

Table 1. Baseline Subject Characteristics vs. 1,25(OH)₂D in Hisayama Subjects (n=2,417)

Variables	Serum 1,25(OH) ₂ D level (pg/ml)				P for trend
	≥79.3 (n=610)	66.8–79.2 (n=602)	56.5–66.7 (n=603)	<56.5 (n=602)	
Age (years)	61±11	60±11	60±11	59±12	0.01
Women	51.0	53.8	65.0	66.8	<0.001
Serum creatinine (mg/dl)	0.66±0.14	0.66±0.14	0.65±0.13	0.66±0.13	0.21
eGFR (ml·min ⁻¹ ·1.73 m ⁻²)	85±18	83±16	83±16	82±16	0.01
Proteinuria	7.1	4.7	5.1	6.8	0.96
SBP (mmHg)	134±21	131±21	130±21	129±21	<0.001
DBP (mmHg)	80±12	79±11	78±11	77±12	<0.001
Antihypertensive medication use	25.9	20.9	18.7	20.1	0.01
Hemoglobin A1c (%)	5.5±0.8	5.5±0.7	5.4±0.8	5.5±0.9	0.98
Serum TC (mg/dl)	204±32	205±36	206±36	203±35	0.64
Serum HDL-C (mg/dl)	64±16	62±16	64±17	62±15	0.04
BMI (kg/m ²)	23.0±3.1	23.2±3.4	23.2±3.3	23.6±3.7	0.03
Smoking habits	20.7	23.4	20.7	21.1	0.86
Alcohol intake	54.4	49.2	39.8	39.2	<0.001
Regular exercise	12.5	12.0	9.8	9.6	0.06

Data given as mean±SD or %.

1,25(OH)₂D, 1,25-dihydroxyvitamin D; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol.

sociated with an increased risk of deterioration in kidney function or the development of end-stage kidney disease.^{18–21}

These findings raise the possibility that 1,25(OH)₂D level has an impact on the progression of kidney disease, but most of these studies were conducted in high-risk subjects, and there are limited longitudinal studies evaluating this issue in general populations, especially in Asia. In the present study, we investigated the association between serum 1,25(OH)₂D level and the development of CKD stage 3–5 in the general Japanese population.

Methods

Subjects

The Hisayama Study is an ongoing population-based prospective cohort study of cardiovascular disease and its risk factors in the town of Hisayama, which is located in a suburb of the Fukuoka metropolitan area on Kyushu Island, Japan. The population of the town is approximately 8,000, and full community surveys of the residents have been repeated since 1961.^{22,23} In 2002 and 2003, a screening survey for the present study was performed in the town. A detailed description of this survey was published.²⁴ Briefly, a total of 3,328 residents aged ≥40 years (77.6% of the total population of this age group) underwent examination. After we excluded 30 subjects who did not consent to participate in the study, one subject for whom no blood sample was obtained, five subjects with frozen blood samples inadequate for measuring serum 1,25(OH)₂D, and 473 subjects with an estimated glomerular filtration rate (eGFR) <60 ml·min⁻¹·1.73 m⁻², the remaining 2,819 participants (1,195 men and 1,624 women) were enrolled in the study. Of those, 400 subjects did not undergo the examination in 2007 and two subjects had no available eGFR data in 2007. The final subject group enrolled was 2,417 subjects (988 men and 1,429 women).

Follow-up

The subjects were followed up prospectively via annual repeated health examinations. Their health status was checked

yearly by mail or telephone for any subjects who did not undergo the annual examination in that year, or who moved out of town. We also established a daily monitoring system among the study team, local physicians, and the members of the town's health and welfare office.

Risk Factor Measurements

A self-administered questionnaire concerning the current use of anti-hypertensive agents, smoking habit, and alcohol intake was checked by trained interviewers at the screening. These variables were classified as being either habitual or not. The subjects engaging in sports or other forms of exercise ≥3 times a week during their leisure time constituted the regular exercise group. Blood pressure was measured three times using an automated sphygmomanometer with subjects in the sitting position after at least 5 min rest. The mean of the three measurements was used for the present analysis. Body height and weight were measured in light clothing without shoes, and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Blood samples were collected from an antecubital vein after overnight fast. Part of the serum was stored at –80°C until measurement of 1,25(OH)₂D. Fresh voided urine samples were collected at the examination, and proteinuria was defined as 1+ or more using a reagent strip. Serum creatinine concentration was measured using the enzymatic method. Hemoglobin A1c was measured on high-performance liquid chromatography. Total cholesterol and high-density lipoprotein cholesterol (HDL-C) was determined enzymatically. Frozen serum samples were thawed in 2010 and assayed for serum 1,25(OH)₂D level with a radioimmunoassay kit (TFB, Tokyo, Japan).

