Title of the symposium on "*Genomics in CKD*"

Genome-wide Association Study of the Risk of Chronic Kidney Disease and Kidney-related Traits in the Japanese Population: J-Kidney-Biobank.

Hajime Nagasu, Yuka Sugawara, Hirakawa Yosuke, Naoki Kashihara

Takashi Wada, Miho Shimizu, Motoko Yanagita, Yuichiro Kitai,Ichiei Narita, Shin Goto, Jun Wada, Satoshi Yamaguchi, Asami Ueno, Toshiaki Nakano, Hiromasa Kitamura, Shoichi Maruyama, Sawako Kato, Hirokazu Okada, Hiroaki Amano, Daichi Fukaya, Koichi Tamura, Hiromichi Wakui, Shinya Taguchi, Takashi Yokoo, Yukio Maruyama, Akira Fukui, Kazuhiko Tsuryuya, Masaomi Nangaku

TSN/APCN
COI disclosure

presenter：　Hajime Nagasu

I have no relevant financial relationship to disclose any COI for this presentation.

Genomic Characteristics and Evolutionary Adaptation in Japanese

Category	Features and Findings
Research Infrastructure	Built upon large cohorts like BioBank Japan (BBJ) and ToMMo. ToMMo established a cohort of 150,000 healthy Japanese individuals, with 100,000 whole genomes sequenced.
Very Recent Selection	Strong signatures of natural selection identified, dating back only **2,000–3,000 years**, distinct from European populations.
Major Selected Loci	The three loci showing the strongest natural selection signatures genome-wide: 1. **ADH clusters** (4q23) 2. **MHC region** (6p21) 3. **BRAP-ALDH2** (12q24)
Metabolic Adaptation	Selection signatures show strong overlap with traits related to **alcohol and nutrition metabolism**. Alleles in *ADH1B* and *ALDH2* associated with lower alcohol consumption are under strong **positive selective pressure**.
Population Structure	The genetic differences induced by recent selection manifest as heterogeneity in Derived Allele Frequencies (DAF) between the **Honsyu** and **Ryukyu (Okinawa)** clusters.

Today's Topics

J-kidney biobank

↓

Genomic Characteristics of the Japanese Population
~non renal disease~

↓

Genomic Characteristics of the Japanese Population
~renal disease~

Today's Topics

J-kidney biobank

Genomic Characteristics of the Japanese Population
~non renal disease~

Genomic Characteristics of the Japanese Population
~renal disease~

J-Kidney-Biobank: JKB

A total of 12 universities in Japan participated and contributed to sample collection. Patients clinically diagnosed with CKD by physicians were included according to the enrollment criteria. The participating institutions are listed below.

1. **Kawasaki Medical School**
2. **Kanazawa University**
3. **Kyoto University**
4. **Niigata University**
5. **Okayama University**
6. **Kyushu University**
1. **Nagoya University**
7. **Saitama Medical University**
8. **Yokohama City University**
9. **The Jikei University School of Medicine**
10. **Nara Medical University**
11. **The University of Tokyo**

Japan kidney biobank

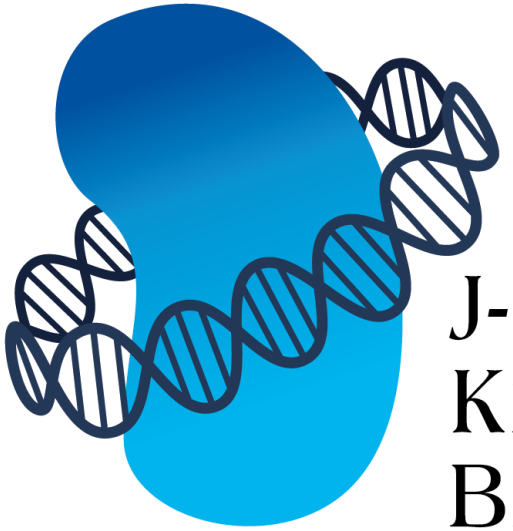
J-Kidney-Biobank

- Genome
- Metablome (Urine and plasma)
- Proteome (plasma)
- Clinical data including laboratory data.

We have collected detailed longitudinal clinical data along with a subset of CT imaging. This enables integrated, multifaceted analyses and allows surrogate endpoints—such as eGFR slope and reduction in proteinuria—to be evaluated.

APCN x TSN 2025, December 7, 16:00-17:15
Session: CKD cohort registration experience

From Concept to Discovery: The Journey and Learnings of the J-Kidney-Biobank.



J-Kidney-Biobank

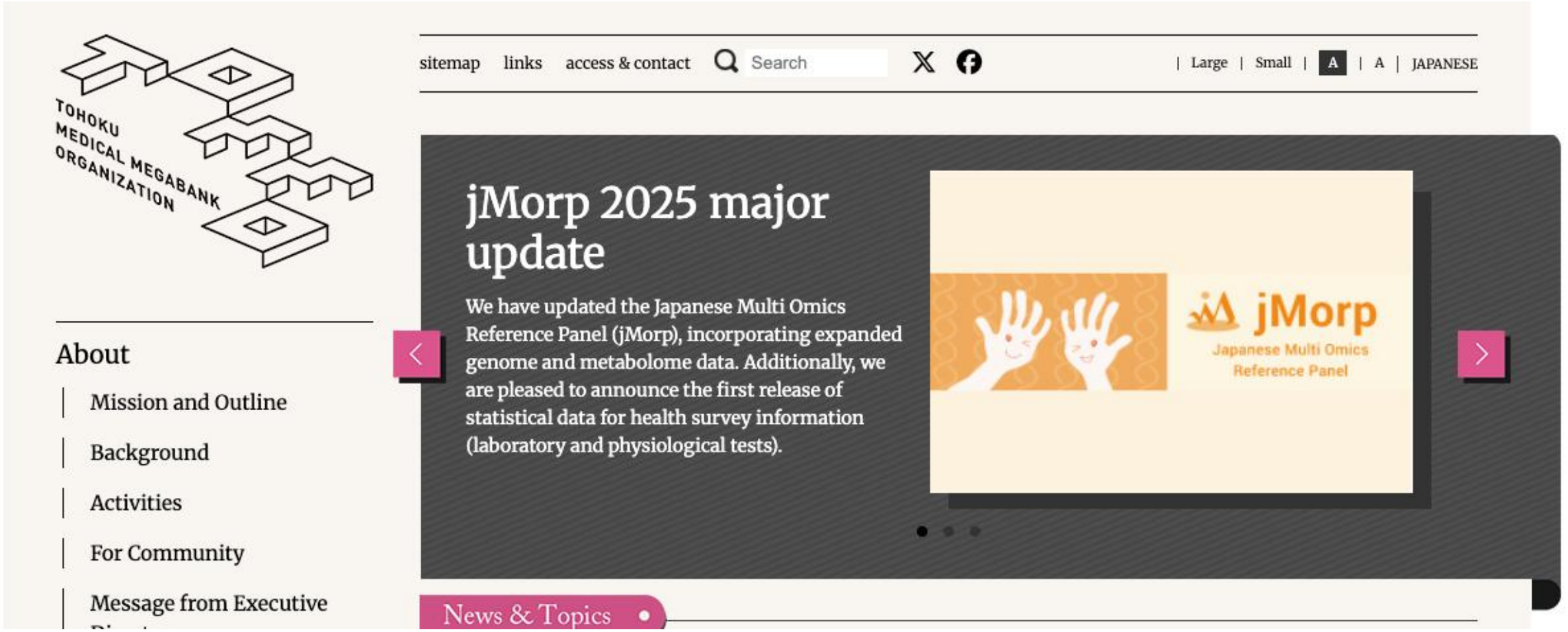
Yuka Sugawara

Division of Nephrology and Endocrinology,
The University of Tokyo Graduate School of Medicine,
Tokyo, Japan.

東京大学 THE UNIVERSITY OF TOKYO

東大病院 The University of Tokyo Hospital

Tohoku Medical Megabank Organization
ToMMo



The Tohoku Medical Megabank Project (TMM) was established following the 2011 Great East Japan Earthquake and Tsunami with two primary objectives.

Tohoku Medical Megabank Organization
ToMMo

The Tohoku Medical Megabank Project (TMM) was established following the 2011 Great East Japan Earthquake and Tsunami with two primary objectives:

1. **Reconstruction of Healthcare Services:** To rapidly reconstruct and revitalize community medical services in the areas severely affected by the disaster.
2. **Establishment of a Novel System:** To establish a cutting-edge medical system aligned with the global trend toward large-scale medical information technology and genomic epidemiology.

The TMM project was envisioned as a necessary step beyond simply restoring lost functions, addressing both the catastrophic damage to medical facilities and the severe decline and outflow of medical professionals in the Tohoku region. By becoming a future-oriented medical hub, the project aims to serve as a driving force to attract and retain essential medical personnel.

Today's Topics

J-kidney biobank

Genomic Characteristics of the Japanese Population ~non renal disease~

Genomic Characteristics of the Japanese Population ~renal disease~

Non-Renal Disease and Genetic Characteristics in Japanese

Category	Features and Findings
Heart Failure (HF) GWAS	Japanese GWAS (16,251 HF cases) identified **18 genome-wide significant loci** for all-cause HF, including 5 novel loci.
EAS-Specific HF Loci	Genes such as *AOPEP*, *CSMD1*, *DPY19L4*, *NEBL*, and *SPRED2* were specifically highlighted as significant only in the **East Asian (EAS)** population.
Differential *TTN* Effect Size	A common *TTN* variant (rs1484116) has a lower risk allele frequency in EAS (0.315) vs. EUR (0.800) but exhibits a **higher effect size in Japanese** for HFrEF (Heart failure with reduced ejection fraction).
Paroxysmal Atrial Fibrillation (PAF)	Whole-exome sequencing in a Japanese cohort (N=2348) identified genetic factors associated with PAF risk.
Novel PAF-Related Genes	**Four novel genes—ZNF785, SMPD3, GFRA4, and LGALS1**—were significantly associated with PAF risk in this Japanese population.

