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Preventing Diabetes with Chinese Herbal Medicine: A Target Trial Emulation from Real-World Data

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Abstract

Background: Prediabetes is a high-risk precursor of type 2 diabetes mellitus (T2DM). Chinese herbal medicine (CHM) is widely used in China for glycaemic regulation, yet its causal effect on diabetes prevention remains uncertain because observational evidence is prone to immortal-time and prevalent-user bias. We emulated a target trial to estimate the effect of initiating CHM on progression from prediabetes to T2DM.

Methods: Using the Xiamen Regional Health Care Database (2010–2023), we identified adults with newly diagnosed prediabetes and emulated a target trial comparing CHM initiation within 30 days versus no CHM use. Follow-up began on day 31. The primary outcome was incident T2DM; secondary outcomes were all-cause and cardiovascular mortality. Cox proportional hazards models estimated hazard ratios (HRs) after 1:1 propensity score matching, with sensitivity analyses (1:2/1:3 matching, four inverse-probability-of-treatment-weighting variants, and 30/60/90/180-day exposure windows), subgroup analyses, and exploratory individual-herb analyses.

Results: After matching, 5,369 CHM users and 5,369 non-users were compared. CHM initiation was associated with a lower risk of progression to T2DM (HR 0.89, 95% CI 0.84–0.95; $P<0.001$; incidence 115.55 vs 129.54 per 1,000 person-years). The association was consistent across sensitivity analyses (HR 0.89–0.93). Effect modification by body mass index was observed (interaction $P=0.009$; BMI ≥24 kg/m^2 HR 0.84 vs BMI <24 kg/m^2 HR 0.95). All-cause (HR 1.04, $P=0.600$) and cardiovascular (HR 0.99, $P>0.900$) mortality were neutral. Among the ten most frequently prescribed herbs, Gan-Cao, Fu-Ling, and Dang-Gui showed significant inverse associations.

Conclusions: In this target trial emulation, initiating CHM was associated with a modestly lower risk of progression to T2DM, with a stronger signal in overweight individuals and no short-term increase in mortality, supporting CHM as a complementary option in stratified prediabetes prevention.

Keywords

Chinese herbal medicine; Prediabetes; Type 2 diabetes mellitus; Target trial emulation; Propensity score matching; Real-world data; Causal inference

Background

Prediabetes is an intermediate hyperglycaemic state between normal glucose regulation and diabetes, encompassing impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). Driven by population ageing, urbanisation, and lifestyle changes, its prevalence continues to rise and has become a major global public-health challenge. The International Diabetes Federation (IDF) estimated in the 11th edition of the IDF Diabetes Atlas (2025) that approximately 589 million adults aged 20–79 years lived with diabetes worldwide in 2024 (about 1 in 9), a figure projected to reach 853 million by 2050; concurrently, an estimated 1.12 billion adults had prediabetes [1]. China bears the heaviest diabetes burden globally: the IDF 2025 estimates about 148 million Chinese adults with diabetes (age-standardised prevalence 11.9%) and about 274 million with prediabetes (117 million with IFG and 157 million with IGT), with nearly half (49.7%) of diabetes cases undiagnosed [1]. Based on a nationally representative cross-sectional survey covering 31 provinces in 2015–2017, the prevalence of prediabetes among Chinese adults reached 35.2% (95% CI 33.5%–37.0%), meaning more than one-third of adults are in this intermediate state [2]. A 2024 review by Ning Guang's group in *The Lancet Public Health* further noted that the prevalence of diabetes in China has risen rapidly from less than 1% in 1980 to 12.4% in 2018, giving the country the world's largest diabetes population (about 22% of the global total) [3].

Crucially, prediabetes is neither benign nor static. It is a high-risk transitional stage toward type 2 diabetes mellitus (T2DM), with an annual conversion rate of approximately 4%–19% [4,35]. Equally important, the vascular and metabolic complications of diabetes begin to emerge during the prediabetic stage: the Australian AusDiab population study found that 6.7% of 1,027 individuals with IGT or IFG already had retinopathy, which was associated with prevalent stroke [5]; IDF data indicate that nearly half of Chinese diabetes patients may have one or more complications at diagnosis [1]. At the same time, prediabetes is reversible—the Diabetes Prevention Program (DPP) long-term follow-up showed that regression from prediabetes to normal glucose regulation reduced the 10-year risk of diabetes by 56% [6]. Timely interruption of progression at the prediabetic stage is therefore of great clinical and economic importance. Lifestyle intervention (weight loss, physical activity, and a balanced diet) is the recommended first-line strategy; the U.S. DPP randomised trial demonstrated a 58% reduction in T2DM incidence [7,31], and metformin is an established option for high-risk individuals (31% reduction in the DPP) [7,31]. In practice, however, sustained lifestyle change is difficult without continued professional support [7], and pharmacologic coverage is limited, leaving a substantial prevention gap.

Chinese herbal medicine (CHM) offers a complementary pathway for prediabetes management that aligns naturally with the traditional Chinese medicine principle of "treating disease before it occurs" (治未病)—prediabetes is a typical "pre-disease" (欲病) stage to which the concepts of preventing disease before onset and preventing progression after onset closely correspond [12]. CHM is widely used in China for

glycaemic regulation, and real-world evidence increasingly supports its potential benefit. For example, a population-based cohort study in mainland China found that CHM use among individuals with prediabetes was associated with a substantially lower risk of T2DM (adjusted hazard ratio 0.32, 95% CI 0.27–0.38) compared with initiation of Western glucose-lowering medications [8]. More direct evidence comes from the FOCUS randomised clinical trial led by Chinese investigators: a multicentre, double-blind, placebo-controlled study conducted at 35 centres in 21 cities enrolling 889 participants with impaired glucose tolerance and multiple metabolic abnormalities, which showed that Jinlida granules reduced the risk of diabetes by 41% (hazard ratio 0.59, 95% CI 0.46–0.74; median follow-up 2.20 years) [9]. Real-world evidence that treats clinical practice itself as the exposure can objectively evaluate the effectiveness of CHM and endow the findings with external validity, and is therefore highly valued in the Chinese medicine community [12].

Nevertheless, causal interpretation of such observational findings remains limited. Conventional cohort designs are susceptible to confounding and, in particular, to two types of bias that can seriously distort effect estimates: immortal-time bias and prevalent-user bias [10–12]. Randomised controlled trials (RCTs), the gold standard for causal inference, are costly, require long follow-up, and have limited generalisability, making them difficult to apply to long-term diabetes-prevention endpoints [9,12]. Target trial emulation (TTE) was formalised by Hernán and Robins in 2016 [10] and further systematised in 2022 as a framework for drawing causal conclusions from observational data [11]; it provides a rigorous solution by conceiving the causal question as a hypothetical, ideally conducted pragmatic RCT and then emulating that target trial using real-world data, with explicit specification of eligibility, treatment strategies, assignment, follow-up, outcomes, causal contrast, and analysis plan (the "3–7–2" implementation framework proposed by Lu et al. [12]), deliberately controlling for immortal-time and prevalent-user bias. TTE has had substantial impact in pharmacoepidemiology—the RCT-DUPLICATE initiative emulated 32 RCTs using non-randomised databases and showed that, when study design and measurement were closely replicated, observational results agreed closely with RCTs (Pearson correlation coefficient 0.93) [13]—and is receiving growing attention in Chinese medicine research [12]. To our knowledge, however, it has not yet been applied to assess whether CHM prevents progression from prediabetes to T2DM.

To fill this gap, we conducted the present study using the Xiamen Regional Health Care Database (Xiamen Municipal Health Commission). Established in 2006, this population-level medical data system assigns a unique resident health identifier to every citizen and integrates four platforms—the electronic health record platform, the primary healthcare management platform, the maternal and child health management platform, and the resident health management platform [14]. Building on this infrastructure, the DEEP cohort constructed by the teams of Sun Xin and Tan Jing at West China Hospital of Sichuan University covers approximately 5 million Xiamen residents and longitudinally records drug prescriptions across primary, secondary, and tertiary care (more than 13.28 million prescriptions from 2013 to 2021, including 655 herbal medicines and 847

Chinese patent medicines) [14]. The representativeness and completeness of this platform are corroborated by independent studies: a real-world study based on the Xiamen resident health information system estimated the T2DM prevalence trend rising from 4.04% in 2014 to 4.84% in 2019 [15]; and an analysis using Xiamen's regional electronic health records (covering 90% of registered patients since 2012, 503 community centres, and 63 general hospitals) confirmed the accessibility and reliability of the system for chronic-disease management [16]. This infrastructure contains detailed CHM prescription records, offering a rare opportunity to emulate a target trial at the population level. Using this real-world resource, we conducted a target trial emulation comparing CHM versus no CHM for the risk of progression from prediabetes to T2DM, with all-cause and cardiovascular mortality as secondary outcomes.

