Development, Popularization and Application of An Online OvAge Calculator Based on Subject Self-reporting System

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Research

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Abstract

Background: At present, there are many clinical markers and models to assess ovarian reserve, but none of them are ideal. The number of clinical samples is a key factor limiting the specificity and sensitivity of the markers and models, and traditional methods of subject recruitment are time and vigor. In addition, the model of ovarian reserve assessment for Chinese women need to be further explored.

Objective: To explore the possibility of self-reporting for subjects through the WeChat mini program, and provide more data support for further optimization of the OvAge model, and to develop a predictive model of ovarian reserve that is specific to Chinese women.

Methods: In this paper, with reference to the existing OvAge model, we developed an online OvAge calculator based on the WeChat mini program for data collection, and then applied the generalized linear model theory to obtain a predictive model of ovarian reserve which is in line with the characteristics of Chinese women.

Results: Compared to traditional recruiting methods, the online OvAge calculator is able to collect a large number of samples in a short period of time, which is efficient and convenient. Optimized model of estimated OvAge =exp (3.5254-0.001*PRL-0.0231*AMH). This model showed a high statistical significance for each marker included in the equation. We applied the final equation on diminished ovarian reserve and polycystic ovary syndrome datasets and obtained a mean of predicted ovarian age significantly different from the mean of chronological age in both groups.

Conclusions: The OvAge calculator based on the WeChat mini program is a novel online subject self-reporting system that can collect a large number of samples in a short period of time, continuously optimize the model and update the mini program version, which is economical, time-saving and efficient., and is worthy of promotion. In addition, the optimized OvAge model is suitable for Chinese women and provides a reference for clinical assessment of ovarian reserve.

Introduction

Female reproductive senescence is a physiological process in which the quality and quantity of oocytes decline over time and do not regenerate [1]. In reproductive medicine, the concept of ovarian reserve is used to describe the reproductive potential of women and to measure the possibility of successful pregnancy with the help of assisted reproductive technology [2]. Models of female ovarian reserve or scoring and staging systems to predict pregnancy outcome have been proposed by scholars in the field of reproduction at home and abroad, such as What's My Fertility, Stages of Reproductive Aging Workshop (STRAW), Ovarian Age (OvAge) and the AFA (anti-Müllerian hormone level–follicle-stimulating hormone level–age) model [3–7]. These models can help women of childbearing age understand the current state of their fertility so that they can plan their fertility rationally. However, in recent years, due to age, genetics, environment, psycho-social, lifestyle, iatrogenic, infection, immunity and other factors, the ovarian age of women of the same age also varies greatly [8–13].

With the liberalization of two-child policy in China and the increase in the number of advanced age pregnant woman, as well as with the socio-economic development and people's demand for quality of life has increased significantly, and with the influence of the various factors mentioned above, it is important to accurately predict the relationship between chronological age and ovarian age in order to assess fertility and predict the timing of menopause, as well as to guide perimenopausal women to undergo menopausal hormone therapy in a timely manner.

Currently, clinical and academic indicators to assess and predict ovarian age include age, anti-Müllerian hormone (AMH), antral follicle counting (AFC), follicle-stimulating hormone (FSH), clomiphene citrate challenge test (CCTest), and Inhibin B (INH B), etc., or a combination of these indicators to obtain scoring systems and staging models to predict ovarian age and pregnancy outcomes [1, 4, 5, 14–16]. Regardless of the predictive efficiency, specificity and sensitivity of these indicators, they are relatively closed to ordinary people, with high thresholds, and cannot be used by the general public, so their practical value is low. The ideal tool should be universally accepted, reproducible, easy to understand and applicable to the general population, and be able to visually predict remaining fertility, time to menopause and reproductive prognosis, and the success rate of assisted reproductive technologies.

With the rapid development of Internet and 5th generation mobile networks, people's lives have become inseparable from the Internet to a certain extent. Due to the huge number of users (over 1 billion monthly active users), convenient payment functions and a relatively open ecological environment, WeChat has become a phenomenon-level application in China [17]. Therefore, we have launched the online OvAge calculator, a self-report system for subjects based on the WeChat mini program. In this way, we can not only quickly collect more data, especially from healthy populations, to further optimize existing models to make it more accurate, but also constantly update and promote the OvAge calculator mini program version based on the data collected, thus increasing its online visibility and providing a new way for clinical recruitment of patients.