Definition of CKD and Decline in eGFR

eGFR was calculated using the following new Japanese equation: eGFR (ml·min⁻¹·1.73 m⁻²)=194×[serum creatinine (mg/dl)]^{-1.094}×[age (years)]^{-0.287}×[0.739 if female].²⁵ CKD stage 3–5 was defined as reduced eGFR (eGFR <60 ml·min⁻¹·1.73 m⁻²) according to the National Kidney Foundation Kidney

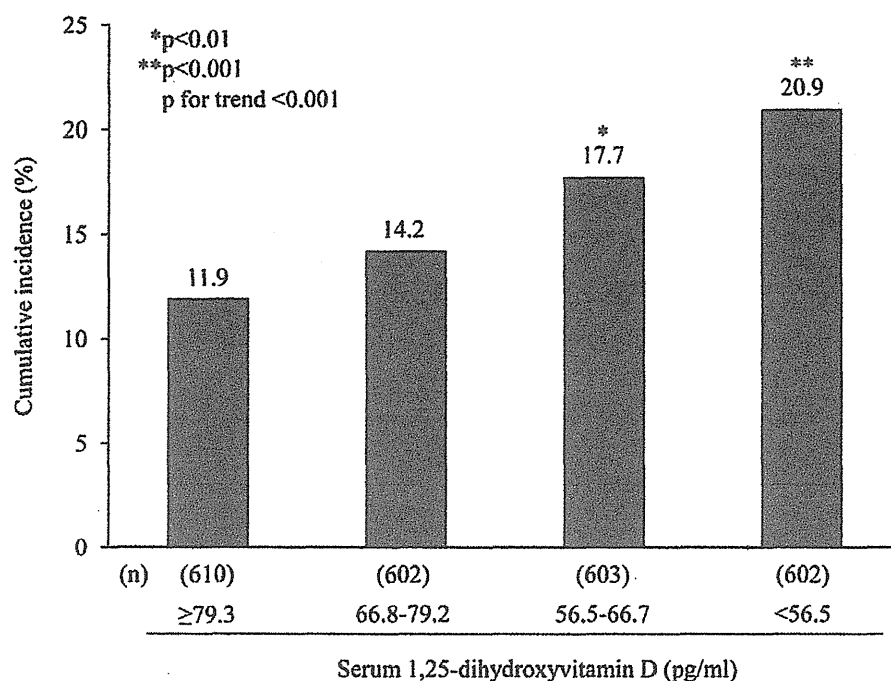


Figure 1. Age- and sex-adjusted 5-year cumulative incidence of chronic kidney disease stage 3-5 according to serum 1,25-dihydroxyvitamin D (1,25(OH)₂D) quartile. *P<0.01, **P<0.001 vs. serum 1,25(OH)₂D ≥79.3 pg/ml.

Disease Outcomes Quality Initiative clinical practice guidelines Improving Global Outcomes definition and classification of CKD.^{26,27} The rate of change in eGFR was calculated as the decline in eGFR using the following equation: change in eGFR (ml·min⁻¹·1.73 m⁻²·year⁻¹)=[eGFR in 2007 (ml·min⁻¹·1.73 m⁻²)-eGFR in 2002 (ml·min⁻¹·1.73 m⁻²)]/follow-up period (years).

The urine albumin-creatinine ratio (ACR, in mg/g) was calculated by dividing urinary albumin by urinary creatinine concentration. Albuminuria was defined as ACR ≥30.0 mg/g, and all CKD was defined as the presence of albuminuria and/or reduced eGFR.

