

# Statistical Analysis Plan (SAP)

**Project Name: POPMIX Cluster Randomized Controlled Trial**

**SAP Version: Version 1.5**

**Date: February 16, 2026**

## **Notes:**

The statistical analysis plan (SAP) applies to the Population Medicine Multimorbidity Intervention in Xishui (POPMIX) Project, which contains four trials that aim to evaluate a uniform integrated intervention package in four distinct populations in Xishui County, i.e., POPMIX-COPD for high-COPD-risk populations, POPMIX-Asthma for suspected asthma populations, POPMIX-Smoking for high-COPD-risk populations who smoke, and POPMIX-MH for high-COPD-risk populations with mental health symptoms.

The protocol papers of the POPMIX Projects have been submitted to *JMIR Research Protocols* (for POPMIX-COPD and POPMIX-MH), *BMJ Open* (for POPMIX-Smoking), and *Trials* (for POPMIX-Asthma). Clinical trial registrations were finished in June 2024, and registrations for POPMIX Projects include:

- POPMIX-COPD: NCT06456996;
- POPMIX-Asthma: NCT06457009;
- POPMIX-Smoking: NCT06458205;
- POPMIX-MH: NCT06458218.

## **Signatures (Hidden according to ClinicalTrials' regulation)**

\*Note: The above investigators are core investigators of the trial and are signed on behalf of the POPMIX study collaboration group.

## Table of contents

1. Introduction.....	5
2. Study Design & Populations.....	6
2.1 Study Overview, Randomization, and Blinding .....	6
2.2 Sample Size Justification .....	6
2.3 Definition of Analysis Populations .....	7
3. Data Handling & Conventions.....	9
3.1 Participants Disposition .....	9
3.2 Missing Data Handling .....	9
4. Detailed Statistical Analysis Methods .....	10
4.1 Screening Analysis.....	10
4.2 Baseline Data Analysis .....	11
4.3 RCT Efficacy Analysis.....	12
4.4 COPD Care Cascade Analysis .....	33
4.5 Regression Discontinuity Design (RDD).....	34
4.6 Instrumental Variable (IV) Analysis .....	36
4.7 Heckman Selection Model Analysis .....	37
4.8 Costing Study.....	37
4.9 Cost-Effectiveness Analysis.....	38
5. Data Management .....	40
5.1 Data Collection .....	40
5.2 Data Storage.....	40
5.3 Study Record Retention .....	40
6. Administrative Aspects .....	41
6.1 Confidentiality .....	41
6.2 Modifications of the Protocol .....	41
6.3 Participant Reimbursement.....	41
6.4 Financial Disclosure and Conflicts of Interest.....	41
7. Use of Data and Publications Policy.....	42

## **List of Abbreviations**

ACT: Asthma Control Test

BMI: Body Mass Index

CONSORT: Consolidated Standards of Reporting Trials

COPD: Chronic Obstructive Pulmonary Disease

COPD-SQ: COPD Screening Questionnaire

cRCT: Cluster Randomized Controlled Trial

CT: Computed Tomography

DSMB: Data and Safety Monitoring Board

ECRHS: European Community Respiratory Health Survey

FEV1: Forced Expiratory Volume in 1 Second

FEV1/FVC: Forced Expiratory Volume in 1 Second to Forced Vital Capacity Ratio

FVC: Forced Vital Capacity

GAD-7: Generalized Anxiety Disorder-7

GLMM: Generalized Linear Mixed Model

ICC: Intraclass Correlation Coefficient

IK: Imbens–Kalyanaraman

ITT: Intent-to-Treat

LATE: Local Average Treatment Effect

LOCF: Last Observation Carried Forward

MAR: Missing at Random

MDD: Minimum Detectable Difference

MI: Multiple Imputation

PHQ-9: Patient Health Questionnaire-9

POPMIX: Population Medicine Multimorbidity Intervention in Xishui County

PP: Per Protocol

QR: Quick Response

RCT: Randomized Controlled Trial

RDD: Regression Discontinuity Design

RR: Relative Risk

2SLS: Two-Stage Least Squares

ICER: Incremental Cost-Effectiveness Ratio

IV: Instrumental Variable

QALY: Quality-Adjusted Life-Year

SAP: Statistical Analysis Plan

WEMWBS: Warwick-Edinburgh Mental Well-being Scale

## **1. Introduction**

This Statistical Analysis Plan (SAP) prespecifies the statistical principles and analytical methods for the Population Medicine Multimorbidity Intervention in Xishui County (POPMIX), a population-based, two-arm, stratified cluster randomized controlled trial conducted in Xishui County, Guizhou Province, China. POPMIX adopts a master trial design comprising four parallel sub-trials: POPMIX-COPD<sup>1</sup>, POPMIX-Asthma, POPMIX-MH<sup>2</sup>, and POPMIX-Smoking.

This SAP is intended to provide a predefined and transparent framework for the analysis of the POPMIX study. It covers the planned analyses of screening data, baseline characteristics, randomized efficacy outcomes, regression discontinuity analyses of selected intervention components, and COPD care cascade analyses. The SAP also defines the main analysis populations, general statistical principles, and approaches for handling missing data and multiplicity.

This SAP was prepared in accordance with the study protocols and will serve as the principal document guiding the statistical analysis of the trial. Unless otherwise specified, primary analyses will follow the intention-to-treat principle and account for the clustered trial design and repeated measurements where applicable. Any deviations from this SAP, as well as any additional analyses not prospectively specified herein, will be clearly identified as post hoc in the final study report.

## **2. Study Design & Populations**

### **2.1 Study Overview, Randomization, and Blinding**

POPMIX is a population-based master trial comprising four parallel sub-trials and conducted within a parallel, two-arm, stratified cluster randomized controlled trial (cRCT) platform in Xishui County, Guizhou Province, China. The 26 townships in Xishui County serve as clusters and were stratified by population size (above or below the county average). Within each stratum, townships were randomly allocated in a 1:1 ratio to the intervention or control arm using a computer-generated randomization sequence generated by an independent statistician.

Given the nature of the intervention, the trial is open-label for participants, healthcare providers, and field workers. However, participants are not explicitly instructed as participants in the intervention group – they receive the informed consent to what they should do and the benefits and rights they have in this trial. We blind the principal investigators, trial methodologist, and all core investigators that are responsible for the study design after implementation, and data analysts/statisticians remain blinded during analysis. Steering Committee and Data Safety and Monitoring Board members are not informed of the exact intervention assignment of each township before database lock.

### **2.2 Sample Size Justification**

The POPMIX project adopts a master trial design comprising four parallel sub-trials: POPMIX-COPD, POPMIX-Asthma, POPMIX-MH, and POPMIX-Smoking. Accordingly, sample size justification was conducted separately for each sub-trial rather than based on a single common endpoint for the overall trial. Each sub-trial was powered according to its own primary endpoint structure and protocol-specified assumptions.

For the POPMIX-COPD sub-trial, the sample size calculation was based on FEV1 as

one of the primary endpoints. Under the protocol-specified assumptions, the minimum required sample size was estimated to be 2,850 high-COPD-risk participants.

For the POPMIX-Asthma sub-trial, the sample size calculation was based on the Asthma Control Test (ACT) score as one of the co-primary endpoints. Under the protocol-specified assumptions, the minimum required sample size was estimated to be 3,988 suspected asthma participants.

For the POPMIX-MH sub-trial, the sample size calculation was based on the Warwick-Edinburgh Mental Well-Being Scale (WEMWBS) as the primary well-being endpoint. Under the protocol-specified assumptions, the minimum required sample size was estimated to be 2,610 high-COPD-risk participants with multimorbid mental health symptoms.

For the POPMIX-Smoking sub-trial, the sample size calculation was based on amount of smoking, defined as the average number of cigarettes smoked per day. Under the protocol-specified assumptions, the minimum required sample size was estimated to be 4,176 high-risk participants.

Therefore, in this SAP, sample size justification will be interpreted as sub-trial-specific, reflecting the different primary endpoints and target populations across the four embedded randomized comparisons, rather than as a single overall sample size for the entire POPMIX master trial.

### **2.3 Definition of Analysis Populations**

The following analysis populations will be defined for the POPMIX master trial and applied, where relevant, across the four parallel sub-trials.

Intent-to-Treat (ITT) Set: The ITT set will include all eligible participants enrolled in randomized clusters and analyzed according to the treatment assignment of their

cluster, regardless of the level of intervention exposure, adherence, or protocol deviations. Unless otherwise specified, analyses of primary and secondary endpoints will be based on the ITT population.