Methods

Study design and data source

We conducted a population-based retrospective cohort study designed to emulate a target trial comparing initiation of Chinese herbal medicine (CHM) with no CHM use among individuals with newly diagnosed prediabetes. This study used data from the Xiamen Regional Health Care Database, a population-based electronic medical record system covering residents of Xiamen, China. The database integrates longitudinal information on demographic characteristics, diagnoses, outpatient and inpatient encounters, medication prescriptions, laboratory measurements, and mortality. Records from different healthcare settings were linked using anonymized individual identifiers.

The study period extended from January 2010 to January 2023. The protocol of the hypothetical target trial and its observational emulation are summarized in Supplementary Table S1. The manuscript was prepared in accordance with the TARGET [22] and STROBE [36] reporting guidelines.

Supplementary Table S1. Specification and emulation of the target trial

Target trial component	Hypothetical target trial	Emulation using the Xiamen Regional Health Care Database
1. Eligibility criteria	Adults aged 18 years or older with newly diagnosed prediabetes, defined as fasting plasma glucose of 5.6-6.9 mmol/L, HbA1c of 5.7%-6.4%, or 2-hour OGTT glucose of 7.8-11.0 mmol/L. Exclude individuals with pre-existing diabetes, severe renal impairment, end-stage renal disease, or insufficient baseline information.	Residents aged 18 years or older who first met the laboratory criteria for prediabetes between January 2010 and January 2023 and had at least 1 year of observable records before baseline. Individuals with diabetes before baseline, baseline eGFR <30 mL/min/1.73 m2, or end-stage renal disease before the index date were excluded. Individuals who developed T2DM, died, or were lost to follow-up during the 30-day exposure-assessment window were also excluded.
2. Treatment strategies	Strategy A: initiate CHM after identification of prediabetes. Strategy B: do not initiate	CHM group: at least one recorded CHM prescription during the 30 days after the

	CHM and continue usual care without CHM.	baseline date. Control group: no recorded CHM prescription during the same 30-day period. Exposure status was fixed at the end of the assessment window, regardless of subsequent discontinuation, initiation, or crossover.
3. Treatment assignment	Eligible participants are randomly assigned at baseline to Strategy A or Strategy B.	Treatment was not randomly assigned. Participants were classified according to observed CHM prescriptions. Propensity score matching and weighting methods were used to balance measured baseline characteristics between the treatment groups.
4. Start and end of follow-up	Follow-up begins at treatment assignment and continues until the outcome, death, loss to follow-up, or the administrative end of the study, whichever occurs first.	Follow-up began on day 31 after the baseline date, after completion of the 30-day exposure-assessment window. Participants were followed until the outcome of interest, death, loss to follow-up, the end of database coverage, or the end of the study period, whichever occurred first.
5. Outcomes	Primary outcome: incident T2DM. Secondary outcomes: all-cause mortality and cardiovascular mortality.	Incident T2DM was defined as the first recorded T2DM diagnosis or the first laboratory measurement meeting a diagnostic threshold: fasting plasma glucose >=7.0 mmol/L, HbA1c >=6.5%, or 2-hour OGTT glucose >=11.1 mmol/L. Mortality outcomes were obtained from data provided by the Xiamen Center for Disease Control and Prevention. Cardiovascular mortality was defined by ICD-10 codes I00-I09, I11, I13, I20-I25, I30-I52, and I60-I69.
6. Causal contrast	Intention-to-treat effect of assignment to CHM initiation versus no CHM initiation among eligible individuals with prediabetes.	Observational analogue of the intention-to-treat effect, comparing participants according to CHM exposure status assigned during the initial 30-day window, regardless of subsequent treatment changes.
7. Analysis plan	Compare time-to-event outcomes between treatment strategies using survival analysis and estimate relative and absolute effects with 95% confidence intervals.	A 1:1 nearest-neighbor propensity score match without replacement was performed on the logit of the propensity score using a caliper of 0.1 standard deviations. Covariate balance was assessed using standardized mean differences. Incidence rates were calculated per 1,000 person-years, and Cox regression was used to estimate hazard ratios with 95% confidence intervals. Subgroup and sensitivity analyses included alternative matching ratios, propensity score weighting methods, and exposure windows of 60, 90, and 180 days.

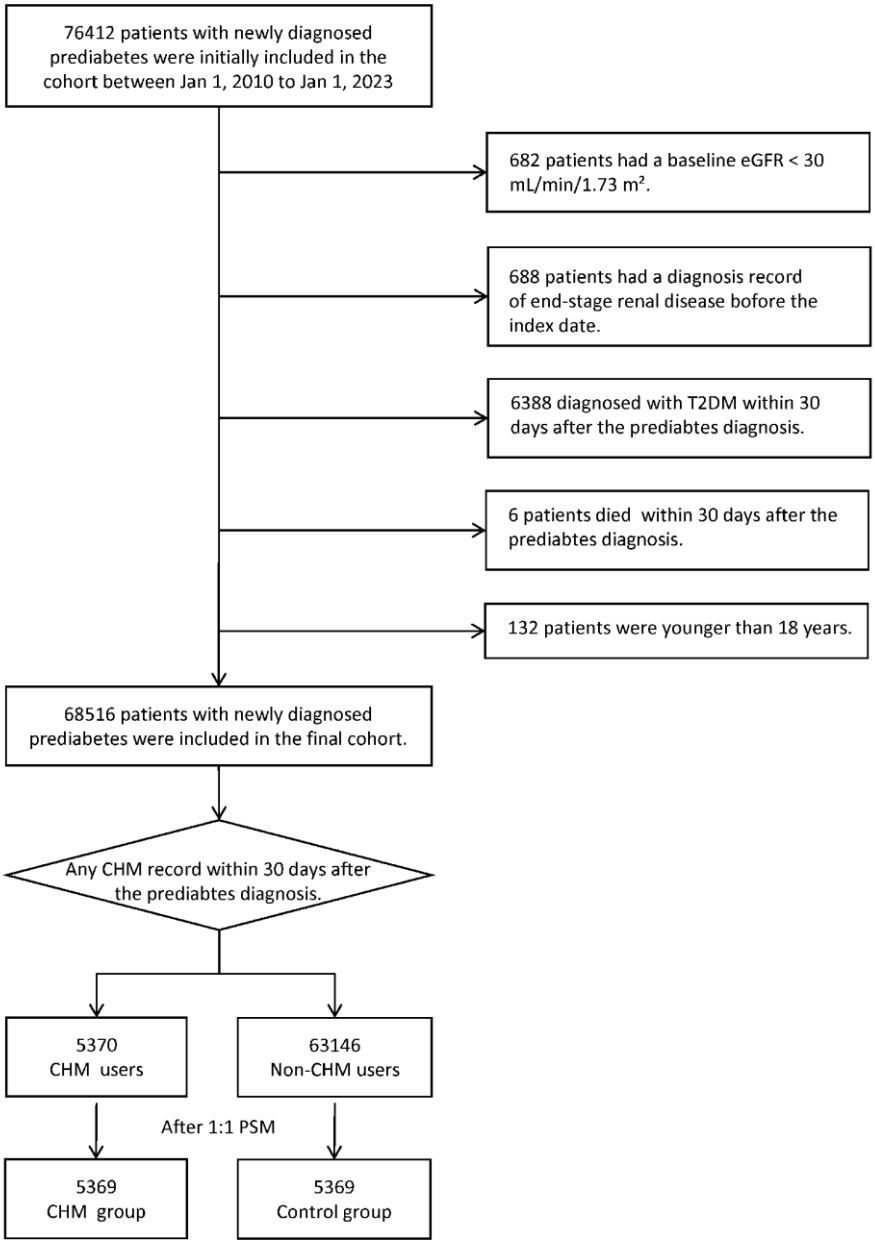
Abbreviations: CHM, Chinese herbal medicine; CI, confidence interval; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; ICD-10, International Classification of Diseases, 10th Revision; OGTT, oral glucose tolerance test; T2DM, type 2 diabetes mellitus.

Eligibility criteria

We identified individuals with newly diagnosed prediabetes based on laboratory measurements recorded in the database. Prediabetes was defined as meeting at least one of the following criteria: fasting plasma glucose of 5.6–6.9 mmol/L, glycated hemoglobin (HbA1c) of 5.7%–6.4%, or a 2-hour plasma glucose concentration of 7.8–11.0 mmol/L during an oral glucose tolerance test (OGTT). The first date on which an individual fulfilled any of these criteria was defined as the baseline date.

Participants were eligible if they were aged 18 years or older and had at least 1 year of observable healthcare records before baseline. We excluded individuals with a diagnosis of diabetes before baseline, including type 1 diabetes, type 2 diabetes mellitus (T2DM), gestational diabetes, or other specified forms of diabetes. Individuals with a baseline estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 or a diagnosis of end-stage renal disease before the index date were also excluded.