Statistical Analysis

Serum 1,25(OH)₂D level was divided into quartiles: ≥79.3, 66.8-79.2, 56.5-66.7, and <56.5 pg/ml. The linear trends in the means and the frequencies of risk factors across serum 1,25(OH)₂D level were tested using a linear regression analysis and a logistic regression analysis, respectively. The age- and sex-adjusted cumulative incidence of CKD stage 3-5 was calculated using the direct method with the age and sex distribution of the overall study group.

Logistic regression analysis was also used to estimate odds ratios (ORs) with 95% confidence intervals (CIs) of CKD stage 3-5, all CKD, and albuminuria according to serum 1,25(OH)₂D level. The relationships between serum 1,25(OH)₂D level and eGFR slope were tested using multiple regression analysis. We calculated the multivariate-adjusted mean of the eGFR slope according to serum 1,25(OH)₂D level with analysis of covariance and compared these values with a Dunnett t-test. SAS (SAS Institute, Cary, NC, USA) was used to perform all statistical analysis. Two-sided P<0.05 was considered significant in all analyses.

Ethics Considerations

This study was conducted with the approval of the Kyushu University Institutional Review Board for Clinical Research. Written informed consent was obtained from all participants.

Results

Baseline subject characteristics according to serum 1,25(OH)₂D concentration quartile are listed in Table 1. Subjects with lower serum 1,25(OH)₂D were younger and were likely to be female. Mean eGFR, systolic and diastolic blood pressure (SBP and DBP), and the frequency of anti-hypertensive medication use were significantly decreased with lower serum 1,25(OH)₂D. Lower serum 1,25(OH)₂D level was also associated with lower mean serum HDL-C and higher mean BMI. The frequency of alcohol intake decreased significantly with lower serum 1,25(OH)₂D.

During the average 5-year follow-up period, 378 subjects experienced CKD stage 3-5 events. The age- and sex-adjusted cumulative incidence of CKD stage 3-5 is shown according to serum 1,25(OH)₂D level in Figure 1. The age- and sex-adjusted cumulative incidence of CKD stage 3-5 was significantly higher in the third and fourth quartile groups than in the highest quartile group. The age- and sex-adjusted ORs increased gradually with lower serum 1,25(OH)₂D level (P for trend <0.001; Table 2). This association remained unchanged after adjusting for potential confounding factors, namely age, sex, SBP, anti-hypertensive medication use, hemoglobin A1c, serum total cholesterol and HDL-C, proteinuria, BMI, smoking habit, alcohol intake, and regular exercise. There was no evidence of heterogeneity in the association between the sexes (P for heterogeneity =0.88). The upward trend in the risk of CKD stage 3-5 with lower serum 1,25(OH)₂D was observed

Table 2. Development of CKD Stage 3–5 vs. 1,25(OH) ₂ D Quartile (n=2,417) [†]											
Serum 1,25(OH) ₂ D (pg/ml)	No. events	No. subjects	Age- and sex-adjusted			Multivariate-adjusted [‡]			Multivariate-adjusted [§]		
			OR (95% CI)	P-value	P-value for trend	OR (95% CI)	P-value	P-value for trend	OR (95% CI)	P-value	P-value for trend
≥79.3	75	610	1.00 (reference)		<0.001	1.00 (reference)		<0.001	1.00 (reference)		0.008
66.8–79.2	84	602	1.20 (0.84–1.70)	0.32		1.27 (0.89–1.82)	0.19		1.31 (0.88–1.93)	0.18	
56.5–66.7	107	603	1.68 (1.20–2.37)	0.003		1.74 (1.23–2.47)	0.002		1.71 (1.17–2.50)	0.006	
<56.5	112	602	1.87 (1.33–2.62)	<0.001		1.90 (1.34–2.70)	<0.001		1.59 (1.08–2.34)	0.02	

[†]Five-year follow-up in Hisayama subjects. [‡]Adjusted for age, sex, SBP, anti-hypertensive medication, HbA1c, serum total cholesterol, serum HDL-C, proteinuria, BMI, smoking habits, alcohol intake, and regular exercise. [§]Adjusted for age, sex, SBP, anti-hypertensive medication, HbA1c, serum total cholesterol, serum HDL-C, proteinuria, BMI, smoking habits, alcohol intake, regular exercise, and baseline eGFR. CI, confidence interval; CKD, chronic kidney disease; OR, odds ratio. Other abbreviations as in Table 1.