Today's Topics

J-kidney biobank

↓

Genomic Characteristics of the Japanese Population
~non renal disease~

↓

Genomic Characteristics of the Japanese Population
~renal disease~

Meta-GWAS analysis of the J-kidney biobank and ToMMo cohorts

ARTICLE

Check for updates

Genome-wide association study of the risk of chronic kidney disease and kidney-related traits in the Japanese population: J-Kidney-Biobank

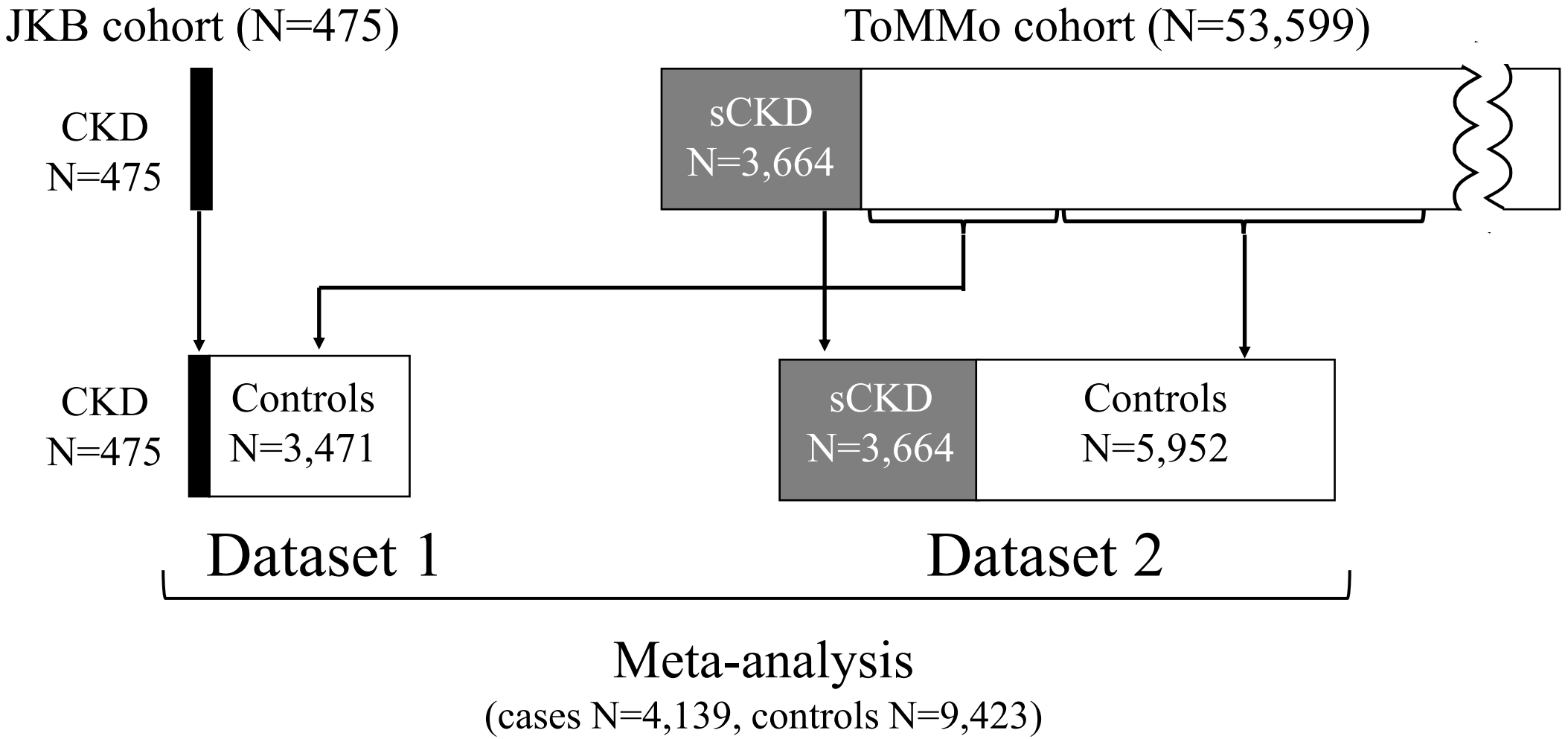
Yuka Sugawara[1], Yosuke Hirakawa[1], Hajime Nagasu[2], Akira Narita[3], Akihiro Katayama[4], Jun Wada[4], Miho Shimizu[5], Takashi Wada[5], Hiromasa Kitamura[6], Toshiaki Nakano[6], Hideki Yokoi[7], Motoko Yanagita[7], Shin Goto[8], Ichiei Narita[8], Seizo Koshiba[3,9], Gen Tamiya[3,10,11], Masaomi Nangaku[1], Masayuki Yamamoto[3,10] and Naoki Kashihara[2]✉

Journal of Human Genetics;
https://doi.org/10.1038/s10038-022-01094-1

Meta-GWAS analysis of the J-kidney biobank and ToMMo cohorts

Supplementary Figure S1. The relationship between the two cohorts and the two datasets.

The cases in dataset 1 were the CKD patients from JKB cohort who are clinically diagnosed as CKD at nephrology units of university hospitals. The cases in dataset 2 were the suspected CKD cases presenting eGFR < 60mL/min/1.73m2 and/or urinary protein ≥ (1+) at the time of recruitment to ToMMo cohort, which is a health check-up cohort. The controls of both datasets were the participants to ToMMo cohort with eGFR > 60 mL/min/1.73m2 and negative urinary protein.



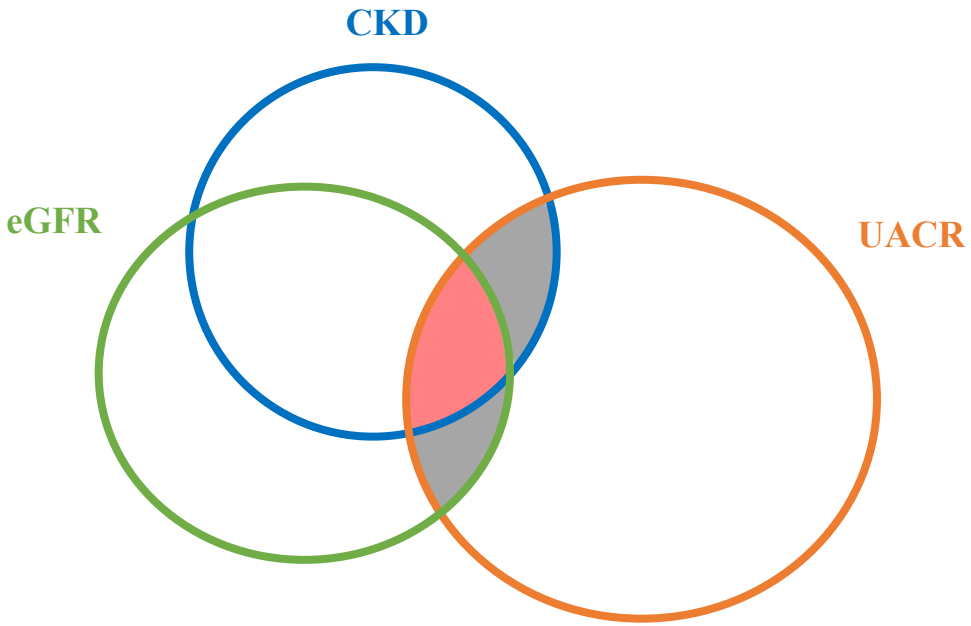
Meta-GWAS analysis of the J-kidney biobank and ToMMo cohorts

Baseline characteristics of participants

	Dataset 1			Dataset 2			Total		
	CKD Cases (N=475)	Controls (N=3 471)	ALL (N=3 946)	sCKD Cases (N=3 664)	Controls (N=5 952)	ALL (N=9 616)	Cases (N=4 139)	Controls (N=9 423)	ALL (N=13 562)
Age, mean (SD)	68.5 (12.0)	61.8 (8.5)	62.6 (9.3)	66.1 (6.8)	61.8 (8.4)	63.4 (8.1)	66.4 (7.6)	61.8 (8.4)	63.2 (8.5)
Female, n (%)	171 (36.0)	2 113 (60.9)	2 284 (57.9)	1 827 (49.9)	3 680 (61.8)	5 507 (57.3)	1 998 (48.3)	5 793 (61.5)	7 791 (57.4)
Participants with eGFR data, n	474	3 470	3 944	3 664	5 952	9 616	4 138	9 422	13 560
eGFR, mean (SD), ml/min/1.73m^2	35.8 (21.6)	78.7 (12.1)	73.5 (19.5)	55.7 (10.4)	78.7 (12.4)	69.9 (16.2)	53.4 (13.7)	78.7 (12.3)	71.0 (17.3)
Participants with UACR data, n	357	3 457	3 814	3 627	5 932	9 559	3 984	9 389	13 373
UACR, mean (SD), mg/gCre	385.0 (271.9)	15.0 (50.3)	49.7 (144.3)	65.5 (219.5)	14.7 (33.1)	34.0 (139.9)	94.2 (242.5)	14.8 (40.3)	38.5 (141.3)

Meta-GWAS analysis of the J-kidney biobank and ToMMo cohorts

CKD related traits



- CKD : Binary variable
- eGFR : Continuous variable
- UACR : Continuous variable

