The Hidden Job Of The Cell's Powerhouse

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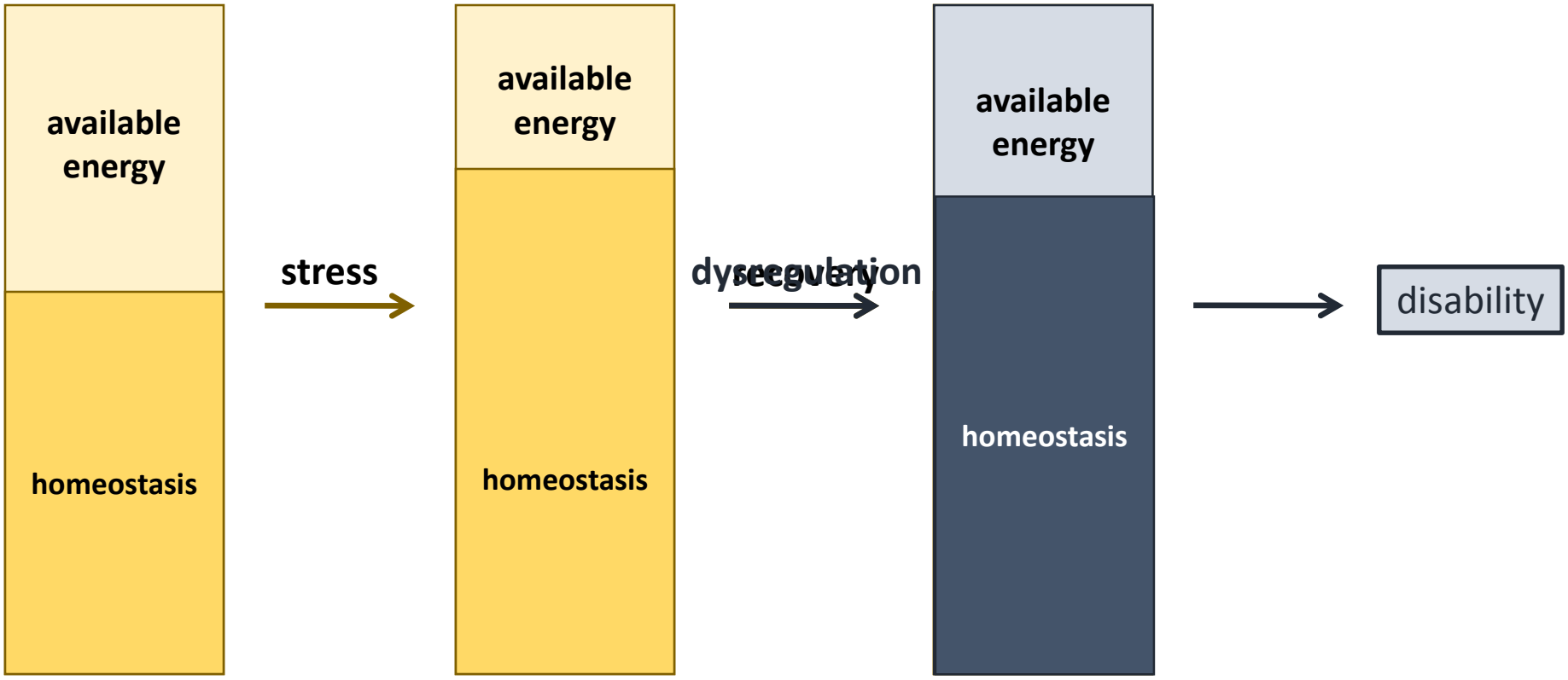
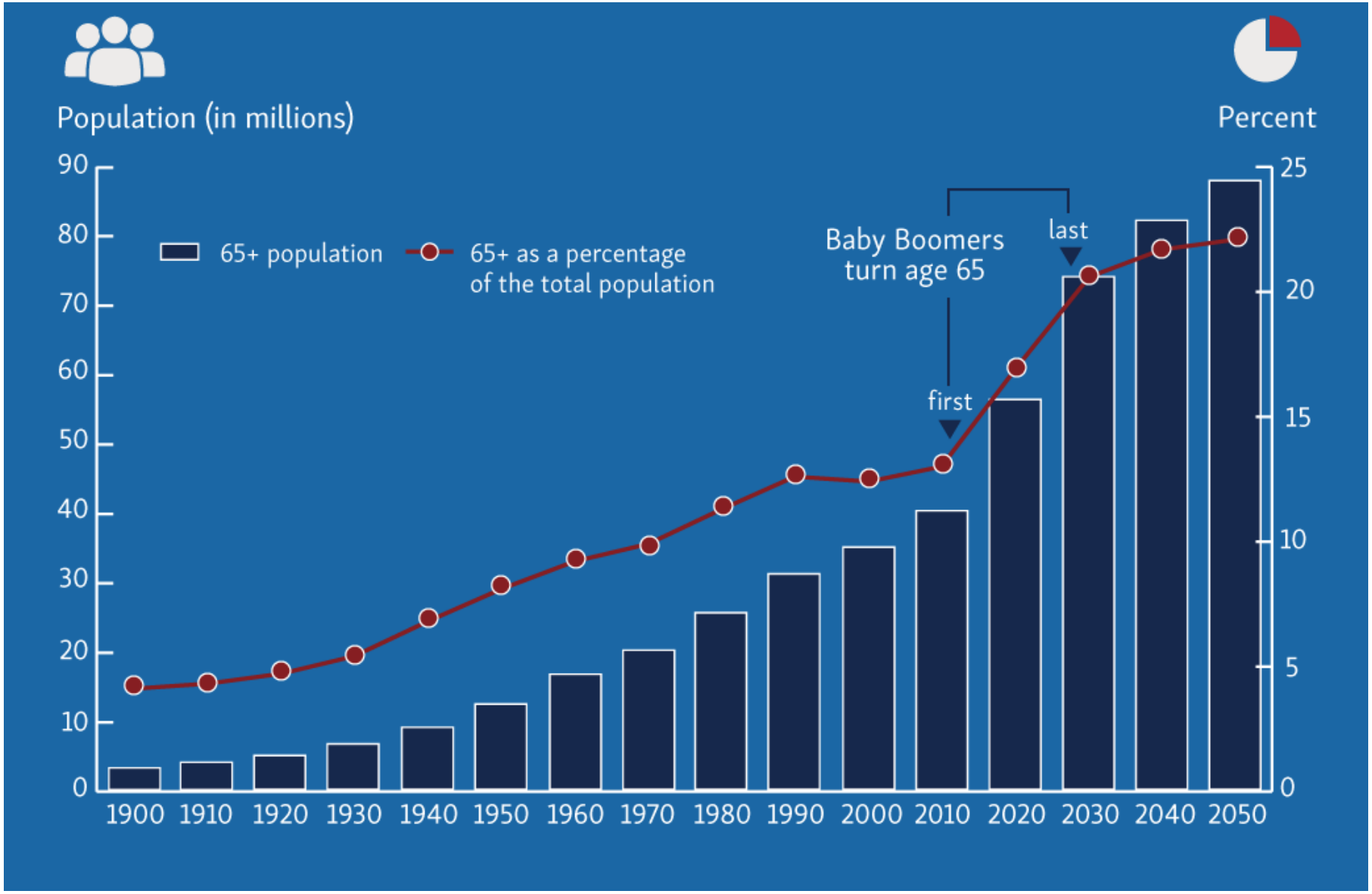
Energy hypothesis of aging



