UiT The Arctic University of Norway

Blood pressure and GFR decline in the general population

Results form the Renal Iohexol Clearance Survey (RENIS)

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Is primary hypertension a cause of nephropathy?

Hypertension and the kidney

- Malignant hypertension is complicated by acute kidney injury

THE NATURAL HISTORY AND COURSE OF HYPERTENSION WITH PAPILLEDEMA (MALIGNANT HYPERTENSION)

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«..the average survival of patients with malignant hypertension is about eight and one-half months. ….»

"…..In our series, **84 per cent** of patients had symptoms due to the effect of the disease on the kidney….."

Hypertension and the kidney

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- Hypertension is a risk factor for both pre-dialytic CKD and ESRD

BLOOD PRESSURE AND END-STAGE RENAL DISEASE IN MEN

MICHAEL J. KLAG, M.D., M.P.H., PAUL K. WHELTON, M.D., BRYAN L. RANDALL, M.S., JAMES D. NEATON, PH.D., FREDERICK L. BRANCATI, M.D., M.H.S., CHARLES E. FORD, PH.D., NEIL B. SHULMAN, M.D., AND JEREMIAH STAMLER, M.D.

(N Engl J Med 1996;334:13-8.)

Elevated Blood Pressure and Risk of End-stage Renal Disease in Subjects Without Baseline Kidney Disease

Chi-yuan Hsu, MD, MSc; Charles E. McCulloch, PhD; Jeanne Darbinian, MPH; Alan S. Go, MD; Carlos Iribarren, MD, MPH, PhD

Arch Intern Med. 2005;165:923-928

- N=316 675, Kaiser Permanente of Northern California
- eGFR>60 and dipstick negative for protein and hematuria at baseline

Are pre-hypertension and hypertension risk-factors for pre-dialytic chronic kidney disease (eGFR<60)?

Garofalo et al.
Am J Kidney Dis
2016, 67(1):89-97.

Hypertension and the kidney

- Malignant hypertension is complicated by acute kidney injury
- Hypertension is a risk factor for progression of chronic kidney disease
- Hypertension is a risk factor for both pre-dialytic CKD and ESRD
- Few persons with primary hypertension will develop ESRD

Do RCTs find an effect of antihypertensive treatment on the risk of CKD or ESKD?

Effects of antihypertensive treatment vs. placebo on renal outcomes in 10 RCTs conducted before 1999

- Hsu 2001, J Human Hypertension
- Antihypertensive treatment vs. placebo before the ACEI/ARB era (mostly adrenergic blockers and diuretics)
- 10 RCTs, 26521 patients, 114 000 person-years., >1 year duration.
- Excluded trials
  - with multiple interventions,
  - that included only patients with CKD
- Different definitions of renal dysfunction across trials
  - increase in BUN and/or creatinine,
  - renal death
  - proteinuria

Effects of antihypertensive treatment vs. placebo on renal outcomes in 10 RCTs conducted before 1999

Hsu CY. Journal of Human Hypertension (2001) 15, 99–106

Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis

Dena Ettehad, Connor A Emdin, Amit Kiran, Simon G Anderson, Thomas Callender, Jonathan Emberson, John Chalmers, Anthony Rodgers, Kazem Rahimi

Lancet 2016; 387: 957–67

Hypertension and the kidney

- Malignant hypertension is complicated by acute kidney injury
- Hypertension is a risk factor for progression of chronic kidney disease
- Hypertension is a risk factor for both pre-dialytic CKD and ESRD
- Few persons with primary hypertension will develop ESRD
- Metaanalyses do not find evidence of an effect of antihypertensive treatment on renal endpoints in patients without diabetes or CKD.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

DOI: 10.1056/NEJMoa1511939

- N=9631 patients with systolic BP > = 130 and increased CVD risk
  - except patients with diabetes
- Intervention: SBP <140 vs. SBP <120.
- HR for primary composite CVD outcome in the intensive-treatment 0.75; 95% CI 0.64 to 0.89.

Table 2. Primary and Secondary Outcomes and Renal Outcomes.

The SPRINT Research Group. N Engl J Med 2015. DOI: 10.1056/NEJMoa1511939

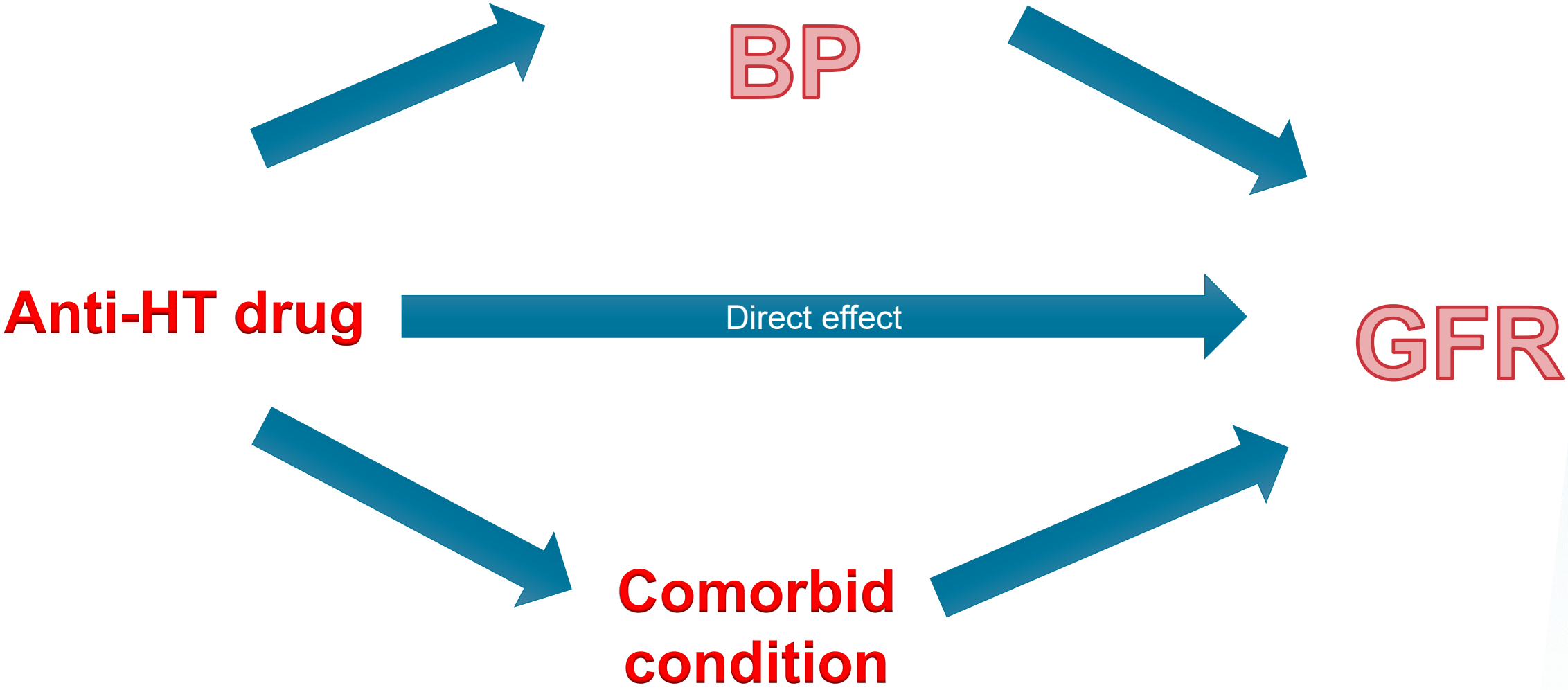
Table 3. Serious Adverse Events, Conditions of Interest, and Monitored Clinical Events.