**Per-Protocol (PP) Set:** The PP set will include participants in the ITT population who had no major protocol deviations, completed the baseline assessment and the relevant primary endpoint assessment, and met the prespecified minimum exposure to key intervention components, where applicable. The PP set will be used primarily for sensitivity analyses of the primary outcomes.



### **3. Data Handling & Conventions**

#### **3.1 Participants Disposition**

The number of participants at each stage of the study will be summarized, including the numbers screened, eligible, enrolled, allocated, followed up, and included in each analysis population, together with reasons for exclusion, withdrawal, and loss to follow-up. Participant disposition will be presented overall and, where relevant, separately for each of the four sub-trials. A CONSORT flow diagram will be used to summarize participant flow through the study.

#### **3.2 Missing Data Handling**

Missing Dates: For partially recorded dates, imputation rules will be applied only when necessary for the derivation of analysis variables. If only the year and month are available, the date may be imputed using a prespecified rule. The specific imputation approach will be documented and applied consistently.

Missing Data: For the primary efficacy analyses, missing outcome data will be handled under the Missing at Random (MAR) assumption using the prespecified regression models, where appropriate. Multiple imputation (MI) will be used as a sensitivity analysis to assess the robustness of the primary findings. Additional sensitivity analyses using alternative assumptions or simpler imputation methods, such as Last Observation Carried Forward (LOCF), may be conducted if considered necessary and will be clearly identified as supplementary.

## 4. Detailed Statistical Analysis Methods

All quantitative analyses will be conducted using Stata (version 17 or above) and/or R (version 4.2 or above). Unless otherwise specified, all statistical tests will be two-sided, with a significance level of 0.05. Where relevant, effect estimates will be reported with 95% confidence intervals (CIs). For analyses based on the representative screening population, weighted estimates will be reported where applicable, with unweighted sample sizes presented for reference.

### 4.1 Screening Analysis

This section describes the distribution of COPD- and asthma-related screening results in the representative general population aged 35 years and above in Xishui County who completed the initial QR code-based screening.

- Endpoints

Screen-positive rate for high risk of COPD (COPD-SQ score  $\geq 16$ ).

Screen-positive rate for suspected asthma (based on the ECRHS questionnaire).

- Statistical Methods

- (1) Characteristics & Stratified Analysis: In addition to summarizing the overall demographic characteristics, the prevalence of high-risk individuals (COPD-SQ  $\geq 16$  and ECRHS results) will be stratified by age group and gender to examine whether specific demographic populations exhibit significantly higher risk levels.
- (2) Questionnaire Correlation Analysis: Given the concurrent availability of COPD-SQ and ECRHS data, the overlap between the population identified as high-risk by the COPD screening tool and those identified by the asthma screening tool will be evaluated (e.g., using Venn diagrams) to explore their correlation.
- (3) Township-level Difference Analysis: The differences in high-risk prevalence across the 26 townships will be compared to identify potential geographic clustering or outliers, even in the absence of altitude data.
- (4) Symptom Distribution Analysis: A descriptive analysis will be conducted to

identify which specific questions/symptoms in the COPD-SQ questionnaire most frequently contribute to high scores within the study population.

## **4.2 Baseline Data Analysis**

This module focuses exclusively on the enrolled cohort (i.e., individuals identified as high-risk for COPD or with suspected asthma from the initial screening). The primary goal is to describe the baseline characteristics of this specific cohort and to test the baseline balance between the intervention and control groups following cluster randomization.

- **Endpoints**

Baseline demographics, clinical parameters (e.g., FEV1, BMI, blood pressure), comorbidity status (e.g., diabetes, hypertension), and questionnaire scores (PHQ-9, GAD-7, WEMWBS).

- **Statistical Methods**

Continuous variables will be summarized as mean  $\pm$  standard deviation or median with interquartile range based on their distribution. To account for the cluster randomization effect, baseline continuous variables between the intervention and control groups will be compared using mixed-effects linear regression (with township as a random effect) or adjusted t-tests/Wilcoxon rank-sum tests. Categorical variables will be summarized as frequencies and percentages, compared via mixed-effects logistic regression or Pearson's  $\chi^2$  /Fisher's exact tests.

- **Additional Analyses**

- (1) **Descriptive and Regression Analyses among Subgroups:** Additional descriptive and regression analyses will be conducted for key subgroups, including participants at high risk of COPD and those diagnosed with COPD at baseline.
- (2) **Clustering Analyses:** Multimorbidity and patient characteristic patterns will be explored using unsupervised clustering methods, such as hierarchical clustering or k-means clustering, to identify distinct subgroups within the high-COPD-risk population. Variables considered may include demographic features, COPD

related indicators, physiological measurements, multimorbidities, and health risk behaviours. Cluster membership will be examined in relation to intervention allocation and baseline outcomes, providing a framework to characterize heterogeneity within the population and to inform subsequent subgroup or exploratory analyses.

- (3) Clustering Analyses interacted with cascade analyses: COPD, hypertension, diabetes cascade among identified clusters to evaluate how different diseases clusters interact with health system indicators.

### 4.3 RCT Efficacy Analysis

The POPMIX project employs a Master Trial design comprising four parallel sub-trials targeting specific high-risk cohorts. Based on the Intent-to-Treat (ITT) principle, Generalized Linear Mixed Models (GLMMs) will be used to evaluate the 12-month efficacy for each sub-trial. The models will include "subject" as a random effect for repeated measures and "township" as a random intercept to control for the intraclass correlation coefficient (ICC). Fixed effects include Intervention group identifiers, Time identifiers, Intervention and Time identifiers interaction term, and randomization stratification factors. To account for multiple testing within each sub-trial, a Bonferroni adjustment will be applied according to the number of primary endpoints, setting the significance threshold at  $p < 0.0167$  (for sub-trials with 3 endpoints) or  $p < 0.025$  (for sub-trials with 2 endpoints).

#### 4.3.1 POPMIX-COPD

Primary outcomes	
<b>Number of chronic conditions controlled</b>	<p>Definition: The number of conditions controlled among seven objectively measured chronic health conditions (COPD, asthma, depression symptoms, anxiety symptoms, BMI, hypertension, and type 2 diabetes)</p> <p>Functional form: Counting data</p> <p>Measurement: Through objective physical examination or a validated scale</p>
<b>COPD screening</b>	<p>Definition: Response to the question "Have you ever had a pulmonary function test?"</p>

<b>FEV<sub>1</sub> measurement</b>	Functional form: Binary
	Measurement: Self-reported response
	Definition: Forced Expiratory Volume in one second
	Functional form: Continuous
	Measurement: Pulmonary function test, portable spirometry
<b>Secondary outcomes</b>	
<b>Quality of life indicators</b>	
<b>Self-rated health status</b>	Definition: General self-assessed health status
	Functional form: Continuous
	Measurement: EQ-5D scale, ranging from 0 to 1 continuously; 0 represents death, and 1 represents perfect health <sup>3</sup>
<b>SGRQ score (for COPD patients only)</b>	Definition: Saint George Respiratory Questionnaire (SGRQ) questionnaire for COPD patients
	Functional form: Continuous
	Measurement: SGRQ score, ranging from 0 to 100, where 0 represents the best possible health status and 100 represents the worst possible health status <sup>4,5</sup>
<b>COPD symptoms</b>	
<b>CAT score (for COPD patients only)</b>	Definition: COPD Assessment Test (CAT) score for COPD patients
	Functional form: Continuous
	Measurement: CAT <sup>6</sup> is a questionnaire for people with COPD. It is designed to measure the impact of COPD on a person's life and how these changes over time; scores range from 0 to 40, with higher scores representing worse COPD conditions
<b>mMRC score</b>	Definition: Modified Medical Research Council (mMRC) questionnaire
	Functional form: Categorical
	Measurement: The mMRC results in a categorical value, with level 0 representing a good respiratory condition and the maximum level 4 representing a very bad respiratory condition
<b>Asthma diagnosis and management</b>	
<b>Asthma diagnosis</b>	Definition: Response to the question "Have you ever been diagnosed as an asthma patient by a professional physician?"
	Functional form: Binary
	Measurement: Self-reported response
<b>ACT score (for asthma patients only)</b>	Definition: Asthma Control Test (ACT) <sup>7</sup> score for asthma patients
	Functional form: Continuous
	Measurement: ACT score, which ranges from 0 to 25 with lower scores representing better controlled asthma
<b>Knowledge of COPD and Asthma</b>	
<b>COPD knowledge</b>	Definition: Responses to excerpted questions of the COPD Knowledge Questionnaire; selected questions ask about information the general population should know about COPD
	Functional form: Continuous

