



Early Reproductive Experience and Risk of Kidney Function Decline in Middle-aged and Older Chinese Women: A Cohort Study

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ABSTRACT

Introduction: Evidence regarding the association between basic reproductive factors (parity, age at first birth) and kidney function remains limited, particularly in Chinese populations.

Patients and Methods: Using data from the China Health and Retirement Longitudinal Study (CHARLS) 2011 baseline and 2015 follow-up, we included 4,180 female participants with serum creatinine measurements (3,057 with cystatin C data for combined eGFR calculation). Exposure variables were parity (≤ 2 vs > 2 children) and age at first birth (AFB) (< 20 , 20-25, > 25 years). Outcomes included estimated glomerular filtration rate (eGFR), incident CKD, and rapid kidney function decline. Multivariable linear and logistic regression models with step-wise covariate adjustment were applied. Sensitivity analyses included creatinine-only eGFR, ANCOVA, z-score standardized eGFR change, and continuous eGFR change models.

Results: The mean age was 57.3 ± 9.2 years; 67.7% were postmenopausal. In the fully adjusted model using combined (creatinine-cystatin C) eGFR, women with parity > 2 had 1.98 mL/min/1.73m² lower baseline eGFR (95%CI: -3.43 to -0.54, $p = 0.007$) compared with parity ≤ 2 . However, parity was not significantly associated with incident CKD (OR = 1.05, $p = 0.910$) or rapid kidney function decline (OR = 0.91, $p = 0.559$). Women with AFB > 25 years had a lower risk of incident CKD (OR = 0.26, 95%CI: 0.08-0.83, $p = 0.023$; 5/677 events) compared with AFB < 20 years (23/432 events). Sensitivity analysis using creatinine-only eGFR showed null associations for parity (beta = -0.12, $p = 0.796$). Subgroup analysis in postmenopausal women showed consistent directions of association.

Conclusions: Higher parity was associated with lower baseline eGFR levels using the combined equation, though this finding was not robust to creatinine-only sensitivity analysis. Older AFB was associated with a lower risk of incident CKD, but the sparse event count warrants cautious interpretation. Reproductive history may be a factor to consider in kidney function assessment for middle-aged and older women.

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Introduction

Chronic kidney disease (CKD) is a major global public health concern, affecting an estimated 850 million people worldwide [1]. CKD is not only a precursor to end-stage renal disease but also an independent risk factor for cardiovascular disease and all-cause mortality [2]. In China, the adult CKD prevalence is approximately 10.8%, affecting over 130 million individuals [3]. Identifying risk factors for CKD is therefore of considerable public health importance for early screening and intervention.

Women experience unique physiological processes throughout their reproductive lifespan, including pregnancy and childbirth. During pregnancy, the maternal kidneys undergo significant adaptive changes, with glomerular filtration rate increasing by 40%-50% [4]. Although this “hyperfiltration” state is necessary to meet fetal metabolic demands, repeated or early pregnancies may cause cumulative damage to the kidneys. Recent studies have demonstrated that adverse pregnancy outcomes such as hypertensive disorders of pregnancy and preeclampsia are

closely associated with increased long-term CKD risk [5, 6]. However, research on the relationship between basic reproductive factors – such as parity and age at first birth – and kidney function remains limited, and existing evidence predominantly derives from Western populations [7].

The China Health and Retirement Longitudinal Study (CHARLS) is a nationally representative longitudinal cohort study [8] that provides an ideal population basis for investigating the relationship between reproductive factors and health outcomes. The present study aimed to explore the association between early reproductive experience and the risk of kidney function decline in middle-aged and older Chinese women, providing evidence-based support for lifecycle health management in women.

Patients and Methods

Study Population

The CHARLS national baseline survey was launched in 2011, employing a multistage stratified cluster probability sampling method covering 450 communities (villages) in 150 counties (districts) across 28 provinces (autonomous regions, municipalities) in China. The target population was adults aged ≥ 45 years and their spouses, yielding nationally representative data [8]. For this study, we selected data from the CHARLS 2011 baseline and 2015 follow-up.

Inclusion criteria were: (1) female sex; (2) serum creatinine measurements available at both 2011 and 2015 (cystatin C was measured in approximately 73% of participants in 2011; thus, the sample for combined eGFR analysis was smaller than the total sample); (3) parity information available (participants with missing AFB were excluded from AFB-specific analyses). Exclusion criteria were: (1) abnormal or missing blood biochemical values (serum creatinine < 0.1 mg/dL or > 25 mg/dL; cystatin C < 0.5 mg/L or > 8 mg/L); (2) reproductive variables outside a plausible physiological range (AFB < 12 years or > 55 years). After screening, 4,180 women were included (Figure 1). This study used publicly available CHARLS data. The original survey was approved by the Biomedical Ethics Review Committee of Peking University (IRB00001052-11015), and all participants provided written informed consent.

Exposure Variables

Parity was defined as the total number of live births and was dichotomized at the sample median

into ≤ 2 and > 2 children. AFB was defined as the mother's age at delivery of her first live-born child and was categorized based on clinical significance and sample distribution into < 20 , 20-25, and > 25 years.

