Rein du sujet âgé: de la physiologie à l'épidémiologie

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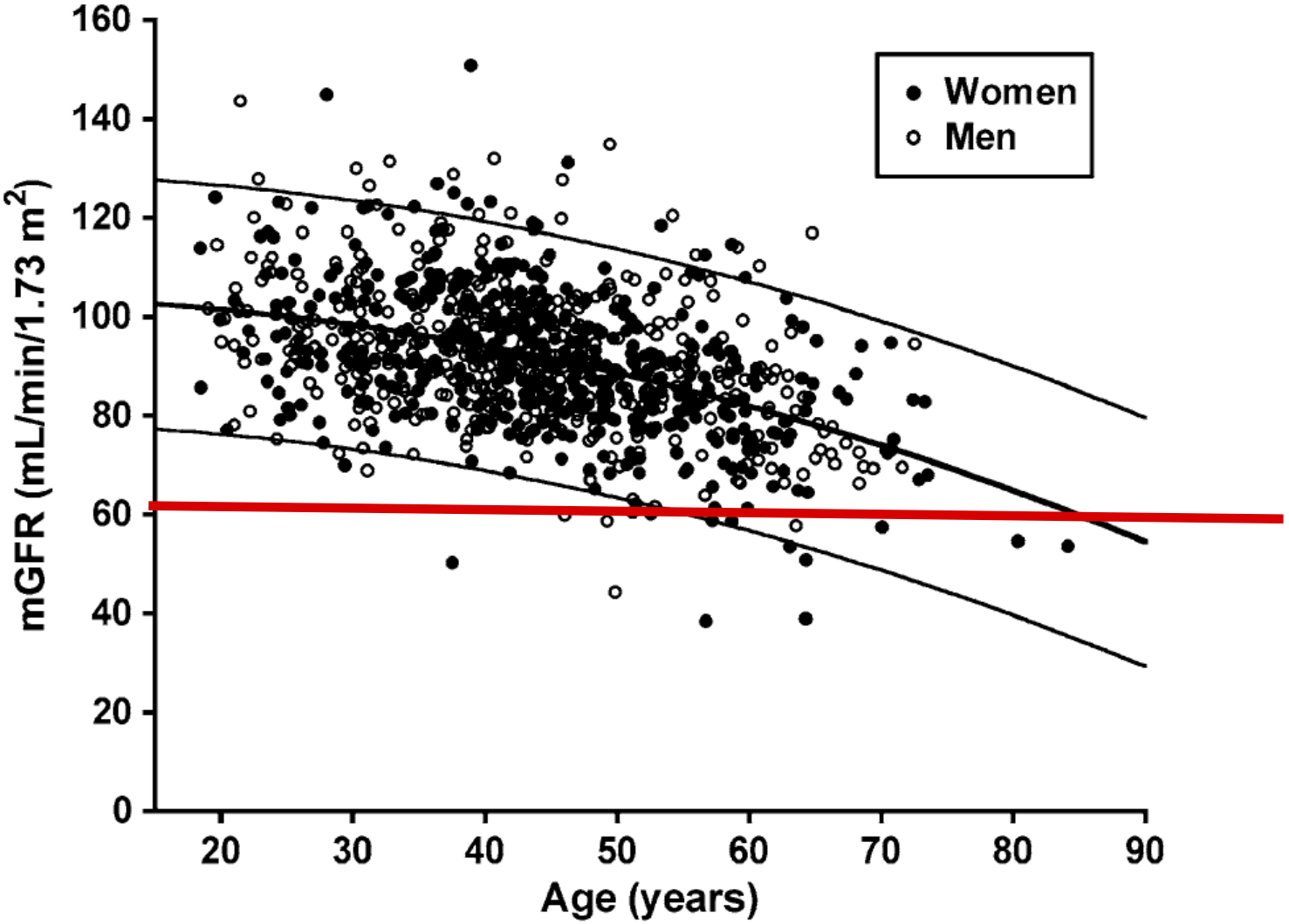
BELGIQUE

PLAN

- Fonction rénale et âge
- Anatomie et âge
- Bases physiologiques
- Mécanismes biologiques
- Estimation du DFG chez le sujet âgé
- Normalité et pathologie
- Impact épidémiologique

La sénescence est un processus inéluctable…

DFG mesuré: étude transversale européenne



DFG mesuré par ^{51}Cr-EDTA chez 904 donneurs vivants

Blake GM et al, Int Urol Nephrol, 2013, p1445

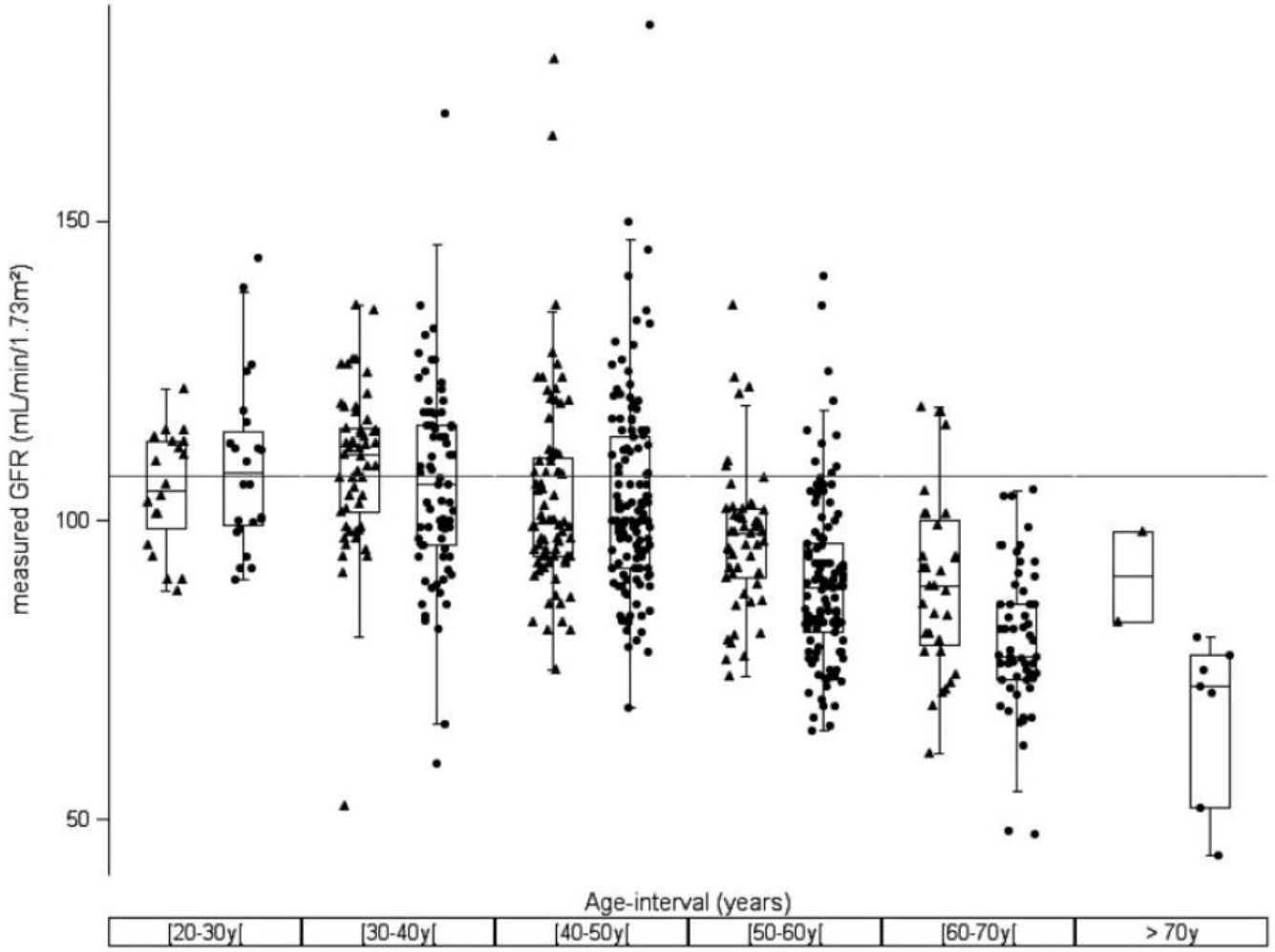


Fig. 1. Box plot for mGFR versus age decades for female (filled circles) and male (filled triangles) potential kidney donors ($n = 633$). A horizontal reference line is drawn at GFR = 107.3 mL/min/1.73 m^2.

Pottel H, Clin Kidney J, 2017, p545

DFG mesuré: étude transversale africaine

Nephrol Dial Transplant (2017) 1–5
doi: 10.1093/ndt/gfx244

ndt
Nephrology Dialysis Transplantation

Measured (and estimated) glomerular filtration rate: reference values in West Africa

Eric Yayo[1], Mireille Ayé[2], Carine Yao[1], Appolinaire Gnionsahé[3], Marie-Laure Attoungbré[1], Etienne Cavalier[4], Hans Pottel[5], Dagui Monnet[1,*] and Pierre Delanaye[6,*]

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*These authors contributed equally to this work as last senior authors.

- 237 sujets sains (donneurs de sang)
- 134 hommes
- Mesure du DFG par clairance plasmatique de l'iohexol

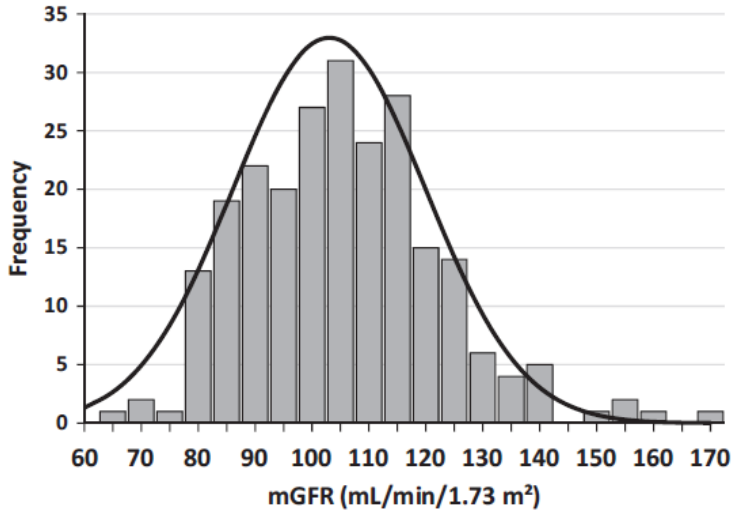

FIGURE 1: Normal distribution of mGFR results in 237 healthy people.

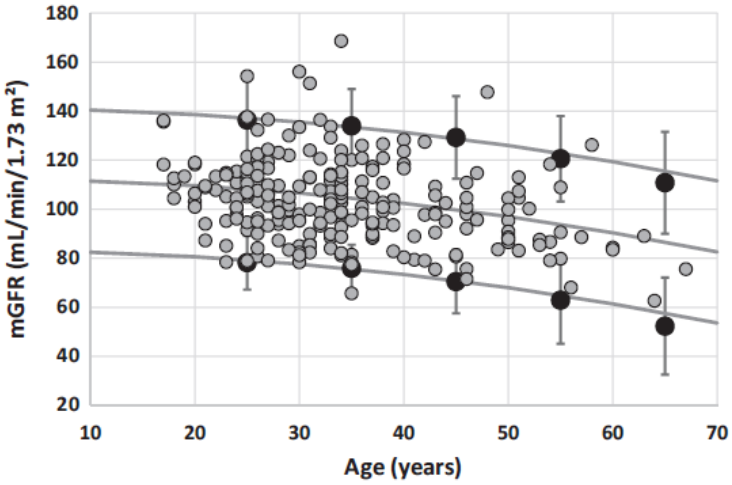

FIGURE 2: mGFR percentiles according to age. The solid grey circles are mGFR results and solid grey lines are 2.5th, 50th and 97.5th percentiles for mGFR in the current African population. The solid black circles with error bars are upper and lower reference limits obtained from the meta-analysis study including 633 Caucasian potential living kidney donors.

DFG estimé: étude transversale

- Population saine aux Pays-Bas
- Equation CKD-EPI
- Pas de diabete, ni d'hypertension, pas de traitement spécifique, pas d'albuminurie
- 1663 hommes 2073 femmes

Nephrol Dial Transplant (2011) 26: 3176–3181
doi: 10.1093/ndt/gfr003
Advance Access publication 16 February 2011

Introduction of the CKD-EPI equation to estimate glomerular filtration rate in a Caucasian population

Jan A.J.G. van den Brand[1], Gerben A.J. van Boekel[1], Hans L. Willems[2], Lambertus A.L.M. Kiemeney[3], Martin den Heijer[3,4] and Jack F.M. Wetzels[1]

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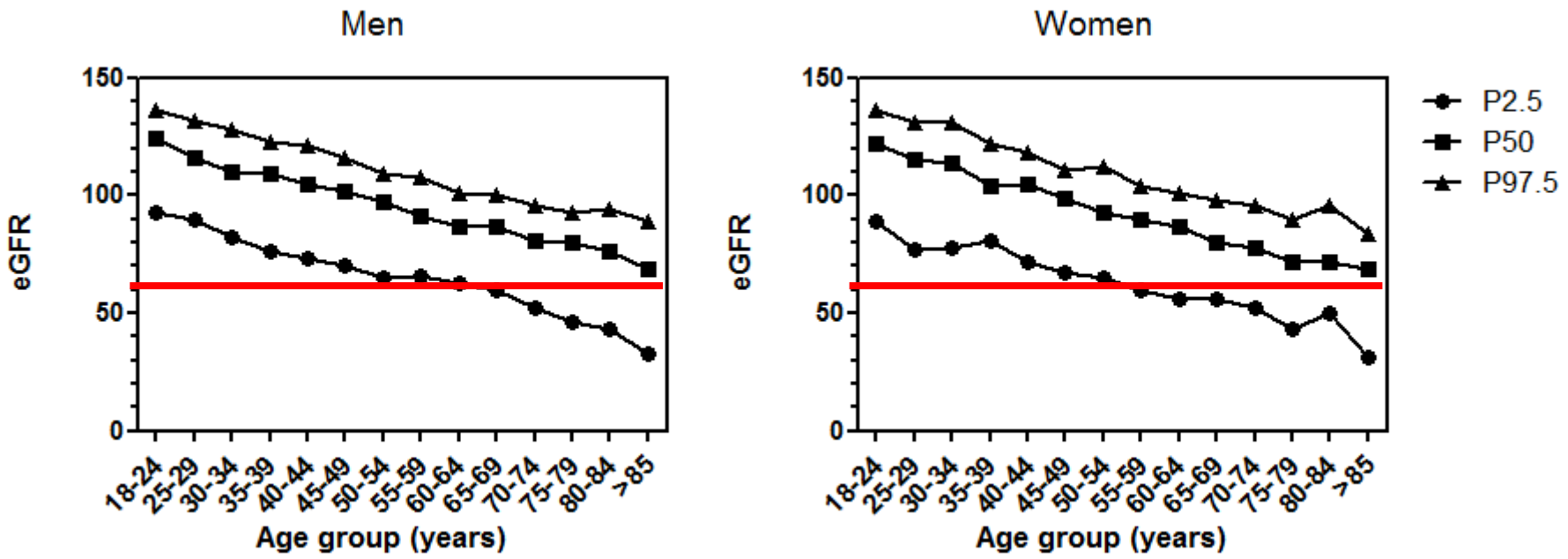

Men
Women
eGFR
150
100
50
0
18-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
>85
Age group (years)
P2.5
P50
P97.5

Déclin du DFG: étude longitudinale

- Baltimore longitudinal study
- 254 hommes « sains » suivis entre 1958 et 1985 (5 mesures ou plus)
- Clairance de créatinine
- Pente de -0,75 mL/min/an
- 1/3 ont un DFG stable

Lindeman RD, J Am Geriatr Soc, 1985, p278

Déclin du DFG: quand? Combien?

