Heliyon 8 (2022) e11919

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

New comprehensive reference values for kidney function indexes across adult and geriatric ages in Chinese popuplation

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HIGHLIGHTS

- Albumin's limits were lower than the national reference intervals (RIs).
- Updating RIs may help to reduce inappropriate application of the albumin.
- Physiological decline with age was in estimate glomerular filtration rate (eGFR).
- Reformulate the RIs for subjects with high uric acid level should be cautious.

ARTICLE INFO

Keywords:
Kidney disease
Reference intervals
Uric acid
Albumin

ABSTRACT

Background and aims: China has the largest number of chronic kidney disease (CKD) patients. Current CKD definition has been challenged recently. We aim to reassess kidney function in healthy Chinese population, to provide a more appropriate reference range (RIs) for diagnosis, treatment, monitoring (or screening) of kidney disease and related research.

Materials and methods: A total of 49627 apparently healthy people aged 18–94 years old were enrolled. Age and sex effects were explored for the kidney function indicators and RIs were calculated non-parametrically.

Results: Albumin's limits were lower than the national RIs, with 5.7 g/L lower in upper limit (UL) and 0.4 g/L lower in lower limit (LL) [RIs: 39.6–49.3 vs 40–55]. The LL of estimate glomerular filtration rate (eGFR) was 80.4 mL/min/1.73 m^2 or 63.3 mL/min/1.73 m^2 at the age of <50 or ≥ 70 years, respectively. Notably, eGFR showed an approximately 0.7 mL/min/1.73 m^2 decrease every year. In addition, eGFR increase 0.35 mL/min/1.73 m^2 per standard deviation increase in blood glucose when uric acid (UA) exceed the RIs.

Conclusion: UA was an important factor affecting eGFR. For healthy elderly in China, albumin's limits were lower than the national RIs, and LLs of eGFR were nearly 60 mL/min/1.73 m^2. Using national RIs for healthy elderly may be overly stringent.

1. Introduction

Chronic kidney disease (CKD) is reported in 10% of adult population [1]. Currently, there are approximately 132.3 million CKD patients in China [2]. Kidneys play key roles in maintaining physiological homeostasis by excreting waste products (such as serum urea, creatinine, and uric acid [UA]) and moderating composition of body fluids (such as calcium, chlorine, and magnesium). Early-stage kidney disease is asymptomatic; therefore, it is imperative to establish laboratory measurements of the these indexes with accurate reference intervals (RIs) for early detection and monitoring of kidney function [3].

Kidney function for general population is mainly determined using serum creatinine and a glomerular filtration rate estimating equation (eGFR). Subjects presenting with eGFR below 60 ml/min/1.73 m^2 for

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https://doi.org/10.1016/j.heliyon.2022.e11919
Received 19 April 2022; Received in revised form 14 November 2022; Accepted 18 November 2022

more than 3 months are known to have CKD [4, 5]. The CKD definition has limitations because it does not differentiate loss of kidney function caused by kidney disease with that caused by kidney aging [6]. The definition of CKD was recently updated and new RIs differ in across population [7]. These differences can be attributed to sex-related physiological differences and different lifestyles, which necessitate use of appropriately subgroup RIs when distinct subpopulation distributions are observed [3, 8]. National standard RIs for creatinine and urea stratified by age (20–59 and 60–79 years) and sex in Chinese adults were published in 2015 [9]. However, studies have not explored age- and sex-specific RIs of comprehensive kidney function indexes for population in China [10].

Establishment of age- and sex-dependent RIs will allow early detection of kidney injury in patients who are ill and/or treated with nephrotoxic drugs [11]. In addition, it will be helpful in clinical management of patients since will prevent over-diagnosis of CKD in the elderly and minimize missed diagnosis of CKD in young and middle-aged adults [3]. In the present study, RIs for routine kidney biomarkers were established using health examination data for healthy people in accordance with CLSI C28-A3 guidelines. Moreover, the effects of four common kidney function indexes on eGFR were evaluated.

2. Materials and methods

2.1. Participants

The study was carried out at Medical Examination Center (MEC). The MEC is part of Guangdong Provincial People's Hospital, a large health management center in southern China. The MEC Laboratory has an efficient and stable quality management system in accordance with ISO15189: 2012 which indicates the requirements for quality and competence in medical laboratories. In addition, the analytes conducted by the laboratory participate in the External Quality Assessment Programs in Laboratory Medicine hold by National Center for Clinical Laboratories (NCCL) every year, and the results are all under control. The center conducts physical examination for about 80,000 subjects every year. Records of 206446 individuals stored in the MEC laboratory information system over a 3-year period (2018.04–2020.12) were retrieved to constitute the original dataset for use in this study.

This study was approved by the Ethics Committee of the Guangdong Provincial People's Hospital (No. KY-Q-2021-126-01) and was conducted in accordance with the ethical guidelines of the Declaration of Helsinki of the World Medical Association. The Ethics Committee also approved the waived written informed patient consent because of the retrospective nature of the study. No identifiable personal data of the patients were available for the analysis.

2.2. Measures

Routine general health examination included demographic information and questionnaires to record underlying diseases (such as comorbidity of hypertension, cardiovascular disease, diabetes mellitus, or kidney disease were identified by taking a careful history). Organ abnormalities were verified by reviewing the ultrasound and/or CT results.

