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Published in:
Journal of Nephrology

DOI:
10.1007/s40620-022-01546-z

Publication date:
2023

Journal of Nephrology (2023) 36:1341–1347
https://doi.org/10.1007/s40620-022-01546-z

ORIGINAL ARTICLE

Prevalence of chronic kidney disease in women of reproductive age and observed birth rates

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Received: 1 October 2022 / Accepted: 1 December 2022 / Published online: 18 January 2023

Abstract

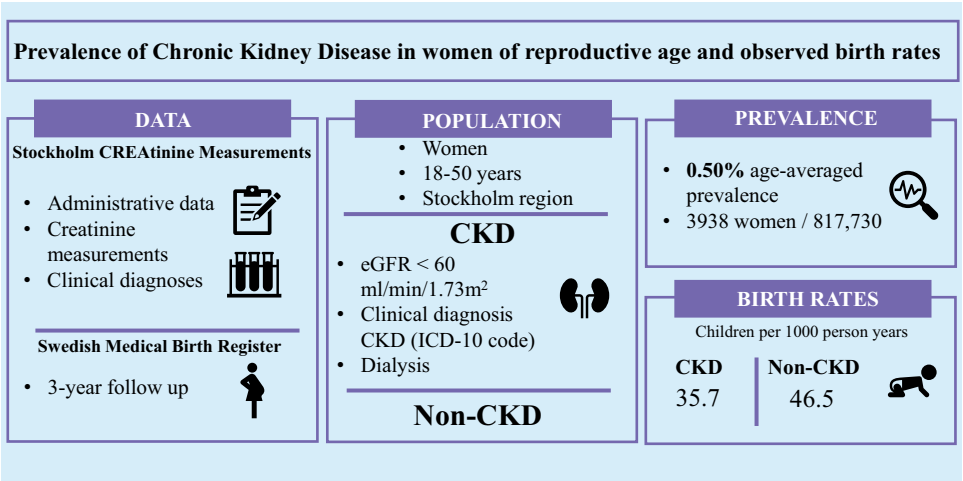
Introduction Women of reproductive age with chronic kidney disease (CKD) are recognised to have decreased fertility and a higher risk of adverse pregnancy outcomes. How often CKD afflicts women of reproductive age is not well known. This study aimed to evaluate the burden of CKD and associated birth rates in an entire region.

Methods This was a retrospective cohort study including women of childbearing age in Stockholm during 2006–2015. We estimated the prevalence of "probable CKD" by the presence of an ICD-10 diagnosis of CKD, a single estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 or history of maintenance dialysis. By linkage with the Swedish Medical Birth Register we identified births during the subsequent three years from study inclusion and evaluated birth rates.

Results We identified 817,730 women in our region, of whom 55% had at least one creatinine measurement. A total of 3938 women were identified as having probable CKD, providing an age-averaged CKD prevalence of 0.50%. Women with probable CKD showed a lower birth rate 3 years after the index date (35.7 children per 1000 person years) than the remaining women free from CKD (46.5 children per 1000 person years).

Conclusion As many as 0.50% of individuals in this cohort had probable CKD, defined on the basis of at least one eGFR<60 ml/min1.73 m^2 test result, dialysis treatment (i.e. CKD stages 3–5) or an ICD-10 diagnosis of CKD. This prevalence is lower than previous estimates. Women with probable CKD, according to a study mainly capturing CKD 3–5, had a lower birth rate than those without CKD, illustrating the challenges of this population to successfully conceive.

