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Glomerular Filtration Rate in Healthy Living Potential Kidney Donors: A Meta-Analysis Supporting the Construction of the Full Age Spectrum Equation

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Key Words
Renal function · Healthy subjects · Aging · Glomerular filtration rate prediction equation

Abstract
Background: Normal kidney function or, more specifically, normal glomerular filtration rate (GFR) in men and women and its decline with age is still much debated today. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation has gender (and race) multiplication factors, accounts for a decline that starts at very young age and assumes that the mean GFR is as high as 120–130 ml/min/1.73 m^2 from a young age. The full age spectrum (FAS) estimated mean GFR is about 107 ml/min/1.73 m^2 at a young age and remains constant until the age of 40 years and then starts to decline both in men and women. The aim of this research study was to give more insight into 'normal' GFR levels and the physiological decrease of kidney function with age and to use a meta-analysis to evaluate the mathematical construction of the FAS and the CKD-EPI equation. ***Methods:*** We conducted a meta-analysis of published GFR measurements in healthy Caucasian living potential kidney donors (n = 5,482, 46.8% men). Only publications dating from 2000 were selected to avoid the possible influence of body surface area changes in the last decades on the indexed GFR, expressed in ml/min/1.73 m^2. ***Results:*** We found that the mean GFR ≈ 107 ml/min/1.73 m^2 up to the age of 40 years, but renal decline begins beyond 40 years. No evidence could be found for any difference between men and women in the separate age groups. ***Conclusions:*** The current meta-analysis supports the mathematical form of the FAS equation, which matches the age/sex dependency of measured GFR for healthy potential living kidney donors.

Introduction

Defining normal kidney function is certainly a difficult task in nephrology. Indeed, renal function is a vast concept, which can be approached in several different ways. Glomerular filtration rate (GFR) is considered as one important parameter to assess global kidney function [1, 2]. Definition of normal kidney function implies that GFR is measured with high precision. However, direct measurement of GFR is not so easy in daily practice and most nephrologists refer to estimated GFR (eGFR), that is, equations based on biomarkers like serum creatinine (Scr) or plasma cystatin C [3–5]. Another difficulty with GFR is the fact that GFR physiologically decreases with aging. In other words, the 'normal' thresholds of GFR are obviously different at 40 versus 80 years [1, 6–8]. Relatively few studies have been published where measured GFR

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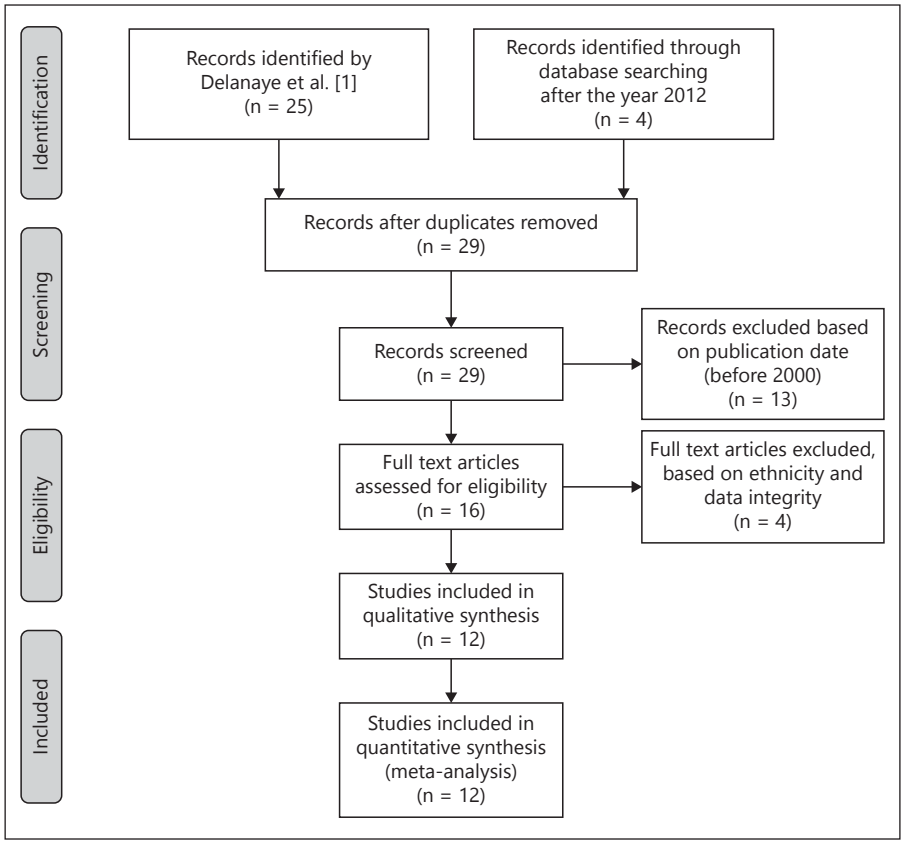

Fig. 1. PRISMA flow diagram.

(mGFR) has been obtained in healthy subjects and, in vast majority of these studies, the samples remain relatively modest [6, 9–20]. We thus believe there is a place for a meta-analysis on this topic, focusing on key points which remain controversial in the literature: what is 'normal' GFR? Is 'normal' GFR different in men and women? When does the physiological decrease in GFR begin? All these questions are also of importance to evaluate and compare the construction of the recommended Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [4] and the new full age spectrum (FAS) equation [21], which was recently proposed to estimate GFR across the entire age spectrum from 2 to old age (FAS-eGFR = $107.3/(Scr/Q) \times 0.988^{(age-40)}$ when age >40 years), where Q is the median Scr concentration for healthy age-matched subjects (0.90 mg/dl for men and 0.70 mg/dl for women). Indeed, the FAS equation and CKD-EPI equation clearly differ in mathematical construction. The FAS equation implies that (i) mean GFR of healthy subjects aged between 18 and 40 years is approximately 107 ml/min/1.73 m^2 and not decreasing from around 125 (at 18 years) to 107 ml/min/1.73 m^2 (at 40 years), as predicted by CKD-EPI, (ii) GFR is not different in men and women, thus, no gender multiplication factor at the GFR level is required and (iii) decline in GFR only begins at 40 years and not already at the age of 18 years, as built in the mathematical construction of the CKD-EPI equation [21]. Moreover, this decline rate is faster in FAS (as expressed by 0.988^{age}) than in the CKD-EPI equation (as expressed by 0.993^{age}).

To answer these much-debated questions, we present a meta-analysis summarizing mGFR data from all currently available relevant studies in healthy living potential kidney donors, allowing for a more comprehensive understanding of the differences between men and women and the evolution of mean GFR of healthy subjects with aging.

Materials and Methods

Search Strategy

The review article of Delanaye et al. [1] listed studies of sufficient size and representative of the general population for which the healthy status of the sample was unquestionable, and where the method used to measure GFR was accurate and the statistical assessment adequate (n = 25; fig. 1). These studies were here identified for the current meta-analysis. Using the search terms 'GFR'

and 'living kidney donors', we searched PubMed/MEDLINE and Web of Science (Web of Knowledge) databases between the year 2000 up to November 2015 and additionally identified 4 studies published after 2012 (the publishing date of the Delanaye review) presenting mGFR in living potential kidney donors (fig. 1).