<b>Asthma knowledge</b>	Measurement: Self-reported responses to questions; scores range from 0 to 7 with higher scores indicating a greater number of correct statements chosen by the respondent <sup>8</sup>
	Definition: Responses to excerpted questions of the Patient-completed Asthma Knowledge Questionnaire (PAKQ); selected questions ask about information the general population should know about asthma
	Functional form: Continuous
	Measurement: Self-reported responses to questions; scores range from 0 to 7 with higher scores indicating a greater number of correct statements chosen by the respondent <sup>9</sup>

#### **COPD care cascade indicators**

<b>Self-awareness of COPD</b>	Definition: Response to the question “Have you ever been diagnosed with COPD?” Functional form: Binary Measurement: Self-reported response
<b>COPD treatment adherence</b>	Definition: Whether an individual diagnosed with COPD is currently following a treatment plan prescribed by a doctor or other healthcare professional Functional form: Binary Measurement: Self-reported response
<b>COPD control</b>	Definition: Response to the question “Has the number of acute exacerbations decreased in the past six months?” Functional form: Binary Measurement: Self-reported response

#### **Physical health indicators**

<b>Blood pressure</b>	Definition: Systolic and diastolic blood pressure (mmHg) Functional form: Continuous Measurement: Omron portable automatic blood pressure monitor
<b>Blood glucose</b>	Definition: Reference standard for average plasma glucose concentration over a period of time, typically reflecting the preceding 8–12 hours for fasting blood glucose and the immediate glycemic status for random blood glucose Functional form: Continuous Measurement: Blood glucose meter
<b>Waist circumference</b>	Definition: Waist circumference (cm) Functional form: Continuous Measurement: Soft measuring tape
<b>BMI</b>	Definition: Body mass index (BMI): weight divided by height squared (kg/m <sup>2</sup> ) Functional form: Continuous Measurement: Height and weight were measured using an automated body composition analyzer
<b>Smoking dependence</b>	Definition: A scale that measures the degree of smoking dependence

Functional form: Continuous

Measurement: Score on the Chinese version of the Fagerström Test for Nicotine Dependence (FTND),<sup>10,11</sup> which ranges from 0 to 15 with higher scores representing more severe nicotine dependence; additionally measured by score on the Heaviness of Smoking Index (HSI),<sup>12</sup> which ranges from 0 to 6 with higher scores representing worse nicotine dependence

#### **Mental health indicators**

<b>Depression symptoms</b>	<p>Definition: Emotional disorders, including sadness, loss, and anger</p> <p>Functional form: Continuous</p> <p>Measurement: Score on Patient Health Questionnaire-9 items (PHQ-9),<sup>13</sup> which ranges from 0 to 27 with higher scores representing more severe depression symptoms</p>
<b>Anxiety symptoms</b>	<p>Definition: Unpleasant state of inner turmoil</p> <p>Functional form: Continuous</p> <p>Measurement: Score on General Anxiety Disorder-7 (GAD-7),<sup>14</sup> which ranges from 0 to 21 with higher scores representing more severe anxiety symptoms</p>
<b>Warwick-Edinburgh Mental Well-being Scale (WEMWBS)</b>	<p>Definition: Score reflecting overall mental health state</p> <p>Functional form: Continuous</p> <p>Measurement: Score on the Warwick Edinburgh Mental Well-being Scale,<sup>15</sup> which ranges from 14 to 70 with lower scores representing worse general mental health</p>

#### **Care cascade indicators for hypertension and type 2 diabetes mellitus**

<b>High blood pressure (HBP) screening</b>	<p>Definition: Response to the question “Have you ever had your blood pressure measured by a doctor, nurse, or other healthcare professional?”</p> <p>Functional form: Binary</p> <p>Measurement: Self-reported response</p>
<b>HBP diagnosis</b>	<p>Definition: Response to the question “Have you ever been diagnosed with hypertension by a doctor?”</p> <p>Functional form: Binary</p> <p>Measurement: Self-reported response</p>
<b>HBP treatment</b>	<p>Definition: Response to the question “Are you currently taking any antihypertensive medication prescribed by a doctor or other healthcare professional?”</p> <p>Functional form: Binary</p> <p>Measurement: Self-reported response</p>
<b>HBP control</b>	<p>Definition: Blood pressure within the normal range at the end-of-year follow-up</p> <p>Functional form: Binary</p> <p>Measurement: Blood pressure measurement</p>
<b>Type 2 diabetes mellitus (T2DM)</b>	<p>Definition: Response to the question “Have you ever had your blood glucose measured by a doctor, nurse, or other healthcare</p>

<b>screening</b>	professional?” Functional form: Binary Measurement: Self-reported response
<b>T2DM diagnosis</b>	Definition: Response to the question “Have you ever been diagnosed with T2DM by a doctor?” Functional form: Binary Measurement: Self-reported response
<b>T2DM treatment</b>	Definition: Response to the question “Are you currently receiving a type 2 diabetes treatment plan prescribed by a doctor or other healthcare professional?” Functional form: Binary Measurement: Self-reported response
<b>T2DM control</b>	Definition: Blood glucose within the normal range at the end-of-year follow-up Functional form: Binary Measurement: Blood glucose measurement
<b>Health risk behaviors</b>	
<b>Smoking status</b>	Definition: Response to the question “Do you currently smoke?” Functional form: Binary Measurement: Self-reported response
<b>Physical proof of cigarettes</b>	Definition: Response to the question “Can you show me your cigarettes?” Functional form: Binary Measurement: Self-reported response and visible proof of cigarette possession to study field workers
<b>Amount of smoking</b>	Definition: Average number of cigarettes smoked per day Functional form: Continuous Measurement: Self-reported response
<b>Drinking status</b>	Definition: Frequency of alcohol consumption over the past three months Functional form: Categorical Measurement: Self-reported response; the possible response options are: 0 = Never drink alcohol 1 = Once per month 2 = 2–3 times per month 3 = Once per week 4 = 2–3 times per week 5 = 4–6 times per week 6 = Once per day 7 = Twice per day 8 = More than twice per day 9 = Other, please specify
<b>Sugar consumption</b>	Definition: Frequency of consumption of sugary foods/drinks



	Functional form: Categorical
	Measurement: Self-reported response; the possible response options are:
	1 = almost every day/daily (6-7 days)
	2 = often (4-5 days)
	3 = sometimes (2-3 days)
	4 = rarely or never (0-1 day)
<b>Salted vegetables consumption</b>	Definition: Frequency of consumption of salted vegetables
	Functional form: Categorical
	Measurement: Self-reported response; the possible response options are:
	1 = almost every day/daily (6-7 days)
	2 = often (4-5 days)
	3 = sometimes (2-3 days)
	4 = rarely or never (0-1 day)
<b>Vegetable consumption</b>	Definition: Frequency of consumption of vegetables
	Functional form: Categorical
	Measurement: Self-reported response; the possible response options are:
	1 = almost every day/daily (6-7 days)
	2 = often (4-5 days)
	3 = sometimes (2-3 days)
	4 = rarely or never (0-1 day)
<b>Physical exercise</b>	Definition: Hours of physical exercise per week
	Functional form: Count
	Measurement: Self-reported response; the possible response options are:
	1 = almost every day/daily (6-7 days)
	2 = often (4-5 days)
	3 = sometimes (2-3 days)
	4 = rarely or never (0-1 day)
<b>Healthcare utilization indicators</b>	
<b>Number of outpatient visits</b>	Definition: Number of outpatient visits and type of hospital visited within the past year
	Functional form: Count
	Measurement: Survey data
<b>Number of inpatient visits</b>	Definition: Number of inpatient visits and type of hospital visited within the past year
	Functional form: Count
	Measurement: Survey data
<b>Medical expenditure within a family over the past year</b>	Definition: Healthcare-related expenditures
	Functional form: Continuous
	Measurement: Insurance/outpatient/inpatient data
<b>Socioeconomic profile indicators</b>	

<b>Productivity loss</b>	<p>Definition: Productivity loss due to illness or health problems</p> <p>Functional form: Continuous</p> <p>Measurement: Score on the simplified Chinese version of the Work Productivity and Activity Impairment-General Health (WPAI-GH) (v2.0) questionnaire, with higher scores representing greater impairment and less productivity<sup>16</sup></p>
<b>Employment status</b>	<p>Definition: Main occupation and type of employment</p> <p>Functional form: Categorical</p> <p>Measurement: Self-reported response</p>
<b>Family level of annual consumption expenditure</b>	<p>Definition: Annual total household expenditure</p> <p>Functional form: Continuous</p> <p>Measurement: Self-reported responses to a series of questions covering local expenditure categories by the household representative</p>