All assays were performed using serum samples obtained from blood collected from patients, and were tested with Vitros 5,1 FS instrument in SST (tube type). A total of 11 key renal-related indicators were evaluated namely: albumin (bromocresol green method), creatinine (enzymic method), total protein (biuret method), urea (urease rate method), UA (uricase method), calcium (Arsenazo III method), chloridion (indirect ion selective electrode), magnesium (Xylidyl Blue method), phosphorus (molybdate method), potassium (indirect ion selective electrode), and sodium (indirect ion selective electrode). All reagents for the corresponding assays were purchased from Beckman Coulter©, and the assays were performed on the Beckman Coulter AU5800 Chemistry System. Quality control is conducted twice a day, in the morning and afternoon respectively. Sample testing only after ensuring all the items are under control. The instrument is regularly maintained on a daily, weekly, monthly, quarterly, and annual basis, and calibrated once a year. The calibration results meet the requirements of the industry standards "YY/T 0654–2017 Automatic Biochemical Analyzer" and "YY/T 0589–2016 Electrolyte Analyzer". The number of available test results ranged from 669 (such as magnesium) to 49,498 (such as UA) for each test.

eGFR was estimated using a recent equation developed by CKD-EPI [12] and was expressed in milliliter per minute per 1.73 m^2. The equation used was as follows: $eGFR = 142 \times \min(creatinine/kappa, 1)^{alpha} \times \max(creatinine/kappa, 1)^{-1.2} \times 0.9938^{Age} \times SexFactor$.

In the equation, age is expressed in years and creatinine level is expressed in mg/dL. The following values were used for females: SexFactor = 1.012; alpha = -0.241; kappa = 0.7. The values used for males were as follows: SexFactor = 1; alpha = -0.302; kappa = 0.9.

2.3. Current RIs

RIs currently in use at MEC were derived mainly from the operation procedures for clinical examination, and the adults' RIs for common clinical biochemistry tests in China [9, 13].

2.4. Control of analytical quality

Internal quality control was performed by daily assay of commercial quality control materials at 2 concentrations of the different parameters. External quality assessment schemes included several programs, conducted according to the different quantities. These programs were organized by the public health authorities such as Guangdong Center for Clinical Laboratories and National Center for Clinical Laboratory.

2.5. Selection of non-diseased individuals

Participants in the present study were free of symptoms of acute illness (such as fever, sore throat, body aches, and diarrhea) and malignancies at the time of physical examination. Subjects aged 18–94 years old, and had data on at least one kidney function index were initially included in the study. A schematic representation of the multistep selection procedure is presented in Figure 1. Imaging results of the thyroid, liver, heart, and urinary systems were confirmed by two attending physicians. Liver dysfunction was defined as alanine aminotransferase (ALT) exceeding 9–50 U/L for males, ALT level exceeding 7–40 U/L U/L for females, aspartate aminotransferase (AST) level exceeding 15–40 U/L for males, AST level exceeding 13–35 U/L for females, total bilirubin exceeding 5–21 umol/L, or direct bilirubin >3.4 umol/L, in addition to abnormal imaging findings. Hyperlipidemia was defined as total cholesterol >6.22 mmol/L, triglycerides>1.7 mmol/L, low density lipoprotein >4.14 mmol/L or undergoing treatment for hyperlipidemia.

The multivariate algorithm described below was used to select a set of individuals suitable for determination of the relevant RIs for each test. The indirect derivation of RIs from the laboratory information system was reported previously [14, 15]. The value of the index was used to calculate the new reference range only when all statistically significant related variables of the index were in the existing RIs. For example, albumin was significantly correlated to the other 7 indicators (Figure 2). Therefore, any single value of albumin was included in the set of the reference values for albumin only if creatinine, total protein, urea, UA, calcium, chloridion, and magnesium values determined using the same blood sample from the same patient were within the appropriate current RIs. Conversely, if 1 of the values of the 7 correlated parameters exceeded the RIs, then the albumin value was not included in the set of values selected for generating the new RI.

2.6. Statistical analyses

Continuous data were expressed as mean ± standard deviation for normally distributed variables and as median with interquartile range