Adapted from: Ruggiero C, Ferrucci L. J Gerontol A Biol Sci Med Sci. 2006.

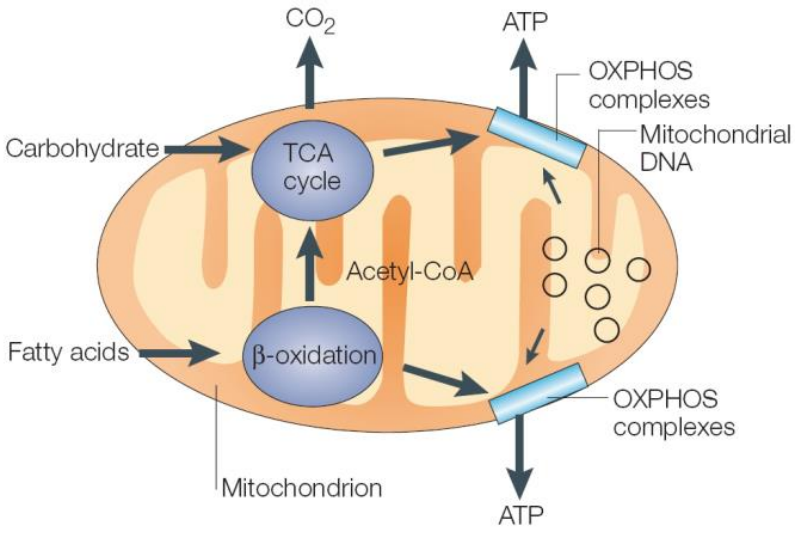
Public Health Significance



Federal Interagency Forum on Aging-Related Statistics. Older Americans 2017.

What are Mitochondria?

- "Powerhouse of the cell" (primary site of ATP synthesis in aerobic metabolism)
- Tens to thousands exist within each cell in your body
- Each mitochondrion has it's own DNA
- Other roles
  - Cell-to-cell communication
  - Programmed cell death



Hypothesis

Given the central role of the mitochondria in energy production and maintenance, we hypothesize that the number of mitochondria will influence aging and age-related disease.

How do we measure the number of mitochondria?

- Mitochondria have their own DNA (mtDNA)
- Nuclear DNA (nucDNA) is always in 2 copies (inherited from Mom and Dad)
- The ratio of the mtDNA to nucDNA gives a standardized measure of mtDNA.
- Can be measured in DNA extracted from blood.

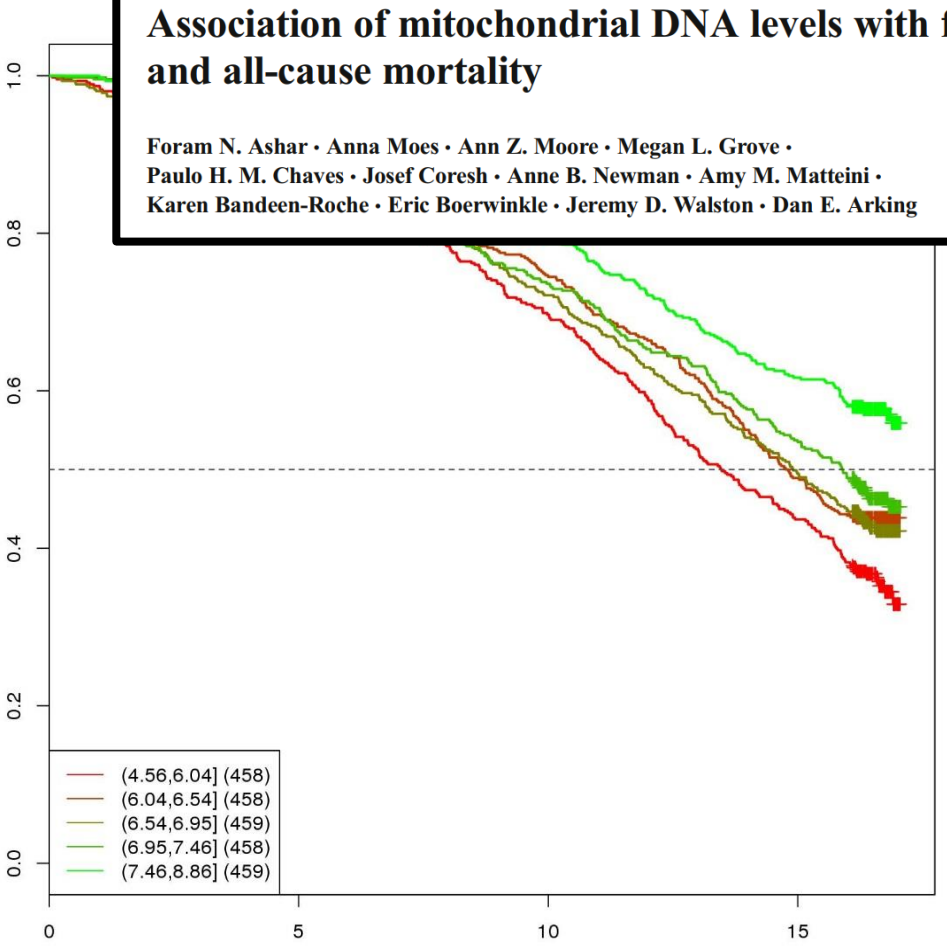
J Mol Med (2015) 93:177–186
DOI 10.1007/s00109-014-1233-3