In this paper, we have developed an online OvAge calculator based on the WeChat mini program in combination with the existing OvAge model, which allows subjects to obtain their ovarian age and provide them with professional medical advice by simply entering the corresponding values on several physical examination report. The novel approach of collecting basic data and gynecological examination reports from Chinese women through the online OvAge calculator will explore the possibility of a self-reporting system for subjects through the WeChat mini program and provide more data support for further optimization of the online OvAge Calculator, as well as for the development and popularization of the mini program software version, creating a new approach to web-based platform for clinical recruitment of patients, and providing new ideas for clinical research.

Materials And Methods

1. Indicators

For the data collected in this study, basal AMH, FSH, LH (Luteinizing hormone), E_2 (Estradiol), P (Progesterone), T (Testosterone), PRL (Prolactin) and vitamin D were measured in all women between day 2 and day 4 of menstrual cycle. The same day of hormonal assay, a single experienced investigator performed all the ultrasound scans. The height and weight were also recorded. All indicators are measured by qualified professional technicians in the laboratory, and the operation is carried out in strict accordance with the reagent kit and instrument instructions.

2. Population data collection

2.1 Phase I data collection

From May 1 to June 30, 2020, the data of subjects (including healthy, PCOS (Polycystic ovary syndrome) and DOR (Diminished ovarian reserve) populations) were collected in the outpatient department of gynecology and reproductive medicine of Jiangsu Province Hospital of Chinese Medicine to compare their chronological age with their predicted ovarian age. The experimental design fully considered the principles of safety and fairness, and the research did not pose any harm or risk to subjects. The recruitment was based entirely on the principles of voluntary and informed consent, the privacy was protected to the greatest extent possible. There is also no conflict of interest.

2.2 Phase Ⅱ data collection

Between July 1 and August 31, 2020, paid recruitments of subject were conducted through a contract research organization (CRO) company to collect physical examination data from healthy women. All tests were performed in the Laboratory of Jiangsu Province Hospital of Chinese Medicine.

2.3 Phase Ⅲ data collection

Since the first two phases were collected inefficiently, we tried a brand-new online OvAge calculator ——a subject self-reporting system based on WeChat mini program. We proposed the functions and requirements of the OvAge calculator, handed over to a professional software development company for completion, using JavaScript and WXML (WeiXin markup language) development languages, the base software version 1.0.0, which went live on September 23, 2020, with a collection time of two weeks (the current version is 1.0.5).

3. Populations

The age range of those who participated in this study through the three recruitment methods described above was 15 to 55 years.

Inclusion criteria for the selection of the training subjects for this model were: with history of spontaneous conception(s), intact ovaries and regular menses with a mean interval of 21 to 35 days.

Exclusion criteria were: estrogen or progestin use or in breastfeeding the two months before enrollment, pregnancy, history of female infertility, endometriosis, presence of ovarian follicles measuring more than 10 mm at study entry ultrasonography and other cystic masses of the ovary, history of ovarian surgery, PCOS, gynecological malignancy, previous radiation or chemotherapy, autoimmune disease, known chronic, systemic, metabolic and endocrine disease including hyperandrogenism, hyperprolactinemia, diabetes mellitus and thyroid diseases, hypogonadotropic hypogonadism or with history of use of drugs that can cause menstrual irregularity.

PCOS (polycystic ovary syndrome) was diagnosed according to the Rotterdam criteria, when at least 2 of the following 3 features existed: oligo/ amenorrhea, clinical and/or biochemical hyperandrogenism, and polycystic ovaries morphology (PCOM) [18].

The diagnosis of DOR has not been standardized, and there are no international criteria. In combination with the current guidelines of the national ART surveillance system (NASS) and society for assisted reproductive technology (SART), the diagnostic criteria used in this study were age ≥40 years, basal FSH ≥12 mIU/mL, AFC≤5~7; AMH≤1.1 ng/mL, any 2 or more of the 4 items can be determined as DOR [19].