A 30-day exposure-assessment window was applied after the baseline date. To align eligibility assessment, exposure classification, and the beginning of follow-up, we further excluded individuals who developed T2DM, died, or were discontinued database coverage / no subsequent records during the exposure window. The detailed cohort-selection process is presented in Figure 1.



199

200

201 **Treatment strategies**

202 CHM exposure was assessed during the 30 days following the baseline date. Participants
203 with at least one recorded CHM prescription during this period were assigned to the
204 CHM group, whereas those without a CHM prescription were assigned to the control
205 group.CHM prescriptions were identified using the standard drug coding system of the
206 Xiamen Regional Health Care Database, which classifies pharmaceutical products into

CHM herbal medicines, Chinese patent medicines, and Western medications based on their therapeutic category.

Exposure status was determined at the end of the 30-day assessment window and retained throughout follow-up, irrespective of subsequent treatment discontinuation, initiation, or crossover. This approach was intended to estimate the observational analogue of an intention-to-treat effect of initiating CHM after identification of prediabetes.

Follow-up

Follow-up began on day 31 after the baseline date, thereby aligning the start of outcome ascertainment with the completion of exposure classification. For each outcome, participants were followed until the first occurrence of that outcome, death, loss to follow-up, the end of database coverage, or the end of the study period, whichever occurred first. In analyses of incident T2DM, participants who died without developing T2DM were censored on the date of death.

For sensitivity analyses using exposure-assessment windows of 60, 90, and 180 days, CHM exposure was reassessed within the corresponding window, and follow-up began on the day immediately after the end of that window. Participants who developed T2DM, died, or were lost to follow-up during the relevant exposure window were excluded from the corresponding analysis.

Outcomes

The primary outcome was incident T2DM during follow-up. Incident T2DM was defined as the first recorded diagnosis of T2DM or the first laboratory measurement meeting the diagnostic criteria for T2DM. The laboratory criteria comprised fasting plasma glucose ≥7.0 mmol/L, HbA1c ≥6.5%, or 2-hour OGTT plasma glucose ≥11.1 mmol/L. The outcome date was defined as the earliest date on which any diagnostic or laboratory criterion was met.

The secondary outcomes were all-cause mortality and cardiovascular mortality. Mortality status and the underlying cause of death were obtained through linkage with mortality data provided by the Xiamen Center for Disease Control and Prevention. Cardiovascular mortality was defined using International Classification of Diseases, 10th Revision codes I00–I09, I11, I13, I20–I25, I30–I52, and I60–I69.

Baseline covariates

Baseline covariates were selected a priori based on clinical knowledge, previous evidence, and their potential associations with both CHM initiation and study outcomes. Covariates were ascertained during the 1-year period preceding the baseline date.

Demographic and socioeconomic characteristics included sex, age, ethnicity, marital status, smoking history, drinking history, and health insurance type. Clinical characteristics included body mass index (BMI), myocardial infarction, stroke, heart failure, hypertension, hyperlipidemia, gouty arthritis, and cancer.

Baseline medication use included metformin, sulfonylureas, dipeptidyl peptidase-4 inhibitors, glinides, aspirin, proton-pump inhibitors, diuretics, β-blockers, calcium-channel blockers, and renin–angiotensin system inhibitors. Healthcare utilization was characterized by the numbers of outpatient visits and inpatient admissions and the frequencies of HbA1c, lipid, serum creatinine, and uric acid testing.

Laboratory measurements included total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, serum creatinine, uric acid, HbA1c, plasma glucose, and 2-hour OGTT glucose. When multiple measurements were available during the baseline period, the measurement closest to the baseline date was used.

Statistical analysis

Missing values for baseline BMI and other laboratory measurements were addressed using multiple imputation by chained equations. The imputation model included CHM exposure, study outcomes, baseline covariates, and variables predictive of the incomplete measurements or their missingness. Imputation was conducted before propensity score estimation and outcome analysis.

Propensity scores were estimated using multivariable logistic regression, with CHM use as the dependent variable and all prespecified baseline covariates as independent variables. In the primary analysis, CHM users were matched 1:1 to control participants using nearest-neighbor matching on the logit of the propensity score, without replacement. A caliper width of 0.1 standard deviations of the logit of the propensity score was applied. Participants without an eligible match within the specified caliper were excluded from the matched analysis.

Baseline characteristics were summarized according to CHM exposure before and after propensity score matching. Continuous variables were reported as means with standard deviations, whereas categorical variables were presented as frequencies and percentages. Between-group balance was evaluated using standardized mean differences (SMDs), with an absolute SMD <0.10 indicating adequate covariate balance. Love plots were generated to visualize the SMDs before and after matching.

Person-time was calculated from the beginning of follow-up until the outcome or censoring. Incidence rates were calculated as the number of events divided by accumulated person-time and expressed per 1,000 person-years with 95% confidence intervals (CIs). Follow-up duration was summarized using the median and interquartile range. Cumulative event probabilities were estimated using Kaplan–Meier methods and presented graphically.

Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% CIs for the associations of CHM use with incident T2DM, all-cause mortality, and cardiovascular mortality.

Subgroup analyses

Subgroup analyses for incident T2DM were conducted according to sex, age, and BMI. HRs and 95% CIs were estimated within each subgroup. Potential heterogeneity in the association between CHM use and T2DM was evaluated using multiplicative interaction terms between CHM exposure and the corresponding subgroup variable. Given the number of comparisons, subgroup analyses were considered exploratory, and interpretation emphasized the interaction tests rather than the statistical significance of individual stratum-specific estimates.

Sensitivity analyses

Several sensitivity analyses were performed to assess the robustness of the primary findings. First, the propensity score-matching ratio was changed from 1:1 to 1:2 and 1:3. Second, alternative propensity score-weighting approaches were applied, including unstabilized inverse probability of treatment weighting, stabilized inverse probability of treatment weighting, truncated inverse probability of treatment weighting, and overlap weighting. Covariate balance and weight distributions were evaluated for each weighted analysis.

Third, the exposure-assessment window was extended from 30 days to 60, 90, and 180 days. For each analysis, exposure classification and the beginning of follow-up were realigned to the end of the corresponding exposure window to avoid immortal time bias.

Finally, exploratory analyses were conducted for the ten most frequently prescribed individual Chinese herbs. For each herb, a separate 1:1 propensity score match was performed within the full eligible cohort of 68,516 participants, comparing individuals with at least one recorded use of that specific herb during the 30-day exposure window against eligible individuals who did not receive that herb, using the same caliper of 0.1 standard deviations of the logit of the propensity score and the same covariates as the primary analysis. Post-match covariate balance was checked for each herb using standardized mean differences (all SMDs < 0.10). The matched sample sizes ranged from 1,000 to 4,000 pairs depending on herb-specific prevalence in the cohort. Associations with incident T2DM were estimated using Cox proportional hazards regression in each matched dataset. Because individual herbs were commonly prescribed as components of multi-herb formulas, there was substantial overlap in sampled individuals across herb-specific analyses, and because multiple comparisons were performed without formal multiplicity adjustment, these analyses were considered hypothesis-generating.

All statistical analyses were performed using R version 4.4.1. All statistical tests were two-sided, and a *P* value <0.05 was considered statistically significant.

Ethical considerations

This study received approval from the Ethics Committee of the First Affiliated Hospital of Xiamen University, with a waiver of informed consent ([2026] Scientific Research Ethics Review No. (130)). All data were deidentified before analysis, and the study was conducted in accordance with applicable ethical and data-protection requirements.

Results

Study population and baseline characteristics

A total of 76,412 individuals with newly diagnosed prediabetes were initially identified between January 2010 and January 2023. After applying the prespecified exclusion criteria, 68,516 individuals were included in the final cohort, comprising 5,370 CHM users and 63,146 non-CHM users (Figure 1). Propensity score matching generated 5,369 matched pairs.

Before matching, CHM users were slightly older and more likely to be female than non-CHM users. Several differences in medication use, comorbidities, and healthcare utilization were also observed. The largest imbalances were found in the number of outpatient visits (SMD=0.408), inpatient admissions (SMD=0.272), calcium-channel blocker use (SMD=0.255), proton-pump inhibitor use (SMD=0.231), and history of stroke (SMD=0.219). After 1:1 propensity score matching, all measured baseline characteristics were well balanced between the groups, with absolute SMDs below 0.10 (Table 1). The improvement in covariate balance after matching was also evident in the Love plot (Supplementary Figure S1).