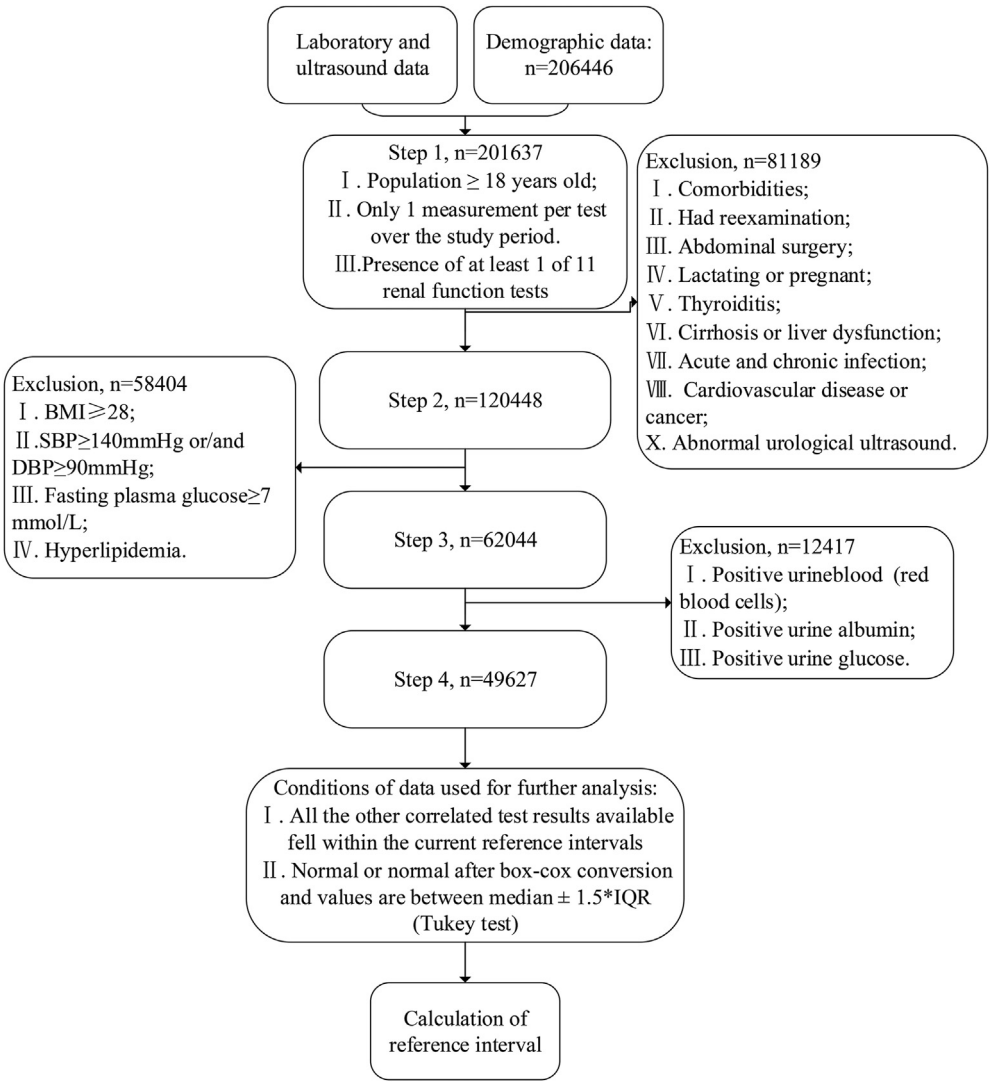

Figure 1. A flow chart showing the participant selection process.

(IQR, 25th and 75th percentiles) for non-normally distributed data. Categorical data were expressed as absolute numbers and percentages. Data normality was assessed using the Kolmogorov–Smirnov test. Correlation between the kidney function indexes was evaluated by Pearson's or Spearman's correlation analysis. Generalized linear model was used to test age trends and sex differences. Multiple linear regression analysis was conducted to explore the relationship between eGFR and other kidney function indexes. Standardized coefficients (βs) were determined. Multicollinearity among the variables was determined by evaluating the variance inflation factors (VIF). A VIF >10 indicated collinearity among the variables. The new RIs were defined as 2.5%–97.5% nonparametric percentiles of the distribution in the sample group and provided 90% RIs. They were computed using the nonparametric rank-based method in accordance with CLSI C28-A3 guidelines [16]. Confidence intervals (90%) for these percentiles across the age groups were determined using bootstrap method. Outliers were determined using Horn's method and Tukey's interquartile fences through Box-Cox transformation of the data. Outlier detection was conducted separately for the males and females and for each age group. A two-tailed P value <0.05 was considered statistically significant. Statistical analyses were performed using R version 4.1.2 (R Foundation for Statistical Computing) and SAS 9.4 (SAS Institute, Inc., Cary, USA).

3. Results

3.1. Characteristics

The stepwise application of different inclusion/exclusion criteria reduced the initial sample group of 206446 persons to a final sample size of 49627 (49627/206446, 24.4%) non-diseased individuals (shown in Figure 1). Male participants with age >50 were more likely to be excluded from the study. The study population was comprised subjects aged 18–49 years old (83.5%), with 26856 males and 22771 females (Table 1). The frequency distribution by age and sex is presented in Figure 3.

3.2. Distribution and proportion of out of range variables

Scatterplot distributions of included subjects grouped by age and sex are shown in Figure 4. Albumin (Figure 4A), urea (Figure 4E), potassium (Figure 4K), and sodium (Figure 4L) values that were within the RI were mainly distributed in the lower half of the interval. On the contrary, calcium (Figure 4G) and chlorine (Figure 4H) values that were within the RI were mainly distributed in the upper half of the interval. Age trends were observed for all indicators except for magnesium (Figure 4I). The