- Débattu dans la littérature
- Continuellement depuis 20 ans
- A partir de 40-50 ans
- A partir de 20 ans puis cela s'accélère vers 40-50 ans
- 6 à 12 mL/min/1.73m² par décade

Delanaye P, Nephrol Dial Transplant, 2012, p2664

Modifications anatomiques

Roseman DA, Nephrol Dial Transplant, 2017, p1344

- Volume rénal par IRM
- 1852 sujets Framingham
- -16 cm³/décade
- Age même après ajustement

Age group	Women		Men	
	n	TKV (cm^3)	*n*	TKV (cm^3)
Overall	981	271 (217, 352)	871	360 (289, 447)
<50 years	53	288 (239, 373)	59	363 (301, 450)
50–59 years	308	284 (230, 368)	241	375 (307, 461)
60–69 years	343	270 (216, 348)	321	366 (297, 454)
≥70 years	277	256 (201, 322)	250	339 (265, 424)

TKV, total kidney volume.

Wang X, Kidney Int, 2014, p677

- Volume rénal par CT-Scan
- 1344 donneurs vivants potentiels
- -22 cm³/décade après 50 ans
- Volume cortical qui diminue
- Parallèlement à diminution DFG

Table 4 | Change in kidney cortical, medullary, and parenchymal volume by age

Kidney volumes	Age <50 years	Age >50 years	Test for change in slope before and after the age of 50 years[a]
Cortical volume	*cc per decade (P-value)*	*cc per decade (P-value)*	*P-value*
Women	−5.6 (0.006)	−17.7 (<0.0001)	0.002
Men	−4.5 (0.07)	−17.9 (0.004)	0.04
Cortical volume per BSA	*cc/m² per decade (P-value)*	*cc/m² per decade (P-value)*	*P-value*
Women	−3.7 (0.0002)	−7.8 (<0.0001)	0.04
Men	−3.2 (0.002)	−9.2 (0.001)	0.07
Medullary volume	*cc per decade (P-value)*	*cc per decade (P-value)*	*P-value*
Women	2.8 (0.008)	−6.1 (0.006)	0.0001
Men	5.1 (0.0004)	0.7 (0.83)	0.25
Medullary volume per BSA	*cc/m² per decade (P-value)*	*cc/m² per decade (P-value)*	*P-value*
Women	1.4 (0.01)	−2.6 (0.04)	0.003
Men	2.0 (0.0006)	0.2 (0.88)	0.41
Parenchymal volume	*cc per decade (P-value)*	*cc per decade (P-value)*	*P-value*
Women	−2.7 (0.32)	−22.6 (<0.001)	0.0002
Men	1.4 (0.68)	−22.7 (0.002)	0.004
Parenchymal volume per BSA	*cc/m² per decade (P-value)*	*cc/m² per decade (P-value)*	*P-value*
Women	−2.2 (0.07)	−9.8 (<0.001)	0.005
Men	−0.8 (0.51)	−10.3 (0.0008)	0.01

Abbreviation: BSA, body surface area.
[a]Based on modeling age as a linear spline with a knot at the age of 50 years.

Hommos MS, J Am Soc Nephrol, 2017, p2838

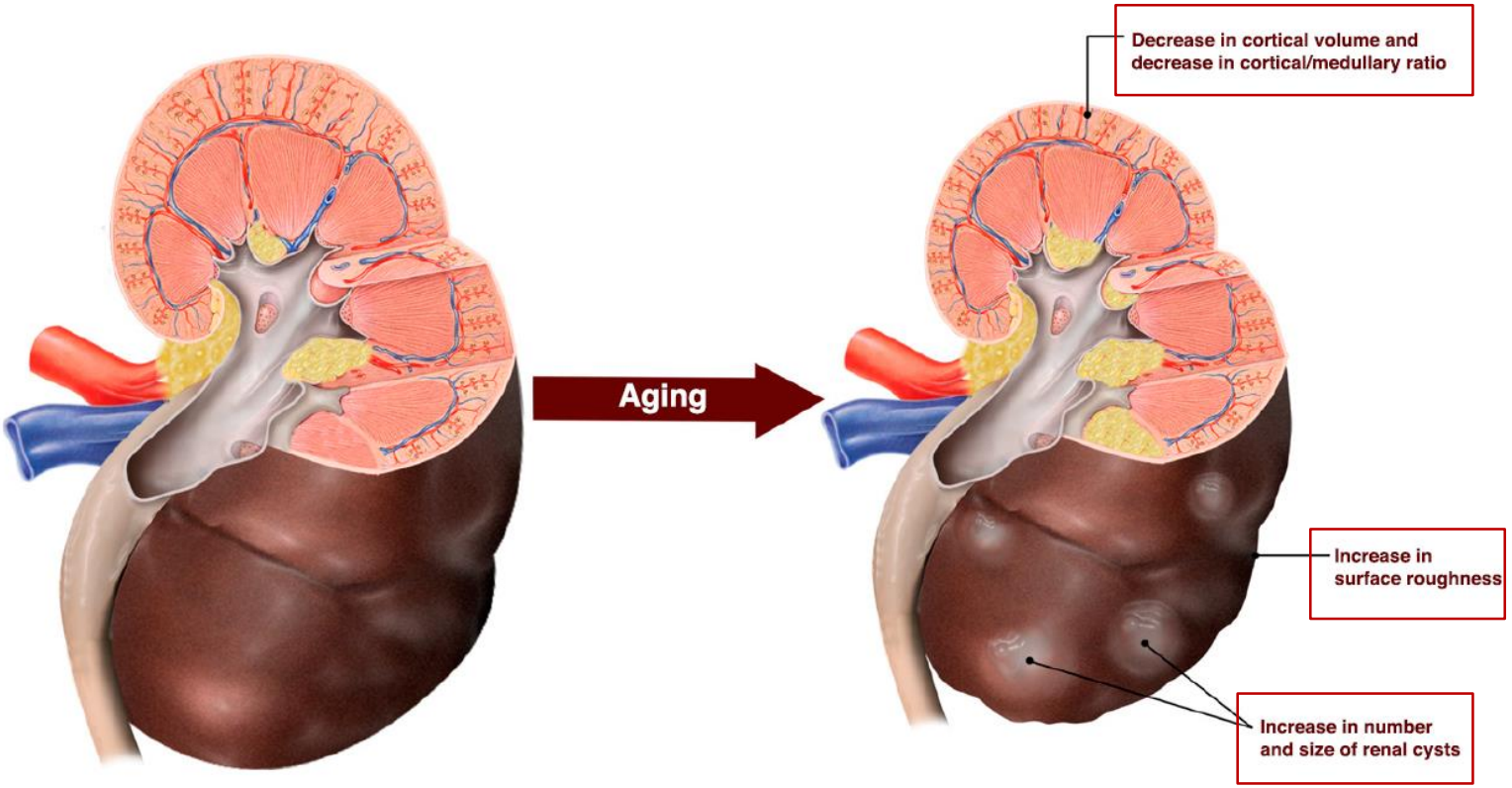


Figure 2. There are degenerative macro-structural changes that occur in the human kidney with even healthy aging. There is cortical volume loss, some increase in medullary volume (not shown), increase in surface roughness, increased sinus fat, and an increase in renal cysts. These findings can be attributed to underlying nephrosclerosis with nephron loss, hypertrophy of remaining tubules, and tubular diverticuli.

Hommos MS, J Am Soc Nephrol, 2017, p2838

Données physiologiques récentes

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Single-Nephron Glomerular Filtration Rate in Healthy Adults

Aleksandar Denic, M.D., Ph.D., Jerry Mathew, M.D.,
Lilach O. Lerman, M.D., Ph.D., John C. Lieske, M.D., Joseph J. Larson, B.S.,
Mariam P. Alexander, M.D., Emilio Poggio, M.D., Richard J. Glassock, M.D.,
and Andrew D. Rule, M.D.

N Engl J Med 2017;376:2349-57.
DOI: 10.1056/NEJMoa1614329

- 1988 donneurs à la Mayo Clinic
- Biopsie rénale au moment du don
- Mesure du DFG par iothalamate et Ct-Scan C+ avec mesure épaisseur corticale avant le don
- Densité des glomérules non sclérotiques x volume cortical = nombre de néphron
- DFG mesuré/nbr de néphron = « Single nephron GFR »

Denic A, N Engl J Med, 2017, p2349

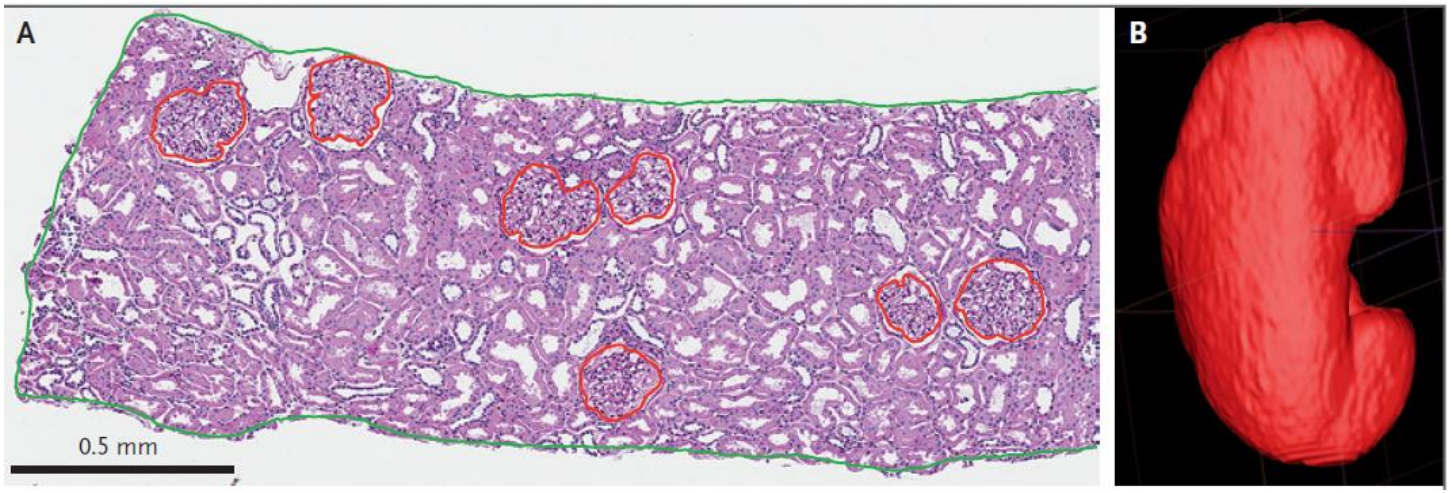


Table 2. Age-Group Differences in the Number of Nephrons per Kidney, the Single-Nephron GFR, and Total GFR among 1388 Living Kidney Donors.

Age Group	No. of Donors	No. of Nephrons	Single-Nephron GFR	Total GFR
			nl/min	*ml/min*
18–29 yr	190	970,000±430,000	79±42	127±25
30–39 yr	339	930,000±350,000	77±36	124±24
40–49 yr	417	850,000±360,000	81±42	114±23
50–59 yr	300	810,000±360,000	80±40	106±20
60–64 yr	73	750,000±310,000	79±36	101±18
65–69 yr	56	720,000±260,000	76±33	95±17

Table 3. Demographic and Clinical Characteristics as Predictors of the Number of Nephrons per Kidney, Single-Nephron GFR, and Total GFR.*

Characteristic	No. of Nephrons		Single-Nephron GFR		Total GFR	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
			nl/min		*ml/min*	
Age, per 10 yr	–60,000	<0.001	1	0.28	–7.1	<0.001
Female sex	–60,000	0.03	6	0.08	–3.8	0.01
Body-mass index, per SD	0	0.85	6	<0.001	9.6	<0.001
Height, per SD†	30,000	0.03	4	0.006	9.2	<0.001
Uric acid, per SD	–40,000	0.002	1	0.42	–3.7	<0.001
Family history of end-stage renal disease	–70,000	<0.001	8	<0.001	0.8	0.43
Mild hypertension	–20,000	0.59	3	0.39	1.5	0.36

* The estimate is the difference with the presence of the characteristic versus its absence (female sex vs. male sex; presence vs. absence of family history of end-stage renal disease; and mild hypertension vs. no hypertension) or with the level increase of the characteristic (for age, body-mass index, height, and uric acid level). The standard deviation (SD) was 4.9 for body-mass index, 9.5 cm for height, and 1.4 mg per deciliter (80 μmol per liter) for uric acid. The analysis was adjusted for each of the other demographic or clinical characteristics in the 1388 donors.

† Statistical significance for the single-nephron GFR was influenced by donors with a height of more than 190 cm.

- Glomerulosclérose augmente avec l'âge (1/20 glomérule à 20 et 5,5 à 70 ans)
- Diminution du nombre de glomérules
- Taille des glomérules reste la même
- Single nephron GFR ne se modifie pas
- Pourquoi? Parce que les besoins physiologiques du rein diminuent avec l'âge?

