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STUDY PROTOCOL

# Evaluating the Safety and Efficacy of Sodium-Glucose Co-transporter 2 Inhibitors in Subjects with Prediabetes: A Protocol for a Randomized Controlled Trial

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## ABSTRACT

***Introduction*:** Prediabetes is a state of subclinical glycemic impairment, bridging normal glucose tolerance and diabetes. Globally, over 30% of individuals exhibit prediabetic conditions, with a significant proportion progressing to diabetes. Prediabetes augments risks of various diseases including cardiovascular and kidney disease. While interventions like lifestyle changes have shown promise in diabetes prevention, their long-term sustainability is challenging. Alternative pharmacological treatments, such as acarbose and metformin, have demonstrated efficacy in certain populations. Sodium-glucose co-transporter 2 inhibitors, a novel class of glucose-lowering agents, have shown potential benefits for heart and kidney health in patients with diabetes. This research aims to evaluate the effectiveness and safety of dapagliflozin in individuals with prediabetes, elucidating its potential role in diabetes prevention strategies.

***Research Design and Methods*:** This prospective trial is being conducted at Peking University Third Hospital. A total of 240 participants with prediabetes will be enrolled and randomly divided into two groups: one receiving dapagliflozin (10 mg/day) with lifestyle education, and the other with lifestyle education alone over a 12-week duration (with male/female = 1:1 in each group). Anthropometric, clinical and laboratory tests, including body mass index, waist circumference, fasting blood glucose, oral glucose tolerance test, insulin, lipid profile, liver and kidney function, sperm quality, will be conducted at the onset and conclusion of the trial. For adherence monitoring, participants will receive phone follow-ups at week 4 and week 8. The primary outcome is the change in 2-h plasma glucose during an oral glucose tolerance test over the study duration. Secondary outcomes encompass changes in various health metrics, including body mass index, lipid profiles, and liver function.

***Planned Outcomes*:** The proposed study is set to refine diabetes prevention strategies on the basis of its potential benefits observed in patients with diabetes.

***Conclusions*:** This will be the first randomized controlled trial to evaluate the safety and effectiveness of sodium-glucose co-transporter 2

Xiaxuan Zhu and Li Xia contributed equally to this work.

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inhibitors compared with lifestyle education for individuals with prediabetes.
***Trial Registration***: ClinicalTrials.gov identifier NCT05914857 (registered 24 July 2023).

**Keywords:** Prediabetes; Sodium-glucose co-transporter 2 inhibitors; Prediabetes management

| Key Summary Points |
| --- |
| Prediabetes is a major risk factor for severe health conditions, including cardiovascular and kidney diseases, cancer, and dementia. |
| Current strategies to prevent the progression from prediabetes to diabetes include lifestyle programs, metformin, and acarbose, but the effectiveness of other interventions is less clear. |
| The randomized controlled trial aims to evaluate the efficacy and safety of sodium-glucose co-transporter 2 inhibitors in people with prediabetes, incorporating a gender-based analysis for personalized benefits and robust safety profiles. |
| The research aims to provide clinically relevant endpoints to translate findings into actionable prevention strategies, focusing on glycemic control, weight loss, and other metabolic parameters. |
| The findings from this study could significantly impact diabetes prevention strategies by introducing sodium-glucose co-transporter 2 inhibitors as a viable option for individuals with prediabetes. |

## INTRODUCTION

Prediabetes is a state characterized by subclinical impairment in glycemic variables that falls between normal glucose tolerance and diabetes. Diagnostic criteria for prediabetes have evolved over time and vary across institutions. Prevalent definitions for prediabetes, proposed by the American Diabetes Association and the World Health Organization, encapsulate conditions such as impaired glucose tolerance (IGT), impaired fasting glucose (IFG), and a glycosylated hemoglobin A1c (HbA1c) level fluctuating between 5.7% and 6.4% [1]. The global prevalence of prediabetes is alarmingly high, with more than 30% of the population demonstrating one or more forms of prediabetic dysglycemia [2, 3]. Moreover, approximately 5–10% of people with impaired glucose regulation progress to diabetes annually [4, 5], up to 70% of individuals with IFG and/or IGT go on to develop clinical type 2 diabetes at some time in the future [5], and the risk significantly increases with higher HbA1c levels or body mass index (BMI) [6]. Additionally, prediabetes is associated with dyslipidemia and microvascular dysfunction, and increases the risk and incidence of atherosclerotic cardiovascular disease, chronic kidney disease, cancer, and dementia [7–10]. Given the escalating prevalence of prediabetes worldwide and its potential complications, identifying and treating individuals with prediabetes is of utmost importance. Recent evidence suggests that it is possible to prevent the progression from prediabetes to diabetes through lifestyle programs and metformin [11]. It is necessary to evaluate whether other interventions are effective, thus providing more evidence for diabetes prevention.