Table 1. Baseline characteristics of the study population before and after propensity score matching

Characteristic	Before propensity score matching			After propensity score matching		
	Non-CHM group (N = 63,146)	CHM group (N = 5,370)	SMD	Non-CHM group (N = 5,369)	CHM group (N = 5,369)	SMD
Female sex	32,291 (51.14%)	2,969 (55.29%)	0.083	3,002 (55.91%)	2,968 (55.28%)	0.013
Age (years)	57.90 (14.37)	59.53 (14.47)	-0.113	59.46 (14.33)	59.54 (14.47)	-0.006
Age >=60 years	30,666	2,797	0.07	2,791 (51.98%)	2,797	0.002

	(48.56%)	(52.09%)			(52.10%)	
Ethnicity			0.019			0.019
Han	40,041 (63.41%)	3,455 (64.34%)		3,405 (63.42%)	3,454 (64.33%)	
Others	23,105 (36.59%)	1,915 (35.66%)		1,964 (36.58%)	1,915 (35.67%)	
Marital status			0.038			0.004
Married	46,539 (73.70%)	3,867 (72.01%)		3,876 (72.19%)	3,867 (72.02%)	
Unmarried/Others	16,607 (26.30%)	1,503 (27.99%)		1,493 (27.81%)	1,502 (27.98%)	
Smoking history			0.095			0.005
Yes	13,473 (21.34%)	944 (17.58%)		933 (17.38%)	944 (17.58%)	
No/Unknown	49,673 (78.66%)	4,426 (82.42%)		4,436 (82.62%)	4,425 (82.42%)	
Drinking history			0.025			0.001
Yes	8,980 (14.22%)	718 (13.37%)		719 (13.39%)	718 (13.37%)	
No/Unknown	54,166 (85.78%)	4,652 (86.63%)		4,650 (86.61%)	4,651 (86.63%)	
Insurance			0.015			0.002
UEBMI	29,358 (46.49%)	2,457 (45.75%)		2,456 (45.74%)	2,457 (45.76%)	
URBMI/Others	31,521 (49.92%)	2,717 (50.60%)		2,715 (50.57%)	2,716 (50.59%)	
Unknown	2,267 (3.59%)	196 (3.65%)		198 (3.69%)	196 (3.65%)	
BMI (kg/m2)	24.39 (3.89)	24.20 (3.93)	0.05	24.27 (3.90)	24.20 (3.93)	0.019
Medication use						
Metformin	10,551 (16.71%)	1,067 (19.87%)	0.082	1,076 (20.04%)	1,067 (19.87%)	0.004
Sulfonylureas	6,789 (10.75%)	833 (15.51%)	0.141	795 (14.81%)	833 (15.51%)	0.02
DPP-4 inhibitors	4,660 (7.38%)	524 (9.76%)	0.085	556 (10.36%)	524 (9.76%)	0.02
Glinides	2,286 (3.62%)	252 (4.69%)	0.054	268 (4.99%)	252 (4.69%)	0.014
Aspirin	11,397 (18.05%)	1,076 (20.04%)	0.051	1,049 (19.54%)	1,075 (20.02%)	0.012
Proton pump inhibitors	18,203 (28.83%)	2,134 (39.74%)	0.231	2,091 (38.95%)	2,133 (39.73%)	0.016
Diuretics	6,471 (10.25%)	712 (13.26%)	0.094	666 (12.40%)	712 (13.26%)	0.026
β-Blocking agents	10,491 (16.61%)	1,093 (20.35%)	0.096	1,071 (19.95%)	1,092 (20.34%)	0.01

Calcium channel blockers	13,401 (21.22%)	1,742 (32.44%)	0.255	1,711 (31.87%)	1,741 (32.43%)	0.012
Renin-angiotensin system inhibitors	13,213 (20.92%)	1,471 (27.39%)	0.152	1,429 (26.62%)	1,471 (27.40%)	0.018
Comorbidities						
Myocardial infarction	2,132 (3.38%)	118 (2.20%)	0.072	92 (1.71%)	118 (2.20%)	0.035
Stroke	11,670 (18.48%)	1,486 (27.67%)	0.219	1,440 (26.82%)	1,485 (27.66%)	0.019
Heart failure	5,349 (8.47%)	420 (7.82%)	0.024	411 (7.66%)	420 (7.82%)	0.006
Hypertension	37,761 (59.80%)	3,603 (67.09%)	0.152	3,599 (67.03%)	3,602 (67.09%)	0.001
Hyperlipidemia	32,330 (51.20%)	3,131 (58.31%)	0.143	3,052 (56.84%)	3,130 (58.30%)	0.029
Gout	5,199 (8.23%)	600 (11.17%)	0.099	542 (10.09%)	600 (11.18%)	0.035
Cancer	8,323 (13.18%)	996 (18.55%)	0.147	1,002 (18.66%)	996 (18.55%)	0.003
Health care utilization						
Outpatient visits			0.408			0.015
<=5	21,029 (33.30%)	1,326 (24.69%)		1,355 (25.24%)	1,326 (24.70%)	
6-10	11,131 (17.63%)	665 (12.38%)		668 (12.44%)	665 (12.39%)	
11-20	14,450 (22.88%)	946 (17.62%)		922 (17.17%)	946 (17.62%)	
>20	16,536 (26.19%)	2,433 (45.31%)		2,424 (45.15%)	2,432 (45.30%)	
Inpatient admissions			0.272			0.037
0	36,462 (57.74%)	2,382 (44.36%)		2,375 (44.24%)	2,382 (44.37%)	
1	19,112 (30.27%)	2,088 (38.88%)		2,159 (40.21%)	2,087 (38.87%)	
>1	7,572 (11.99%)	900 (16.76%)		835 (15.55%)	900 (16.76%)	
Frequency of HbA1c test			0.041			0.02
0	18,307 (28.99%)	1,610 (29.98%)		1,657 (30.86%)	1,609 (29.97%)	
1	31,779 (50.33%)	2,594 (48.31%)		2,549 (47.48%)	2,594 (48.31%)	
>1	13,060 (20.68%)	1,166 (21.71%)		1,163 (21.66%)	1,166 (21.72%)	
Frequency of lipid test			0.118			0.027

0	8,812 (13.95%)	628 (11.69%)		612 (11.40%)	627 (11.68%)	
1	30,803 (48.78%)	2,445 (45.53%)		2,517 (46.88%)	2,445 (45.54%)	
>1	23,531 (37.26%)	2,297 (42.77%)		2,240 (41.72%)	2,297 (42.78%)	
Frequency of creatinine testing			0.137			0.026
0	6,727 (10.65%)	447 (8.32%)		441 (8.21%)	447 (8.33%)	
1	30,173 (47.78%)	2,344 (43.65%)		2,413 (44.94%)	2,343 (43.64%)	
>1	26,246 (41.56%)	2,579 (48.03%)		2,515 (46.84%)	2,579 (48.04%)	
Frequency of uric acid testing			0.183			0.036
0	8,831 (13.99%)	513 (9.55%)		506 (9.42%)	513 (9.55%)	
1	30,605 (48.47%)	2,430 (45.25%)		2,523 (46.99%)	2,429 (45.24%)	
>1	23,710 (37.55%)	2,427 (45.20%)		2,340 (43.58%)	2,427 (45.20%)	
Laboratory test indicators						
Total cholesterol (mmol/L)	4.94 (1.25)	4.98 (1.29)	-0.033	5.02 (1.35)	4.98 (1.29)	0.029
Triglycerides (mmol/L)	1.75 (1.46)	1.71 (1.68)	0.031	1.73 (1.31)	1.71 (1.68)	0.019
HDL-C (mmol/L)	1.30 (0.38)	1.29 (0.39)	0.012	1.29 (0.37)	1.29 (0.39)	-0.014
LDL-C (mmol/L)	2.93 (1.02)	2.97 (1.03)	-0.037	3.00 (1.07)	2.97 (1.03)	0.029
Creatinine (mmol/L)	74.68 (38.73)	74.30 (42.67)	0.009	74.20 (43.59)	74.31 (42.67)	-0.002
Uric acid (mmol/L)	350.56 (105.90)	345.25 (102.69)	0.051	344.48 (104.32)	345.29 (102.67)	-0.008
HbA1c (%)	6.45 (1.21)	6.49 (1.28)	-0.034	6.50 (1.30)	6.49 (1.28)	0.01
Plasma glucose (mmol/L)	6.44 (1.48)	6.43 (1.59)	0.006	6.44 (1.43)	6.43 (1.59)	0.001
2-hour OGTT glucose (mmol/L)	8.82 (1.92)	8.76 (2.00)	0.03	8.79 (1.89)	8.76 (2.00)	0.011

Data are presented as n (%) or mean (SD). SMDs were used to assess covariate balance; an absolute SMD <0.10 was considered indicative of adequate balance. Abbreviations: BMI, body mass index; CHM, Chinese herbal medicine; DPP-4, dipeptidyl peptidase-4; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OGTT, oral glucose tolerance test; PSM, propensity score matching; SMD, standardized mean difference; UEBMI, Urban Employee Basic Medical Insurance; URBMI, Urban and Rural Resident Basic Medical Insurance.