Outcome Variables

The estimated glomerular filtration rate (eGFR) was calculated using the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine-cystatin C combined equation [9]. eGFR outcomes included baseline eGFR and baseline-to-follow-up mean eGFR. Incident CKD was defined as baseline eGFR ≥ 60 mL/min/1.73m² with follow-up eGFR < 60 mL/min/1.73m². Because the combined equation requires both serum creatinine and cystatin C, some participants in 2011 lacked cystatin C measurement, precluding baseline combined eGFR calculation. After excluding participants with missing baseline or follow-up combined eGFR and those with baseline CKD, the at-risk cohort comprised 2,884 individuals. Rapid kidney function decline was defined as annualized eGFR decline > 3 mL/min/1.73m² [10]. Mean eGFR was defined as the arithmetic mean of baseline and follow-up eGFR.

It should be noted that the follow-up combined eGFR was higher than the baseline on average (possibly related to batch differences in cystatin C assay methods between the two survey waves), resulting in a mean eGFR slightly higher than baseline eGFR.

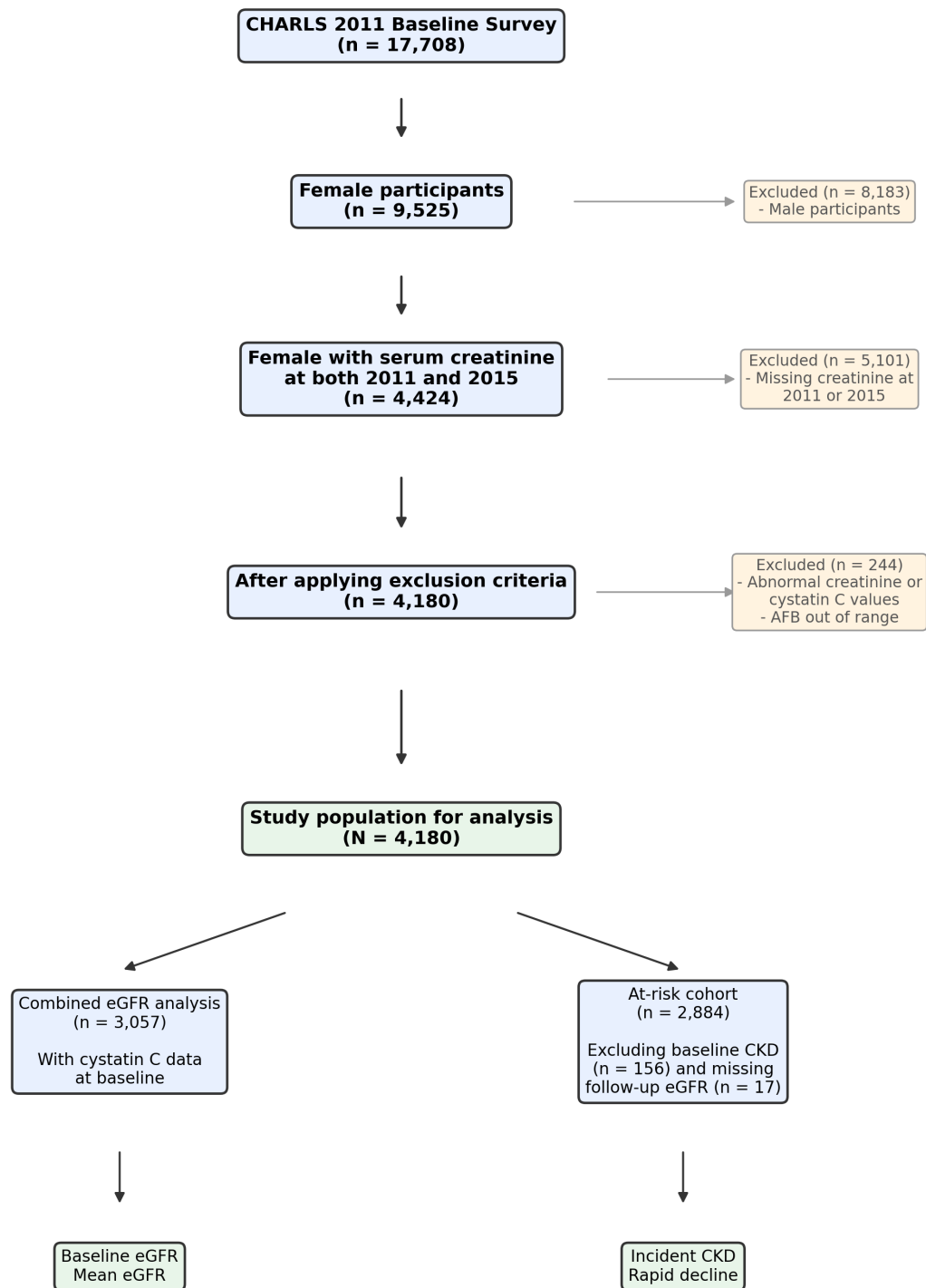
Covariates

Based on prior literature, the following covariates were adjusted: (1) demographic characteristics: age, age-squared, education level, urban/rural residence, marital status; (2) health behaviors: body mass index (BMI), smoking status, drinking status; (3) chronic disease history: hypertension, diabetes, dyslipidemia, heart disease, stroke.

Statistical Analysis

Continuous variables were described as mean $\pm$ standard deviation and compared using independent-samples t-tests. Categorical variables were described as frequency (percentage) and compared using chi-square tests. Multivariable regression models were constructed using a stepwise adjustment strategy informed by directed acyclic graph (DAG) reasoning: Model 1 adjusted for age and age-squared; Model 2 additionally adjusted for education, urban/rural

Figure 1. Flow diagram of participant selection. CHARLS, China Health and Retirement Longitudinal Study; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; AFB, age at first birth.