The recruitment process for outpatient department of gynecology and reproductive medicine, the CRO company, and OvAge WeChat mini program were all based on inclusion and exclusion criteria, and the past history was collected through a professional questionnaire.

4. Statistical analysis, model construction and optimization

A dataset of 149 records of subjects has been analyzed using R language (Version 4.0.2). The whole analysis consists of seven main steps (Figure 1).

(i) The main dataset has been divided into three sub-datasets, according to the preliminary clinical analysis HCs (Healthy Controls), DOR and PCOS. Each subset has been checked to ensure the data quality, in terms of the presence of missing values and consistency in decimal separator. For missing data, multiple imputations are applied.

(ii) For each dataset, descriptive statistics for each variable have been calculated. The rank correlations between the chronological age and the variables have been analyzed by applying Spearman's test and multiple testing with adjusted p-values by Holm's test.

(iii) For describing the relationship between the new response variable here introduced and called OvAge, and the set of inputs, which are the independent variables, we applied the generalized linear model (GLM) theory, which provides a unified methodology for modeling all types of response variables, such as continuous, binary, ordinal response or variables in the form of proportions. Since it has been

hypothesized that, in healthy population, OvAge is equal to chronological age, which is not continuous and non-normal, a Poisson distribution has been chosen as the random component of the GLM for modeling the expected value of OvAge. Identity and logarithm have been chosen as candidate link functions.

(iv) For the Ockham's razor (law of parsimony) and avoiding collinearity problems due to the possible non independence of predictor variables, variable selection methods have been applied. The stepwise selection, least absolute shrinkage and selection operator (LASSO) and sure independence screening (SIS) are considered. The boosting method in machine learning is also considered to construct models, which is an ensemble meta-algorithm in supervised learning and a family of algorithms that convert weak learners to strong ones[20]. The overall best model was chosen using the Akaike information criterion (AIC). For the sake of completeness, for each generated model, 10-fold cross-validated accuracy and leave-one-out accuracy have been calculated too. In particular, in the 10-fold cross-validation, the dataset is divided into 10 groups of approximately equal size and for each group the generalized linear model is fit to nine of the groups (training set) omitting one group that is then used as the test set. In the leave-one-out only one observation is left out as the test set. As further evidence of the significance of the linear terms, ANOVA test (Chi-squared) had been performed for comparing each model to the null model in terms of deviance.

(v) The best model had been re-built taking into account all possible interactions among covariates to assess any improvements in AIC value and accuracy. Interactions terms in the model provide interactive effects and they are considered when main effects are significant.

(v) For evaluating the quality of fit of the final model, several diagnostic statistical techniques had been applied. Influence measures considered are DFBETAS, DFFITS, covariance ratio CR and Cook’s distance D and the leverages h. The R function influence.measures() is used to identify potentially influential observations according to R’s criteria with influence measures above. In a manual and iterative way, identified influential single cases had been first checked by specialists and then removed from the dataset. The final model has been repeatedly updated without influential cases and with the significance of any predictor having a p-value <0.01.

(vii) The final generalized linear model has been applied on POI and PCOS dataset. The hypothesis was that, in the case of POI, the ovarian age is greater than the chronological age and in the case of PCOS the ovarian age is lesser than the chronological age.

Results

1. Quite different in data collected at three different phases

In the phase Ⅰ, 113 women (16 healthy individuals, 45 PCOS and 52 DOR populations) were recruited in our department within two months; And in the phase Ⅱ, a CRO recruitment company took two months to collected 52 healthy women's information. However, in the phase Ⅲ of this study, the online OvAge

calculator based on the WeChat mini grogram has collected data has collected 5,236 cases, including 97 healthy data within two weeks.

2. The OvAge in the literature is not fully adapted to the Chinese population

In the phase Ⅱ of this study, we collected data of 113 women (16 healthy individuals, 45 PCOS and 52 DOR populations) (Table 1).