Two contributing authors (H.P. and P.D.) considered and selected studies as potentially eligible for our meta-analysis by independently reviewing the titles and abstracts of each study identified by the search and then examining the full text. We resolved any disagreement regarding whether a particular study should be included using discussion among all of the contributing authors, followed by a consensus reached by all.

Inclusion and Exclusion Criteria

Only publications written in English and dating from after the year 2000 were selected to avoid the possible influence of body surface area (BSA) changes in the last decades on the indexed GFR, expressed in ml/min/1.73 m^2 [9]. Based on that criterion, 13 studies were excluded (fig. 1). More recent studies presented lower mGFR values as normal compared to prior studies published in the 1950s or before. This observation is explained by the BSA adjustment as BSA has been increased significantly during the last 3 decades and the BSA-unadjusted GFR did not show such a decrease [9, 22].

Only publications involving white and Arabic (Caucasian) living potential kidney donors were selected, because it is suspected that normal GFR could be different according to ethnicity, especially in Asian people [1]. We also excluded abstracts and studies that did not allow the retraction of numbers, mean GFRs and SDs from the published text. Based on these 2 criteria, 4 studies were excluded (fig. 1). Finally, 12 articles were involved in the meta-analysis (fig. 1). For each article, male and female data were presented separately, which leads to a maximum of 2 × 12 = 24 'studies' used in this meta-analysis.

Outcome Measures

We retrieved measured mean GFR (ml/min/1.73 m^2), SD, age group, sex and numbers of men/women in each age group. SD was sometimes obtained from 2.5th or 5th percentile to 95th or 97.5th percentile, using SD = (Pct2.5–Pct97.5)/4 or SD = (Pct5–Pct95)/3.29. We defined age groups as decades: 20–30, 30–40, 40–50, 50–60, 60–70 and ≥70 years, but when case data were not available from these decades, we shifted by maximum 5 years to match the predefined age groups.

Data Extraction

Two contributing authors (H.P. and L.H.) independently extracted the data from the full text and partitioned the numbers into age groups. Any disagreement between the 2 authors was resolved by discussion. For the outcomes of GFR, relevant group means (SD) per age group were extracted from each included study, by inspecting the tables or figures or by reading the text. When mean GFR and/or numbers for men and women were not available from the tables, we made a reasonable estimate from the figures (for mGFR, and by counting subjects, where possible for men and women) and tried to assign correct numbers to age groups for men/women, as much as possible. In case the numbers for men or women were simply not available, neither from tables nor inspection of figures nor by reading the text, we equally distributed men and women among age groups, a subjective decision which we only applied in very few cases, as described in table 1.

Statistical Analysis

All statistical analyses were performed in MS Excel using a self-written macro in Visual Basic for Applications (online suppl. material; for all online suppl. material, see www.karger.com/doi/10.1159/000450893), after the theory outlined by Lipsey and Wilson [23]. Continuous outcomes were analyzed using mean differences and SDs.

Effect sizes for the difference between sexes were calculated along with 95% CIs using a fixed effect model. We assumed that the effect sizes differ only because of sampling error, because we rule out the differences between studies by defining the effect size as the difference between mGFR for both sexes, divided by the pooled SD, and thus the effect size from each study estimates a single common mean. Effect sizes differ from each other because each study used a different sample of participants.

A random-effects model was used to determine the overall mean mGFR and 95% CIs for the means. A random-effects model assumes a genuine diversity in the results of the included studies due to between-study heterogeneity and incorporates a between-study variance (random effect) into the calculation accordingly.

Between-study heterogeneity was evaluated using the χ^2 test based on the Cochran's Q statistic, and an I^2 index was used for assessing heterogeneity, in which an I^2 value of 25, 50 or 75% represented low, moderate or high heterogeneity, respectively. $p < 0.05$ was considered statistically significant, although correction for multiple comparisons is considered during the discussion.

We also investigated the relationship between the outcome mean mGFR and the covariates 'study', 'sex', 'age-group' and 'method' with a weighted generalized linear model (GLM).

Results

Eligible Studies and Study Characteristics

Table 1 gives an overview of the studies and the way we obtained mean GFR, SD and numbers for men and women from the 12 selected publications [6, 9–16, 24–26].

Extracted Data from the Selected Studies

Table 2 gives a detailed overview of the data for mean GFR, SD and numbers of men and women per age group, as we extracted them from these publications. A total of 5,482 (2,565 men and 2,917 women) living kidney donors, who were subdivided to 104 sub-studies (per age group and gender), were involved in this meta-analysis. The data from table 2 were used to answer the research questions of interest.

Is There a Difference between Men and Women in Each Age Group?

We subdivided each publication into a study for men and women as we wanted to evaluate the difference in mean GFR between sexes. The results of this fixed-effects meta-analysis are summarized in table 3. Heterogeneity

Table 1. List of studies included in this meta-analysis and description of the methods used to extract the relevant data. The table and figure numbering refers to the corresponding reference

Study reference	Mean GFR	SD	Numbers and age-groups
Hamilton et al. [10], 2000	Read from table 3	Read from table 3	Read from table 3
Vervoort et al. [24], 2002	Read from table 2	Read from table 2	Read from table 1. All data were for ages (28.2±1.96 × 6.1). M/F were equally distributed into 2 age-groups
Hoang et al. [11], 2003	Read from figure 1 and table 1. Equality for M/F reported in the text	Read from table 1	Read from figure 1 and table 1. Age-dependence reported in table 1 and figure 1
Fehrman-Ekholm and Skeppholm [25], 2004	Read from the text	Read from the text	Read from the text. No difference between M/F reported
Rule et al. [12], 2004	From table 1 at midpoints of age-groups	Calculated as (Pct97.5–Pct2.5)/4	Read from figure 2
Grewal and Blake [13], 2005	103.4 for age >40 years; 103.4–0.91 × (age – 40) for age ≥40 years. No difference between M/F	2 × SD = 28.9	Read from figure 1, respecting totals obtained from the text
Berg [14], 2006	From table 3	From table 3	From table 3
Poggio et al. [9], 2009	Read from table 3 at mid-points of age-groups	Calculated as (Pct95–Pct5)/3.29	Read from figure 1 and table 2 + shifted 5 years
Peters et al. [15], 2012	From table 4 (<30 years and 65+) and figure 4	From table 4 (<30 years and 65+). The same SDs are used for the other age-groups	From table 4 (<30 years and 65+). In the text, it is mentioned that n = 778/543 women/men are aged >40 years
Soares et al. [26], 2013	Read from the text	Read from the text	Read from figure 1 and totals from the text
Blake et al. [6], 2013	103.9–0.0061 × age^2 and read from figure 3	2 × SD = 25.8	Determined from table 1 and below 50 years allocated as 50% (40–50 years), 30% (30–40 years) and 20% (20–30 years), based on the density of the points in figure 2
Holness et al. [16], 2013	From figure 5 and the text and formula (13) for age >40 years: GFR = 170–1.55 × age at midpoints	2 × SD = 27.5 below 40 years and 2 × SD = 36.7 above 40 years	From figure 5 and equally distributed between males and females

Pct = Percentile; M = male; F = female.

(I^2) between studies is presented for information only and was low to moderate. Up to the age of 50 years, there is no difference between men and women (effect sizes are not different from zero). Above 50 years, there is a tendency for a difference of about 3.5 ml/min/1.73 m^2, with a faster renal decline in women than in men. For the age group ≥70 years, only 3 studies had a small number of subjects and none of these studies reported mean mGFRs for men and women separately.

