Introductory Comments

Nicholas J. Schork, Ph.D.

TGen, Phoenix AZ and The City of Hope National Medical Center, Duarte, CA;
UCSD and Scripps Research, La Jolla, CA; St. Johns Health Center, Santa Monica, CA

1. Are Factors Mitigating Disease Generally Age and Context-Dependent?
2. Going From 'Bench to Bedside to Streetside' Requires Integration
3. Surrogate Endpoints, Biological Aging, and Interventions: How and When?

Nutritional Recommendations Should be Age and Context Dependent

AGE CATEGORY	All Ages		0-14		15-24		25-34		35-44		45-54		55-64		65-74		75+	
CAUSE OF DEATH	Rank	#	Rank	#	Rank	#	Rank	#	Rank	#	Rank	#	Rank	#	Rank	#	Rank	#
LOW BIRTH WEIGHT	46	4,110	2	4,107	55	1	62	2	69	0	72	0	72	0	73	0	77	0
BIRTH TRAUMA	55	1,347	4	1,336	56	1	63	2	67	1	71	0	66	4	66	2	67	1
ROAD TRAFFIC ACCIDENTS	19	41,944	5	1,171	1	6,816	3	8,038	3	6,178	9	5,615	18	6,275	27	4,117	34	3,734
HOMICIDE	26	24,573	6	1,011	3	6,466	4	7,125	7	4,482	17	2,541	32	1,753	44	742	50	453
DROWNINGS	44	4,176	7	654	6	546	18	557	25	509	38	508	50	552	52	437	52	413
SUICIDE	16	45,977	8	601	4	6,062	2	8,454	2	7,314	6	7,249	14	7,160	25	4,716	31	4,421
ENDOCRINE DISORDERS	10	55,660	9	559	8	423	8	1,210	10	2,267	13	4,320	11	8,782	10	12,131	13	25,968
INFLUENZA & PNEUMONIA	12	53,617	10	341	17	184	17	574	17	1,135	18	2,502	17	6,276	14	10,449	11	32,156
LEUKEMIA	27	23,422	11	276	12	261	26	346	24	541	29	956	28	2,616	21	5,685	20	12,741
STROKE	3	160,262	12	235	16	188	15	600	11	2,008	8	5,686	9	14,153	6	26,363	4	111,029
FIRES	53	2,951	13	185	20	99	30	158	38	234	45	307	47	640	47	674	48	654
INFLAMMATORY/HEART	24	28,422	14	166	13	237	12	826	16	1,445	21	2,405	22	4,402	22	5,527	19	13,414

AGE CATEGORY	All Ages		0-14		15-24		25-34		35-44		45-54		55-64		65-74		75+	
CAUSE OF DEATH	Rank	#	Rank	#	Rank	#	Rank	#	Rank	#	Rank	#	Rank	#	Rank	#	Rank	#
POISONINGS	9	87,386	19	115	2	6,664	1	20,938	1	21,943	2	18,078	8	15,030	29	3,891	46	727
SUICIDE	16	45,977	8	601	4	6,062	2	8,454	2	7,314	6	7,249	14	7,160	25	4,716	31	4,421
ROAD TRAFFIC ACCIDENTS	19	41,944	5	1,171	1	6,816	3	8,038	3	6,178	9	5,615	18	6,275	27	4,117	34	3,734
COVID-19	2	350,827	20	103	7	501	5	2,254	4	6,079	3	16,964	2	42,090	2	76,277	2	206,559
CORONARY HEART DISEASE	1	382,803	26	24	21	86	10	997	5	5,133	1	18,668	1	53,125	1	81,703	1	223,067
LIVER DISEASE	14	51,575	37	4	27	47	6	1,630	6	4,934	4	9,494	7	16,128	11	11,884	26	7,454
HOMICIDE	26	24,573	6	1,011	3	6,466	4	7,125	7	4,482	17	2,541	32	1,753	44	742	50	453
DIABETES MELLITUS	8	102,187	23	61	10	312	9	1,168	8	2,904	5	7,546	5	18,002	5	27,213	8	44,981
HYPERTENSION	7	119,985	34	5	22	78	13	795	9	2,783	7	7,132	6	16,447	7	21,561	6	71,184
ENDOCRINE DISORDERS	10	55,660	9	559	8	423	8	1,210	10	2,267	13	4,320	11	8,782	10	12,131	13	25,968
STROKE	3	160,262	12	235	16	188	15	600	11	2,008	8	5,686	9	14,153	6	26,363	4	111,029
OTHER INJURIES	23	28,499	3	1,795	5	929	7	1,439	13	1,867	16	2,605	20	4,431	24	5,118	24	10,315
COLON-RECTUM CANCERS	13	53,095	49	1	28	46	21	408	15	1,523	11	4,800	10	10,544	9	13,337	14	22,436
INFLAMMATORY/HEART	24	28,422	14	166	13	237	12	826	16	1,445	21	2,405	22	4,402	22	5,527	19	13,414
INFLUENZA & PNEUMONIA	12	53,617	10	341	17	184	17	574	17	1,135	18	2,502	17	6,276	14	10,449	11	32,156
KIDNEY DISEASE	11	54,306	22	71	23	72	27	345	18	896	20	2,444	16	6,412	12	11,849	10	32,217
HIV/AIDS	41	5,115	44	2	26	53	19	468	19	770	25	1,165	34	1,542	43	833	55	282

AGE CATEGORY	All Ages		0-14		15-24		25-34		35-44		45-54		55-64		65-74		75+	
CAUSE OF DEATH	Rank	#	Rank	#	Rank	#	Rank	#	Rank	#	Rank	#	Rank	#	Rank	#	Rank	#
CORONARY HEART DISEASE	1	382,803	26	24	21	86	10	997	5	5,133	1	18,668	1	53,125	1	81,703	1	223,067
COVID-19	2	350,827	20	103	7	501	5	2,254	4	6,079	3	16,964	2	42,090	2	76,277	2	206,559
LUNG CANCERS	5	136,166	32	6	39	13	32	126	20	756	10	5,058	3	26,664	3	45,572	7	57,971
LUNG DISEASE	4	147,511	30	13	37	14	40	47	32	373	15	2,946	4	18,011	4	37,837	5	88,275
DIABETES MELLITUS	8	102,187	23	61	10	312	9	1,168	8	2,904	5	7,546	5	18,002	5	27,213	8	44,981
STROKE	3	160,262	12	235	16	188	15	600	11	2,008	8	5,686	9	14,153	6	26,363	4	111,029
HYPERTENSION	7	119,985	34	5	22	78	13	795	9	2,783	7	7,132	6	16,447	7	21,561	6	71,184
COLON-RECTUM CANCERS	13	53,095	49	1	28	46	21	408	15	1,523	11	4,800	10	10,544	9	13,337	14	22,436
ENDOCRINE DISORDERS	10	55,660	9	559	8	423	8	1,210	10	2,267	13	4,320	11	8,782	10	12,131	13	25,968
LIVER DISEASE	14	51,575	37	4	27	47	6	1,630	6	4,934	4	9,494	7	16,128	11	11,884	26	7,454
KIDNEY DISEASE	11	54,306	22	71	23	72	27	345	18	896	20	2,444	16	6,412	12	11,849	10	32,217
INFLUENZA & PNEUMONIA	12	53,617	10	341	17	184	17	574	17	1,135	18	2,502	17	6,276	14	10,449	11	32,156
LIVER CANCER	25	28,227	25	33	30	38	35	97	35	321	22	1,424	15	6,806	15	9,988	25	9,520
LYMPHOMAS	21	34,319	28	19	25	63	29	200	30	436	23	1,399	21	4,420	17	9,026	17	18,756
PROSTATE CANCER	22	32,707	50	1	58	1	64	1	53	32	44	326	25	2,944	18	8,083	15	21,319
FALLS	18	42,113	24	47	18	152	24	359	22	625	24	1,282	24	3,140	20	5,925	12	30,583
LEUKEMIA	27	23,422	11	276	12	261	26	346	24	541	29	956	28	2,616	21	5,685	20	12,741
INFLAMMATORY/HEART	24	28,422	14	166	13	237	12	826	16	1,445	21	2,405	22	4,402	22	5,527	19	13,414
OTHER INJURIES	23	28,499	3	1,795	5	929	7	1,439	13	1,867	16	2,605	20	4,431	24	5,118	24	10,315
SUICIDE	16	45,977	8	601	4	6,062	2	8,454	2	7,314	6	7,249	14	7,160	25	4,716	31	4,421
ROAD TRAFFIC ACCIDENTS	19	41,944	5	1,171	1	6,816	3	8,038	3	6,178	9	5,615	18	6,275	27	4,117	34	3,734
OVARY CANCER	33	13,438	38	4	38	14	36	96	36	285	26	1,065	26	2,837	28	4,014	29	5,123
POISONINGS	9	87,386	19	115	2	6,664	1	20,938	1	21,943	2	18,078	8	15,030	29	3,891	46	727
ORAL CANCER	37	10,835	43	2	35	15	42	41	40	187	30	842	27	2,827	31	3,317	35	3,604
OTHER NEOPLASMS	29	16,229	18	129	24	65	31	131	37	251	39	491	35	1,539	32	3,278	23	10,345

