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Age- and gender-specific reference values of estimated GFR in Caucasians: The Nijmegen Biomedical Study

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The Nijmegen Biomedical Study is a population-based cross-sectional study conducted in the eastern part of the Netherlands. As part of the overall study, we provide reference values of estimated glomerular filtration rate (GFR) for this Caucasian population without expressed risk. Age-stratified, randomly selected inhabitants received a postal questionnaire on lifestyle and medical history. In a large subset of the responders, serum creatinine was measured. The GFR was then measured using the abbreviated Modification of Diet in Renal Disease (MDRD) formula. To limit possible bias, serum creatinine was calibrated against measurements performed in the original MDRD laboratory. The study cohort included 2823 male and 3274 female Caucasian persons aged 18–90 years. A reference population of apparently healthy subjects was selected by excluding persons with known hypertension, diabetes, cardiovascular- or renal diseases. This healthy study cohort included 1660 male subjects and 2072 female subjects, of which 869 of both genders were 65 years or older. The median GFR was 85 ml/min/1.73 m^2 in 30–to 34-year-old men and 83 ml/min/1.73 m^2 in similar aged women. In these healthy persons, GFR declined approximately 0.4 ml/min/year. Our study provides age- and gender-specific reference values of GFR in a population of Caucasian persons without identifiable risk.

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In recent years, chronic kidney disease (CKD) has received increasing attention.[1] Patients with CKD are at increased risk for cardiovascular morbidity and mortality.[2] Furthermore, patients with CKD may progress to end-stage renal disease.[3] As early treatment of patients with CKD may reduce cardiovascular risk and delay the onset of end-stage renal disease, it is important to identify patients with CKD in an early stage.[4] To increase the awareness of CKD and improve treatment of patients with CKD, the Kidney Disease Outcomes Quality Initiative (K/DOQI) from the US National Kidney Foundation has developed guidelines for the diagnosis and classification of CKD.[5] K/DOQI has proposed to classify CKD in five stages according to the absence or presence of albuminuria and the level of the glomerular filtration rate (GFR). The guidelines propose that patients with GFR <60 ml/min/1.73 m^2 are at risk and need to be evaluated and properly treated.

Classification of patients with CKD thus necessitates accurate assessment of GFR. For many years, serum creatinine has been used in routine clinical practice as a marker of GFR. It is well recognized that serum creatinine is not an accurate marker of GFR.[6] Serum creatinine is dependent on muscle mass and the relation with GFR is influenced by age, gender, and body weight. Therefore, formulas have been developed for the estimation of GFR. The K/DOQI guidelines advocate to use the recently developed 'Modification of Diet in Renal Disease (MDRD)'-formula for the calculation of GFR. This formula was derived from the MDRD study, which included patients with renal disease, in whom GFR was measured with an accurate, invasive technique using subcutaneous administration of Iothalamate.[7] This formula provides a good estimate of GFR, in particular, in the GFR range <60 ml/min/1.73 m^2.[8,9] It is important to realize that for correct reporting of MDRD-GFR attention must be given to calibration of the creatinine assay against the creatinine assay that was originally used in the original MDRD laboratory.[10] The importance hereof was recently stipulated by a working group.[11]

Many laboratories have adopted this formula and have started automated reporting of calculated MDRD-GFR.[12] It was recently shown that automated reporting of GFR indeed leads to earlier identification of patients with CKD.[13] However, reference values of estimated GFR are virtually lacking. Lack of reference values for estimated GFR hampers the interpretation of reported MDRD-GFR by medical laboratories. Therefore, we have estimated GFR using the MDRD formula for participants of the Nijmegen Biomedical Study. We have calibrated the creatinine assay against the MDRD laboratory. Our data provide reference values of estimated GFR for a Caucasian population.

RESULTS

Age- and gender-specific reference values of GFR

Values of estimated GFR per 5-year age groups are given for men and women in Tables 1a and 1b and 2a and 2b. In Table 1a and 1b, data are given for the disease-free population. Reference values for this 'healthy' population are depicted in Figures 1 and 2. The data in Table 2a and 2b are based on the results obtained in the population with reported comorbidities.