What Is the Mean GFR in Each Age Group?

To answer this research question, we performed a meta-analysis to estimate the mean GFR in the different age groups. The results of the random-effects model are summarized in table 4. Forest plots (fig. 2–6) show the mean mGFR with 95% CIs for the mean for each study, separate for men and women, together with the final mean mGFR (and 95% CI) obtained from the meta-analysis random-effects model. For each age group, large heterogeneity between the studies was observed. Figures 2 and 3 also show the mean mGFR = 107.3 ml/min/1.73 m^2 (vertical line) predicted from the FAS equation and the possible CKD-EPI predictions (shaded area) for the average healthy adult <40 years (corresponding with Scr = 0.90 mg/dl for males and 0.70 mg/dl for females). When the vertical line crosses the horizontal 95% CIs, this indicates that there is no statistically significant difference between the study results and the

Table 2. Data extracted from the selected studies in order of appearance

Study	Age, years	Males			Females		
		n	mGFR	SD	n	mGFR	SD
Hamilton et al. [10], 2000	21–60	130	108	14	42	110	16
^{51}Cr-EDTA	20–30	79	107	14	19	112	18
	30–40	32	108	16	12	106	13
	40–50	13	109	15	9	108	14
	50–60	6	108	12	2	93	12
Vervoort et al. [24], 2002	28.2±6.1	23	104	9	23	109	13
Inulin	20–30	11	104	9	11	109	13
	30–40	12	104	9	12	109	13
Hoang et al. [11], 2003	18–88	104			60		
Inulin	20–30	55	104	15	21	104	15
	30–40	25	104	15	14	104	15
	40–50	7	95	15	5	95	15
	50–60	3	81	17	8	81	17
	60–70	10	81	17	5	81	17
	>70	4	81	17	7	81	17
Fehrman-Ekholm and Skeppholm [25], 2004	71–110	32	67.7	10.8	20	67.7	10.8
Iohexol	>70	32	67.7	10.8	20	67.7	10.8
Rule et al. [12], 2004	18–71	160			205		
Iothalamate	20–30	30	109	13.50	27	109	13.50
	30–40	56	104	13.75	55	104	13.75
	40–50	41	99	13.75	73	99	13.75
	50–60	20	94	13.50	39	94	13.50
	60–70	13	89	13.50	11	89	13.50
Grewal and Blake [13], 2005	19–72	210			218		
^{51}Cr-EDTA	20–30	33	103.4	14.45	13	103.4	14.45
	30–40	76	103.4	14.45	65	103.4	14.45
	40–50	44	98.9	14.45	58	98.9	14.45
	50–60	44	89.8	14.45	58	89.8	14.45
	60–70	13	80.7	14.45	24	80.7	14.45
Berg [14], 2006	21–67	60	105.0	13.00	62	105.0	13.00
Inulin	20–30	12	119	12	12	102	15
	30–40	22	104	13	23	110	12
	40–50	22	100	11	25	105	11
	50–60	4	92	11	2	85	1
Poggio et al. [9], 2009	39±10	411			529		
Iothalamate	20–30	58	111	16.72	46	114	16.72
	30–40	120	107	16.72	138	111	16.72
	40–50	123	103	16.72	165	107	16.72
	50–60	85	93	16.72	137	96	16.72
	60–70	25	88	17.02	43	91	16.72
Peters et al. [15], 2012		819			1,059		
^{51}Cr-EDTA	20–30	105	98.5	13.2	91	100.8	15.4
	30–40	171	102.0	13.2	190	97.0	15.4
	40–50	245	94.0	13.2	349	92.0	15.4
	50–60	245	88.0	13.2	348	82.0	15.4
	60–70	53	78.5	14.3	81	70.9	11.6

Table 2. (continued)

Study	Age, years	Males			Females		
		n	mGFR	SD	n	mGFR	SD
Soares et al. [26], 2013	19–70	123	108	18	162	104	18
^{51}Cr–EDTA	20–30	28	113	18	36	111	18
	30–40	29	113	18	37	111	18
	40–50	28	101	16	37	96	14
	50–60	32	101	16	43	96	14
	60–70	6	101	16	9	96	14
Blake et al. [6], 2013	18–84	436			468		
^{51}Cr–EDTA	20–30	65	104	12.9	63	101	12.9
	30–40	98	97	12.9	98	99	12.9
	40–50	163	92	12.9	154	93	12.9
	50–60	71	89	12.9	108	85	12.9
	60–70	37	81	12.9	33	77	12.9
	>70	2	70	12.9	12	70	12.9
Holness et al. [16], 2013	18–59	57	107	14.9	69	100.7	17.9
^{99m}Tc–DTPA	20–30	21	108.0	13.75	32	108.0	13.75
	30–40	15	108.0	13.75	15	108.0	13.75
	40–50	17	100.3	18.35	17	100.3	18.35
	50–60	4	84.8	18.35	5	84.8	18.35

n = Number of subjects.

Table 3. Meta-analysis results for comparing mean GFR between men and women

Age group, years	#Studies	#M	#F	I^2 (%; p value)	Standardized effect size (95% CI)	p value	Effect size (95% CI), ml/min/1.73 m^2
20–30	11/12	497	371	33.1 (0.134)	–0.03 (–0.16 to 0.11)	0.714	–0.4 (–2.3 to 1.6)
30–40	11/12	656	659	49.4 (0.032)	0.00 (–0.11 to 0.11)	0.969	0.0 (–1.5 to 1.6)
40–50	10/12	703	892	22.3 (0.238)	–0.01 (–0.11 to 0.09)	0.831	–0.1 (–1.6 to 1.3)
50–60	10/12	514	750	50.0 (0.035)	0.23 (0.12 to 0.35)	0.0001	3.4 (1.7 to 5.1)
60–70	7/12	157	206	22.6 (0.257)	0.25 (0.04 to 0.47)	0.020	3.7 (0.6 to 6.9)
>70	3/12	38	39	0.0 (1.000)	0.00 (–0.48 to 0.48)	1.000	0.0 (–6.7 to 6.7)
Total		2,565	2,917				

#Studies = The number of studies or articles involved in the hypothesis of equality (out of 12 selected articles). I^2 (p value) = measure of homogeneity among studies, with p indicating Cochran's Q significance. Standardized effect size = difference in mean mGFR between males (#M) and females (#F) divided by the pooled SD. 95% CI for the effect size. p = p value for testing the hypothesis of equality of mean mGFR between sexes. Effect size = GFR-difference corresponding to the standardized effect size expressed in ml/min/1.73 m^2.

mean mGFR of 107.3 ml/min/1.73 m^2. For subjects >40 years, the grey-shaded areas in figures 4–6 indicate the areas of possible FAS (or CKD-EPI) predictions for that age interval (for the same Scr values). Overlap with the 95% CIs of the studies indicates no statistically significant difference.

When Does Renal Function Start to Decline?