https://www.worldlifeexpectancy.com/usa-cause-of-death-by-age-and-gender

Lingering Effects of Early Genetic Programs, Diets, Behaviors, and Exposures

ORIGINAL ARTICLES

www.jpeds.com • THE JOURNAL OF PEDIATRICS

Childhood Risk Factors and Adulthood Cardiovascular Disease: A Systematic Review

Lindsay R. Pool, PhD[1], Liliana Aguayo, PhD[1,2], Michal Brzezinski, PhD[3], Amanda M. Perak, MD[1,4,5], Matthew M. Davis, MD[1,2,5,6,7], Philip Greenland, MD[1], Lifang Hou, MD, PhD[1,5], Bradley S. Marino, MD[2,4,5,7], Linda Van Horn, PhD[1], Lauren Wakschlag, PhD[6,7], Darwin Labarthe, MD, PhD[1,6], Donald Lloyd-Jones, MD[1,6], and Norrina B. Allen, PhD[1,6]

Childhood Risk Factor	# of papers	Subclinical CVD				Clinical CVD			
		Arterial Stiffness	cIMT	CAC	LV structure and function	CHD	Stroke	Heart failure	CVD Mixed Definition
Increased Adiposity	61	3 papers: higher risk 5 papers: null	19 papers: higher risk 1 papers: null	1 paper: higher risk	11 papers: higher risk	9 papers: higher risk 2 papers: null	6 papers: higher risk 1 papers: null	2 papers: higher risk	10 papers: higher risk
Low Birthweight	28	1 paper: higher risk 1 paper: null	no papers	no papers	1 paper: null	13 papers: higher risk	3 papers: higher risk 1 paper: null	no papers	8 papers: higher risk
Pediatric Hypertension	29	9 papers: higher risk 1 paper: null	10 papers: higher risk 1 paper: null	2 papers: higher risk	7 papers: higher risk 1 paper: null	2 papers: higher risk	no papers	no papers	3 papers: higher risk
Pediatric Hyperlipidemia	16	no papers	10 papers: higher risk	2 papers: higher risk	1 paper: higher risk	1 paper: higher risk	no papers	no papers	3 papers: higher risk
High Glycemic Indicators	2	1 paper: null	1 paper: higher risk	no papers	no papers	no papers	1 paper: higher risk	no papers	no papers
Tobacco Exposure	7	no papers	3 papers: higher risk	1 paper: higher risk	no papers	1 paper: higher risk	1 paper: higher risk	no papers	3 papers: higher risk
Physical Activity	6	4 papers: lower risk	2 papers: lower risk	no papers	no papers	no papers	no papers	no papers	1 paper: null
Dietary Quality	9	3 papers: lower risk 1 paper: null	3 papers: lower risk	no papers	no papers	1 paper: null	2 papers: lower risk	no papers	no papers
Breastfeeding	6	1 paper: null	1 paper: lower risk 1 paper: null	no papers	no papers	1 paper: lower risk 1 paper: null	1 paper: null	no papers	1 paper: null
Low Socioeconomic Status	13	no papers	2 papers: null	no papers	1 paper: higher risk	2 papers: higher risk	2 papers: higher risk	no papers	7 papers: higher risk
Psychosocial Adversity	18	1 paper: higher risk 2 papers: null	4 papers: higher risk	1 paper: higher risk	no papers	3 papers: higher risk	1 paper: higher risk	1 paper: higher risk	5 papers: higher risk 1 paper: null
Metabolic Syndrome	9	1 paper: higher risk	5 papers: higher risk	no papers	no papers	no papers	no papers	no papers	3 papers: higher risk
Other Risk Factor Clustering	7	2 papers: higher risk	6 papers: higher risk	1 paper: higher risk	no papers	no papers	no papers	no papers	no papers

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 19, 2022 VOL. 386 NO. 20

Childhood Cardiovascular Risk Factors and Adult Cardiovascular Events

D.R. Jacobs, Jr., J.G. Woo, A.R. Sinaiko, S.R. Daniels, J. Ikonen, M. Juonala, N. Kartiosuo, T. Lehtimäki, C.G. Magnussen, J.S.A. Viikari, N. Zhang, L.A. Bazzano, T.L. Burns, R.J. Prineas, J. Steinberger, E.M. Urbina, A.J. Venn, O.T. Raitakari, and T. Dwyer

BACKGROUND

Childhood cardiovascul
ease, but links to clinic

METHODS

In a prospective cohort
Cardiovascular Cohort (i
(at the ages of 3 to 19 ye
after a mean follow-up
cholesterol level, triglyce
i3C-derived age- and sex
calculated as the unweig
rable adult combined-ri
jointly with the childh
events and fatal or nonfa
multiple imputation wit

RESULTS

In the analysis of 319 fa
ticipants (49.7% male an
years), the hazard ratios
1.30 (95% confidence in
total cholesterol level to
The hazard ratio for a f
z score was 2.71 (95% C
95% confidence interval
to those in the analyses
among 20,656 participan
of 115 fatal cardiovascul
(31.0±5.6 years of age at
the adjusted hazard rati
3.54 (95% CI, 2.57 to 4.8
with respect to the cha
hood was 2.88 (95% CI,
the analysis of 524 fatal

CONCLUSIONS

In this prospective coh
combined-risk z score
cardiovascular events in

Published by Oxford University Press on behalf of the International Epidemiological Association
© The Author 2012; all rights reserved. Advance Access publication 20 March 2012

International Journal of Epidemiology 2013;**42**:86–96
doi:10.1093/ije/dys004

COHORT PROFILE

Cohort Profile: The International Childhood Cardiovascular Cohort (i3C) Consortium

Terence Dwyer,[1]* Cong Sun,[1†] Costan G Magnussen,[2,3†] Olli T Raitakari,[3,4] Nicholas J Schork,[5] Alison Venn,[2] Trudy L Burns,[6,7] Markus Juonala,[3,8] Julia Steinberger,[9] Alan R Sinaiko,[9] Ronald J Prineas,[10] Patricia H Davis,[11] Jessica G Woo,[12,13] John A Morrison,[12] Stephen R Daniels,[14] Wei Chen,[15] Sathanur R Srinivasan,[15] Jorma SA Viikari[8] and Gerald S Berenson[15]