Stages of CKD

We have used the definitions of the K/DOQI. These definitions require information on proteinuria or hematuria to classify persons as CDK stage 1 or 2. Thus, our data only allow correct classification of persons in stage 3 and above. Figure 3 depicts the prevalence of CKD stage 3–5 (GFR <60 ml/min/1.73 m^2) in our population of disease-free subjects. As expected, the prevalence increases with age, reaching 42% in men and 44% in women of age 85 and higher.

DISCUSSION

Our data provide reference values for MDRD-GFR using data of an apparently healthy Caucasian population. We have used the abbreviated MDRD equation that is nowadays most regularly used. The MDRD formula provides the best estimate of GFR, particularly in the range of GFR <60 ml/min/1.73 m^2.[8,9] Awareness of CKD has increased in the past decade. Especially, the publication of guidelines by the K/DOQI from the National Kidney Foundation has fostered interest in CKD worldwide.[5]

Table 1a | Estimated GFR in non-diseased caucasian males of the Nijmegen Biomedical Study

Age (years)	*N*	Mean ± s.d.	Range	P5	P25	P50	P75	P95
18–24	94	100 ± 13	72–137	77	90	99	109	121
25–29	96	93 ± 13	67–125	74	82	90	102	117
30–34	118	86 ± 13	63–133	68	77	85	93	107
35–39	125	85 ± 14	61–118	65	74	85	95	110
40–44	143	84 ± 13	54–124	66	76	83	92	106
45–49	160	83 ± 13	50–123	63	73	82	91	105
50–54	143	79 ± 12	46–120	60	71	78	87	97
55–59	158	76 ± 13	27–118	58	68	75	84	98
60–64	149	75 ± 15	48–199	59	67	73	83	95
65–69	154	75 ± 14	51–165	56	66	74	82	97
70–74	102	71 ± 12	38–102	54	64	70	79	92
75–79	112	70 ± 13	41–110	45	62	70	79	91
80–84	73	67 ± 15	41–129	43	58	69	77	87
>85	33	62 ± 16	34–101	35	47	65	72	92

GFR, glomerular filtration rate.
Values are given as means (s.d.), ranges and 5th, 25th, 50th, 75th, and 95th percentile.

Table 1b | Estimated GFR in non-diseased females of the Nijmegen Biomedical Study

Age (years)	*N*	Mean ± s.d.	Range	P5	P25	P50	P75	P95
18–24	187	91 ± 15	58–186	72	80	90	99	112
25–29	159	85 ± 13	55–140	63	76	83	93	107
30–34	171	85 ± 15	53–153	63	74	83	93	113
35–39	193	79 ± 13	55–165	63	72	76	85	102
40–44	195	77 ± 12	48–117	58	67	77	84	100
45–49	227	74 ± 10	47–109	56	67	74	81	91
50–54	191	73 ± 13	51–152	56	64	71	79	93
55–59	174	70 ± 12	48–149	53	63	69	76	89
60–64	180	68 ± 12	41–148	50	61	68	75	84
65–69	156	66 ± 10	44–102	52	60	65	71	85
70–74	95	66 ± 11	40–96	49	58	64	73	85
75–79	77	62 ± 11	37–100	45	54	61	69	82
80–84	40	64 ± 14	46–114	46	56	62	73	88
>85	27	59 ± 14	30–87	36	48	61	69	78

GFR, glomerular filtration rate.
Values are given as means (s.d.), ranges and 5th, 25th, 50th, 75th, and 95th percentile.

Table 2a | Estimated GFR in caucasian males with reported comorbidity of the Nijmegen Biomedical Study

Age (years)	N	Mean ± s.d.	Range	P5	P25	P50	P75	P95
18–24	1	—	—	—	—	77	—	—
25–29	8	—	15–128	—	—	86	—	—
30–34	4	—	74–107	—	—	98	—	—
35–39	15	86 ± 12	69–106	69	78	81	98	106
40–44	29	81 ± 17	13–118	63	75	83	88	98
45–49	39	78 ± 14	53–135	54	70	77	85	102
50–54	66	76 ± 14	50–107	52	66	75	86	97
55–59	100	76 ± 13	30–108	58	68	75	86	98
60–64	150	71 ± 14	42–106	50	61	71	80	98
65–69	182	68 ± 15	6–112	44	59	69	78	89
70–74	194	66 ± 15	25–112	40	58	66	76	91
75–79	180	62 ± 15	23–105	36	53	62	73	84
80–84	150	60 ± 16	15–102	31	48	61	72	84
>85	45	56 ± 16	11–87	29	48	55	64	84

GFR, glomerular filtration rate.
Values are given as means (s.d.), ranges and 5th, 25th, 50th, 75th, and 95th percentile. For age classes with $N < 10$ only medians and range is given.