#### 4.3.2 POPMIX-Asthma

<b>Primary outcomes</b>	
<b>Number of chronic conditions controlled</b>	<p>Definition: The number of conditions controlled among seven objectively measured chronic health conditions (COPD, asthma, depression symptoms, anxiety symptoms, BMI, hypertension, and type 2 diabetes)</p> <p>Functional form: Counting data</p> <p>Measurement: Through objective physical examination or a validated scale</p>
<b>Lung function testing</b>	<p>Definition: Response to the question “Have you ever had a pulmonary function test?”</p> <p>Functional form: Binary</p> <p>Measurement: Self-reported response</p>
<b>ACT score</b>	<p>Definition: Asthma Control Test (ACT) score</p> <p>Functional form: Continuous</p> <p>Measurement: ACT score, ranging from 0 to 25 with lower scores representing better controlled asthma<sup>7</sup></p>
<b>Secondary outcomes</b>	
<b>Quality of life indicators</b>	
<b>Self-rated health status</b>	<p>Definition: General self-assessed health status</p> <p>Functional form: Continuous</p> <p>Measurement: EQ-5D scale, ranging from 0 to 1 continuously; 0 represents death, and 1 represents perfect health<sup>3</sup></p>
<b>Respiratory symptoms</b>	
<b>mMRC score</b>	<p>Definition: mMRC questionnaire</p> <p>Functional form: Categorical</p> <p>Measurement: Modified Medical Research Council, categorical value, level 0 represents a good respiratory condition, while the</p>

maximum level 4 represents a very bad respiratory condition.

<b>Asthma care cascade indicators</b>	
<b>Asthma screening</b>	<p>Definition: Response to the question “Have you ever been screened for bronchial asthma by a doctor?”</p> <p>Variable type: Binary</p> <p>Measurement: Self-reported response</p>
<b>Asthma diagnosis</b>	<p>Definition: Response to the question “Have you ever diagnosed as asthma patient by professional physician?”</p> <p>Functional form: Binary</p> <p>Measurement: Self-reported response</p>
<b>Asthma treatment</b>	<p>Definition: Response to the question “Have you followed the treatment therapy from the professional physicians for asthma?”</p> <p>Variable type: Binary</p> <p>Measurement: Self-reported response</p>
<b>Asthma control</b>	<p>Definition: Asthma Control Test (ACT) score <math>\geq 20</math>, corresponding to “controlled” asthma</p> <p>Variable Type: Binary</p> <p>Measurement: ACT score ranges from 5 to 25, with higher scores representing better asthma control</p>
<b>Knowledge of asthma</b>	
<b>Asthma knowledge</b>	<p>Definition: Responses to excerpted questions of the Patient-completed Asthma Knowledge Questionnaire (PAKQ); selected questions ask about information the general population should know about asthma</p> <p>Functional form: Continuous</p> <p>Measurement: Self-reported responses to questions; scores range from 0 to 7 with higher scores indicating a greater number of correct statements chosen by the respondent</p>
<b>Knowledge and awareness of COPD</b>	
<b>Self-awareness of COPD</b>	<p>Definition: Response to the question “Have you ever been diagnosed with COPD?”</p> <p>Functional form: Binary</p> <p>Measurement: Self-reported response</p>
<b>COPD knowledge</b>	<p>Definition: Responses to excerpted questions of the COPD Knowledge Questionnaire; selected questions ask about information the general population should know about COPD</p> <p>Functional form: Continuous</p> <p>Measurement: Self-reported responses to questions; scores range from 0 to 7 with higher scores indicating a greater number of correct statements chosen by the respondent</p>
<b>Physical health indicators</b>	
<b>FEV<sub>1</sub> measurement</b>	<p>Definition: Forced Expiratory Volume in one second</p> <p>Functional form: Continuous</p> <p>Measurement: Pulmonary function test, portable spirometry</p>

<b>Blood pressure</b>	<p>Definition: Systolic and diastolic blood pressure (mmHg)</p> <p>Functional form: Continuous</p> <p>Measurement: Omron portable automatic blood pressure monitor</p>
<b>Blood glucose</b>	<p>Definition: Reference standard for average plasma glucose concentration over a period of time, typically reflecting the preceding 8–12 hours for fasting blood glucose and the immediate glycemic status for random blood glucose</p> <p>Functional form: Continuous</p> <p>Measurement: Blood glucose meter</p>
<b>Waist circumference</b>	<p>Definition: Waist circumference (cm)</p> <p>Functional form: Continuous</p> <p>Measurement: Soft measuring tape</p>
<b>BMI</b>	<p>Definition: Body mass index (BMI): weight divided by height squared (<math>\text{kg/m}^2</math>)</p> <p>Functional form: Continuous</p> <p>Measurement: Height and weight were measured using an automated body composition analyzer</p>
<b>Smoking dependence</b>	<p>Definition: A scale that measures the degree of smoking dependence</p> <p>Functional form: Continuous</p> <p>Measurement: Score on the Chinese version of the Fagerström Test for Nicotine Dependence (FTND),<sup>10,11</sup> which ranges from 0 to 15 with higher scores representing more severe nicotine dependence; additionally measured by score on the Heaviness of Smoking Index (HSI),<sup>12</sup> which ranges from 0 to 6 with higher scores representing worse nicotine dependence</p>
<b>Mental health indicators</b>	
<b>Depression symptoms</b>	<p>Definition: Emotional disorders, including sadness, loss, and anger</p> <p>Functional form: Continuous</p> <p>Measurement: Score on Patient Health Questionnaire-9 items (PHQ-9),<sup>13</sup> which ranges from 0 to 27 with higher scores representing more severe depression symptoms<sup>13</sup></p>
<b>Anxiety symptoms</b>	<p>Definition: Unpleasant state of inner turmoil</p> <p>Functional form: Continuous</p> <p>Measurement: Score on General Anxiety Disorder-7 (GAD-7),<sup>14</sup> which ranges from 0 to 21 with higher scores representing more severe anxiety symptoms<sup>14</sup></p>
<b>Warwick-Edinburgh Mental Well-being Scale (WEMWBS)</b>	<p>Definition: Score reflecting overall mental health state</p> <p>Functional form: Continuous</p> <p>Measurement: Score on the Warwick Edinburgh Mental Well-being Scale, which ranges from 14 to 70 with lower scores representing worse general mental health<sup>15</sup></p>
<b>Care cascade indicators for hypertension and type 2 diabetes mellitus</b>	
<b>High blood pressure</b>	<p>Definition: Response to the question “Have you ever had your</p>

<b>(HBP) screening</b>	blood pressure measured by a doctor, nurse, or other healthcare professional?" Functional form: Binary Measurement: Self-reported response
<b>HBP diagnosis</b>	Definition: Response to the question "Have you ever been diagnosed with hypertension by a doctor?" Functional form: Binary Measurement: Self-reported response
<b>HBP treatment</b>	Definition: Response to the question "Are you currently taking any antihypertensive medication prescribed by a doctor or other healthcare professional?" Functional form: Binary Measurement: Self-reported response
<b>HBP control</b>	Definition: Blood pressure within the normal range at the end-of-year follow-up Functional form: Binary Measurement: Blood pressure measurement
<b>Type 2 diabetes mellitus (T2DM) screening</b>	Definition: Response to the question "Have you ever had your blood glucose measured by a doctor, nurse, or other healthcare professional?" Functional form: Binary Measurement: Self-reported response
<b>T2DM diagnosis</b>	Definition: Response to the question "Have you ever been diagnosed with T2DM by a doctor?" Functional form: Binary Measurement: Self-reported response
<b>T2DM treatment</b>	Definition: Response to the question "Are you currently receiving a type 2 diabetes treatment plan prescribed by a doctor or other healthcare professional?" Functional form: Binary Measurement: Self-reported response
<b>T2DM control</b>	Definition: Blood glucose within the normal range at the end-of-year follow-up Functional form: Binary Measurement: Blood glucose measurement
<b>Health risk behaviors</b>	
<b>Smoking status</b>	Definition: Response to the question "Do you currently smoke?" Functional form: Binary Measurement: Self-reported response
<b>Amount of smoking</b>	Definition: Average number of cigarettes smoked per day Functional form: Continuous Measurement: Self-reported response
<b>Drinking status</b>	Definition: Frequency of alcohol consumption over the past three months