The current paradigm for diabetes prevention in high-risk individuals focuses on weight loss through dietary changes and physical activity. While lifestyle-centric weight-loss strategies have exhibited initial success, sustainability often poses a challenge [12, 13]. In some cases, pharmacologic treatments, such as acarbose and metformin, which have been used to control blood glucose in patients with diabetes, are used to prevent diabetes. Acarbose is currently the only drug approved for the treatment of IGT in China [14]. The multicenter randomized clinical trial (RCT) STOP-NIDDM has demonstrated that acarbose reduces the risk of IGT progressing to diabetes by 25% over 3.3 years [15]. Furthermore, findings from the Acarbose Cardiovascular Evaluation study have revealed that acarbose substantially decreases the incidence of diabetes,

although it does not significantly reduce the risk of major adverse cardiovascular events in Chinese patients with IGT and coronary heart disease [16]. Metformin is another recommended medication for patients with prediabetes [17], with RCTs demonstrating its efficacy in preventing insulin resistance syndrome, microvascular diseases, and heart attacks [18, 19]. In an open-label, multicenter RCT study, metformin plus lifestyle intervention reduces the risk of developing diabetes compared with lifestyle intervention alone in Chinese individuals with impaired glucose regulation [20]. Although metformin has exhibited a favorable safety profile, it still induces discomforting side effects such as diarrhea and nausea in some individuals [21]. For individuals who cannot tolerate metformin or have contraindications, sodium-glucose cotransporter 2 (SGLT2) inhibitors present a potential alternative.

SGLT2 inhibitors have been initially used as a novel class of glucose-lowering agents by acting on SGLT2 in the renal tubules and inhibiting the reabsorption of filtered glucose in the kidneys. While safety concerns have been raised, including volume depletion, diabetic ketoacidosis, genitourinary infections, and hyperkalemia [22], large-scale clinical trials have not shown a substantial increase in adverse reactions compared to placebo groups [23, 24]. In addition to glucose-lowering effects independent of insulin secretion, the advantages of SGLT2 inhibitors for diabetes management include weight loss without major hypoglycemic events, cardiovascular benefits supported by clinical trials, and prevention of nephropathy and renal function decline among patients with or without diabetes [23–27]. Large RCTs, including DAPA-HF [28], DAPA-CKD [24], EMPEROR-Reduced [29], EMPEROR-Preserved [30], and EMPA-KIDNEY [31], conducted for at least 52 weeks, have demonstrated that SGLT2 inhibitors significantly reduce the risk of diabetes development in adults with either chronic kidney disease or heart failure. Additionally, in individuals without heart and kidney disease, a 14-day treatment of individuals with insulin resistance using dapagliflozin resulted in significant metabolic adaptations in whole-body and skeletal muscle substrate metabolism [32]. Overall, SGLT2 inhibitors have demonstrated safety and additional benefits in patients without diabetes, particularly those with heart or kidney failure.

Despite the accumulated knowledge of SGLT2 inhibitors, their overall effectiveness and safety in improving the metabolism of people with prediabetes remain uncertain. Therefore, the objective of this RCT is to rigorously assess the impact of SGLT2 inhibitors on individuals with prediabetes. By investigating the safety and efficacy of SGLT2 inhibitors on glycemic control, we aim to contribute to the understanding of SGLT2 inhibitors as a potential intervention for prediabetes, ultimately informing diabetes prevention strategies.

## METHODS

This prospective, single-center, parallel-group trial is being conducted at the Peking University Third Hospital. This trial is registered with ClinicalTrials.gov (NCT05914857). The study methods have been reported in accordance with the CONsolidated Standards Of Reporting Trials (CONSORT) statement (Supplementary Material) [33, 34]. Figure 1 shows the flow diagram of the study. This study protocol is reported according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines for defining items of the clinical trial (Supplementary Material) [35].

### Trial Design and Ethical Approvals

A total of 240 people with prediabetes who meet the predefined inclusion and exclusion criteria will be randomly assigned to the intervention or control group in a 1:1 ratio. The intervention group will receive dapagliflozin (10 mg/day) along with lifestyle education, while the control group will undergo lifestyle education alone (with male/female = 1:1 in each group). The trial will span a duration of 12 weeks to closely monitor changes in metabolic parameters, including glucose levels. The study is being conducted in accordance with the Declaration of Helsinki, and ethical approval has been obtained from the Peking University Third Hospital Medical Science Research Ethics