The SPRINT Research Group. N Engl J Med 2015. DOI: 10.1056/NEJMoa1511939

- Elevated BP is not a sufficient cause of medium-term CKD or ESKD

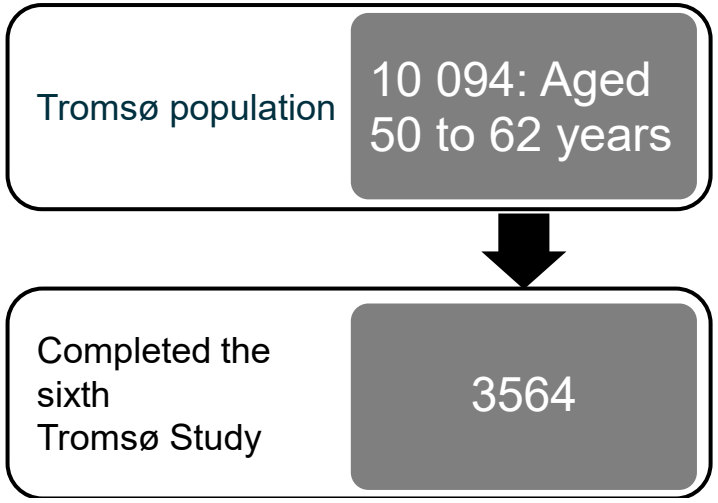
Limitations of RCTs of GFR and antihypertensive treatment

- Short follow-up (median 3.4 years in Ettehad et al)
- Use of estimated instead of measured GFR

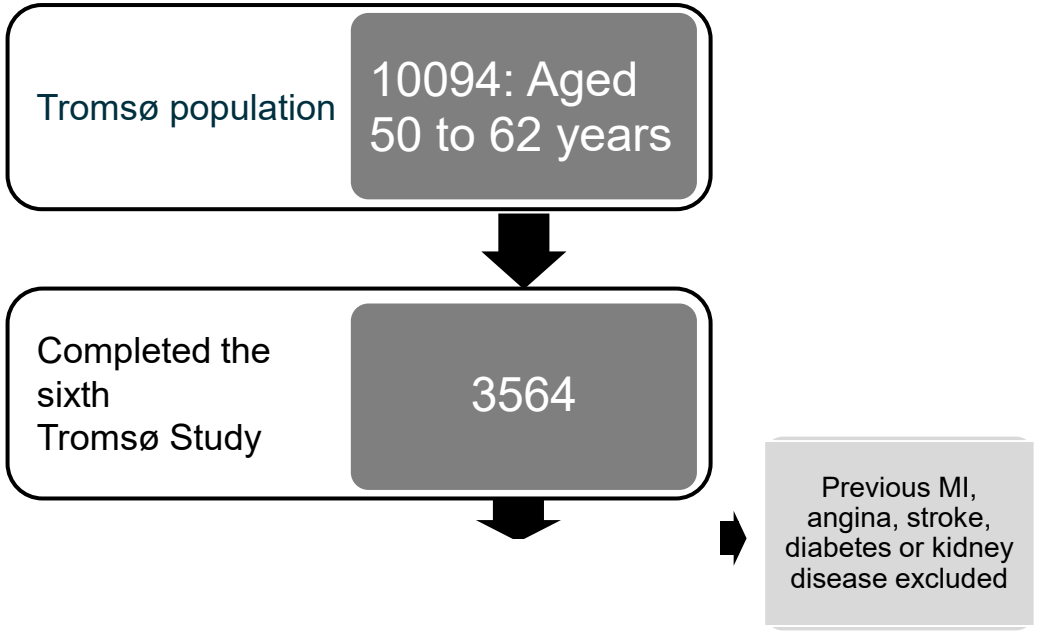

BP
Anti-HT drug
Direct effect
GFR
Comorbid condition

Limitations of RCTs of GFR and antihypertensive treatment

- Short follow-up (median 3.4 years in Ettehad et al)
- Use of estimated instead of measured GFR
- Indirect effects through comorbid conditions (CVD, diabetes…)



The Renal Iohexol Clearance Survey (RENIS)