	Functional form: Categorical
	Measurement: Self-reported response; the possible response options are:
	0 = Never drink alcohol
	1 = Once per month
	2 = 2–3 times per month
	3 = Once per week
	4 = 2–3 times per week
	5 = 4–6 times per week
	6 = Once per day
	7 = Twice per day
	8 = More than twice per day
	9 = Other, please specify
<b>Sugar consumption</b>	Definition: Frequency of consumption of sugary foods/drinks
	Functional form: Categorical
	Measurement: Self-reported response; the possible response options are:
	1 = almost every day/daily (6-7 days)
	2 = often (4-5 days)
	3 = sometimes (2-3 days)
	4 = rarely or never (0-1 day)
<b>Salted vegetables consumption</b>	Definition: Frequency of consumption of salted vegetables
	Functional form: Categorical
	Measurement: Self-reported response; the possible response options are:
	1 = almost every day/daily (6-7 days)
	2 = often (4-5 days)
	3 = sometimes (2-3 days)
	4 = rarely or never (0-1 day)
<b>Vegetable consumption</b>	Definition: Frequency of consumption of vegetables
	Functional form: Categorical
	Measurement: Self-reported response; the possible response options are:
	1 = almost every day/daily (6-7 days)
	2 = often (4-5 days)
	3 = sometimes (2-3 days)
	4 = rarely or never (0-1 day)
<b>Physical exercise</b>	Definition: Hours of physical exercise per week
	Functional form: Count
	Measurement: Self-reported response; the possible response options are:
	0 = No related physical activity
	1 = Vigorous physical activity (e.g., lifting heavy objects, aerobic exercise, fast cycling)

2 = Moderate physical activity (e.g., lifting light objects, cycling at normal speed, playing doubles tennis; excluding walking)

3 = Light physical activity (e.g., walking)

<b>Healthcare utilization indicators</b>	
<b>Number of outpatient visits</b>	Definition: Number of outpatient visits and type of hospital visited within the past year Functional form: Count Measurement: Survey data
<b>Number of inpatient visits</b>	Definition: Number of inpatient visits and type of hospital visited within the past year Functional form: Count Measurement: Survey data
<b>Medical expenditure within a family over the past year</b>	Definition: Healthcare-related expenditures Functional form: Continuous Measurement: Survey/insurance/outpatient/inpatient data
<b>Socioeconomic profile indicators</b>	
<b>Productivity loss</b>	Definition: Productivity loss due to illness or health problems Functional form: Continuous Measurement: Score on the simplified Chinese version of the Work Productivity and Activity Impairment-General Health (WPAI-GH) (v2.0) questionnaire, with higher scores representing greater impairment and less productivity <sup>16</sup>
<b>Employment status</b>	Definition: Main occupation and type of employment; Functional form: Categorical Measurement: Self-reported response
<b>Family level of annual consumption expenditure</b>	Definition: Annual total household expenditure Functional form: Continuous Measurement: Self-reported responses to a series of questions covering local expenditure categories by the household representative

#### 4.3.3 POPMIX-MH

<b>Primary outcomes</b>	
<b>Depression symptoms</b>	Definition: Emotional disorders, including sadness, loss, and anger Functional form: Continuous Measurement: Score on Patient Health Questionnaire-9 items (PHQ-9), <sup>17</sup> which ranges from 0 to 27 with higher scores representing more severe depression symptoms
<b>Anxiety symptoms</b>	Definition: Unpleasant state of inner turmoil Functional form: Continuous Measurement: Score on General Anxiety Disorder-7 (GAD-7), <sup>18</sup> ranging from 0 to 21, which ranges from 0 to 21 with higher scores representing more severe anxiety symptoms

<b>Warwick-Edinburgh Mental Well-being Scale, WEMWBS</b>	<p>Definition: Score reflecting overall mental health state</p> <p>Functional form: Continuous</p> <p>Measurement: Score on the Warwick Edinburgh Mental Well-being Scale,<sup>19</sup> which ranges from 14 to 70 with lower scores representing worse general mental health</p>
<b>Secondary outcomes</b>	
<b>Quality of life indicators</b>	
<b>Number of chronic conditions controlled</b>	<p>Definition: The number of conditions controlled among seven objectively measured chronic health conditions (COPD, asthma, depression symptoms, anxiety symptoms, BMI, hypertension, and type 2 diabetes)</p> <p>Functional form: Counting data</p> <p>Measurement: Through objective physical examination or a validated scale</p>
<b>Self-rate health status</b>	<p>Definition: General self-assessed health status</p> <p>Functional form: Continuous</p> <p>Measurement: EQ-5D scale, ranging from 0 to 1 continuously; 0 represents death, and 1 represents perfect health</p>
<b>COPD symptoms</b>	
<b>mMRC score</b>	<p>Definition: Modified Medical Research Council (mMRC) questionnaire</p> <p>Functional form: Categorical</p> <p>Measurement: The mMRC results in a categorical value, with level 0 representing a good respiratory condition and the maximum level 4 representing a very bad respiratory condition</p>
<b>CAT score</b>	<p>Definition: COPD Assessment Test (CAT) score for COPD patients</p> <p>Functional form: Continuous</p> <p>Measurement: CAT<sup>20</sup> is a questionnaire for people with COPD. It is designed to measure the impact of COPD on a person's life and how these changes over time; scores range from 0 to 40, with higher scores representing worse COPD conditions</p>
<b>Knowledge and awareness of COPD</b>	
<b>Self-awareness of COPD</b>	<p>Definition: Response to the question "Have you ever been diagnosed with COPD?"</p> <p>Functional form: Binary</p> <p>Measurement: Self-reported response</p>
<b>COPD knowledge</b>	<p>Definition: Responses to excerpted questions of the COPD Knowledge Questionnaire; selected questions ask about information the general population should know about COPD</p> <p>Functional form: Continuous</p> <p>Measurement: Self-reported responses to questions; scores range from 0 to 7 with higher scores indicating a greater number of correct statements chosen by the respondent<sup>21</sup></p>



Care cascade indicators for COPD	
<b>COPD screening</b>	<p>Definition: Response to the question “Have you ever had a pulmonary function test?”</p> <p>Functional form: Binary</p> <p>Measurement: Self-reported response</p>
<b>COPD treatment adherence</b>	<p>Definition: Whether an individual diagnosed with COPD is currently following a treatment plan prescribed by a doctor or other healthcare professional.</p> <p>Functional form: Binary</p> <p>Measurement: Self-reported response</p>
<b>COPD control</b>	<p>Definition: Response to the question “Has the number of acute exacerbations decreased in the past six months?”</p> <p>Functional form: Binary</p> <p>Measurement: Self-reported response</p>
Physical health indicators	
<b>FEV1 measurement</b>	<p>Definition: Forced Expiratory Volume in one second (FEV1)</p> <p>Functional form: Continuous</p> <p>Measurement: Pulmonary function test, portable spirometry</p>
<b>Blood pressure</b>	<p>Definition: Systolic and diastolic blood pressure (mmHg)</p> <p>Functional form: Continuous</p> <p>Measurement: Omron portable automatic blood pressure monitor</p>
<b>Blood glucose</b>	<p>Definition: Reference standard for average plasma glucose concentration over a period of time, typically reflecting the preceding 8–12 hours for fasting blood glucose and the immediate glycemic status for random blood glucose</p> <p>Functional form: Continuous</p> <p>Measurement: Blood glucose meter</p>
<b>Waist circumference</b>	<p>Definition: Waist circumference (cm)</p> <p>Functional form: Continuous</p> <p>Measurement: Soft measuring tape</p>
<b>BMI</b>	<p>Definition: Body mass index (BMI): weight divided by height squared (<math>\text{kg/m}^2</math>)</p> <p>Functional form: Continuous</p> <p>Measurement: Height and weight were measured using an automated body composition analyzer</p>
<b>Smoking Dependence</b>	<p>Definition: A scale that measures the degree of smoking dependence</p> <p>Functional form: Continuous</p> <p>Measurement: Score on the Chinese version of the Fagerström Test for Nicotine Dependence (FTND),<sup>10,11</sup> which ranges from 0 to 15 with higher scores representing more severe nicotine dependence; additionally measured by score on the Heaviness of Smoking Index (HSI),<sup>12</sup> which ranges from 0 to 6 with higher scores representing worse nicotine dependence</p>