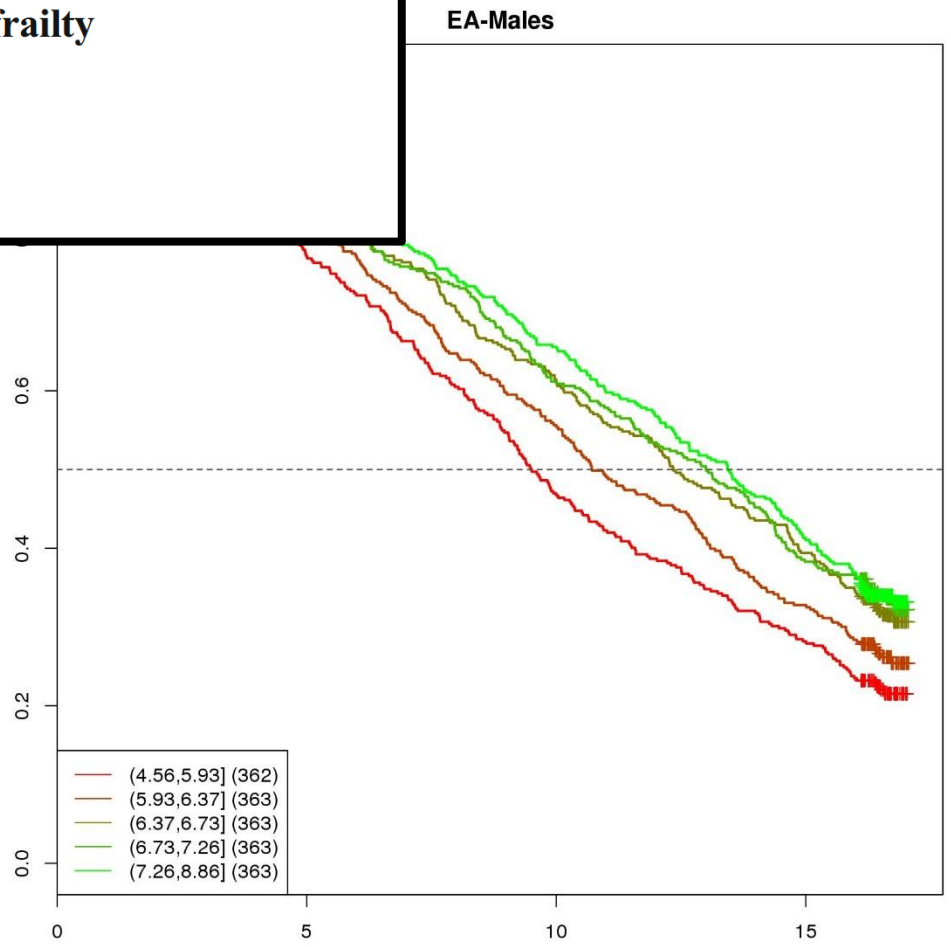
JMolMed

ORIGINAL ARTICLE

Association of mitochondrial DNA levels with frailty and all-cause mortality

Foram N. Ashar · Anna Moes · Ann Z. Moore · Megan L. Grove · Paulo H. M. Chaves · Josef Coresh · Anne B. Newman · Amy M. Matteini · Karen Bandeen-Roche · Eric Boerwinkle · Jeremy D. Walston · Dan E. Arking