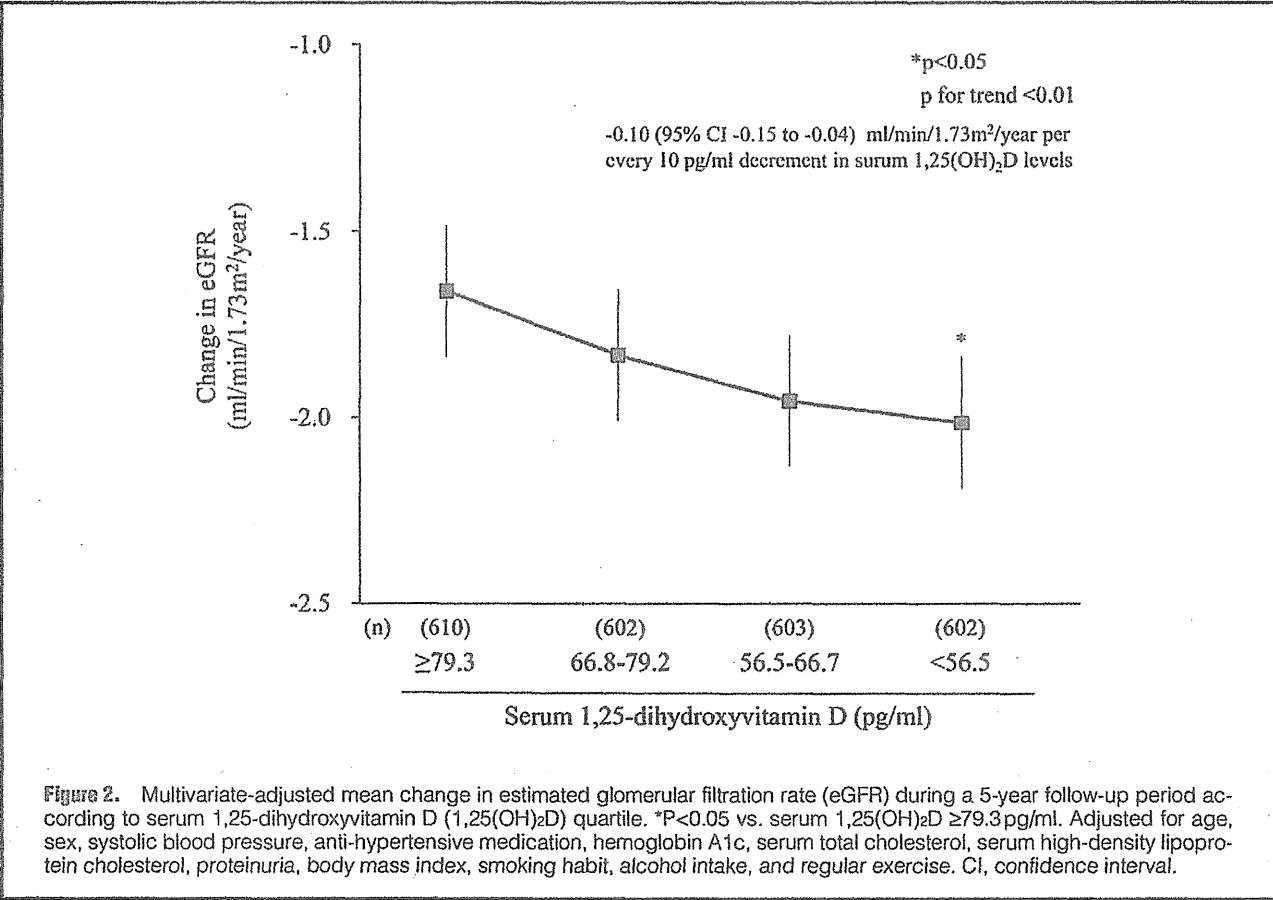


Figure 2. Multivariate-adjusted mean change in estimated glomerular filtration rate (eGFR) during a 5-year follow-up period according to serum 1,25-dihydroxyvitamin D (1,25(OH)₂D) quartile. *P<0.05 vs. serum 1,25(OH)₂D ≥79.3 pg/ml. Adjusted for age, sex, systolic blood pressure, anti-hypertensive medication, hemoglobin A1c, serum total cholesterol, serum high-density lipoprotein cholesterol, proteinuria, body mass index, smoking habit, alcohol intake, and regular exercise. CI, confidence interval.

after adjusting for the aforementioned covariates plus baseline eGFR, although the lowest quartile had a lower OR than the second lowest quartile.