Subgroup: Postmenopausal women (n = 2,829)

residence, and marital status (a priori confounders); Model 3 additionally adjusted for BMI, smoking, and drinking (proximal risk factors); Model 4 (fully adjusted) additionally adjusted for hypertension, diabetes, dyslipidemia, heart disease, and stroke. Of note, these chronic diseases may lie on the causal pathway between reproductive factors and kidney function (i.e., as potential mediators); accordingly, Model 3 estimates the total effect while Model 4 estimates the direct effect not mediated through cardiometabolic conditions.

For continuous outcomes (eGFR), multivariable linear regression was used, reporting regression coefficients (beta) with 95% confidence intervals (CI). For binary outcomes (incident CKD, rapid kidney function decline), multivariable logistic regression was used, reporting odds ratios (OR) with 95% CI. To verify robustness, all analyses were repeated in the postmenopausal women subgroup ($n = 2,829$). Regression analyses used complete-case analysis. Due to partial missing data for AFB ($n = 233$), the effective sample size for AFB analyses was slightly smaller than for parity analyses. The highest missing rates among covariates were for smoking (14.2%) and BMI (11.7%), resulting in a reduced effective sample for the fully adjusted model.

For the z-score standardized sensitivity analysis, baseline and follow-up eGFR were standardized separately within participants with both measurements for each eGFR equation by subtracting the wave-specific mean and dividing by the wave-specific standard deviation. The standardized change outcome was calculated as follow-up z-score minus baseline z-score. This approach evaluates relative change within each survey wave and reduces the influence of systematic wave-level shifts in cystatin C measurement.

For the continuous eGFR change analysis, raw change was calculated as follow-up eGFR minus baseline eGFR in mL/min/1.73m² and modeled using multivariable linear regression with the same Model 4 covariates. A positive coefficient indicates a more favorable change, whereas a negative coefficient indicates a greater decline. Statistical analyses were performed using Python 3.11 (statsmodels 0.14.0). All tests were two-sided with $\alpha = 0.05$.

Results

Baseline Characteristics

A total of 4,180 women were included, with a mean age of 57.3 ± 9.2 years; 67.7% were postmenopausal.

Table 1. Baseline Characteristics of Study Participants ($n = 4,180$)

Variable	Value
Age (years)	57.3 ± 9.2
Postmenopausal	2,829 (67.7)
Education	
Primary school or below	3,366 (80.5)
Junior high school	574 (13.7)
Senior high school or above	240 (5.7)
Residence	
Urban	1,449 (34.7)
Rural	2,731 (65.3)
Married	3,306 (79.1)
BMI (kg/m ²)	24.1 ± 3.9
Smoking (ever or current)	37 (0.9)
Drinking (ever or current)	510 (12.2)
Chronic diseases	
Hypertension	1,662 (39.8)
Diabetes	673 (16.1)
Dyslipidemia	474 (11.3)
Heart disease	571 (13.7)
Stroke	94 (2.2)
Parity	
≤2 children	1,837 (43.9)
>2 children	2,343 (56.1)
Age at first birth	
<20 years	603 (14.4)
20-25 years	2,316 (55.4)
>25 years	1,028 (24.6)
Missing	233 (5.6)
Baseline eGFR (mL/min/1.73m ²)	91.9 ± 18.3
Mean eGFR (mL/min/1.73m ²)	93.9 ± 17.0
Baseline CKD	156 (5.1)
Incident CKD*	74 (2.6)
Rapid kidney function decline*	349 (12.1)

Table 1 note: Continuous data are presented as mean $\pm$ SD; categorical data are presented as n (%). Percentages are based on the total sample of 4,180. BMI non-missing $n = 3,693$; smoking non-missing $n = 3,587$ (593 missing, 14.2%; the very low smoking prevalence of $37/3,587 = 1.0\%$ among non-missing reflects low female smoking rates in China); drinking non-missing $n = 3,896$; AFB non-missing $n = 3,947$. Baseline eGFR and CKD based on 3,057 participants with combined eGFR data. Mean eGFR based on 3,036 participants. *At-risk cohort ($n = 2,884$) as denominator.

Table 2. Multivariable Regression Analysis of the Association Between Parity and Kidney Function

Outcome	Model 1 beta/OR (95%CI)	Model 4 beta/OR (95%CI)
eGFR (beta)		
Baseline eGFR	-1.46 (-2.72 to -0.21)*	-1.98 (-3.43 to -0.54)**
Mean eGFR	-1.55 (-2.67 to -0.42)**	-1.74 (-3.04 to -0.45)**
Binary outcomes (OR)		
Incident CKD	1.17 (0.59 to 2.35)	1.05 (0.46 to 2.37)
Rapid decline	1.03 (0.79 to 1.34)	0.91 (0.67 to 1.24)

Table 2 note: Reference group: parity ≤ 2 . Model 1: adjusted for age and age². Model 4: additionally adjusted for education, urban/rural residence, marital status, BMI, smoking, drinking, hypertension, diabetes, dyslipidemia, heart disease, and stroke. Effective sample sizes – Model 4: baseline eGFR n = 2,251; mean eGFR n = 2,237; binary outcomes n = 2,153. Model 1: baseline eGFR n = 3,057; mean eGFR n = 3,036; binary outcomes n = 2,884. * $p < 0.05$; ** $p < 0.01$.