[1]Environmental and Genetic Epidemiology Research Group, Murdoch Children's Research Institute, Royal Children's Hospital, Melbourne, Victoria, Australia, [2]Menzies Research Institute Tasmania, University of Tasmania, Hobart, Tasmania, Australia, [3]Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, Finland, [4]Department of Clinical Physiology, Turku University Hospital, Turku, Finland, [5]The Scripps Research Institute, La Jolla, CA, USA, [6]Department of Epidemiology, College of Public Health, University of Iowa, Iowa City, IA, USA, [7]Department of Pediatrics, Carver College of Medicine, University of Iowa, Iowa City, IA, USA, [8]Department of Medicine, University of Turku, Turku University Hospital, Turku, Finland, [9]Department of Pediatrics, University of Minnesota Amplatz Children's Hospital, Minneapolis, MN, USA, [10]Wake Forest University School of Medicine, Winston-Salem, NC, USA, [11]Department of Neurology, Carver College of Medicine, University of Iowa, Iowa City, IA, USA, [12]The Heart Institute, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA, [13]Division of Biostatistics and Epidemiology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA, [14]Department of Pediatrics, University of Colorado School of Medicine, The Children's Hospital, Denver, CO, USA and [15]Tulane Center for Cardiovascular Health, Department of Epidemiology, Tulane University, New Orleans, LA, USA

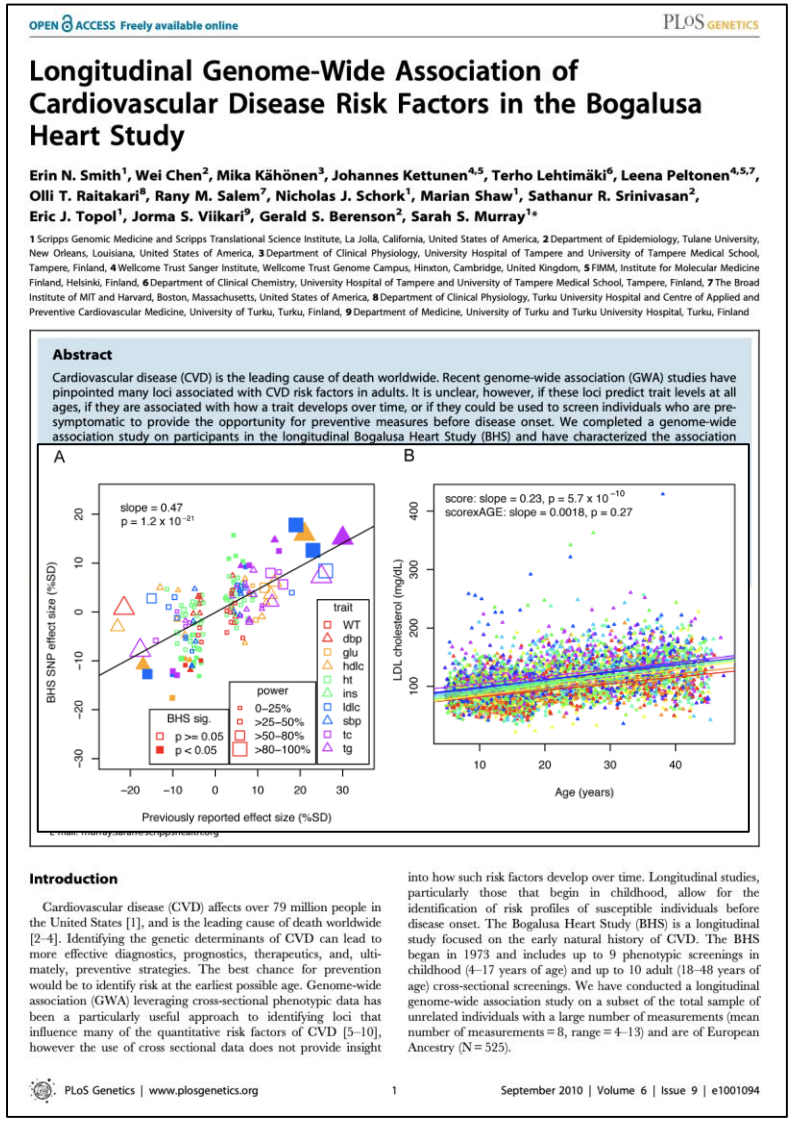
*Corresponding author. Murdoch Children's Research Institute, Royal Children's Hospital, Flemington Road, Parkville, Melbourne 3052, Australia. E-mail: terry.dwyer@mcri.edu.au
†These authors contributed equally to this work

Table 1 Summary of the i3C Consortium Studies

Study	Country	Sampling frame	Baseline in childhood and adolescence: Sample with one major CVD risk factor (*N*)[a]	Sample with three major CVD risk factors (*N*)[b]	Study years	Age (years)	Follow-up in adulthood: Sample with three major CVD risk factors (*N*)[b]	Study years	Age (years)
Muscatine Study[c]	USA	School based	11 377	11 377	1970–81	5–18	2547	1982–91	20–39
							865	1992–2008	29–55
BHS[c,d]	USA	School based	12 164	12 164	1973–94	4–17	1203	2001–02	23–43
							1052	2003–05	26–47
							914	2007–10	29–51
YFS	Finland	Random sample from five centres	3596	3596	1980	3–18	2283	2001	24–39
							2204	2007	30–45
							Ongoing	2010	33–48
CDAH Study	Australia	School based	8498	1714	1985	7–15	2410	2004–06	26–36
Minneapolis Children's Studies[c,d]	USA	School based	1207 (10 423 screened)	0	1978–89	6–9 to 17–20	679	1993–96	21–24
							359	2007–11	35–38
		School based	357 (12 043 screened)	357	1996	11–14	230	2004	19–24
Princeton LRC/PFS[c,d]	USA	School based	6775 (Visit 1)	1729 (Visit 2)[e]	1973–76	5–19	623[e]	1999–2004	30–48
							600 (ongoing)	2011–12	43–57
NGHS[d]	USA	Cincinnati, OH: School based	871	705–871	1987–96	9–19	653	1997–2002	20–24
							~650	2002–07	24–28
		Richmond, CA: School based	879	823–871			–	–	–
		Washington, DC: Sample from HMO	629	550–629			–	–	–

BHS: Bogalusa Heart Study; CDAH Study: Childhood Determinants of Adult Health Study; NGHS: National Heart, Lung, and Blood Institute Growth and Health Study; YFS: Young Finns Study; Princeton LRC/PFS: National Heart, Lung, and Blood Institute Princeton Lipid Research Clinics Study/Princeton Follow-up Study; HMO: health maintenance organization.
[a]Sample with measurement of at least one major CVD risk factor (blood pressure, lipids or adiposity measures including skinfold thickness or BMI).
[b]Sample with measurement of all three major CVD risk factors.
[c]Other generations and family data available.
[d]Biracial cohort: black and white.
[e]An additional 557 participants aged 5–19 years were measured in the LRC family study (Visit 3) along with their siblings already counted in the 1729 above. Blood pressure was not measured at Visit 3. Of these 557 siblings, 221 were recontacted in the 1999–2004 follow-up.

The Need for Integration Across the Age, Genetic and Non-Genetic Spectrum



OPEN ACCESS Freely available online — PLoS GENETICS

Longitudinal Genome-Wide Association of Cardiovascular Disease Risk Factors in the Bogalusa Heart Study

Erin N. Smith[1], Wei Chen[2], Mika Kähönen[3], Johannes Kettunen[4,5], Terho Lehtimäki[6], Leena Peltonen[4,5,7], Olli T. Raitakari[8], Rany M. Salem[7], Nicholas J. Schork[1], Marian Shaw[1], Sathanur R. Srinivasan[2], Eric J. Topol[1], Jorma S. Viikari[9], Gerald S. Berenson[2], Sarah S. Murray[1]*