Graphical Abstract



Keywords Chronic kidney disease · Women of reproductive age · Pregnancy · Birth rate · Prevalence

Extended author information available on the last page of the article

Introduction

Women of reproductive age with chronic kidney disease (CKD) require additional considerations related to good clinical practice management [1]. For example, becoming pregnant might be complicated by decreased fertility due to hormonal changes associated with impaired renal function [2, 3]. Many women experience some sexual dysfunction, such as reduced libido, difficulty with arousal, dyspareunia and anorgasmia [2]. If women with CKD successfully conceive, the pregnancy carries risks for both mother and child, including higher risk of hypertensive disorders of pregnancy, fetal growth restriction, preterm delivery and longer hospital stays [4, 5]. Furthermore, it is estimated that in women with CKD stages 3–5, pregnancy advances the need for kidney replacement therapy by 2.5–4.7 years [6] and even in the earlier stages a decline in kidney function may be seen after delivery [7, 8].

Although the growing prevalence of CKD is attracting more attention, data regarding the impact of CKD in women of reproductive age are limited. In 2020 the Global Burden of Disease Chronic Kidney Disease Collaboration reported on global, regional, and national overviews of the burden of disease of CKD and emphasised the importance of data on CKD for health system planning [9]. In 2018, World Kidney Day focussed on women's kidney health and reported that CKD affects approximately 195 million women [10, 11].

Prevalence of CKD is reported to affect 0.2–6.0% of women of reproductive age but data are derived from expert opinion and one systematic review [12–17], and accurate assessment of the true population prevalence is lacking. Furthermore, there are limited data describing population birth rates in women with CKD. Therefore, this study aims to provide insight into the prevalence of CKD in women of reproductive age by taking into consideration clinical diagnoses and estimated glomerular filtration rate (eGFR) test results. Secondly, we evaluated birth rates of women identified as having probable CKD.

Methods

Data sources

We used data from the Stockholm CREAtinine Measurements (SCREAM) cohort, which includes all individuals in the region of Stockholm, Sweden, who accessed healthcare between 1 January, 2006 and 31 December, 2019 [18]. Through linkage with administrative databases, we were able to ascertain information on demographics and medical history, using de-identified personal identification numbers. Additionally, linkage with the Swedish Renal Registry allowed ascertainment of kidney replacement therapy. Moreover, SCREAM was linked with the Swedish Medical Birth Register (SMBR). The SMBR contains data on mother and infants from 1973 onwards, with information on maternal identification, social factors, maternal history, pregnancy, delivery and the infant [19]. According to SMBR data, the most frequent time for an initial visit to an antenatal clinic was after 10 full weeks of pregnancy, and 90% of women made a first visit in the first 12 weeks of pregnancy. All data were de-identified prior to this study and it was approved by the regional ethical review boards and the Swedish National Board of Welfare.

Study design

Reproductive age was defined to be between 18–50 years, as we lacked information on menarche and menopause. We included women aged between 18–50 years during the period of 01-01-2006 to 31-12-2015, registered in the population census of Stockholm region. No more women were added following 2015 to allow a minimum follow-up of 3 years for the evaluation of pregnancy rates. Women who were tested for creatinine at age 18–50 were included at their creatinine test date (index date). If a woman was tested more than once, we randomly chose one of the available tests in R. Women without a creatinine test were matched on their month and year of birth to women who did have a test. Subsequently, they were assigned the same index date as their match. Supplementary Figure S1 graphically explains the construction of the cohort.

Study outcomes

The primary study outcome was the prevalence of probable CKD, defined as a composite of a relevant International Classification of Diseases, Tenth Revision (ICD-10) diagnosis of CKD (at any time prior to the index date), a history of maintenance dialysis by linkage with the Swedish Renal registry or an index eGFR below 60 mL/min/1.73 m^2 [20]. Because of low albuminuria testing rates in healthcare, we were unable to use this biomarker to evaluate CKD stages 1 and 2 [20]. We chose this composite definition in acknowledgement that CKD awareness in healthcare is low and most persons with CKD do not carry a clinical diagnosis. According to KDIGO guidelines, a CKD diagnosis might be issued when abnormalities of kidney structure or function are present for more than 3 months [20]. However, routinely collected health care data do not capture a random sample of the population, but rather of a subgroup of patients who interact with the health care system. Thus, a single creatinine measurement in our study may misclassify cases. However, and in agreement with a

recent consensus report [21], we believe that identifying young women with repeated eGFR tests within a short period of time is likely to pre-select a sicker, non-representative population. For these reasons our outcome cannot be taken as a differential diagnosis and we refer to it as "probable CKD".