The selected studies for the age groups 20–30 and 30–40 years were the same, which allowed us to test equality of mean GFR between these age groups, controlling for study and sex. The overall effect size was 0.12 with 95% CI 0.03–0.21 (p = 0.012) indicating that there is a slight sta-

Table 4. Meta-analysis results for mean GFR, CKD-EPI and FAS estimation in ml/min/1.73 m^2

Age group, years	#Studies	CKD-EPI	FAS	Mean mGFR	95% CI
20–30	22/24	114–125	107.3	106.7	104.6–108.9
30–40	22/24	107–117	107.3	104.9	102.8–107.0
40–50	20/24	99–109	95–107	99.0	96.5–101.6
50–60	18/24	93–101	84–95	90.7	88.1–93.3
60–70	14/24	86–95	75–84	84.0	79.5–88.5
>70	6/24	70–88	52–75	69.4	66.1–72.7

I^2 >75% in all age-groups, indicating that high heterogeneity among studies was observed. #Studies = The number of studies involved in the meta-analysis for the corresponding age-group (out of 12 × 2 = 24 male/female datasets). CKD-EPI and FAS = eGFR-prediction range for the corresponding age-group. 95% CI for the mean mGFR.

tistically significant but clinically meaningless difference of 1.8 ml/min/1.73 m^2 between the mean GFR of both age groups; however, when correcting for multiple comparisons, this p value turns into a non-significant difference.

With the only exception of the study by Vervoort et al. [24], all studies for the age groups 30–40 and 40–50 years were the same, which allowed us again to test the equality of mean GFR between these age groups. The overall effect size was 0.39 (95% CI of 0.31–0.47; $p < 0.0001$) indicating that there was a strong statistically significant (and clinically relevant) difference of 5.9 ml/min/1.73 m^2 between the mean GFR of both age groups.

All studies for the age groups 40–50 years were compared with the age groups 50–60 years yielding an overall effect size of 0.53 with 95% CI of 0.45–0.61 ($p < 0.0001$) indicating that the decrease accelerates as mean mGFR is significantly different (7.8 ml/min/1.73 m^2) from the previous age group with a larger effect size.

Finally, the comparison between age groups 50–60 and 60–70 years (for all studies, except for Vervoort et al. [24], Hamilton et al. [10], Berg [14] and Holness et al. [16] who did not have kidney donors in the last age group) gives an overall effect size of 0.55 with 95% CI of 0.42–0.67 ($p < 0.0001$) corresponding to a difference of 8.2 ml/min/1.73 m^2 indicating that the decrease goes on at the same rate.

Sensitivity Analysis

We performed a sensitivity analysis, leaving out one study (both men and women) at a time to evaluate the influence of one particular study on the overall results. In the age groups 20–30, 30–40, 50–60 and 60–70 years, the largest influence was obtained from the study of Peters et al. [15], with a significant decrease in heterogeneity I^2 when omitted. In the age group of 40–50 years, the study of Poggio et al. [9] showed the largest influence, and when omitted, heterogeneity I^2 = 90.3% decreased to 82.2%. The sensitivity analysis raised the question whether there was an effect of the method used.

Is There an Effect of the Method Used?

This question is difficult to answer without the individual patient data. However, we realized that most of the studies were obtained with ^{51}Cr-EDTA (50/104 = 48.1%), followed by inulin (24/104 = 23.1%), iothalamate (20/104 = 19.2%), ^{99m}Tc-DTPA (8/104 = 7.7%) and iohexol (2/104 = 1.9%). We performed a fixed-effect analysis in each age group for the ^{51}Cr-EDTA studies, the inulin studies and the iothalamate studies, pooling studies on men and women (table 5).

The mean GFRs obtained in each age group by ^{51}Cr-EDTA are significantly lower than those obtained with iothalamate. In 2 age groups, ^{51}Cr-EDTA is also significantly lower than the inulin reference method. The conclusion is that there is a significant difference between GFR methods with underestimation for ^{51}Cr-EDTA and overestimation of iothalamate compared to the inulin reference method.

Meta-Regression

A weighted GLM (weights were defined as $w_i = 1/(SD_i^2/n_i)$) explains 99% of the variation in mGFR, with 'age group', 'study' and the interaction term 'age group' × 'study' explaining, respectively, 50.3, 42.0 and 4.3% of the variation in mGFR. This reflects the age decline of mGFR and the heterogeneity between the studies at hand. 'Sex' only explained 0.5% of the total variation and the interaction terms 'study' × 'sex' and 'sex' × 'age' only contributed 1.5 and 0.5% to the explained variation, respectively, confirming that there is no difference between men and