Figure 1. Flowchart of study cohort selection. CHM, Chinese herbal medicine; eGFR, estimated glomerular filtration rate; PSM, propensity score matching; T2DM, type 2 diabetes mellitus.

Primary and secondary outcomes

During follow-up, 2,084 incident T2DM events occurred over 18,035 person-years in the CHM group, compared with 2,178 events over 16,813 person-years in the non-CHM group. The corresponding incidence rates were 115.55 (95% CI 110.70–120.62) and 129.54 (95% CI 124.21–135.10) per 1,000 person-years, respectively. CHM use was associated with a lower risk of progression to T2DM (HR 0.89, 95% CI 0.84–0.95; *P*<0.001; Table 2). Consistently, the Kaplan–Meier curves showed a higher probability of remaining free from T2DM among CHM users than among non-CHM users (log-rank *P*=0.00019; Figure 2A).

Table 2. Associations of Chinese herbal medicine use with incident type 2 diabetes and mortality outcomes after 1:1 propensity score matching

Outcome	**CHM group**			**Non-CHM group**			**Effect estimate**		
	Events/person-years	Median follow-up, years (SD)	Incidence rate per 1,000 person-years (95% CI)	Events/ person-years	Median follow-up, years (SD)	Incidence rate per 1,000 person-years (95% CI)	HR	95% CI	P value
Incident T2DM	2,084/18,035	3.36 (3.00)	115.55 (110.70-120.62)	2,178/16,813	3.13 (2.54)	129.54 (124.21-135.10)	0.89	0.84-0.95	<0.001
All-cause mortality	409/23,425	4.36 (3.34)	17.46 (15.85-19.24)	377/21,898	4.08 (2.77)	17.22 (15.56-19.04)	1.04	0.91-1.20	0.600
Cardiovascular mortality	111/23,425	4.36 (3.34)	4.74 (3.93-5.71)	106/21,898	4.08 (2.77)	4.84 (4.00-5.86)	0.99	0.76-1.29	>0.900

Incidence rates are expressed per 1,000 person-years. HRs were estimated using Cox regression in the 1:1 propensity score-matched cohort, with the non-CHM group as the reference. Abbreviations: CHM, Chinese herbal medicine; CI, confidence interval; HR, hazard ratio; SD, standard Deviation; T2DM, type 2 diabetes mellitus.

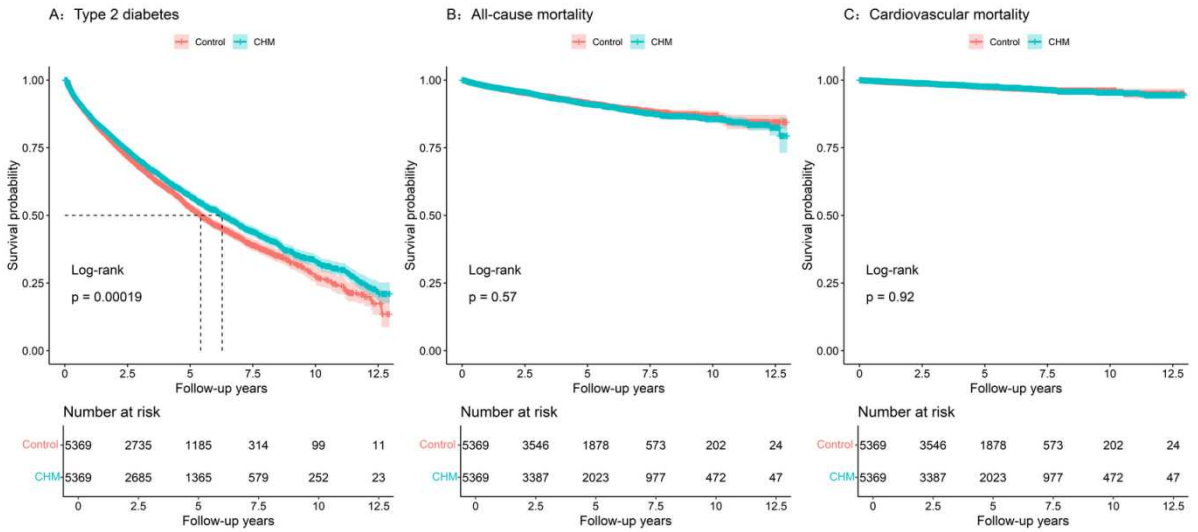


Figure 2. Kaplan–Meier curves for study outcomes in the propensity score-matched cohort. Kaplan–Meier curves comparing CHM users with non-CHM users for (A) progression to type 2 diabetes mellitus, (B) all-cause mortality, and (C) cardiovascular mortality. Numbers of participants at risk are presented below each panel. Differences between the groups were evaluated using log-rank tests. CHM, Chinese herbal medicine; T2DM, type 2 diabetes mellitus.

No evidence of an association was observed between CHM use and mortality. A total of 409 all-cause deaths occurred in the CHM group and 377 in the non-CHM group, corresponding to incidence rates of 17.46 and 17.22 per 1,000 person-years, respectively. The HR for all-cause mortality was 1.04 (95% CI 0.91–1.20; *P*=0.600). Cardiovascular mortality occurred in 111 CHM users and 106 non-CHM users, with incidence rates of 4.74 and 4.84 per 1,000 person-years, respectively. The corresponding HR was 0.99 (95% CI 0.76–1.29; *P*>0.900; Table 2). The Kaplan–Meier curves were also similar between the groups for all-cause mortality (log-rank *P*=0.57) and cardiovascular mortality (log-rank *P*=0.92; Figures 2B and 2C).

Subgroup analyses

The association between CHM use and incident T2DM was generally consistent across the examined subgroups (Table 3). Similar estimates were observed in men (HR 0.89, 95% CI 0.82–0.98) and women (HR 0.89, 95% CI 0.82–0.96), with no evidence of interaction by sex (*P* for interaction=0.991).

Table 3. Subgroup analyses of the association between Chinese herbal medicine use and incident type 2 diabetes after 1:1 propensity score matching

Outcome	CHM group			Non-CHM group			Effect estimate		P for interaction
	Events/person-years	Median follow-up, years (SD)	Incidence rate per 1,000 person-years (95% CI)	Events/person-years	Median follow-up, years (SD)	Incidence rate per 1,000 person-years (95% CI)	HR	95% CI	P value
Overall	2,084/18,035	3.36 (3.00)	115.55 (110.70-120.62)	2,178/16,813	3.13 (2.54)	129.54 (124.21-135.10)	0.89	0.84 - 0.95	<0.001
Male	983/7,948	3.31 (3.06)	123.68 (116.18-131.66)	999/7,194	3.04 (2.52)	138.87 (130.52-147.75)	0.89	0.82 - 0.98	0.013
Female	1,101/10,087	3.40 (2.95)	109.15 (102.89-115.79)	1,179/9,620	3.20 (2.54)	122.56 (115.76-129.76)	0.89	0.82 - 0.96	0.005
Age >=45 years	1,702/14,267	3.16 (2.87)	119.30 (113.76-125.10)	1,814/13,850	3.04 (2.45)	130.97 (125.08-137.14)	0.91	0.85 - 0.97	0.006
Age >=60 years	1,103/8,233	2.94 (2.71)	133.97 (126.30-142.12)	1,148/7,940	2.84 (2.33)	144.58 (136.46-153.19)	0.93	0.85 - 1.01	0.071
BMI <24 kg/m2	1,098/8,545	3.18 (2.89)	128.50 (121.12-136.33)	1,094/8,043	3.05 (2.52)	136.02 (128.19-144.32)	0.95	0.87 - 1.03	0.196
BMI >=24 kg/m2	986/9,490	3.54 (3.10)	103.90 (97.61-110.59)	1,084/8,770	3.21 (2.55)	123.60 (116.46-131.18)	0.84	0.77 - 0.91	<0.001

Incidence rates are expressed per 1,000 person-years. HRs were estimated using Cox regression in the 1:1 propensity score-matched cohort, with the non-CHM group as the reference. P values for interaction assess heterogeneity in the association across the corresponding subgroup categories. Subgroup analyses were exploratory. Abbreviations: BMI, body mass index; CHM, Chinese herbal medicine; CI, confidence interval; HbA1c, glycated hemoglobin; HR, hazard ratio; SD, standard Deviation; T2DM, type 2 diabetes mellitus.

Among participants aged ≥45 years, CHM use was associated with a lower risk of T2DM (HR 0.91, 95% CI 0.85–0.97). The estimate was attenuated among those aged ≥60 years and its CI included the null (HR 0.93, 95% CI 0.85–1.01). The reported interaction *P* value was 0.053.

Evidence of heterogeneity was observed according to BMI (*P* for interaction=0.009). The association was stronger among participants with BMI ≥24 kg/m^2 (HR 0.84, 95% CI 0.77–0.91), whereas no clear association was observed among those with BMI <24 kg/m^2 (HR 0.95, 95% CI 0.87–1.03).