<b>Healthcare utilization indicators</b>	
<b>Number of outpatient visits</b>	<p>Definition: Number of outpatient visits and type of hospital visited within the past year</p> <p>Functional form: Count</p> <p>Measurement: Survey data</p>
<b>Number of inpatient visits</b>	<p>Definition: Number of inpatient visits and type of hospital visited within the past year</p> <p>Functional form: Count</p> <p>Measurement: Survey data</p>
<b>Medical expenditure within a family over the past year</b>	<p>Definition: Healthcare-related expenditures</p> <p>Functional form: Continuous</p> <p>Measurement: Insurance/outpatient/inpatient data</p>
<b>Socioeconomic profile indicators</b>	
<b>Productivity loss</b>	<p>Definition: Productivity loss due to illness or health problems</p> <p>Functional form: Continuous</p> <p>Measurement: Score on the simplified Chinese version of the Work Productivity and Activity Impairment-General Health (WPAI-GH) (v2.0) questionnaire, with higher scores representing greater impairment and less productivity</p>
<b>Care cascade indicators for hypertension and type 2 diabetes mellitus</b>	
<b>High blood pressure (HBP) Screening</b>	<p>Definition: Response to the question “Have you ever had your blood pressure measured by a doctor, nurse, or other healthcare professional?”</p> <p>Functional form: Binary</p> <p>Measurement: Self-reported response</p>
<b>HBP diagnosis</b>	<p>Definition: Response to the question “Have you ever been diagnosed with hypertension by a doctor?”</p> <p>Functional form: Binary</p> <p>Measurement: Self-reported response</p>
<b>HBP treatment</b>	<p>Definition: Response to the question “Are you currently taking any antihypertensive medication prescribed by a doctor or other healthcare professional?”</p> <p>Functional form: Binary</p> <p>Measurement: Self-reported response</p>
<b>HBP control</b>	<p>Definition: Blood pressure within the normal range at the end-of-year follow-up</p> <p>Functional form: Binary</p> <p>Measurement: Blood pressure measurement</p>
<b>Type 2 diabetes mellitus (T2DM) screening</b>	<p>Definition: Response to the question “Have you ever had your blood glucose measured by a doctor, nurse, or other healthcare professional?”</p> <p>Functional form: Binary</p> <p>Measurement: Self-reported response</p>
<b>T2DM diagnosis</b>	<p>Definition: Response to the question “Have you ever been</p>

	diagnosed with T2DM by a doctor?”
	Functional form: Binary
	Measurement: Self-reported response
<b>T2DM treatment</b>	Definition: Response to the question “Are you currently receiving a type 2 diabetes treatment plan prescribed by a doctor or other healthcare professional?”
	Functional form: Binary
	Measurement: Self-reported response
<b>T2DM control</b>	Definition: Blood glucose within the normal range at the end-of-year follow-up
	Functional form: Binary
	Measurement: Blood glucose measurement
<b>Health risk behaviors</b>	
<b>Smoking status</b>	Definition: Response to the question “Do you currently smoke?”
	Functional form: Binary
	Measurement: Self-reported response
<b>Amount of smoking</b>	Definition: Average number of cigarettes smoked per day
	Functional form: Continuous
	Measurement: Self-reported response
<b>Drinking status</b>	Definition: Frequency of alcohol consumption over the past three months
	Functional form: Categorical
	Measurement: Self-reported response; the possible response options are:
	0 = Never drink alcohol
	1 = Once per month
	2 = 2–3 times per month
	3 = Once per week
	4 = 2–3 times per week
	5 = 4–6 times per week
	6 = Once per day
	7 = Twice per day
	8 = More than twice per day
	9 = Other, please specify
<b>Sugar consumption</b>	Definition: Frequency of consumption of sugary foods/drinks
	Functional form: Categorical
	Measurement: Self-reported response; the possible response options are:
	1 = almost every day/daily (6-7 days)
	2 = often (4-5 days)
	3 = sometimes (2-3 days)
	4 = rarely or never (0-1 day)
<b>Salted vegetables consumption</b>	Definition: Frequency of consumption of salted vegetables
	Functional form: Categorical

	Measurement: Self-reported response; the possible response options are: 1 = almost every day/daily (6-7 days) 2 = often (4-5 days) 3 = sometimes (2-3 days) 4 = rarely or never (0-1 day)
<b>Vegetable consumption</b>	Definition: Frequency of consumption of vegetables Functional form: Categorical Measurement: Self-reported response; the possible response options are: 1 = almost every day/daily (6-7 days) 2 = often (4-5 days) 3 = sometimes (2-3 days) 4 = rarely or never (0-1 day)
<b>Physical exercise</b>	Definition: Hours of physical exercise per week Functional form: Count Measurement: Self-reported response; the possible response options are: 1 = almost every day/daily (6-7 days) 2 = often (4-5 days) 3 = sometimes (2-3 days) 4 = rarely or never (0-1 day)

#### 4.3.4 POPMIX-Smoking

Primary outcomes	
<b>Amount of smoking</b>	Definition: Average number of cigarettes smoked per day Functional form: Continuous Measurement: Self-reported response
<b>Smoking dependence</b>	Definition: A scale that measures the degree of smoking dependence Functional form: Continuous Measurement: Score on the Chinese version of the Fagerström Test for Nicotine Dependence (FTND), which ranges from 0 to 15 with higher scores representing more severe nicotine dependence; additionally measured by score on the Heaviness of Smoking Index (HSI), which ranges from 0 to 6 with higher scores representing worse nicotine dependence
Secondary outcomes	
Quality of life indicators	
<b>Self-rated health status</b>	Definition: General self-assessed health status Functional form: Continuous Measurement: EQ-5D scale, ranging from 0 to 1 continuously; 0 represents death, and 1 represents perfect health

<b>Number of chronic conditions controlled</b>	<p>Definition: The number of conditions controlled among seven objectively measured chronic health conditions (COPD, asthma, depression symptoms, anxiety symptoms, BMI, hypertension, and type 2 diabetes)</p> <p>Functional form: Counting data</p> <p>Measurement: Through objective physical examination or a validated scale</p>
<b>Smoking-related indicators</b>	
<b>Physical proof of cigarettes</b>	<p>Definition: Response to the question “Can you show me your cigarettes?”</p> <p>Functional form: Binary</p> <p>Measurement: Self-reported response and visible proof of cigarette possession to study field workers</p>
<b>Knowledge and awareness of COPD</b>	
<b>Self-awareness of COPD</b>	<p>Definition: Response to the question “Have you ever been diagnosed with COPD?”</p> <p>Functional form: Binary</p> <p>Measurement: Self-reported response</p>
<b>COPD knowledge</b>	<p>Definition: Responses to excerpted questions of the COPD Knowledge Questionnaire; selected questions ask about information the general population should know about COPD</p> <p>Functional form: Continuous</p> <p>Measurement: Self-reported responses to questions; scores range from 0 to 7 with higher scores indicating a greater number of correct statements chosen by the respondent</p>
<b>Care cascade indicators for COPD</b>	
<b>COPD screening</b>	<p>Definition: Response to the question “Have you ever had a pulmonary function test?”</p> <p>Functional form: Binary</p> <p>Measurement: Self-reported response</p>
<b>COPD treatment adherence</b>	<p>Definition: Whether an individual diagnosed with COPD is currently following a treatment plan prescribed by a doctor or other healthcare professional</p> <p>Functional form: Binary</p> <p>Measurement: Self-reported response</p>
<b>COPD control</b>	<p>Definition: Response to the question “Has the number of acute exacerbations decreased in the past six months?”</p> <p>Functional form: Binary</p> <p>Measurement: Self-reported response</p>
<b>Physical health indicators</b>	
<b>FEV<sub>1</sub> measurement</b>	<p>Definition: Forced Expiratory Volume in one second</p> <p>Functional form: Continuous</p> <p>Measurement: Pulmonary function test, portable spirometry</p>
<b>Blood pressure</b>	<p>Definition: Systolic and diastolic blood pressure (mmHg)</p>