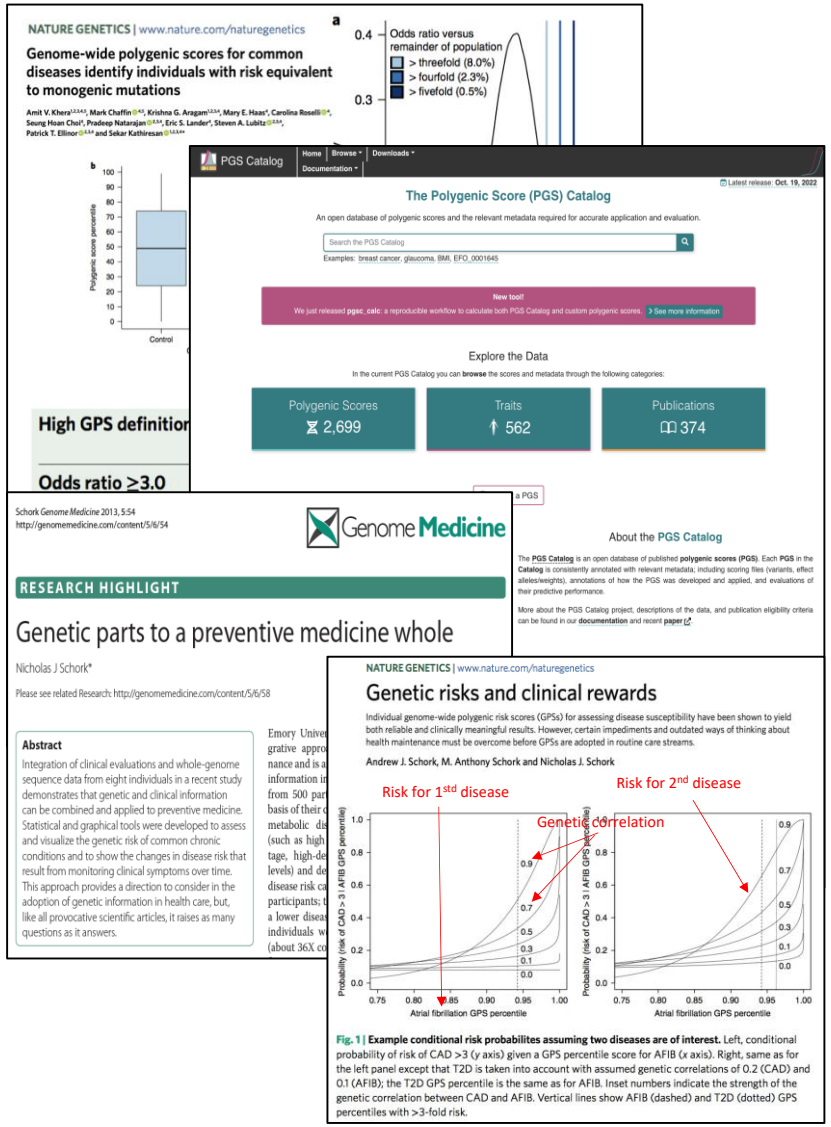
1 Scripps Genomic Medicine and Scripps Translational Science Institute, La Jolla, California, United States of America, **2** Department of Epidemiology, Tulane University, New Orleans, Louisiana, United States of America, **3** Department of Clinical Physiology, University Hospital of Tampere and University of Tampere Medical School, Tampere, Finland, **4** Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, United Kingdom, **5** FIMM, Institute for Molecular Medicine Finland, Helsinki, Finland, **6** Department of Clinical Chemistry, University Hospital of Tampere and University of Tampere Medical School, Tampere, Finland, **7** The Broad Institute of MIT and Harvard, Boston, Massachusetts, United States of America, **8** Department of Clinical Physiology, Turku University Hospital and Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, Finland, **9** Department of Medicine, University of Turku and Turku University Hospital, Turku, Finland

Abstract

Cardiovascular disease (CVD) is the leading cause of death worldwide. Recent genome-wide association (GWA) studies have pinpointed many loci associated with CVD risk factors in adults. It is unclear, however, if these loci predict trait levels at all ages, if they are associated with how a trait develops over time, or if they could be used to screen individuals who are pre-symptomatic to provide the opportunity for preventive measures before disease onset. We completed a genome-wide association study on participants in the longitudinal Bogalusa Heart Study (BHS) and have characterized the association

Introduction

Cardiovascular disease (CVD) affects over 79 million people in the United States [1], and is the leading cause of death worldwide [2–4]. Identifying the genetic determinants of CVD can lead to more effective diagnostics, prognostics, therapeutics, and, ultimately, preventive strategies. The best chance for prevention would be to identify risk at the earliest possible age. Genome-wide association (GWA) leveraging cross-sectional phenotypic data has been a particularly useful approach to identifying loci that influence many of the quantitative risk factors of CVD [5–10], however the use of cross sectional data does not provide insight into how such risk factors develop over time. Longitudinal studies, particularly those that begin in childhood, allow for the identification of risk profiles of susceptible individuals before disease onset. The Bogalusa Heart Study (BHS) is a longitudinal study focused on the early natural history of CVD. The BHS began in 1973 and includes up to 9 phenotypic screenings in childhood (4–17 years of age) and up to 10 adult (18–48 years of age) cross-sectional screenings. We have conducted a longitudinal genome-wide association study on a subset of the total sample of unrelated individuals with a large number of measurements (mean number of measurements = 8, range = 4–13) and are of European Ancestry (N = 525).



NATURE GENETICS | www.nature.com/naturegenetics

Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations

Amit V. Khera[1,2,3,4,5], Mark Chaffin[1,4,5], Krishna G. Aragam[1,2,3,4], Mary E. Haas[6], Carolina Roselli[1,4], Seung Hoan Choi[1], Pradeep Natarajan[1,2,3,4], Eric S. Lander[4], Steven A. Lubitz[1,2,3,4], Patrick T. Ellinor[1,2,3,4] and Sekar Kathiresan[1,2,3,4,5]*

PGS Catalog — Home | Browse | Downloads | Documentation

The Polygenic Score (PGS) Catalog

An open database of polygenic scores and the relevant metadata required for accurate application and evaluation.

Search the PGS Catalog

Examples: breast cancer, glaucoma, BMI, EFO_0001645

New tool!

We just released pgsc_calc: a reproducible workflow to calculate both PGS Catalog and custom polygenic scores. See more information

Explore the Data

In the current PGS Catalog you can browse the scores and metadata through the following categories:

Polygenic Scores	Traits	Publications
2,699	562	374

About the PGS Catalog

The PGS Catalog is an open database of published polygenic scores (PGS). Each PGS in the Catalog is consistently annotated with relevant metadata; including scoring files (variants, effect alleles/weights), annotations of how the PGS was developed and applied, and evaluations of their predictive performance.

More about the PGS Catalog project, descriptions of the data, and publication eligibility criteria can be found in our documentation and recent paper

Schork Genome Medicine 2013, 5:54
http://genomemedicine.com/content/5/6/54

Genome Medicine

RESEARCH HIGHLIGHT

Genetic parts to a preventive medicine whole

Nicholas J Schork*

Please see related Research: http://genomemedicine.com/content/5/6/58

Abstract

Integration of clinical evaluations and whole-genome sequence data from eight individuals in a recent study demonstrates that genetic and clinical information can be combined and applied to preventive medicine. Statistical and graphical tools were developed to assess and visualize the genetic risk of common chronic conditions and to show the changes in disease risk that result from monitoring clinical symptoms over time. This approach provides a direction to consider in the adoption of genetic information in health care, but, like all provocative scientific articles, it raises as many questions as it answers.