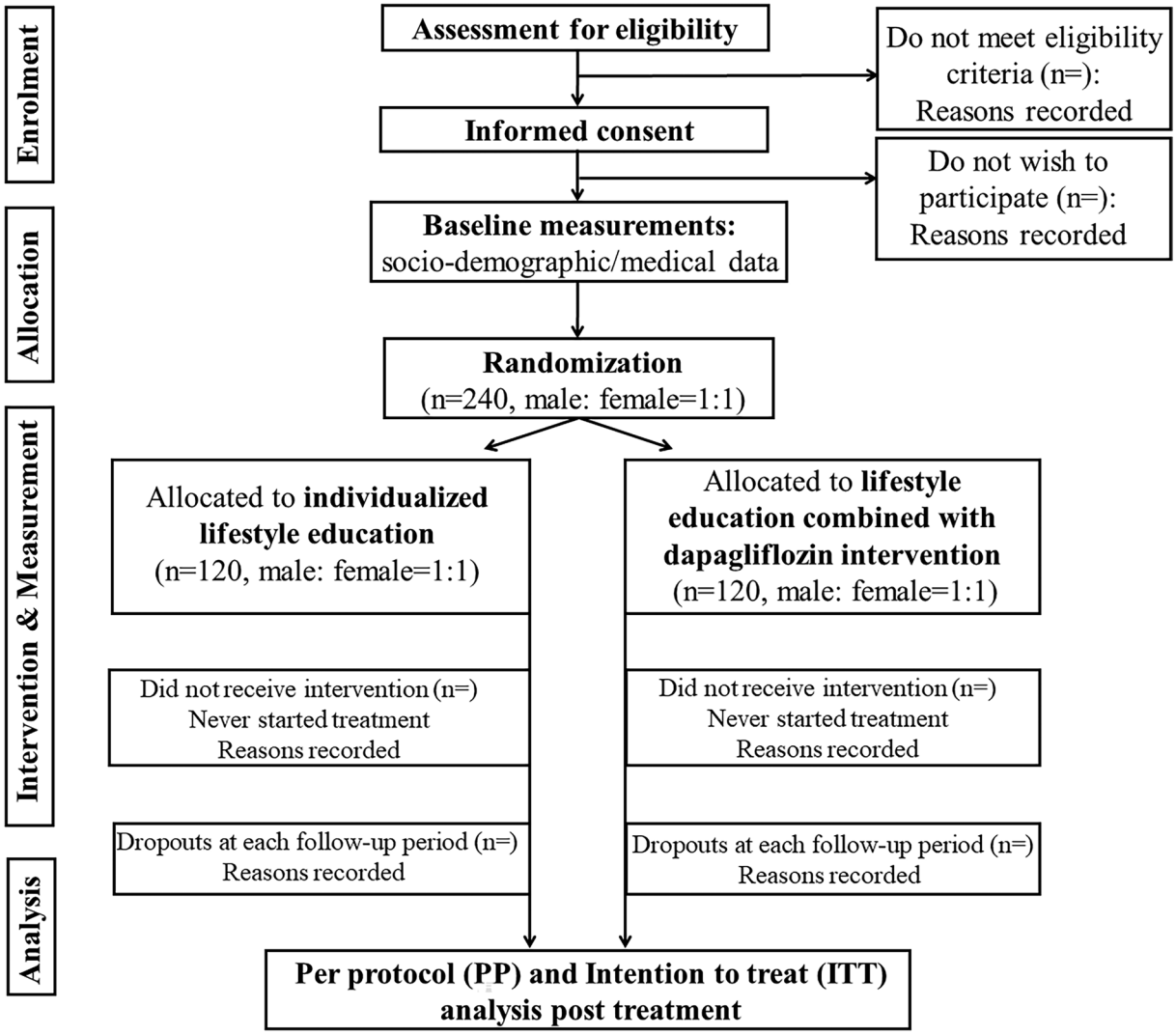


**Fig. 1** Enrollment and follow-up: CONSORT flow diagram describing anticipated progress of participants through the trial

Committee (reference number CN-032), with the approval number IRB00006761-M2022520. Any study discontinuation, completion, or changes in conduct (e.g., protocol revisions) must be promptly reported to the committee for approval. Immediate notification is required if changes are made to mitigate risks to subjects.

### Participant Eligibility

Eligible participants will meet the following criteria:

1. Age between 18 and 65 years

2. Diagnosed with prediabetes based on the combined criteria of American Diabetes Association and World Health Organization within the last 6 months:
    - Fasting blood glucose between 6.1 and 7.0 mmol/L (110–125 mg/dL)
    - 2-h plasma glucose (2 h-PG) on a 75-g oral glucose tolerance test (OGTT) between 7.8 and 11.1 mmol/L (140–199 mg/dL)
    - HbA1c between 5.7% and 6.4% (39–46 mmol/mol)

Fulfillment of at least two criteria above is required for diagnosis. If only one criterion is met initially, the diagnosis must be confirmed by repeating the test on a different day.