The secondary outcome was the birth rate of women with and without CKD, defined as the total number of births per 1000 women per year as determined from the Swedish Medical Birth Register [19]. We also evaluated birth rates stratified by women with a CKD diagnosis and/or an eGFR ≥ 45 mL/min/1.73 m^2 and women with eGFR < 45 mL/min/1.73 m^2. We assumed that women with a CKD diagnosis but no eGFR tests would be in earlier stages of their disease, and we assigned women who received a kidney transplant to their evaluated eGFR. Participants were not censored, since inclusion implies that the subjects are alive and aged between 18–50 years at the index date. If participants died during the three-year follow-up, it implies that no birth is registered in the time after death.

Covariates

Covariates in this study included age, highest attained education, eGFR and medical history. eGFR was calculated using the 2009 Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI) formula [22] from plasma creatinine. Plasma creatinine measurements were performed by enzymatic or corrected Jaffe methods traceable to isotope dilution mass spectroscopy standards. Medical history was defined using the presence of ICD-10 codes and Anatomical Therapeutical Chemical classifications for drugs. Definitions are detailed in Supplementary Table S1.

Statistical analysis

We summarized study population characteristics overall, by the presence of CKD and by severity of probable kidney disease using median [interquartile range] for continuous variables and absolute counts and percentages for categorical data. For CKD prevalence, we reported overall counts and the age-averaged prevalence to adjust for the uneven age distribution in the cohort. A linear regression model was fitted to identify the increase in prevalence and 95% confidence interval (CI) per additional year in age. Counts were reported for the births in the CKD and non-CKD population. Birth rate was calculated per 1000 person years. All analyses were performed using R version 4.2.1 [23].

Results

Demographic data of the study population were collected for 817,730 women in the cohort, of whom 55% had at least one creatinine measurement. (Table 1). As many as 3938 women (0.48%) met our criteria of CKD, with ascertainment and overlapping shown in Supplementary Figure S2. Women with CKD were older, had a lower proportion of attained university education and more comorbid conditions.

Prevalence of CKD

The crude prevalence of women that met our CKD criteria was 0.48% (age-adjusted prevalence of CKD was 0.50%). CKD prevalence ranged from 0.18% (in women aged 18) to 0.94% (in women aged 46). Figure 1 graphically depicts this, with an average increasing prevalence of 0.024% 95% CI [0.022–0.0226] per year older.

Women with CKD were also classified according to severity (Table 1). Of these women, 19.5% were classified with CKD stage 3b or worse (eGFR < 45 mL/min/1.73 m^2), and the remaining with CKD stage 3a or better (eGFR ≥ 45 mL/min/1.73 m^2). Women with more severe CKD were older and had more comorbidities, such as hypertension, diabetes mellitus and heart diseases.

Regarding birth rates, all study participants were followed up for exactly three years after index date to evaluate birth rates. During this time, a total of 101,655 women had 114,027 children from 112,511 pregnancies. Women with CKD (any sign of CKD) had a lower 3-year birth rate (35.7 children per 1000 person years) than the remaining women free from CKD (46.5 children per 1000 person years). Figure 2 further stratifies by estimated CKD severity and shows relatively comparable birth rates of women free from CKD and women with eGFR ≥ 45 ml/min/1.73 m^2. By contrast, birth rates of women with eGFR < 45 ml/min/1.73 m^2 were considerably lower. Figure 3 shows complementary findings throughout the spectrum of eGFR by age categories.

