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Circulating and Urinary Creatine Levels in the All of Us Research Program

David Nedeljkovic[1], Sergej M. Ostojic[1,2,3*]

[1]*Applied Bioenergetics Lab, Medical Polyclinic Fizikus, Belgrade, Serbia*
[2]*Faculty of Health Sciences, University of Pécs, Pécs, Hungary*
[3]*Department of Nutritional Sciences, Texas Tech University, Lubbock, TX*

Abstract

Creatine is central to human bioenergetics, yet circulating creatine remains largely uncharacterized in population settings. Using data from the All of Us Research Program, we examined serum/plasma and urinary creatine in a demographically diverse U.S. cohort. We identified 246 adults with 1,576 serum or plasma creatine measurements and harmonized values across assay formats. Participant-level mean serum creatine was right-skewed in the full cohort but clustered tightly after exclusion of individuals with kidney disease. In adults without renal pathology (n=139), circulating creatine occupied a narrow physiological range (mean 0.94 mg/dL; median 0.90 mg/dL; interquartile range 0.76-1.10 mg/dL), indicating strong homeostatic regulation. In contrast, urinary creatine, assessed in 2,044 participants, displayed wide interindividual variability with a long upper tail. These findings establish the first population-scale reference framework for creatine in blood and urine and define ~ 1mg/dL as a pragmatic physiological anchor for circulating creatine in adults without kidney disease.(**International Journal of Biomedicine. 2026;16(2):281-283.**)

Keywords: creatine • bioenergetics • population • kidney disease

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Introduction

Creatine is a central component of human bioenergetics, functioning as a rapidly mobilizable phosphate buffer that stabilizes ATP availability in tissues with high, fluctuating energy demands,[1] including skeletal muscle, brain, myocardium, and immune cells. Through the phosphocreatine-creatine kinase system, creatine supports energy transfer, contributes to redox balance, and participates in osmotic and signaling processes.[2] In humans, creatine homeostasis reflects the interplay between endogenous synthesis and dietary intake from animal-source foods, positioning creatine at the intersection of metabolism and nutrition.

Despite this central role, circulating creatine remains remarkably understudied. In routine clinical practice, creatinine is ubiquitously measured as a marker of renal function, yet serum or plasma creatine itself is rarely assessed and is not part of standard chemistry panels. Measurement is typically confined to specialized contexts,[3] such as the evaluation of rare inborn errors of creatine metabolism or selected neuromuscular disorders. Consequently, population-based reference data for circulating creatine are lacking. Existing knowledge derives largely from small experimental cohorts or athletic populations. One of the few population-oriented reports from a French adult cohort suggested relatively low, tightly distributed circulating creatine concentrations[4] but was limited in size and demographic scope. Whether such narrow distributions generalize to diverse real-world populations remains unknown. As a result, even basic descriptors, such as typical concentration, interindividual variability, and physiological range of serum creatine in community-dwelling adults, remain undefined.

This gap has important implications. Circulating creatine integrates endogenous synthesis, dietary exposure, tissue uptake, and renal handling, and may therefore reflect systemic bioenergetic status. Without normative data, it is difficult to contextualize individual values or relate circulating creatine to diet, age, sex, metabolic health, or disease risk. The

***Corresponding author:** Prof. Sergej M. Ostojic, MD, PhD, FACP. E-mail addresses: sergej.ostojic@chess.edu.rs and sergej.ostojic@etk.pte.hu*

absence of reference distributions also constrains translational work on supplementation and fortification strategies, as well as on the emerging concept of creatine as a conditionally essential nutrient across the life course. Large-scale population resources now make it feasible to address this deficiency. The All of Us Research Program provides harmonized electronic health record data and laboratory measurements from a large, demographically diverse cohort of U.S. adults (https://allofus.nih.gov/), enabling empirical characterization of circulating metabolites under real-world clinical conditions. Importantly, this setting allows separation of physiological variability from pathological influences,[5] particularly renal disease, which profoundly affects creatine handling and may dominate the upper tail of observed distributions.