Fasting blood glucose and HbA1c levels will be assessed following an overnight 8–12 h fasting, usually conducted in the morning. 2 h-PG on a 75-g OGTT will be measured 2 h after ingesting 75 g anhydrous glucose powder dissolved in 300 mL water, following overnight fasting.

Participants will be recruited by the researchers, and study documentation will be provided in advance. Those interested in participating will be scheduled for an appointment to discuss the study and provided written informed consent before engaging in any trial-related activities.

## Participant Exclusion and Discontinuation Criteria

### *Exclusion Criteria*

1. Diagnosed with diabetes
2. Taking antidiabetic, lipid-affecting, or weight-loss medications within the 6 months prior to screening (including traditional Chinese medicine, and excluding thiazide diuretics at a daily dose of ≤ 12.5 mg)
3. Patients with acute infection, surgery, acute alcoholism, or mental illness
4. Patients with liver and kidney dysfunction, severe chronic gastrointestinal disease, uncontrolled thyroid disease, cancer, or on ventilator support
5. Systolic blood pressure ≥ 180 mmHg (1 mmHg = 0.133 kPa) or diastolic blood pressure ≥ 110 mmHg at screening
6. Electrocardiogram within 12 weeks before screening indicating arrhythmia requiring urgent diagnosis or treatment (e.g., clinically newly identified severe arrhythmia or conduction disturbance), myocardial infarction, unstable angina, or stroke requiring cardiovascular and cerebrovascular intervention
7. A history of traumatic amputation within the past year, or active skin ulcers, osteomyelitis, gangrene, or critical lower limb ischemia within the past 6 months
8. Enrolled in drug/device clinical studies (including vaccines) within 12 weeks before screening
9. Pregnant or lactating individuals, or those planning a pregnancy
10. Allergic constitution or multidrug allergy
11. Receiving bariatric surgery within the past 2 years
12. Receiving unsatisfactory pre-trial adherence evaluations that might hinder participants from following and completing the trial

### *Discontinuation Criteria*

1. Pregnancy
2. Inability to follow lifestyle instructions as per protocol
3. Patients with severe cardiovascular events or pulmonary embolism
4. Loss of contact with participants
5. Subjects request early withdrawal from the study (for reasons other than adverse reactions or a lack of efficacy)
6. Other reasons (recorded in the case report form)

A candidate participant who is already engaging in exercise or following a specific diet may still be eligible for participation in the study. Their exercise and dietary patterns will be systematically monitored and documented before and throughout the study. These data will be analyzed in the results after the completion of all recruitments.

### *Patient Withdrawal*

Patients may opt to discontinue their participation in the trial at any point. Withdrawal from the trial is permitted and may be advised under certain circumstances, including adverse events, safety concerns, or a lack of adherence to the trial protocol.

### *Eliminated Cases*

Participants who do not complete the trial as planned and have incomplete observation records are eliminated. Subjects who discontinue the trial as a result of serious adverse reactions should be classified as adverse reaction cases and should not be included in the per-protocol (PP) analysis.

## Design of the Intervention

Participants are stratified by gender and then randomly allocated to the intervention and control groups. The intervention group receives dapagliflozin 10 mg/day alongside lifestyle education, while the control group is given lifestyle education alone. Participants will be assigned randomly to either the intervention or control group by employing a random number table.

Dapagliflozin (Forxiga®) will be administered orally as 10-mg tablets, once daily.

## Lifestyle Education

Recommended lifestyle interventions include a sensible diet, controlling calorie intake (reducing total dietary calories by at least 400–500 kcal per day), and engaging in moderate-to-high intensity physical activity for more than 30 min per day, according to the Intervention for Adults with Pre-diabetes: A Chinese Expert Consensus [14]. We will provide lifestyle education, including instructions on physical activity and diet intake, at the start of the intervention. We will follow up their adherence to lifestyle modifications during two phone follow-ups and the end visit. Study participants should be instructed not to donate blood or blood products during the study.

Physical activity: For optimal physical fitness, it is highly recommended to incorporate a combination of aerobic and resistance exercises daily for a minimum of 30 min. Aerobic exercises, including brisk walking, jogging, cycling, and swimming, should be performed at least three times weekly. Resistance exercises, which entail the utilization of resistance training equipment or free weights (such as dumbbells and barbells), should be integrated into the exercise regimen at least twice a week, in conjunction with regular aerobic exercise.

Dietary intervention: The daily total energy requirement is recommended to comprise 45–60% from carbohydrates, 25–35% from fats, and 15–20% from protein. The daily dietary energy intake is advised to be reduced by a minimum of 300 kcal. Furthermore, it is crucial to limit the intake of saturated fatty acids to less than 30% of the total fat intake and restrict daily salt intake to no more than 6 g. It is not advisable to consume alcohol; if consumed, it must be included in the total energy intake (7 kcal/g).