<b>Blood glucose</b>	<p>Functional form: Continuous</p> <p>Measurement: Omron portable automatic blood pressure monitor</p> <p>Definition: Reference standard for average plasma glucose concentration over a period of time, typically reflecting the preceding 8–12 hours for fasting blood glucose and the immediate glycemic status for random blood glucose</p> <p>Functional form: Continuous</p> <p>Measurement: Blood glucose meter</p>
<b>Waist circumference</b>	<p>Definition: Waist circumference (cm)</p> <p>Functional form: Continuous</p> <p>Measurement: Soft measuring tape</p>
<b>BMI</b>	<p>Definition: Body mass index (BMI): weight divided by height squared (<math>\text{kg}/\text{m}^2</math>)</p> <p>Functional form: Continuous</p> <p>Measurement: Height and weight were measured using an automated body composition analyzer.</p>
<b>Healthcare utilization indicators</b>	
<b>Number of outpatient visits</b>	<p>Definition: Number of outpatient visits and type of hospital visited within the past year</p> <p>Functional form: Count</p> <p>Measurement: Survey data</p>
<b>Number of inpatient visits</b>	<p>Definition: Number of inpatient visits and type of hospital visited within the past year</p> <p>Functional form: Count</p> <p>Measurement: Survey data</p>
<b>Medical expenditure within a family over the past year</b>	<p>Definition: Healthcare-related expenditures</p> <p>Functional form: Continuous</p> <p>Measurement: Insurance/outpatient/inpatient data</p>
<b>Mental health indicators</b>	
<b>Depression symptoms</b>	<p>Definition: Emotional disorders, including sadness, loss, and anger</p> <p>Functional form: Continuous</p> <p>Measurement: Score on Patient Health Questionnaire-9 items (PHQ-9), which ranges from 0 to 27 with higher scores representing more severe depression symptoms</p>
<b>Anxiety symptoms</b>	<p>Definition: Unpleasant state of inner turmoil</p> <p>Functional form: Continuous</p> <p>Measurement: Score on General Anxiety Disorder-7 (GAD-7), which ranges from 0 to 21 with higher scores representing more severe anxiety symptoms</p>
<b>Warwick-Edinburgh Mental Well-being Scale (WEMWBS)</b>	<p>Definition: Score reflecting overall mental health state</p> <p>Functional form: Continuous</p> <p>Measurement: Score on the Warwick Edinburgh Mental Well-being Scale, which ranges from 14 to 70 with lower scores</p>

representing worse general mental health

#### **Socioeconomic profile indicators**

**Productivity loss** Definition: Productivity loss due to illness or health problems  
Functional form: Continuous  
Measurement: Score on the simplified Chinese version of the Work Productivity and Activity Impairment-General Health (WPAI-GH) (v2.0) questionnaire, with higher scores representing greater impairment and less productivity

#### **Care cascade indicators for hypertension and type 2 diabetes mellitus**

**High blood pressure (HBP) screening** Definition: Response to the question “Have you ever had your blood pressure measured by a doctor, nurse, or other healthcare professional?”

Functional form: Binary

Measurement: Self-reported response

**HBP diagnosis** Definition: Response to the question “Have you ever been diagnosed with hypertension by a doctor?”

Functional form: Binary

Measurement: Self-reported response

**HBP treatment** Definition: Response to the question “Are you currently taking any antihypertensive medication prescribed by a doctor or other healthcare professional?”

Functional form: Binary

Measurement: Self-reported response

**HBP control** Definition: Blood pressure within the normal range at the end-of-year follow-up

Functional form: Binary

Measurement: Blood pressure measurement

**Type 2 diabetes mellitus (T2DM) screening** Definition: Response to the question “Have you ever had your blood glucose measured by a doctor, nurse, or other healthcare professional?”

Functional form: Binary

Measurement: Self-reported response

**T2DM diagnosis** Definition: Response to the question “Have you ever been diagnosed with T2DM by a doctor?”

Functional form: Binary

Measurement: Self-reported response

**T2DM treatment** Definition: Response to the question “Are you currently receiving a type 2 diabetes treatment plan prescribed by a doctor or other healthcare professional?”

Functional form: Binary

Measurement: Self-reported response

**T2DM control** Definition: Blood glucose within the normal range at the end-of-year follow-up

Functional form: Binary

	Measurement: Blood glucose measurement
<b>Health risk behaviors</b>	
<b>Smoking status</b>	Definition: Response to the question “Do you currently smoke?” Functional form: Binary Measurement: Self-reported response
<b>Drinking status</b>	Definition: Frequency of alcohol consumption over the past three months Functional form: Categorical Measurement: Self-reported response; the possible response options are: 0 = Never drink alcohol 1 = Once per month 2 = 2–3 times per month 3 = Once per week 4 = 2–3 times per week 5 = 4–6 times per week 6 = Once per day 7 = Twice per day 8 = More than twice per day 9 = Other, please specify
<b>Sugar consumption</b>	Definition: Frequency of consumption of sugary foods/drinks Functional form: Categorical Measurement: Self-reported response; the possible response options are: 1 = almost every day/daily (6-7 days) 2 = often (4-5 days) 3 = sometimes (2-3 days) 4 = rarely or never (0-1 day)
<b>Salted vegetables consumption</b>	Definition: Frequency of consumption of salted vegetables Functional form: Categorical Measurement: Self-reported response; the possible response options are: 1 = almost every day/daily (6-7 days) 2 = often (4-5 days) 3 = sometimes (2-3 days) 4 = rarely or never (0-1 day)
<b>Vegetable consumption</b>	Definition: Frequency of consumption of vegetables Functional form: Categorical Measurement: Self-reported response; the possible response options are: 1 = almost every day/daily (6-7 days) 2 = often (4-5 days) 3 = sometimes (2-3 days) 4 = rarely or never (0-1 day)



<b>Physical exercise</b>	Definition: Hours of physical exercise per week Functional form: Count Measurement: Self-reported response; the possible response options are: 0 = No related physical activity 1 = Vigorous physical activity (e.g., lifting heavy objects, aerobic exercise, fast cycling) 2 = Moderate physical activity (e.g., lifting light objects, cycling at normal speed, playing doubles tennis; excluding walking) 3 = Light physical activity (e.g., walking)
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- **Additional longitudinal analyses among subgroups**

Exploratory analyses will examine trajectories and short-term burden of lung function, symptoms, and acute exacerbations among COPD patients categorized by baseline multimorbidity status. Appropriate mixed-effects models will be used for these analyses, with adjustment for relevant baseline covariates and the clustered trial design.

#### **4.4 COPD Care Cascade Analysis**

This module adopts a mixed-methods approach to evaluate the continuum of care for individuals with COPD. The quantitative component delineates the funnel-shaped attrition across the healthcare system, while the qualitative component explores the underlying mechanisms and barriers leading to dropout at each node.

##### **4.4.1 Quantitative Cascade Analysis**

The care cascade uses confirmed patients as the baseline denominator (Stage 1). To ensure population representativeness, survey weighting (based on age and gender distribution of Xishui County) will be applied to calculate absolute proportions and relative attrition rates for the following stages:

1. **Patients:** Individuals with post-bronchodilator  $FEV_1/FVC < 0.7$  or CT diagnosis.
2. **Spirometry Testing:** Patients who reported ever having undergone a pulmonary function test.

3. Diagnosis: Patients who reported ever having been formally diagnosed with COPD.

4. Treatment: Patients currently receiving prescribed effective treatment for COPD.

5. Control (Two-tier assessment):

5a. Control (No severe exacerbation): 0 hospitalizations due to COPD in the past 6 months.

5b. Control (No any exacerbation): 0 total exacerbations in the past 6 months.

Poisson regression models with robust standard errors will be employed to explore the factors influencing dropout (attrition) at each stage. The models will estimate the Relative Risk (RR) of failing to transition to the next stage, adjusting for socio-demographics, comorbidities, and health literacy.

#### 4.4.2 Qualitative Thematic Analysis

To explain the "gaps" identified in the quantitative cascade, semi-structured interviews will be conducted with four key stakeholder groups: patients, high-COPD-risk individuals, community health workers and health administrators.

- Data Analysis

Transcripts will be analyzed using Practical Thematic Analysis with the assistance of NVivo software.

- Focus

The analysis will identify Barriers and Facilitators at each stage of the cascade. Triangulation will be used to compare perspectives across different stakeholder groups to ensure validity.

#### 4.5 Regression Discontinuity Design (RDD)

This module uses the quasi-experimental variation created by pre-specified eligibility thresholds within the POPMIX intervention package to estimate the local causal effects of selected targeted management components. The rationale is that participants located narrowly on either side of a clinical cutoff are expected to be comparable in

underlying risk, such that any discontinuous change in the probability of receiving the corresponding management component at the threshold can be interpreted as exogenous. This analysis is restricted to intervention components for which assignment was determined by a continuous clinical or questionnaire-based running variable with a clearly defined cutoff. By comparing outcomes for individuals just above and just below the predefined threshold, we will estimate the Local Average Treatment Effect (LATE) of the targeted sub-intervention localized at that cutoff.