To analyze sensitivity, we assessed the association between serum 1,25(OH)₂D level and the likelihood of albuminuria and all CKD in 1,945 participants without all CKD for 5 years. The multivariate-adjusted OR for the development of all CKD was 1.38 (95% CI: 1.00–1.90) in the lowest quartile and 1.41 (95% CI: 1.03–1.93) in the second-lowest quartile compared to the highest quartile, after adjusting for potential confounding factors. In contrast, no significant association was found between serum 1,25(OH)₂D level and the multivariate-adjusted OR of albuminuria (Table S1).

We also carried out slope analysis, in which the relationship

between serum 1,25(OH)₂D level and the decline in eGFR was examined using a multiple regression model after adjusting for the aforementioned potential confounding factors (Figure 2). We found that lower serum 1,25(OH)₂D was significantly associated with a greater decline in eGFR (P for trend <0.01); the difference in the multivariate-adjusted mean of the decline in eGFR was significant in the subjects with serum 1,25(OH)₂D <56.5 pg/ml compared to those with serum 1,25(OH)₂D ≥79.3 pg/ml.

The amount of change in eGFR was −0.10 ml·min^{−1}·1.73 m^{−2}·year^{−1} (95% CI: −0.15 to −0.04) per 10 pg/ml decrement in serum 1,25(OH)₂D level. This relationship was not altered substantially after adjusting for eGFR at baseline in addition to the covariates included in the model for Figure 2

(Figure S1). The sensitivity analyses using the Chronic Kidney Disease Epidemiology Collaboration equation for eGFR calculation instead of the Japanese equation also identified a significant relationship between eGFR level and mean change in eGFR: ≥ 79.3 pg/ml, -1.1 (95% CI: -1.2 to -1.0); 66.8 – 79.2 pg/ml, -1.2 (95% CI: -1.3 to -1.1); 56.5 – 66.7 pg/ml, -1.3 (95% CI: -1.4 to -1.2); and <56.5 pg/ml, -1.4 (95% CI: -1.5 to -1.3); P for trend <0.001 .

In the subgroup analyses stratified by sex, age, diabetes, and hypertension, there was no evidence of a significant difference in the association of serum 1,25(OH) $_2$ D level with the risk of the development of CKD stage 3–5 or the eGFR slope between the subgroups (all P for heterogeneity >0.18 ; Tables S2,S3).

Discussion

The present results clearly show that lower serum 1,25(OH) $_2$ D is significantly associated with an increased risk of development of CKD stage 3–5. Additionally, the subjects with lower serum 1,25(OH) $_2$ D had a greater decline in eGFR. These relationships remained significant after adjusting for potential confounding factors. To the best of our knowledge, this is the first study to investigate the relationship between serum 1,25(OH) $_2$ D level and the incidence of CKD stage 3–5 prospectively in a community-based Asian population.

Several epidemiological studies examined the association of serum 25(OH)D or 1,25(OH) $_2$ D level with the development of CKD. In the Cardiovascular Health Study, lower serum 25(OH)D level was associated with a greater decline in eGFR among 1,705 community-dwelling older adults in the USA.¹⁸ The Third National Health and Nutrition Examination Survey in the USA also found that lower serum 25(OH)D level was a significant risk factor for development of end-stage kidney disease.¹⁹ A hospital-based prospective study conducted in 168 subjects in Italy found that lower serum 1,25(OH) $_2$ D level, as well as serum 25(OH)D level, was significantly linked to an increased risk of progression from moderate–severe CKD to end-stage kidney disease.²⁰ In the Homocysteinemia in Kidney and End Stage Renal Disease Study of 1,099 US patients with advanced CKD, lower serum 1,25(OH) $_2$ D level was associated with an increased risk of end-stage kidney disease.²¹ These findings are in accord with the present results.

