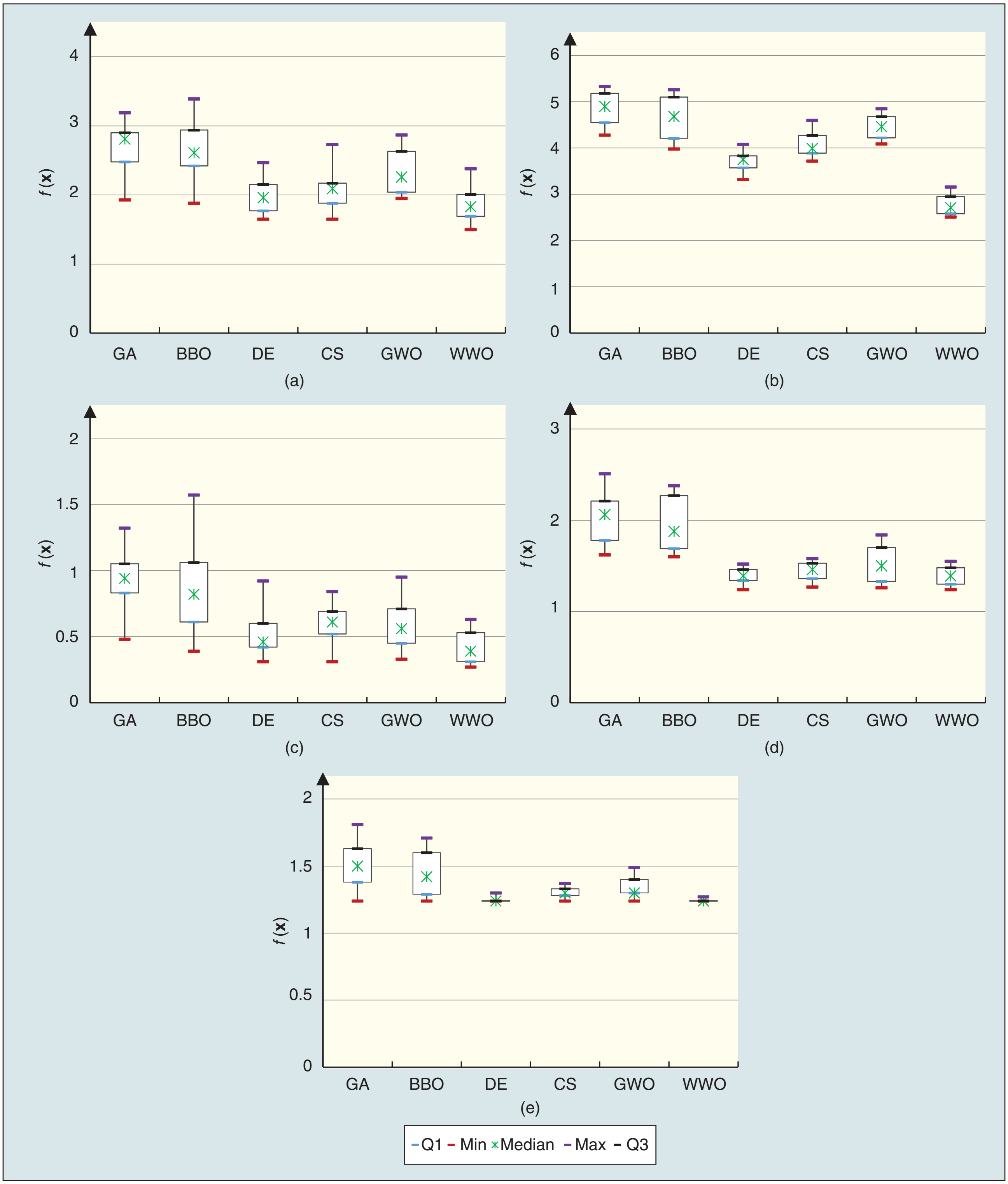

FIGURE 4 Comparison of the resulting objective function values obtained by the algorithms for prevention program optimization. Each box plot shows the maximum, minimum, median, first quartile (Q1), and third quartile (Q3) of objective function values over the 30 runs of an algorithm. (a) Hangzhou, 1st round. (b) Hangzhou, 2nd round. (c) Hangzhou, 3rd round. (d) Shaoxing, 1st round, and (e) Shaoxing, 2nd round.