- Statistical Methods

The pre-specified RDD thresholds to be evaluated are shown below (Table 1). For each cutoff, the primary specification will be a local linear regression discontinuity model estimated within a data-driven bandwidth around the threshold. The outcome will be the corresponding 12-month endpoint, and separate local models will be fitted for each cutoff. Outcomes will include COPD-related indicators, health behavior outcomes, mental health measures, BMI-related outcomes, blood pressure control, blood glucose control, multimorbidity control status, health economic outcomes and health-related quality of life.

Table 1. Pre-specified Thresholds for RDD

Targeted intervention component	Running variable	Cutoff
Mental health digital intervention and health education	WEMWBS score	45
Weight abnormality intervention	BMI (kg/m <sup>2</sup> )	18.5 and 24.0
Hypertension management and education	Mean systolic blood pressure / mean diastolic blood pressure	140 mmHg / 90 mmHg
Diabetes management and education	Fasting blood glucose / random blood glucose	7.0 mmol/L / 11.1 mmol/L
Encouragement and referral for computed tomography and formal diagnosis, together with health education	Post-bronchodilator FEV1/FVC	0.7

- Robustness and Validity Checks

Bandwidth selection will be based on an Imbens–Kalyanaraman or comparable

mean squared error–optimal procedure, with robust bias-corrected 95% confidence intervals reported. Sensitivity analyses will re-estimate the local effect using narrower and wider bandwidths, local quadratic specifications, and alternative kernel functions. The validity of the design will be assessed by visual inspection of outcome and treatment-probability plots around the cutoff, continuity testing of baseline covariates, and density testing of the running variable around the threshold to evaluate potential manipulation. Because some intervention rules may generate imperfect compliance with the threshold-based recommendation, the RDD estimand will be interpreted as the local intention-to-treat effect of threshold eligibility

#### **4.6 Instrumental Variable (IV) Analysis**

This module is designed to address non-compliance in the real-world delivery of the POPMIX intervention package. Because some participants in intervention clusters may not actually receive or engage with the intervention package as intended, the intention-to-treat analysis may underestimate the causal effect of actual exposure to the integrated package. Therefore, randomized assignment will be used as an instrumental variable for actual receipt of the overall intervention package to estimate the local average treatment effect among compliers.

- **Statistical Methods**

For continuous outcomes, the primary IV analysis will use two-stage least squares. In the first stage, actual receipt of the integrated intervention package will be regressed on randomized cluster assignment, with adjustment for township-size stratification and prespecified baseline covariates. In the second stage, the predicted value of intervention receipt from the first stage will be used to estimate the causal effect on the corresponding 12-month outcome. For binary outcomes, a linear probability IV model will be used as the primary specification to preserve interpretability of the complier-average causal effect. Standard errors will be clustered at township level. First-stage coefficients and standard weak-instrument diagnostics will be reported. The IV estimand will be interpreted

as the local average treatment effect of the overall integrated intervention package among participants whose actual receipt of the package was affected by randomized assignment.

#### **4.7 Heckman Selection Model Analysis**

A Heckman two-step selection model will be employed to assess and correct for potential sample selection bias arising from incomplete or unsuccessful pulmonary function testing among individuals at high risk for COPD. This analysis is motivated by the fact that COPD status based on spirometry can only be observed among participants who completed pulmonary function testing, while some high-risk individuals may not undergo or successfully complete testing. If pulmonary function test completion is associated with participant characteristics that are also related to COPD prevalence or risk-factor profiles, analyses restricted to participants with observed spirometry results may be biased. In the first stage, a Probit selection equation will be fitted to estimate the probability of completing pulmonary function testing, using observed baseline characteristics associated with testing uptake or successful test completion; if appropriate exclusion-restriction variables are available, they will be considered for the selection equation. The inverse Mills ratio derived from this model will then be incorporated into the second-stage outcome model to evaluate the extent of selection bias and to obtain bias-corrected estimates for COPD-related analyses. Consistent with the study proposal, the results from the spirometry-only analysis and the Heckman-corrected analysis will, where feasible, be compared with analyses based on the broader set of participants with CT-supported diagnostic information, including those who did not complete pulmonary function testing, to assess the validity and robustness of the selection correction approach.

#### **4.8 Costing Study**

This module will estimate the economic cost of implementing the POPMIX multicomponent intervention package in Xishui County. In line with the trial design and intervention structure, the costing study will identify, measure, and value the

resources required for screening, intervention delivery, follow-up, referral coordination, and provider incentive mechanisms across county, township, village, and household levels. The primary costing perspective will be that of programme implementation and health service management, supplemented by patient-borne costs where these are available from the trial data.

- **Cost Components**

Cost components will be summarized at an aggregate level and may include project and programme implementation costs, health service delivery costs, and patient- or household-borne costs, as applicable. Depending on data availability and final analytic definitions, these costs may cover management and administrative inputs, personnel and training, examinations and clinical services, medicines and related supplies, transport or travel-related costs, and other direct or indirect costs relevant to intervention delivery or care seeking. Resource use and unit cost information will be derived from available financial and administrative records, implementation documentation, and questionnaire-based data where appropriate.

- **Statistical Methods**

Total and mean per-participant costs will be estimated overall and, where relevant, by intervention component. Cost summaries will be reported by trial arm and by major intervention category. Between-group differences in mean cost will be estimated with 95% confidence intervals using non-parametric bootstrap methods with resampling at township level to reflect the clustered design.

#### **4.9 Cost-Effectiveness Analysis**

This module will evaluate the economic value of the POPMIX intervention package by jointly comparing costs and health outcomes between the intervention and control groups over the trial follow-up period. The primary within-trial economic evaluation will be conducted over 12 months, consistent with the trial observation window. Given the collection of EQ-5D-5L data and the project's stated objective of assessing sustainability and economic value, the primary economic outcome will be

quality-adjusted life-years (QALYs), supplemented by cost-effectiveness analyses using selected trial primary outcomes relevant to population medicine decision-making.

- Endpoints

The primary economic endpoint will be QALYs calculated from EQ-5D-5L utility values over 12 months using the area-under-the-curve approach. The cost endpoint will comprise total costs from the program implementation and health service management perspective, as defined in Section 4.8, including all intervention-related costs and health care utilization costs incurred during the 12-month follow-up period.

- Statistical Methods

Incremental cost, incremental effect, and the incremental cost-effectiveness ratio (ICER) will be estimated by comparing mean costs and mean outcomes between study arms. Uncertainty will be characterized using non-parametric bootstrap methods with township-level resampling to generate confidence intervals, cost-effectiveness planes, and cost-effectiveness acceptability curves over a range of willingness-to-pay thresholds.

## **5. Data Management**

### **5.1 Data Collection**

Study data will be collected using questionnaires, physical examinations, and clinical assessments at protocol-specified time points. Data entry will be performed by trained study staff using the electronic data capture (EDC) system. Built-in checks will identify missing, inconsistent, or out-of-range values, and any discrepancies will be resolved by the quality control personnel through verification against the original source documents.

### **5.2 Data Storage**

All study data will be stored in secure, password-protected electronic systems with role-based access. Participants will be identified by unique study IDs, and personal identifiers will be stored separately from the main dataset. Access to identifiable data is restricted to authorized personnel only.

### **5.3 Study Record Retention**

Essential study documents and source records will be retained in secure storage according to institutional and regulatory requirements. Records will be archived after study completion and retained for at least five years after publication of the main study results, unless a longer retention period is required.



## **6. Administrative Aspects**

### **6.1 Confidentiality**

Participant confidentiality will be strictly maintained. Identifiable information will not be included in analysis datasets. All data used for analysis or publication will be anonymized or de-identified, and access to identifiable records will be limited to authorized personnel.

### **6.2 Modifications of the Protocol**

Any important protocol modification will be submitted to the relevant ethics committee for review and approval before implementation, unless immediate action is required for participant safety.

### **6.3 Participant Reimbursement**

No direct financial compensation will be provided for participation unless approved under local study procedures. Reasonable reimbursement for direct participation-related costs may be provided according to ethics approval and local regulations.

### **6.4 Financial Disclosure and Conflicts of Interest**

Investigators and subinvestigators will disclose any financial or other interests that could influence study conduct, analysis, or reporting. Any identified conflicts will be managed according to institutional and ethics requirements.

## **7. Use of Data and Publications Policy**

Study data will be used primarily for analyses prespecified in the protocol and SAP. Any additional analyses not prospectively specified will be clearly identified as exploratory or post hoc. Study findings will be disseminated through peer-reviewed publications, conference presentations, and other appropriate scientific channels. Reported results will be presented in aggregate form without identifying individual participants. Authorship and publication decisions will follow internationally accepted academic standards.

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