Table 2b | Estimated GFR in caucasian females with reported comorbidity of the Nijmegen Biomedical Study

Age (years)	N	Mean ± s.d.	Range	P5	P25	P50	P75	P95
18–24	7	—	84–142	—	—	102	—	—
25–29	15	81 ± 9	65–101	65	73	83	85	101
30–34	33	79 ± 16	39–127	60	72	78	86	111
35–39	50	77 ± 12	51–113	58	68	76	83	92
40–44	43	79 ± 17	57–159	64	70	75	86	102
45–49	60	70 ± 15	5–90	52	64	70	78	87
50–54	101	72 ± 11	42–100	56	63	71	80	93
55–59	106	70 ± 12	28–98	51	62	70	77	91
60–64	141	67 ± 12	27–98	48	61	67	75	86
65–69	154	63 ± 14	23–111	42	53	63	72	88
70–74	166	61 ± 12	16–94	43	53	62	70	79
75–79	131	59 ± 14	26–97	36	50	59	69	86
80–84	100	56 ± 15	26–91	29	46	55	65	82
>85	95	55 ± 15	21–95	29	45	53	64	82

GFR, glomerular filtration rate.
Values are given as means (s.d.), ranges and 5th, 25th, 50th, 75th, and 95th percentile. For age classes with $N < 10$ only median and range are given.

The K/DOQI guidelines have proposed a classification scheme, and defined five stages of CKD according to the presence of proteinuria and the level of GFR. Patients with GFR < 60 ml/min/1.73 m^2 (stages 3 and higher) are considered to be at high risk for cardiovascular morbidity, mortality, and end-stage renal disease and should receive special attention, directed at the identification and treatment of cardiovascular risk factors. Many reports have recently been published describing the prevalence of CKD in various populations.[14–16]

However, these figures must be interpreted with caution. First, most studies have calculated GFR using uncalibrated creatinine assays.[14–16] The importance of proper calibration of the creatinine assays has recently been stressed.[17,18] The impact of the differences in creatinine assays is illustrated in a recent study. Clase *et al.*[16] calculated the prevalence of CKD in a non-diabetic US population using data from National Health and Nutrition Examination Survey III. Using uncalibrated creatinine, they noted a 26.7% prevalence of CKD stages 3–5 in 60- to 69-year-old Caucasian men. This figure dropped to 7.4% when using calibrated creatinine.[19,20] Most studies published in recent years are flawed by the use of improper creatinine values.

Secondly, K/DOQI guidelines do not take age in account when classifying patients. As GFR decreases with age, the number of persons with CKD stages 3–5 (diseased) increases with age, as shown by many investigators and as illustrated in Figure 3. However, our data indicate that the 60 ml/min/1.73 m^2 cannot be used to define a diseased population. Our reference values illustrate that MDRD-GFR decreases with age. A GFR of 60 ml/min/1.73 m^2 is within the normal reference range for men >60 years and women >50 years. Our data suggest that recommendations to define kidney disease must be changed. In a recent study, the use of a threshold value of 60 ml/min/1.73 m^2 independent of age was also questioned.[21] Using a database of the VA system in the US containing creatinine data of predominantly male persons, it was shown that a GFR of 50–59 ml/min/1.73 m^2 was associated with an increased mortality risk only in younger persons (age 18–54 years). For older persons, GFR