C'est la situation physiologique
Si HTA, diabète et/ou obésité=> augmentation de la taille des glomérules pour compenser la fibrose plus importante

Denic A, N Engl J Med, 2017, p2349

Sénescence tubulaire et endocrinienne

- Le débit plasmatique diminue aussi avec l'âge (de 50% entre 20 et 90ans)
- Diminution du nombre de tubules et fibrose
- Protéinurie stable ou augmente tout en restant dans les normes
- Diminution dans la capacité à concentrer ou diluer les urines
- Equilibre sodé maintenu mais réponse aux modification plus lentes
- Potassium: diminution capacité sécrétoire distale (diminution NA/K ATPase, et diminution aldo)
- Diminution modérée de l'ammoniogénèse dans le tube proximal et de l'activité de H+ ATPase du tube collecteur
- Concentration plus basse d'aldostérone, diminution synthèse 1 alpha hydroxylase et de klotho

Davies DF, J Clin Invest, 1950, p496
Gekle M, Exp Gerontol, 2017, p153
Bolignano D, Ageing Res Rev, 2014, p65

Mécanismes biologiques de la sénescence rénale

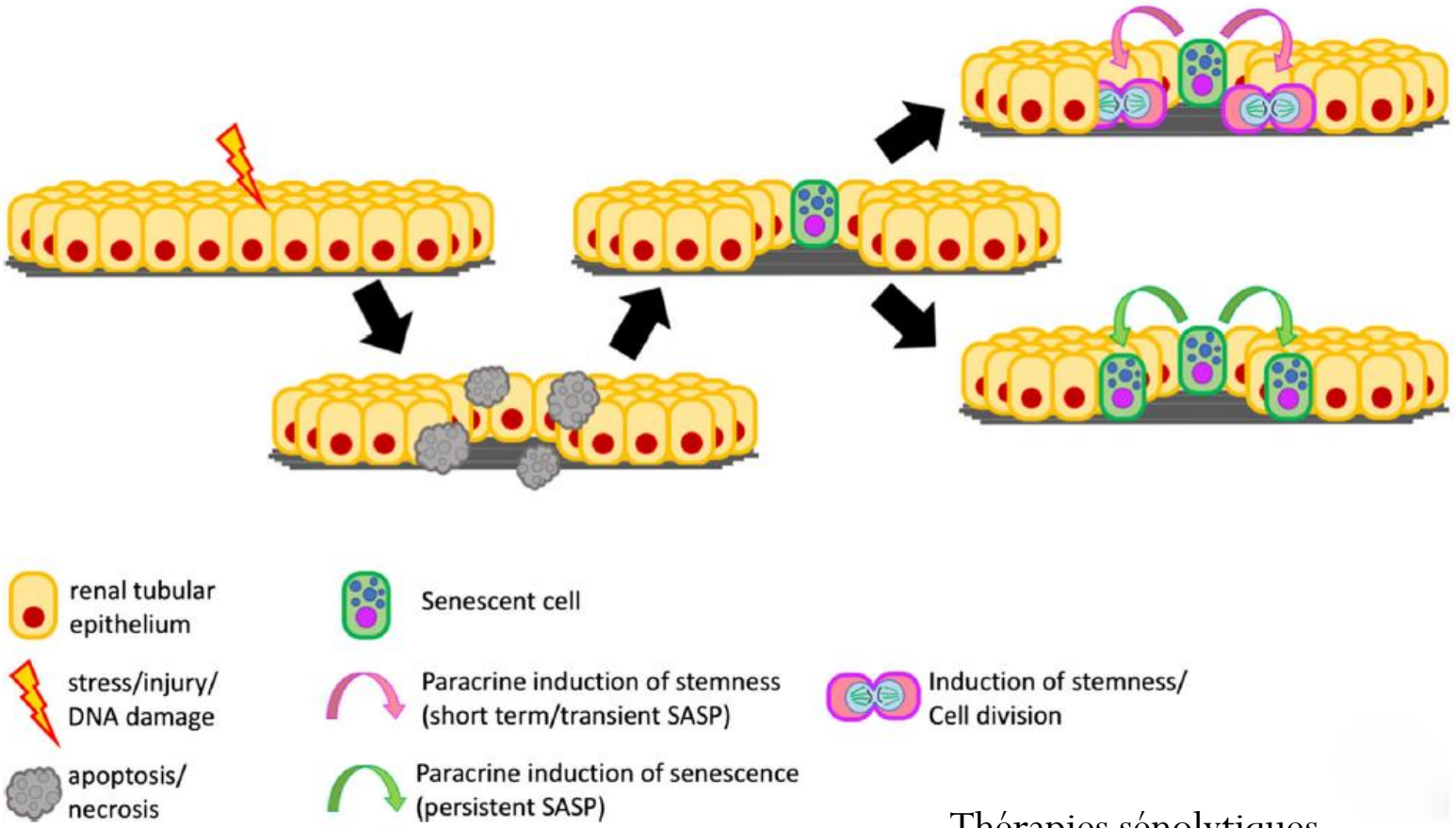


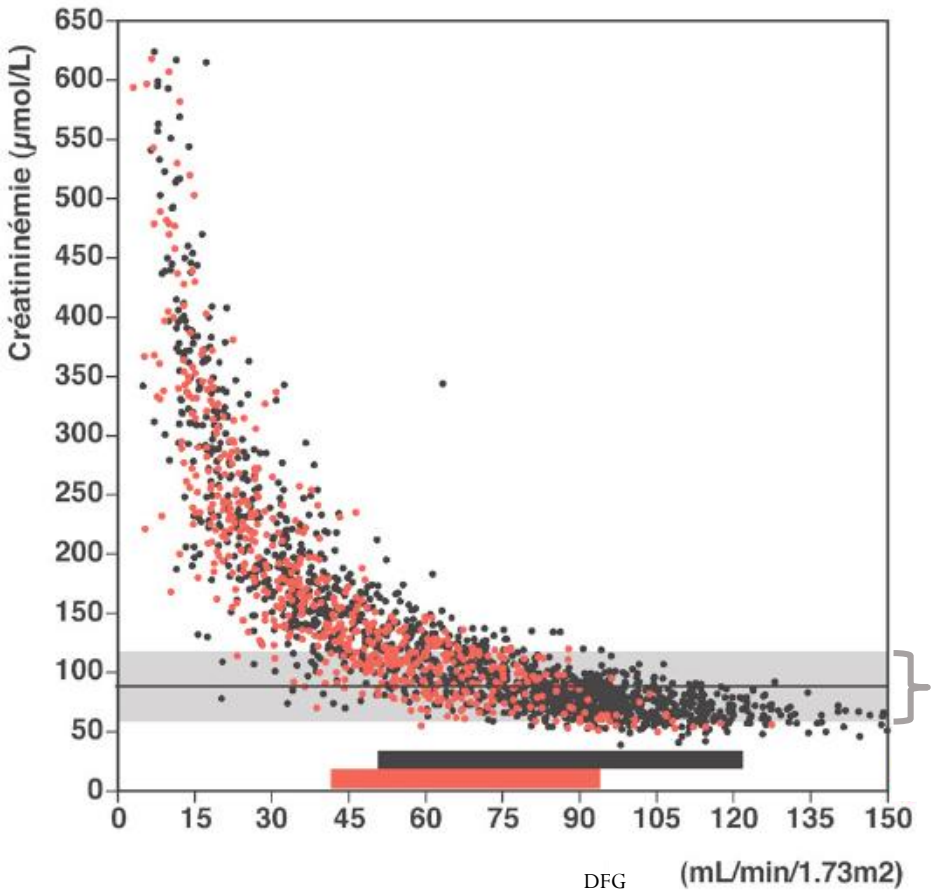
Fig. 3 Paracrine effects of senescent cells in early and late phases of tissue injury

Thérapies sénolytiques…

Valentijn FA, J Cell Commun Signal, 2018, ePUB
Bitzer M, Adv Chron Kidney Dis, 2016, p12

Estimation du DFG chez le sujet âgé

- DFG mesuré diminue avec l'âge
- Les valeurs normales de créatinine sérique ne changent pas avec l'âge (cystatine C)
- Pourquoi? Dépendance à la masse musculaire
- Implication? Il faut un facteur âge dans l'équation



NephroTest Cohort (France)
Quel DFG correspond à une créatinine de 80 µmol/L (0.9 mg/dL)?

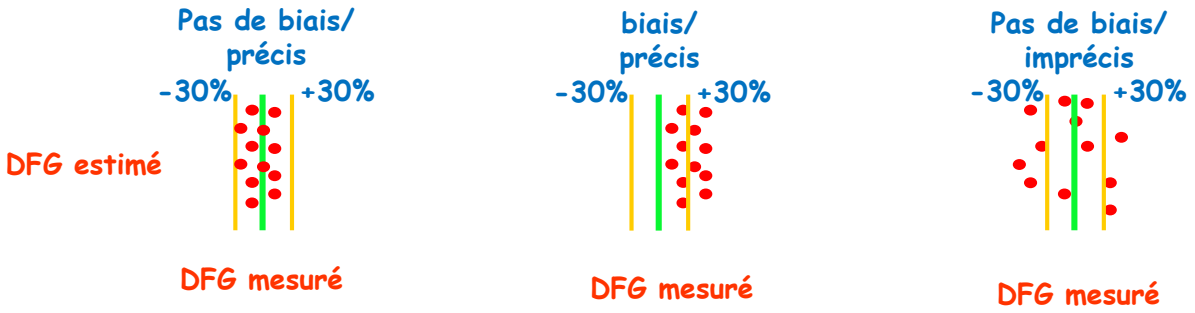
IC 95% pour sujets<65 ans
IC 95% pour sujets>65 ans

Valeurs normales de créatinine

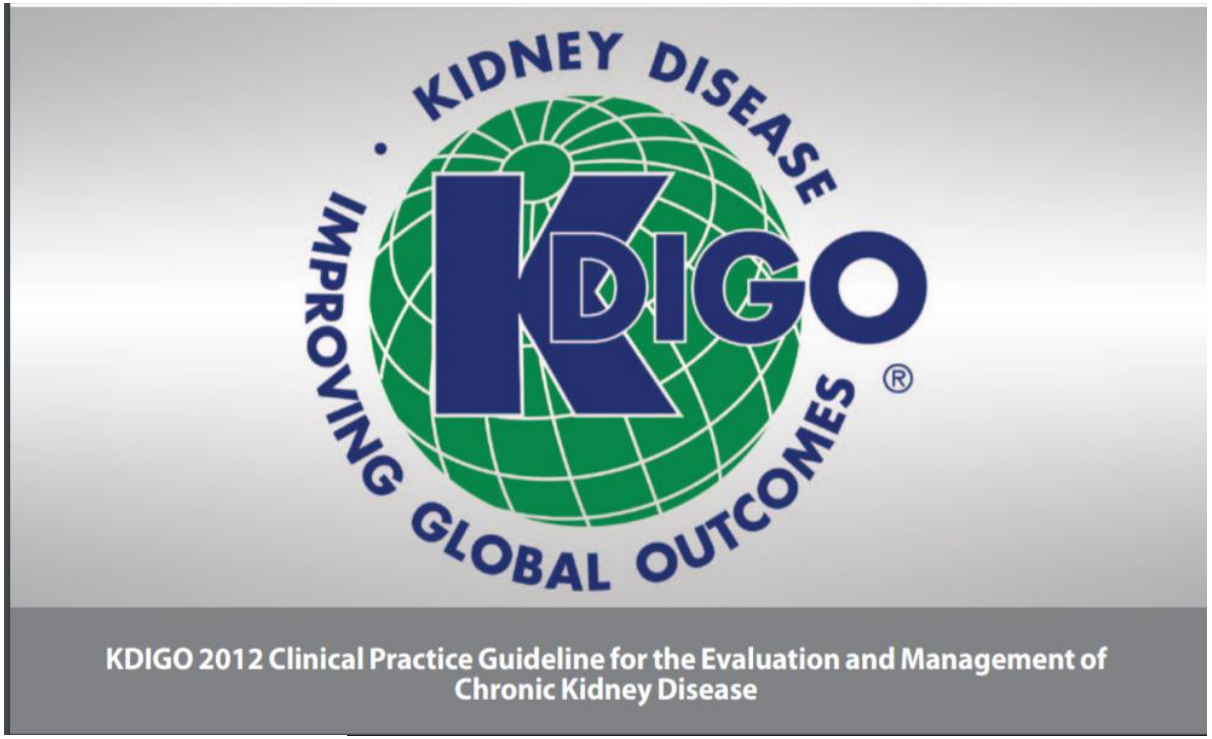
Avec l'aimable permission de Marc Froissart

Statistiques

- corrélation: une condition "*sine qua non*" mais insuffisante!
- Biais: différence moyenne entre 2 valeurs = erreur systématique
- Précision: SD autour de ce biais = erreur aléatoire
- Exactitude 30% = % du DFG estimée dans ± 30% du DFG mesuré



Bland JM, Altman DG, Lancet, 1986, 8476, 307
Delanaye P, Nephrol Dial Transplant, 2013, 28, 1396



Kidney International Supplements (2013) **3,** 3; doi:10.1038/kisup.2012.75

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- report $eGFR_{creat}$ in adults using the 2009 CKD-EPI creatinine equation. An alternative creatinine-based GFR estimating equation is acceptable if it has been shown to improve accuracy of GFR estimates compared to the 2009 CKD-EPI creatinine equation.

Cockcroft and Gault

$$\text{GFR (ml/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{7.2 \times \text{SCr (mg/dl)}} \times 0.85 \text{ if woman}$$

4-Variable MDRD study equation (IDMS traceable)

$$\text{GFR (ml/min/1.73 m}^2) = 175 \times \text{SCr (mg/dl)}^{-1.154} \times \text{age}^{-0.203} \times 0.742 \text{ (if woman)} \times 1.21 \text{ for Black-American}$$

Table 2. **The CKD-EPI Equation for Estimating GFR on the Natural Scale***

Race and Sex	Serum Creatinine Level, *μmol/L (mg/dL)*	Equation
Black		
Female	≤62 (≤0.7)	$GFR = 166 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 166 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 163 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 163 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$
White or other		
Female	≤62 (≤0.7)	$GFR = 144 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 144 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 141 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 141 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$

Annals of Internal Medicine | ORIGINAL RESEARCH

Two Novel Equations to Estimate Kidney Function in Persons Aged 70 Years or Older

Elke S. Schaeffner, MD, MS*; Natalie Ebert, MD, MPH*; Pierre Delanaye, MD, PhD; Ulrich Frei, MD; Jens Gaedeke, MD; Olga Jakob; Martin K. Kuhlmann, MD; Mirjam Schuchardt, PhD; Markus Tölle, MD; Reinhard Ziebig, PhD; Markus van der Giet, MD; and Peter Martus, PhD

BIS1:

$3736 \times \text{créatinine}^{-0.87} \times \text{age}^{-0.95} \times 0.82$ (si femme)

Ann Intern Med. 2012;157:471-481

CKD-EPI Equation *vs* BIS Equation

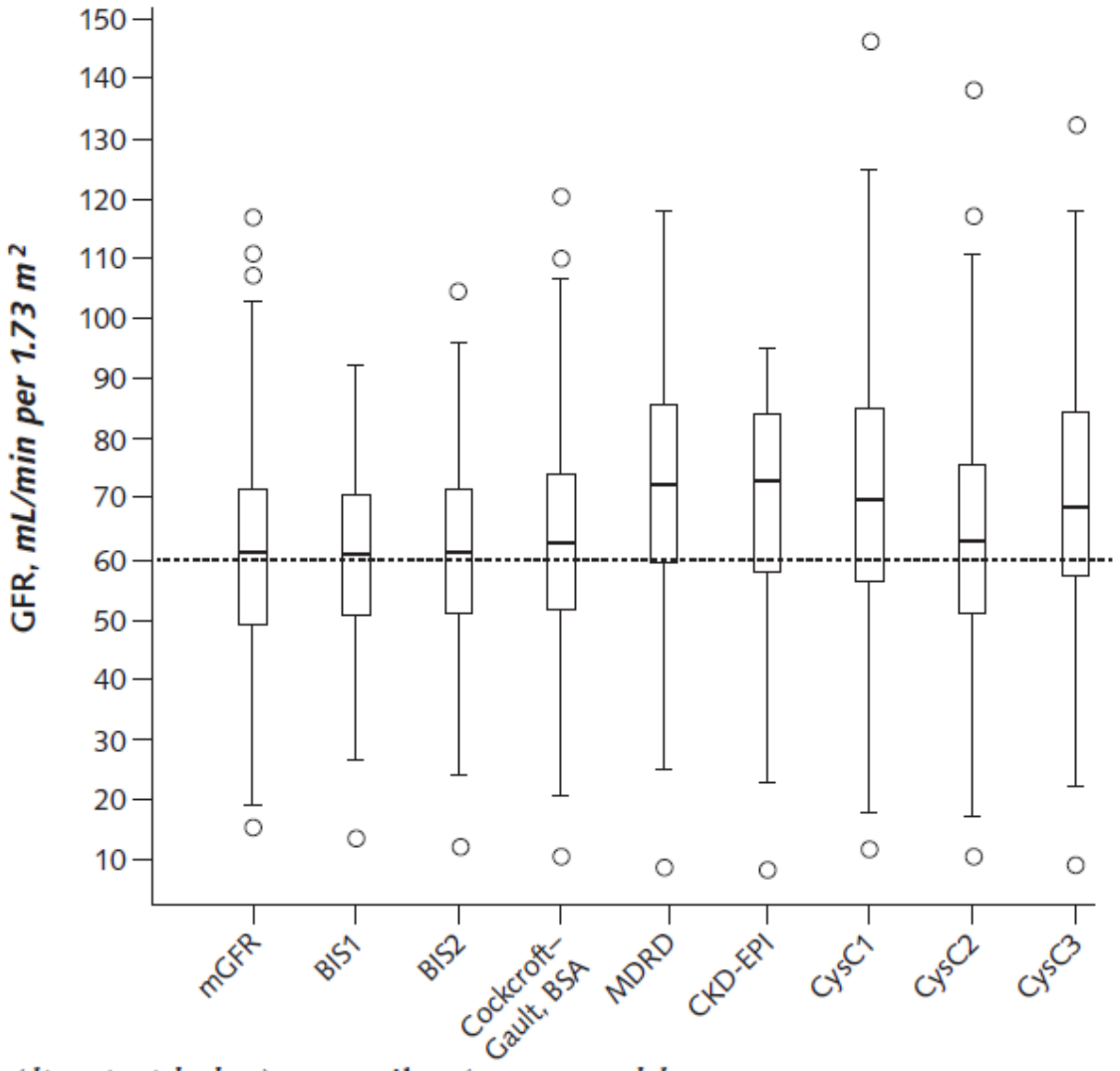
n=5504

- Mean Age: 47
- Mean GFR: 68 ml/min/1.73m^2
- Reference: Iothalamate
- Creatinine Assay: Multiple – recalibration

n=570

- Mean Age: 78.5
- Mean GFR: 60 ml/min/1.73m^2
- Reference: Iohexol
- Creatinine Assay:
- IDMS - Enzymatic

Figure 1. **Comparison of mGFR with eGFR equations in the validation sample.**



Boxes indicate medians (*line inside box*), quartiles (*upper and lower margins of box*). Antennae are defined by the rule upper–lower box margin ± 1.5 × interquartile range. Circles indicate outliers.