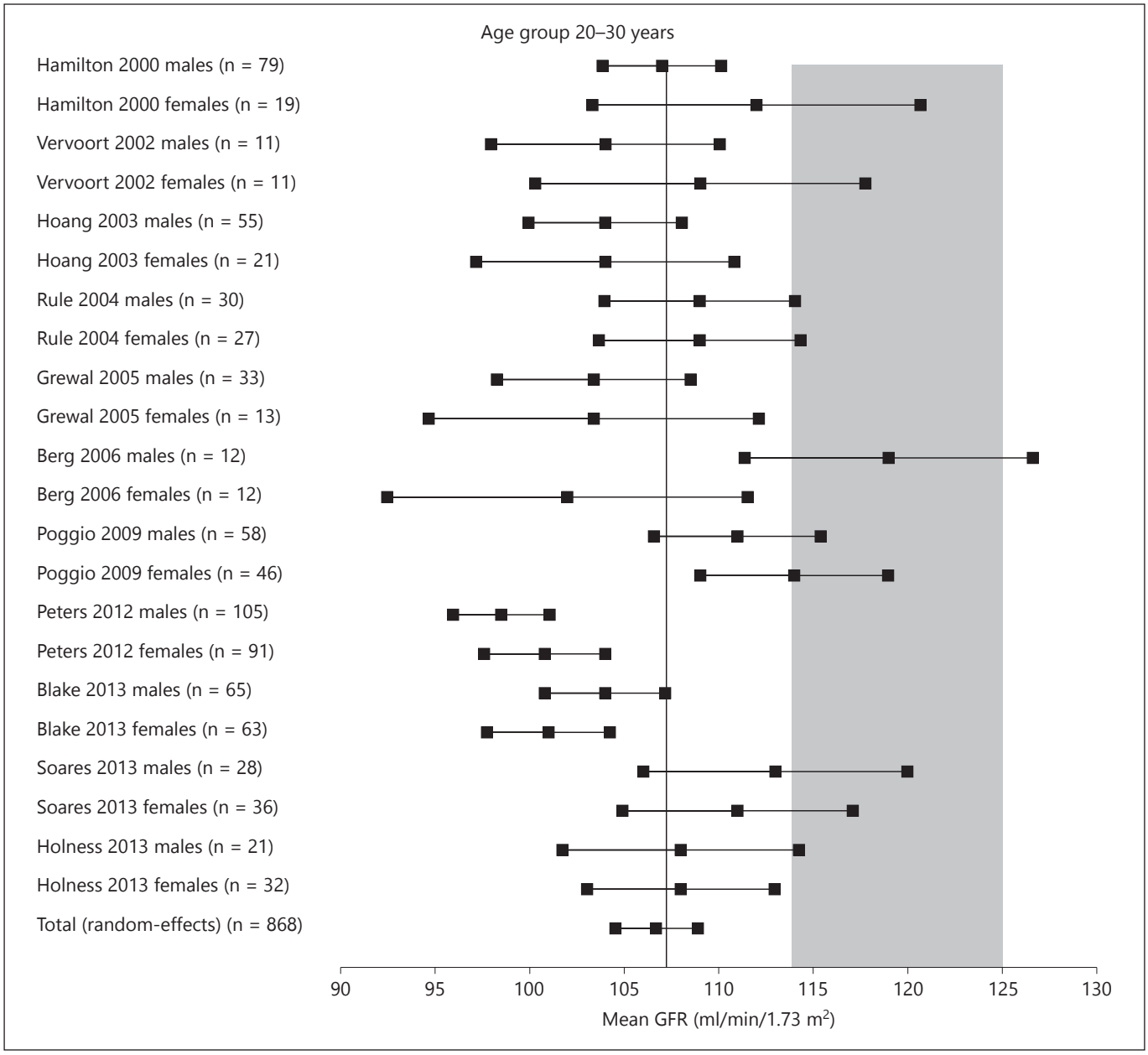

Fig. 2. Forest plot for the age group 20–30 years. The vertical black line gives the FAS prediction for the mean GFR of 107.3 ml/min/1.73 m^2, corresponding to Scr = 0.90 mg/dl for men and 0.70 mg/dl for women, the median Scr values for healthy Caucasian people. The grey-shaded region gives the possible CKD-EPI predictions (114–125 ml/min/1.73 m^2) for this age group, for the same Scr values.

women in the different age groups. If we replaced 'study' by 'method', the model still explained 88% of the total variation in mGFR, with 'age group' (59%) and 'method' (26%) as the only significant variables in the model. In this model, no significant interaction terms were observed. This confirms that the measurement method has an important effect on the reported mGFR values.

Publication Bias

The danger of unsystematic reviews, with only a portion of relevant studies included, is that they could introduce (publication) bias. One simple way of assessing the likely presence of publication bias is to examine a funnel plot [27, 28]. An asymmetric funnel indicates a relationship between effect size and precision in the

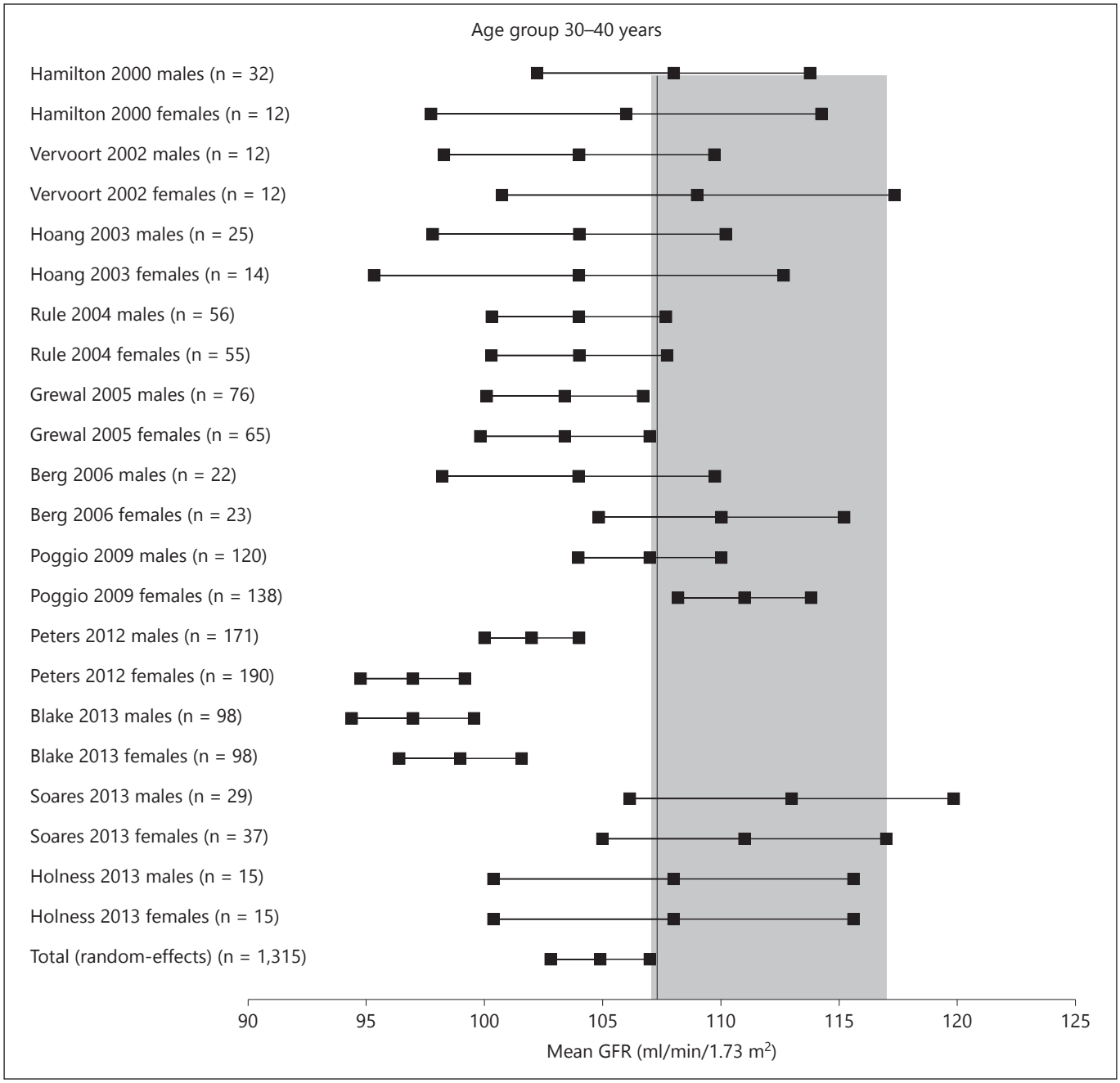

Fig. 3. Forest plot for the age group 30–40 years. The vertical line represents the FAS prediction for the mean GFR of 107.3 ml/min/1.73 m^2, corresponding to Scr = 0.90 mg/dl for men and 0.70 mg/dl for women, the median Scr values for healthy Caucasian people. The grey-shaded region gives the possible CKD-EPI predictions (107–117 ml/min/1.73 m^2) for this age-group, for the same Scr values.

studies at hand. The funnel plots (online suppl. material) for each age group up to 50 years for the difference between men and women were not asymmetric. However, beyond 50 years, the number of studies rapidly decreased and the funnel plots became asymmetric, a sign of a possible publication bias or the shift to positive effect sizes for the studies still present may also indicate a more rapid decline of the renal function in women compared to men.