Table 1
Baseline characteristics in the phase Ⅱ of study participants

Category	Healthy women (n = 16)	DOR women (n = 52)	PCOS women (n = 45)
Age	32.13 ± 3.86	39.12 ± 6.65	28.11 ± 3.28
AMH (ng/mL)	3.64 ± 3.42	1.02 ± 1.03	12.79 ± 3.43
FSH (mIU/mL)	6.28 ± 2.00	22.70 ± 11.64	5.80 ± 1.87
PRL (ng/mL)	14.28 ± 5.13	12.43 ± 4.51	10.72 ± 4.78
AFC	5.63 ± 2.09	3.42 ± 1.39	9.14 ± 4.37
BMI	23.39 ± 4.22	23.36 ± 2.81	26.58 ± 6.41

With the data collected in the phase Ⅱ, we compared and validated their chronological age and predicted ovarian age, using the model of a previous study to obtain OvAge in the literature[5]. There is a statistically significant difference between the chronological age and OvAge in the literature of PCOS patients, and the OvAge in the literature is smaller than the actual chronological age, which is the same as the prediction ($p = 0.0000003$). And there is also a statistically significant difference between these two indicators of DOR patients ($p = 0.000004$). There is no statistical difference between the chronological age and OvAge in the literature of healthy individuals, although it is the same as expected, we could find that these two indicators still vary somewhat and is not entirely consistent (Table 2).

Table 2
Comparison of chronological age and OvAge in the literature

Category	Chronological age	OvAge in the literature	*P* value
Healthy women (n = 16)	32.13 ± 3.74	36.02 ± 7.87	0.09
DOR women (n = 52)	39.12 ± 6.58	44.36 ± 3.93	< .001
PCOS women (n = 45)	28.11 ± 3.19	22.74 ± 8.14	< .001

3. Optimization of the generalized linear model theory of OvAge

In order to speed up the data collection process, we developed an online OvAge calculator based on the WeChat mini program (Fig. 2).

There are 52 and 97 observations in the phase and phase data sets, respectively. Age is the dependent variable, and we consider independent variables which can be obtained for the test data set with 35 observations. Following independent variables are included for modelling: BMI, P, T, E2, PRL, LH, FSH, AMH and New. The independent variable New is considered for the correction of effects from different sources of data. New = 0 denotes phase data, and New = 1 denotes phase data. Following the previous study [5], we consider normal linear regression, Possion generalized linear models with log and identity link functions for modelling Age with previous independent variables. We first use stepwise linear regression based on AIC (Akaike information criterion) values for variable selection to construct regression models of only phase data (i.e. observations with New = 0). The best result models for normal linear regression, Poisson generalized linear models with log and identity link functions are denoted as mod1a, mod2a and mod3a, respectively (Table 3). Only PRL and AMH variables are included in mod1, mod2 and mod3. PRL is not statistically significant and AMH is significant. Next, we use the same variables in the models of only phase data to fit corresponding models (mod1b, mod2b and mod3b) for both phase and phase data. We considered to add the New variable and its corresponding interaction terms with other variables into the models, however, no significant variable effects related to the New variable were found, which means there are no differences of effects of AMH and PRL between phase and phase data. Some improvements in the prediction are obtained with the assessment of the MSE, RMSE and MAE for the test/validation data set of 35 observations by comparing pairs of models for phase data only and both phase and data (i.e. mod1a vs. mod1b, etc.). The results are shown in Tables 3 and 4 as follows.

From Table 4, models for both phase and data predict better than models for phase data only. Based on results of Table 3, effects of PRL in models for only phase data change to be close to zeros in corresponding models for phase and data. This illustrates that involving more observations from phase data for modelling corrects the non-significant effect in the models to approach the theoretical value 0, which means no effect. On the other hand, the p-values of significant effects of AMH in models for phase data only become smaller with more asterisks in corresponding models for both phase and , which gives more confidence of the estimated significant effects. This shows that involving more observations from phase data makes the p-values of significant effects in the models become smaller, because the standard errors of estimated effects in the models become smaller due to the increase of the sample size.

Based the results of AIC, BIC and the prediction errors MSE, RMSE and MAE, mod2b is the best among all models considered. The model is estimated OvAge = exp (3.5254 − 0.001*PRL-0.0231*AMH).