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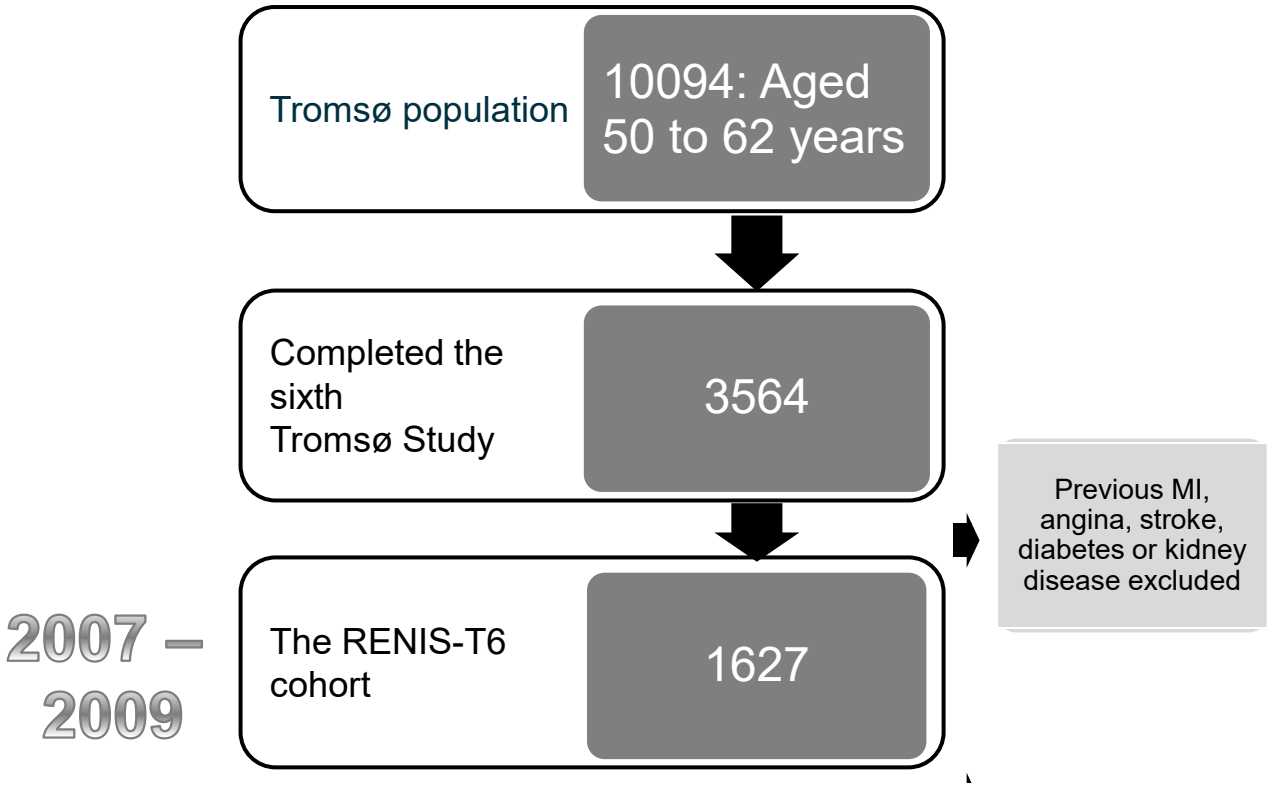

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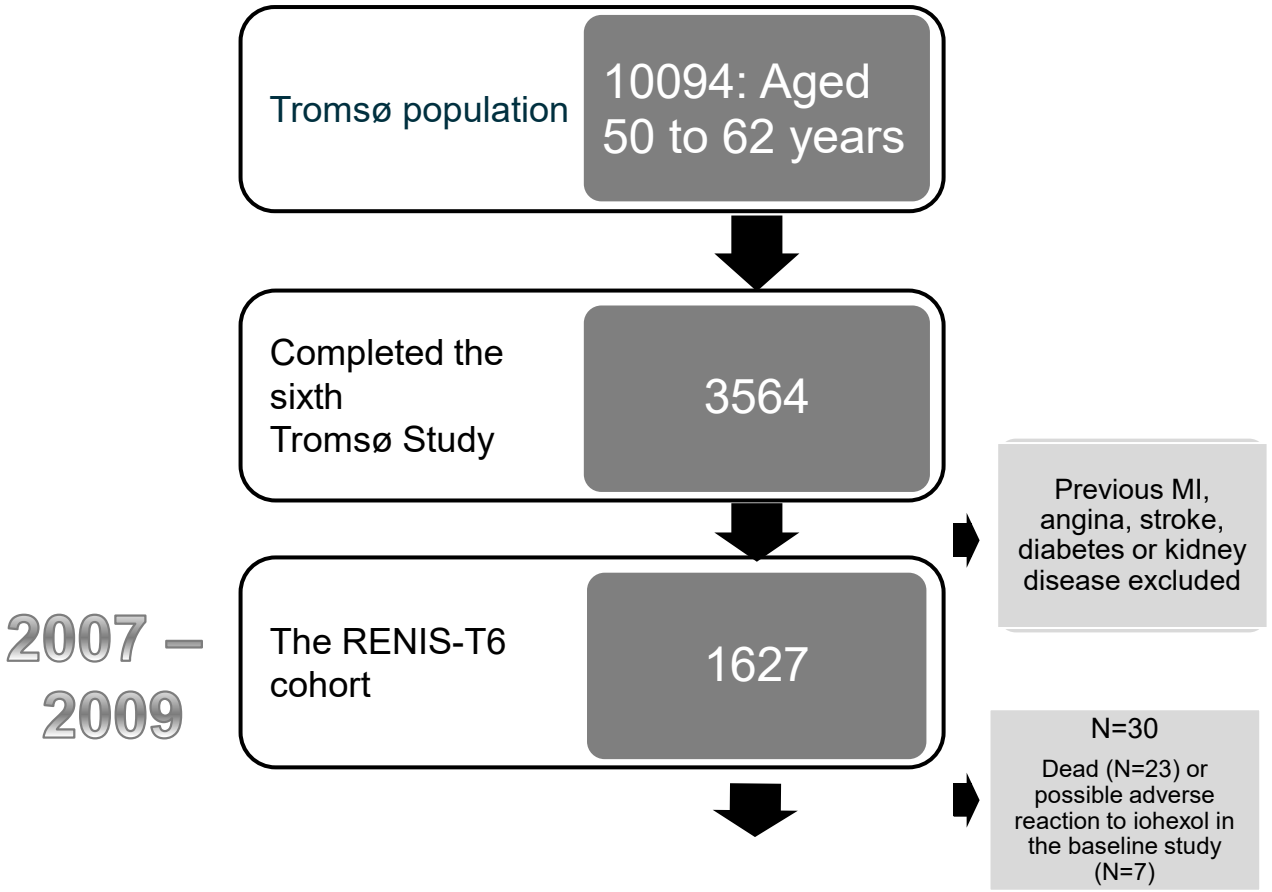