Table 2. Loci associated with the incidence of CKD

rsID	Chr.	Position (Hg19)	Gene	Ref/Alt	Frequency		GWAS meta-analysis	
					8.3kJPN	gnomAD	β	*p*-value
rs116802592	1	11979466	*KIAA2013*	C/T	0.0439	0.0142	0.0949	2.18×10^{-17}
rs1048619	3	16269117	*GALNT15**	G/T	0.0554	0.1210	0.058	1.77×10^{-8}
rs73200720	3	192665070	*MB21D2*†	C/T	0.0122	0.0191	0.1199	2.39×10^{-9}
rs10031236	4	190298297	*FRG1*†	T/C	0.9751	0.8372	0.1118	4.93×10^{-15}
rs9689694	6	150091773	*PCMT1*	C/T	0.7243	0.5028	-0.0331	1.15×10^{-9}
rs76762104	7	26431321	*SNX10*†	T/G	0.0072	0.0266	-0.3154	4.37×10^{-25}
rs757889	8	1504024	*DLGAP2**	T/C	0.9337	0.8607	0.058	8.76×10^{-10}
rs7048659	9	117533289	*TNSF15*	T/C	0.0235	0.4087	-0.0821	3.20×10^{-8}
rs28488438	9	140268976	*EXD3*	C/T	0.0254	0.0450	0.0775	4.40×10^{-8}
rs3782886	12	112110489	*BRAP **	T/C	0.2131	0.0187	-0.0361	7.54×10^{-10}

Genomic control correction was applied to each *p*-value. There were 429 significant SNPs on chromosome 6, 149–150 Mb. Among these, rs9689694, with the smallest *p*-value, is listed in the table.
Similarly, there were 16 significant SNPs on 112 Mb of chromosome 12, of which rs3782886 had the smallest *p*-value, as listed in the table.
8.3kJPN, 8.3KJPN whole-genome variation panel; Chr., chromosome; gnomAD, gnomAD v2.1.1; CKD, chronic kidney disease; SNP, single nucleotide polymorphism; GWAS, genome-wide association study; *, One or multiple SNPs associated with CKD have been previously reported within 1 Mbp of the locus. †, The nearest gene name is shown if the SNP with the smallest *p*-value is located in the intergenic region.

10 loci associated with CKD

Table 3. Loci associated with eGFR

rsID	Chr.	Position (Hg19)	Gene	Ref/Alt	Frequency		GWAS meta-analysis	
					8.3kJPN	gnomAD	β	*p*-value
rs116802592	1	11979466	*KIAA2013*	C/T	0.0439	0.0142	-2.6321	2.14×10^{-8}
rs140327554	1	78309785	*NSRP1P1**	TAAAA/TAAA	0.3102	0.117	1.2513	3.27×10^{-8}
-	2	217654793	*RPL31P14**	CAA/CA	0.4718	-	-1.1482	7.61×10^{-9}
rs4715517	6	54973761	*HCRTR2**	C/A	0.0667	0.0077	-2.1673	4.39×10^{-8}
rs374648186	6	150107532	*PCMT1*	T/C	0.5734	0.3054	-1.4632	8.12×10^{-10}
rs10277115	7	1285195	*UNCX**	A/T	0.3241	0.5826	1.2478	3.51×10^{-9}
rs76762104	7	26431321	*SNX10*†*	T/G	0.0072	0.0266	14.7294	1.22×10^{-14}
rs3782886	12	112110489	*BRAP**	T/C	0.2131	0.0187	1.8793	7.97×10^{-15}
rs77924615	16	20392332	*PDILT-UMOD**	G/A	0.2260	0.1640	1.3304	2.92×10^{-8}

9 with eGFR levels

Table 4. Loci associated with UACR

rsID	Chr.	Position (Hg19)	Gene	Ref/Alt	Frequency		GWAS meta-analysis	
					8.3kJPN	gnomAD	β	*p*-value
rs191954357	1	34847375	*RP4-657M3.2, MIR552*	C/T	-	0.0023	117.946	1.17×10^{-9}
rs61732477	1	113741619	*RP11-389O22.5*	T/C	-	0.0281	57.4107	1.05×10^{-8}
rs77307668	1	146622739	*PRKAB2*	A/G	0.0154	0.0037	-39.8705	3.24×10^{-8}
-	2	74321359	*TET3*	G/A	-	3.18×10^{-5}	-45.6043	5.95×10^{-9}
rs142587251	2	147482206	*RP11-638D14.1*	G/A	-	0.0016	65.7656	4.68×10^{-9}
rs763997494	2	197904396	*ANKRD44*	TGTGTGTGC/T	0.0059	0.0065	136.023	7.59×10^{-9}
rs13115639	4	16569606	*LDB2*	G/A	0.0777	0.0479	18.4621	3.18×10^{-8}
rs10031236	4	190298297	*FRG1* *†	T/C	0.9751	0.8372	29.5671	3.83×10^{-8}
rs1383220102	5	44451469	*FGF10*†	CT/C	0.0079	0.0021	133.934	2.30×10^{-9}
rs748100735	5	138886722	*AC010378.2*	C/T	0.0122	0.0002	58.0022	2.26×10^{-10}
rs149509413	5	171924465	*AC011407.1*	T/C	0.0121	-	43.1525	2.69×10^{-8}
rs183062876	6	24023427	*RP11-31K13.1, NRSN1*	C/G	-	0.0012	-71.9094	7.61×10^{-9}
-	6	114096716	*MARCKS* †	Del/CTTTTTTT	-	-	96.0015	7.27×10^{-10}
rs145244410	6	167905133	*TCP10, RP11-351J23.2*	C/G	-	0.0271	-120.117	1.87×10^{-8}
rs76762104	7	26431321	*SNX10* *†	T/G	0.0072	0.0266	-100.5	1.70×10^{-11}
-	8	124611215	*KLHL38* *†	Del/AATA…(111bp)	-	-	58.351	9.75×10^{-10}
rs576217269	10	124430036	*DMBT1, C10orf120*	C/T	-	0.0048	62.9036	3.81×10^{-9}
rs184385689	12	127001150	*RP11-407A16.1*	A/G	-	0.0003	-42.6178	8.87×10^{-9}
-	15	55641464	*RP11-139H15.6* *	T/G	-	-	-69.2692	4.00×10^{-10}
rs527994431	16	10685260	*EMP2*†	C/T	0.0144	0.00003	39.8073	4.02×10^{-8}
rs73977230	17	10905596	*RP11-963H4.8*	C/T	-	0.0221	64.5706	9.34×10^{-9}
rs569245088	18	2510795	*METTL4* *	G/A	-	3.18×10^{-5}	57.0629	4.57×10^{-8}

22 with UACR

Figure 1. The GWAS meta-analysis for the multiple kidney-related traits.