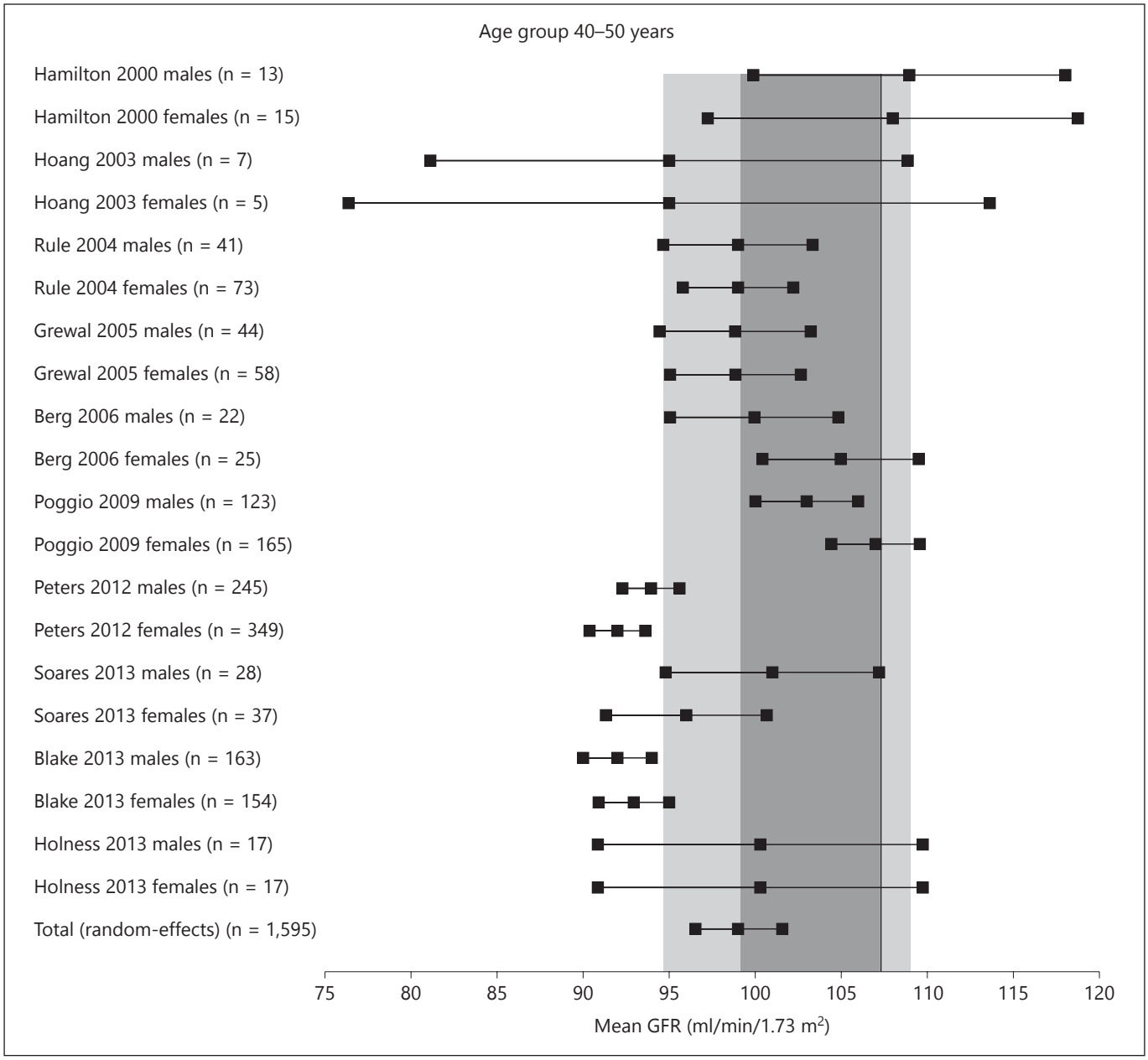

Fig. 4. Forest plot for the age group 40–50 years. The grey areas give the range of mean GFR values 95–107 predicted by the FAS equation and by the CKD-EPI equation 99–109 for this age group, for the median Scr values for healthy Caucasian people. The vertical line represents the FAS prediction of 107.3 ml/min/1.73 m^2 up to the age of 40 years.

Discussion

In the current meta-analysis, we confirmed several important facts regarding normal GFR. First, normal GFR is around 107 ml/min/1.73 m^2, both in men and women, until 40 years and at this age, the mean GFR value tends to decrease progressively. The mean GFR of 107 ml/min/1.73 m^2 was first suggested by original data obtained by Piepsz et al. [29, 30] from children in 2006. The results of our meta-analysis (data from 12 selected articles) confirm that mGFR in adults aged between 20 and 30 years is well (or at least not different from) 107 ml/min/1.73 m^2. For subjects aged between 30 and 40 years, the mean mGFR was only slightly significantly dif-

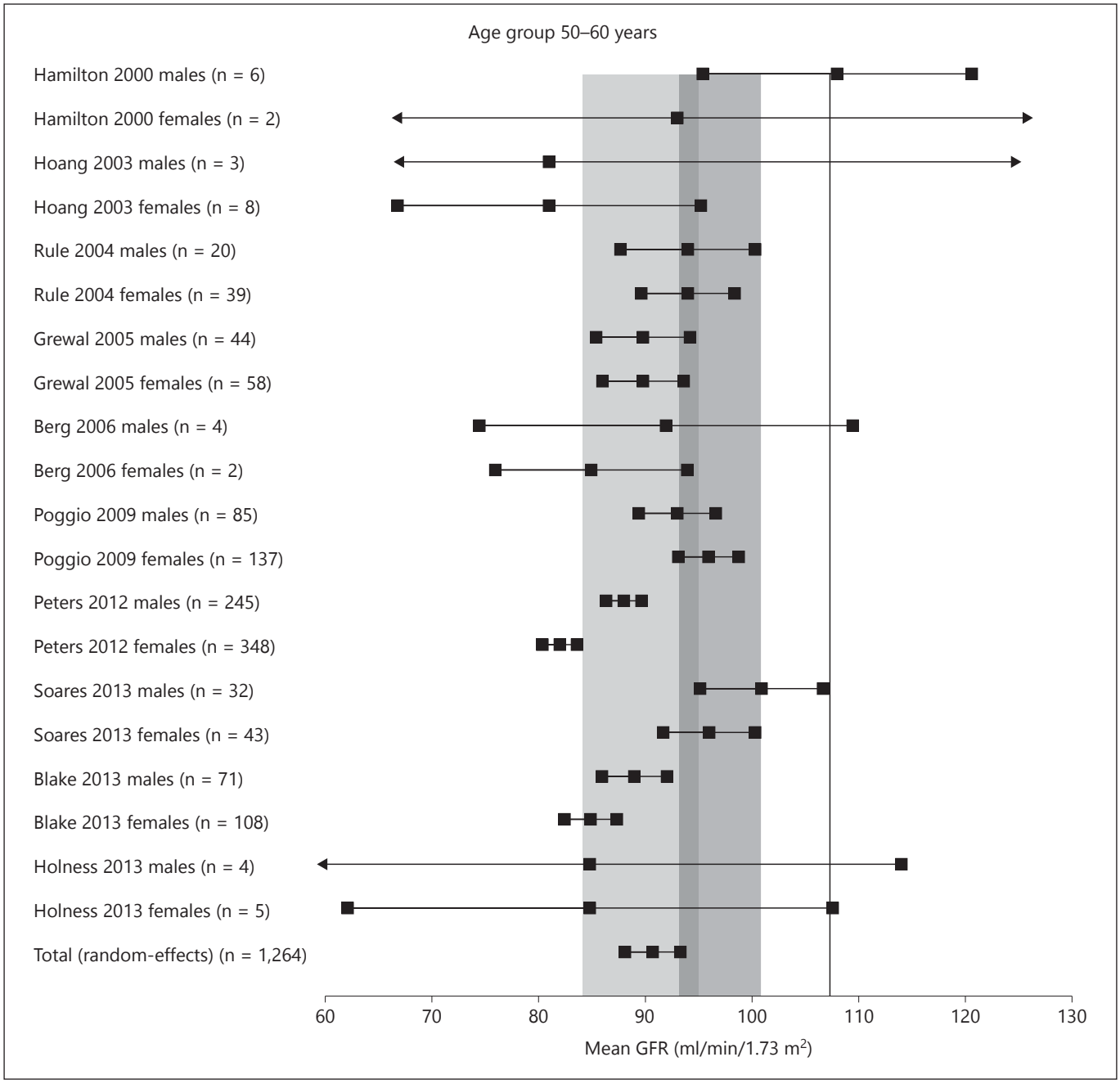

Fig. 5. Forest plot for the age-group 50–60 years. The grey areas give the range of mean GFR values 84–95 predicted by the FAS equation and by the CKD-EPI equation 93–101 for this age group, for the median Scr values for healthy Caucasian people. The vertical line represents the FAS prediction of 107.3 ml/min/1.73 m^2 up to the age of 40 years.

