Xanthine oxidoreductase inhibitors suppress the onset of exercise-induced AKI in high HPRT activity *Urat1*-*Uox* double knockout mice

Supplemental Information

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Supplemental Methods

- **In vivo experimental protocols.**

Supplemental Figure Legends

- **Supplemental Figure 1.**

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  Correlation of IL-1β and Na^+-K^+-ATPase (NKA) protein with UA kinetic and renal injury parameters in the post-exercise group.

Supplemental Methods

In vivo experimental protocols.

Study 1: Male low hypoxanthine phosphoribosyltransferase (HPRT) activity *Uox*-KO mice (n=8) and *Urat1*-*Uox* double knockout (DKO) mice (n=5) were fed standard powder chow (CRF-1). Blood or pooled and spot urine samples were collected.

Study 2: Female high HPRT activity *Uox*-KO (n=6) and *Urat1*-*Uox* DKO mice (n=6) were used in the forced swimming test. The blood and pooled urine samples were collected before (pre) and after (post) the forced swimming test, respectively.

Supplemental Figure Legends

Supplemental Figure 1

Growth curves of male and female HPRT activity *Uox*-KO and *Urat1*-*Uox* DKO mice. The growth curves of male and female mice from 6 to 20 weeks were similar between the *Uox*-KO and *Urat1*-*Uox* DKO group. Data represent means ± SEM of 3 to 8 mice per group.

Supplemental Figure 2

UA kinetic profiling of male low HPRT activity *Urat1*-*Uox* DKO mice.

(A) Plasma UA (mg/dL), (B) urinary UA/Cr ratio, (C) fractional excretion of UA (FE_{UA}; %) and (D) plasma Cr (mg/dL) in male low HPRT activity *Uox*-KO (n=8), and *Urat1*-*Uox* DKO mice (n=5). (E) HPRT activity (nmol/min/mg erythrocyte) in male low HPRT activity *Uox*-KO, and *Urat1*-*Uox* DKO mice (n=5 per group). Data represent means ± SEM. NS., not significant ($p > 0.05$). UA, urate; Cr, creatinine.

Supplemental Figure 3

Exercise-induced acute kidney injury (EIAKI) of female high HPRT activity *Urat1-Uox* DKO mice. (A) Plasma Cr (mg/dL), (B) Cr clearance (CL_{Cr}; mL/min/kg), (C) plasma UA (mg/dL), (D) urinary UA/Cr ratio, (E) FE_{UA} (%) and (F) UA clearance (CL_{UA}; mL/min/kg) in female high HPRT activity *Uox*-KO (n=6) and *Urat1-Uox* DKO mice (n=6) pre- and post-exercise. A-F data represent means ± SEM; data were analyzed using 2-way ANOVA with Tukey's *post hoc* test in A-F. Significantly different from pre-exercise group ($^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$), and change in *Uox*-KO group ($^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$). NS, not significant ($p > 0.05$). UA, urate; Cr, creatinine; WT, wild-type.