TABLE 2 Age distribution, percentage with underlying diseases, and TCM constitution distribution of residents using diversified programs and residents using the unified program.

AGE		0–6	7–13	14–19	20–39	40–59	≥60	DISEASED		
HANGZHOU	DIVERSIFIED	10.88%	8.06%	7.83%	28.80%	33.82%	10.62%	5.27%		
	UNIFIED	11.03%	8.63%	8.01%	28.63%	32.60%	11.10%	6.30%		
SHAOXING	DIVERSIFIED	11.17%	7.50%	7.99%	26.89%	35.53%	10.92%	4.12%		
	UNIFIED	11.51%	7.64%	7.84%	25.79%	35.60%	11.60%	4.38%		
TCM CONSTITUTION		MILD	YANG DEFICIENCY	YIN DEFICIENCY	PHLEGM DAMPNESS	WET & HEAT	QI STAGNATION	QI DEFICIENCY	BLOOD STASIS	SPECIAL
HANGZHOU	DIVERSIFIED	35.26%	9.56%	5.17%	5.69%	10.59%	9.04%	11.35%	10.38%	6.88%
	UNIFIED	32.05%	9.88%	5.30%	5.98%	11.25%	8.86%	11.58%	10.66%	7.54%
SHAOXING	DIVERSIFIED	40.34%	9.21%	4.16%	5.13%	10.76%	8.07%	9.86%	10.19%	7.01%
	UNIFIED	39.53%	9.10%	4.48%	5.12%	11.28%	7.76%	9.34%	9.75%	7.28%

which are always the smallest among the six algorithms. These three instances have the same number N of programs and similar numbers of residents, but the constraints of the second-round instance is the most rigorous, while the constraints of the third-round instance is the least rigorous. The differences among the comparative algorithms are the largest on the second-round instance and the smallest on the third one. On the second-round instance, the performance advantages of WWO over the other algorithms are also the most significant. This demonstrates that the proposed WWO algorithm is efficient in solving complex instances of the problem.

On the two instances in Shaoxing, the median objective function values of WWO are 1.39 and 1.24, respectively, which are also the smallest among the six algorithms. In the second-round instance, the resources required by the basic prevention programs do not exceed the available resources too much; on this relatively simple instance, all algorithms achieve the same minimum objective function value of 1.24, which has been verified to be the exact optimal objective function value. However, only the median objective function values of DE and WWO are 1.24, and the maximum objective function value of WWO is less than that of DE. In summary, the results show that the proposed WWO algorithm exhibits the best performance on all instances.

C. Results of Prevention Program Implementation

We compare the actual prevention effects of the diversified TCM prevention programs developed using our method with those of the unified TCM prevention program released by Zhejiang Provincial Health Commission. We collect data of 36,138 residents from 71 communities in Hangzhou and 10,530 residents from 23 communities in Shaoxing who adopt the unified prevention program. Table II presents the distribution of basic characteristics in the residents using the different prevention policies. In either region, the two groups have similar age distribution, percentage with moderate and severe underlying diseases, and TCM constitution distribution (note that some particular people can have more than one TCM constitution). Therefore, the comparison of the effects of diversified and unified programs on the two different groups is justified, as a resident can take only one prevention program.

Table III presents the comparison results. In Hangzhou, during February and March, 2019, among 4,625 residents adopting diversified prevention programs, there is no reported case of COVID-19. During the same period, among 36,138 residents adopting the unified prevention program, there are six COVID-19 cases, including five imported cases and one local case. In Shaoxing, among 1,227 residents adopting our diversified prevention programs, there is also no reported case of COVID-19. During the same period, among 10,530 residents adopting the unified prevention program, there are two imported cases. According to the results in Table III, in terms of incidence rate, the effects of diversified TCM prevention programs are obviously better than those of the unified TCM prevention program in both regions.