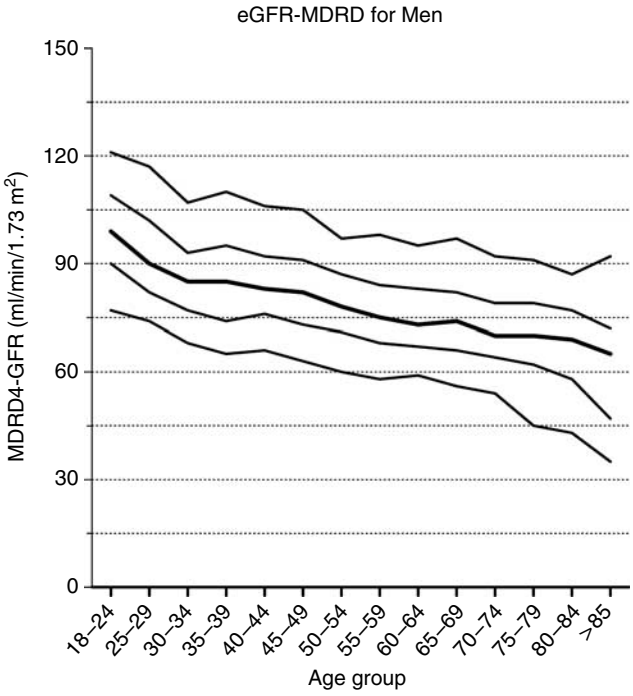

Figure 1 | Reference values of estimated GFR for non-diseased Caucasian males. Median values and 5, 25, 75, and 95 percentiles are shown for persons grouped in 5 years age classes.

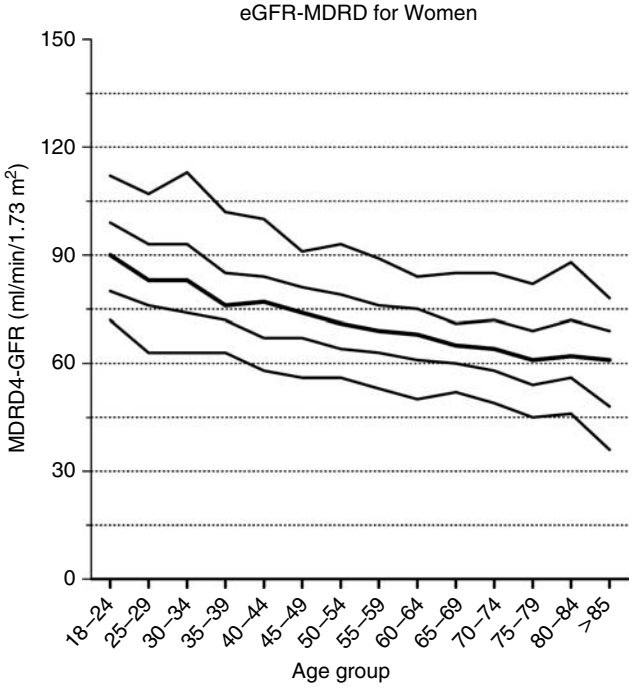

Figure 2 | Reference values of estimated GFR for non-diseased Caucasian females. Median values and 5, 25, 75, and 95 percentiles are shown for persons grouped in 5 years age classes.

values below 50 ml/min/1.73 m^2 (age 55–74) or 40 ml/min/1.73 m^2 proved better thresholds. These figures compare nicely with our reference values, clearly falling below the 5% percentile.

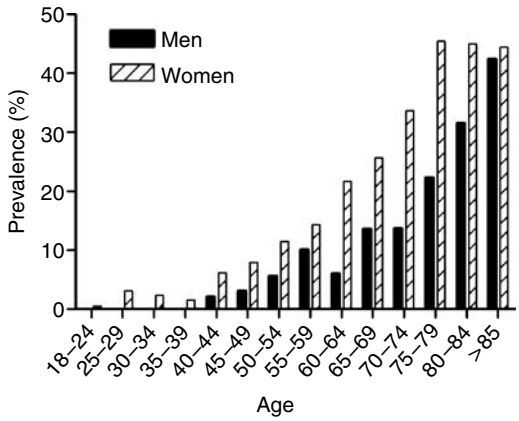

Figure 3 | Prevalence of CKD stages 3–5 (GFR $<$60 ml/min/1.73 m^2) according to age in the non-diseased Caucasian Nijmegen Biomedical Study population. Black bars represent men and open bars women.

Admittedly, there is debate on the use of formulas for estimating GFR. Newer formulas have been developed, however, their performance compared with the MDRD formula has been questioned. In a recent study Hallan *et al.*[22] showed that the MDRD formula (using calibrated creatinine) gives nearly unbiased estimates of GFR, whereas all other formula had a much larger negative bias especially in the elderly.