Table 3
Summary of the fitted models for phase Ⅰ and phase Ⅱ data

	mod1a	mod1b	mod2a	mod2b	mod3a	mod3b
(Intercept)	32.3968 ***	33.8402 ***	3.4846 ***	3.5254 ***	32.2573 ***	33.6966 ***
	(1.9030)	(0.8489)	(0.0568)	(0.0264)	(1.7938)	(0.8367)
PRL	0.1483	-0.0016	0.0043	-0.0001	0.1438	-0.0017
	(0.0872)	(0.0072)	(0.0024)	(0.0002)	(0.0867)	(0.0071)
AMH	-0.8752 *	-0.7045 ***	-0.0287 **	-0.0231 ***	-0.8163 **	-0.6608 ***
	(0.3296)	(0.1968)	(0.0103)	(0.0064)	(0.2971)	(0.1872)
N	52	149	52	149	52	149
AIC	338.0059	946.6072	334.9155	941.3778	335.5451	942.2076
BIC	345.8108	958.6230	340.7692	950.3897	341.3988	951.2194
*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$.						

Table 4
Prediction assessments of fitted models for the validation dataset of 35 observations

Models	MSE	RMSE	MAE
mod1a	69.2735	8.3231	5.3830
mod1b	32.0149	5.6582	4.1787
mod2a	117.1521	10.8237	5.9000
mod2b	31.7237	5.6324	4.1703
mod3a	67.7729	8.2324	5.3772
mod3b	32.6351	5.7127	4.2063
Mod1a vs mod1b, mod2a vs mod2b, mod3a vs mod3b. The smaller the MSE (mean square error), RMSE (root mean square error) and MAE (mean absolute error), the better the prediction.			

Discussion

This study explores the possibility of a novel self-reporting system for subjects through the WeChat mini program based on the online OvAge calculator, which can collect many samples in a short period of time, continuously optimize the model and update the version of the software, which is economical, time-saving and efficient.

It is well known that the age of human organs is not completely consistent with the chronological age, and the ovaries are no exception [5, 21–23]. The reproductive aging process of women is not only related to age, genes, environment, pressure, diet structure, but also to pathological factors. Therefore, the process of female reproductive aging at the same age is quite different, and the ovarian reserve is extremely different [8, 10, 11, 13]. In the light of such differences, it is worthwhile to investigate and address how to visually and accurately represent women's ovarian reserve, fertility, and menopause period. In addition, coupled with the opening of the two-child policy, changes in bearing concept and and the increase in the number of advanced-age women preparing for pregnancy, is of great practical importance in enabling Chinese women to quickly and visually find out their ovarian age and potential fertility. So far, however, there are no models with satisfactory sensitivity and specificity through single or joint indicators. The ideal marker should be able to assess both qualitative and quantitative aspects of ovarian reserve, synthesize all relevant information, and respond with clear understanding. In 2015, Venturella et al. proposed "OvAge", which is more in line with the current requirements [5]. Our prospectively evaluated and optimized OvAge model is universally accepted, reproducible, easy to interpret. It is a digital model for the general population, and can provide reliable information on follicle number and quality, residual fertility, menopause time, and reproductive prognosis. In the previous work, we found that for both PCOS and DOR populations, the ovarian age calculated by the existing OvAge model is significantly less than or greater than their chronological age, which can reflect the ovarian function and potential fertility of both groups to a certain extent; whereas for healthy Chinese women, there is no significant difference between their ovarian age and chronological age. Although it is the same as expected, there is still some difference between the two indicators, which is not entirely consistent. It may be that this formula is not entirely applicable to Chinese women, suggesting that the generalized linear model in the literature has certain reliability, and it has practical application in calculating ovarian age by combining clinical and laboratory tests with ultrasound data. However, the study has limitations in terms of geography, population and sample size.