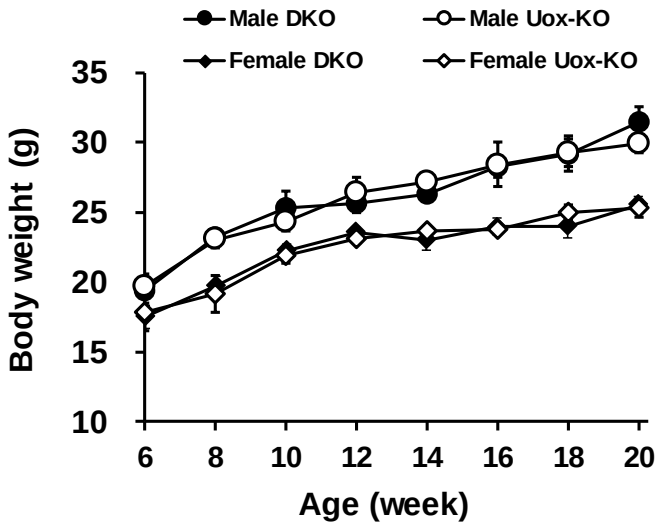
Supplemental Figure 4

Correlation of renal functional makers with UA kinetic parameters in high HPRT activity *Uox*-KO and *Urat1-Uox* DKO mice before (pre) and after (post) the forced swimming test. The correlation of plasma Cr with (A) plasma UA, (B) urinary UA/Cr ratio, (C) FE_{UA} and (D) CL_{UA}, the correlation of BUN with (E) plasma UA, (F) urinary UA/Cr ratio, (G) FE_{UA} and (H) CL_{UA}, the correlation of Cr clearance (CL_{Cr}) with (I) plasma UA, (J) urinary UA/Cr ratio, (K) FE_{UA} and (L) CL_{UA} in *Uox*-KO (n=8) and *Urat1-Uox* DKO mice (n=9) before (pre) and after (post) the forced swimming test. Data were analyzed using scatter plots. The coefficient of determination and *p* value are shown in each panel.