The majority were rural residents (65.3%) with primary school education or below (80.5%). Regarding parity, 43.9% had ≤ 2 children and 56.1% had > 2 children. For AFB, 14.4%, 55.4%, and 24.6% were in the < 20 , 20-25, and > 25 years groups, respectively (233 missing, 5.6%).

All 4,180 participants had serum creatinine results, of whom 3,057 (73.0%) also had baseline cystatin C data for combined eGFR calculation. Among these 3,057 participants, baseline eGFR was 91.9 ± 18.3 mL/min/1.73m², and baseline CKD prevalence (eGFR < 60 mL/min/1.73m²) was 5.1% (n = 156). After excluding participants with missing baseline or follow-up combined eGFR and those with baseline CKD, the at-risk cohort comprised 2,884 individuals. During approximately 4 years of follow-up, the cumulative incidence of incident CKD was 2.6%, and rapid kidney function decline was 12.1%. Baseline characteristics are shown in Table 1.

Parity and Kidney Function

Table 2 shows the association between parity and kidney function outcomes. In Model 1 (age-adjusted only), parity > 2 was significantly negatively associated with both baseline eGFR and mean eGFR ($p < 0.05$). After stepwise adjustment for sociodemographic characteristics, health behaviors, and chronic diseases, effect sizes remained stable and slightly increased, suggesting that the adjustment variables had a suppressive confounding effect on the parity-eGFR association.

In the fully adjusted model (Model 4), women with parity > 2 had 1.98 mL/min/1.73m² lower baseline eGFR (95%CI: -3.43 to -0.54, $p = 0.007$) and 1.74

mL/min/1.73m² lower mean eGFR (95%CI: -3.04 to -0.45, $p = 0.008$) compared with parity ≤ 2 . The associations between parity and incident CKD (OR = 1.05, 95%CI: 0.46-2.37, $p = 0.910$) and rapid kidney function decline (OR = 0.91, 95%CI: 0.67-1.24, $p = 0.559$) were not statistically significant (Table 2).

Event counts by parity group in the at-risk cohort: incident CKD occurred in 13/1,247 (1.0%) women with parity ≤ 2 and 61/1,637 (3.7%) with parity > 2 ; rapid decline occurred in 140/1,247 (11.2%) and 209/1,637 (12.8%), respectively.

Age at First Birth and Kidney Function

Table 3 presents the association between AFB and kidney function outcomes. In the fully adjusted model, compared with AFB < 20 years, women with AFB > 25 years had 1.71 mL/min/1.73 m² higher mean eGFR (95%CI: -0.17 to 3.60, $p = 0.075$), showing a marginally significant trend.

For incident CKD, compared with the AFB < 20 years, the AFB > 25 years group had a 74% reduction in risk (OR = 0.26, 95%CI: 0.08-0.83, $p = 0.023$). The associations between AFB and rapid kidney function decline did not reach statistical significance (20-25 years: OR = 0.92, 95%CI: 0.63-1.34, $p = 0.673$; > 25 years: OR = 0.79, 95%CI: 0.51-1.23, $p = 0.303$) (Table 3).

Event counts by AFB group in the at-risk cohort: incident CKD occurred in 23/432 (5.3%) women with AFB < 20 years, 44/1,617 (2.7%) with AFB 20-25 years, and 5/677 (0.7%) with AFB > 25 years. The very low event count (n=5) in the AFB > 25 group warrants caution in interpreting the OR estimate. Rapid decline occurred in 60/432 (13.9%), 200/1,617 (12.4%), and 69/677 (10.2%), respectively.

Table 3. Multivariable Regression Analysis of the Association Between AFB and Kidney Function (Model 4)

Outcome	<20 years (Ref)	20-25 years beta/OR (95%CI)	>25 years beta/OR (95%CI)
eGFR (beta)			
Baseline eGFR	0	0.62 (-1.21 to 2.44)	1.51 (-0.60 to 3.61)
Mean eGFR	0	0.51 (-1.13 to 2.15)	1.71 (-0.17 to 3.60)
Binary outcomes (OR)			
Incident CKD	1	0.92 (0.46 to 1.83)	0.26 (0.08 to 0.83)*
Rapid decline	1	0.92 (0.63 to 1.34)	0.79 (0.51 to 1.23)

Table 3 note: Model 4: adjusted for age, age², education, urban/rural residence, marital status, BMI, smoking, drinking, hypertension, diabetes, dyslipidemia, heart disease, stroke. Effective sample sizes: baseline eGFR n=2,149; mean eGFR n=2,136; binary outcomes n=2,055. * $p < 0.05$.

Table 4. Subgroup Analysis in Postmenopausal Women (n=2,829, Model 4)

Exposure	Outcome	beta/OR (95%CI)	P value
Parity (>2 vs ≤2)			
	Baseline eGFR	-1.99 (-3.80 to -0.18)	0.031
	Mean eGFR	-1.80 (-3.44 to -0.16)	0.031
	Incident CKD	0.66 (0.27 to 1.61)	0.365
	Rapid decline	0.78 (0.54 to 1.14)	0.203
AFB (>25 vs <20 years)			
	Baseline eGFR	2.24 (-0.27 to 4.75)	0.08
	Mean eGFR	2.41 (0.14 to 4.67)	0.038
	Incident CKD	0.21 (0.06 to 0.81)	0.023
	Rapid decline	0.85 (0.50 to 1.45)	0.554

Table 4 note: Model 4: fully adjusted. Effective sample sizes – Parity analysis: baseline eGFR n = 1,537; mean eGFR n = 1,528; binary outcomes n = 1,459. AFB analysis: baseline eGFR n = 1,475; mean eGFR n = 1,467; binary outcomes n = 1,401. AFB shows extreme group comparison only (> 25 vs < 20 years); 20-25 years results available in Table 3.