COMPARATIVE ACCURACY-30%
- CKD-EPI vs BIS -

- *Koppe L et al. J Nephrol, 2013*
  - **n=224, Mean Age=75** 72% vs 76%
- *Lopes M et al. BMC Nephrology, 2013*
  - **n=95, Mean Age=85** 75% vs 80%
- *Alshoer I et al. AJKD, 2014*
  - **n=394, Median Age=80** 83% vs 88%
- *Vidal-Petiot E et al. AJKD, 2014*
  - **N=609, Mean Age=76** 82% vs 84%

Comparing GFR Estimating Equations Using Cystatin C and Creatinine in Elderly Individuals

Li Fan,*† Andrew S. Levey,* Vilmundur Gudnason,‡§ Gudny Eiriksdottir,‡ Margret B. Andresdottir,‖ Hrefna Gudmundsdottir,§‖ Olafur S. Indridason,‖ Runolfur Palsson,§‖ Gary Mitchell,¶ and Lesley A. Inker*

J Am Soc Nephrol 26: 1982–1989, 2015.

N=805
+74 y

Equation	Bias Median Difference	Precision IQR	Accuracy P_{30}
eGFRcr			
CKD-EPI	−2.7 (−3.3 to −2.1)	12.1 (11.2 to 13.4)	91.7 (89.9 to 93.4)
Japanese	10.5 (9.8 to 11.2)[c]	10.9 (9.7 to 12.1)[a]	86.3 (83.9 to 88.6)[c]
BIS	5.7 (5.1 to 6.4)[c]	11.9 (10.6 to 12.7)[a]	95.8 (94.4 to 97.1)[b]

[a]No different than CKD-EPI.
[b]Better than CKD-EPI.
[c]Worse than CKD-EPI.

Ulf Nyman*, Anders Grubb, Anders Larsson, Lars-Olof Hansson, Mats Flodin, Gunnar Nordin, Veronica Lindström and Jonas Björk

The revised Lund-Malmö GFR estimating equation outperforms MDRD and CKD-EPI across GFR, age and BMI intervals in a large Swedish population

Clin Chem Lab Med 2014, 52(6), 815-824

Revised Lund-Malmö Study equation (LM Revised) [34]

$e^{X-0.0158\times Age+0.438\times \ln(Age)}$

Female	pCr<150 µmol/L:	$X=2.50+0.0121\times(150-pCr)$
Female	pCr≥150 µmol/L:	$X=2.50-0.926\times\ln(pCr/150)$
Male	pCr<180 µmol/L:	$X=2.56+0.00968\times(180-pCr)$
Male	pCr≥180 µmol/L:	$X=2.56-0.926\times\ln(pCr/180)$

- Lund-Malmo study
- n=3495 (chez 2847 sujets), iohexol, créatinine standardisée
- DFG moyen = 52 mL/min/1,73 m²

Nephrol Dial Transplant (2016) 31: 798–806
doi: 10.1093/ndt/gfv454
Advance Access publication 29 February 2016

An estimated glomerular filtration rate equation for the full age spectrum

Hans Pottel[1], Liesbeth Hoste[1], Laurence Dubourg[2], Natalie Ebert[3], Elke Schaeffner[3], Bjørn Odvar Eriksen[4], Toralf Melsom[4], Edmund J. Lamb[5], Andrew D. Rule[6], Stephen T. Turner[6], Richard J. Glassock[7], Vandréa De Souza[8], Luciano Selistre[9], Christophe Mariat[10], Frank Martens[11] and Pierre Delanaye[12]

Example 1: A healthy 18-year-old male with a body height (L) of 180 cm and SCr of 0.90 mg/dL:

Paediatric equation (Schwartz): $eGFR = 0.413 \times L/SCr = 0.413 \times 180/0.90 = 83$ mL/min/1.73 m^2.

Adult equation (CKD-EPI): $eGFR = 141 \times (0.90/0.90)^{-1.209} 0.993^{18} = 124$ mL/min/1.73 m^2.

+50%

N=6870, 735 children

Nephrol Dial Transplant (2017) 1–9
doi: 10.1093/ndt/gfx272

ndt
Nephrology Dialysis Transplantation

Comparison of glomerular filtration rate estimating equations derived from creatinine and cystatin C: validation in the Age, Gene/Environment Susceptibility-Reykjavik elderly cohort

Jonas Björk[1,2], Anders Grubb[3], Vilmundur Gudnason[4,7], Olafur S. Indridason[5], Andrew S. Levey[6], Runolfur Palsson[5,7] and Ulf Nyman[8]

[1]Clinical Studies Sweden, Forum South, Skåne University Hospital, Lund, Sweden, [2]Division of Occupational and Environmental Medicine, Lund University, Lund, Sweden, [3]Department of Clinical Chemistry, Skåne University Hospital, Lund University, Lund, Sweden, [4]Icelandic Heart Association, Kopavogur, Iceland, [5]Division of Nephrology, Landspitali–The National University Hospital of Iceland, Reykjavik, Iceland, [6]Division of Nephrology, Tufts Medical Center, Boston, Massachusetts, USA, [7]University of Iceland, Reykjavik, Iceland and [8]Department of Translational Medicine, Division of Medical Radiology, Lund University, Malmö, Sweden

Table 2. Bias (median eGFR−mGFR, mL/min/1.73 m^2), precision (IQR, mL/min/1.73 m^2), absolute accuracy (median, percent) and P_{30} accuracy (percentage of GFR estimated within 30% of mGFR) of GFR estimating equations based on creatinine and the combination of creatinine and cystatin C in the AGES-Kidney cohort ($n = 805$)

Variables	LMR_{Cr}	FAS_{Cr}	$CKD\text{-}EPI_{Cr}$	$MEAN_{LMR+CAPA}$	FAS_{Cr+Cys}	$CKD\text{-}EPI_{Cr+Cys}$
Bias	−4.8 (−5.4 to − 4.2)[a]	−5.7 (−6.3 to − 5.1)[a]	2.7 (2.1 to 3.3)	−2.7 (−3.2 to − 2.1)[a]	−5.9 (−6.5 to − 5.4)[a]	0.6 (−0.1 to 1.2)
Precision	10.8 (10.1 to 11.5)[b]	10.7 (9.9 to 11.9)[b]	12.1 (11.2 to 13.4)	9.3 (8.5 to 10.1)[c]	10.0 (9.1 to 10.9)[c]	10.2 (9.0 to 11.1)
Absolute accuracy	11.4 (10.3 to 12.3)[c]	12.1 (11.1 to 13.2)[a]	10.2 (9.3 to 11.0)	8.5 (8.0 to 9.2)[c]	11.3 (10.5 to 12.3)[a]	8.1 (7.5 to 8.9)
P_{30} accuracy	95.0 (93.5 to 96.5)[b]	95.8 (94.4 to 97.2)[b]	91.7 (89.9 to 93.4)	97.3 (96.2 to 98.4)[b]	97.8 (96.7 to 98.8)[b]	96.1 (94.8 to 97.4)

Data are presented with 95% CIs.
[a]Significantly worse ($P < 0.05$) than corresponding CKD-EPI equation.
[b]Significantly better ($P < 0.05$) than corresponding CKD-EPI equation.
[c]No statistical difference ($P \geq 0.05$) compared with corresponding CKD-EPI equation.

Jonas Björk, Sten Erik Bäck, Natalie Ebert, Marie Evans, Anders Grubb, Magnus Hansson, Ian Jones, Edmund J. Lamb, Peter Martus, Elke Schaeffner, Per Sjöström and Ulf Nyman*

GFR estimation based on standardized creatinine and cystatin C: a European multicenter analysis in older adults

5 cohortes > 70 y

Créatinine

Biais: pire pour CKD-EPI

Précision: mieux pour LM et FAS

Exactitude: LM>FAS>CKD-EPI

Cystatine C

Pas de différence avec créat

Combinée

+5 to 10% comparée à la créatinine

LM+CAPA légèrement meilleures

Table 2: Bias, precision and accuracy (95% confidence intervals) of creatinine, cystatin C and combined-marker equations in adults ≥70 years.

Equations	Bias	Precision	Absolute accuracy	P_{15} accuracy	P_{30} accuracy
Creatinine (n = 3226)					
BIS1	1.7 (1.2 to 2.0)	11.6 (11.1–12.1)	14.8 (14.1–15.5)	50.7 (48.9–52.4)	77.5 (76.1–78.9)
BIS1 (no Berlin data, n = 2569)	2.0 (1.6 to 2.4)	11.6 (11.1–12.1)	16.3 (15.5–17.1)	46.6 (44.7–51.1)	73.8 (72.1–75.5)
CKD-EPI	3.6 (3.2 to 4.0)	12.3 (11.9–13.0)	16.3 (15.6–17.0)	46.3 (44.6–48.0)	76.4 (74.9–77.9)
FAS	0.6 (0.3 to 0.9)	11.1 (10.6–11.5)	14.0 (13.4–14.5)	53.3 (51.5–55.0)	80.9 (79.5–82.3)
LMR	−0.7 (−1.0 to −0.4)	10.5 (10.1–11.0)	13.8 (13.3–14.3)	54.2 (52.4–55.9)	83.5 (82.2–84.8)
LMR (no Lund data, n = 2309)	−1.0 (−1.5 to −0.6)	11.0 (10.5–11.6)	13.9 (13.3–14.4)	53.9 (51.8–55.9)	83.7 (82.2–85.2)
Cystatin C (n = 2638)					
CAPA	−1.4 (−1.8 to −1.0)	11.9 (11.3–12.6)	15.7 (14.9–16.5)	48.2 (46.3–50.1)	80.3 (78.8–81.8)
CAPA (no Lund data, n = 1721)	1.0 (0.5 to 1.6)	13.1 (12.3–13.8)	14.1 (13.3–15.0)	52.3 (49.9–54.7)	82.5 (80.7–84.3)
CKD-EPI	−2.7 (−3.1 to −2.3)	11.8 (11.3–12.5)	16.4 (15.7–17.1)	46.1 (44.2–48.0)	78.8 (77.3–80.4)
FAS	−1.1 (−1.6 to −0.8)	12.2 (11.7–12.8)	15.1 (14.3–16.0)	49.8 (47.9–51.8)	80.9 (79.4–82.4)
Creatinine + cystatin C (n = 2638)					
BIS2	−1.2 (−1.5 to −0.8)	10.5 (10.0–11.0)	12.1 (11.6–12.8)	58.4 (56.5–60.3)	85.7 (84.4–87.0)
BIS2 (no Berlin data, n = 1981)	−1.9 (−2.3 to −1.4)	10.9 (10.4–11.4)	14.0 (13.2–14.7)	52.7 (50.5–54.9)	82.6 (80.9–84.3)
CKD-EPI	−0.1 (−0.4 to 0.2)	10.2 (9.6–10.8)	12.8 (12.3–13.3)	56.8 (54.9–58.7)	86.8 (85.5–88.1)
FAS	−0.8 (−1.1 to −0.5)	10.1 (9.7–10.7)	12.2 (11.5–12.7)	58.7 (56.8–60.6)	85.7 (84.4–87.1)
$MEAN_{LMR+CAPA}$	−1.0 (−1.3 to −0.6)	9.2 (8.8–9.6)	11.9 (11.3–12.4)	61.4 (59.6–63.3)	88.7 (87.5–89.9)
$MEAN_{LMR+CAPA}$ (no Lund data, n = 1721)	0.1 (−0.3 to 0.6)	9.7 (9.1–10.3)	11.1 (10.6–11.8)	63.6 (61.4–65.9)	89.0 (87.5–90.5)

Median bias (eGFR–mGFR) and precision (interquartile range) expressed in mL/min/1.73 m^2, and median absolute accuracy ([eGFR–mGFR]/mGFR) expressed in percent, and P_{15} and P_{30} accuracy (percentage of GFR estimates within 15% and 30% of measured GFR).

Validité de la formule CKD-EPI et MDRD reste à prouver

chez le sujet africain âgé

Validité des nouvelles formules reste à prouver

dans le contexte africain

Valeur ajoutée de la cystatine C reste à prouver

(« cost effectiveness »?)

Dans le contexte africain

Facteur ethnique CKD/EPI - MDRD

RESEARCH LETTER

Performance of GFR Estimating Equations in African Europeans: Basis for a Lower Race Factor Than in African Americans

Flamant M et al Am J Kidney Dis, 2013, 62, p179

Néphrologie & Thérapeutique 12 (2016) 454–459

ELSEVIER

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Article original

Inadéquation du facteur ethnique pour l'estimation du débit de filtration glomérulaire en population générale noire-africaine : résultats en Côte d'Ivoire

Inadequacy of the African-American ethnic factor to estimate glomerular filtration rate in an African general population: Results from Côte d'Ivoire

Éric Sagou Yayo [a], Mireille Aye [a], Jean-Louis Konan [a], Arlette Emième [b], Marie-Laure Attoungbre [a], Appolinaire Gnionsahé [c], Étienne Cavalier [d], Dagui Monnet [a], Pierre Delanaye [e,*]

Performance of glomerular filtration rate estimation equations in Congolese healthy adults: the inopportunity of the ethnic correction.