	Q1	Q5
15-year survival	43%	61%
50% survival (yrs)	13.5	>16.5

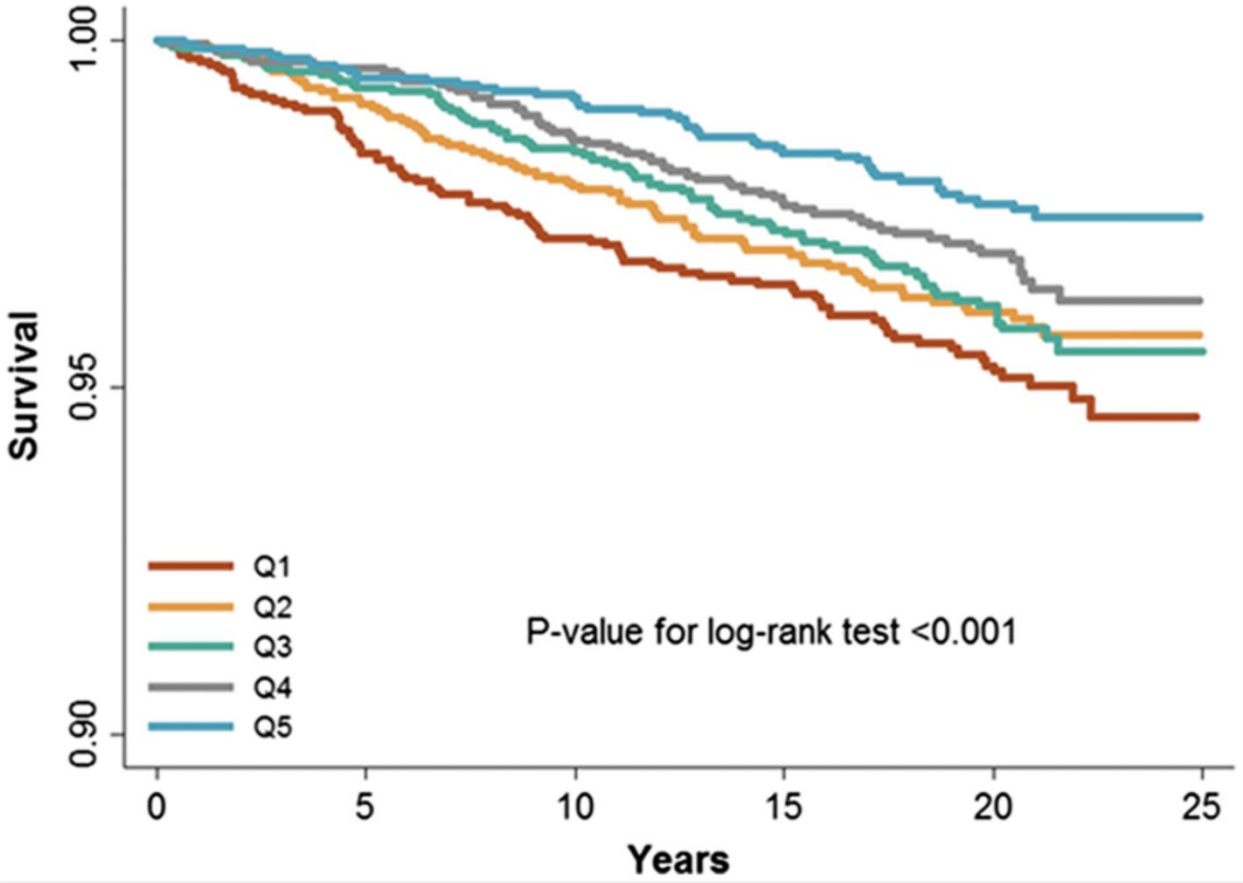
	Q1	Q5
15-year survival	27%	41%
50% survival (yrs)	9.5	13.5