Several possible explanations have been proposed for the mechanism underlying the association between serum 1,25(OH) $_2$ D level and the risk of CKD. Experimental studies have suggested that 1,25(OH) $_2$ D can regulate the proliferation of vascular smooth muscle cells and vascular inflammation, which may promote systemic arteriosclerosis.^{28,29} Several epidemiological studies reported that decreased eGFR is closely correlated with systemic atherosclerosis.^{30,31} These properties may play a key role in the pathogenesis of CKD by promoting arteriosclerosis within the kidney. 1,25(OH) $_2$ D also promotes the survival of podocytes by inducing differentiation and preventing apoptosis, and reduces glomerulosclerosis, intestinal fibrosis, and albuminuria in animal models.^{32–36} Through these mechanisms, lower serum 1,25(OH) $_2$ D level may cause arteriosclerosis, glomerulosclerosis, and intestinal fibrosis, resulting in CKD.

It has been recognized that subjects with lower eGFR at baseline are likely to have lower serum 1,25(OH) $_2$ D, raising the possibility that the present findings merely reflect that subjects with lower eGFR at baseline develop CKD more quickly.^{37,38} To avoid this possibility, we excluded the subjects with eGFR <60 ml \cdot min $^{-1}$ \cdot 1.73 m $^{-2}$, because serum 1,25(OH) $_2$ D

decreases progressively when eGFR falls below 60 ml \cdot min $^{-1}$ \cdot 1.73 m $^{-2}$, and we adjusted the risk estimates for eGFR level at baseline.^{37,38}

We also compared decline in eGFR across serum 1,25(OH) $_2$ D level. Even after taking these precautions into consideration, we found that lower serum 1,25(OH) $_2$ D level was a significant risk factor for the development of CKD stage 3–5. Nevertheless, confounding may still exist in the association between serum 1,25(OH) $_2$ D level and CKD stage 3–5. Further intervention studies addressing whether treatment to combat lower 1,25(OH) $_2$ D level reduces the risk of CKD are necessary to clarify this issue.

Several limitations of the present study should be noted. First, it is possible that the present results are biased by the exclusion of the 402 subjects who did not return to the follow-up examination; of these, 148 subjects died during the follow-up period. The excluded subjects had lower serum 1,25(OH) $_2$ D and eGFR, suggesting that a high-risk group for the development of CKD stage 3–5 was excluded in this study. Second, serum 1,25(OH) $_2$ D level was based on a single measurement at baseline, as was the case in most of the prior epidemiologic studies. This may cause a misclassification of serum 1,25(OH) $_2$ D level. These limitations could have weakened the association found in this study, biasing the results toward the null hypothesis. We therefore believe these biases would not alter the conclusion. Last, we have no information about the type of underlying renal disease. Such information could be obtained by detailed clinical examination, including renal biopsy and ultrasonography, but these diagnostic procedures are not considered feasible for a cohort study recruited from a general population, such as the present one.

Conclusions

Lower serum 1,25(OH) $_2$ D level is a significant risk factor for the development of CKD stage 3–5 in the general Asian population. At present, the extent to which raising serum 1,25(OH) $_2$ D level can attenuate the risk of CKD stage 3–5 is not known. A clinical trial raising serum 1,25(OH) $_2$ D level is needed to clarify whether higher serum 1,25(OH) $_2$ D level will result in an improved renal prognosis.

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Supplementary Files

Supplementary File 1

- Table S1. Development of all CKD and albuminuria vs. serum 1,25(OH)₂D during 5-year follow-up
- Table S2. Multivariate-adjusted OR and 95% CI for development of CKD stage 3–5 vs. 1,25(OH)₂D
- Table S3. Multivariate-adjusted mean change in eGFR (95% CI) vs. 1,25(OH)₂D in 5-year follow-up
- Figure S1. Multivariate-adjusted mean change in estimated glomerular filtration rate (eGFR) during a 5-year follow-up period according to serum 1,25-dihydroxyvitamin D (1,25(OH)₂D) quartile after adjusting for eGFR at baseline in addition to the covariates included in the model for Figure 2.

Please find supplementary file(s);
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「身体活動・不活動量，運動量の実態とその変化が生活習慣病発症に及ぼす影響と
運動介入支援の基盤構築に関する研究」

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