Discussion

To the best of our knowledge, this is the first study that attempts to comprehensively quantify the prevalence of CKD in women of reproductive age and their birth rates. We found an age-averaged prevalence of 0.50% in women of reproductive age (18–50 years), which is lower than most described estimates [12, 17]. Piccoli et al. (2010), suggested a 3% prevalence of CKD in women of childbearing age [12] following the redefinition of CKD by the KDOQI guidelines. This estimate was extrapolated from a previous estimate of 1% based on expert opinion. Our study evaluated the presence of probable CKD by three complementary sources: clinical diagnoses, low eGFR or current dialysis. While we believe these sources may have reliably captured women with detected CKD, we cannot exclude the presence of undetected CKD given that screening for CKD is low in society and the disease is free of symptoms until late stages,

Table 1 Characteristics of women of childbearing age in Stockholm region during 2006–2015, overall and by the presence of chronic kidney disease (CKD)

	Overall	Free from CKD[a]	With any sign of probable CKD[a]	With a CKD diagnosis and/or eGFR ≥ 45 ml/min/1.73 m^2	With eGFR < 45 ml/min/1.73 m^2 or on dialysis
Number of individuals	817,730	813,792	3938	3105	833
Median age [IQR]	32.0 [23.0, 43.0]	32.0 [23.0, 43.0]	41.0 [31.0, 47.0]	40.0 [30.0, 47.0]	43.0 [34.0, 48.0]
Age category (%)					
18–19 years	11.0	11.0	4.2	4.6	2.8
20–29 years	31.9	32.0	17.5	18.9	12.4
30–39 years	25.1	25.2	24.5	25.2	22.0
40–50 years	32.0	31.9	53.7	51.3	62.9
Highest attained education (%)					
Compulsory school	3.6	3.6	6.5	7.2	3.8
Secondary school	30.9	30.8	39.7	38.3	45.3
University	65.5	65.6	53.8	54.5	50.9
Medical history, *n* (%)					
Chronic kidney disease	2209 (0.3)	0 (0.0)	2209 (56.1)	1880 (60.5)	329 (39.5)
Maintenance dialysis	66 (< 0.1)	0 (0.0)	66 (1.7)	0 (0.0)	66 (7.9)
History of kidney transplantation	226 (< 0.1)	18 (< 0.1)	208 (5.3)	124 (4.0)	84 (10.1)
Hypertension	4350 (0.5)	3863 (0.5)	487 (12.4)	263 (8.5)	224 (26.9)
Diabetes mellitus	3887 (0.5)	3625 (0.4)	262 (6.7)	154 (5.0)	108 (13.0)
Myocardial infarction	421 (0.1)	389 (0.0)	32 (0.8)	19 (0.6)	13 (1.6)
Peripheral vascular disease	300 (< 0.1)	254 (< 0.1)	46 (1.2)	22 (0.7)	24 (2.9)
Cerebrovascular disease	1234 (0.2)	1190 (0.1)	44 (1.1)	25 (0.8)	19 (2.3)
Heart failure	502 (0.1)	419 (0.1)	83 (2.1)	41 (1.3)	42 (5.0)
Median eGFR [IQR]	109.2 [97.7, 119.7]	109.2 [97.9, 119.8]	58.5 [47.9, 103.1]	74.7 [56.3, 108.6]	29.4 [17.2, 38.9]
eGFR category, *n* (%)					
< 15 ml/min/1.73 m^2	119 (0.0)	0 (0.0)	119 (3.0)	0 (0.0)	119 (14.3)
15–29	240 (0.0)	0 (0.0)	240 (6.1)	0 (0.0)	240 (28.8)
30–44	408 (0.0)	0 (0.0)	408 (10.4)	0 (0.0)	408 (49.0)
45–59	1340 (0.2)	0 (0.0)	1340 (34.0)	1340 (43.2)	0 (0.0)
60–89	62,856 (7.7)	62,486 (7.7)	370 (9.4)	370 (11.9)	0 (0.0)
> 90	387,518 (47.4)	386,259 (47.5)	1259 (32.0)	1259 (40.5)	0 (0.0)
Not tested for creatinine	365,183 (44.7)	365,047 (44.9)	136 (3.5)	136 (4.4)	0 (0.0)