Successfully recruiting qualified subjects is an important part of the success of a trial. An accurate and scientific model that can rapidly predict ovarian age is based on data from a large sample of subjects. The traditional methods of recruiting subjects mainly include self-recruitment by research centers, hospital departments and cooperation with third party CRO companies [24, 25]. Research centers or hospital departments recruit by themselves and small CRO companies are small in size, lack influence and publicity, are regionally based, so they cannot do cannot do nationwide recruitment, while large CRO companies have many staffs and resources, but are more expensive and generally have limited funding for pilot projects. The recruitment costs depend on the number of blood collection sites, the density, the cycle of the cleaning period and the difficulty of the test itself. The cost of recruiting a subject generally ranging from 5,000 to 12,000 RMB. In addition to the later screening and operation fees, the total costs of recruitment are quite expensive. Some CRO companies also have poor gatekeeping in the recruitment process, caring only about the number of subjects enrolled, pursuing financial gain while masking factors that may affect the outcome, leading to not only higher screening ratios, but also increasing the cost of the trial [26].

Based on traditional recruitment methods, we first tried WeChat, which is the most widely used in China, as a medium for trial recruitment, and creatively developed an online OvAge calculator based on WeChat mini program. The self-reporting system for subjects allow her to get their own ovarian age and fertility guidelines simply by entering the values reported in the physical examination, completing a simple questionnaire and signing an informed consent form. Not only will it ensure fair participation of subjects in the trial, but it will also significantly improve the efficiency of the recruitment process. In addition, as it is self-reported by the subjects, it saves on clinical recruitment costs. The online OvAge calculator integrates an inclusion and exclusion module, which is associated with the subject's personal information. After each test screening, it automatically records the parameters that make the subject unsuitable for the test, and adds the label "unsuitable for the test" to the database in the background, but does not display it to the subject in the front-end, which not only protects the safety interests of the subject, but also improves the screening success rate and reduces the difficulty of statistics later. In the phase □ of this study, 113 subjects (16 healthy individuals, 45 PCOS and 52 DOR populations) were recruited in our department within two months. In the phase □, 52 healthy women's data were collected over two months at a cost of ¥52,000 by partnering with a CRO recruitment company. The subject self-reporting system, the online OvAge calculator based on the WeChat mini grogram, has collected data from 97 healthy women within two weeks and is running reliably and has greatly improved efficiency. In addition, the users of the system are authorized staff members, and the network used is located in a hospital network environment and is specially encrypted. The subject self-reporting system will improve the efficiency and effectiveness of subject recruitment for clinical trials in practice, resulting in cost savings and improved efficiency and management.

After the optimized OvAge model, for the healthy women, the predicted ovarian age fits significantly better with the actual chronological age. Conversely, for PCOS patients, the ovarian age was less than the actual chronological age, which was statistically different, and for patients in the DOR group, the ovarian age was greater than the actual chronological age, which was also statistically different. In addition, constructing a predictive model of ovarian function based on ovarian reserve in healthy women is important for accurate assessment of ovarian reserve function, and there is some influence of race on ovarian reserve function. This large-scale prospective study based on the Chinese population is of great significance in developing an age model of ovarian reserve based on the characteristics of Chinese women. Compared with the results of previous studies, this study not only optimized the OvAge model, but also added indicators such as family history, nutritional status, psychological factors and body mass index, which are highly correlated with fertility. The OvAge model was continuously optimized with large samples and large data, and the subject self-reporting system and the version of the WeChat mini program were updated simultaneously to establish an ovarian age calculator and an early warning model in accordance with Chinese population data, in order to detect the decline in ovarian reserve function and intervene in time to improve reproductive potential, predict the timing of menopause, improve reproductive prognosis and increase the success rate of assisted reproductive technology. The online OvAge calculator also has some limitations, such as the fact that subjects have to get a report of the physical examination before they can enter a value, which causes some subjects to exit the mini program

when they click on it and find that there is no corresponding report. The authenticity of the data needs to be further ascertained, and although we provide a button to upload the report, not many are willing to do so.

Conclusions

In this paper, combined with the existing OvAge model, we developed an online OvAge calculator based on WeChat mini program, then collected basic data and gynecological examination reports of Chinese women through the online application, which is a novel way to explore the possibility of self-reporting system for subjects, and to provid more data support for further optimizing the OvAge model, to provide more evidence for the development and popularization of the online OvAge calculator, and create a new way of web-based clinical subject recruitment, and provide new ideas for clinical research.