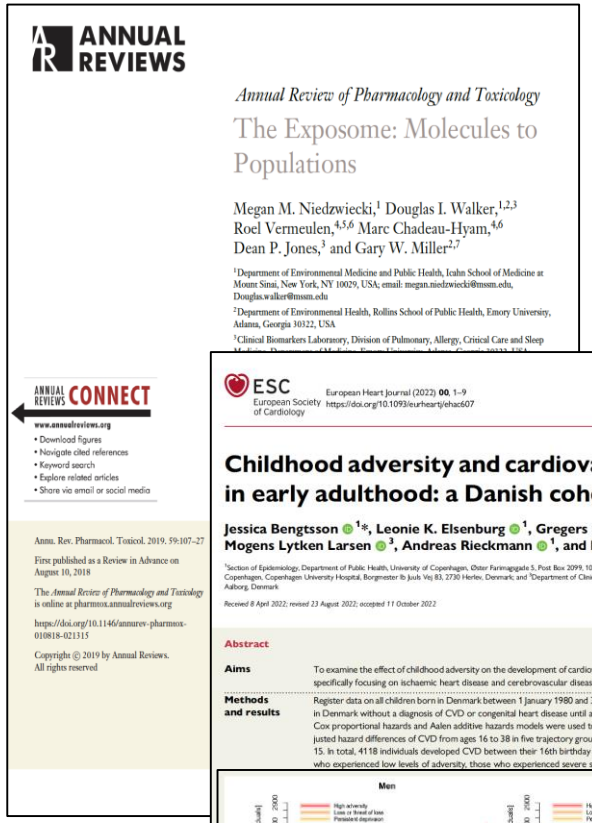
NATURE GENETICS | www.nature.com/naturegenetics

Genetic risks and clinical rewards

Individual genome-wide polygenic risk scores (GPSs) for assessing disease susceptibility have been shown to yield both reliable and clinically meaningful results. However, certain impediments and outdated ways of thinking about health maintenance must be overcome before GPSs are adopted in routine care streams.

Andrew J. Schork, M. Anthony Schork and Nicholas J. Schork

Fig. 1 | Example conditional risk probabilites assuming two diseases are of interest. Left, conditional probability of risk of CAD >3 (*y* axis) given a GPS percentile score for AFIB (*x* axis). Right, same as for the left panel except that T2D is taken into account with assumed genetic correlations of 0.2 (CAD) and 0.1 (AFIB); the T2D GPS percentile is the same as for AFIB. Inset numbers indicate the strength of the genetic correlation between CAD and AFIB. Vertical lines show AFIB (dashed) and T2D (dotted) GPS percentiles with >3-fold risk.



ANNUAL REVIEWS

Annual Review of Pharmacology and Toxicology

The Exposome: Molecules to Populations

Megan M. Niedzwiecki,[1] Douglas I. Walker,[1,2,3] Roel Vermeulen,[4,5,6] Marc Chadeau-Hyam,[4,6] Dean P. Jones,[3] and Gary W. Miller[2,7]

[1]Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA; email: megan.niedzwiecki@mssm.edu, Douglas.walker@mssm.edu

[2]Department of Environmental Health, Rollins School of Public Health, Emory University, Atlanta, Georgia 30322, USA

[3]Clinical Biomarkers Laboratory, Division of Pulmonary, Allergy, Critical Care and Sleep

ANNUAL REVIEWS CONNECT

www.annualreviews.org

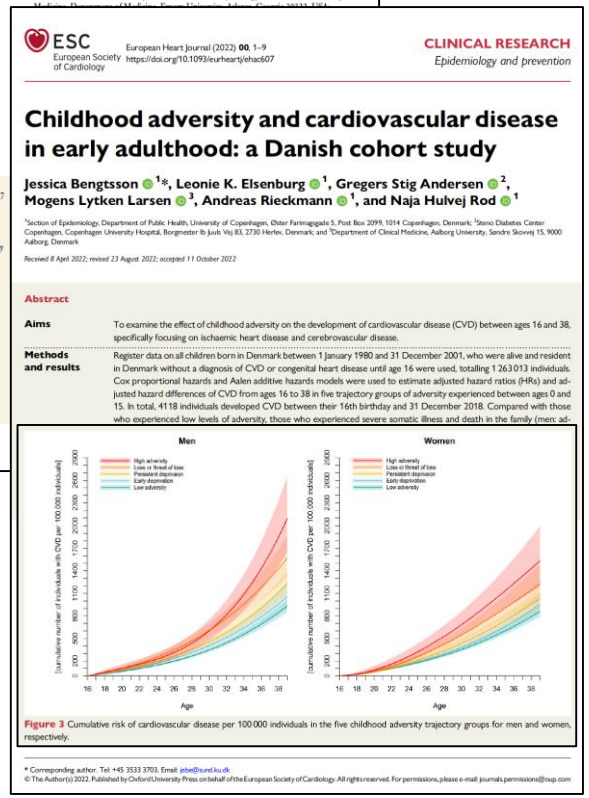
- Download figures
- Navigate cited references
- Keyword search
- Explore related articles
- Share via email or social media

Annu. Rev. Pharmacol. Toxicol. 2019. 59:107–27

First published as a Review in Advance on August 10, 2018

The *Annual Review of Pharmacology and Toxicology* is online at pharmtox.annualreviews.org

https://doi.org/10.1146/annurev-pharmtox-010818-021315



ESC European Society of Cardiology

European Heart Journal (2022) 00, 1–9 https://doi.org/10.1093/eurheartj/ehac607

CLINICAL RESEARCH
Epidemiology and prevention

Childhood adversity and cardiovascular disease in early adulthood: a Danish cohort study

Jessica Bengtsson[1]*, Leonie K. Elsenburg[1], Gregers Stig Andersen[2], Mogens Lytken Larsen[3], Andreas Rieckmann[1], and Naja Hulvej Rod[1]

[1]Section of Epidemiology, Department of Public Health, University of Copenhagen, Øster Farimagsgade 5, Post Box 2099, 1014 Copenhagen, Denmark; [2]Steno Diabetes Center Copenhagen, Copenhagen University Hospital, Borgmester Ib Juuls Vej 83, 2730 Herlev, Denmark; and [3]Department of Clinical Medicine, Aalborg University, Sandre Skovvej 15, 9000 Aalborg, Denmark

Received 8 April 2022; revised 23 August 2022; accepted 11 October 2022

Abstract

Aims To examine the effect of childhood adversity on the development of cardiovascular disease (CVD) between ages 16 and 38, specifically focusing on ischaemic heart disease and cerebrovascular disease.

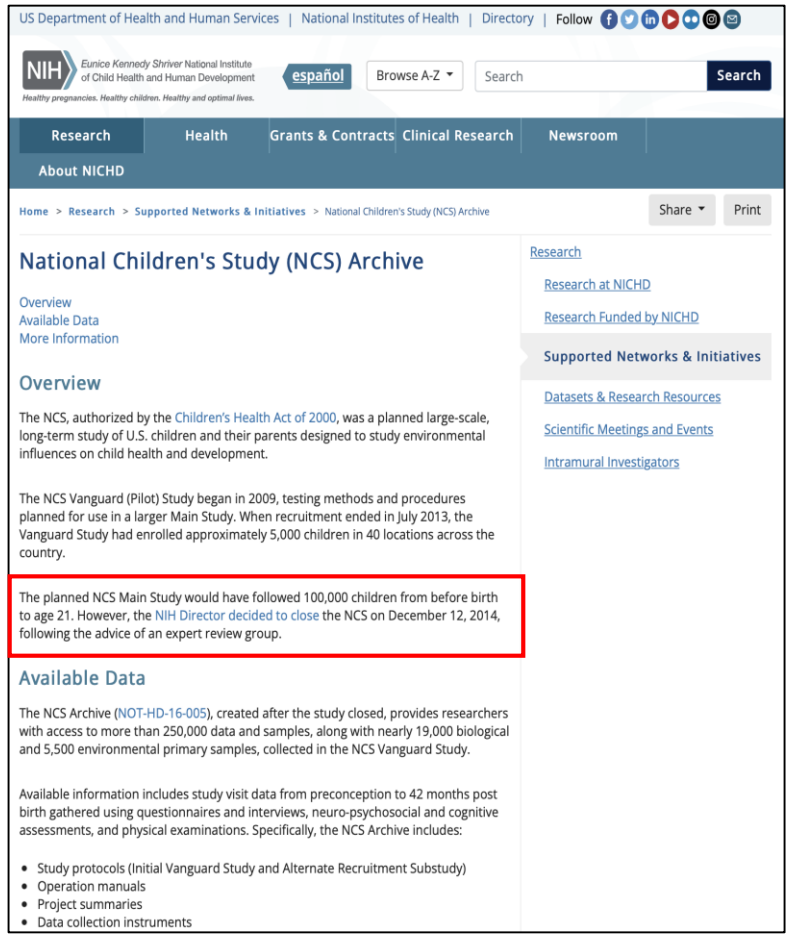
Methods and results Register data on all children born in Denmark between 1 January 1980 and 31 December 2001, who were alive and resident in Denmark without a diagnosis of CVD or congenital heart disease until age 16 were used, totalling 1 263 013 individuals. Cox proportional hazards and Aalen additive hazards models were used to estimate adjusted hazard ratios (HRs) and adjusted hazard differences of CVD from ages 16 to 38 in five trajectory groups of adversity experienced between ages 0 and 15. In total, 4118 individuals developed CVD between their 16th birthday and 31 December 2018. Compared with those who experienced low levels of adversity, those who experienced severe somatic illness and death in the family (men: ad-