Justine B. Bukabau[1], Ernest K. Sumaili[1], Etienne Cavalier[2], Hans Pottel[3], Bejos Kifakiou[1], Aliocha Nkodila[1], Jean Robert R. Makulo[1], Vieux M. Mokoli[1], Chantal V. Zinga[1], Augustin L. Longo[1], Yannick M. Engole[1], Yannick M. Nlandu[1], François B. Lepira[1], Nazaire M. Nseka[1], Jean Marie Krzesinski[4], Pierre Delanaye[4].

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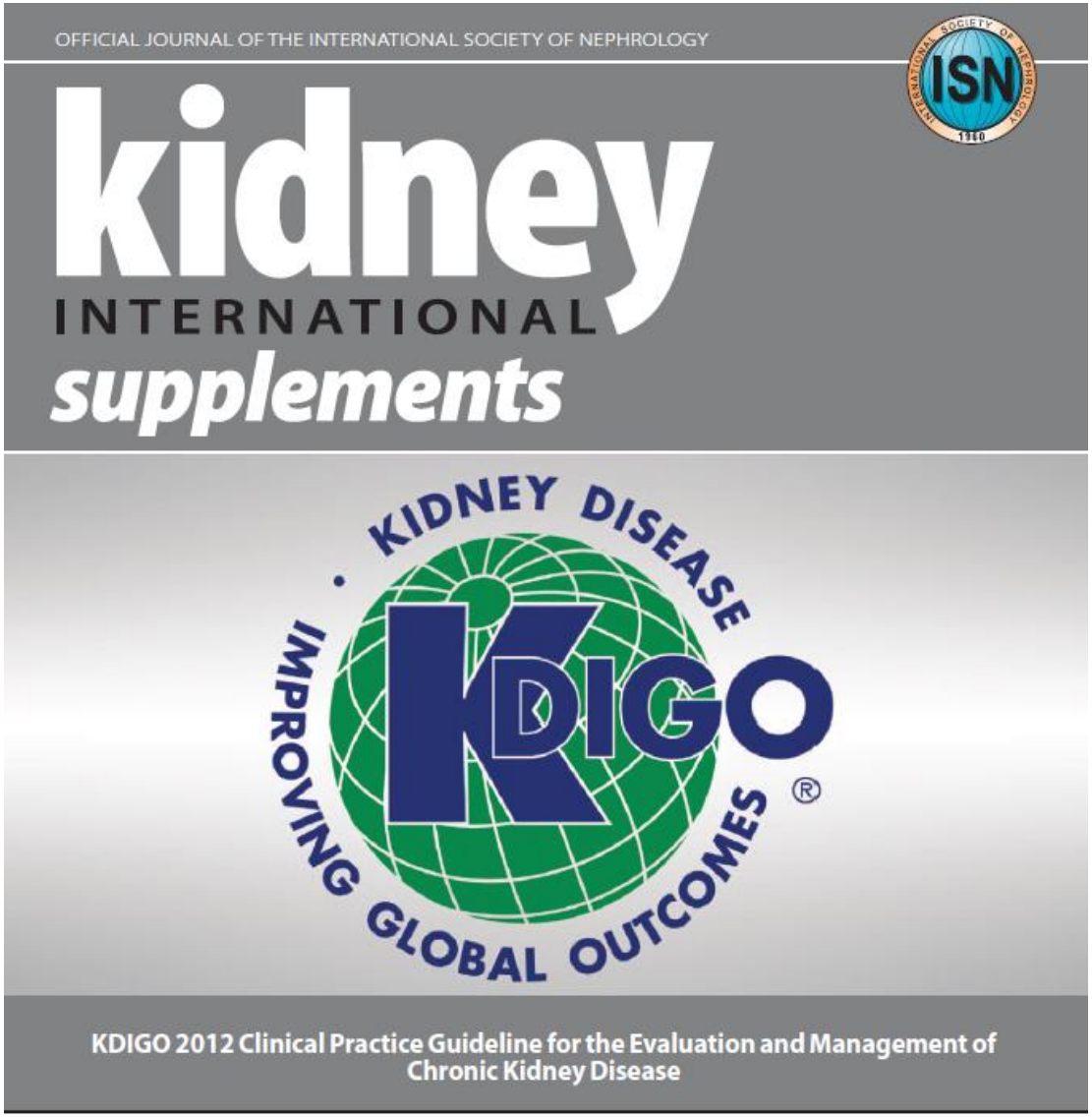
4. Division of Nephrology-Dialysis-Transplantation, University of Liège, CHU Sart Tilman (ULg CHU), Liège, Belgium

Accepté dans PlosOne

NON

DFG: “Normalité” et pathologie

- Difficile (au du moins pas si facile)
- Important


OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY
ISN
kidney
INTERNATIONAL
supplements
KIDNEY DISEASE
IMPROVING GLOBAL OUTCOMES
KDIGO
KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease
VOLUME 3 | ISSUE 1 | JANUARY 2013
http://www.kidney-international.org

GFR categories in CKD **Chronic Kidney Disease**

GFR category	GFR (ml/min/1.73 m^2)	Terms
G1	≥90	Normal or high
G2	60–89	Mildly decreased*
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.
*Relative to young adult level
In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

1.4.1: Evaluation of chronicity

1.4.1.1: In people with GFR <60 ml/min/1.73 m^2 (GFR categories G3a-G5) or markers of kidney damage, review past history and previous measurements to determine duration of kidney disease. (*Not Graded*)

- If duration is >3 months, CKD is confirmed. Follow recommendations for CKD.
- If duration is not >3 months or unclear, CKD is not confirmed. Patients may have CKD or acute kidney diseases (including AKI) or both and tests should be repeated accordingly.

60 mL/min/1.73 m²

Justification de cette valeur cible

- Moitié du DFG normal mesuré
- Simplicité
- DFG < 60 mL/min/1.73 m² est associé à une surmortalité

Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis

Caroline S Fox, Kunihiro Matsushita, Mark Woodward, Henk J G Bilo, John Chalmers, Hiddo J Lambers Heerspink, Brian J Lee, Robert M Perkins, Peter Rossing, Toshimi Sairenchi, Marcello Tonelli, Joseph A Vassalotti, Kazumasa Yamagishi, Josef Coresh, Paul E de Jong, Chi-Pang Wen, Robert G Nelson, for the Chronic Kidney Disease Prognosis Consortium

Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without hypertension: a meta-analysis

Bakhtawar K Mahmoodi, Kunihiro Matsushita, Mark Woodward, Peter J Blankestijn, Massimo Cirillo, Takayoshi Ohkubo, Peter Rossing, Mark J Sarnak, Bénédicte Stengel, Kazumasa Yamagishi, Kentaro Yamashita, Luxia Zhang, Josef Coresh, Paul E de Jong, Brad C Astor, for the Chronic Kidney Disease Prognosis Consortium

ONLINE FIRST

Age and Association of Kidney Measures With Mortality and End-stage Renal Disease

BMJ 2013;346:f324 doi: 10.1136/bmj.f324 (Published 29 January 2013)

RESEARCH

Associations of estimated glomerular filtration rate and albuminuria with mortality and renal failure by sex: a meta-analysis

Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis

*Chronic Kidney Disease Prognosis Consortium**

Lancet 2010; 375: 2073–81

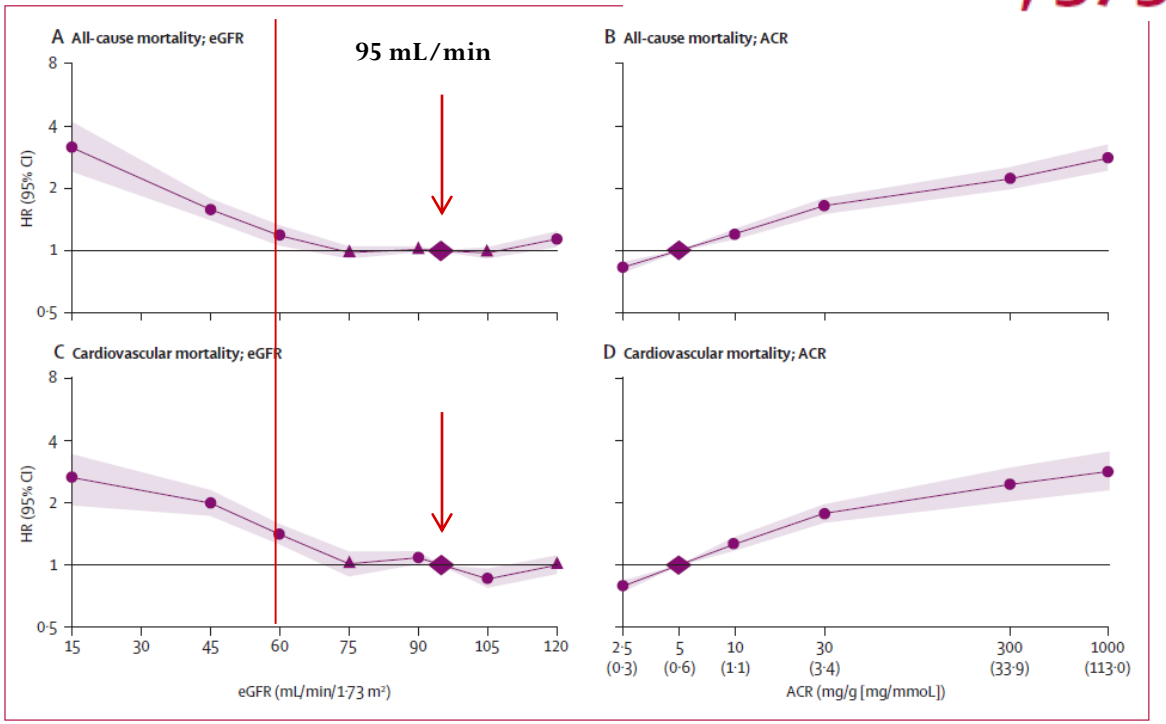


Figure 2: **Hazard ratios and 95% CIs for all-cause and cardiovascular mortality according to spline estimated glomerular filtration rate (eGFR) and albumin-to-creatinine ratio (ACR)**

Hazard ratios and 95% CIs (shaded areas) according to eGFR (A, C) and ACR (B, D) adjusted for each other, age, sex, ethnic origin, history of cardiovascular disease, systolic blood pressure, diabetes, smoking, and total cholesterol. The reference (diamond) was eGFR 95 mL/min/1·73 m² and ACR 5 mg/g (0·6 mg/mmol), respectively. Circles represent statistically significant and triangles represent not significant. ACR plotted in mg/g. To convert ACR in mg/g to mg/mmol multiply by 0·113. Approximate conversions to mg/mmol are shown in parentheses.

- 105,872 sujets de 14 études avec ACR
- 1,128,310 sujets de 7 études avec tigette

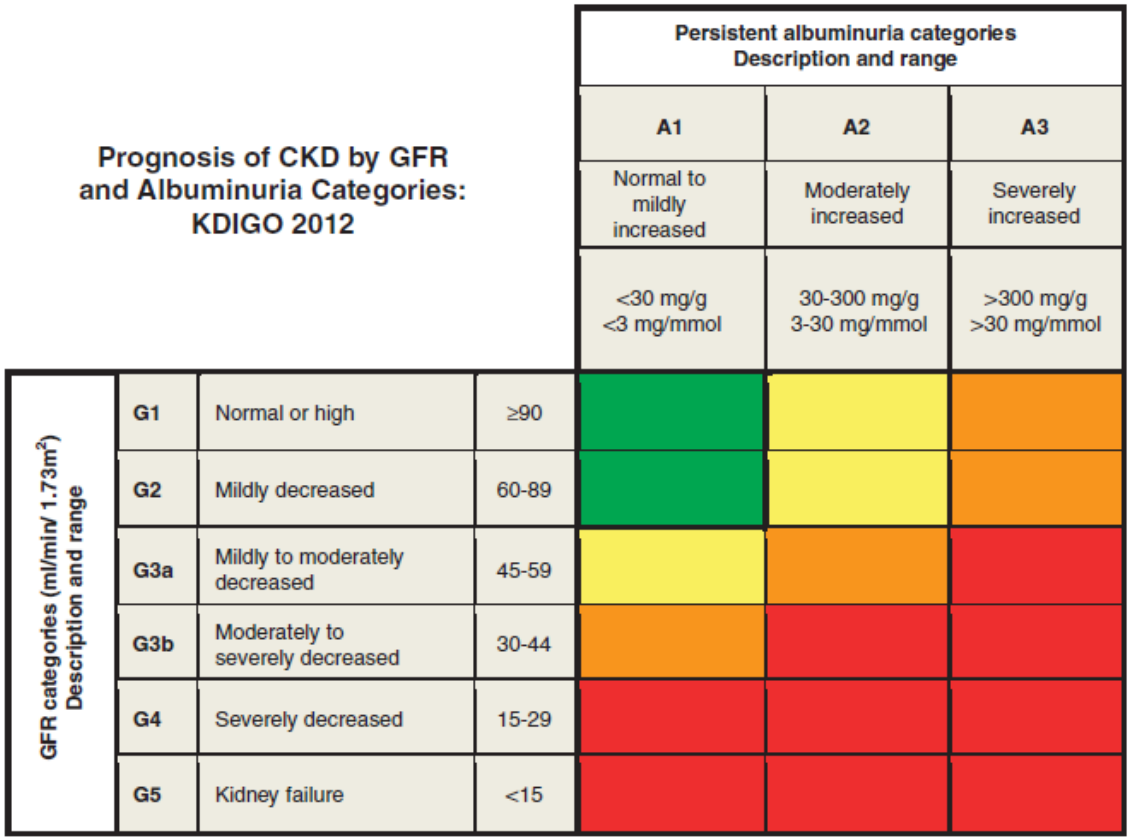
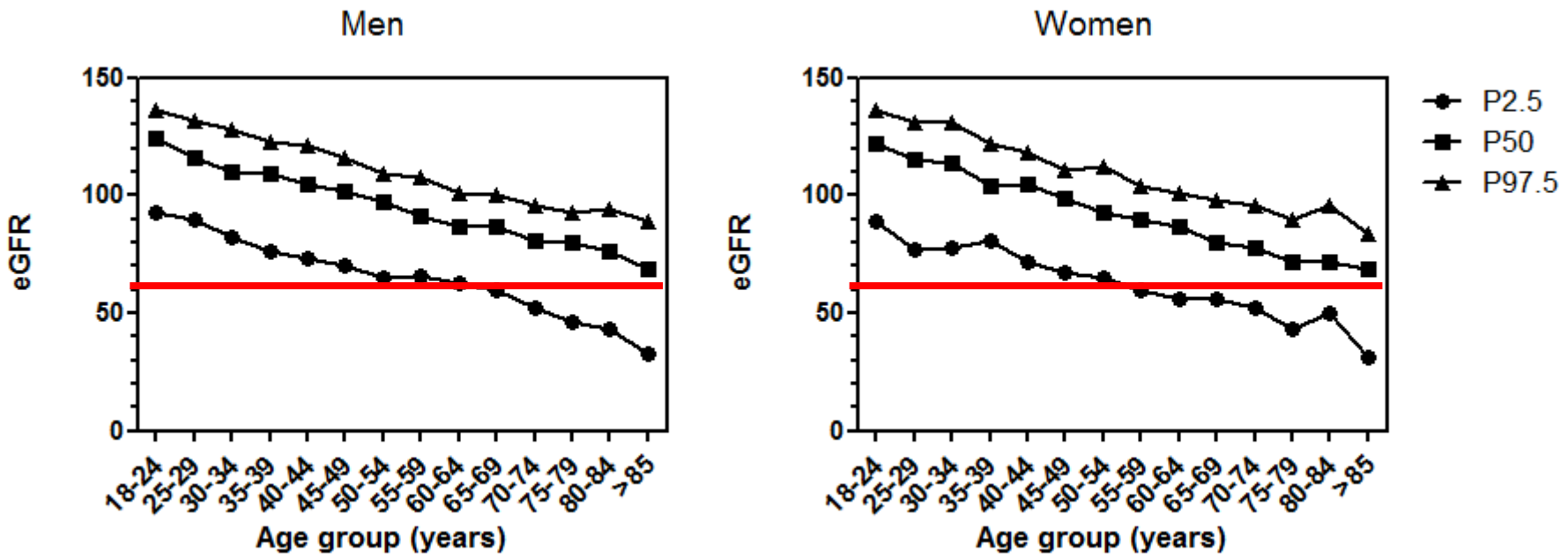


Figure 9 | Prognosis of CKD by GFR and albuminuria category. Green, low risk (if no other markers of kidney disease, no CKD); Yellow, moderately increased risk; Orange, high risk; Red, very high risk. CKD, chronic kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes. Modified with permission from Macmillan Publishers Ltd: *Kidney International*. Levey AS, de Jong PE, Coresh J, et al.[30] The definition, classification, and prognosis of chronic kidney disease: a KDIGO controversies conference report. Kidney Int 2011; 80: 17-28; accessed http://www.nature.com/ki/journal/v80/n1/full/ki2010483a.html

- Echantillon impressionnant mais…
- Observationnel
- DFG estimé
- Jaffe et pas (très bien) calibré
- Pas de confirmation à 3 mois

Pourquoi se focaliser sur le sujet âgé?