## Adherence Evaluation

### *Pre-trial Assessment*

During the initial visit, subjects will be evaluated for various factors to select participants with good adherence. These factors include their occupation, regularity of daily life (potential hindrance due to occupational commitments impacting exercise and dietary goals), awareness of prediabetic state and its risks, inclination towards improving their current health condition, and ease of communication. Individuals with factors suggesting they might struggle with adherence will be excluded.

### *In-trial Assessment*

During the period of the trial, patients will receive telephone follow-ups to assess their adherence to study interventions. Key self-reported measures include medication

adherence, frequency, and reasons for non-adherence; weekly physical exercise frequency, duration, and type; and dietary habits, encompassing frequency of dining out, consumption of high-fat/oil foods, and overall diet maintenance. Patients will self-report over the telephone how many pills they have left, which will be cross-referenced with expected amounts to assess medication adherence.

For some eligible patients, objective measures will be integrated: data from a designated physical activity app to assess exercise habits, and meal photographs to evaluate dietary adherence.

These multifaceted evaluations ensure a robust assessment of adherence, reinforcing the reliability and validity of study results.

The gathered adherence data will contribute to a comprehensive understanding of participants' adherence to the study interventions. This methodology ensures a rigorous evaluation of adherence throughout the trial, contributing to the reliability and validity of the study findings.

## Baseline Measurements and Randomization

Baseline assessments encompass both clinical and laboratory measurements. We will record age, sex, BMI, waist circumference, and blood pressure. At the start and the end of the trial, we will collect serum and urine samples to evaluate glucose and other metabolism parameters and collect semen samples for evaluation safety of male reproductive function.

The eligible participants will be allocated concealed and randomized in a 1:1 ratio. Randomization will be stratified by gender. Prior to this, a predetermined list comprising 120 research subject numbers was established separately for each gender. A random number table method was employed to generate random digits. Subjects were allocated into one of two groups, intervention group and control group, on the basis of the parity of the generated random digits—subjects assigned odd numbers were placed in the intervention group, while those with even numbers were assigned to the control group.

The assignment of medications was predetermined for the groups: the intervention group received dapagliflozin 10 mg/day alongside lifestyle education, while the control group is given lifestyle education. Subsequently, research personnel who were not part of the trial recruiters or intervention allocators preserved a record of the random allocation scheme within sealed opaque envelopes.

### *Clinical Measures*

Measurements will be performed by trained study physicians, following standard protocols. Clinical measures will encompass BMI, waist circumference, blood pressure, along with participants' medical history and medication intake. Participants will be measured barefoot and in light clothing. Weight will be recorded to the nearest 100 g using a calibrated electronic scale. Height will be assessed to the nearest 0.1 cm with a calibrated wall-mounted stadiometer. BMI ($kg/m^2$) will be calculated as weight divided by square height. Blood pressure (mmHg) will be taken once seated using a calibrated automatic oscillometric sphygmomanometer and systolic and diastolic blood pressure will be recorded. In the standing position with feet 25–30 cm apart, waist circumference is measured at the midpoint between the lowest rib margin and the anterior superior iliac spine and will be measured to the nearest 0.1 cm using a non-stretchable fiberglass tape. Comprehensive patient data collection will comprise demographic and medical history, inclusive of age, gender, smoking history, history of cardiovascular disease, biochemical hypoglycemia, severe liver disease, malignancy, stroke, genitourinary infection, and usage of hypoglycemic and/or weight-loss drugs.

### *Laboratory Measures*

Laboratory measurements will be conducted at the study initiation (before medication intake) and the study end (following a 12-week intervention period). The measurements included blood glucose and other metabolic parameters.

Venous blood samples will be collected from all participants. Whole blood samples will be used to ascertain the complete blood count (automated hematology analyzer) and to assess HbA1c (ion-exchange high-performance liquid

chromatography method). Plasma will be used to evaluate blood glucose level, including fasting blood glucose, OGTT measurements at 0.5 h, 1 h, and 2 h glucose (glucose oxidase method). Serum will be collected for other biochemistry tests. Fasting insulin levels alongside insulin at each OGTT time point will be measured (the Siemens Insulin Assay Kit, chemiluminescence assay). The lipid profile includes total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglyceride (turbidimetric immunoassay). Liver function includes alanine aminotransferase (lactate dehydrogenase method) and aspartate aminotransferase (malate dehydrogenase method). Kidney function will be reflected by blood creatinine levels (picric acid method). Sex hormones including follicle-stimulating hormone, luteinizing hormone, prolactin, estradiol, progesterone, and testosterone will be quantified (Roche Diagnostics; chemiluminescent assay). The blood samples for sex hormone detection in women should be collected under fasting conditions between 8:00 and 10:00 AM on days 2 to 5 of the menstrual cycle. For those experiencing amenorrhea exceeding 60 days or postmenopausal individuals, blood samples should be obtained before 10:00 AM on any day.