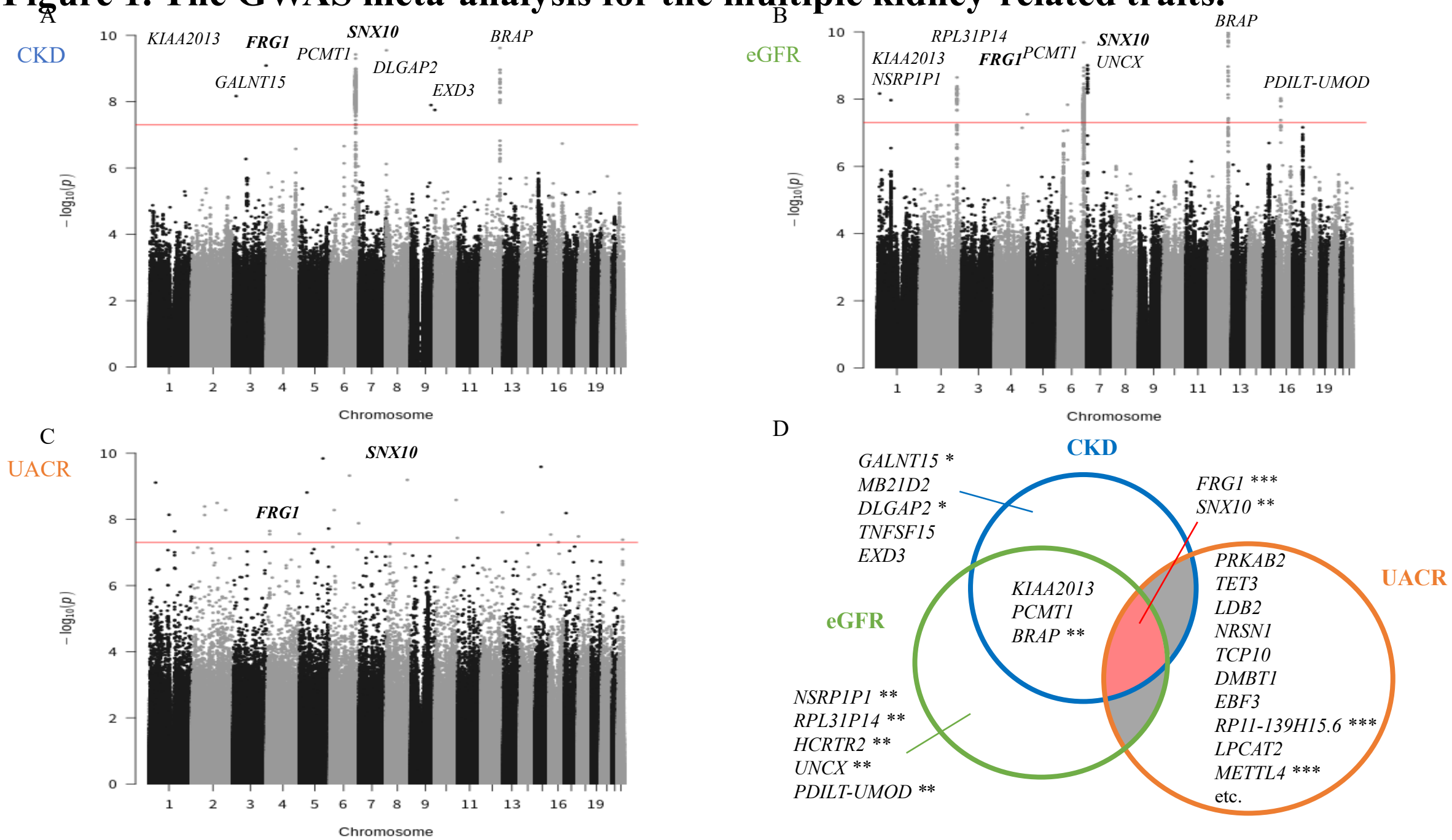
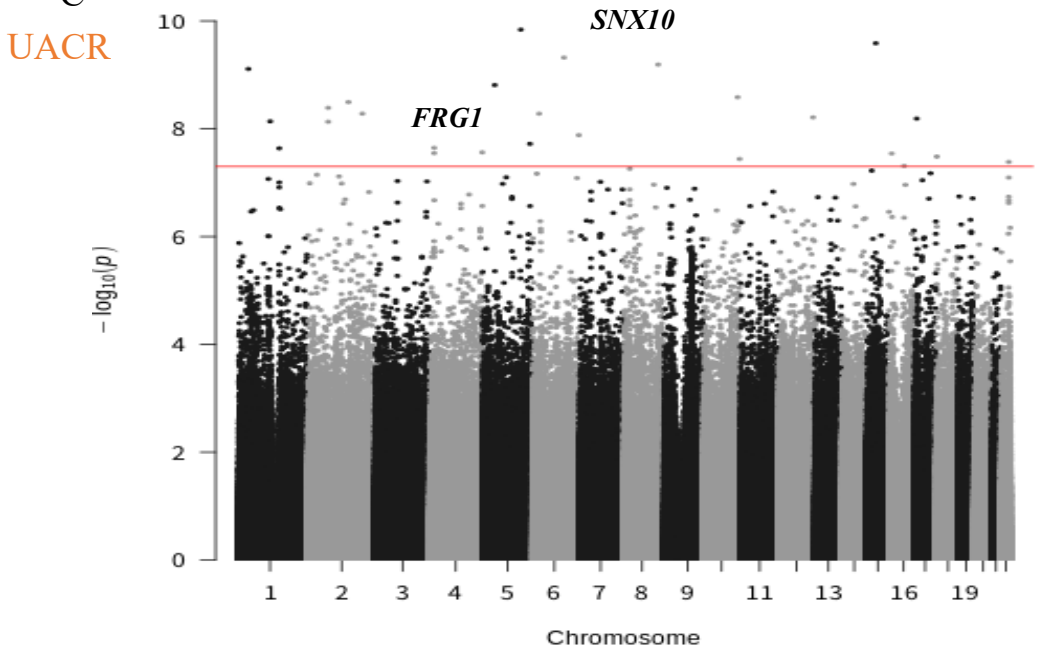


Figure 1. The GWAS meta-analysis for the multiple kidney-related traits.

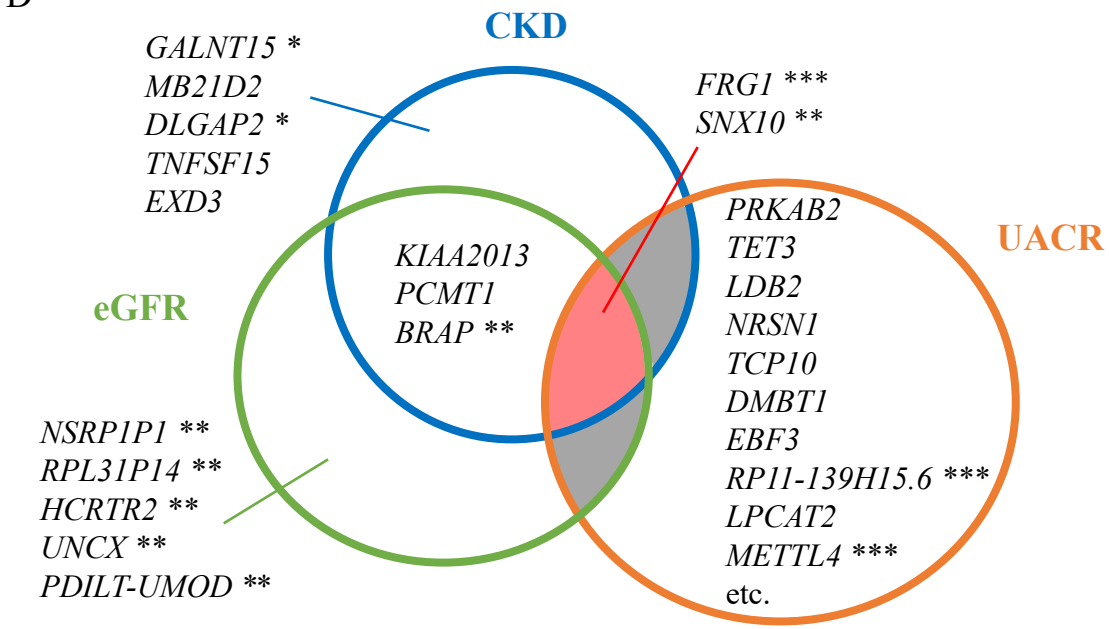
Loci that attained genome-wide significance for more than two traits (BRAP, FRG1, KIAA2013, PCMT1, and SNX10) are shown in bold. Loci previously reported to be associated with each of the three traits are identified with asterisks (CKD*, eGFR, UACR***).**

Half of the CKD-associated loci overlapped with eGFR-associated loci, whereas most UACR-associated loci were distinct.

C



D



Conclusion from this study

- As a result, **10 loci associated with CKD** risk, **9 with eGFR levels**, and **22 with UACR** were identified. Of these, 22 loci were previously unreported, indicating unique genetic features of CKD in the Japanese population.
- Notably, about half of the CKD-associated loci overlapped with eGFR-associated loci, whereas **most UACR-associated loci were distinct**, suggesting that reduction of eGFR and increased albuminuria may arise from different genetic architectures.
- These findings provide important insights into CKD pathophysiology in the Japanese population and support future progress in personalized medicine.

J Hum Genet. 2023 Feb;68(2):55-64.

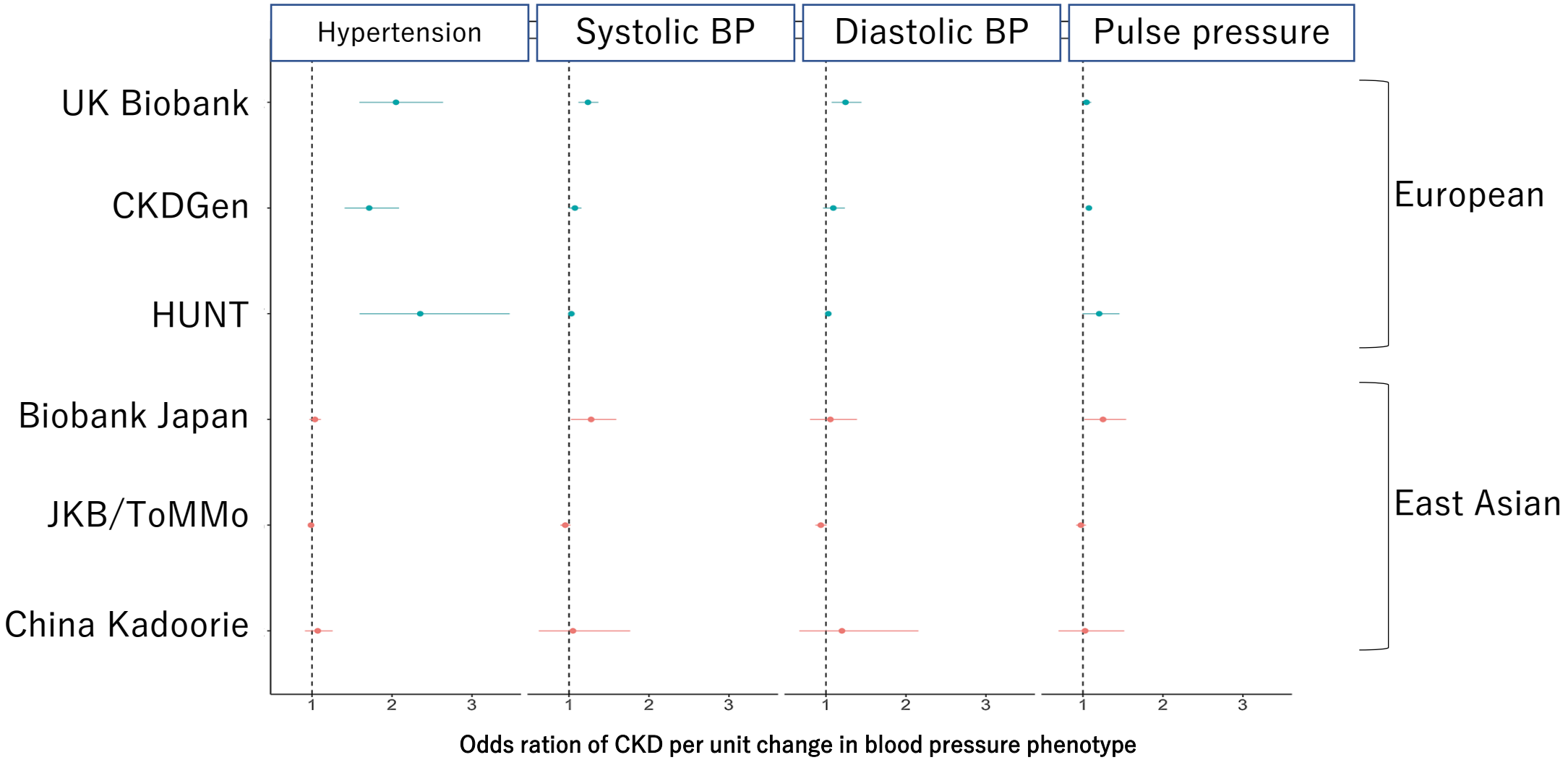
International Journal of Epidemiology, 2021, 1995–2010
doi: 10.1093/ije/dyab203
Advance Access Publication Date: 20 October 2021
Original article

Mendelian Randomization

Trans-ethnic Mendelian-randomization study reveals causal relationships between cardiometabolic factors and chronic kidney disease

Population	N_case	N_control	Sample_size	Consortium
European	6985	397602	404587	UKBB
European	3292	64476	67768	HUNT study
European	41395	439303	480698	CKDGen
East Asian	848	94887	95735	China Kadoorie Biobank
East Asian	4046	9423	13469	**J-Kidney-Biobank/ToMMo**
East Asian	8586	133808	142394	BioBank Japan

Int J Epidemiol. 2022 Jan 6;50(6):1995.