ESC European Society of Cardiology
European Heart Journal (2017) **38**, 3443–3448
doi:10.1093/eurheartj/ehx354

CLINICAL RESEARCH
Prevention and epidemiology

Association between mitochondrial DNA copy number and sudden cardiac death: findings from the Atherosclerosis Risk in Communities study (ARIC)

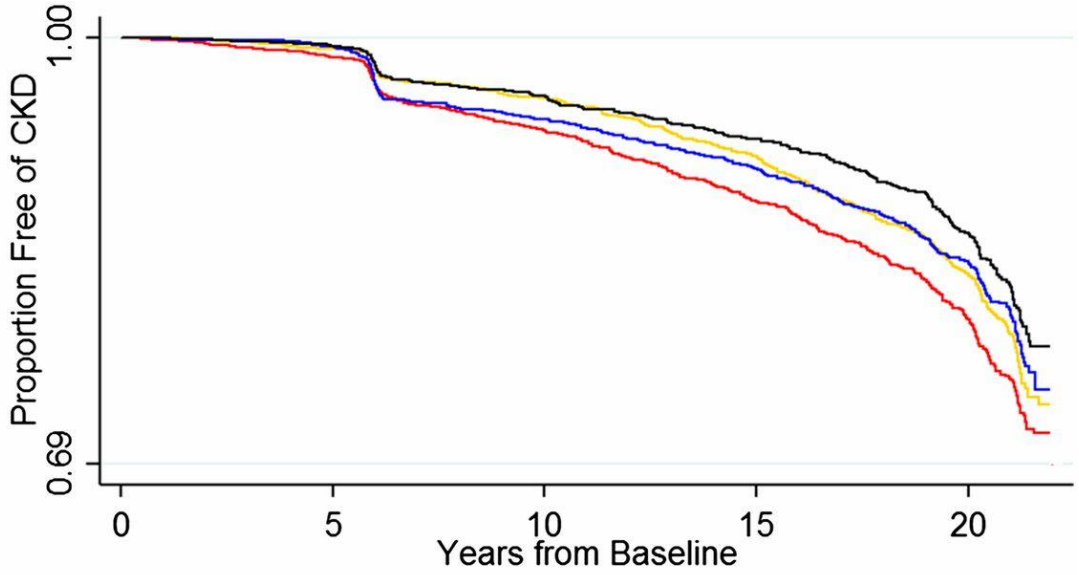
Yiyi Zhang[1], Eliseo Guallar[1], Foram N. Ashar[2], Ryan J. Longchamps[2], Christina A. Castellani[2], John Lane[3], Megan L. Grove[4], Josef Coresh[1], Nona Sotoodehnia[5], Leonard Ilkhanoff[6,7], Eric Boerwinkle[4,8], Nathan Pankratz[3], and Dan E. Arking[2]*



CLINICAL EPIDEMIOLOGY www.jasn.org

Association between Mitochondrial DNA Copy Number in Peripheral Blood and Incident CKD in the Atherosclerosis Risk in Communities Study

Adrienne Tin,* Morgan E. Grams,† Foram N. Ashar,‡ John A. Lane,§ Avi Z. Rosenberg,‖¶ Megan L. Grove,** Eric Boerwinkle,** Elizabeth Selvin,* Josef Coresh,* Nathan Pankratz,§ and Dan E. Arking‡