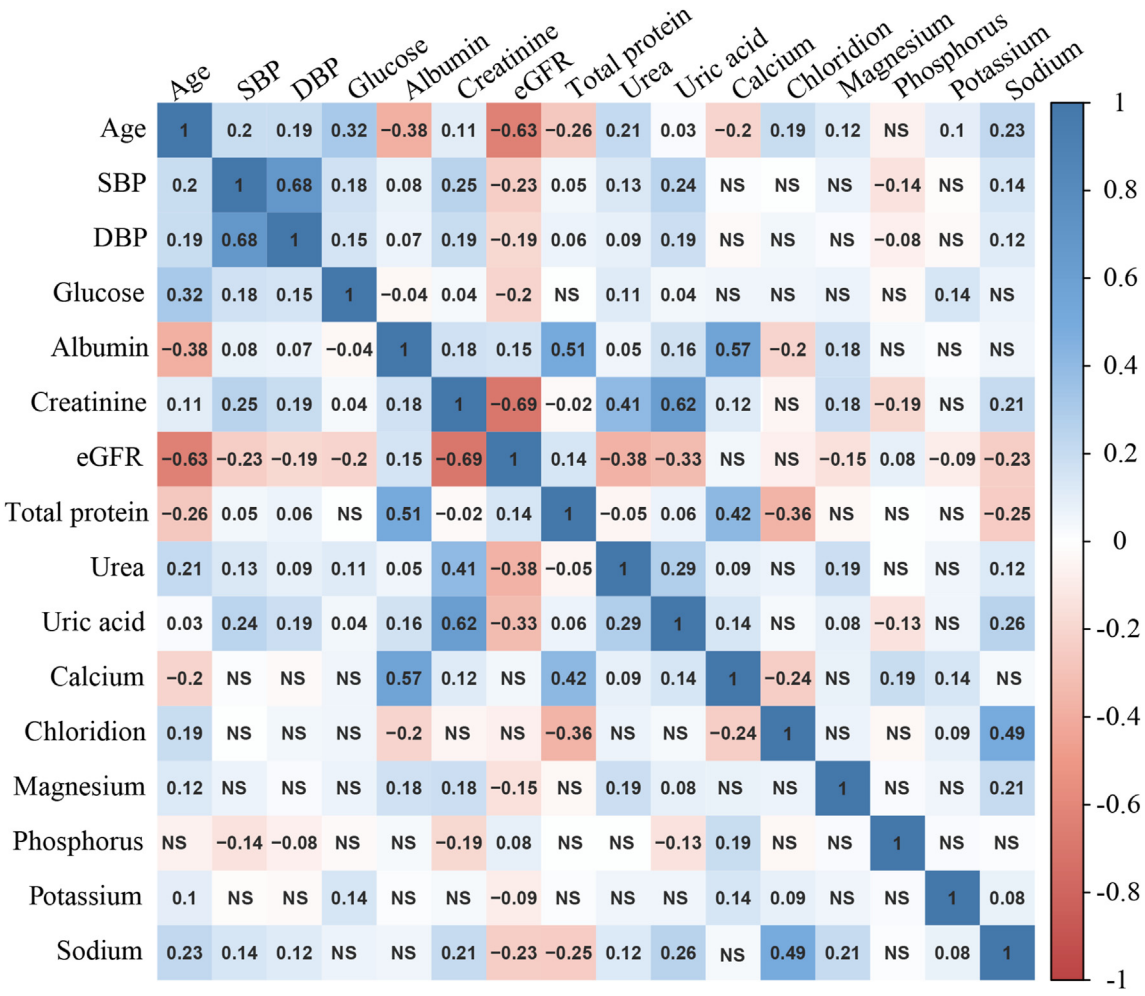

Figure 2. Spearman's correlation matrix of the kidney function indexes. Note: The label "NS" means that there was no statistically significant correlation between the two indicators; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate.

indicators showed significant differences between females and males except for total protein (Figure 4D), calcium (Figure 4G), chloridion (Figure 4H), magnesium (Figure 4I), potassium (Figure 4K), and sodium (Figure 4L). Male subjects exhibited higher levels of creatinine (Figure 4B), urea (Figure 4E) and UA (Figure 4F) relative to the levels in females. The proportion of out of range (OOR) variables in the study population were less than 5.0%. The OOR of eGFR (Figure 4C) was 0.30%, implying that most study subjects did not present with CKD. OORs of chloridion and sodium were 5.97%, and 7.31%, respectively. The OOR for UA was 32.38%, with 42.44% for males and 20.50% for females.

3.3. Reference values by sex and age

The number of useful results in each sample group was variable owing to the selection processes for non-disease individuals. These results are presented in Table 2. Age partitions were determined by visual inspection for the indicators that showed an age trend. Most indicators changed around the age of 50. RIs were computed according to the age and sex groups for the albumin, creatinine, eGFR total protein, urea, UA, calcium, phosphorus and sodium (interactions between age and sex, all P value $<$ 0.05). The findings showed no sex difference in the indicators and all were stable throughout the age, with only 1 broad partition required for magnesium.

The new RIs were narrower except for UA, and most of the new RIs did not exceed the current RIs except for albumin, urea, UA, chloridion and sodium. UL and LL of albumin were lower compared with the current limits, with 5.7 g/L lower in UL and 0.4 g/L lower LL compared with the current values [RIs: 39.6–49.3 vs 40–55]. ULs of chloridion were 0.7 mmol/L higher compared with the current UL values [RIs: 100.9–108.7 vs 96–108]. LLs of urea and sodium in males aged ≥60 were 0.23 mmol/L lower [RIs: 3.37–8.9 vs 3.6–9.5] and 1.2 mmol/L lower compared with the current LL values [RIs: 135.8–143.2 vs 137.0–147.0], respectively. ULs and LLs of UA were significantly higher relative to the current values for both males [RIs: 282.0–584.8 vs 208–428] and females [RIs: 20.5–442.5 vs 155–357] (Table 2). Comparison of the proportion exceeding the UL or LL between the study population and the excluded population is presented in supplemental Table A.1.

3.4. Factors related to eGFR decline

All VIF values of the clinical items were below 3, indicating that no collinearity existed in these clinical variables. Therefore, a linear model was used for analysis in this study. Calcium and the other five ion indicators had a relatively small sample size; thus they were not included in the multiple linear regression analysis. eGFR decreased by approximately 0.7 mL/min/1.73 m^2 every year for the healthy persons in adjusted model. In the multiple linear regression analysis (Table 3), the negative associations of UA levels and eGFR were statistically significant after adjusting for confounding factors in people with normal UA level (β = -0.03, $P < 0.001$), as well as in people with high UA level (β = -0.03, $P <$ 0.001).

Table 1. Demographics of study population.

