

Lifecourse Journey in Cystinosis

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Introduction

Lifecourse research first studied social & cultural influences on health and now includes effects of maternal, prenatal, postnatal, infancy/childhood, adolescent, early adult & aging environmental exposures across the life continuum.¹² It is a multidisciplinary approach to developmental & biologic trajectories which are considered over time. As defined, it involves studies of biological, environmental, genetic, epigenetic, behavioral, & psychosocial pathways that operate across an individual's lifecourse as well as across generations, to influence the development of chronic disease.³⁴ Conceptual models include cohorts of subjects with early life exposures, birth weights, socioeconomic status, & identified conditions that are entered into a registry for investigations using multivariate analyses.

There are critical time points along the continuum for unique exposures called allostatic loads, to have additive influences on the subsequent phenotype or expression of outcomes. Allostatic loads⁵ are defined as accumulated biologic stresses, including those related to social determinants of health⁶ and adverse childhood events (ACES), that may affect genes throughout

¹ Brinkley, T. E., Justice, J. N., Basu, S., Bauer, S. R., Loh, K. P., Mukli, P. & Kritchevsky, S. B. (2022). Research priorities for measuring biologic age: summary and future directions from the Research Centers Collaborative Network Workshop. *GeroScience*, 44(6), 2573-2583.

² Baird, J., Jacob, C., Barker, M., Fall, C. H., Hanson, M., Harvey, N. C., ... & Cooper, C. (2017, March). Developmental origins of health and disease: a lifecourse approach to the prevention of non-communicable diseases. In *Healthcare* (Vol. 5, No. 1, p. 14). MDPI.

³ Michels, K. B. (2003). Early life predictors of chronic disease. *Journal of women's health*, 12(2), 157-161.

⁴ Hanson HA, Leiser CL, Bandoli G, Pollock BH, Karagas MR, Armstrong D, Dozier A, Weiskopf NG, Monaghan M, Davis AM, Eckstrom E, Weng C, Tobin JN, Kaskel F, Schleiss MR, Szilagyi P, Dykes C, Cooper D, Barkin SL. Charting the life course: Emerging opportunities to advance scientific approaches using life course research. *J Clin Transl Sci*. 2020 Jun 15;5(1):e9. <https://doi.org/10.1017/cts.2020.492>

⁵ Zhen Wah Tan, Wei-Ven Tee, Enrico Guarnera, Lauren Booth, Igor N Berezovsky, AlloMAPS: allosteric mutation analysis and polymorphism of signaling database, *Nucleic Acids Research*, Volume 47, Issue D1, 08 January 2019, Pages D265–D270, <https://doi.org/10.1093/nar/gky1028>

⁶ Gustafsson PE, San Sebastian M, Janlert U, Theorell T, Westerlund H, Hammarström A. Life-course accumulation of neighborhood disadvantage and allostatic load: empirical integration of three social determinants of health frameworks. *Am J Public Health*. 2014 May;104(5):904-10. doi: 10.2105/AJPH.2013.301707. Epub 2014 Mar 13. PMID: 24625161; PMCID: PMC3987591.

the lifecourse. Biomarkers of these exposures & their epigenetic mechanisms⁷ at critical stages of the lifecourse will advance our knowledge of health & disease.

Application to cystinosis

- Identify what critical time points and factors such as: epigenetic, environmental, psychosocial, are affected in cystinosis.
- Apply what is known regarding multiorgan involvement during growth & development in cystinosis & how best to examine them using principles of lifecourse research.
- Establish secured shared registries and databases using the electronic medical record, biobanks, and other longitudinal cohorts for future development of targeted lifecourse research at ideal windows.
- Using big data opportunities develop predictive/prognostic modeling of multiorgan involvement.

Conclusion:

From newborn screening allowing early diagnosis and treatment⁸ to increased understanding of the long-term sequelae of cystinosis in adulthood, a lifecourse perspective adds a vital perspective to understanding and managing the disease over time.

Priority areas for future research around cystinosis include individual level and transgenerational research, identification of time points and ideal windows for intervention, use of big data, omics, lifespan template for EMRs, and development of biomarkers and measures.

⁷ Rastegar, M., & Yasui, D. H. (2021). Epigenetic Mechanisms and Their Involvement in Rare Diseases. *Frontiers in Genetics, 12*, 755076.

⁸ Hohenfellner, K., Elenberg, E., Ariceta, G., Nesterova, G., Soliman, N. A., & Topaloglu, R. (2022). Newborn Screening: Review of its Impact for Cystinosis. *Cells, 11*(7), 1109.