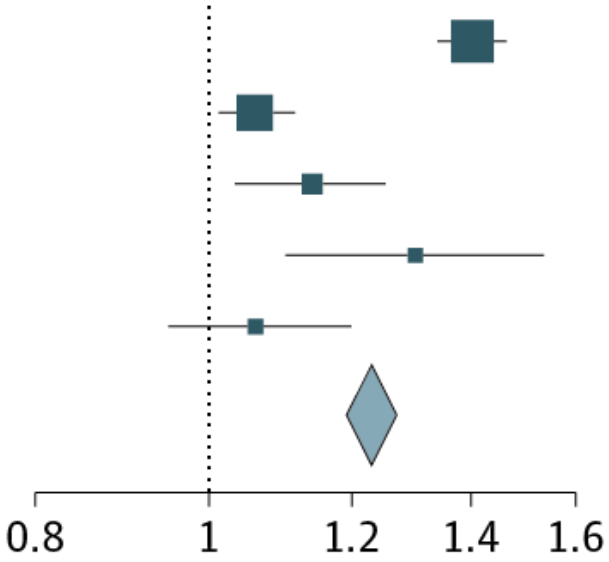
JAMA Cardiology | Original Investigation

Association of Mitochondrial DNA Copy Number With Cardiovascular Disease

Foram N. Ashar, PhD; Yiyi Zhang, PhD; Ryan J. Longchamps, BS; John Lane, BA; Anna Moes, MS; Megan L. Grove, MS; Josyf C. Mychaleckyj, MA, DPhil; Kent D. Taylor, PhD; Josef Coresh, MD, PhD; Jerome I. Rotter, MD; Eric Boerwinkle, PhD; Nathan Pankratz, PhD; Eliseo Guallar, MD, DrPH; Dan E. Arking, PhD

C Incident cardiovascular disease

Cohort	No.	Events	HR (95% CI)
ARIC	10150	1500	1.40 (1.34-1.46)
CHS	4126	1743	1.06 (1.01-1.12)
MESA	5887	422	1.14 (1.03-1.25)
<65 y	3236	142	1.30 (1.10-1.53)
≥65 y	2651	280	1.06 (0.95-1.20)
Meta-analysis	**20163**	**3665**	**1.23 (1.19-1.26)**



Approximately 70% higher risk of CVD comparing bottom 20% to top 20% of samples.

Does including mtDNA-CN in the ACC/AHA risk score improve sensitivity and specificity for initiating statin therapy?

Table 4. Net Reclassification Index[a] and IDI Comparing AHA Risk Score With and Without mtDNA-CN in the Pooled Cohorts

	AHA Risk Score + mtDNA-CN				Recalibrated AHA Risk Score + mtDNA-CN			
Event	<5% Risk	5% to <7.5% Risk	≥7.5% Risk	Total	<5% Risk	5% to <7.5% Risk	≥7.5% Risk	Total
Persons without event, No.								
<5% Risk	4833	241	13	5087	6236	202	9	6447

Overall, a net of 15 individuals with events were appropriately upclassified, and 221 individuals without events were appropriately downclassified.

Using a hard cutoff of 7.5% 10-year CVD risk for starting statin therapy, a net of 6 additional individuals would appropriately take a statin, and 139 would be appropriately not recommended to take a statin.

	Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value
NRI Categorical	0.032 (0.015-0.049)	<.001	0.022 (0.004-0.039)	.02
NRI Continuous	0.194 (0.130-0.258)	<.001	0.156 (0.092-0.220)	<.001
IDI	0.009 (0.005-0.012)	<.001	0.004 (0.002-0.007)	<.001

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; IDI, integrated discrimination improvement; mtDNA-CN, mitochondrial DNA copy number; NRI, net reclassification index.

[a] Categorical NRI with <5.0% and 5% to <7.5% risk cutoffs. Ten-year hard atherosclerotic cardiovascular disease risk was estimated in the pooled cohorts using Cox proportional hazards regression, using similar criteria as the 2013 AHA/ACC guidelines.[15]

Excluded individuals whose risk score would not impact therapy decisions based on the 2013 ACC/AHA guidelines (i.e., prevalent CVD, age >75 years, prevalent diabetes, LDL≥190, or LDL<70)

Conclusions

- mtDNA-CN is a novel independent risk factor for aging-related disease (frailty, mortality, CVD, SCD), with potential clinical utility (CVD)

- Mendelian Randomization is suggestive for causality – important when considering drug therapy for patients

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