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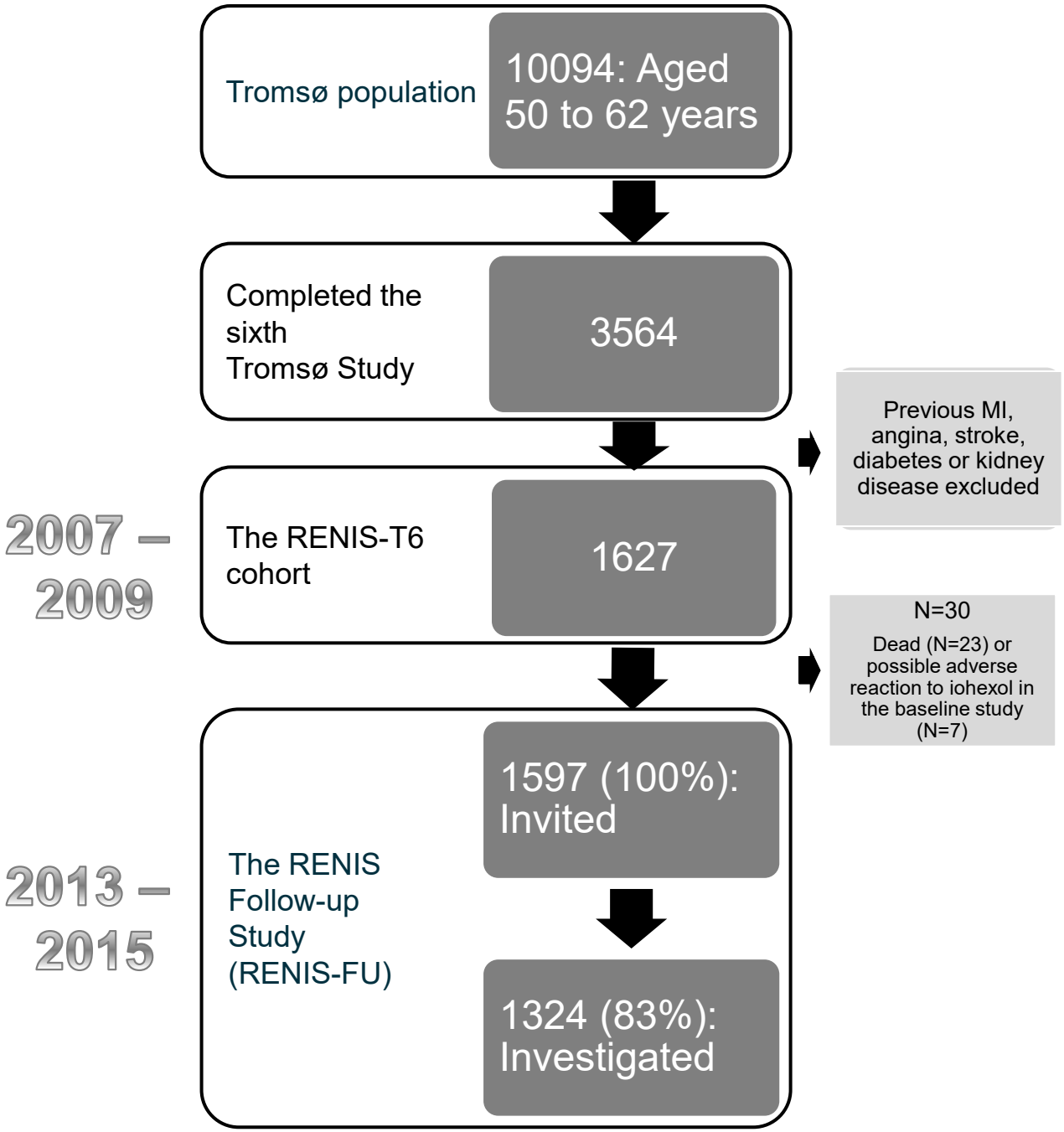
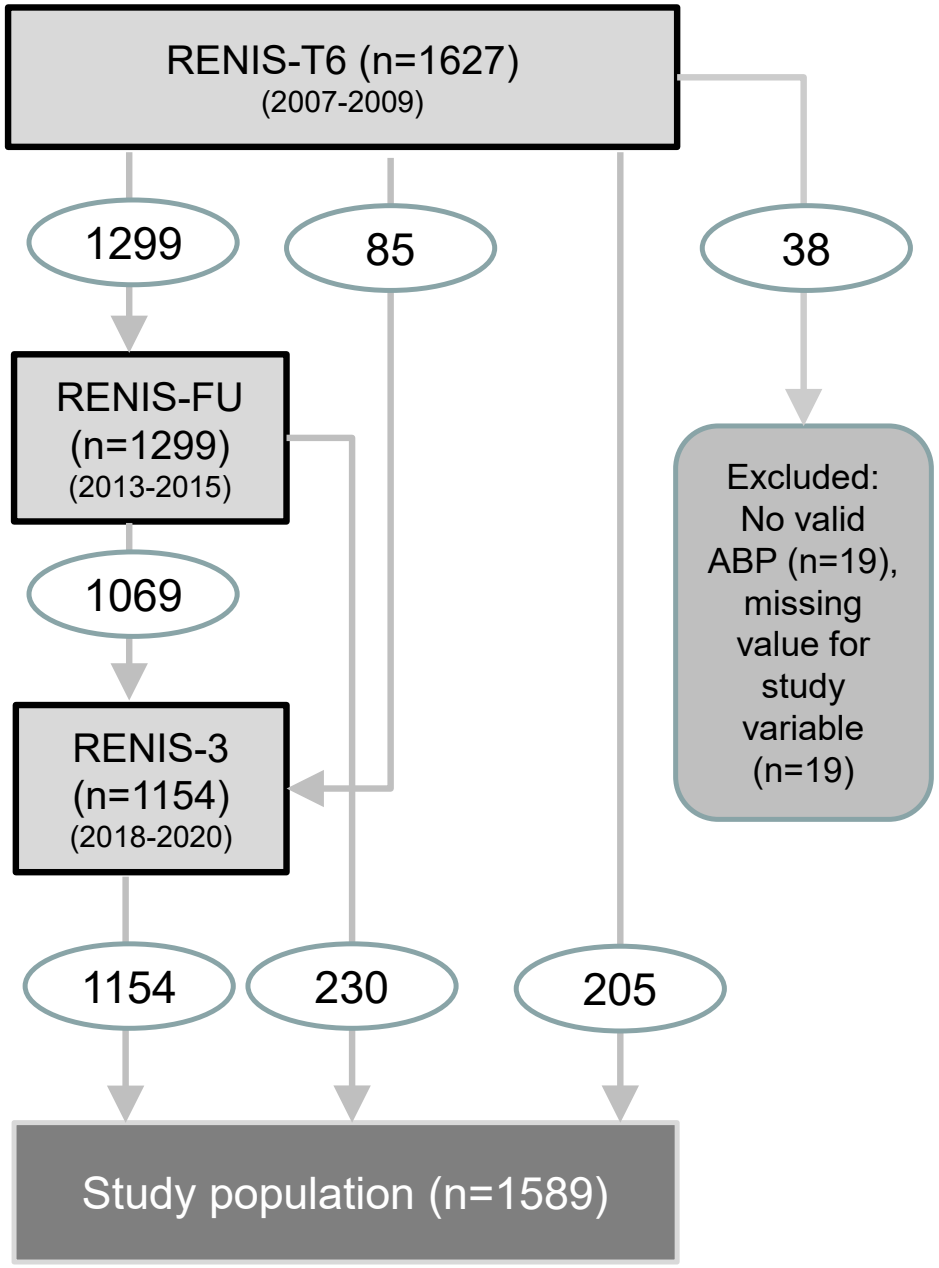