Sensitivity analyses

The primary finding remained consistent across multiple sensitivity analyses (Table 4). Changing the propensity score-matching ratio to 1:2 or 1:3 produced identical HRs of 0.91, with 95% CIs excluding 1. Results obtained using alternative propensity score-weighting approaches were also similar. The HRs were 0.93 with unstabilized, stabilized, and truncated inverse probability of treatment weighting and 0.89 with overlap weighting.

Table 4. Sensitivity analyses of the association between Chinese herbal medicine use and incident type 2 diabetes

Analysis	**CHM group**			**Non-CHM group**			**Effect estimate**		
	Events/person-years	Median follow-up, years (SD)	Incidence rate per 1,000 person-years (95% CI)	Events/person-years	Median follow-up, years (SD)	Incidence rate per 1,000 person-years (95% CI)	HR	95% CI	P value
1:2 propensity score matching	2,084/18,035	3.36 (3.00)	115.55 (110.70-120.62)	4,316/33,931	3.16 (2.54)	127.20 (123.46-131.05)	0.91	0.86-0.96	<0.001
1:3 propensity score matching	2,084/18,035	3.36 (3.00)	115.55 (110.70-120.62)	6,443/50,510	3.14 (2.54)	127.56 (124.48-130.71)	0.91	0.86-0.95	<0.001
Unstabilized IPTW	25,721/225,673	3.36 (3.00)	113.97 (112.59-115.38)	26,780/219,355	3.21 (2.55)	122.09 (120.63-123.56)	0.93	0.88-0.98	0.006
Stabilized IPTW	2,016/17,687	3.36 (3.00)	113.98 (109.11-119.07)	24,681/202,163	3.21 (2.55)	122.08 (120.57-123.62)	0.93	0.89-0.98	0.006
Truncated IPTW	1,919/16,946	3.36 (3.00)	113.24 (108.29-118.42)	24,681/202,162	3.21 (2.55)	122.09 (120.57-123.62)	0.93	0.88-0.97	0.002
Overlap weighting	1,861/16,165	3.36 (3.00)	115.13 (110.01-120.48)	1,937/15,018	3.21 (2.55)	128.98 (123.36-134.85)	0.89	0.85-0.94	<0.001

60-day exposure window	2,412/21,716	3.37 (2.94)	111.07 (106.72-115.59)	2,515/20,348	3.16 (2.51)	123.60 (118.86-128.53)	0.9	0.85-0.95	<0.001
90-day exposure window	2,665/24,484	3.36 (2.90)	108.85 (104.79-113.06)	2,770/23,475	3.22 (2.49)	118.00 (113.68-122.48)	0.92	0.87-0.97	0.003
180-day exposure window	3,037/30,621	3.42 (2.84)	99.18 (95.71-102.77)	3,247/30,279	3.38 (2.48)	107.24 (103.61-110.99)	0.92	0.88-0.97	0.001

Incidence rates are expressed per 1,000 person-years. Event counts and person-years in weighted analyses represent weighted quantities. HRs were estimated using Cox regression, with the non-CHM group as the reference. For alternative exposure windows, CHM exposure was reassessed during the corresponding window and follow-up began immediately after the end of that window. Abbreviations: CHM, Chinese herbal medicine; CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; SD, standard Deviation.

Extending the CHM exposure-assessment window did not materially alter the results. The HR was 0.90 (95% CI 0.85–0.95) using a 60-day window, 0.92 (95% CI 0.87–0.97) using a 90-day window, and 0.92 (95% CI 0.88–0.97) using a 180-day window. Across all sensitivity analyses, the estimated HRs ranged from 0.89 to 0.93 and remained statistically compatible with a lower risk of T2DM among CHM users.

Exploratory analyses of individual herbs

In exploratory analyses of the ten most frequently prescribed Chinese herbs, use of Gan-Cao (Glycyrrhiza uralensis), Fu-Ling (Wolfiporia cocos), and Dang-Gui (Angelica sinensis) was associated with a lower risk of incident T2DM after propensity score matching (Table 5). The corresponding HRs were 0.89 (95% CI 0.82–0.97), 0.90 (95% CI 0.82–0.98), and 0.87 (95% CI 0.78–0.98), respectively.

Table 5. Associations of the ten most frequently prescribed individual Chinese herbs with incident type 2 diabetes after propensity score matching

Chinese herb	**CHM group**			**Non-CHM group**			**Effect estimate**		
	Events/person-years	Median follow-up, years (SD)	Incidence rate per 1,000 person-years (95% CI)	Events/person-years	Median follow-up, years (SD)	Incidence rate per 1,000 person-years (95% CI)	HR	95% CI	P value
Gan-Cao (Glycyrrhiza uralensis)	1,071/9,281	3.33 (2.99)	115.40 (108.69-122.52)	1,125/8,745	3.13 (2.51)	128.64 (121.34-136.39)	0.89	0.82-0.97	0.009

Fu-Ling (Wolfiporia cocos)	892/7,336	3.14 (2.93)	121.59 (113.87-129.84)	947/6,955	2.98 (2.43)	136.16 (127.76-145.12)	0.9	0.82 - 0.98	0.021
Huang-Qi (Astragalus mongholicus)	767/6,095	3.10 (2.89)	125.84 (117.24-135.07)	807/5,964	3.03 (2.48)	135.31 (126.29-144.98)	0.93	0.85 - 1.03	0.200
Bai-Zhu (Atractylodes macrocephala)	655/5,248	3.15 (2.92)	124.81 (115.61-134.74)	682/5,189	3.11 (2.57)	131.43 (121.93-141.68)	0.95	0.85 - 1.06	0.300
Di-Huang (Rehmannia glutinosa)	508/4,393	3.43 (3.08)	115.64 (106.01-126.14)	509/4,009	3.13 (2.54)	126.96 (116.40-138.49)	0.91	0.80 - 1.03	0.120
Bai-Shao (Paeonia lactiflora)	578/4,599	3.21 (2.94)	125.68 (115.84-136.35)	572/4,364	3.04 (2.52)	131.07 (120.76-142.27)	0.96	0.86 - 1.08	0.500
Dang-Gui (Angelica sinensis)	566/4,759	3.23 (2.85)	118.93 (109.53-129.15)	605/4,457	3.02 (2.50)	135.74 (125.34-147.00)	0.87	0.78 - 0.98	0.022
Chen-Pi (Citrus reticulata)	518/4,149	2.96 (2.78)	124.85 (114.55-136.08)	548/4,236	3.03 (2.44)	129.37 (118.98-140.67)	0.97	0.86 - 1.09	0.600
Dan-Shen (Salvia miltiorrhiza)	421/3,585	3.51 (3.05)	117.43 (106.74-129.20)	426/3,189	3.12 (2.53)	133.58 (121.48-146.89)	0.88	0.77 - 1.01	0.062
Dang-Shen (Codonopsis pilosula)	510/4,059	3.04 (2.84)	125.65 (115.20-137.04)	539/4,017	3.01 (2.47)	134.18 (123.32-146.00)	0.94	0.83 - 1.06	0.300

Incidence rates are expressed per 1,000 person-years. For each herb, users were compared with propensity score-matched nonusers of that herb. HRs were estimated using Cox regression, with nonusers as the reference. Individual herbs were frequently co-prescribed as components of multi-herb formulas; therefore, the estimates should not be interpreted as independent effects of single herbs. These analyses were exploratory, and P values were not adjusted for multiple comparisons. Abbreviations: CHM, Chinese herbal medicine; CI, confidence interval; HR, hazard ratio; SD, standard Deviation; T2DM, type 2 diabetes mellitus.

No clear associations were observed for Huang-Qi, Bai-Zhu, Di-Huang, Bai-Shao, Chen-Pi, Dan-Shen, or Dang-Shen, although the estimate for Dan-Shen suggested a possible inverse association (HR 0.88, 95% CI 0.77–1.01; *P*=0.062). Because the analyses were exploratory, individual herbs were commonly co-prescribed, and no adjustment was made for multiple comparisons, these findings should be interpreted cautiously.

Discussion

In this population-based cohort study conducted within a target trial emulation framework, initiation of Chinese herbal medicine (CHM) after the identification of prediabetes was associated with a modestly lower risk of progression to type 2 diabetes mellitus (T2DM). After 1:1 propensity score matching, 5,369 CHM users were compared with 5,369 non-users. CHM initiation within the 30-day exposure window was associated with an approximately 11% lower hazard of incident T2DM (hazard ratio [HR] 0.89, 95% confidence interval [CI] 0.84–0.95; $P<0.001$). The protective association was consistent on both absolute and survival scales: incidence rates were 115.55 and 129.54 per 1,000 person-years in the CHM and non-CHM groups, respectively (absolute difference ≈14 per 1,000 person-years), and Kaplan–Meier curves showed a higher probability of remaining free from T2DM among CHM users (log-rank $P=0.00019$; Figure 2A). The effect size was relatively modest, and this should be interpreted in light of the study design. Exposure was broadly defined as any recorded CHM prescription within 30 days, capturing highly heterogeneous formulations (decoctions, granules, and proprietary products) with variable composition and dosing; in addition, an intention-to-treat strategy was adopted, whereby participants were classified by baseline exposure status and subsequent discontinuation or crossover was not tracked. Both features introduce dilution bias toward the null [11,27]. That a statistically significant 11% reduction was nevertheless detected under this conservative specification suggests the signal is unlikely to be a design artifact and more plausibly reflects a conservative estimate of the average causal effect of initiating CHM in real-world practice.