Subgroup Analysis in Postmenopausal Women

To verify the robustness of results, the above analyses were repeated in a subgroup of 2,829 postmenopausal women (effective sample sizes for each outcome were lower due to complete-case analysis; see Table 4 notes). Results showed that associations between parity, AFB, and kidney function were consistent in direction with the full sample. Women with parity >2 had 1.99 mL/min/1.73m² lower baseline eGFR ($p = 0.031$) and 1.80 mL/min/1.73m² lower mean eGFR ($p = 0.031$). Women with AFB > 25 years had 2.41 mL/min/1.73m² higher mean eGFR ($p = 0.038$) and a 79% reduction in incident CKD risk (OR = 0.21, 95%CI: 0.06-0.81, $p = 0.023$). The association with rapid kidney function decline did not reach statistical significance (OR = 0.85, $p = 0.554$) (Table 4).

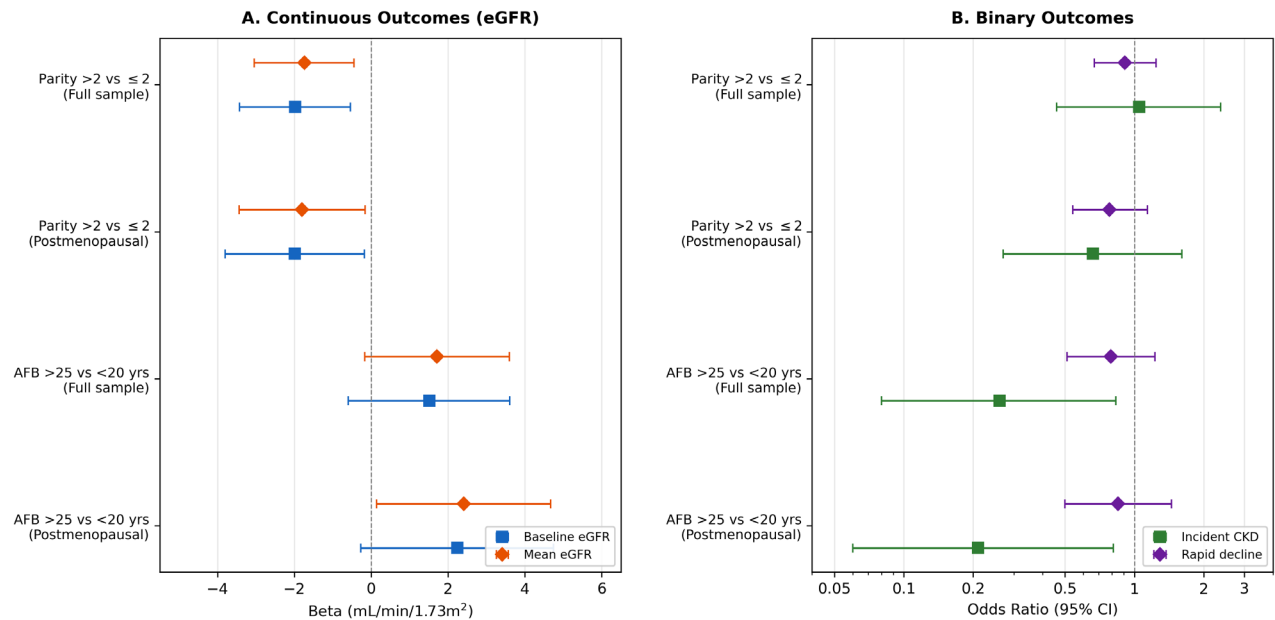
Summary of Main Findings

Figure 2 summarizes the main effect estimates from the fully adjusted models in both the full sample and the postmenopausal subgroup. The forest plot illustrates two consistent patterns: higher parity was associated with lower eGFR (panel A, left of reference line), while later AFB was associated with higher eGFR and reduced incident CKD risk (Panel B, OR < 1).

Sensitivity Analyses

To address the potential impact of cystatin C assay batch differences between the 2011 and 2015 survey waves, all primary analyses were repeated using the CKD-EPI 2021 creatinine-only equation [9]. The mean change in creatinine-only eGFR between waves

Figure 2. Forest plot of the associations between reproductive factors and kidney function outcomes (fully adjusted Model 4). Panel A shows beta coefficients for continuous eGFR outcomes; Panel B shows odds ratios for binary outcomes (incident CKD and rapid kidney function decline) on a logarithmic scale. Error bars represent 95% confidence intervals. The dashed reference lines indicate null effects (beta = 0 and OR = 1, respectively). eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; AFB, age at first birth; CI, confidence interval.



was -3.93 mL/min/1.73m² (consistent with age-related decline), in contrast to the +3.91 mL/min/1.73m² increase observed with the combined equation. Using creatinine-only eGFR, the association between parity > 2 and baseline eGFR was fully attenuated (beta = -0.12, 95%CI: -1.01 to 0.78, *p* = 0.796; *n* = 3,053). The association between AFB >25 years and incident CKD was also attenuated (OR = 0.64, 95%CI: 0.34-1.23, *p* = 0.182). However, AFB >25 years was significantly associated with reduced risk of rapid kidney function decline using creatinine-only eGFR (OR = 0.65, 95%CI: 0.47-0.91, *p* = 0.011), a finding that was not significant in the combined eGFR analysis.