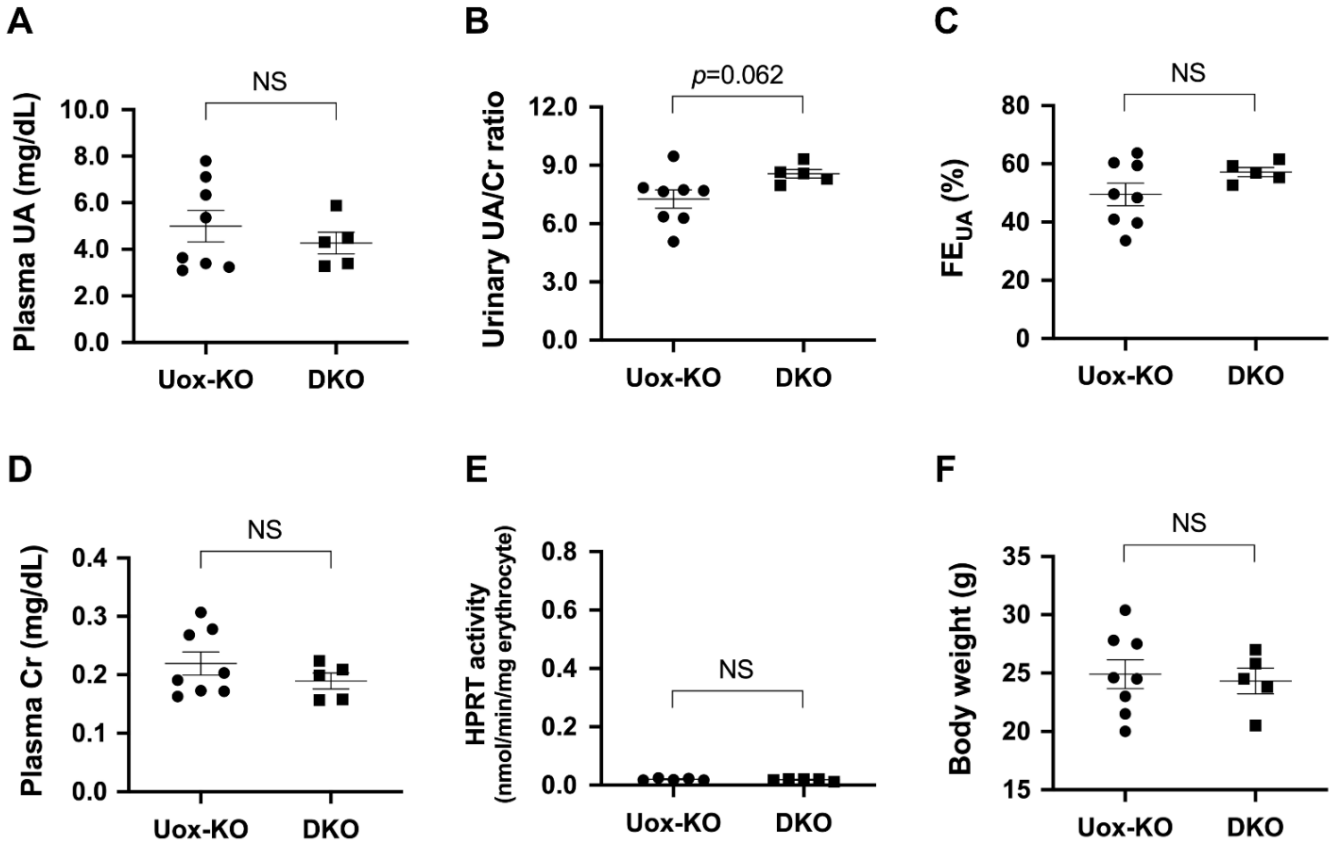
Supplemental Figure 5

Correlation of IL-1β and Na^+-K^+-ATPase (NKA) protein with UA kinetic and renal

injury parameters in the post-exercise group. The correlation of IL-1β protein with (A) plasma UA, (B) urinary UA/Cr ratio, (C) FE_{UA}, (D) plasma Cr, (E) BUN, and (F) CL_{Cr} in WT (n=8), high HPRT activity *Uox*-KO (n=8) and *Urat1-Uox* DKO mice (n=9) after (post) the forced swimming test. The correlation of Na^+-K^+-ATPase (NKA) protein with (G) plasma UA, (H) urinary UA/Cr ratio, (I) FE_{UA}, (J) plasma Cr, (K) BUN, and (L) CL_{Cr} in WT (n=8), high HPRT activity *Uox*-KO (n=8) and *Urat1-Uox* DKO mice (n=9) after (post) the forced swimming test. Data were analyzed using scatter plots. The coefficient of determination and *p* value are shown in each panel.



Supplemental Figure 1



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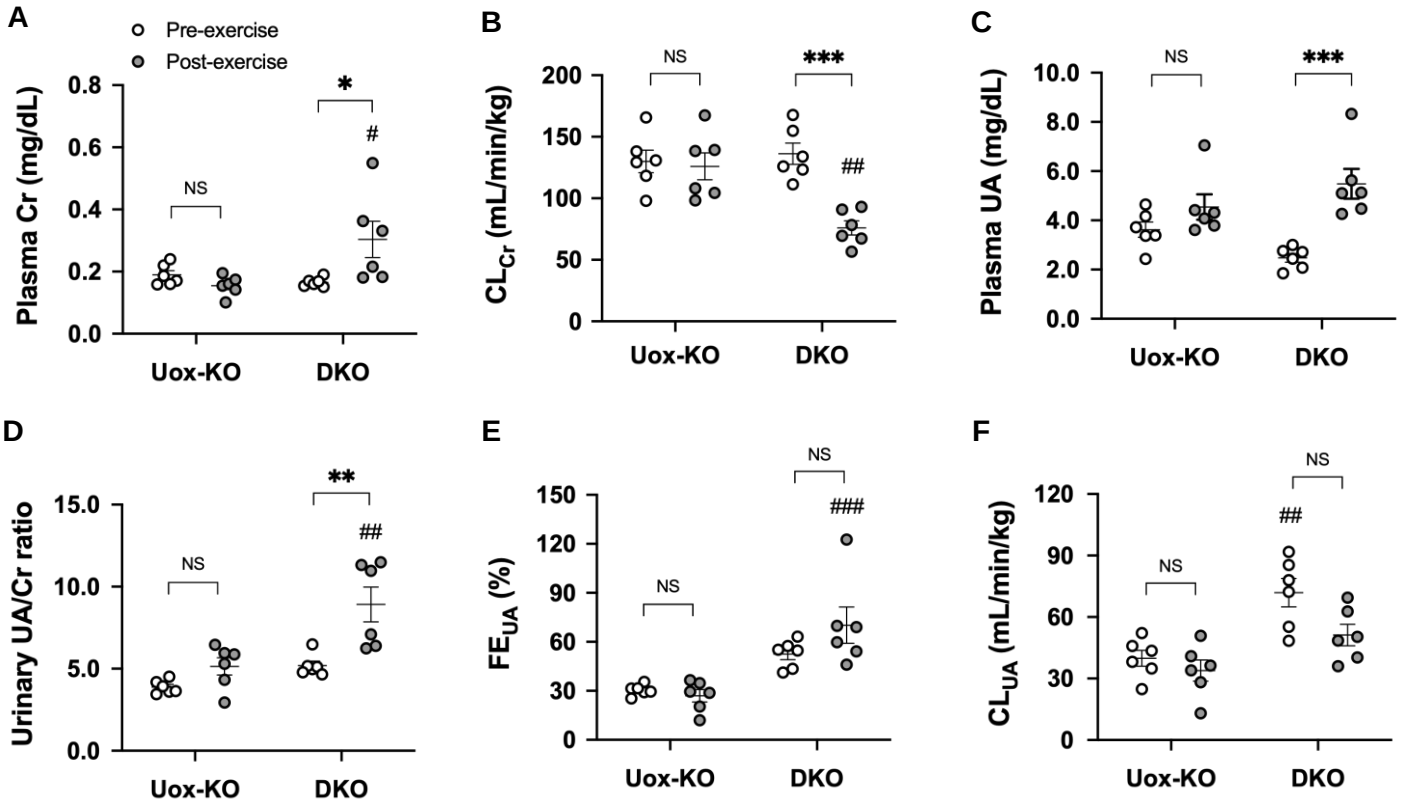