An important feature of this study was the choice of individuals who did not initiate CHM as the comparator. This comparison reflects a clinically relevant decision encountered in the routine management of prediabetes: whether to initiate CHM in addition to the usual care received after prediabetes is identified. Lifestyle modification remains the foundation of prediabetes management, whereas glucose-lowering medications are generally reserved for patients selected by diabetes risk, comorbidities, and preference, and are not routinely initiated in every patient with prediabetes. Comparing CHM users exclusively with Western glucose-lowering medication users would therefore restrict the study population to those for whom pharmacologic intervention had already been selected and would address a different clinical question. Our comparator broadens the applicability of the findings to the general prediabetes population and provides evidence on the potential value of initiating CHM under real-world conditions [11,27].

The robustness of the primary finding was supported by the convergence of multiple identification strategies. In sensitivity analyses, 1:1, 1:2, and 1:3 propensity score matching yielded HRs of 0.89, 0.91, and 0.91, respectively; the four inverse probability of treatment weighting variants gave HRs from 0.89 (overlap weighting) to 0.93 (unstabilized, stabilized, and truncated weighting), with overlap weighting coinciding exactly with the primary estimate [40]. Matching and weighting rely on different

assumptions about ignorability, and their convergence reduces concern that a single, misspecified identifying assumption generated a false-positive result [23,24]. Extending the exposure-assessment window from 30 to 60, 90, and 180 days produced HRs of 0.90, 0.92, and 0.92, with unchanged direction and significance, indicating that the 30-day window was not the source of a positive finding. Covariate balance improved substantially after matching: the largest pre-match imbalances were observed for number of outpatient visits (standardized mean difference [SMD] 0.408), inpatient admissions (0.272), calcium-channel blocker use (0.255), proton-pump inhibitor use (0.231), and history of stroke (0.219), whereas all measured covariates had absolute SMDs below 0.10 after 1:1 matching (Table 1; Supplementary Figure S1). Missing baseline body mass index and laboratory values were addressed by multiple imputation by chained equations before propensity score estimation, limiting bias from missingness [22].

Subgroup analyses revealed a clinically meaningful effect modification by body mass index. A statistically significant interaction was observed across BMI strata (*P* for interaction=0.009): the association was strongest among participants with BMI ≥24 kg/m^2 (HR 0.84, 95% CI 0.77–0.91; *P*<0.001), whereas it attenuated and crossed the null among those with BMI <24 kg/m^2 (HR 0.95, 95% CI 0.87–1.03; *P*=0.196). This is compatible with the greater insulin resistance and larger metabolic dysregulation amenable to intervention in overweight and obese individuals [33]. No interaction was detected by sex (men: HR 0.89, *P*=0.013; women: HR 0.89, *P*=0.005; *P* for interaction=0.991). Age-related effects were borderline: among participants aged ≥45 years the HR was 0.91 (95% CI 0.85–0.97; *P*=0.006; *P* for interaction=0.053), and among those aged ≥60 years the estimate shifted toward the null (HR 0.93, 95% CI 0.85–1.01; *P*=0.071), an observation that requires consideration of competing risks and follow-up structure (see below).

In contrast, no association was observed between CHM use and mortality. A total of 409 all-cause deaths occurred in the CHM group and 377 in the non-CHM group, corresponding to incidence rates of 17.46 and 17.22 per 1,000 person-years (HR 1.04, 95% CI 0.91–1.20; *P*=0.600). Cardiovascular mortality occurred in 111 and 106 participants, respectively (rates 4.74 and 4.84 per 1,000 person-years; HR 0.99, 95% CI 0.76–1.29; *P*>0.900). Kaplan–Meier curves were similar between groups (log-rank *P*=0.57 and 0.92 for all-cause and cardiovascular mortality, respectively). The neutral mortality result carries two implications. First, it is reassuring from a safety perspective: CHM use in routine practice was not associated with short-term increases in mortality. Second, it is an expected null: as discussed below, mortality is a very long-latency endpoint in diabetes prevention, and the neutral finding more likely reflects follow-up duration and event structure than a true absence of effect.

Exploratory analyses of the ten most frequently prescribed individual herbs suggested that Gan-Cao (Glycyrrhiza uralensis; HR 0.89, *P*=0.009), Fu-Ling (Wolfiporia cocos; HR 0.90, *P*=0.021), and Dang-Gui (Angelica sinensis; HR 0.87, *P*=0.022) were each associated with a lower risk of incident T2DM, whereas Dan-Shen (Salvia miltiorrhiza) was marginally suggestive (HR 0.88, *P*=0.062) [34]. The remaining seven herbs yielded

point estimates in the protective direction that did not reach significance (Huang-Qi (*Astragalus membranaceus*; anti-diabetic phytochemical constituents reviewed [39]) 0.93, Bai-Zhu 0.95, Di-Huang 0.91, Bai-Shao 0.96, Chen-Pi 0.97, Dang-Shen 0.94). These three significant signals may map onto distinct pharmacologic nodes: glycyrrhizin and its derivatives improve insulin signaling through the PI3K/Akt pathway and inhibit key gluconeogenic enzymes [17]; triterpenoids from *Poria* are identified α-glucosidase inhibitors that delay intestinal glucose absorption [19]; and Angelica polysaccharides alleviate hyperglycemia by remodeling the gut microbiota (e.g., restoring *Bifidobacterium* and *Akkermansia*) with short-chain fatty acid metabolites acting on the gut–pancreas axis to promote GLP-1 [18]. Together they span three complementary mechanisms—improving insulin resistance, delaying glucose absorption, and modulating the gut microbiome. It must be emphasized, however, that these estimates reflect the signal of "formulas containing the herb" rather than the independent causal effect of a single herb, and that no adjustment was made for multiple comparisons; any significant result may therefore include false positives. Their value lies in prioritizing subsequent formula-deconstruction and active-component studies, not in supporting the independent use of individual herbs [43].

Our findings are consistent with emerging clinical and real-world evidence that CHM may delay progression to diabetes. In the FOCUS randomized clinical trial, Jinlida granules reduced the risk of diabetes among participants with impaired glucose tolerance and multiple metabolic abnormalities compared with placebo (HR 0.59, 95% CI 0.46–0.74) [9], accompanied by improvements in fasting and postprandial glucose, HbA1c, insulin resistance, waist circumference, and lipid profiles. A recent population-based cohort study from Yinzhou reported a lower risk of T2DM among prediabetes patients using traditional Chinese medicine compared with those initiating Western glucose-lowering medications (HR 0.32, 95% CI 0.27–0.38) [8]. The association observed in our study (HR 0.89) was smaller than both but in the same direction. This "conventional cohort (0.32) → randomized trial (0.59) → target trial emulation (0.89)" gradient corresponds reasonably to the strictness of bias control across designs: conventional observational cohorts are susceptible to immortal-time and prevalent-user biases that can underestimate the hazard ratio [10,25,26,27]; randomized trials have the highest internal validity but smaller, selected samples and a single formulation under controlled conditions; our study eliminated immortal-time bias through an explicit 30-day exposure window and uniform day-31 follow-up and balanced measured covariates through PSM/IPTW, yielding a more conservative estimate [10,11,27]. The three sets of results are not contradictory but together delineate the credible interval of the CHM prediabetes-prevention effect. Our "no-CHM" comparator further clarifies that the 0.89 estimate reflects the incremental association of adding CHM in a broad prediabetes population rather than a head-to-head comparison with active Western pharmacotherapy [8].

Compared with non-CHM prevention strategies, our 11% reduction is considerably more modest than the 58% reduction with lifestyle intervention and 31% with metformin in the Diabetes Prevention Program [7], and lower than the 25% reduction

(HR 0.75) with acarbose among impaired-glucose-tolerance participants in STOP-NIDDM [32]. The difference mainly reflects that our estimate is a real-world intention-to-treat effect that includes heterogeneous, potentially non-standardized CHM formulations and permits crossover, rather than the efficacy of a controlled intervention; CHM is therefore more appropriately positioned as a complement to, rather than a substitute for, lifestyle and evidence-based pharmacotherapy.