- La senescence n'est pas une maladie en soi
- C'est un facteur de risque (non modifiable)
- La valeur seuil de 60 mL/min est-elle justifiée?


Men
Women
eGFR
150
100
50
0
18-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
>85
Age group (years)
P2.5
P50
P97.5

Quid de l'argument pronostique?

ORIGINAL CONTRIBUTION

ONLINE FIRST

Age and Association of Kidney Measures With Mortality and End-stage Renal Disease

Stein I. Hallan, MD, PhD
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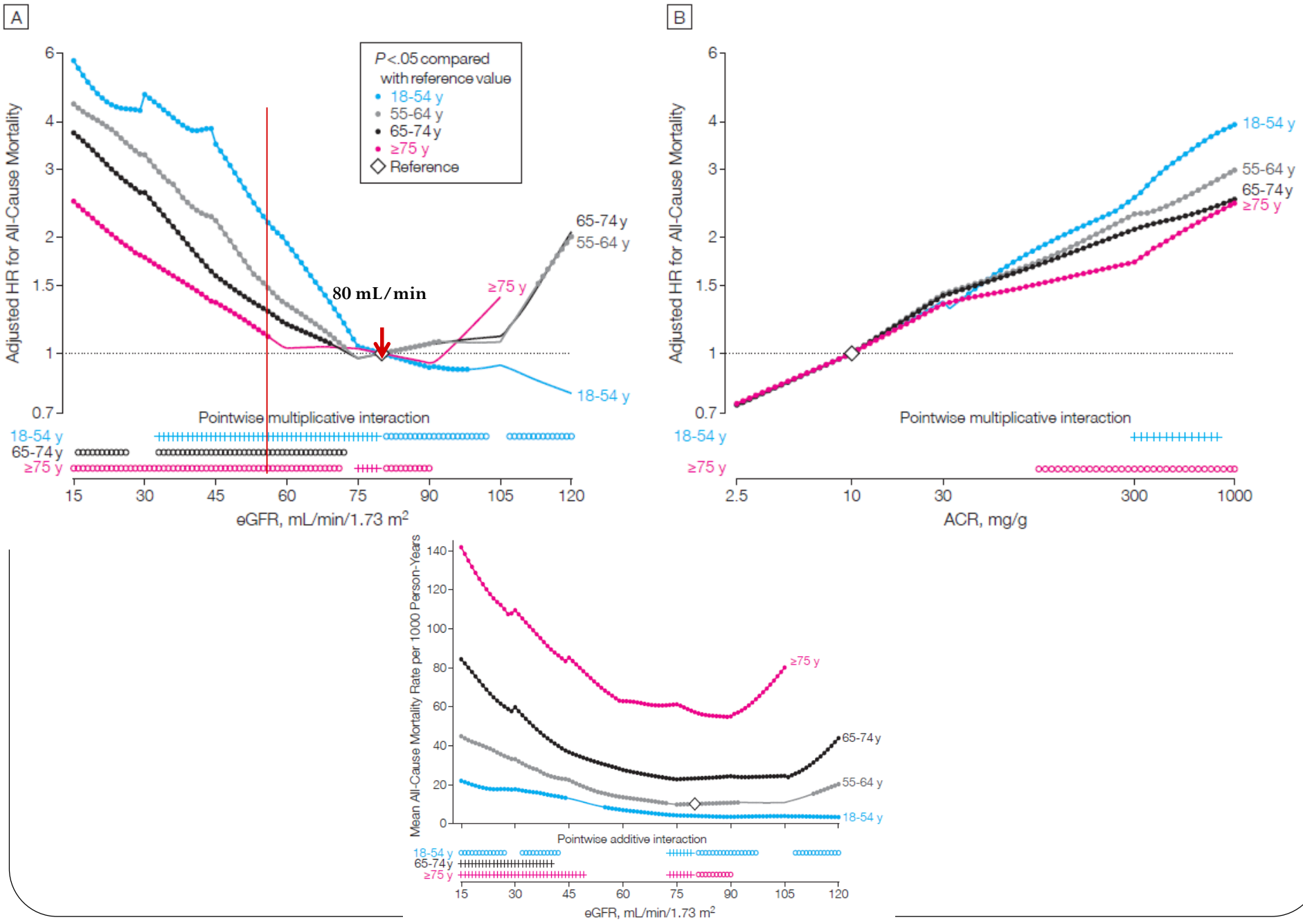
for the Chronic Kidney Disease Prognosis Consortium

JAMA. 2012;308(22):2349-2360

N=2,051,044
33 cohortes de population générale ou à risque
13 CKD cohortes MRC
Suivi moyen: 5.3 ans

Figure 1. Adjusted Hazard Ratios (HRs) for All-Cause Mortality and Mean Mortality Rates According to eGFR and ACR Within Each Age Category

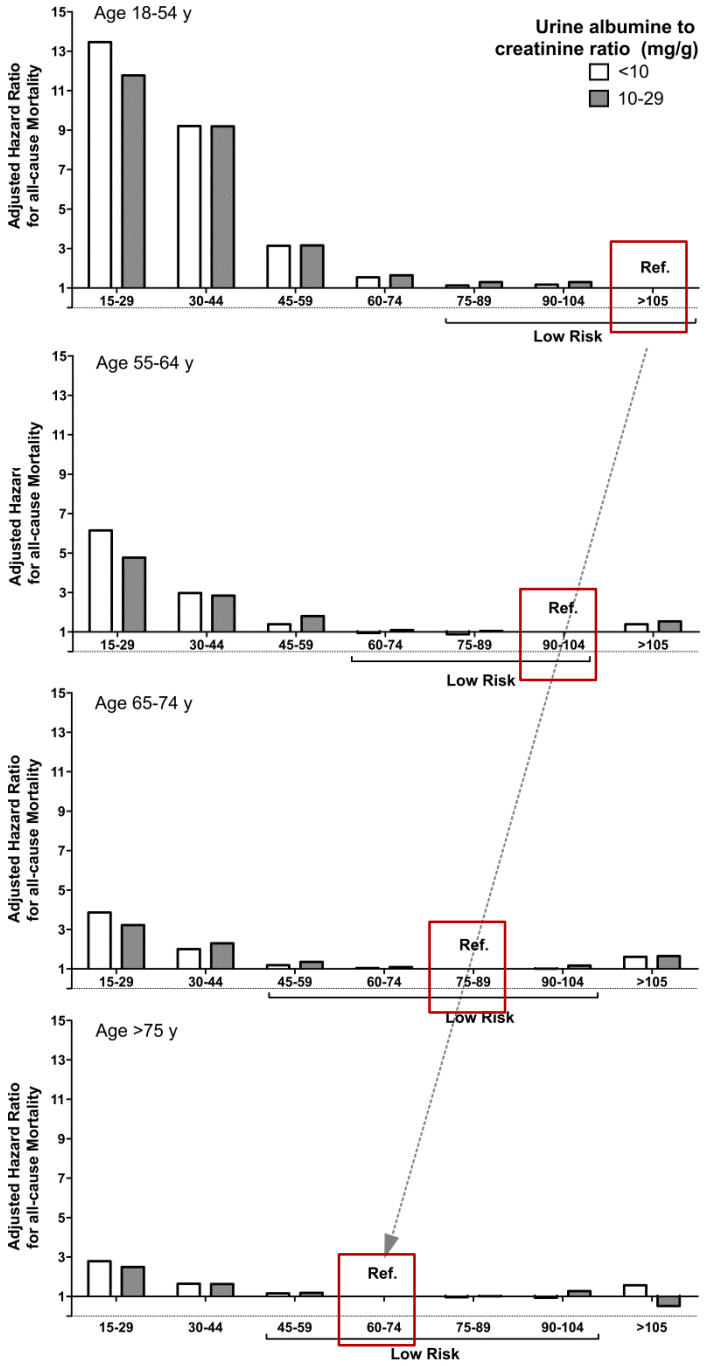


Age 18-54 y =>

Age 55-64 y =>

Age 65-74 y =>

Age >75 y =>



eGFR

JAMA. 2012;308(22):2349-2360

Courtesy from Andrew Rule, Mayo Clinic

Adv Chronic Kidney Dis. 2016, 23, p19

Delanaye P, Clin Biochem Rev, 2016, 37, p17

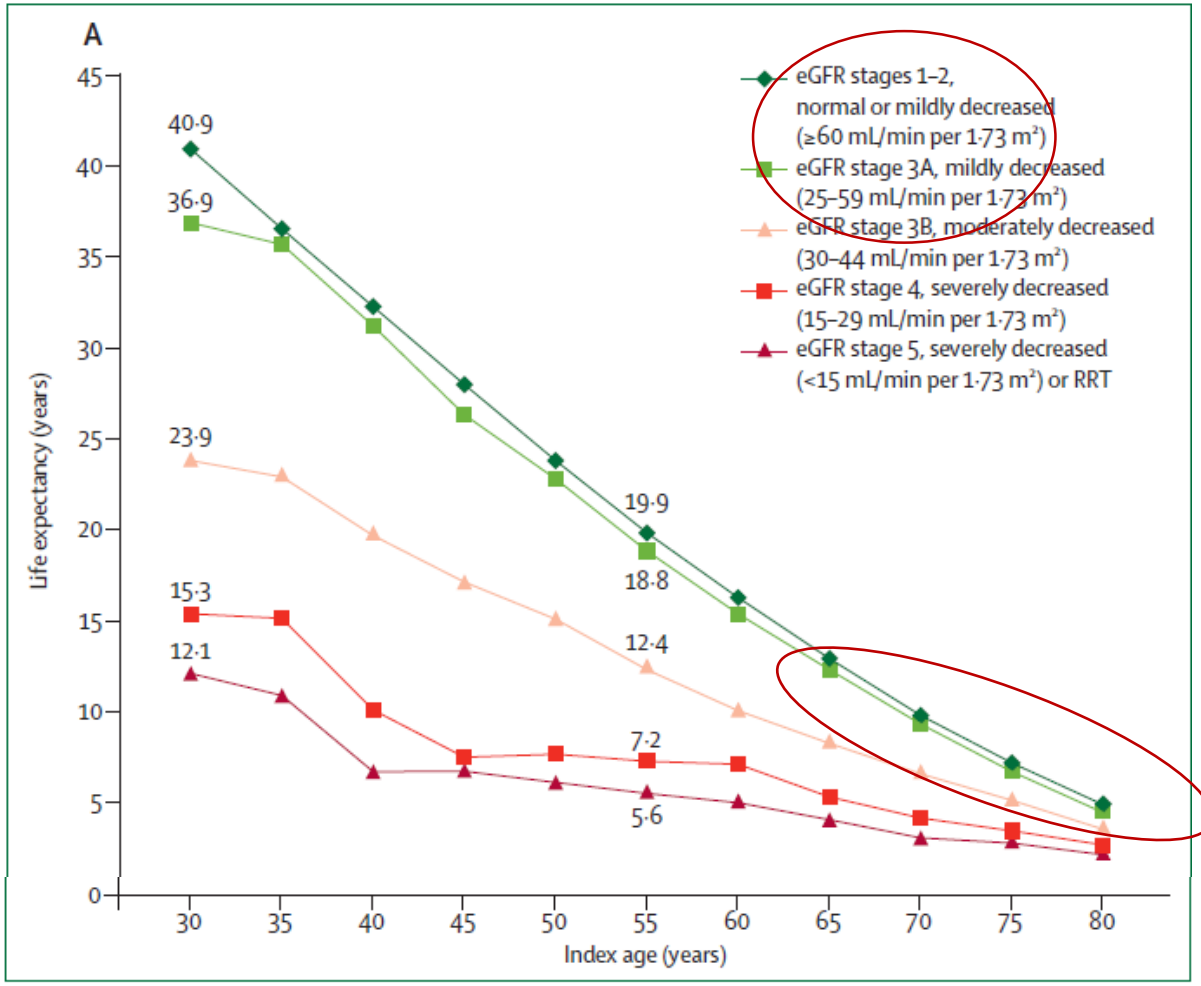


Figure 2: **Life expectancy, according to chronic kidney disease stages (Canadian data)**
(A) eGFR stages and (B) albuminuria stages. Data are adjusted per eGFR and albuminuria stage for sex to the WHO world average in 2000–05. eGFR=estimated glomerular filtration rate. RRT=renal replacement therapy. Based on data in references 24 and 25 (appendix pp 1–2).

Life expectancy for stage 3A

Gansevoort R et al, Lancet, 2013, p339

Est-ce important ou purement sémantique?