The different causal relationship between hypertension and CKD in Europeans and East Asians suggests that blood pressure may affect CKD differently depending on ancestry.

Int J Epidemiol. 2022 Jan 6;50(6):1995.

Meta-analysis in East Asia

- Addressing the current shortage of large-scale meta-GWAS studies aimed at identifying CKD-related genetic components characteristic of East Asia.

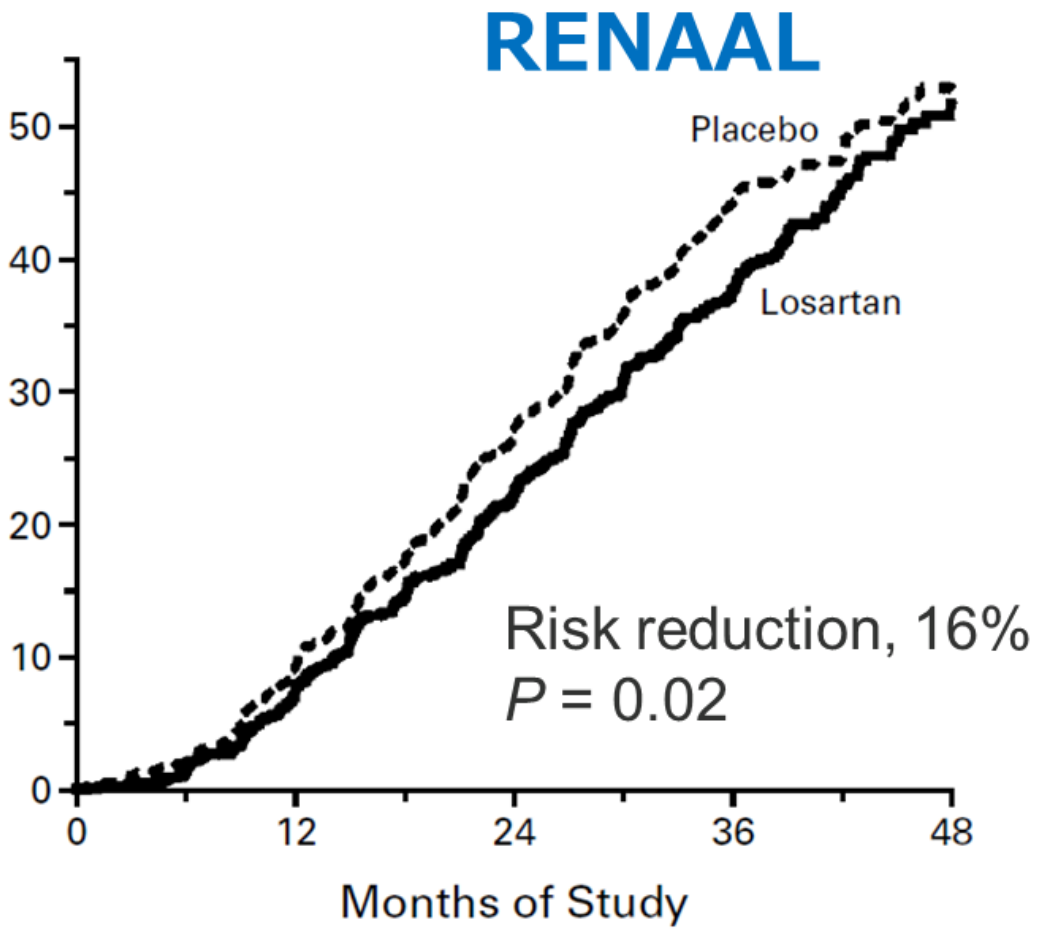
- Evaluating whether findings reported in major international studies (Nat Commun 2019; Nat Genet 2019) are reproducible in East Asian cohorts and conducting additional analyses such as PRS calculations.

The following cohorts are participating:

- **Biobank Japan**
- **Iwate Tohoku Medical Megabank Organization**
- **J-MICC**
- **JPSC-AD**
- **China Kadoorie Biobank from China**
- **KNOW-CKD/Koges from Korea**
- **Taiwan Biobank from Taiwan**

on going!!

Randomized controlled trials (RCTs) demonstrating the renal protective effects of ARBs in patients with diabetic kidney disease.

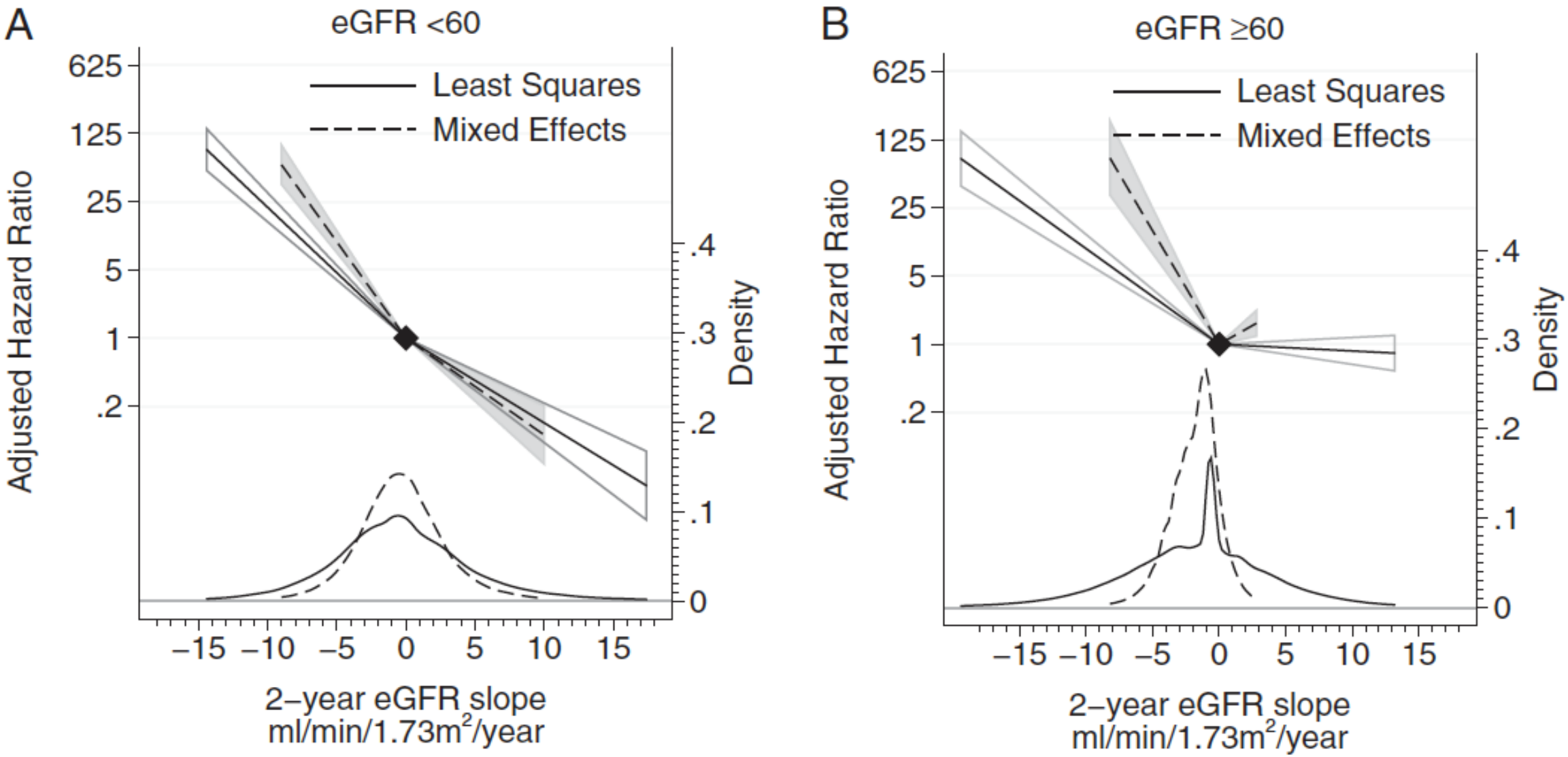


Kidney specific hard endpoints

1) Doubling of serum creatinine
2) Progression to End-Stage Kidney Disease
3) Kidney-related death / Renal death

N Engl J Med. 2001 Sep 20;345(12):861-9.