ANCOVA analysis (follow-up eGFR adjusted for baseline eGFR and Model 4 covariates) showed no significant associations for either exposure using either eGFR equation (parity: *p* = 0.371 for combined, *p* = 0.797 for creatinine-only; AFB >25: *p* = 0.223 for combined, *p* = 0.075 for creatinine-only).

When parity was treated as a continuous variable (per-child increment), each additional child was associated with 0.59 mL/min/1.73m² lower baseline combined eGFR (95%CI: -1.09 to -0.08, *p* = 0.024), supporting a dose-response relationship. However, the P-for-trend across four parity categories (0-1, 2, 3-4, 5+) did not reach statistical significance.

In paired participants with cystatin C data at both waves (*n* = 3,044), mean cystatin C was 0.96 mg/L (SD 0.24) in 2011 and 0.86 mg/L (SD 0.22) in 2015. The 2015-2011 paired average difference was -0.10 mg/L (SD 0.21; 95%CI: -0.108 to -0.093), and the Kolmogorov-Smirnov test comparing the two wave distributions showed *D* = 0.233 (*p* < 0.001), supporting a systematic distributional shift between waves (Table 5).

Z-score standardized eGFR change analyses did not show significant associations between parity and relative kidney function change. For parity > 2 versus ≤ 2 children, the beta was 0.015 (95%CI: -0.059 to 0.090, *p* = 0.688; *n* = 2,237) using combined eGFR and -0.007 (95%CI: -0.075 to 0.062, *p* = 0.850; *n* = 3,037) using creatinine-only eGFR. For AFB > 25 versus < 20 years, the beta was 0.024 (95%CI: -0.084 to 0.131, *p* = 0.667; *n* = 2,136) using combined eGFR and 0.067 (95%CI: -0.036 to 0.169, *p* = 0.202; *n* = 2,893) using creatinine-only eGFR (Table 6).

Linear regression of standardized eGFR change, calculated as follow-up eGFR z-score minus baseline eGFR z-score. Baseline and follow-up eGFR were standardized independently within participants with both measurements for each equation. Model 4 adjusted for age, age-squared, education, residence,

Table 5. Cystatin C distribution comparison, 2011 vs 2015 waves

Metric	Wave 2011	Wave 2015	Paired diff
n	3,044	3,044	
mean	0.957	0.856	
SD	0.243	0.217	
median	0.93	0.83	
Q1	0.82	0.72	
Q3	1.06	0.95	
min	0.36	0.4	
max	5.97	3.7	
skewness	4.192	2.598	
kurtosis	65.461	18.078	
KS_D			0.233
KS_p			1.37E-72
paired_diff_mean			-0.101
paired_diff_SD			0.212
paired_diff_95CI_lower			-0.108
paired_diff_95CI_upper			-0.093

Table 5 note: Cystatin C values are in mg/L. Paired difference is 2015 minus 2011. KS_D and KS_p are from the two-sample Kolmogorov-Smirnov test comparing wave distributions among participants with cystatin C measurements at both 2011 and 2015 waves.

Table 6. Z-score standardized eGFR sensitivity analysis (Model 4)

Exposure	eGFR equation	Beta	Lower 95%CI	Upper 95%CI	p value	n
parity >2 vs ≤2	combined	0.015	-0.059	0.09	0.688	2,237
AFB 20-25 vs <20	combined	-0.012	-0.106	0.082	0.801	2,136
AFB >25 vs <20	combined	0.024	-0.084	0.131	0.667	2,136
parity >2 vs ≤2	creatinine-only	-0.007	-0.075	0.062	0.85	3,037
AFB 20-25 vs <20	creatinine-only	0.078	-0.013	0.168	0.091	2,893
AFB >25 vs <20	creatinine-only	0.067	-0.036	0.169	0.202	2,893

Table 7. Continuous eGFR change linear regression (Model 4)

Exposure	eGFR equation	Beta	Lower 95%CI	Upper 95%CI	p value	n
parity >2 vs ≤2	combined	0.229	-1.147	1.605	0.744	2,237
AFB 20-25 vs <20	combined	-0.207	-1.94	1.526	0.815	2,136
AFB >25 vs <20	combined	0.488	-1.502	2.477	0.631	2,136
parity >2 vs ≤2	creatinine-only	-0.111	-1.142	0.919	0.832	3,037
AFB 20-25 vs <20	creatinine-only	1.209	-0.157	2.575	0.083	2,893
AFB >25 vs <20	creatinine-only	1.135	-0.41	2.68	0.15	2,893

Table 7 note: Continuous raw eGFR change models similarly showed no significant association for parity. For parity > 2 versus ≤ 2 children, the beta was 0.229 mL/min/1.73m² (95%CI: -1.147 to 1.605, $p = 0.744$; $n = 2,237$) using combined eGFR and -0.111 mL/min/1.73m² (95%CI: -1.142 to 0.919, $p = 0.832$; $n = 3,037$) using creatinine-only eGFR. For AFB > 25 versus < 20 years, the beta was 0.488 (95%CI: -1.502 to 2.477, $p = 0.631$; $n = 2,136$) using combined eGFR and 1.135 (95%CI: -0.410 to 2.680, $p = 0.150$; $n = 2,893$) using creatinine-only eGFR (Table 7). Detailed numerical estimates are reported in Tables 5-7 below.

marital status, BMI, smoking, drinking, hypertension, diabetes, dyslipidemia, heart disease, and stroke.