Limitations of RCTs of GFR and antihypertensive treatment

- Short follow-up
- Use of estimated instead of measured GFR
- Indirect effects through comorbid conditions (CVD, diabetes…)
- Lack of ambulatory BP (ABP) measurements


RENIS-T6 (n=1627)
(2007-2009)
1299
85
38
RENIS-FU
(n=1299)
(2013-2015)
1069
RENIS-3
(n=1154)
(2018-2020)
Excluded:
No valid
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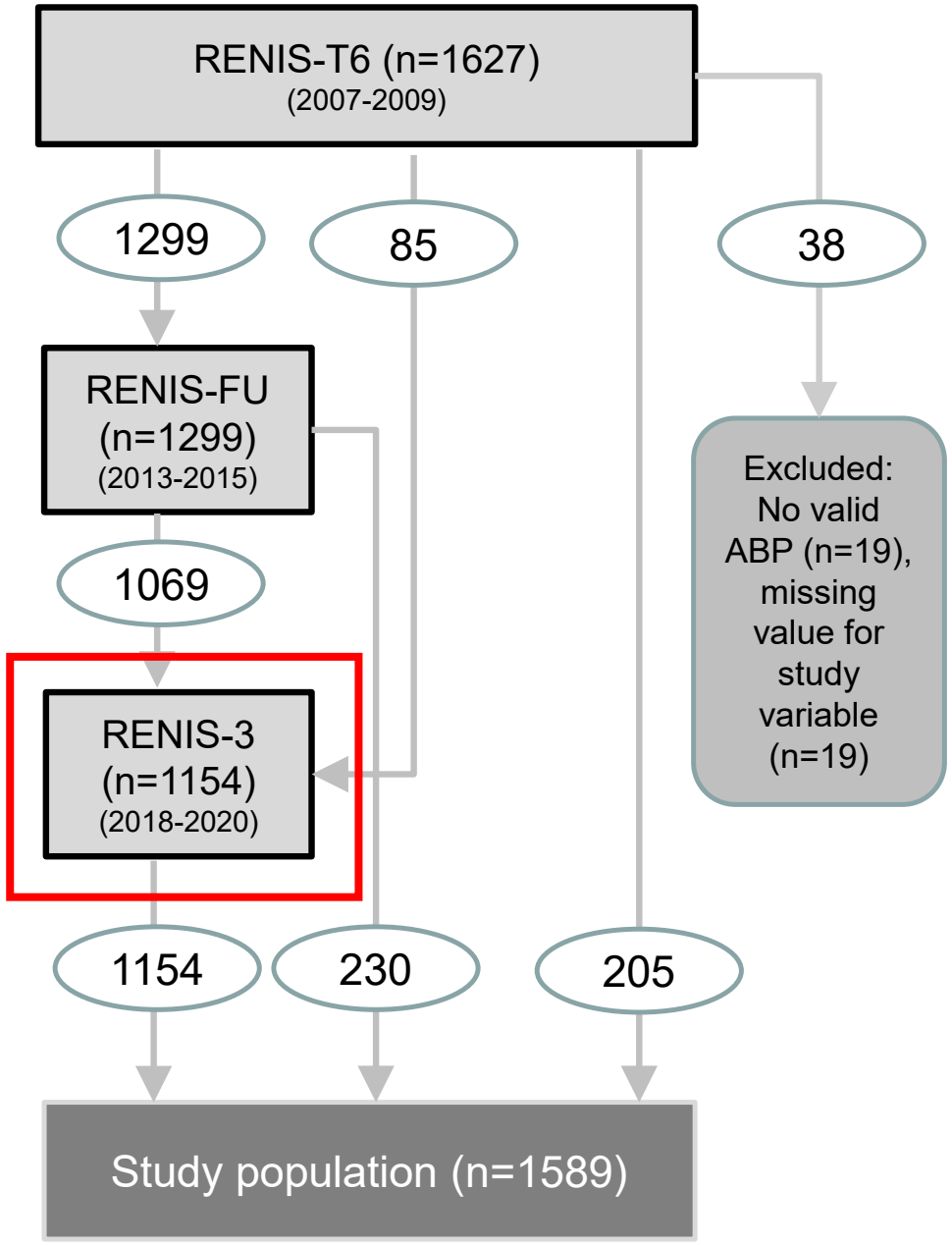
value for
study
variable
(n=19)
1154
230
205
Study population (n=1589)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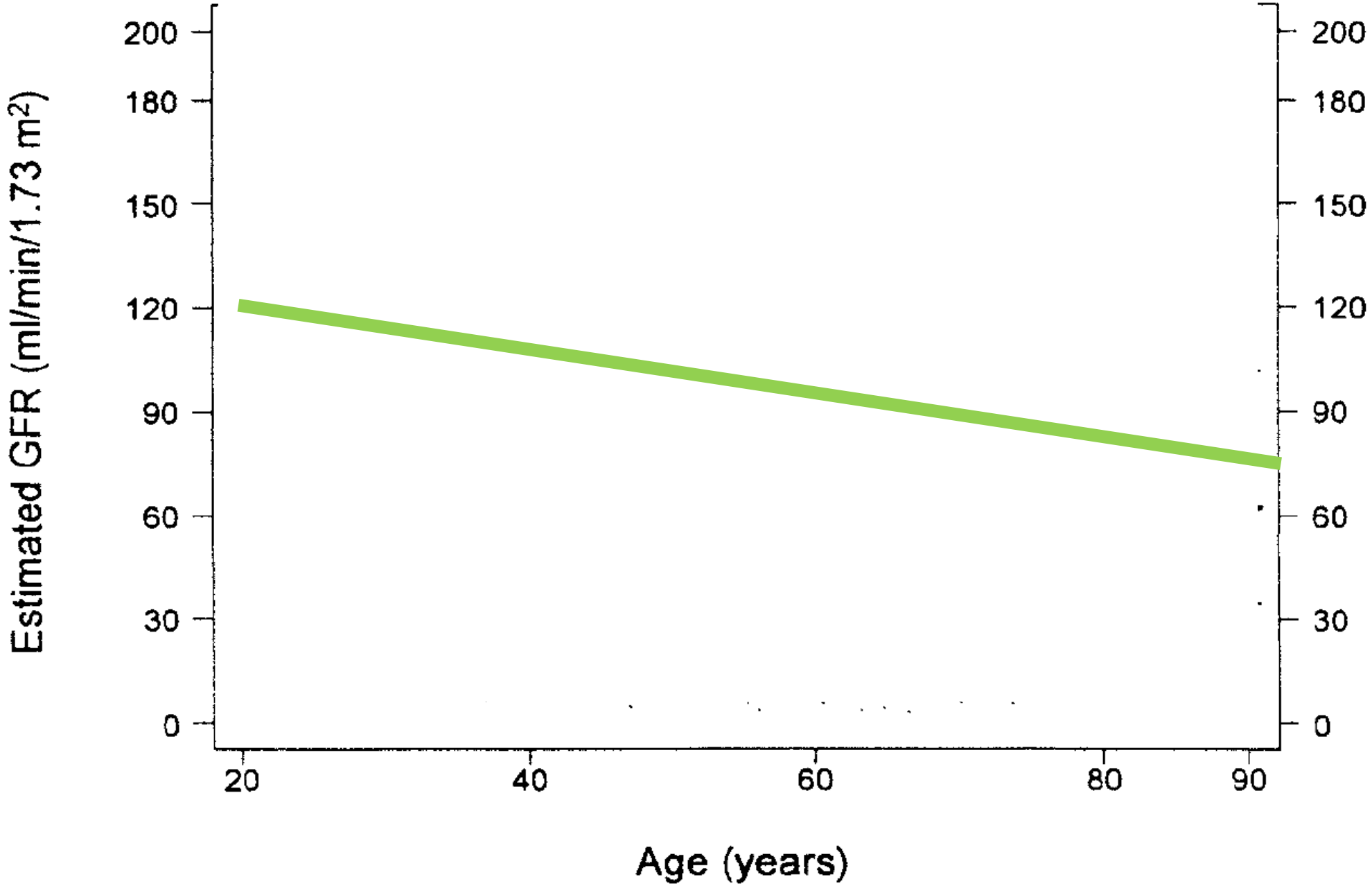
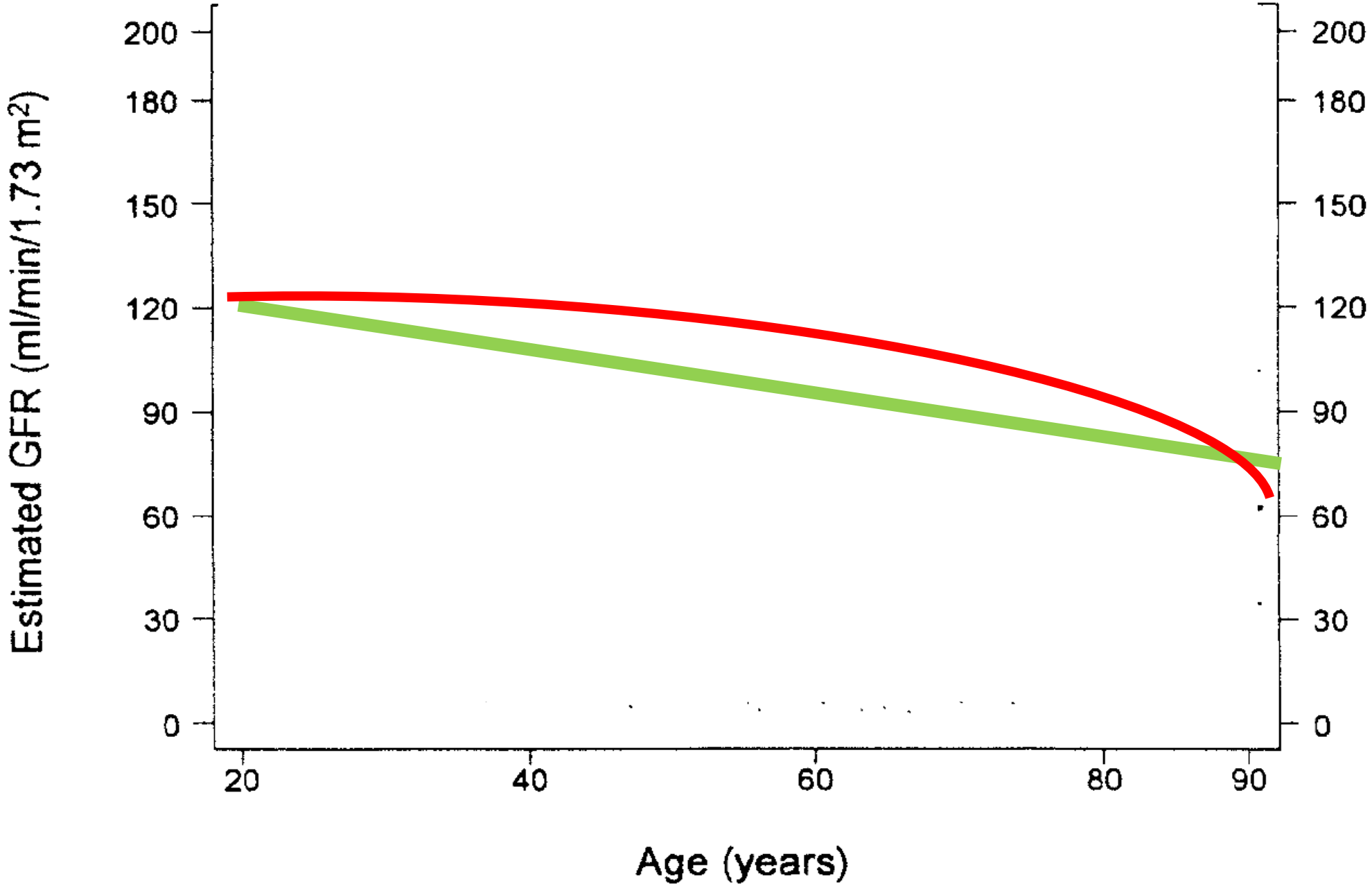