The neutral mortality result is consistent with the experience of long-term prevention trials, in which survival and cardiovascular benefits of diabetes prevention typically require 10–20 years of follow-up to become detectable—the Da Qing 20-year and 30-year follow-ups and the DPP/DPPOS 10-year and 15-year follow-ups all indicated that mortality or microvascular differences emerged only at later time points [6,28,29,30]. In the present study, median T2DM follow-up was 3.13–3.36 years and mortality follow-up 4.08–4.36 years, with a cardiovascular death rate below 5 per 1,000 person-years, consistent with limited power to detect a mortality difference over this interval.

Several results remain unresolved and warrant further clarification. First, the attenuated effect in the elderly deserves scrutiny. The HR of 0.93 (CI crossing 1; P=0.071) in the ≥60 group and the borderline interaction (P=0.053) in the ≥45 group are both marginal. Older individuals carry a higher risk of all-cause death; in our cohort, 409 deaths occurred in the CHM group and 377 in the non-CHM group over a mean 4.36 and 4.08 years of follow-up, respectively, and death as a competing event for T2DM may underestimate cumulative incidence and bias the HR toward 1 [41]. We recommend replicating the elderly analysis with a competing-risk model (cumulative incidence function) and extending follow-up to distinguish true nullity from event-structure-driven neutrality. Second, the herb exploration yielded only three significant signals without multiple-comparison adjustment, and exposure was defined as "prescription containing the herb" rather than independent single-herb treatment, so the findings reflect combined-formula signals. Dan-Shen, marginally suggestive (P=0.062), merits replication in larger samples [34]. Clarifying pathways include decoction deconstruction to identify core herb pairs or groups, randomized trials of the significant formulas, and embedding mechanistic subcohorts (fecal microbiota sequencing, serum metabolomics, inflammatory and islet-function markers) to directly test the proposed pathways [17–19]. Third, although the stronger effect in the BMI ≥24 subgroup reached statistical significance (interaction P=0.009), subgroup analyses are exploratory, and their generalizability should be confirmed in independent cohorts using established subgroup-credibility criteria [43].

This study has several limitations. First, as with all observational studies, residual confounding cannot be excluded despite extensive adjustment and post-match SMDs below 0.10. The pre-match outpatient-visit SMD of 0.408 indicates that CHM choosers had higher healthcare utilization; although this was balanced by matching, unmeasured healthy behaviors, diet, or "prevention"-oriented health beliefs may persist and overestimate the true effect [42]. To quantify this, the primary HR of 0.89 (0.84–0.95) yields an E-value of approximately 1.50 at the point estimate and 1.67 at the confidence limit, implying that an unmeasured confounder would require a hazard ratio of at least

1.50 to fully explain the association; the all-cause mortality upper confidence limit of 1.20 corresponds to an E-value of 1.70, suggesting the neutral mortality conclusion is also reasonably robust to moderately strong residual confounding [20,21]. The E-value, however, cannot replace a prospective design. Second, exposure heterogeneity and the intention-to-treat specification warrant caution. The "any CHM prescription" definition mixed highly heterogeneous interventions, diluting the within-group true effect (a conservative bias), and we estimated only the ITT effect without modeling treatment switches during follow-up (per-protocol effects would require g-methods such as inverse probability of censoring weighting [11,40]); no dose–response relation was constructed, and prescription records did not fully capture adherence, treatment duration, dose, or CHM obtained outside the healthcare system, so exposure misclassification would generally attenuate the observed difference. Third, outcome ascertainment relied on ICD-10 E11 codes or the first glucose-lowering prescription; some progressors who did not seek timely care were classified as non-progressors, which tends to conservatively bias the effect estimate [15]. Fourth, the number of deaths and the short follow-up, together with competing risks, limit mortality analysis; moreover, the study was conducted within a single regional healthcare system (Xiamen, an affluent coastal area) whose CHM accessibility, diet, and prescribing traditions differ from northern, western, and rural China [3,15], so external validation in other populations is warranted. As partial mitigation, we applied multiple imputation, adhered to the TARGET reporting guideline [22], and included an extensive set of demographic, clinical, laboratory, medication, and healthcare-utilization covariates [14–16]; these measures, however, cannot remove the structural limitations above.

For researchers in the field, this study illustrates the feasibility and rigor of applying the target trial emulation framework to evaluate a complex traditional medicine intervention, and provides effect-modification evidence (with the BMI ≥24 subgroup prioritized) for "which prediabetes patients are more likely to benefit," which can directly inform subgroup hypotheses in subsequent cohorts and trials. For researchers in adjacent fields—real-world evidence methodology and big-data chronic-disease prevention—it illustrates how a regional-level healthcare database can be transformed into a target trial that answers causal questions, with methodological value transferable to the evaluation of other complex interventions such as acupuncture [14–16]. For clinicians, public health practitioners, and policymakers, the findings suggest that initiating CHM in real-world practice is associated with a lower risk of prediabetes progression, with a stronger signal in the overweight subgroup and no short-term increase in mortality, supporting the inclusion of CHM as a complementary option in stratified prediabetes prevention pathways and "prevention before disease" practice [37,38]; realization requires evidence-based guidelines and reimbursement design, with confirmation studies prioritized in the subgroups showing the strongest benefit signals.

Prior evidence on CHM for prediabetes progression came mainly from single-center randomized trials (e.g., FOCUS [9]) or conventional observational cohorts (e.g., Long et al. [8]); the former are limited in generalizability and the latter prone to design bias that can inflate effects. Building on these, the present study integrated the target trial

emulation framework, a regional big-data platform, a grid of PSM/IPTW sensitivity analyses, and exploration of effect modification and herb composition, filling the gap of "evaluating the causal effect of CHM under strict bias control using real-world big data while characterizing effect heterogeneity and compositional signals," and thereby yielding conclusions with both internal validity and external relevance, and providing a demonstration of TARGET-compliant causal evaluation for complex traditional medicine interventions [22].

In light of the unresolved and limited aspects above, we suggest several directions. First, external validation cohorts should be established on multi-region platforms with different economic and geographic profiles to test the reproducibility of the effect and its effect modification. Second, competing-risk models with extended follow-up should be applied in the elderly subgroup to confirm whether the age-related attenuation is real. Third, building on the herb signals, decoction-deconstruction and core-formula randomized trials should be conducted. Fourth, mechanistic subcohorts (microbiota, metabolomics, inflammatory and islet-function markers) should be embedded in real-world cohorts to convert proposed pharmacologic pathways into human evidence. Fifth, cumulative CHM exposure metrics should be constructed to support dose–response analysis.

In conclusion, this target trial emulation study based on the Xiamen regional health database suggests that initiating CHM in real-world management of prediabetes is associated with an approximately 11% lower risk of progression to T2DM (HR 0.89; E-value 1.50), with a stronger signal in the high-metabolic-burden BMI ≥24 kg/m^2 subgroup, whereas all-cause and cardiovascular mortality were neutral. The findings provide preliminary real-world evidence supporting the inclusion of CHM in stratified prediabetes prevention strategies and demonstrate the application of the target trial emulation framework to complex traditional medicine interventions.

Conclusions

This target trial emulation study based on the Xiamen regional health database suggests that initiating CHM in real-world management of prediabetes is associated with an approximately 11% lower risk of progression to T2DM (HR 0.89; E-value 1.50), with a stronger signal in the high-metabolic-burden BMI ≥24 kg/m^2 subgroup, whereas all-cause and cardiovascular mortality were neutral. The findings provide preliminary real-world evidence supporting the inclusion of CHM in stratified prediabetes prevention strategies and demonstrate the application of the target trial emulation framework to complex traditional medicine interventions.

List of abbreviations

CHM: Chinese herbal medicine; T2DM: type 2 diabetes mellitus; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; OGTT: oral glucose tolerance test; HbA1c: glycated hemoglobin; BMI: body mass index; eGFR: estimated glomerular filtration rate;

SMD: standardized mean difference; PSM: propensity score matching; IPTW: inverse probability of treatment weighting; HR: hazard ratio; CI: confidence interval; DEEP: Drug Exposures and Pregnancy outcomes cohort; IDF: International Diabetes Federation; DPP: Diabetes Prevention Program; FOCUS: a randomized clinical trial of Jinlida for diabetes prevention; RCT: randomized controlled trial; TTE: target trial emulation.

Declarations

Ethics approval and consent to participate

This study received approval from the Ethics Committee of the First Affiliated Hospital of Xiamen University, with a waiver of informed consent ([2026] Scientific Research Ethics Review No. (130)). All data were deidentified before analysis, and the study was conducted in accordance with applicable ethical and data-protection requirements.

Availability of data and materials

The data used in this study were obtained from the Xiamen Regional Health Care Database and are not publicly available owing to patient privacy protections and the data-use agreement with the data custodian. The minimal dataset supporting the conclusions of this article is available from the corresponding author upon reasonable request and with permission of the Xiamen Municipal Health Commission.

Competing interests

The authors declare that they have no competing interests.

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