Abbreviations

OvAge: Ovarian age; AMH: Anti-Müllerian hormone; AFC: Antral follicle counting; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; PRL: Prolactin; E_2: Estradiol; T: Testosterone; P: Progesterone; PCOS: Polycystic ovary syndrome; DOR: Diminished ovarian reserve; CRO: Contract research organization

Declarations

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None

Authors' contributions

WWX, QLR and HW conceived and designed the study. WWX, ZZ, WQ, JJ, HYZ and QLR recruited participants and collected and examined samples. WQ and FS analyzed the data. WWX, WQ and HW wrote the manuscript. All authors reviewed the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by Chinese Clinical Trial Registry (registration No. ChiCTR2000037522) and Medical ethics committee of Jiangsu Province Hospital of Chinese Medicine (approved No. 2019NL-152-02) and informed consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

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Figures

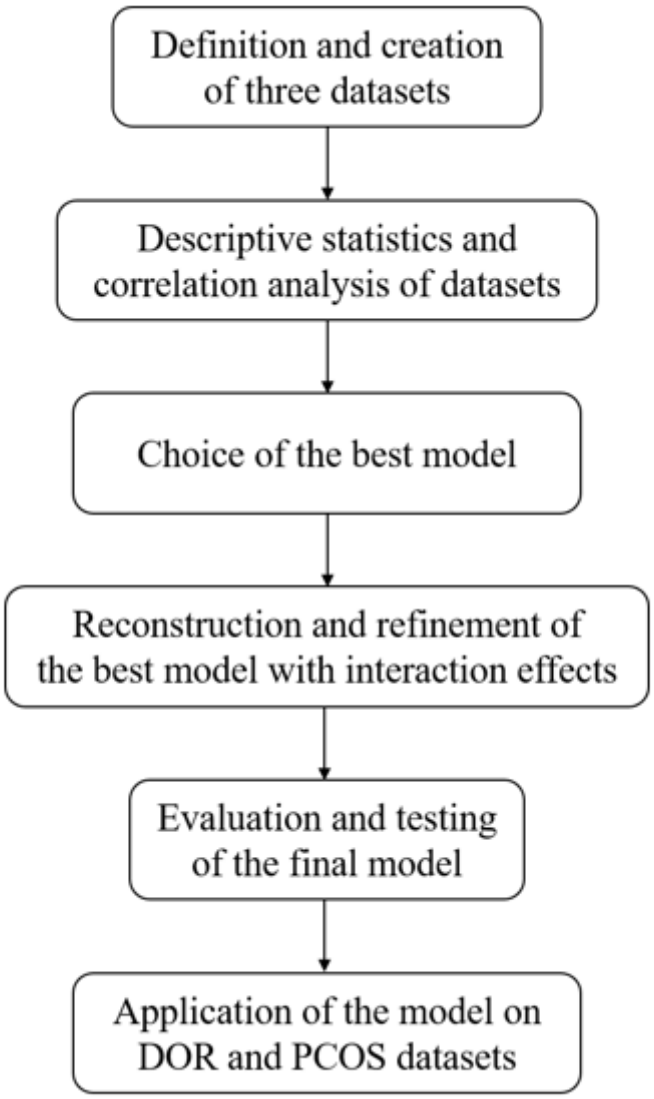
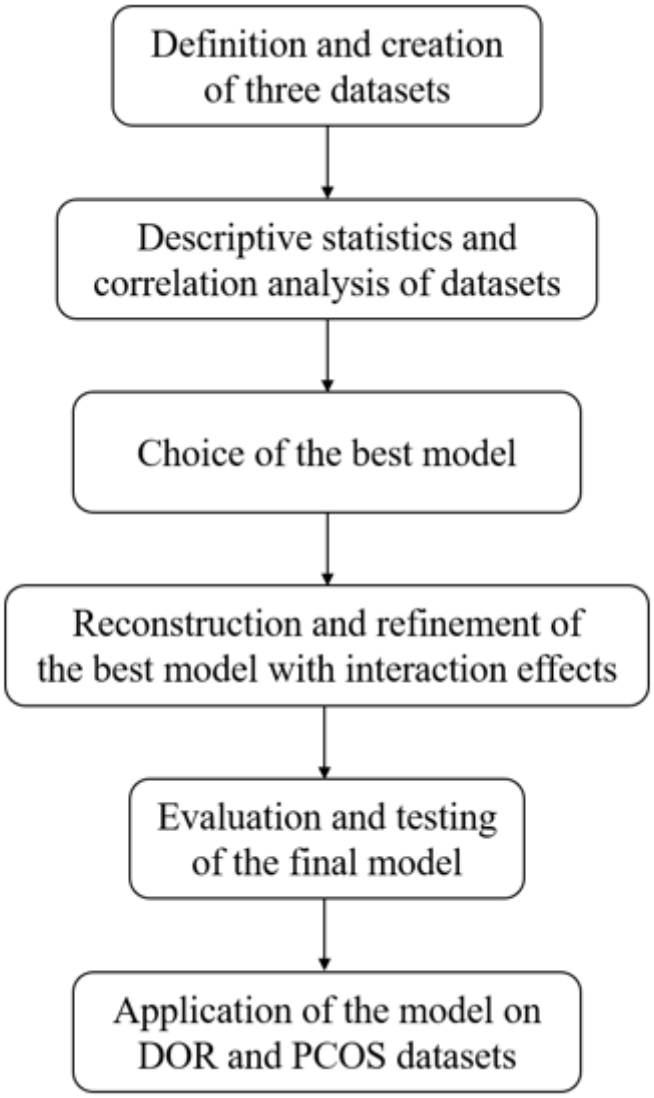