Estimated GFR (ml/min/1.73 m²)
200
180
150
120
90
60
30
0
20
40
60
80
90
Age (years)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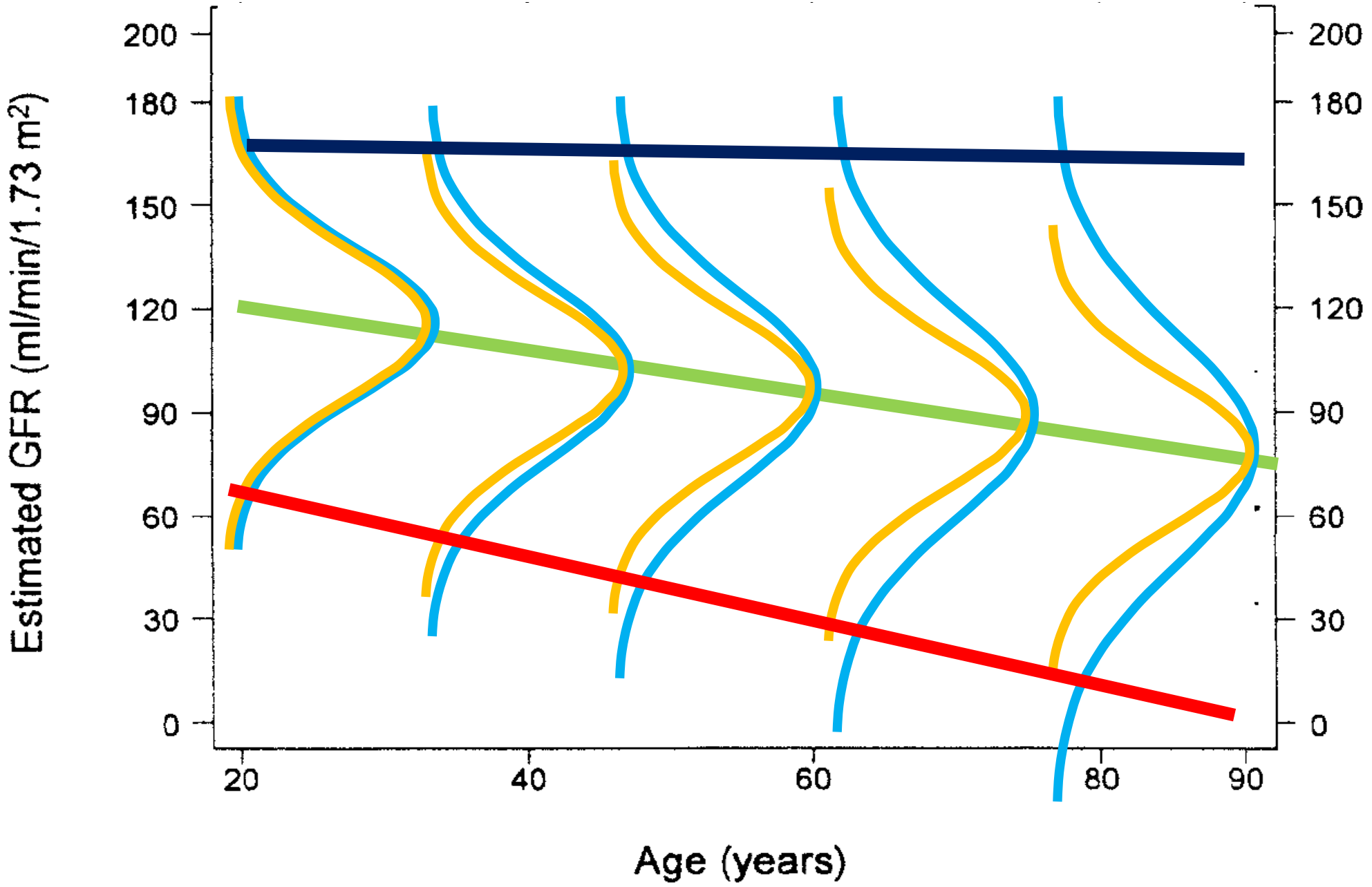
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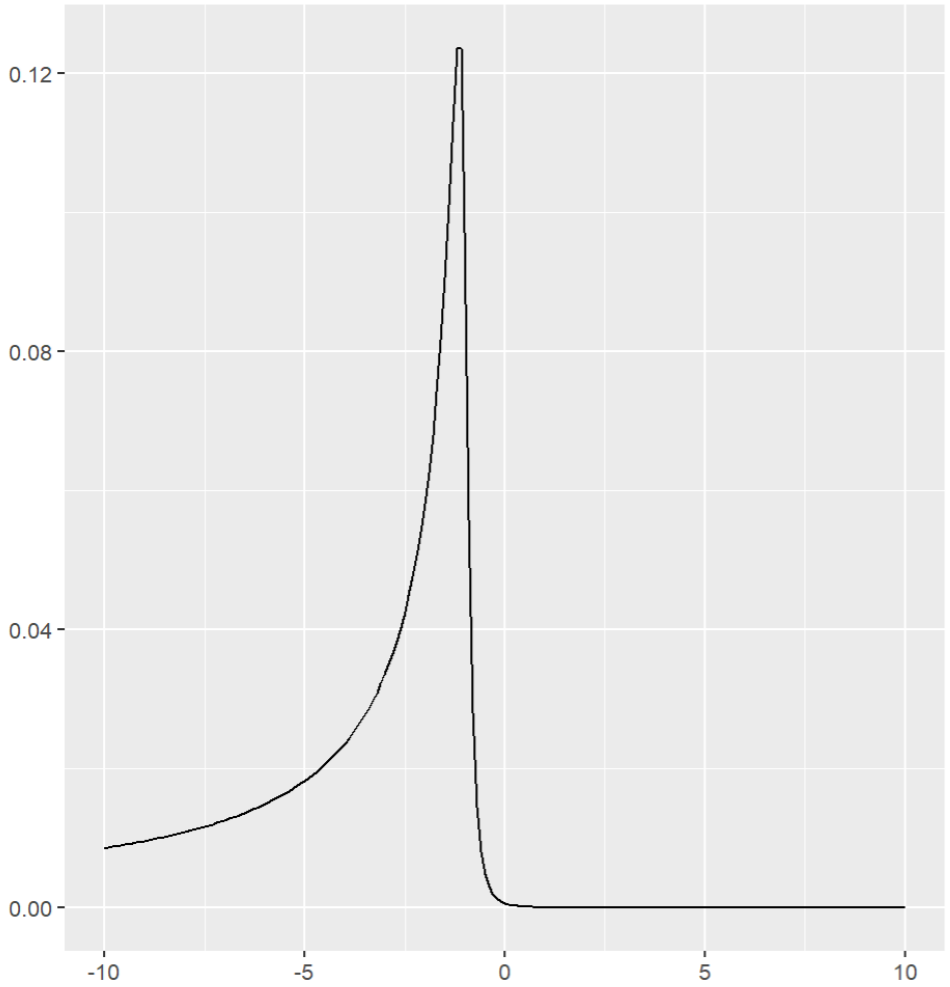
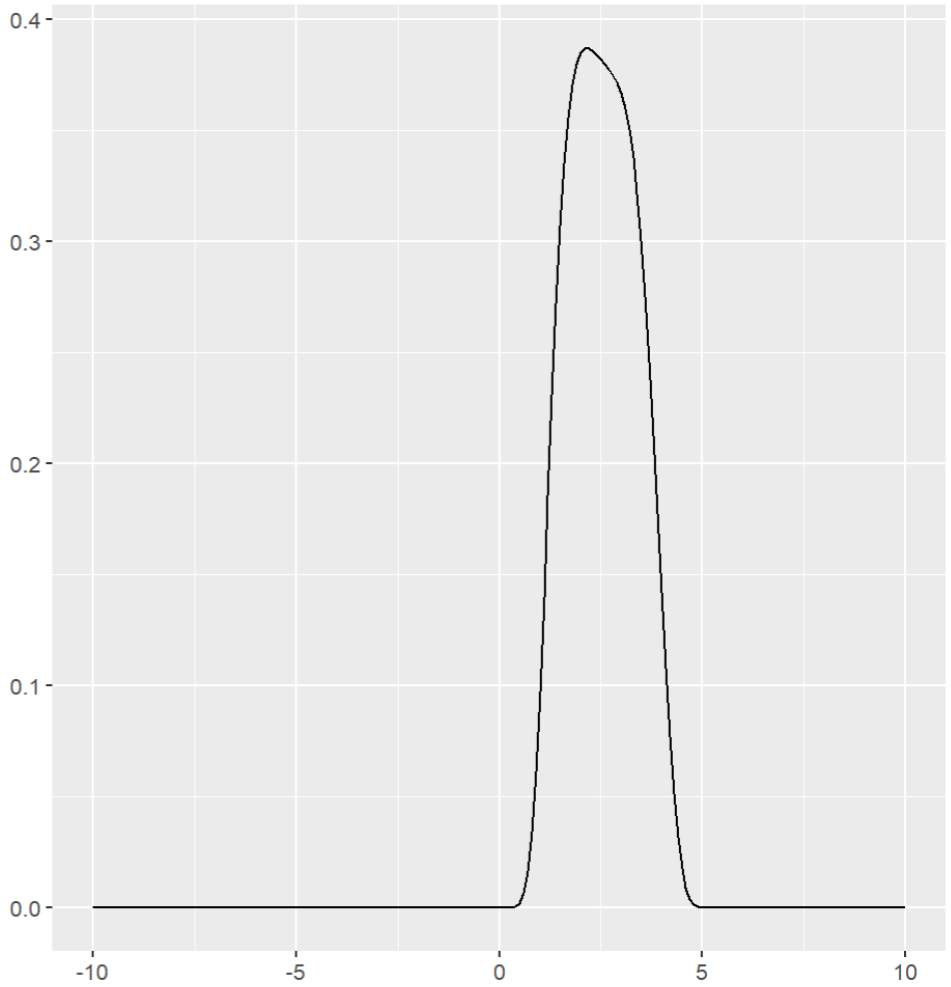

0.12
0.08
0.04
0.00
-10
-5
0
5
10


0.4
0.3
0.2
0.1
0.0
-10
-5
0
5
10

Conclusions

- Elevated daytime ABP is associated with a shift in the GFR distribution towards lower GFR.

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- Elevated daytime ABP is associated with a shift in the GFR distribution towards lower GFR.

- Elevated daytime ABP is associated with only a modest acceleration of GFR decline in most people.

Remaining issues

- What is the effect on GFR of time-dependent BP and antihypertensive treatment?
- Which environmental and/or genetic factors interacts with BP to cause CKD in some persons?
- Will we ever see a long-term RCT of antihypertensive treatment in primary hypertension with effect on GFR as the primary endpoint?

The RENIS-T6 team (2007-2009)

The RENIS-FU team (2013-2015)

The RENIS-3 team (2018-2020)

The RENIS-4 team (2023-2025) !!

The RENIS-4 team (2023-2025)!!