Analysis in cohorts: associations between population distribution of change in glomerular filtration rate (GFR) slope and end-stage kidney disease



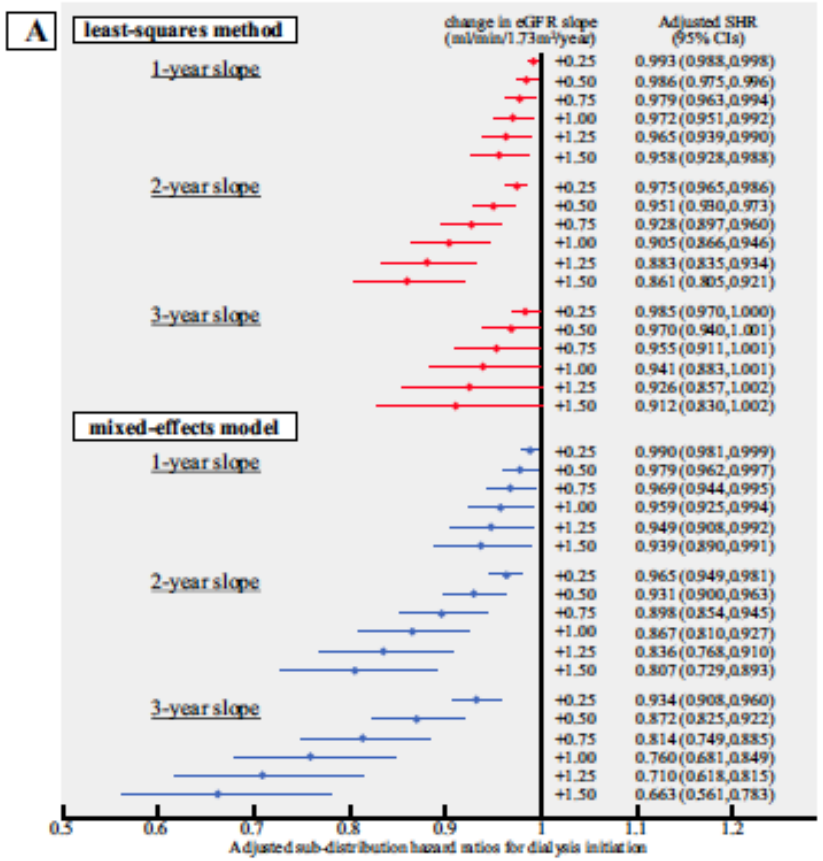
Clinical and Experimental Nephrology (2023) 27:847–856
https://doi.org/10.1007/s10157-023-02376-4

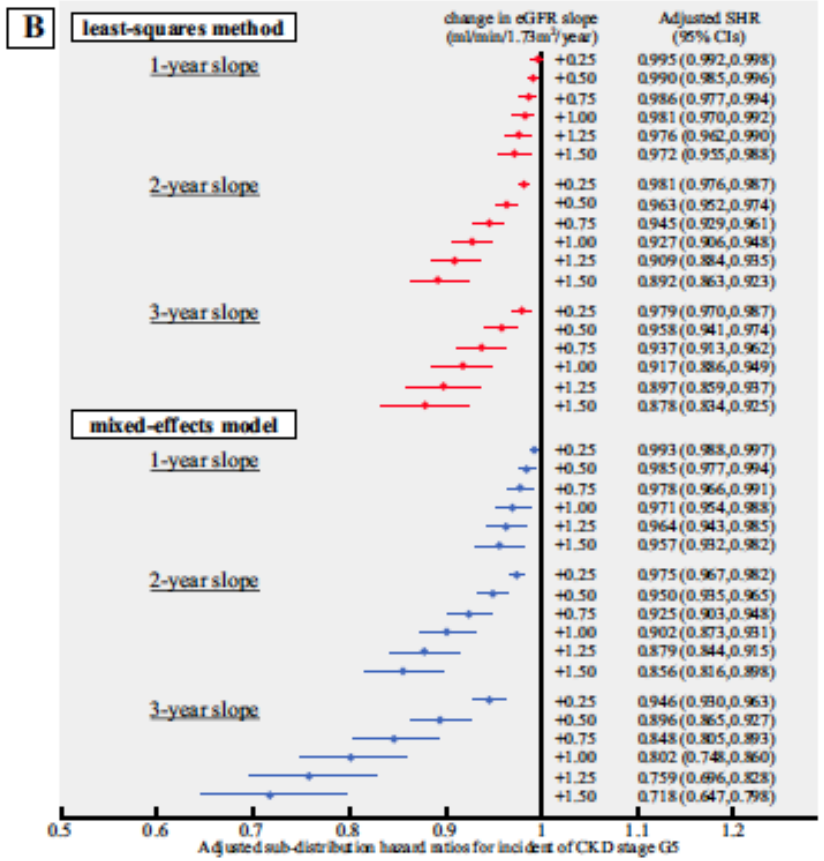
ORIGINAL ARTICLE

eGFR slope as a surrogate endpoint for clinical study in early stage of chronic kidney disease: from The Japan Chronic Kidney Disease Database

Seiji Itano[1] · Eiichiro Kanda[2] · Hajime Nagasu[1] · Masaomi Nangaku[3] · Naoki Kashihara[1]

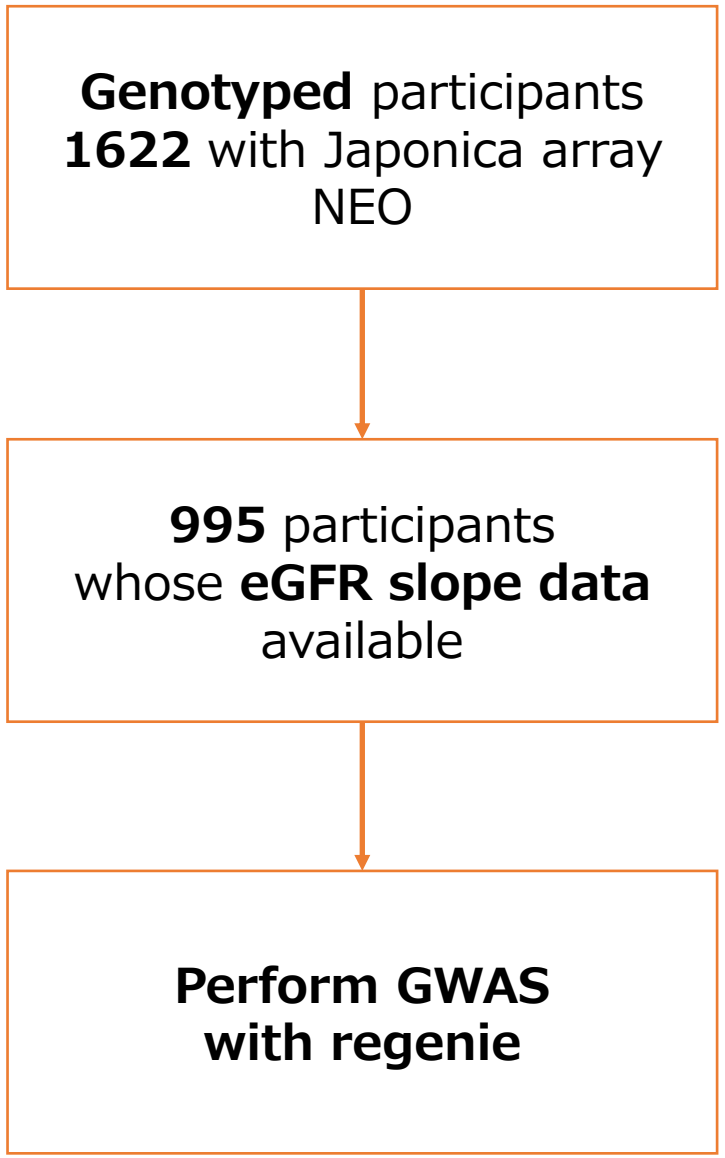
Clinical and Experimental Nephrology (2023) 27:847–856