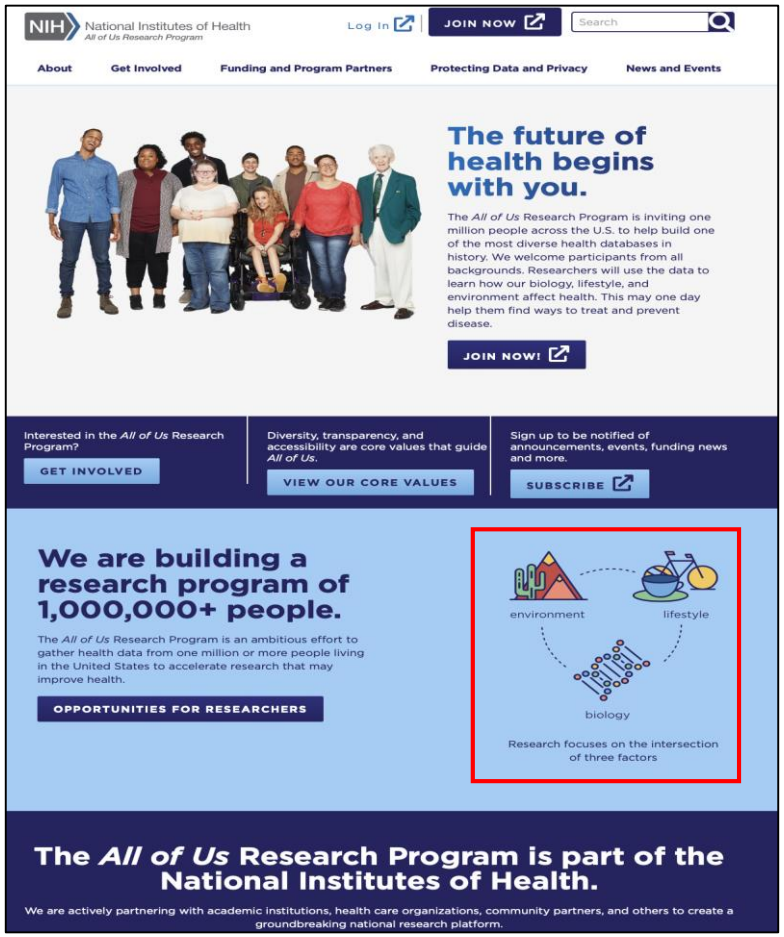
Figure 3 Cumulative risk of cardiovascular disease per 100 000 individuals in the five childhood adversity trajectory groups for men and women, respectively.

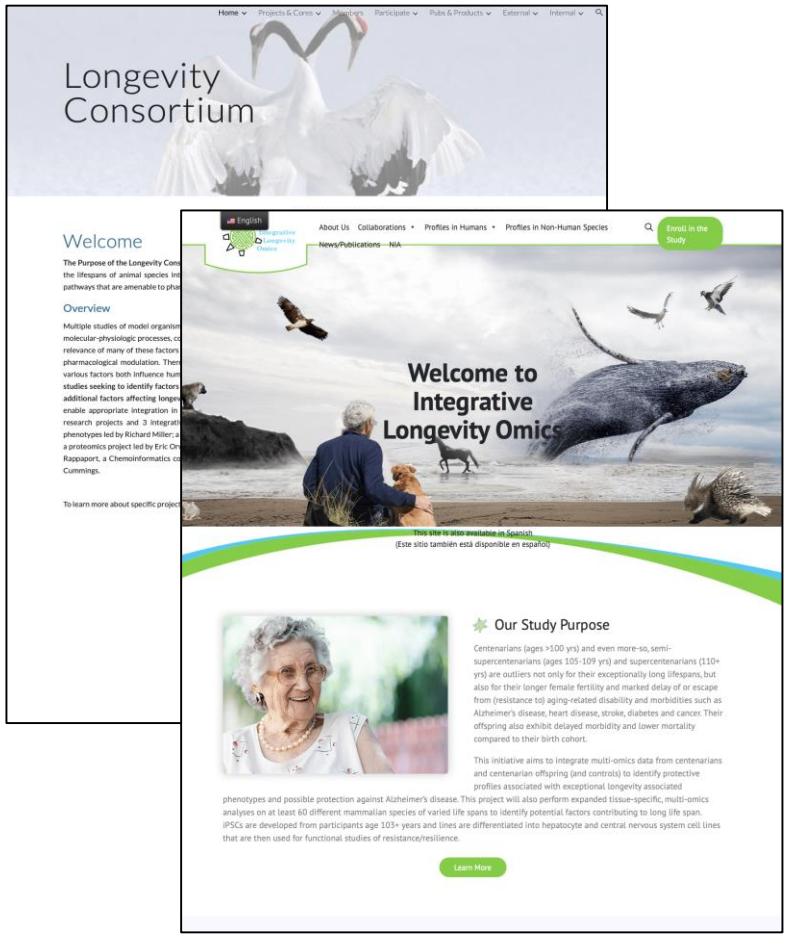
* Corresponding author. Tel: +45 3533 3703, Email: jebe@sund.ku.dk

Better integration is needed to identify and exploit *g x e* interactions, nuanced behaviors, social factors, aging effects, and general context-specificity that could lead to interventions designed to optimize individual health and longevity

Are Large-Scale National Government Subsidized Longitudinal Studies Good?







Will such studies reveal greater heterogeneity and a need for the ‘personalization’ of nutritional and medical interventions?

Estimating Life Expectancy for Different Age Cohorts and Dietary Changes

PLOS MEDICINE

RESEARCH ARTICLE

Estimating impact of food choices on life expectancy: A modeling study

Lars T. Fadnes[1,2]*, **Jan-Magnus Økland**[1,3], **Øystein A. Haaland**[1,3☯], **Kjell Arne Johansson**[1,2,3☯]

1 Department of Global Public Health and Primary Care, University of Bergen, Norway, 2 Bergen Addiction Research, Department of Addiction Medicine, Haukeland University Hospital, Bergen, Norway, 3 Bergen Center for Ethics and Priority Setting, University of Bergen, Norway

☯ These authors contributed equally to this work.
* lars.fadnes@uib.no

Abstract

Background

Interpreting and utilizing the findings of nutritional research can be challenging to clinicians, policy makers, and even researchers. To make better decisions about diet, innovative methods that integrate best evidence are needed. We have developed a decision support model that predicts how dietary choices affect life expectancy (LE).