[a]CKD was defined by the presence of a CKD diagnosis, an eGFR < 60 ml/min/1.73 m^2 or current dialysis

nor can we exclude possible misclassification by identifying probable CKD with a single eGFR test. The overall prevalence of CKD, with age-specific subgroups has been investigated in a meta-analysis of global scale [16]. The authors reported a prevalence of CKD in women aged 20–49 years ranging from 2.7% to 8.2% in high-income countries, which is also higher than in our study. However, the meta-analysis included studies with different inclusion and exclusion criteria, some based on claims, other on eGFR using different eGFR equations, which taken together, prevent us from making a direct comparison.

We found lower birth rates for these women with probable CKD, particularly for those with eGFR < 45 ml/min/1.73 m^2. This expands previous studies [2, 12], but due to missing data on prevalence of CKD in women of reproductive age, only subcategories of CKD have been studied which are more clearly defined, i.e., women on dialysis or with a transplant history. National conception rates of 72.5–79.5 per 1000 women per year were reported by the National Registry Data from the United Kingdom and Italy [2, 24], compared to 0.7–1.4 per 1000 women per year in women receiving dialysis and 5.5–8.3 per 1000 women per year in women with kidney transplants. The higher birth rate identified in our cohort compared to others is likely to be explained by the inclusion of women with less severe CKD rather than solely focusing on kidney replacement therapy. Other explanations

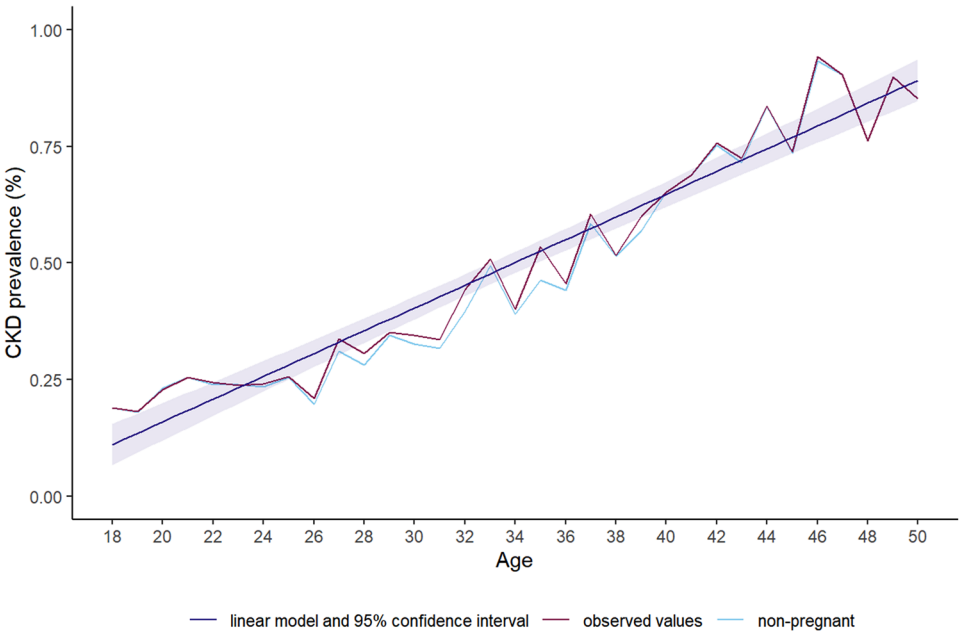


Fig. 1 Prevalence of probable CKD in women of reproductive age. An increasing prevalence of 0.024% per year is observed. The light purple area shows the 95% confidence interval. Light blue line shows sensitivity analysis excluding women who were pregnant at the index date