Nevertheless, due to the low incidence rate of COVID-19 in China and the limited number of residents in this study, the comparison of incidence rates does not have sufficient statistical significance. Thus, we also conduct a questionnaire survey on the effects of prevention programs. There are two questions, the first is "TCM prevention program helps me improve health conditions," and the second is "TCM prevention program helps me

TABLE 3 Comparison of the effects of our diversified TCM prevention programs with those of the unified TCM prevention program.

		RESIDENTS	CASES	INCIDENCE RATE	LOCAL CASES	LOCAL INCIDENCE RATE
HANGZHOU	DIVERSIFIED	4,625	0	**0**	0	**0**
	UNIFIED	36,138	6	0.0166%	1	0.00277%
SHAOXING	DIVERSIFIED	1,227	0	**0**	0	**0**
	UNIFIED	10,530	2	0.0190%	0	0

prevent COVID-19." Each answer has seven choices: strongly agree, agree, weakly agree, neutral, weakly disagree, disagree, and strongly disagree.

There are a total of 7,358 residents, including 2,550 adopting diversified programs and 4,808 adopting the unified program, participating in the survey. Fig. 5 presents the survey results of the first question: among the participants adopting diversified programs, 73% give positive answers (18% strongly agree, 44% agree, and 11% weakly agree), which is significantly higher than the 59% among the participants adopting the unified program who give positive answers (16% strongly agree, 31% agree, and 12% weakly agree). Fig. 6 presents the results of the second question. Among the participants adopting diversified programs, 78% give positive answers (23% strongly agree, 41% agree, and 14% weakly agree), which is significantly higher than the 63% among the participants adopting the unified program who give positive answers (20% strongly agree, 29% agree, and 14% weakly agree). In summary, the survey results demonstrate that the residents adopting diversified programs are more satisfied with the effects of COVID-19 prevention and health condition improvement than those adopting the unified program.

V. Conclusion

In this study, we propose an intelligent optimization method to develop diversified TCM prevention programs for COVID-19. First, we use a fuzzy clustering method to divide the population based on combined modern medicine and TCM health characteristics. Based on the clustering results, TCM experts develop diversified prevention programs, which are then evolved by an interactive optimization method until all the resource constraints are satisfied. The method has been used for improving community prevention of COVID-19 in Zhejiang province, China, during the peak of the pandemic.