Methods and findings

Based on meta-analyses and data from the Global Burden of Disease study (2019), we used life table methodology to estimate how LE changes with sustained changes in the intake of fruits, vegetables, whole grains, refined grains, nuts, legumes, fish, eggs, milk/dairy, red meat, processed meat, and sugar-sweetened beverages. We present estimates (with 95% uncertainty intervals [95% UIs]) for an optimized diet and a feasibility approach diet. An optimal diet had substantially higher intake than a typical diet of whole grains, legumes, fish, fruits, vegetables, and included a handful of nuts, while reducing red and processed meats, sugar-sweetened beverages, and refined grains. A feasibility approach diet was a midpoint between an optimal and a typical Western diet. A sustained change from a typical Western diet to the optimal diet from age 20 years would increase LE by more than a decade for women from the United States (10.7 [95% UI 8.4 to 12.3] years) and men (13.0 [95% UI 9.4 to 14.3] years). The largest gains would be made by eating more legumes (females: 2.2 [95% UI 1.1 to 3.4]; males: 2.5 [95% UI 1.1 to 3.9]), whole grains (females: 2.0 [95% UI 1.3 to 2.7]; males: 2.3 [95% UI 1.6 to 3.0]), and nuts (females: 1.7 [95% UI 1.5 to 2.0]; males: 2.0 [95% UI 1.7 to 2.3]), and less red meat (females: 1.6 [95% UI 1.5 to 1.8]; males: 1.9 [95% UI 1.7 to 2.1]) and processed meat (females: 1.6 [95% UI 1.5 to 1.8]; males: 1.9 [95% UI 1.7 to 2.1]). Changing from a typical diet to the optimized diet at age 60 years would increase LE by 8.0 (95% UI 6.2 to 9.3) years for women and 8.8 (95% UI 6.8 to 10.0) years for men, and 80-year-olds would gain 3.4 years (95% UI females: 2.6 to 3.8/ males: 2.7 to 3.9). Change from typical to feasibility approach diet would increase LE by 6.2 (95% UI 3.5 to 8.1) years for 20-year-old women from the United States and 7.3 (95% UI 4.7

Check for updates

OPEN ACCESS

Citation: Fadnes LT, Økland J-M, Haaland ØA, Johansson KA (2022) Estimating impact of food choices on life expectancy: A modeling study. PLoS Med 19(2): e1003889. https://doi.org/10.1371/journal.pmed.1003889

Academic Editor: Luigi Fontana, The University of Sydney, AUSTRALIA

Received: September 20, 2021

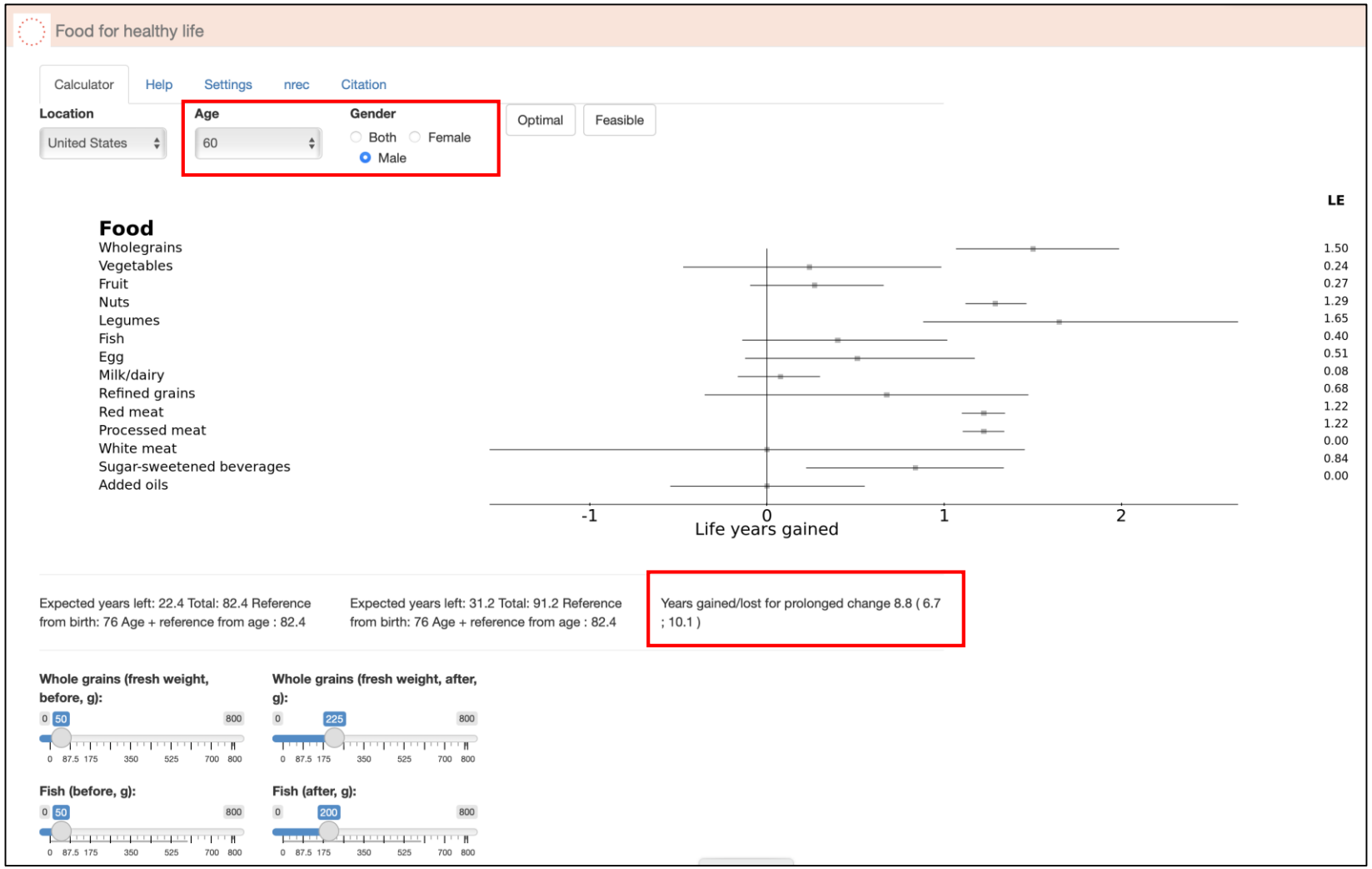
Accepted: December 11, 2021

Published: February 8, 2022

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: https://doi.org/10.1371/journal.pmed.1003889

Data Availability Statement: All relevant data are within the manuscript and its Supporting information files.

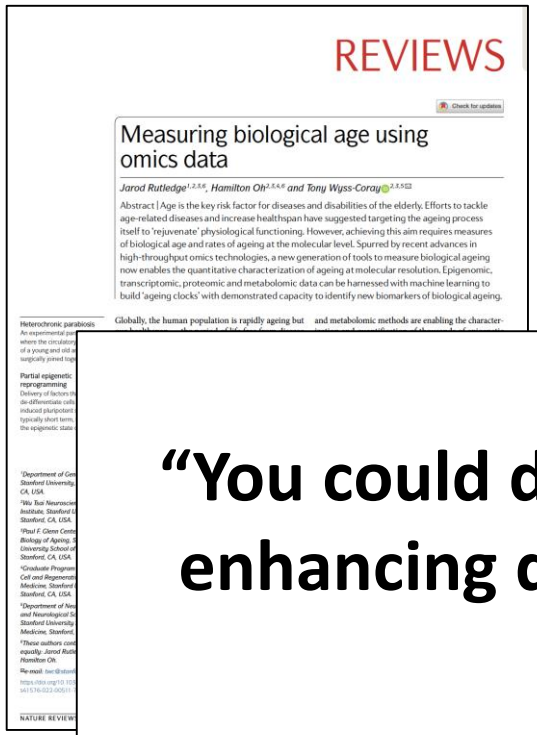
Funding: The authors received no specific funding for this work.



- How reliable are the data used? What about interactions with, e.g., SES, genetic predisposition, etc.?
- Could/should such estimates be personalized with many more factors considered based on more data?