Indicators, median (IQR) or as showed	Pre-exclusions			Post-exclusion		
	All	Men	Women	All	Men	Women
N	201637	112758	88879	49627	26856	22771
Age, median (IQR)	43.6(33.7–56.7)	44.3(34.1–57.2)	42.6(33.2–56.0)	36.0(29.6–45.2)	36.7(30.1–46.9)	35.3(29.1–43.1)
Age group, n(%)						
18–49	127244(63.1)	69602(61.7)	57642(64.9)	41423(83.5)	21556(80.3)	19867(87.2)
50–69	56923(28.2)	32206(28.6)	24717(27.8)	7193(14.5)	4557(17.0)	2636(11.6)
≥70	17470(8.7)	10950(9.7)	6520(7.3)	1011(2.0)	743(2.8)	268(1.2)
SBP, mmHg	122(111–136)	126(115–138)	117(106–131)	115(107–124)	119(111–127)	111(103–119)
DBP, mmHg	74(67–82)	77(70–85)	71(64–79)	70(64–76)	72(66–78)	68(62–74)
Glucose, mmol/L	4.8(4.4–5.2)	4.8(4.4–5.3)	4.7(4.4–5.1)	4.6(4.3–4.9)	4.6(4.3–4.9)	4.6(4.3–4.9)
Albumin, g/L	44.3(42.6–46.1)	44.8(43.1–46.6)	43.6(42–45.3)	44.4(42.7–46.1)	44.9(43.3–46.6)	43.8(42.2–45.5)
Creatinine, μmol/L	70.7(57.5–83.1)	81(73.3–89.4)	57.2(51.2–63.9)	69.8(57.0–82)	80.8(73.9–88.4)	56.3(51.0–62.2)
eGFR, ml/(min*1.73m2)	106.3(94.1–117.2)	102.6(90.7–113.6)	111.1(99.1–120.4)	112.2(101.2–120.3)	107.1(96.4–116.4)	117.1(108.4–123.2)
Protein, total, g/L	75.4(72.6–78.4)	75.4(72.5–78.3)	75.5(72.7–78.5)	75.1(72.3–78.0)	75.0(72.1–77.7)	75.4(72.6–78.3)
Urea, mmol/L	4.9(4.2–5.8)	5.1(4.4–6)	4.6(3.8–5.4)	4.7(4–5.5)	5.0(4.4–5.8)	4.3(3.7–5.0)
Uric acid, μmol/L	377.7(310.8–450.9)	427.0(371.0–489.0)	315(271.0–368.0)	359.6(297.7–428)	412.4(362.0–467.3)	300.6(262.0–345.0)
Calcium, total, mmol/L	2.38(2.32–2.43)	2.38(2.33–2.44)	2.36(2.31–2.42)	2.4(2.3–2.4)	2.4(2.3–2.4)	2.4(2.3–2.4)
Chloridion, mmol/L	104.4(103–105.8)	104.2(102.8–105.6)	104.8(103.5–106.2)	104.5(103.2–105.9)	104.5(103.0–105.8)	104.6(103.5–105.9)
Magnesium, mmol/L	0.91(0.86–.095)	0.91(0.87–0.95)	0.90(0.85–0.94)	0.9(0.9–1.0)	0.9(0.9–1.0)	0.9(0.9–0.9)
Phosphorus, mmol/L	1.13(1.03–1.23)	1.09(0.99–1.19)	1.20(1.11–1.30)	1.1(1.0–1.2)	1.1(1.0–1.2)	1.2(1.1–1.3)
Potassium, mmol/L	4.10(3.91–4.32)	4.11(3.93–4.34)	4.07(3.88–4.30)	4.1(3.9–4.3)	4.1(3.9–4.3)	4.1(3.9–4.3)
Sodium, mmol/L	140.0(138.6–141.3)	140(138.7–141.3)	139.8(138.4–141.2)	139.8(138.4–141.0)	140.2(138.9–141.2)	139.1(137.7–140.6)

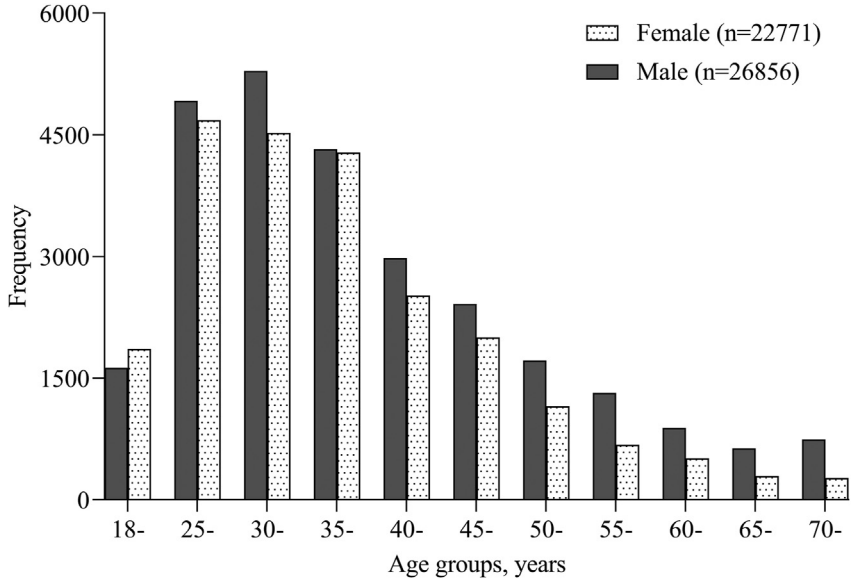

Figure 3. Distribution by age classes and sex of the final population in the study.

4. Discussion

In the present study, age- and sex-specific RIs of kidney function indexes were determined for a healthy population in China. LLs of eGFR for all age groups were above 60 mL/min/1.73 m^2. Albumin values that were within the RI were predominantly found in the lower half of the interval, with 5.7 g/L less UL and 0.4 g/L less LL compared with the current RIs. The findings showed that eGFR of included subjects decreased by approximately 0.7 mL/min/1.73 m^2 every year.

The new UL in the current study for albumin was lower than the current UL. Notably, the difference was more significant among women and older people. Although albumin was significantly positively correlated with eGFR in the present study, it had not significant effect in the adjusted model. This implies that albumin does not independently affect eGFR for a health population. Lang et al. reported that albumin levels ranges of 38.1–40.0 and 40.0–42.0 g/L were not significantly associated with increased odds of rapid kidney function decline and increased risk of incident CKD relative to levels >42.1 g/L [17]. This indicated that a moderate reduction in albumin level does not increase the risk of CKD. However, irrational application of albumin is widespread in clinical practice, especially in the elderly, due to lack of understanding of the physiological function, pharmacological action and medication indication of human serum albumin [18]. Therefore, it is necessary to update the RIs of albumin to reduce inappropriate application of the albumin to healthy elderly subjects. Serum total protein levels decrease gradually with age owing to the decrease in volume and number of liver cells with