Methods

Using All of Us data, we identified 246 adults with serum or plasma creatine measurements, contributing 1,576 tests. Creatine was captured using LOINC-derived OMOP concepts for mass- and molar-based serum/plasma assays. Units were overwhelmingly recorded as milligrams per deciliter, with a small number labeled as micromoles per liter; a subset lacked standardized unit metadata. Given the dominance of a single assay stream and the consistency of observed value ranges, unmapped numeric values were conservatively harmonized to mg/dL, yielding standardized creatine concentrations for 1,574 of 1,576 records and retaining all participants. To avoid over-weighting individuals with frequent clinical testing and to approximate each participant's typical creatine exposure, creatine was summarized at the participant level as the mean of all available values.

Results

In the full cohort, participant-level mean creatine was right-skewed (mean 2.28 mg/dL; median 1.09 mg/dL; range 0.19-22.2 mg/dL). Trimming extreme values using a ±3SD criterion identified four outliers (1.6%). The outlier-trimmed distribution remained right-skewed but more compact (mean 2.08 mg/dL; median 1.05 mg/dL). A more restrictive ±2SD sensitivity filter further reduced the mean (1.46 mg/dL) while leaving the median (~1.0 mg/dL) and interquartile range essentially unchanged, demonstrating that the central tendency is stable and that the mean is highly sensitive to a small right tail. Renal pathology emerged as the dominant determinant of this tail. After exclusion of all participants with any recorded diagnosis of chronic kidney disease, renal failure, end-stage renal disease, or dialysis, 139 individuals remained (52% female). The mean age was 50.5±14.8 years, with a median of 49.1 years (interquartile range 41.0-62.0; range 21.2-95.8 years). In this kidney disease-free subcohort, circulating creatine clustered tightly around ~1mg/dL (mean 0.94 mg/dL; median 0.90 mg/dL; interquartile range 0.76-1.10 mg/dL; range 0.19-2.80 mg/dL). Both the mean and dispersion were markedly attenuated relative to the unfiltered cohort, indicating that impaired renal handling is a major contributor to elevated values in the population. In adults without diagnosed kidney disease, circulating creatine occupies a narrow and apparently conserved physiological window.

Urinary creatine exhibited a contrasting profile. We identified 3,939 urinary creatine tests from 2,100 individuals. The vast majority represented spot urine creatine concentrations, predominantly in mg/dL; a minority corresponded to 24-hour excretion formats and were excluded from concentration-based analyses. After harmonization, 3,850 tests from 2,044 participants were retained. Across all tests, urinary creatine showed a broad, right-skewed distribution (mean 92 mg/dL; median 71 mg/dL; range 2-595 mg/dL). Participants contributed a median of one test, indicating that the population profile is not driven by frequent testers. Aggregation at the participant level yielded a similar distribution. Application of a ±3SD criterion identified 32 extreme values (1.6% of individuals). Exclusion of these outliers yielded a physiologically coherent reference distribution in 2,012 participants, with a mean urinary creatine concentration of 86.2±58.0 mg/dL (median 72.9 mg/dL, interquartile range 41.8-115.7 mg/dL; range 2.2-295.1 mg/dL), revealing substantial biological dispersion and a long upper tail even after removal of extremes, consistent with wide interindividual variability in creatine handling under everyday conditions.

Figure 1 illustrates the population distributions of creatine concentrations, showing serum/plasma creatine in adults without kidney disease and spot urinary creatine after outlier trimming.