Surrogate
ΔeGFR slope
0.5–1.0
ml/min /1.73 m2/yr

Flow diagram for eGFR slope GWAS in JKB

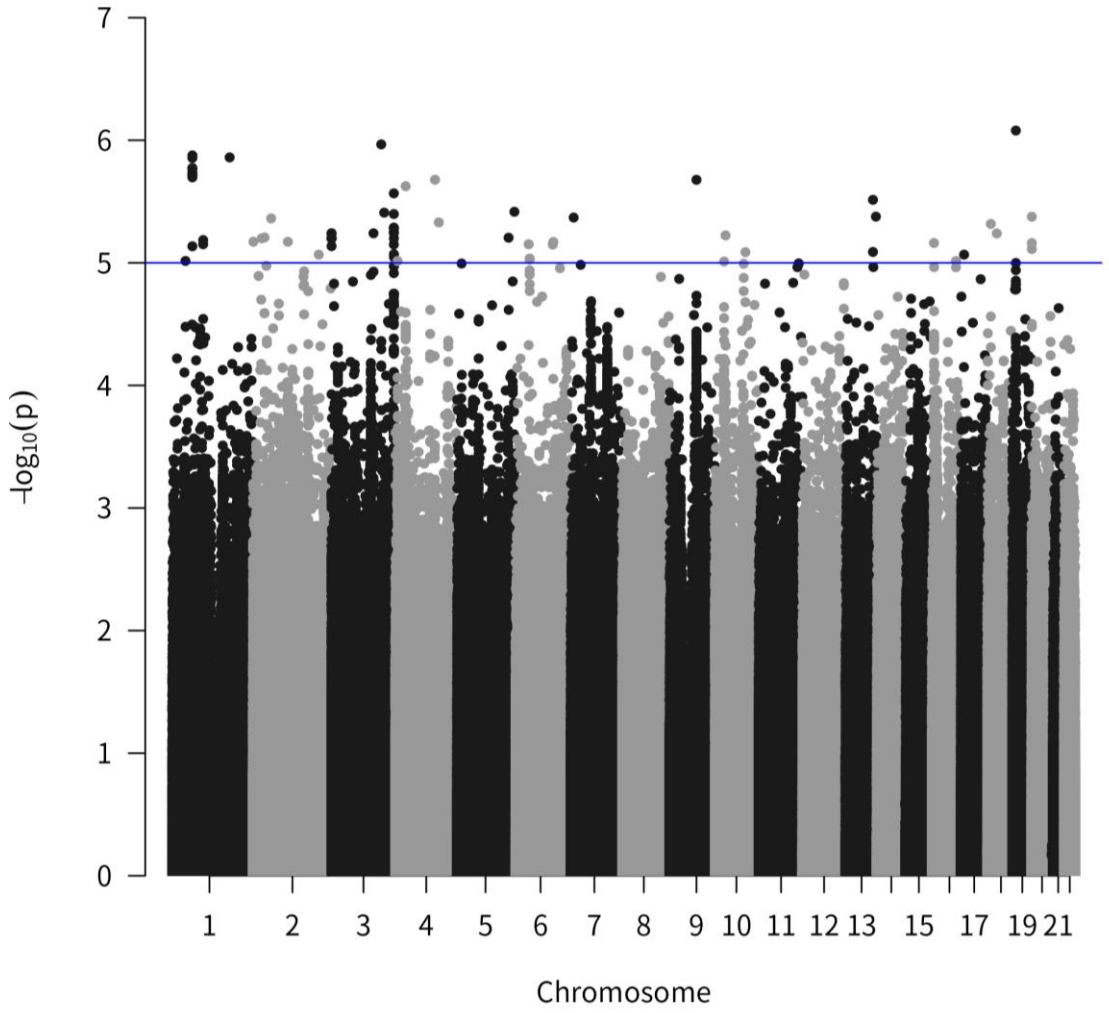


All of the participants were hospital diagnosed CKD.

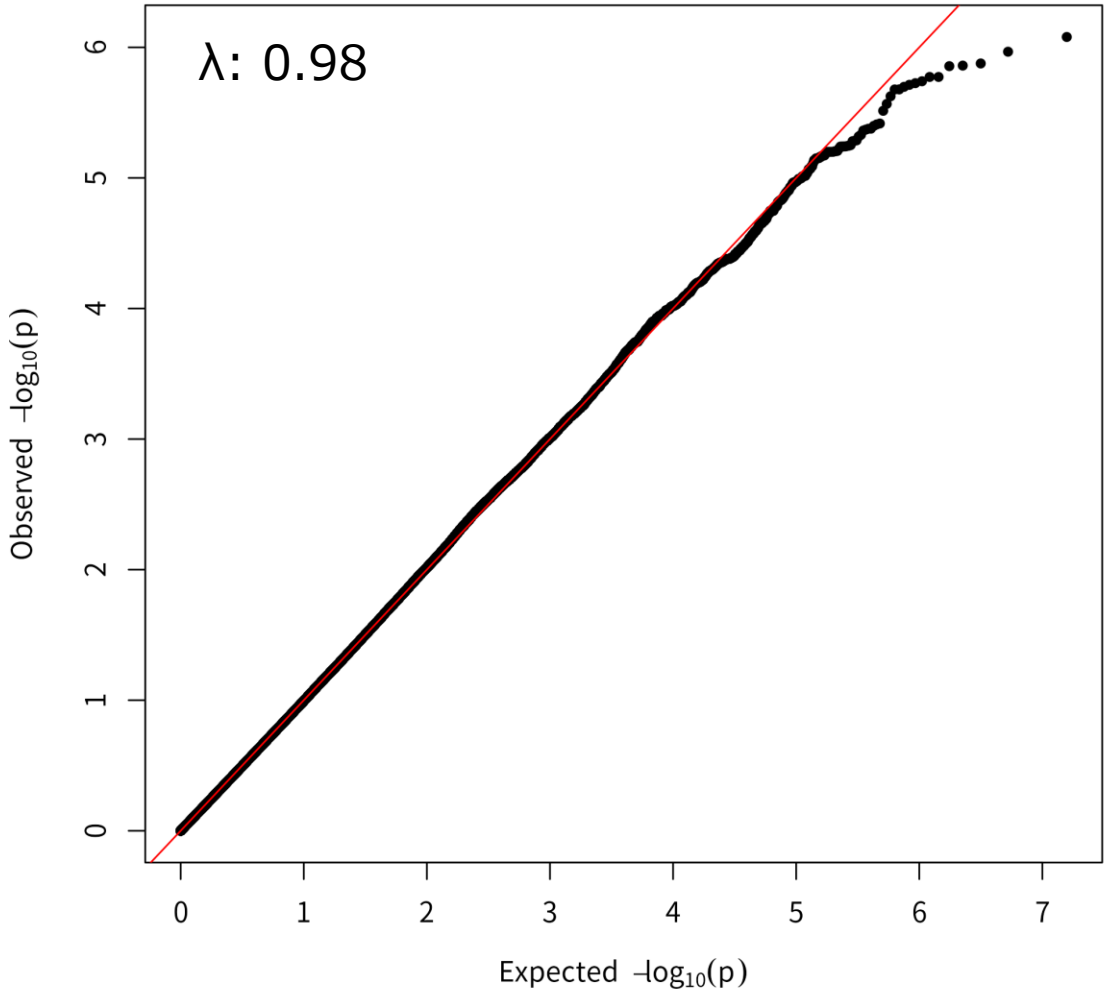
We collected no relatives, but max PI_HAT was 0.278 (the second highest was 0.143)

Covariates : Age, Sex, PC1-20
Original GWAS result includes 14,269,263 variants.

Result of GWAS – MAF >= 0.05 & Info >= 0.3



Number of SNPs : 7,891,598

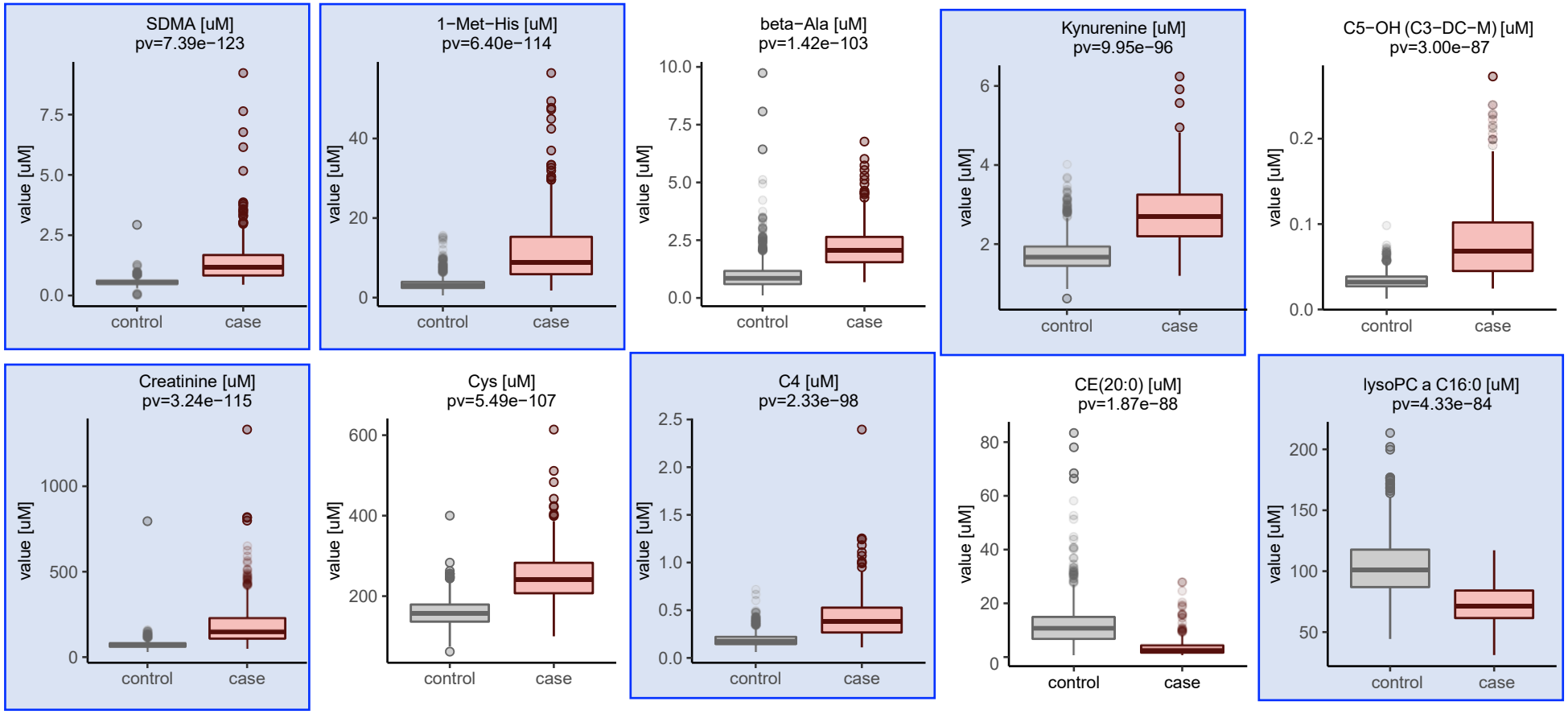


on going!!

Comparison of blood metabolite levels between patients with kidney disease and healthy controls (ToMMo)

Top 10 metabolites

case: 269, control: 943



The metabolites in the blue box have been previously reported.