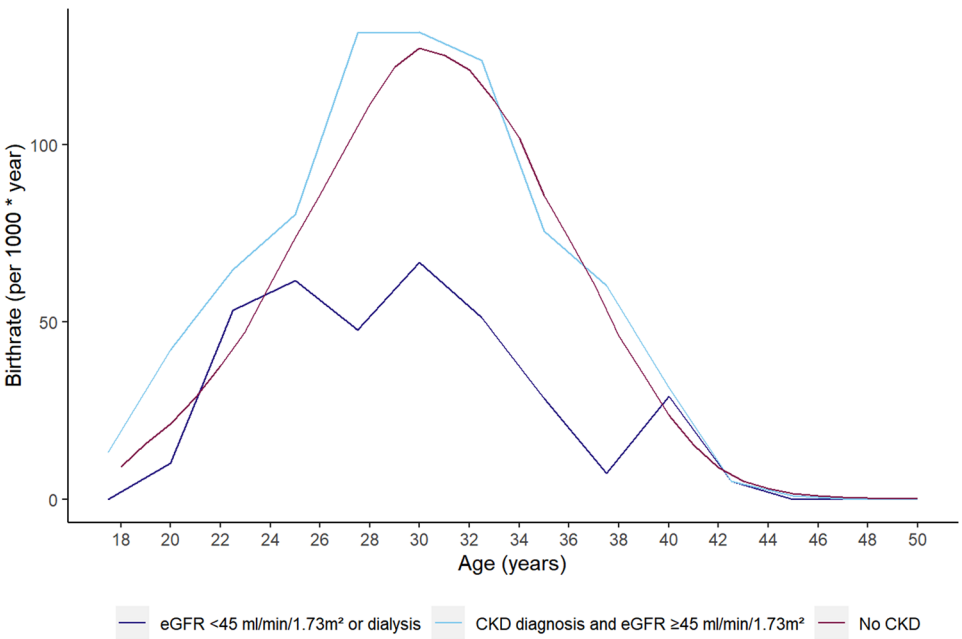


Fig. 2 Birth rate per 1000 person years in women with eGFR < 45 ml/min/1.73 m^2 compared to women with eGFR ≥ 45 ml/min/1.73 m^2 or without CKD, by age. A comparable birth rate is seen in women with an eGFR ≥ 45 ml/min/1.73 m^2 and in women free from CKD, whereas women with an eGFR < 45 ml/min/1.73 m^2 show considerably lower birth rates

may be the evaluation of different age ranges (age 18–50 rather than 20–45) and the study of *birth rates* rather than *pregnancy rates*. Our data contain minimal information on pregnancy termination before 10 weeks and therefore did not allow us to study pregnancy rates. A recent study reported a 98% live birth rate in women with CKD [6], which suggests that the birth rate should be slightly lower than the pregnancy rate. As seen in our results, Fig. 3 suggests that mostly kidney function lower than 45 ml/min/1.73 m^2 affects the birth rate and therefore explains the higher birth rates in our CKD population. Finally, we studied the birth rate of the region of Stockholm, compared to national pregnancy rates, which could partially explain the lower birth rate in both the CKD and overall population, because studies show lower birth rates in urban areas than in rural ones [25].

Our study has several strengths. First, we had access to complete administrative databases which allowed the creation of a large real-life cohort. We confirmed our findings with demographic data from the Swedish Government to validate our birth rate findings [26], and the calculated birth rates are shown in Supplementary Table S2. About 55% of the female residents of the Stockholm region