ferent from 107 ml/min/1.73 m^2 but this difference is clearly not relevant from a clinical point of view, as the mean mGFR was 104.9 ml/min/1.73 m^2. Moreover, the study by Peters et al. [15] has the largest impact (weight) on the meta-analysis results, since this is the study with the largest number of subjects, but at the same time, this study consistently showed the lowest mean mGFR values for all age groups. Without the Peters data, the mean mGFR in the 30–40 years age group becomes 105.6 with a 95% CI of 103.4–107.8, which includes 107.3 ml/min/1.73 m^2. This mean of 107.3 ml/min/1.73 m^2 is exactly the GFR value predicted by the FAS equation at

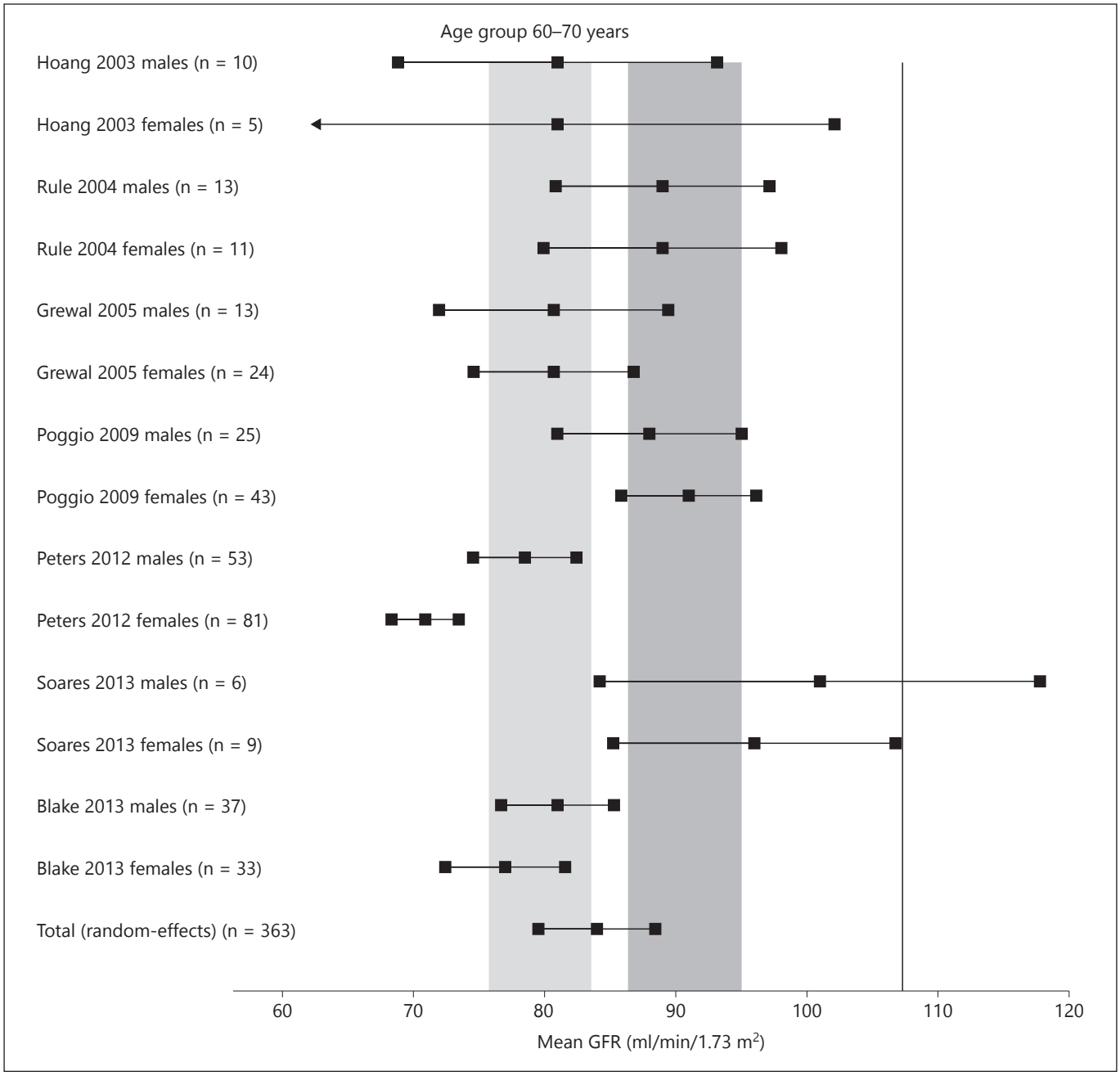

Fig. 6. Forest plot for the age group 60–70 years. The grey areas give the range of mean GFR values 75–84 predicted by the FAS equation and by the CKD-EPI equation 86–95 for this age group, for the median Scr values for healthy Caucasian people. The vertical line represents the FAS prediction of 107.3 ml/min/1.73 m^2 up to the age of 40 years.

Scr = 0.70 mg/dl (women) and Scr = 0.90 mg/dl (men), the median Scr values for healthy Caucasian people [21]. These results of the meta-analysis support the construction of the FAS equation. On the other hand, the mean GFR predicted by the CKD-EPI equation for the average healthy adult subject (Scr = Q) evolves from 122.5 (men) and 125.1 ml/min/1.73 m^2 (women) at the age of 20 years to 106.5 (men) and 108.7 ml/min/1.73 m^2 (women) at the age of 40 years, a difference of 13%. The high values of about 120–125 ml/min/1.73 m^2 at young adult age and the decline of about 13% are not supported by the findings of the current meta-analysis results.

Table 5. Meta-analysis results for the mean mGFR and 95% CIs per age group for the different mGFR methods

Age, years	^{51}Cr-EDTA	Inulin	Iothalamate
20–30	103.0 (101.8–104.2)[a]	106.2 (103.8–108.6)	110.8 (108.4–113.2)[a]
30–40	100.8 (99.9–101.8)[a, b]	105.9 (103.6–108.3)[a]	107.1 (105.6–108.7)[b]
40–50	93.9 (93.0–94.7)[a, b]	101.7 (98.8–104.7)[a]	103.0 (101.4–104.5)[b]
50–60	86.9 (86.0–87.8)[a]	85.0 (83.7–86.4)[b]	94.6 (92.8–96.5)[a, b]
60–70	76.8 (75.2–78.4)[a]	81.0	89.6 (86.4–92.8)[a]

[a, b] Same symbol denotes a statistically significant difference (at row level): for example, for the 20–30 years age group, 103.0 is significantly different from 110.8, but not from 106.2.