Linear regression of raw eGFR change, calculated as follow-up eGFR minus baseline eGFR in mL/min/1.73 m². Positive beta values indicate a more favorable eGFR change; negative beta values indicate greater decline. Model 4 adjusted for age, age-squared, education, residence, marital status, BMI, smoking, drinking, hypertension, diabetes, dyslipidemia, heart disease, and stroke.

Discussion

Reproductive History and Kidney Function in Chinese Women

CKD has become a major public health threat in China, and women may be subject to long-term effects of reproductive experience on kidney function due to unique physiological processes, including pregnancy and childbirth [1-4]. Using a nationally representative CHARLS sample, this study systematically investigated the association between reproductive history and kidney function in middle-aged and older Chinese women. We found that higher parity (> 2 children) was independently associated with lower eGFR levels, older AFB (> 25 years) was associated with higher eGFR levels and lower incident CKD risk, and these associations remained consistent in the postmenopausal subgroup.

The finding that women with parity > 2 had approximately 2 mL/min/1.73m² lower baseline eGFR is modest at the individual level but may have population-level implications. Given that healthy adults experience an age-related eGFR decline of approximately 0.75-1.0 mL/min/1.73m² per year [11], this

difference corresponds to roughly 2-3 years of age-related eGFR decline at the population level, though the cross-sectional nature of this finding precludes causal interpretation. Previous studies have also reported that delayed menarche age and shorter reproductive lifespan are associated with increased CKD prevalence [12], suggesting that female reproductive factors have long-term effects on kidney function. Healthcare providers may consider incorporating reproductive history into comprehensive health assessments for middle-aged and older women. Notably, this association was observed only with the combined (creatinine-cystatin C) eGFR equation and was not replicated using creatinine-only eGFR (beta = -0.12, $p = 0.796$), requiring careful interpretation.

The creatinine discrepancy may reflect limitations of creatinine-based eGFR in this demographic rather than the simple absence of a true association. Serum creatinine is strongly influenced by muscle mass, diet, and frailty, whereas cystatin C and combined creatinine-cystatin C equations can provide additional information when creatinine is insensitive to early kidney dysfunction [20, 21]. This issue is particularly relevant for middle-aged and older women, among whom sarcopenia and low muscle mass may lower serum creatinine and thereby overestimate kidney function. In older adults, cystatin C has been shown to predict mortality and cardiovascular outcomes, and equations incorporating cystatin C have been developed specifically to improve kidney function estimation in older populations [20-22]. A longitudinal cohort study further showed that low muscle mass and muscle wasting can cause substantial overestimation of creatinine-based eGFR, supporting the use of muscle mass-independent markers such as cys-

tin C in low-muscle-mass settings [23]. In the present study, the creatinine-only null result may therefore reflect reduced sensitivity to early eGFR differences in older women, rather than the absence of any biological association between reproductive history and kidney function. At the same time, the cystatin C wave shift cautions against overinterpreting longitudinal combined-eGFR outcomes.

Potential Mechanisms

The association between higher parity and lower kidney function may involve multiple mechanisms: (1) each pregnancy is accompanied by significant renal hemodynamic changes, and repeated “hyperfiltration” states may accelerate glomerular sclerosis [13]; (2) higher parity is often associated with lower socioeconomic status and poorer access to prenatal care, increasing the risk of pregnancy complications [14]; (3) multiple pregnancies may indirectly damage kidney function through increased metabolic burden [6]. Notably, the associations between parity and incident CKD or rapid kidney function decline were not significant, suggesting that the impact of parity on kidney function is primarily reflected in cross-sectional level differences rather than accelerated decline [15].

Several factors may explain the null longitudinal findings for parity. First, the acknowledged cystatin C assay batch effect between the 2011 and 2015 waves – evidenced by a mean increase of 3.91 mL/min/1.73m² in combined eGFR despite expected age-related decline – may have systematically misclassified longitudinal outcomes. The creatinine-only eGFR, unaffected by this batch effect, showed a mean decline of 3.93 mL/min/1.73m², consistent with normal aging. When creatinine-only eGFR was used, the parity-eGFR association was entirely attenuated (beta = -0.12, $p = 0.796$). Second, reverse causation cannot be excluded: women with chronic conditions, poorer perceived health, or early kidney impairment may have selected lower parity or delayed first birth, especially when reproductive decisions were shaped by family, policy, and access to care. Third, birth cohort confounding is a concern in the Chinese context, where older cohorts experienced both higher parity (pre-family planning era) and greater age-related kidney function decline. Although age and age-squared were adjusted, residual confounding by birth cohort remains possible. Fourth, with only 74 incident CKD events in the combined eGFR risk set, statistical power was limited for detecting modest associations.