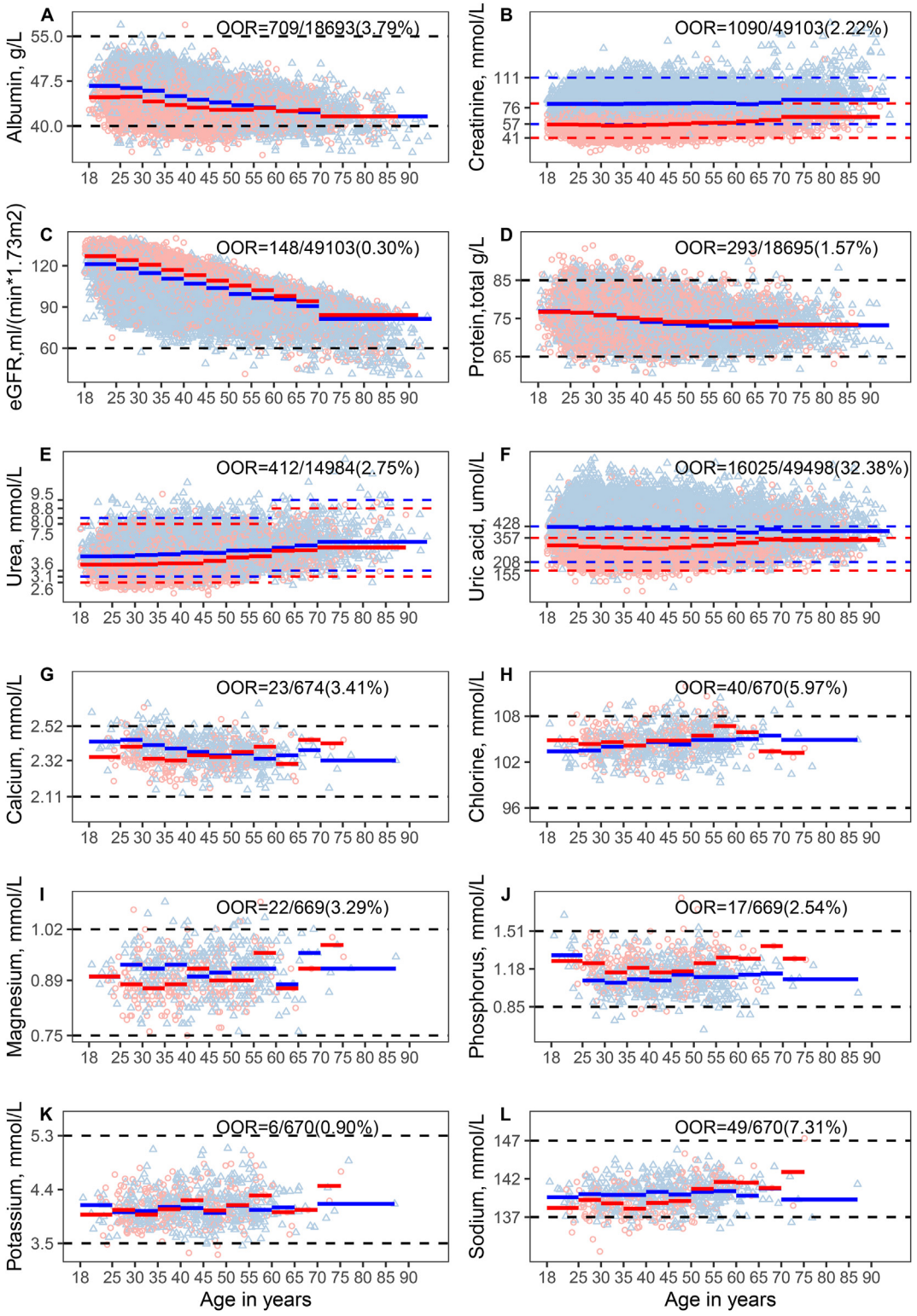

Figure 4. Scatterplot distributions for the kidney function indexes of the study population over 18- to 94-year age range. Note: age groups were defined from 18-24 years old, with 5-year age-bands up to a final category of ≥70 years; △ Male, ○ Female; – Blue short line, median value for males; – Red short line, median value for females; – – Dashed line, lower and upper reference limits: black indicates all, blue indicates male and red indicates female; OOR, out of the range (the percent of individuals outside the current RIs).

age; as a result, serum total protein components decrease slightly. The new UL of total protein for elderly individuals aged ≥60 years in eastern China was similar to the value obtained in a CHR Tian's study (RI: 67.7–83.2 vs 54.1–82.3 g/L) [19].

The finding of the current study showed that the ULs of UA for both males and females were relatively high. Xia et al conducted a nationwide multicenter RIs study and the findings indicated that the UL of UA was higher relative to the clinical decision limits for Guangzhou, even they

Table 2. Age- and sex-specific new reference intervals for the renal function indexes.