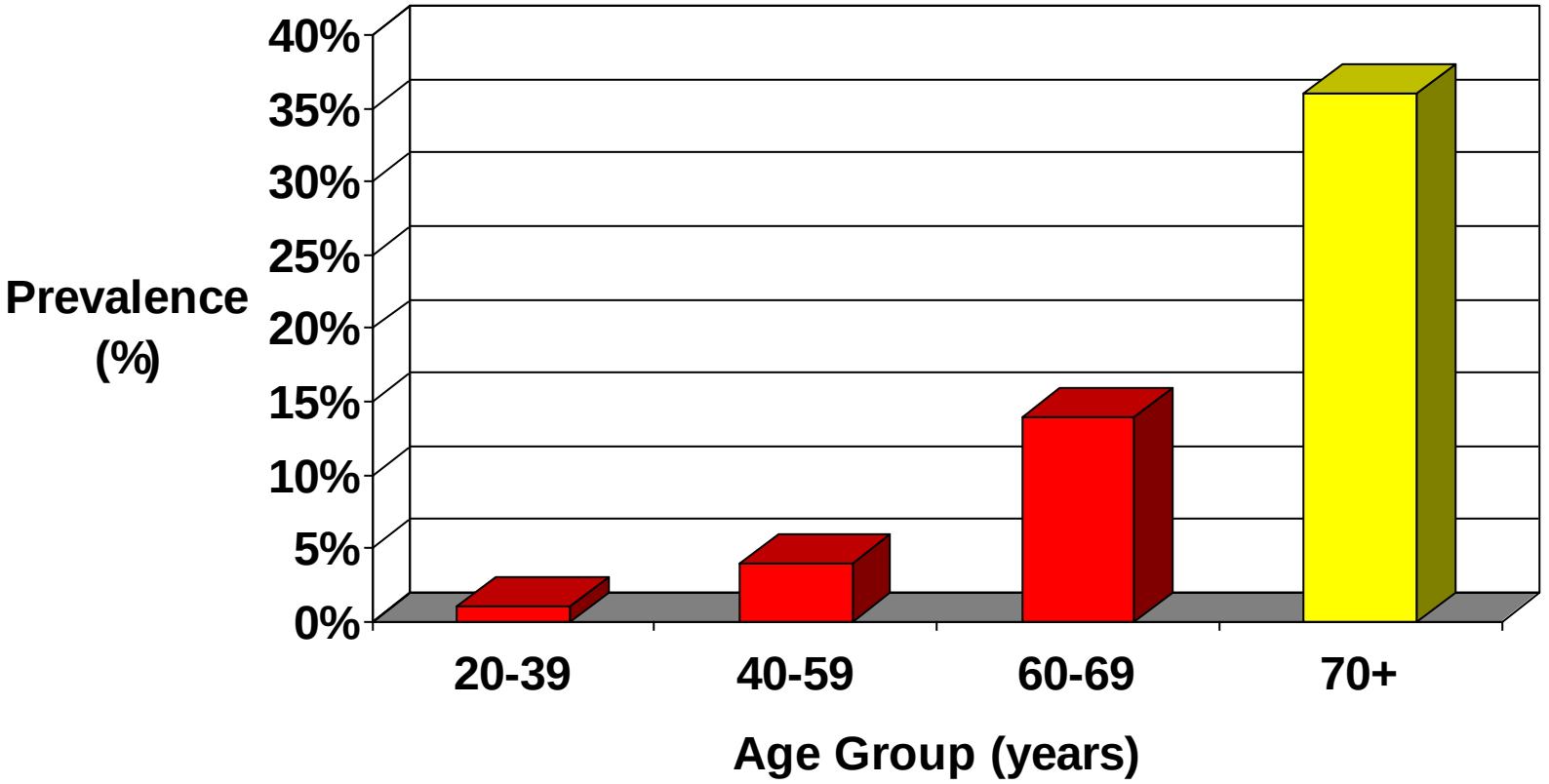
Prévalence de la MRD: 11.5%

Prévalence de la MRC sur le critère DFG estimé uniquement: 4.8%

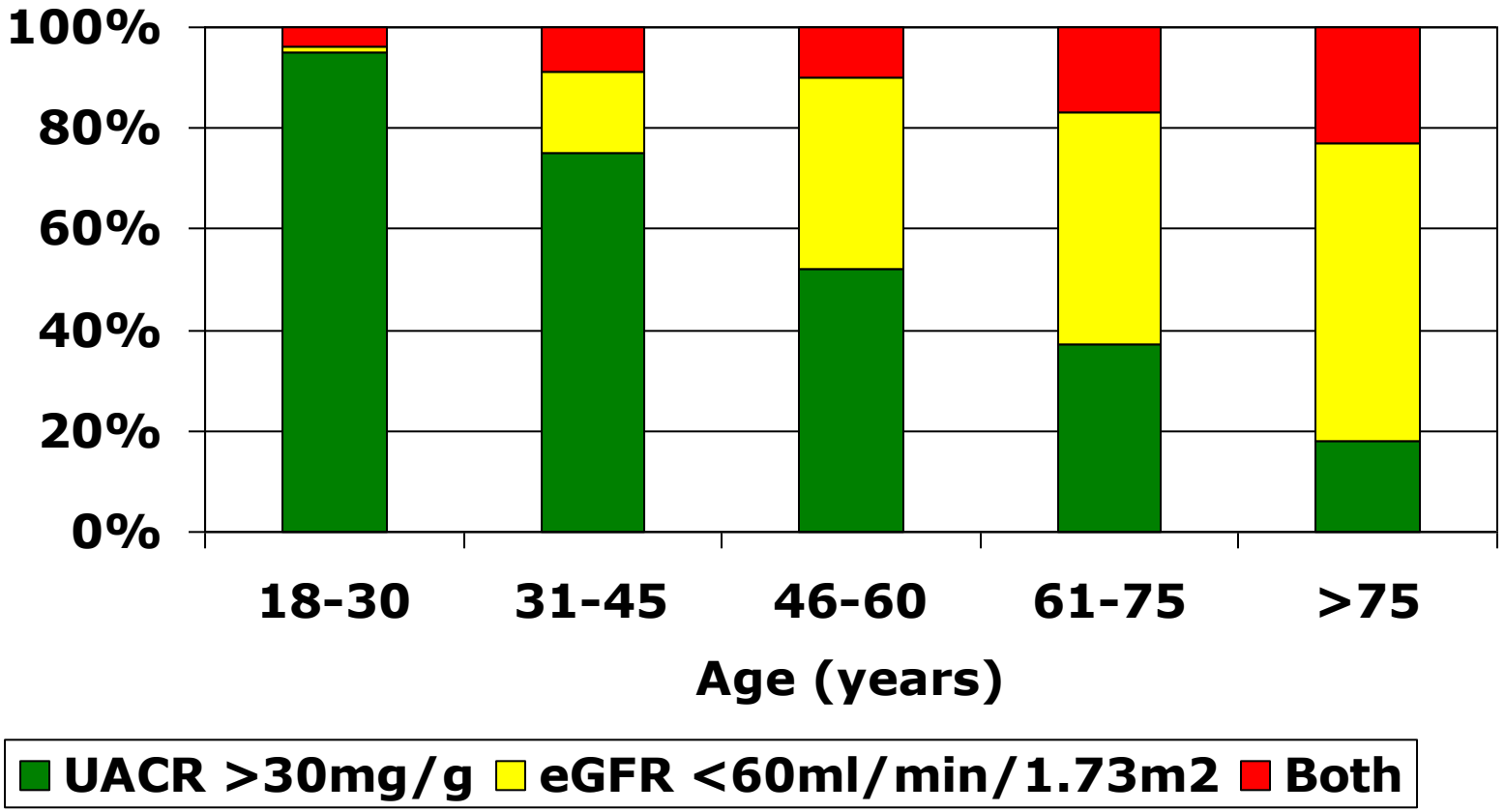
Percentage of US Population by eGFR and Albuminuria Category: KDIGO 2012 and NHANES 1999-2006

GFR categories (ml/min/ 1.73m^2) Description and range				Persistent albuminuria categories Description and range			
				A1	A2	A3	
				Normal to mildly increased	Moderately increased	Severely increased	
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30mg/mmol	
	G1	Normal or high	≥90	55.6	1.9	0.4	57.9
	G2	Mildly decreased	[illegible]	[illegible]	[illegible].2	0.3	35.4
	G3a	Mildly to moderately decreased	45-59	3.6	[illegible].8	0.2	4.6
	G3b	Moderately to severely decreased	[illegible]	[illegible].0	[illegible].4	0.2	1.6
	G4	Severely decreased	15-29	0.2	0.1	0.1	0.4
	G5	Kidney failure	<15	0.0	0.0	0.1	0.1
				93.2	5.4	1.3	100.0

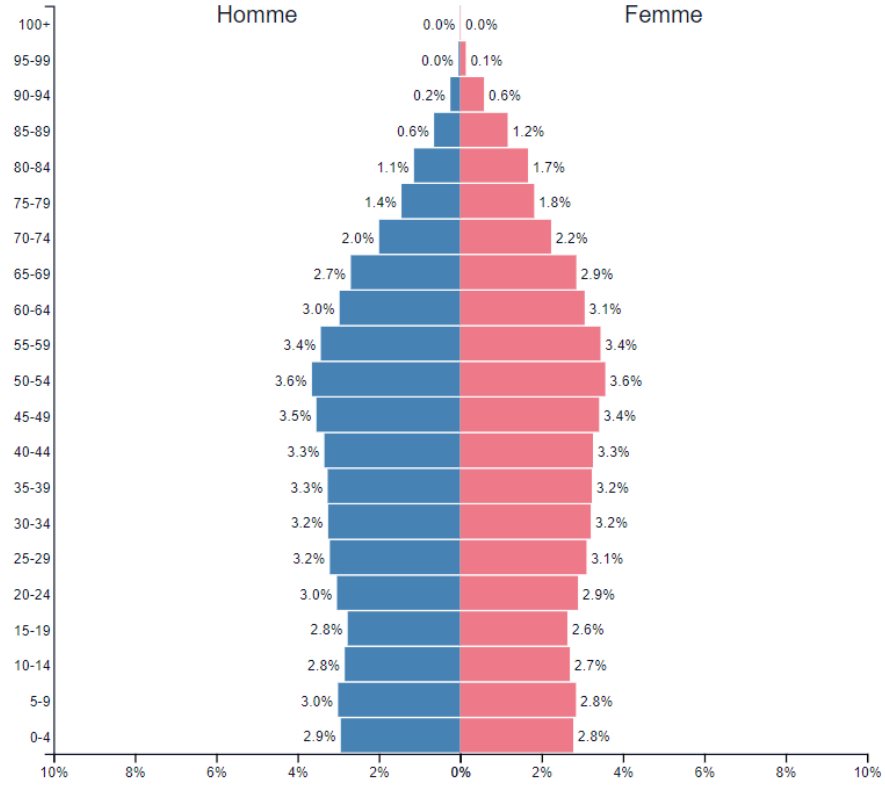
Prevalence du stade 3 selon l'âge (étude NHANES)

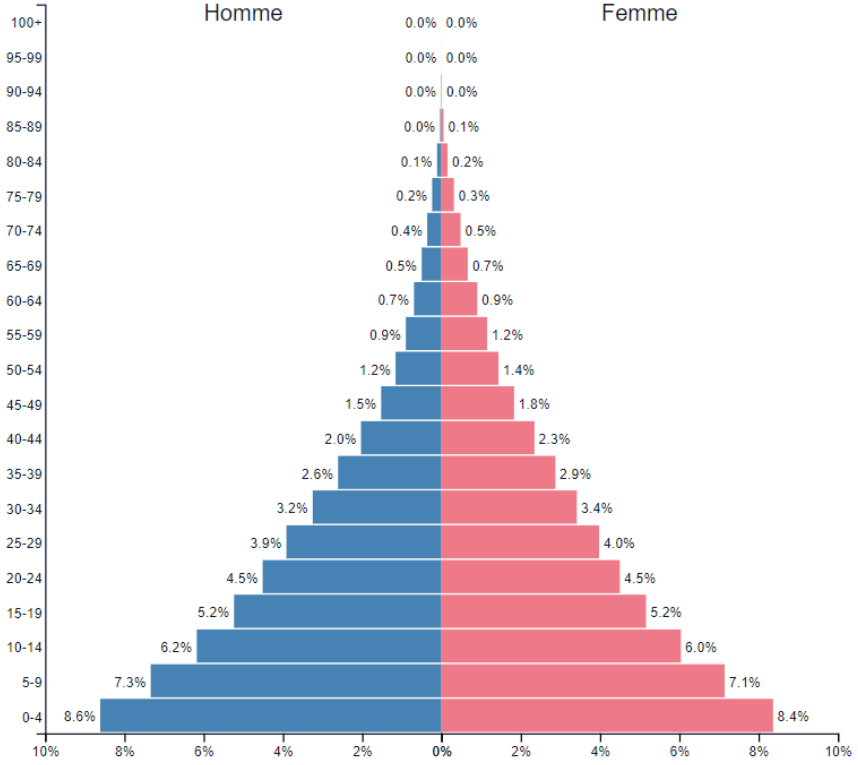


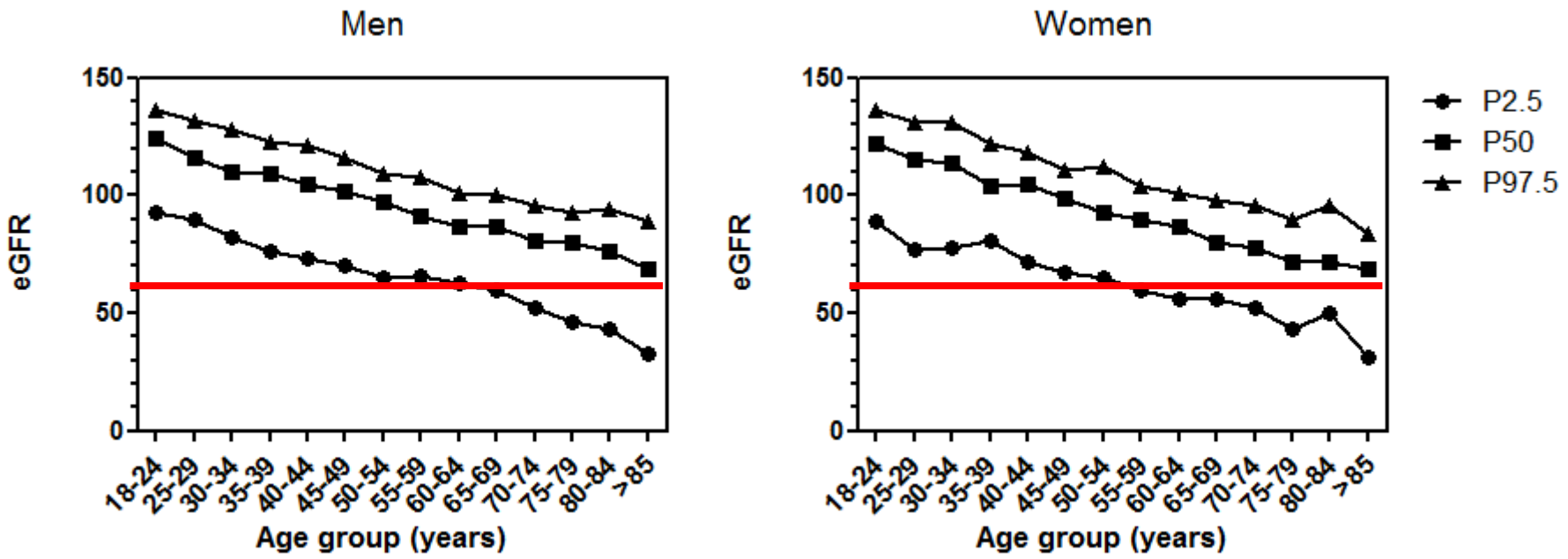
Critères de MRC (GFR v albumninurie)



Courtesy by RJ Glassock, Adapted from James MT, et al Lancet 375:1296, 2010


Homme
Femme
100+ 0.0% 0.0%
95-99 0.0% 0.1%
90-94 0.2% 0.6%
85-89 0.6% 1.2%
80-84 1.1% 1.7%
75-79 1.4% 1.8%
70-74 2.0% 2.2%
65-69 2.7% 2.9%
60-64 3.0% 3.1%
55-59 3.4% 3.4%
50-54 3.6% 3.6%
45-49 3.5% 3.4%
40-44 3.3% 3.3%
35-39 3.3% 3.2%
30-34 3.2% 3.2%
25-29 3.2% 3.1%
20-24 3.0% 2.9%
15-19 2.8% 2.6%
10-14 2.8% 2.7%
5-9 3.0% 2.8%
0-4 2.9% 2.8%
10% 8% 6% 4% 2% 0% 2% 4% 6% 8% 10%