In terms of urinary evaluations, participants' urine samples will be subjected to routine testing (automated urinalysis instrument). Urine creatinine levels will be gauged (picric acid method), and albumin/creatinine ratio levels will be measured to monitor for early signs of proteinuria.

Fecal samples from participants will undergo routine examinations under microscopic observations.

For male volunteers aged between 18 and 50 years, semen samples will be analyzed with the sperm quality analyzer and computer-aided semen analysis system. After collection, these samples will undergo incubation at 37 °C for 0.5–1 h and will be checked for the absence of liquefaction before centralized assessment at the Department of Reproduction Center at Peking University Third Hospital.

Upon collection, all specimens—with the exception of semen samples—will be processed promptly within 2 h at the centralized laboratory of the Department of Laboratory Medicine at Peking University Third Hospital. Following their analyses, all samples, including the semen samples, will be stored in the Peking University Third Hospital Biobank for a maximum duration of 15 years, subject to ethical board clearance. At the conclusion of this period, any remaining samples will be disposed in accordance with relevant guidelines.

## Intervention Visits

Regular telephone follow-ups are carried out at week 4 and week 8 to assess medication adherence, potential adverse drug reactions, and physical activity. Table 1 delineates the specific content arrangements within the follow-up procedures. Figure 2 provides a comprehensive visualization of the study's sequential assessments and informational components.

## Study Outcomes

### *Primary Outcome*

The primary efficacy endpoint is the change of 2 h-PG during OGTT from baseline to study end (12 weeks).

There are several reasons. First, we are monitoring fasting blood glucose, 2 h-PG, and HbA1c levels to assess the potential of SGLT2 inhibitors in restoring normal glycemic control among individuals with prediabetes. It is worth noting that individuals with IGT outnumber those with IFG in the prediabetic population [36]. Additionally, previous studies have shown that 2 h-PG serves as a strong predictor of cardiovascular events in individuals with coronary heart disease, underscoring its clinical significance [37]. Moreover, the 2 h-PG is widely used as a surrogate marker for assessing glycemic control and is recommended in guidelines for evaluating prediabetes and diabetes [14, 38, 39]. Therefore, we have chosen 2 h-PG level during OGTT as the primary endpoint.

### *Secondary Outcomes*

Secondary efficacy outcomes include changes in fasting blood glucose, HbA1c, BMI, waist circumference, fasting insulin, OGTT-2 h insulin, blood lipid profile (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein

**Table 1** Patient evaluation follow-up schedule

| | Visit 1<br>Primary assessment | Visit 2<br>Week 0<br>Start of interventions | Visit 3<br>Week 4<br>First phone follow-up | Visit 4<br>Week 8<br>Second phone follow-up | Visit 5<br>Week 12<br>End of interventions |
|---|---|---|---|---|---|
| Subject screening | √ | | | | |
| Informed consent | √ | | | | |
| Adherence evaluation | √ | √ | √ | √ | √ |
| Randomization | | √ | | | |
| Individual intervention for each group | | √ | √ | √ | √ |
| Medical history collection | √ | | | | |
| Vital signs and weight | | √ | √ | √ | √ |
| HbA1c and OGTT | | √ | | | √ |
| Other laboratory tests | | √ | | | √ |
| Exercise and diet recording | | √ | √ | √ | √ |
| Patient education | | √ | √ | √ | |
| Treatment optimization | | | √ | √ | |
| Pregnancy outcome collection | | | √ | √ | √ |
| Adverse event recording | | | √ | √ | √ |