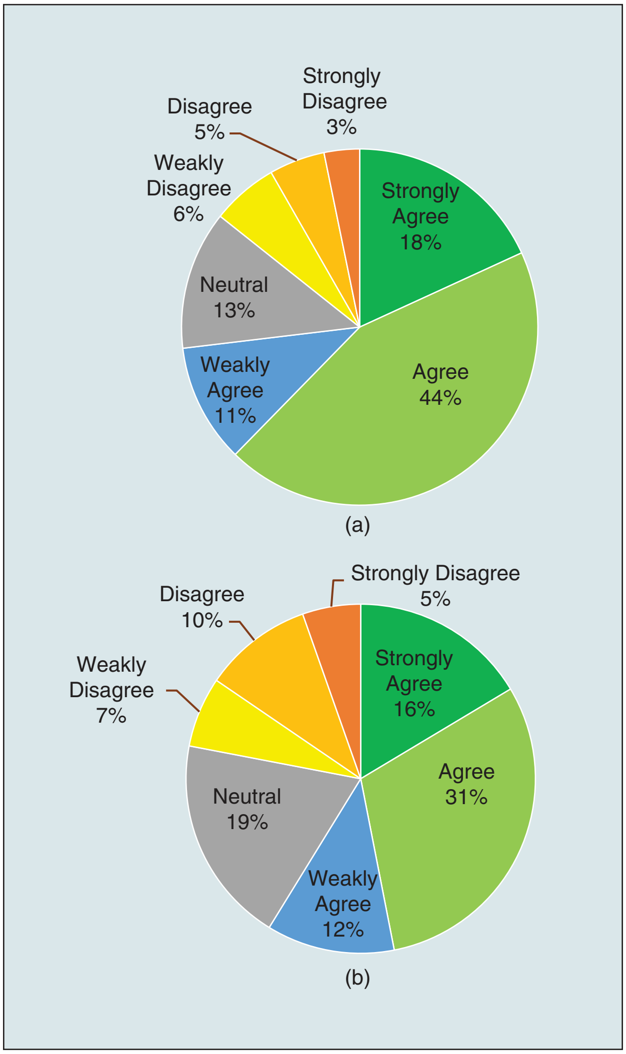

FIGURE 5 Distribution of different answers to the question "TCM prevention program helps to improve health conditions." (a) Participants adopting diversified prevention programs. (b) Participants adopting the unified prevention program.

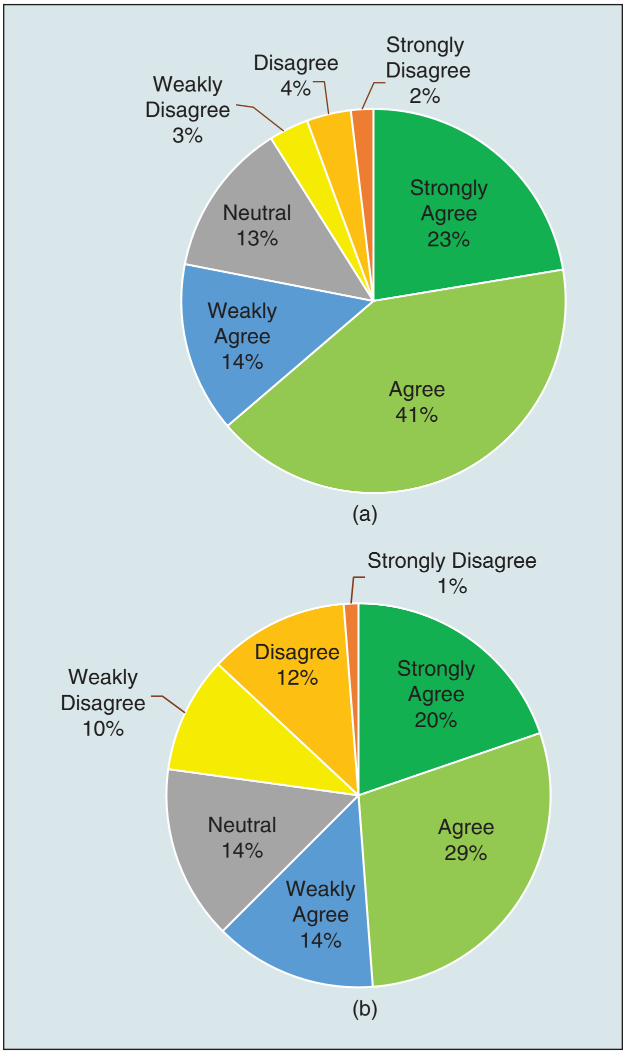

FIGURE 6 Distribution of different answers to the question "TCM prevention program helps to prevent COVID-19." (a) Participants adopting diversified prevention programs. (b) Participants adopting the unified prevention program.

The reported work is an emergency study aiming at COVID-19. We are continuously improving it in the following aspects: (1) using health big-data analytics to enhance the feature sets and incorporating multi-view learning to improve clustering; (2) incorporating more TCM knowledge to interactive optimization to reduce the efforts of TCM experts; (3) combining medical knowledge with machine learning to evaluate the effects of TCM prevention programs in a more accurate way. It is expected that the proposed method can be extended to the prevention and control of more epidemics in the future.

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