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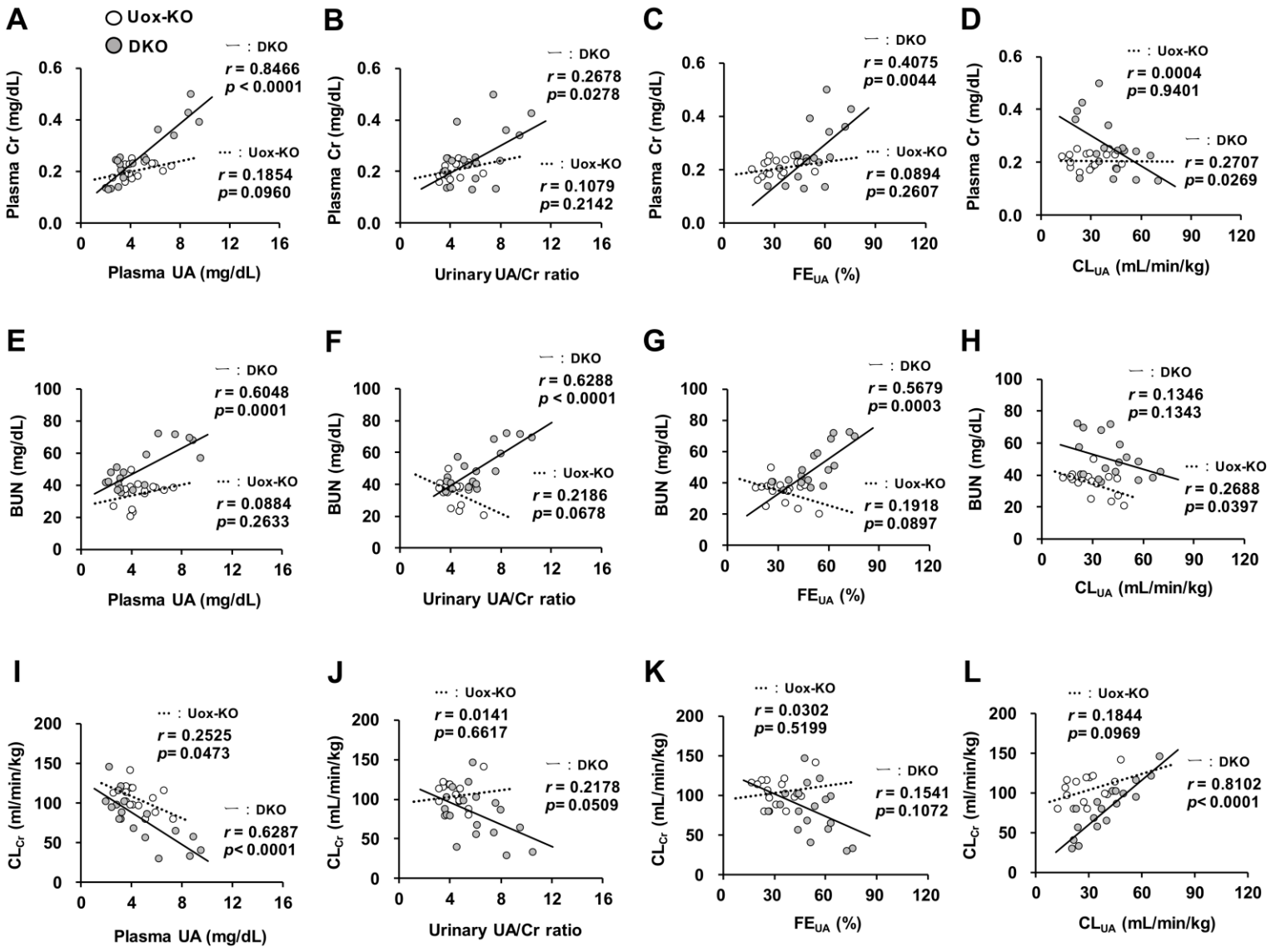
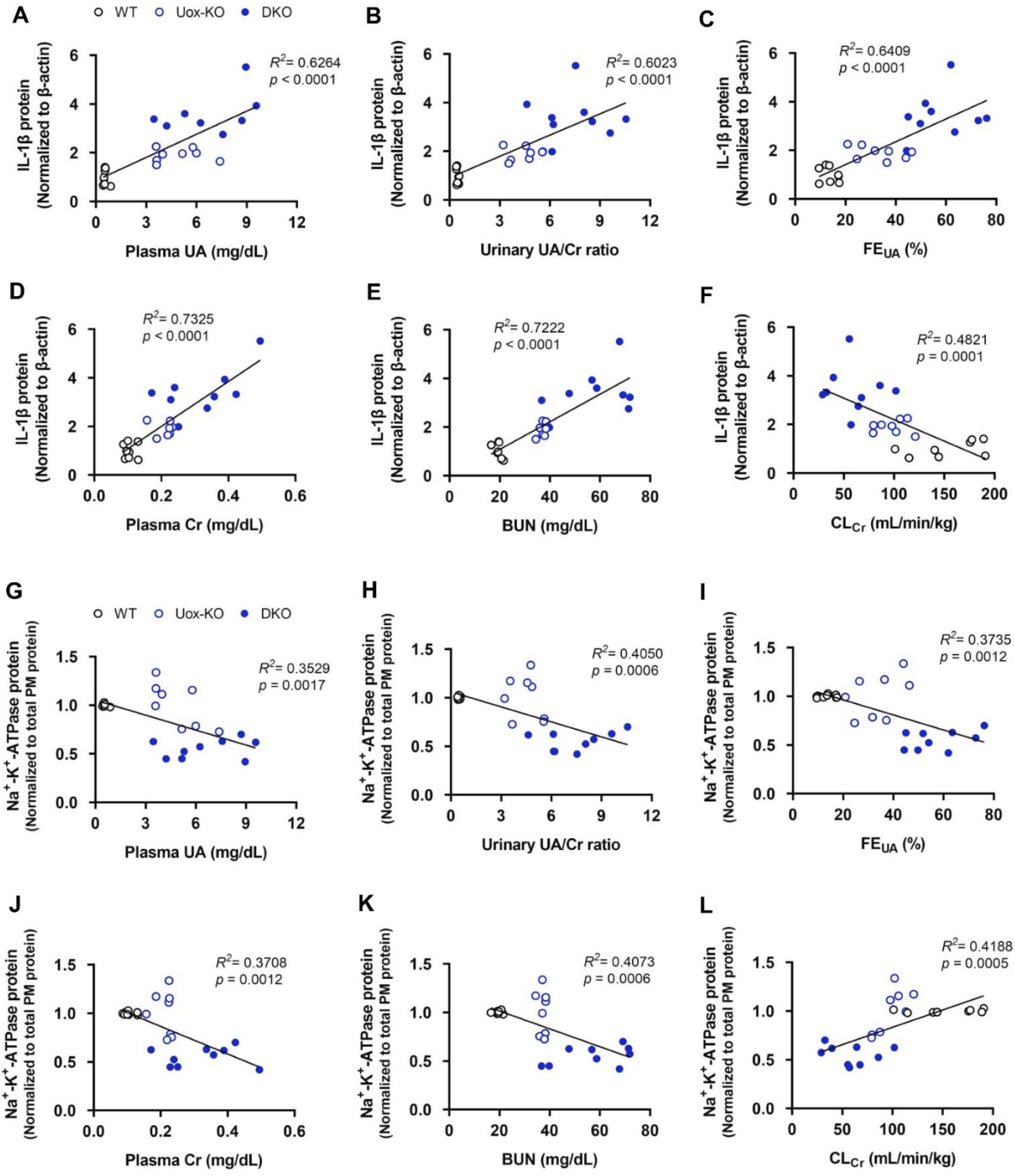


Supplemental Figure 4



Supplemental Figure 5