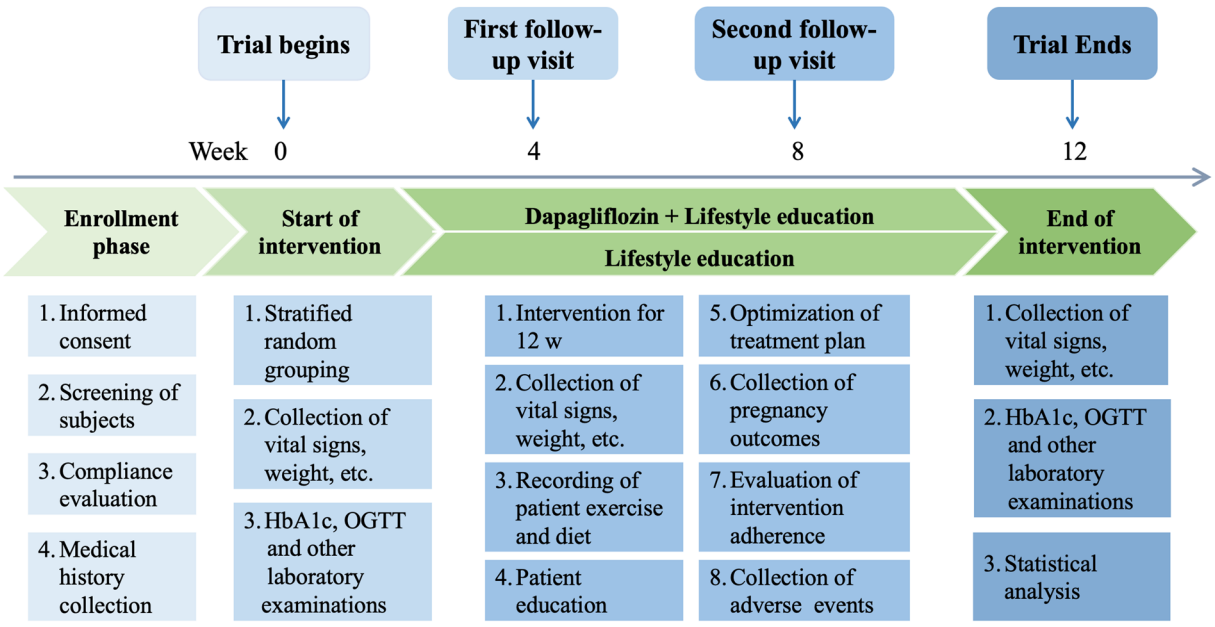


**Fig. 2** Protocol summary for the randomized controlled trial of dapagliflozin in subjects with prediabetes

cholesterol, and triglyceride), and blood pressure (including diastolic blood pressure and systolic blood pressure).

The safety profile is evaluated through changes in liver function (alanine aminotransferase and aspartate aminotransferase levels), kidney function (creatinine, calculated estimated glomerular filtration rate, and albumin/creatinine ratio), urine routine tests, sex hormones, sperm-related parameters (count and function), and self-reported adverse events.

## Quality Control

To maintain the highest quality in data collection and analysis throughout the study, we will implement comprehensive quality control strategies. These strategies will focus on reinforcing standardized procedures and minimizing both inter- and intraobserver variations.

(a) Ethical approval: We submit the research plan to the Medical Science Research Ethics Committee of Peking University Third Hospital for thorough review and approval to ensure the study complies with all ethical standards and regulations.
(b) Researcher training: Prior to data collection, all researchers will undergo comprehensive training to ensure accurate and consistent recording and evaluation of each case. In preparation for this, we design a case report form informed by extensive consultations with experts and a thorough review of relevant literature, intending to ensure data accuracy and reliability.
(c) Participant retention strategies: We recognize the importance of minimizing participant attrition to maintain the robustness of our results. Therefore, we will implement public awareness and education campaigns targeting our participants to increase their understanding of the study's importance and reduce the rate of dropout.
(d) Data management: To ensure the accuracy and reliability of all recorded outcomes, this study will implement a double data entry method, aiming to elevate the standards of data quality.

## Sample Size Estimation

Sample size estimation for this trial was conducted on the basis of the primary efficacy endpoint: the change of 2 h-PG during OGTT from baseline to 12-week intervention. Both treatment and control groups are expected to experience a reduction in 2 h-PG levels. However, the dapagliflozin group is anticipated to show a greater reduction by 0.86 mmol/L compared to the control group. This estimate is adapted from previous RCTs involving metformin as a reference therapeutic agent [40]. Gender stratification will maintain a 1:1 male-to-female ratio, facilitating the exploration of potential gender-based differences in adverse effects, particularly those related to the genitourinary system. Six sex hormone tests and semen analysis are included in the study's metrics to monitor these gender-specific adverse effects, as supported by relevant literature [41].

For sample size calculation, we employ the following formula for a two-sample $t$ test:

$$n = 2 \times \left(\frac{Z_{\alpha/2} + Z_{\beta}}{\Delta/\sigma}\right)^2,$$

where $Z_{\alpha/2} = 1.96$ for a two-sided $\alpha$ level of 0.05, $Z_{\beta} = 0.84$ for a power of 80%, $\Delta = 0.86$ mmol/L (expected difference), and $\sigma = 1.52$ (standard deviation). The formula yields $n = 49$ participants per group.

Considering a dropout rate of 15%, the sample size per group needs adjustment to accommodate potential participant attrition. The adjustment increases the necessary number of participants per group from 49 to 58. To ensure robustness, we will include 60 participants for each gender in each group. Consequently, the adjusted total sample size for the trial will be 240 participants, comprising 60 men and 60 women in both the intervention and control groups.

Recruitment advertisements targeting potential participants will be disseminated through various channels, ensuring the attainment of the predetermined sample size necessary to maintain the study's validity and robustness.

### Statistical Analysis

Statistical analysis will be performed using SPSS 25.0 software. The independent sample *t* test, chi-square test, Spearman's correlation analysis, and binary logistic regression analysis will be used for comparative and correlation analysis respectively. A *P* value of less than or equal to 0.05 will be considered statistically significant.