Homme
Femme
100+ 0.0% 0.0%
95-99 0.0% 0.0%
90-94 0.0% 0.0%
85-89 0.0% 0.1%
80-84 0.1% 0.2%
75-79 0.2% 0.3%
70-74 0.4% 0.5%
65-69 0.5% 0.7%
60-64 0.7% 0.9%
55-59 0.9% 1.2%
50-54 1.2% 1.4%
45-49 1.5% 1.8%
40-44 2.0% 2.3%
35-39 2.6% 2.9%
30-34 3.2% 3.4%
25-29 3.9% 4.0%
20-24 4.5% 4.5%
15-19 5.2% 5.2%
10-14 6.2% 6.0%
5-9 7.3% 7.1%
0-4 8.6% 8.4%
10% 8% 6% 4% 2% 0% 2% 4% 6% 8% 10%


Men
Women
eGFR
150
100
50
0
18-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
>85
Age group (years)
P2.5
P50
P97.5

ARTICLE IN PRESS

www.kidney-international.org clinical investigation

Chronic kidney disease, hypertension, diabetes, and obesity in the adult population of Morocco: how to avoid "over"- and "under"-diagnosis of CKD

Mohammed Benghanem Gharbi[1,6], Monique Elseviers[2,6], Mohamed Zamd[1], Abdelali Belghiti Alaoui[3], Naïma Benahadi[3], El Hassane Trabelssi[3], Rabia Bayahia[4], Benyounès Ramdani[1] and Marc E. De Broe[5,6]

[1]Faculty of Medicine and Pharmacy, University Hassan II, Casablanca, Morocco; [2]Department of Biostatistics, Center for Research and Innovation in Care, University of Antwerp, Antwerp, Belgium; [3]Ministry of Health, Rabat, Morocco; [4]Faculty of Medicine and Pharmacy, University Mohammed V, Rabat, Morocco; and [5]University of Antwerp, Antwerp, Belgium

Kidney Int. 2016 Jun;89(6):1363-71.

- Deux villes marocaines
- 26-70 ans, n=10,524
- Créatinine and disptick
- Chronicité confirmée à 3 mois

Chronicity of decreased eGFR was investigated in 78.9% of the subjects ($n = 285$) with CKD3A, 3B, 4, and 5. The remaining were deceased or lost to follow-up. The majority (75%) of false positives were found in the subjects with CKD3A. Thirty-two percent of the CKD3A subjects and 7.4% of the CKD3B subjects had an eGFR >60 ml/min/1.73 m^2 when reinvestigated after 3 months or longer. Subjects with CKD4 and 5 ($n = 51$) remained in these low eGFR categories, and 11 were on dialysis, died, or lost to follow-up after 3 months or longer.

32% faux + si pas de confirmation

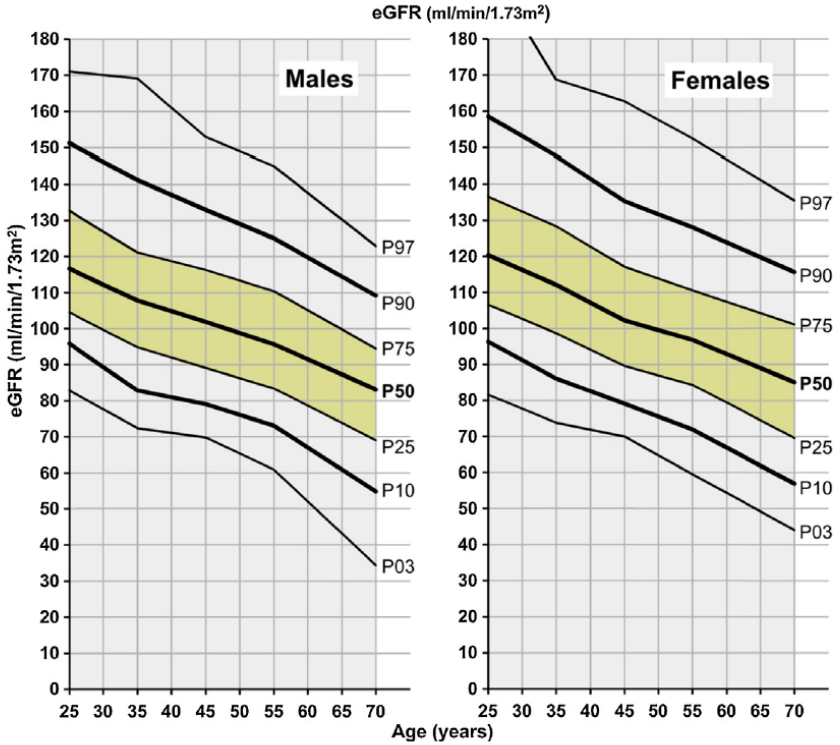
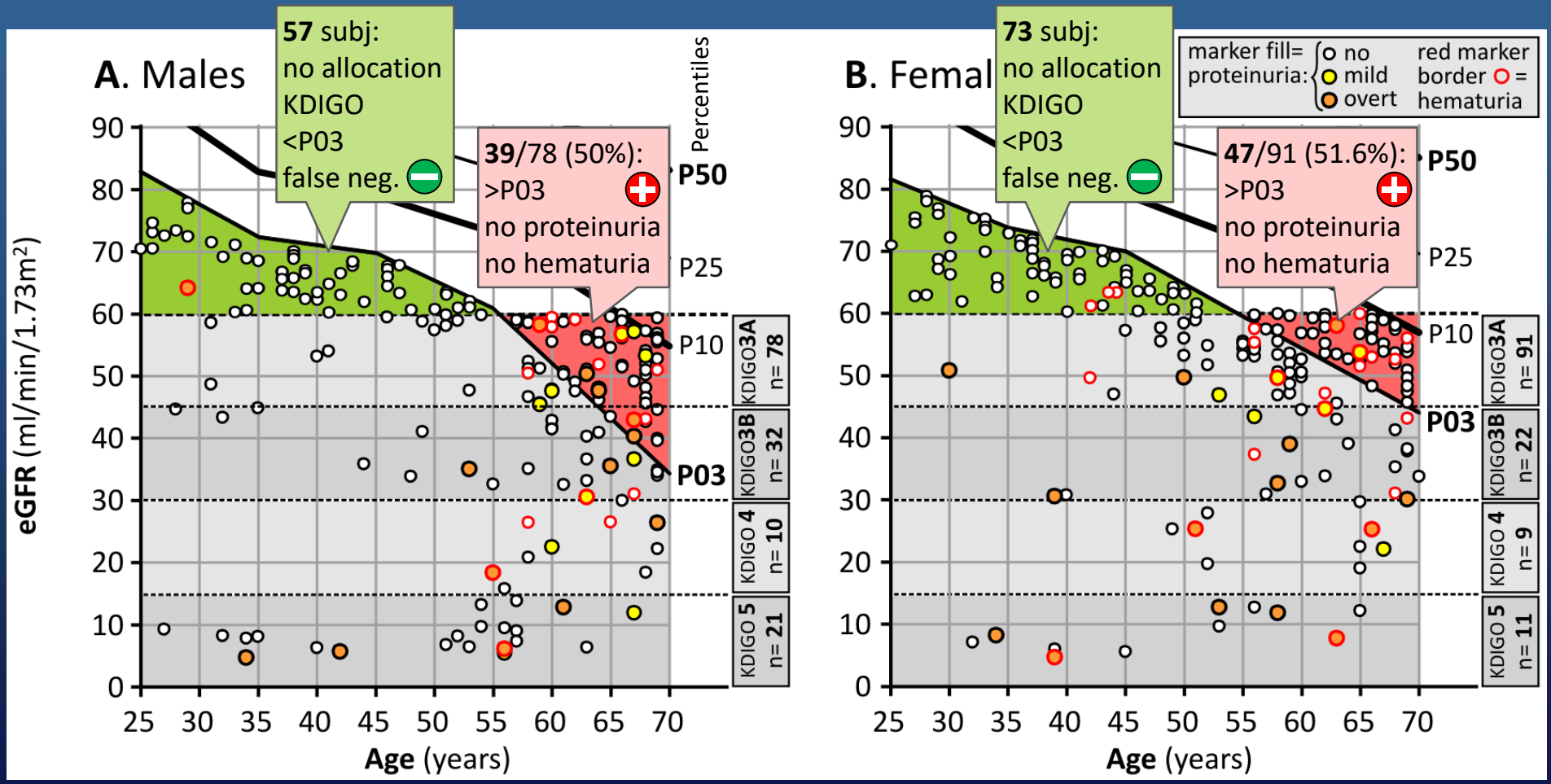


Fig. 2. Estimated glomerular filtration rate (eGFR) distribution showing the 3rd, 10th, 25th, 50th, 75th, 90th and 97th percentile within the gender and age categories ($n = 10{,}524$). The "normal" decline in eGFR of the study population is 0.75 mL/min/1.73 m^2 per year.
From [22] with permission.

False negatives ⊖ and false positives ⊕ by using the arbitrary threshold of eGFR for classifying CKD3-5



Kidney Int. 2016 Jun;89(6):1363-71.

Thanks to Pr De Broe

Alternatives

- Percentiles
- Stade 3A (sans autre atteinte rénale) n'est plus considéré comme MRC si + 65 ans
- Valeur seuil de MRC est 45 mL/min/1.73m² pour les plus de 65 ans
- Valeur seuil de MRC est de 75 mL/min/1.73m² pour les – de 40 ans

Delanaye P, Clin Biochem Rev, 2016, 37, p17
Delanaye P, Nephrol Dial Transplant, 2013, 28, 1396
Glassock RJ, JAMA, 2016

Conclusions

- La sénescence rénale s'accompagne d'une diminution physiologique du DFG
- La sénescence rénale s'accompagne de modifications macro- et micro-anatomiques
- Le rein âgé est plus à risque de MRC, d'IRA…mais n'est pas malade en soi
- Le seuil unique (60 mL/min/1.73m²) rend mal compte de la physiologie du rein âgé (mais aussi de celle du jeune!!)

Il n'y a pas de normes. Tous les hommes sont des exceptions à une règle qui n'existe pas.

(Fernando Pessoa)

Merci de votre attention

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SFNDT 2020 à Liège

Nous serons heureux de vous accueillir!

Research

Original Investigation

Interpreting Treatment Effects From Clinical Trials in the Context of Real-World Risk Information

End-Stage Renal Disease Prevention in Older Adults

Ann M. O'Hare, MA, MD; John R. Hotchkiss, MD; Manjula Kurella Tamura, MD, MPH; Eric B. Larson, MD, MPH; Brenda R. Hemmelgarn, MD, PhD; Adam Batten, BA; Thy P. Do, PhD; Kenneth E. Covinsky, MD, MPH

JAMA Intern Med. 2014;174(3):391-397.

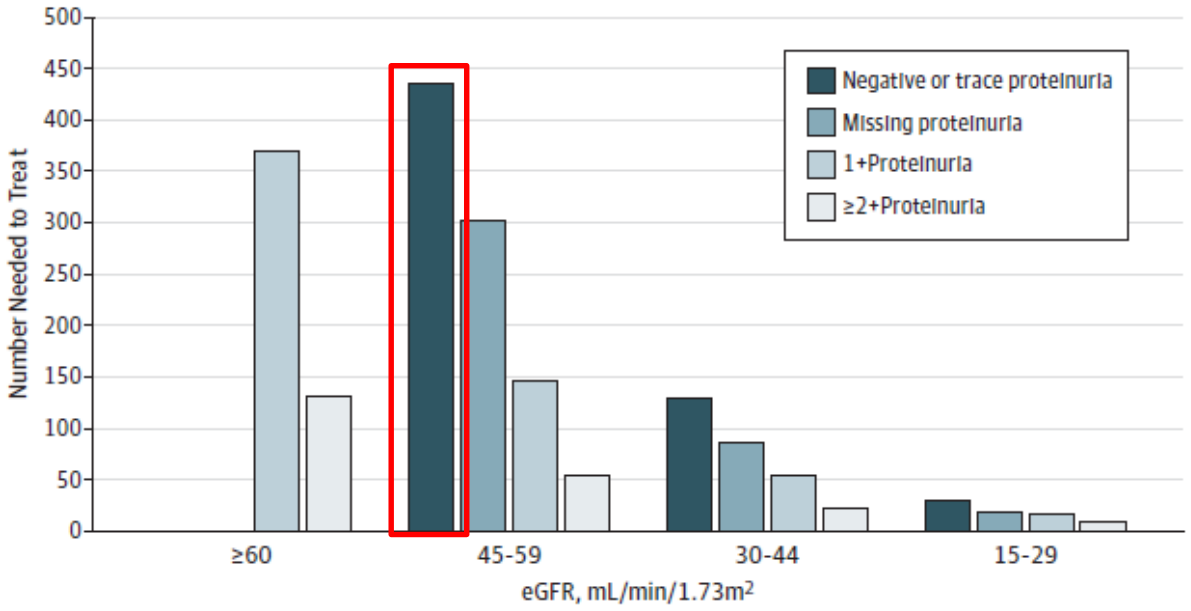
VA
Age>70 ans
Âge moyen: 77.8 ± 4.6 ans
DFG estimé: 48 ± 11.7 ml/min/1.73 m²
n=371.470

IEC ou SARTANS et prevention IRCT

Table 1. Entry Criteria and Outcomes of Major Trials Reporting a Protective Effect of ACE Inhibitors or ARBs on Progression to ESRD

				Entry Criteria				Mortality, %		ESRD, %		ESRD Outcomes[a]		
Source	No. of Patients	Intervention	Mean FU, y	Age, y	DM	Renal Function	Dipstick Proteinuria Measurement	Control Group	INT Group	Control Group	INT Group	RRR, %	ARR, %	NNT
Brenner et al,[18] 2001	1513	Losartan potassium vs placebo	3.4	31-70	Yes	Scr level, 1.3-3.0 mg/dL	ACR >300 mg/g	20.3	21.0	25.5	19.6	23.0	5.9	17
Lewis et al,[19] 1993	409	Captopril vs placebo	3.0	18-49	Yes	Scr level, ≤2.5 mg/dL	Urine protein level, ≥500 mg/g	6.9	3.9	15.4	9.7	37.0	5.7	18
Ruggenenti et al,[20] 1999	352	Ramipril vs placebo	2.6	18-70	Type 1 DM excluded	CrCl, 20-70 mL/min	Stratum 1: urine protein level ≥1 and <3 g/d	0	1.0	20.7	9.1	56.0	11.6	9
Agodoa et al,[21] 2001	1094	Ramipril vs amlodipine besylate	3.0	18-70	No	GFR, 20-65 mL/min/ 1.73 m^2	Urinary ratio of protein to creatinine levels, ≤2.5 mg/mg	6.0	4.1	14.8	10.8	27.0	4.0	25

Figure. Number Needed to Treat (NNT) to Prevent 1 Case of End-Stage Renal Disease (ESRD) Over 10 Years



The NNT is calculated assuming a 30% reduction in relative risk over 10 years.