Indicators	Current reference intervals			Reference intervals of our study					
	Sex group	Age range, years	Reference intervals	Sex group	Age range, years	n	Median	Lower (90% CI)	Upper (90% CI)
Albumin[#†‡], g/L	All	All	40.0–55.0	All	18–94	11905	44.3	39.6(39.5–39.7)	49.3(49.1–49.4)
				Male	18–49	4362	45.4	41.1(41.0–41.3)	49.9(49.8–50.1)
				Male	50–94	1098	43.0	39.0(38.9–39.4)	47.2(46.9–47.5)
				Female	18–49	5723	43.9	39.5(39.4–39.6)	48.6(48.4–48.7)
				Female	50–94	706	42.7	39.2(39.0–39.5)	47.2(47.0–47.5)
Creatinine[#†‡], μmol/L	Male	All	57–111	Male	18–94	14880	79.0	61.5(61.2–61.8)	100.6(100.3–101.0)
	Female	All	41–81	Female	18–94	17271	55.6	42.0(41.8–42.2)	73.3(72.9–73.6)
				Male	18–69	14492	79.0	61.4(61.1–61.6)	100.2(99.8–100.5)
				Male	70–94	405	81.2	60.1(59.0–62.0)	116.7(110.6–121.8)
				Female	18–69	17141	55.6	42.0(41.8–42.3)	73.1(72.8–73.4)
				Female	70–94	139	61.3	42.6(40.4–43.5)	88.7(79.9–94.8)
eGFR[#†‡],ml/(min*1.73m^2)	All	≥18	60	All	18–94	31787	114.1	82.3(81.9–82.7)	129.9(129.7–130.0)
				Male	18–49	11815	112.4	85.3(84.9–85.6)	127.5(127.3–127.8)
				Male	50–59	1742	100.4	75.8(75.4–76.6)	109.9(109.4–110.5)
				Male	60–69	884	94.8	72.0(70.4–74.1)	103.5(102.9–104.1)
				Male	70–94	387	86.3	63.3(62.7–65.2)	98.1(97.3–99.1)
				Female	18–49	15083	118.9	94.3(93.6–94.8)	131.2(130.9–131.4)
				Female	50–59	1236	104.7	80.4(78.1–81.1)	112.4(112.0–112.9)
				Female	60–69	474	97.6	74.3(72.5–76.0)	105.0(104.6–105.5)
				Female	70–94	130	89.2	65.3(63.6–68.7)	98.8(95.9–100.1)
Protein, total[#†‡], g/L	All	All	65.0–85.0	All	18–94	11574	75.1	67.7(67.6–67.8)	83.2(83.0–83.3)
				Male	18–49	4383	75.1	67.7(67.5–67.9)	82.9(82.5–83.2)
				Male	50–94	1020	73.0	66.9(66.5–67.2)	81.3(81.0–82.1)
				Female	18–49	5513	75.5	68.2(68.0–68.4)	83.6(83.4–83.8)
				Female	50–94	651	74.1	67.5(67.0–67.9)	82.9(82.1–83.7)
Urea[#†‡], mmol/L	Male	15–59	3.1–8.0	Male	18–59	4187	4.94	3.27(3.22–3.31)	7.40(7.26–7.50)
	Male	60–120	3.6–9.5	Male	60–94	294	5.53	3.37(3.06–3.54)	8.90(8.86–9.27)
	Female	15–59	2.6–7.5	Female	18–59	4523	4.20	2.73(2.69–2.76)	6.57(6.50–6.64)
	Female	60–120	3.1–8.8	Female	60–94	161	5.23	3.26(2.99–3.31)	8.68(8.36–9.43)
Uric acid[#†‡], μmol/L	Male	All	208–428	Male	18–94	25372	412.3	282.0(280.6–283.5)	584.8(581.7–588.2)
	Female	All	155–357	Female	18–94	21079	301.0	200.5(199.4–201.8)	442.5(440.0–445.0)
				Male	18–49	20587	414.7	284.3(282.6–285.9)	587.4(584.0–591.4)
				Male	50–94	4789	403.0	273.7(269.6–277.5)	578.0(573.0–582.9)
				Female	18–49	18461	298.5	199.8(198.6–201.0)	437.9(436.0–440.4)
				Female	50–94	2618	319.2	206.7(201.4–210.5)	471.2(462.6–477.2)
Calcium, total[#‡], mmol/L	All	≥13	2.11–2.52	All	18–94	358	2.37	2.21(2.20–2.21)	2.51(2.49–2.53)
				Male	18–49	124	2.39	2.21(2.19–2.21)	2.53(2.48–2.55)
				Male	50–94	70	2.36	2.21(2.18–2.23)	2.49(2.47–2.52)
				Female	18–49	140	2.35	2.21(2.19–2.22)	2.50(2.47–2.53)
				Female	50–94	25	2.38	2.23(2.18–2.27)	2.55(2.50–2.59)
Chloridion[#‡], mmol/L	All	All	96–108	All	18–94	556	104.6	101.2(101.1–101.5)	108.7(108.3–108.9)
				All	18–49	391	104.4	101.1(100.8–101.5)	108.9(108.6–109.5)
				All	50–94	166	105.0	101.3(100.6–101.7)	109.0(107.7–109.6)
Magnesium, mmol/L	All	All	0.75–1.02	All	18–94	358	0.91	0.80(0.79–0.81)	1.02(1.00–1.04)
Phosphorus[#†‡], mmol/L	All	>12	0.85–1.51	All	18–94	417	1.14	0.85(0.81–0.88)	1.43(1.40–1.45)
				Male	18–49	132	1.10	0.79(0.72–0.84)	1.42(1.40–1.45)
				Male	50–94	88	1.09	0.84(0.80–0.91)	1.31(1.28–1.34)
				Female	18–49	165	1.17	0.90(0.87–1.00)	1.43(1.40–1.48)
				Female	50–94	30	1.28	0.91(0.80–1.00)	1.60(1.50–1.68)
Potassium[#], mmol/L	All	All	3.50–5.30	All	18–94	556	4.08	3.65(3.61–3.67)	4.70(4.63–4.74)
				All	18–49	384	4.07	3.64(3.60–3.67)	4.67(4.64–4.72)
				All	50–94	171	4.12	3.71(3.65–3.77)	4.81(4.79–4.98)
Sodium[#‡], mmol/L	All	All	137.0–147.0	All	18–94	377	139.4	135.9(135.5–136.2)	143.2(143.1–143.7)
				Male	18–49	121	139.6	136.6(135.9–137.2)	143.2(143.1–143.8)
				Male	50–94	81	140.2	136.3(135.7–136.4)	142.5(141.7–142.7)
				Female	18–49	148	138.6	135.5(135.2–136.1)	141.8(141.2–142.0)
				Female	50–94	21	141.0	138.4(138.3–138.4)	143.7(143.7–144.1)

Note: [#]The age trend was statistically significant ($P < 0.05$); [†]Sex difference was statistically significant ($P < 0.05$). [‡]Interaction between age and sex was statistically significant ($P < 0.05$).

Table 3. Multiple linear regression analysis for the association between eGFR and clinical variables in the apparently health population.