The second key message of our meta-analysis is that mean mGFR is not different between men and women, at least not before the age of 50 years [9, 31], and thus, there is no need to build in an extra multiplication factor for gender at the GFR level, when the correction for differences in Scr generation has already been done at the Scr level. At this point, we have to comment on the indexation by BSA. Indeed, if non-indexed GFR is considered, there is an expected difference of mGFR in men and women as body size is different according to gender. This point has been nicely illustrated in the RENIS cohort study [31]. Also, we and others have criticized the indexation of GFR by BSA. If indexation of mGFR is necessary when the GFR of one given subject needs to be compared with another one, using the BSA is certainly not the best physiological tool to index and other authors have proposed other variables like height or total body water [22, 31]. However, we must admit that indexation by BSA is still the most used, both in clinical research and in daily practice. The BSA indexation is also included in data sets used to develop eGFR equations [4]. Moreover, the impact of BSA (or the errors induced by BSA indexation) will be clinically relevant only in very low and very high BSA values [22, 31]. Because the subjects included from the 12 selected articles analyzed in this meta-analysis have normal or near normal BSA values, the absence of a difference in normal mGFR between men and women can be considered as a good reflection of reality. Berg [14] observed a faster decline rate in men than in women in the age range 20–50 years, but not in the years beyond 50 years, which she explained as that women seemed to be protected in the pre-menopausal period, probably by estrogens. We did not observe a difference between men and women up to the age of 50 years, and beyond 50 years, the current meta-analysis showed a small (3.5 ml/min/1.73 m^2) but significant difference between men and women in the age groups 50–60 and 60–70 years with a faster decline in women than in men, a finding also reported in a Brazilian [26] and a Chinese population [32]. Women seem to be no longer protected in the post-menopausal period. Clearly, these contradictory results need more investigation.

From this meta-analysis, we also confirmed data from several (but not all) studies suggesting that mGFR progressively declines from the age of 40 years [2, 11, 13, 17, 20, 33]. Indeed, we clearly showed that mGFR is not different in healthy subjects aged between 20 and 30 years on one side and between 30 and 40 years on the other side. Only after 40 years, the mGFR observed is significantly lower than in these youngest. This observation also justifies the mathematical construction of the FAS equation, which models the decline in GFR from 40 years on [21]. Indeed, the FAS equation does not predict a decline between 20 and 40 years. If we use the mean mGFR observed in this meta-analysis at the age of 35 years (mGFR = 104.9 ml/min/1.73 m^2) and at 75 years (mGFR = 69.4 ml/min/1.73 m^2), we can calculate the average mGFR decline. The mean GFR decline over this 40-year period is (69.4–104.9)/40 = –0.89 ml/min/1.73 m^2/year. Over the same period and for mean normal Scr values, the FAS equation predicts an average decline rate of (70.3–107.3)/40 = –0.92 ml/min/1.73 m^2/year. These results are very close to each other, whereas the same calculation with the CKD-EPI equation will result in a decline of (83.3–110.3)/40 = –0.68 ml/min/1.73 m^2/year (for men). This larger difference from the meta-analysis result can be explained by the fact that the CKD-EPI equation used a statistical model with a constant decline rate of GFR with aging over the 18–75 year age period. The alternative construction of the FAS equation shows no age dependency up to 40 years and a faster decline rate constant (0.988^{age}) beyond that age. In other words, the CKD-EPI age term (0.993^{age}) has to balance the different age decline rates of the 20–40 years versus the 40–75 years age range into one overall 'mean' decline rate factor. The age knot at 40 years is the most

important difference between the FAS and CKD-EPI equations. The current independent meta-analysis supports the age-knotted form of the FAS equation.

mGFR can be obtained with different methods [34]. The gold standard method is the urinary clearance of inulin [2]. This method is however cumbersome and costly and other biomarkers like iothalamate, iohexol, ^{51}Cr-EDTA and ^{99}Tc-DTPA [34] can be used. Each marker, including inulin, can be used in different protocols with or without urine collections (i.e., plasma vs. renal clearance) [35]. All the biomarkers and most of the methods can be considered as 'reference method' [34]. However, the way GFR is measured in every single centre is unfortunately not standardized. Moreover, it is clear from the literature that each method can give slightly different results [34, 36, 37]. It is thus not surprising that we found different mGFR values according to the reference method considered in the present meta-analysis. Compared to inulin results, iothalamate clearances give higher mGFR values, which may also partially explain the higher estimations by CKD-EPI (which was developed on iothalamate data). From the literature, this result is expected as it has been suggested that iothalamate is secreted by renal tubules, leading to a slight overestimation of GFR measured by inulin [34, 38], while results from studies using ^{51}Cr-EDTA clearances give lower mGFR than inulin. Such observation was observed by pioneers in ^{51}Cr-EDTA like Brochner-Mortensen [39]. The differences observed between methods in the present meta-analysis must be interpreted very carefully. Indeed, because of the lack of standardization in measuring GFR, differences can be due not only because different filtration markers were used but also because of the methodology used to calculate GFR: plasma versus renal clearances, choice of sampling times, analytical methods to measure plasma levels etc. [34, 35, 37, 40]. The number of studies in the current meta-analysis is too low to consider all these potential methodological biases.

There are limitations to our meta-analysis. First, the populations concerned in the meta-analysis are, for the majority, subject candidates for living kidney donation. Sensu stricto, they can be considered as not equivalent to the normal general population. Second, the number of healthy subjects >65 years remains limited. We clearly need additional studies in this specific population. Third, we limited our meta-analysis to Caucasians. Some limited data from the literature suggest that normal mGFR in African subjects could be the same [9, 41] but a dedicated research in this population would be welcome as data are clearly lacking. Limited data are also available from Asian populations. Normal mGFR could be slightly lower in such Asian populations. Different hypotheses to explain such results are lower BSA in this population, low protein diet or different methods to measure GFR [1, 32, 42, 43]. Also in this population, additional research seems necessary. Fourth, all the studies included in this meta-analysis are cross-sectional. Therefore, the mean decline in mGFR in ml/min/1.73 m^2/year described here (–0.89 ml/min/1.73 m^2/year between 35 and 75 years), even if not very different from few available data in longitudinal studies, must be interpreted with caution [44–46]. Lastly, the current meta-analysis does not allow the investigation of the Scr dependency in the eGFR equations, which is also different between the FAS and CKD-EPI equations.

In conclusion, the current meta-analysis confirms that normal mean mGFR is the same in men and women, below the age of 50 years, is not different from the value of 107 ml/min/1.73 m^2 proposed from pediatric data up to the age of 40 years and starts to decline significantly beyond 40 years. This meta-analysis also underlines the necessity of future research in other ethnicities, in healthy subjects >65 years and in a longitudinal design. The results of the current meta-analysis also support the mathematical construction of the new FAS equation recently proposed to estimate GFR with a good precision and accuracy from infancy to older age [21].

Disclosure Statement

The authors declare no conflicts of interest.

Statement of Ethics

This retrospective study on anonymous data did not require informed consent nor review/approval by the appropriate ethics committee.

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