Enhancing Genetic Studies with Metabolic Simulations

The Challenge with Standard MGWAs

Findings are statistical correlations, not proven causes

This can lead to false positives where an association appears significant only by chance.

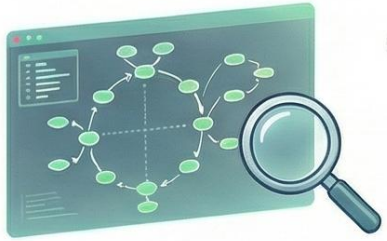
Small sample sizes can miss true genetic associations

This results in false negatives, overlooking important relationships between variants and metabolites.

Experimentally validating thousands of potential links is daunting

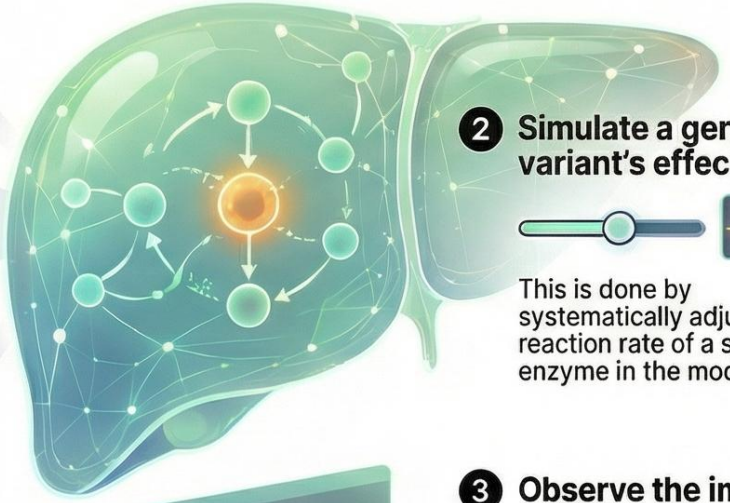
The vast number of combinations makes it difficult to prioritize research efforts effectively.

The Solution: Metabolic Pathway Simulations



1 Model a metabolic pathway in a computer

A model of the human liver cell folate cycle was used for this study.



2 Simulate a genetic variant's effect

This is done by systematically adjusting the reaction rate of a specific enzyme in the model.

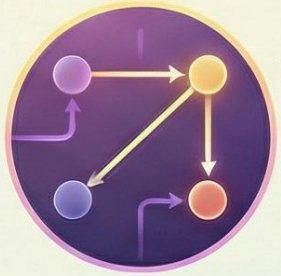
3 Observe the impact on metabolite levels

The simulation predicts how metabolite concentrations change in response to the "genetic variant".

Key Benefits of the Simulation Approach

Validates and explains real-world data

The simulation accurately replicated MGWA5 results, confirming known gene-metabolite relationships.



Uncovers connections missed by MGWAS

Simulations revealed significant metabolite fluctuations for pairs considered insignificant in MGWAS.

Classifies enzymes to prioritize research

Enzymes were grouped by their impact: wide, targeted, or minimal, focusing future studies.

Acknowledgement

J-Kidney-Biobank Recruitment Sites

Kawasaki Medical School
Naoki KASHIHARA
★**Hajime NAGASU**

Kanazawa University
Takashi WADA
Miho SHIMIZU

Kyoto University
Motoko YANAGITA
Yuichiro KITAI

Niigata University
Ichiei NARITA
Shin GOTO

Okayama University
Jun WADA
Satoshi YAMAGUCHI
Asami UENO

Kyushu University
Toshiaki NAKANO
Hiromasa KITAMURA

Nagoya University
Shoichi MARUYAMA
Sawako KATO

Saitama Medical University
Hirokazu OKADA
Hiroaki AMANO
Daichi FUKAYA

Yokohama City University
Koichi TAMURA
Hiromichi WAKUI
Shinya TAGUCHI

The Jikei University School of Medicine
Takashi YOKOO
Yukio MARUYAMA
Ryo FUKUI

Nara Medical University
Kazuhiko TSURUYA
Kenichi SAMEJIMA
Kaori TANABE

The University of Tokyo
Masaomi NANGAKU
Yosuke HIRAKAWA

Tohoku Medical Megabank

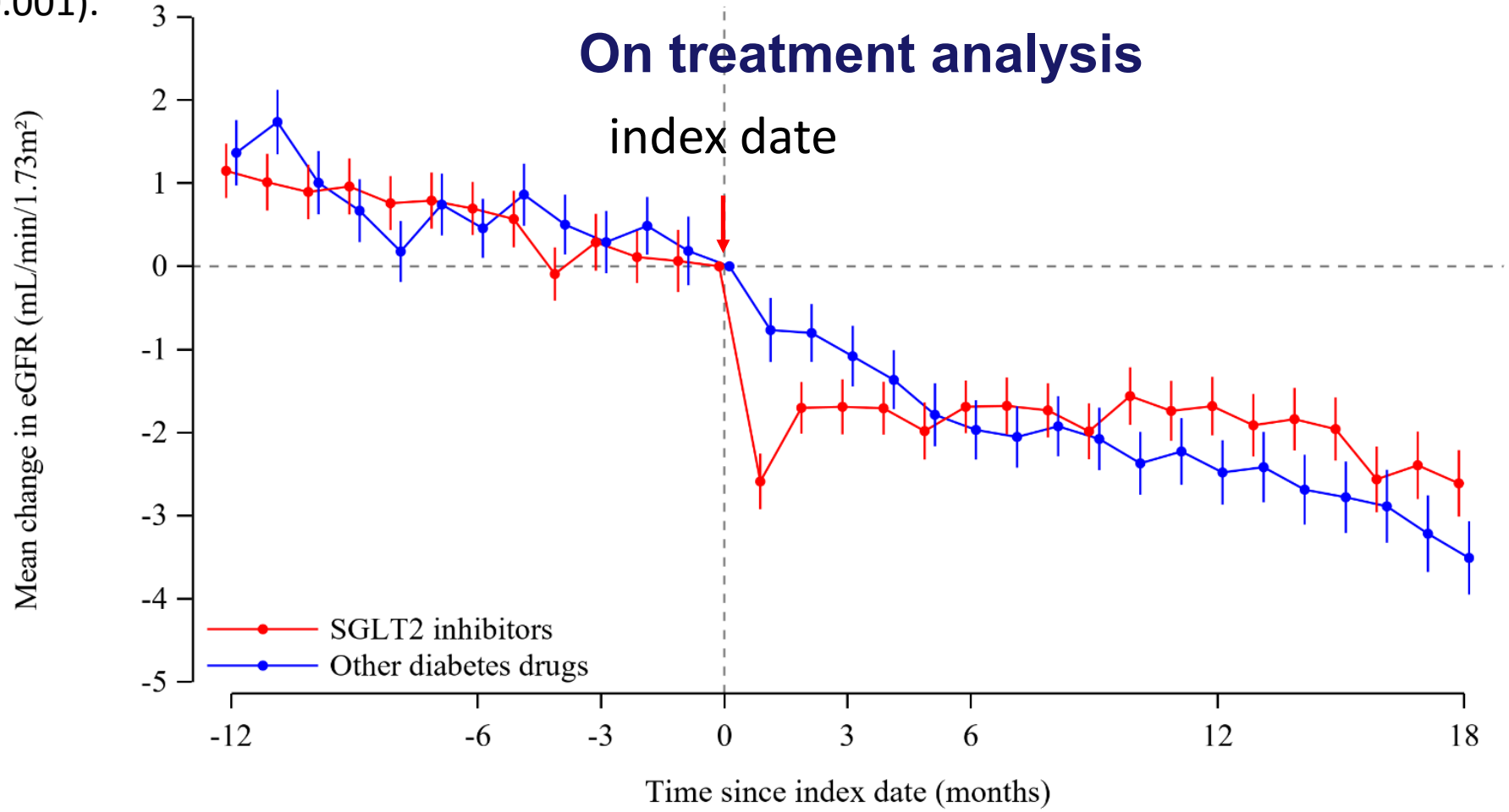
Masayuki YAMAMOTO
Seizo KOSHIBA
Gen TAMIYA
Mika SAKURAI
Akira NARITA

We thank everyone involved in this study!!

Thank you ☺

Change in eGFR over time before and after initiation of SGLT2 inhibitors or other diabetes drugs

- The between-group difference in the rate of eGFR decline **was 0.75 mL/ min/1.73 m^2 per year** , favoring SGLT2 inhibitors (P < 0.001).



Number at risk								
SGLT2 inhibitors	453	497	396	716	439	503	368	256
Other diabetes drugs	294	400	334	576	366	394	308	213

Renal Disease and Disease-Associated SNPs in Japanese

Category	Features and Findings
Large-Scale CKD GWAS	Meta-analysis of the largest Japanese genome cohorts (N ≥ 100,000) provided novel genomic loci associated with kidney function.
Novel SCr Locus	**CD36** was identified as a **novel genetic locus** (>1 Mb away from known loci) associated with serum creatinine (SCr). This finding is biologically plausible due to *CD36*'s role in oxidized LDL uptake and kidney fibrosis.
PCMT1 and BRAP Loci	**PCMT1**, which encodes an enzyme repairing age-damaged proteins, was significantly associated with CKD and eGFR. The causal SNP in the region including *ALDH2* and *NAA25* was likely identified on **BRAP**.
UACR Characteristics	Loci associated with **UACR** (Urine Albumin-to-Creatinine Ratio) showed genetic characteristics largely **distinct** from those associated with eGFR/CKD risk.
Monogenic CKD	Approximately **10%** of adult CKD patients are due to monogenic diseases, with most cases attributable to only **~7 limited causative genes**. The most common single gene cause is **ADPKD** (Autosomal Dominant Polycystic Kidney Disease).