We will conduct an intention-to-treat (ITT) analysis, where all participants will be included in the analysis according to their randomization group, regardless of whether they received the intervention or completed the study. We will also conduct a PP analysis, which will include only participants who completed the study as per the protocol without major deviations.

For handling missing data, we will employ multiple imputation techniques, which allow for the estimation of missing values by leveraging observed data and making informed assumptions regarding the reasons for data absence. This approach is particularly advantageous in scenarios where covariates themselves have missing values or when covariates that change over time can predict future instances of missing data [42]. Imputations will be performed with the Multiple Imputation by Chained Equations (MICE) package in R software [43].

### Trial Status

The trial is currently in the recruitment phase. We expect to complete patient enrollment intervention and follow-up period by March 2025, adhering to the original schedule.

## DISCUSSION

Previous research has substantiated the potential of SGLT2 inhibitors in managing diabetes, primarily via improving glycemic control, reducing body weight, and attenuating blood pressure [23–27]. Despite these promising findings, the effectiveness and safety of SGLT2 inhibitors in treating prediabetes, a condition afflicting a rapidly expanding population, remain unclear. Therefore, we are launching a single-center, stratified RCT to fill this knowledge gap. This protocol details our prospective study, which focuses on assessing the effects and safety of dapagliflozin, a commonly used SGLT2 inhibitor, in individuals with prediabetes. Prediabetes is a critical stage where effective interventions could potentially halt the progression to full-blown diabetes [11, 44]. Moreover, extensive research has proved that SGLT2 inhibitors offer beneficial effects on cardiovascular outcomes and renal function in both patients with and without diabetes [23, 24, 45]. Hence, our RCT is designed to specifically assess the multiorgan impact of SGLT2 inhibitors on subjects with prediabetes.

Our research has several noteworthy strengths. First, we will implement a stratified analysis of our study population, with a particular interest in investigating the differential benefits among gender groups. Through evaluating sex hormone biomarkers and semen quality, we aim for a robust safety profile that informs gender-specific treatment recommendations. Second, our study goes beyond glycemic control by also evaluating weight loss and other metabolic parameters. This comprehensive approach aims to enrich our understanding of the efficacy and safety of SGLT2 inhibitors in individuals with prediabetes.

Our study also has limitations that should be noted. First, the intervention duration of 12 weeks may be short for observing the long-term outcome of SGLT2 inhibitors on the efficacy and safety profiles in individuals with prediabetes. Second, the trial is initiated by the investigators rather than pharmaceutical companies, and it is not possible to fulfill a placebo-controlled trial. Additionally, single-center recruitment, with the limitation of small sample, regional restriction, etc., may limit the applicability of our findings across broader populations.

In summary, the study aims to evaluate the effectiveness and safety of SGLT2 inhibitors in improving the metabolism of people with prediabetes. The results are intended to be readily translatable to prevention strategies by focusing on practical and clinically relevant endpoints. The investigation will focus on the impact of SGLT2 inhibitors on glycemic control weight loss, and other metabolic parameters, thereby

potentially informing and transforming diabetes prevention strategies.

## CONCLUSION

This protocol lays the groundwork for a prospective RCT designed to rigorously evaluate the benefits and risks of SGLT2 inhibitors in individuals with prediabetes, with potential implications for safe and effective prediabetes management. Through a gender-specific stratified analysis and a comprehensive range of metabolic outcome measures, our study holds the potential to refine and inform current diabetes prevention strategies.

## ACKNOWLEDGEMENTS

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***Author Contributions.*** Rui Wei led the conception and design of the trial. Xiaxuan Zhu, Li Xia and Deshan Yin closely participated in the data analysis and interpretation, as well as facilitating the delivery of the intervention sessions. Xiaxuan Zhu and Li Xia drafted the manuscript. Rui Wei and Jin Yang ensured the study's alignment with principles of equity, diversity, and inclusion. Rui Wei revised the draft. All authors read and approved the final manuscript.

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***Data Availability.*** Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

***Declarations***

***Conflict of Interest.*** Xiaxuan Zhu, Li Xia, Deshan Yin, Jin Yang, and Rui Wei declare that they have no competing interests.

***Ethical Approval.*** Approval to conduct the study was gained from the Peking University Third Hospital Medical Science Research Ethics Committee (reference number CN-032), with the Approval Number IRB00006761-M2022520. Prior to any study-related activities, all potential participants will be recruited by the researchers and thoroughly informed about the study's objectives, procedures, potential risks, and benefits. Written informed consent will be obtained from all participants, ensuring their voluntary participation and understanding of their rights to withdraw from the study at any time without any consequences. This consent process is designed to protect the participants' autonomy and confidentiality, with all data collected being anonymized to ensure privacy.



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