Our study has several limitations. We have used a questionnaire to ascertain the health status of the participants. Thus, persons who are unaware of a underlying comorbidity may be incorrectly classified as 'healthy'. Participants were also asked if they had seen their family physician or a hospital specialist within 3 or 12 months before the study, respectively. Fifty-three percent of the study participants denied any contact with such health-care professionals. Limiting the analysis to this subgroup had no major effect: only for the age groups $>$80 years (with few remaining persons), the fifth percentile was higher at values of 45 ml/min/1.73 m^2. We have measured serum creatinine at one time point only. Correct classification of CKD stage 3–5 requires decreased GFR values for a period of at least three months. Therefore, we may have overestimated the true prevalence of CKD stages 3–5 in our population. As our healthy study participants had not used medication or contacted a physician in the 3 months before the study, the likelihood of major classification errors is small. Of note, our data do not necessarily reflect true GFR. The seemingly lower estimated GFR in women may thus be the consequence of the well-known underestimation of true GFR by the MDRD formula in women.[8,23] Lastly, our data cannot be applied to other, non-Caucasian populations.

In conclusion, we provide age- and sex-specific values of estimated GFR using the MDRD formula with proper calibration of creatinine. These values should allow a better interpretation of reported GFR data of individual patients. As such, the data should help in guiding treatment of the individual patients.

MATERIALS AND METHODS

Sample design

Details of the Nijmegen Biomedical Study have been described before.[24] In brief, the Nijmegen Biomedical Study is a population-based cross-sectional study conducted by the Radboud University Nijmegen Medical Centre. Approval to conduct the study was obtained from the Institutional Review Board. Nijmegen is a town in the eastern part of The Netherlands with 156 000 inhabitants, approximately 87% of Caucasian descent. Age and sex stratified randomly selected adult (age 18 years and older) inhabitants of Nijmegen ($n = 22\,452$) received an invitation to fill out a postal questionnaire on lifestyle and medical history. The following questions were used to collect data on pre-existent renal and vascular disease:

'Have you ever been diagnosed by a physician with any of the underlying diseases: myocardial infarction, stroke or cerebrovascular disease, diabetes, hypertension, or any kidney disease'. In addition, specific information was gathered on the use of any drug therapy in the last 6 months.

The response to the questionnaire was 41.7% ($n = 9371$). In addition, 68.9% of the responders donated 2×8.5 ml blood ($n = 6455$). No physical examination was carried out. Serum creatinine was measured in these samples. We limited the analysis for this paper to the 6097 Caucasian participants with valid data, of whom 2823 were male and 3272 female. Of this population, 2365 reported an underlying condition (hypertension $n = 1032$, diabetes $n = 358$, myocardial infarction $n = 362$, stroke $n = 127$, kidney disease $n = 145$, or the use of diuretic, antihypertensive, or antirheumatic drugs $n = 347$). The remaining 3732 participants (1660 male, 2072 female) were defined as the disease-free population.

Laboratory methods

Serum creatinine was measured by a kinetic alkaline picrate method on an Aeroset auto-analyser of Abbott. In view of the importance of interlaboratory and methodological differences in the creatinine assays on results of estimated GFR creatinine data obtained by the Jaffe method were calibrated against the Roche enzymatic creatinine assay. We also have sent 40 serum samples to the Cleveland Clinic Laboratory, which is the original MDRD laboratory. The Cleveland Clinic Laboratory has measured serum creatinine using a Beckman-modified kinetic alkaline picrate reaction.

Calculations

We observed the following relationship between the Roche enzymatic creatinine assay and the Jaffe alkaline picrate assay, yielding the following equation: y (Nijmegen enzymatic) $= 1.266 \times$ (Nijmegen Jaffe) -29.

Comparison between creatinine measured in our laboratory and in the Cleveland Clinic Laboratory revealed y (creatinine Cleveland) $= 1.021 \times$ (Nijmegen enzymatic) $+ 11$.

For calculation of GFR, we used serum creatinine values calibrated to the original MDRD laboratory values.

GFR was calculated using the abbreviated MDRD formula: $186 \times$ (serum creatinine (in μmol/l)/88.4)$^{-1.154} \times$ (age (in years))$^{-0.203}$ $\times 0.742$ (if female).

Patients were classified in stages of GFR according to the classification of CKD as defined by the K/DOQI guidelines. Notably, as we have no information on urinary protein excretion, we only provide data on the prevalence of CKD stages 3–5.

We calculated means with standard deviation and 5th, 25th, 50th, 75th, and 95th percentile using STATA software (Version 9.1).

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