Older AFB (> 25 years) was associated with higher eGFR levels and lower incident CKD risk, with women having AFB > 25 years showing only 0.26 times the incident CKD risk of those with AFB < 20 years. This is consistent with findings from the UK Biobank, where Han et al. reported that each 5-year delay in AFB was associated with approximately 10% lower CKD risk [7]. A Korean study of postmenopausal women also found that longer reproductive lifespan was associated with lower CKD risk [16]. The protective effect of older AFB may involve both biological and social mechanisms. Biologically, adolescent pregnancy occurs when renal development is not yet complete, and the pregnancy burden during this period may cause greater irreversible damage to renal reserve function [17]. Because normal pregnancy requires major renal vasodilation and hyperfiltration, a first pregnancy during late adolescence could, as a hypothesis-generating mechanism, blunt renal reserve or reduce later capacity to tolerate hemodynamic stress [4, 24]. Socially, women with older AFB generally have higher education levels and health literacy [18]. In this CHARLS cohort, AFB > 25 years may also mark better early-life nutrition, more stable social circumstances before childbearing, and greater ability to access medical care. The association persisted after adjustment for socioeconomic factors in the fully adjusted model, suggesting that biological mechanisms may contribute. However, residual confounding by socioeconomic factors remains a concern. In the CHARLS generation, higher parity and younger AFB are strongly correlated with lower socioeconomic status, limited healthcare access, nutritional deficiencies, and heavy manual labor during early life – all of which are independent risk factors for kidney disease. Although we adjusted for education and urban/rural residence, these covariates may not fully capture the cumulative life-course disadvantage that shapes both reproductive patterns and long-term health outcomes. The biological and social pathways through which reproductive factors affect kidney function are likely intertwined and cannot be fully disentangled in observational data.

In the postmenopausal subgroup, effect sizes for parity and eGFR were similar to the full sample, and the protective effects of AFB > 25 years on mean eGFR and incident CKD remained significant. Estrogen exerts multiple protective effects on the kidneys, including suppression of renin-angiotensin system activity and reduction of oxidative stress and inflammation [19]. The sharp decline in estrogen levels after

menopause may amplify the negative effects of prior reproductive exposures on kidney function. This finding suggests that postmenopausal women may be a high-risk group for reproductive factor-related kidney damage, and healthcare providers should incorporate reproductive history into kidney function risk assessment during perimenopausal health management.

Pregnancy complications remain an important source of unmeasured confounding. Hypertensive disorders of pregnancy, preeclampsia, and gestational diabetes are biologically plausible drivers of later CKD and may also be associated with parity, AFB, socioeconomic status, and access to prenatal care [5, 6]. CHARLS did not collect detailed pregnancy-complication histories, so we could not distinguish whether the observed associations reflect reproductive timing and parity themselves, cumulative exposure to complicated pregnancies, or shared upstream life-course determinants. This limitation is particularly important for interpreting mechanisms, and future cohorts with obstetric history data should evaluate these complications directly.

Strengths and Limitations

This study has several strengths: (1) the use of a nationally representative CHARLS sample provides good generalizability; (2) the combination of baseline and follow-up eGFR data to construct longitudinal outcome variables (incident CKD and rapid kidney function decline) addresses limitations of previous cross-sectional studies; (3) the stepwise adjustment strategy allows observation of the influence of confounding factors on the association.

Several limitations should be acknowledged: (1) the combined eGFR calculation relies on cystatin C, and potential batch differences in cystatin C assay methods between the two CHARLS survey waves may have affected the 2015 combined eGFR values (follow-up mean eGFR was higher than baseline), potentially influencing the classification of binary outcomes. As detailed in the Sensitivity Analyses section, the parity-eGFR association was not robust to creatinine-only eGFR analysis, suggesting that cystatin C measurement variability may have contributed to the observed associations. The creatinine-only analysis did, however, reveal a significant association between later AFB and reduced rapid kidney function decline (OR = 0.65, $p = 0.011$) that was not detected with the combined equation; (2) the association between eGFR and parity is based on cross-sectional baseline

data and cannot establish causality; (3) reproductive history was self-reported and may be subject to recall bias; (4) effect sizes were small, limiting individual-level clinical significance; (5) CHARLS did not collect detailed information on pregnancy complications, limiting mechanistic exploration; (6) sparse longitudinal events constrained inference, especially for AFB, where only 5 incident CKD events occurred in the AFB > 25 subgroup. Therefore, the OR of 0.26 should be interpreted as hypothesis-generating rather than definitive evidence of protection; (7) the study population was Chinese, and caution should be exercised in generalizing results. Future studies should pursue longer longitudinal follow-up, incorporate detailed pregnancy complication data, and further elucidate the biological mechanisms through which reproductive factors affect kidney function.

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Author contributions

Juhong Zhu conceptualized the study, performed data analysis, and drafted the manuscript. Haiyang Zheng and Ying Wan contributed to data interpretation and critically revised the manuscript. Yuanmei Zhang contributed to study design and data collection. Weiyue Huang supervised the study, contributed to the study design, and provided a critical review of the manuscript. All authors have read and approved the final version.

Conflict of interest

The authors declare no conflicts of interest.

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Data availability statement

The China Health and Retirement Longitudinal Study (CHARLS) data used in this study are publicly available and can be accessed at <http://charls.pku.edu.cn/> upon registration.

Ethics statement

This study used publicly available CHARLS data. The original CHARLS survey was approved by the Biomedical Ethics Review Committee of Peking University (IRB00001052-11015). All participants provided written informed consent.

Use of artificial intelligence

DeepSeek (DeepSeek-AI, Hangzhou, China) was used to assist with translating the manuscript from Chinese to English. All AI-generated translations were reviewed, verified, and edited by the authors, who take full responsibility for the accuracy and integrity of the final manuscript.

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