Parameter	Uric acid in the RIs, n = 7972*				Uric acid above the RIs, n = 3974*			
	β	SE	Standardized β	P value	β	SE	Standardized β	P value
Intercept	155.15	2.79	0.00	<0.001	149.29	4.73	0.00	<0.001
Sex, ref = male	2.71	0.30	0.10	<0.001	3.58	0.49	0.11	<0.001
Age, years	-0.72	0.01	-0.62	<0.001	-0.71	0.02	-0.58	<0.001
SBP, mmHg	0.01	0.01	0.01	0.258	0.02	0.02	0.01	0.357
DBP, mmHg	0.03	0.02	0.02	0.046	0.00	0.03	0.00	0.870
Glucose, mmol/L	0.39	0.22	0.01	0.081	1.58	0.35	0.06	<0.001
Albumin, g/L	0.01	0.05	0.00	0.786	-0.03	0.09	-0.01	0.730
Protein, total, g/L	-0.12	0.03	-0.04	<0.001	-0.03	0.05	-0.01	0.513
Urea, mmol/L	-1.73	0.09	-0.15	<0.001	-2.49	0.16	-0.19	<0.001
Uric acid, μmol/L	-0.03	0.00	-0.13	<0.001	-0.03	0.00	-0.14	<0.001

Note: *Number of samples with complete data.

have applied rigorous multiple selection to reduce the influence of unhealthy people [20, 21]. Notably, each SD increase of the UA concentration was associated with a 0.13 mL/min/1.73 m^2 decline in the adjusted model, even for people with normal UA levels. Previous findings indicate a direct causal relationship between serum urate levels and development of CKD [22]. Kuwabara et al. reported that asymptomatic hyperuricemia was significantly associated with new onset of cardiometabolic diseases in population without comorbidities, especially in the elderly [23]. Gengxu Li et al. observed that UA level promoted progression and deterioration of renal disease in T2DM patients [24]. Therefore, it is important to carefully reformulate the RIs for subjects from China with high average UA level.

Age-specific eGFR thresholds are recommended to prevent overdiagnosis of CKD in older adults and under-diagnosis of CKD in young adults [6, 25, 26]. The present results showed a physiological increase in creatinine levels in the elderly aged ≥70 years. This is attributed to the physiological aging of the kidney. Similarly, a study reported higher creatinine levels in the elderly population without cardiovascular disease [8]. Creatinine obtained in the present study were lower compared with those reported by Chan et al. in Hong Kong [27], and Yang et al. in northern China [27, 28], but were higher relative to Ris obtained from a study conducted in eastern China [29]. In addition, Lili Yue et al. reported that the LL of eGFR was <60 mL/min/1.73 m^2 and 45 mL/min/1.73 m^2 at the age of ≥40 and ≥65 years, respectively, which are significantly lower compared with the LL of eGFR obtained in our study [10]. These results further indicate the importance of establishing RIs for serum creatinine and eGFR for the China population.

Urea is a marker of kidney function that indicates protein degradation. The results showed that urea level increased with age, with the highest concentrations occurring in the elderly aged ≥80 years. This finding is similar to previous finding [3, 30] and is attributed to decrease in fractional urea excretion with age. Female and male subjects were assigned to two distinct group based on age. This finding differs from results reported by Guo et al. who described a combined RI for male and female [29]. Male subjects had higher RIs compared with females and this sex differences were observed in all the age partitions, which can partially explained by persistent higher whole-body protein turnover in females [31].

Scatter plots of calcium, chlorine, magnesium, phosphorus, potassium, and sodium showed narrow intervals and little change with age. These insignificant changes showed that electrolytes were highly regulated to remain stable throughout adulthood. Calculation of RIs revealed that several age and sex partitions were required to reflect minor fluctuations in electrolyte concentrations. For instance, calcium, phosphorus, and sodium each required 4 partitions, whereas potassium required 2. These findings are consistent with the range of reference values that are typical for healthy individuals [20, 28]. A previous large study comprising >7000 adults aged 20–79 years reported a similar electrolyte profile, in which at least 6 age partitions were established for electrolytes [32]. This finding further indicates the requirement of a large sample population to fully capture such minor fluctuations. The slight increases in electrolyte concentrations observed with advancing age can be attributed to different stages of kidney function and regulation during aging. This is particularly evident for sodium levels in women. On the contrary, magnesium required only 1 interval spanning the entire age range, indicating that it is highly regulated during development, maturation, and aging.

This study mainly focused on age-specific and sex-specific RIs of kidney function indexes with the largest sample in South China. The present study had some limitations. First, the kidney function indexes did not include cystatin C, thus they may not reflect the true GFR. Second, subjects unaware of an underlying disease may incorrectly be classified as healthy. A careful selection was conducted to ascertain the health status of participants, and further exclusions were conducted based on related variables. Although all tests were recommended by the attending physician, the researcher had the right to increase or decrease the number of tests. In the current study, it was not possible to ensure that all indicators were normal owing to lack of related dat. Third, the small sample size of some subgroups may not provide sufficient power to detect differences in sex or age. Fourth, the results in this study may not be representative for other types of methods as the choice of method may affect the test results.

In summary, the finding of the present study indicate the normal range of kidney function indicators for China population. GFR declined approximately 0.72 mL/min/1.73 m^2 every year in the subjects included in the present study with normal UA levels. The LLs of eGFR were >60 mL/min/1.73 m^2 at all age groups. Notably, the results showed that the new UL of albumin was 5.7 g/L less than the current UL, and the difference was more significant among females and elderly people. The findings indicate that it is importance to establish age and sex dependent threshold values of kidney function indexes for residents of China. Further prospective studies should be conducted to determine the RIs of UA in the population of China.

Declarations

Author contribution statement

Huixian Li; Haiqing Zheng; Qianyun Deng: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Jinghua Li, Zixia Wang, and Hui Li: Performed the experiments; Contributed reagents, materials, analysis tools or data.

Huiying Liang, Zhiming Ye, Bing Gu: Conceived and designed the experiments; Analyzed and interpreted the data.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

Supplementary content related to this article has been published online at https://doi.org/10.1016/j.heliyon.2022.e11919.

Acknowledgements

We appreciated Dr. Meng Yue for her opinions for the article. In particular, we thank our colleagues from the MEC for their statistical support.

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