Figure 1

Flowchart for optimizing the OvAge model



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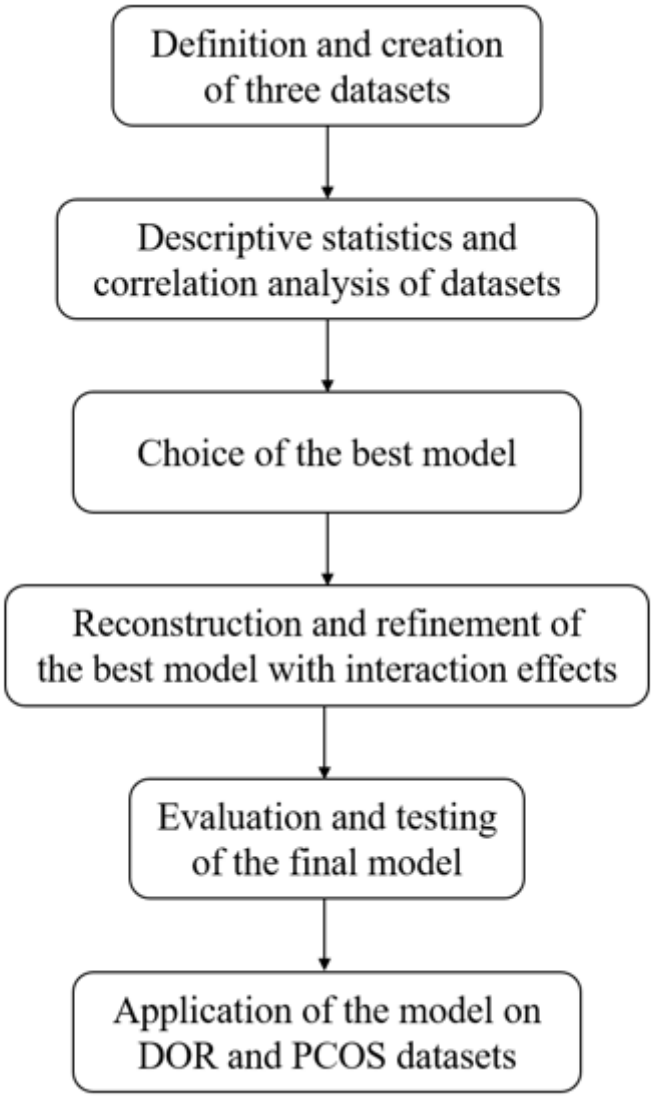

Figure 1

Flowchart for optimizing the OvAge model

Figure 2

Self-reporting system for subjects based on WeChat mini program——the online OvAge calculator. a, QR code of online OvAge calculator; b, Main interface of the online OvAge calculator; c, Data Acquisition Module; d, Questionnaire module.

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