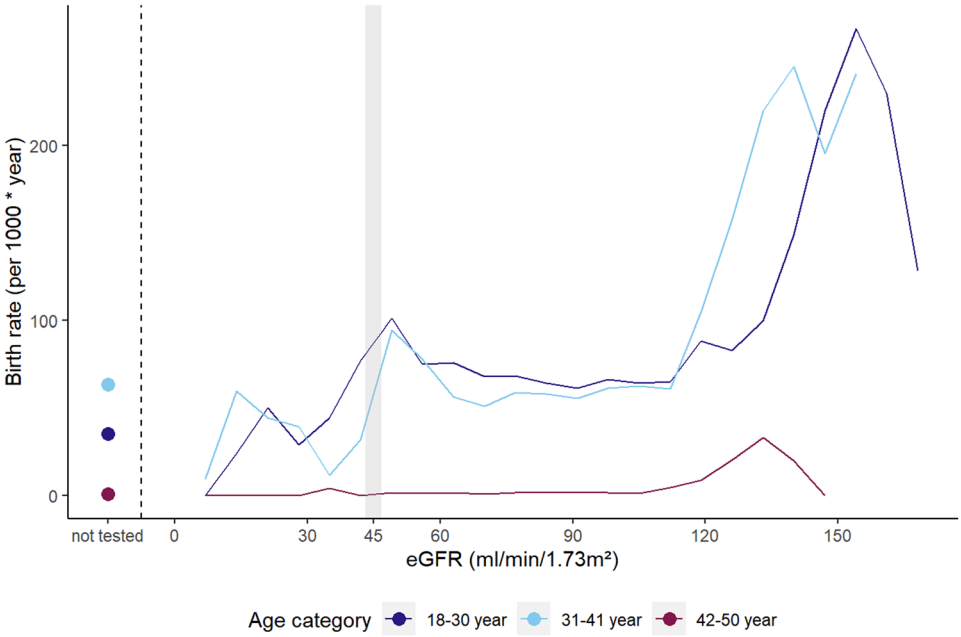


Fig. 3 Birth rates in women of different ages, by eGFR. All age categories show a higher birth rate when eGFR increases. Grey area represents suggested threshold of 45 ml/min/1.73 m^2. High birth rate with eGFR above 120 ml/min/m^2 may be attributed to renal physiology in women already pregnant at the index date

aged between 18 and 50 years had a recorded creatinine measurement, which is a large proportion of the population and reflects the commonness of creatinine testing in healthcare. However, creatinine testing was not done in all women, hence our broader definition was enriched with issued CKD diagnoses. Our study also has some limitations. Because testing is infrequent in young women, we could not evaluate a point prevalence, but rather a period prevalence. A second limitation is the reliance on a single eGFR test to determine kidney function, but we argued earlier on the selection bias inferred by retrospectively selecting women with frequent healthcare contacts requiring eGFR testing [21].

In conclusion, we observed a prevalence of 0.50% of "probable CKD", according to a definition mainly capturing CKD in stages 3–5, in women of reproductive age in the Stockholm population, which is lower than previous estimates. Women with CKD, in particular with eGFR < 45 ml/min/1.73 m^2, had a lower birth rate compared to women free from this condition, illustrating challenges with reduced fertility, however, this figure may also reflect individual choice not to conceive in the presence of advanced CKD.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40620-022-01546-z.

Acknowledgements Research reported in this publication was supported by the Swedish Research Council (#2019-01059), the Swedish Heart and Lung Foundation and the Westman Foundation. R.J.J. has been supported by grants from the Minerva Scholarship Fund and the Leiden University Fund (LUF) International Study Fund (LISF). W.A.L Vrijlandt has been supported by a grant from the J.K. De Cock-Hadders Stichting. The funders of this study had no role in the study design, data collection, analysis, interpretation, writing of the report, or the decision to submit the report for publication.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by WALV, PJWSV, RJJ and FM. The first draft of the manuscript was written by WALV and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding The authors have no relevant financial or non-financial interests to disclose.

Data availability Authors can confirm that all relevant data are included in the article and/or its supplementary information files.

Declarations

Conflict of interest The authors report no conflicts of interest.

Ethics approval All data were de-identified prior to this study and the study was approved by the regional ethical review boards and the Swedish National Board of Welfare. This study was performed in accordance with the declaration of Helsinki.

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