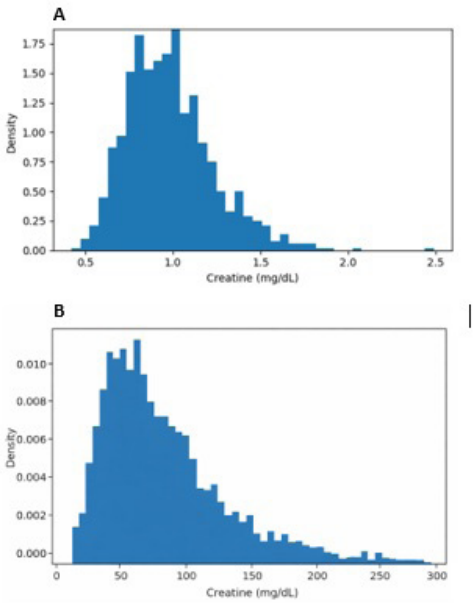

Figure 1. *Population distributions of circulating and urinary creatine. Panel A shows the distribution of participant-level mean serum/plasma creatine in adults without diagnosed kidney disease, demonstrating tight clustering around ~1 mg/dL and a narrow interquartile range. Panel B depicts spot urinary creatine concentration after exclusion of 24-h formats and ±3SD outliers, revealing a broad, right-skewed distribution. These distributions contrast the narrow physiological range of circulating creatine with the wide biological dispersion of urinary creatine under real-world conditions.*

Discussion

Together, these findings provide the first population-scale reference framework for creatine in human circulation and urine. The tight clustering of serum/plasma creatine around ~1mg/dL in adults without kidney disease suggests a narrow physiological range, consistent with tight homeostatic regulation across synthesis, intake, tissue uptake, and renal clearance.[3] In contrast, urinary creatine displays wide interindividual variability, likely reflecting differences in muscle mass, dietary exposure, endogenous synthesis, and renal handling under real-world conditions. Several limitations warrant consideration. All of Us laboratory data originate from routine clinical care and are not standardized for research purposes; assay platforms and calibration vary across sites. Unit metadata were incomplete for a subset of records, requiring conservative harmonization assumptions. Kidney disease was identified through diagnostic coding and may not capture subclinical impairment. Finally, the cohort reflects individuals engaged with the healthcare system and may not represent the healthiest segment of the population.

Despite these constraints, this analysis establishes the first empirical population anchors for creatine in adults. The observation that circulating creatine in individuals without kidney disease clusters tightly around ~1mg/dL defines a pragmatic physiological reference point. These data allow individual values to be interpreted in a biologically meaningful context and provide a foundation for translational studies linking creatine biology to diet, aging, metabolic health, and functional outcomes. In this light, circulating creatine may be viewed not merely as a biochemical curiosity, but as a systemic indicator of human bioenergetic status.

Ethics Statement

This research was conducted using data from the All of Us Research Program, obtained via the All of Us Researcher Workbench. The program operates under a central Institutional Review Board (IRB) protocol reviewed and approved by the Advarra IRB (IRB# IRB00009605), in accordance with the U.S. Department of Health and Human Services regulations for the protection of human subjects (45 CFR 46). The All of Us IRB provides single IRB oversight for all research activities involving program data. This study met the criteria for exempt human subjects' research as defined by the Common Rule and did not require additional IRB review at the authors' home institution. All data were de-identified and analyzed in compliance with the program's Data Use Agreement and ethical standards.

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Data Availability Statement

The datasets supporting the conclusions of this study are publicly available and can be accessed through the All of Us Research Program via a secure, cloud-based Researcher Workbench at https://www.researchallofus.org/. The authors do not own the data. For further information, please contact the corresponding author.

AI Statement

During the preparation of this manuscript, the authors used ChatGPT (OpenAI) for language editing, figure formatting, and grammatical refinement. All AI-assisted content was reviewed, verified, and revised by the authors, who take full responsibility for the accuracy, integrity, and final content of the manuscript.

Author Contributions

David Nedeljkovic: Investigation, Data curation, Formal analysis, Writing – original draft.
Sergej M. Ostojic (SMO): Supervision, Conceptualization, Writing – review and editing.

SMO serves on scientific advisory boards related to creatine. SMO is an inventor on creatine-related intellectual property and has received research funding on creatine from public agencies and industry partners. SMO co-founded a venture developing creatine-enriched food products

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Conflict of Interest

The authors have declared no conflict of interest.

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