Surrogate Endpoints for Long-term Outcomes and Longitudinal Trajectories

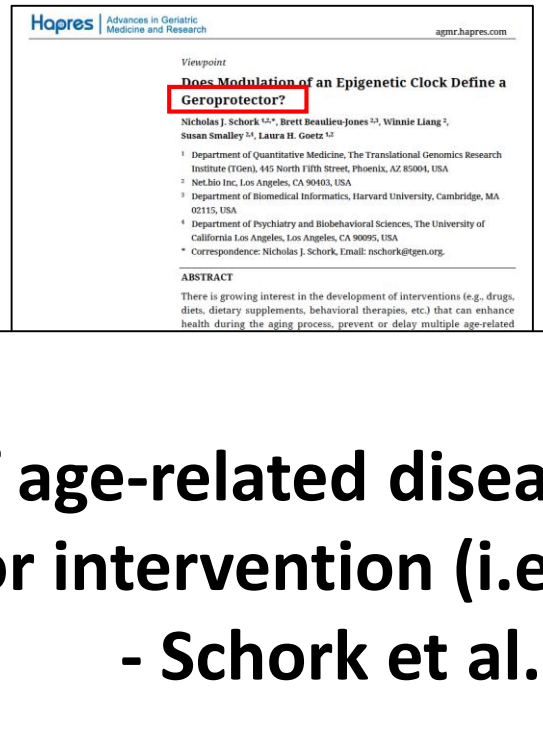
- Time lapse between change in the molecular milieu and change in the clinically-relevant phenotype?
- How long does it take before the system is sustainably healthy with continued use of intervention?


REVIEWS

Measuring biological age using omics data

Jarod Rutledge[1,2,3,6], Hamilton Oh[2,3,4,6] and Tony Wyss-Coray[2,3,5]

Abstract | Age is the key risk factor for diseases and disabilities of the elderly. Efforts to tackle age-related diseases and increase healthspan have suggested targeting the ageing process itself to 'rejuvenate' physiological functioning. However, achieving this aim requires measures of biological age and rates of ageing at the molecular level. Spurred by recent advances in high-throughput omics technologies, a new generation of tools to measure biological ageing now enables the quantitative characterization of ageing at molecular resolution. Epigenomic, transcriptomic, proteomic and metabolomic data can be harnessed with machine learning to build 'ageing clocks' with demonstrated capacity to identify new biomarkers of biological ageing.


Hapres | Advances in Geriatric Medicine and Research

agmr.hapres.com

Viewpoint

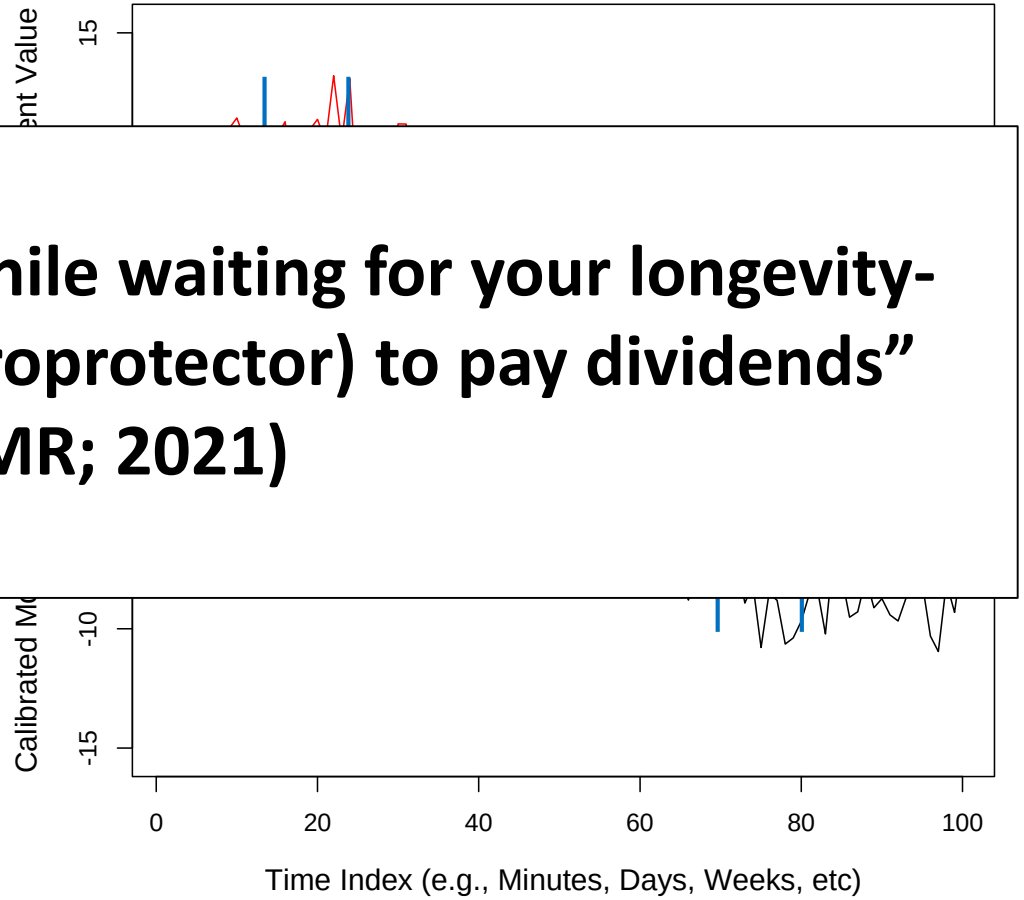
Does Modulation of an Epigenetic Clock Define a Geroprotector?

Nicholas J. Schork[1,2,*], Brett Beaulieu-Jones[2,3], Winnie Liang[2], Susan Smalley[2,4], Laura H. Goetz[1,2]

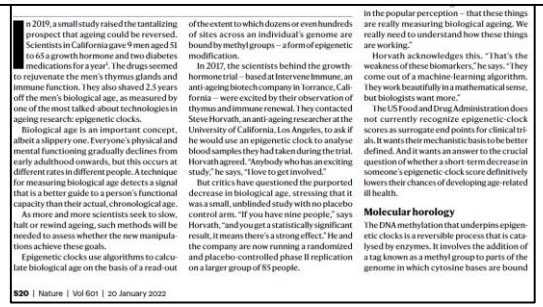
[1] Department of Quantitative Medicine, The Translational Genomics Research Institute (TGen), 445 North Fifth Street, Phoenix, AZ 85004, USA
[2] Net.bio Inc, Los Angeles, CA 90403, USA
[3] Department of Biomedical Informatics, Harvard University, Cambridge, MA 02115, USA
[4] Department of Psychiatry and Biobehavioral Sciences, The University of California Los Angeles, Los Angeles, CA 90095, USA
* Correspondence: Nicholas J. Schork, Email: nschork@tgen.org.

ABSTRACT

There is growing interest in the development of interventions (e.g., drugs, diets, dietary supplements, behavioral therapies, etc.) that can enhance health during the aging process, prevent or delay multiple age-related



"You could die of age-related disease while waiting for your longevity-enhancing diet or intervention (i.e., geroprotector) to pay dividends"
- Schork et al. (AGMR; 2021)


In 2019, a small study raised the tantalizing prospect that ageing could be reversed. Scientists in California gave 9 men aged 51 to 65 a growth hormone and two diabetes medications for a year[1]. The drugs seemed to rejuvenate the men's thymus glands and immune function. They also shaved 2.5 years off the men's biological age, as measured by one of the most talked-about technologies in ageing research: epigenetic clocks.

Biological age is an important concept, albeit a slippery one. Everyone's physical and mental functioning gradually declines from early adulthood onwards, but this occurs at different rates in different people. A technique for measuring biological age detects a signal that is a better guide to a person's functional capacity than their actual, chronological age.

As more and more scientists seek to slow, halt or rewind ageing, such methods will be needed to assess whether the new manipulations achieve these goals.

Epigenetic clocks use algorithms to calculate biological age on the basis of a read-out of the extent to which dozens or even hundreds of sites across an individual's genome are bound by methyl groups – a form of epigenetic modification.

In 2017, the scientists behind the growth-hormone trial – based at Intervene Immune, an anti-ageing biotech company in Torrance, California – were excited by their observation of thymus and immune renewal. They contacted Steve Horvath, an anti-ageing researcher at the University of California, Los Angeles, to ask if he would use an epigenetic clock to analyse blood samples they had taken during the trial. Horvath agreed. "Anybody who has an exciting study," he says, "I love to get involved."

But critics have questioned the purported decrease in biological age, stressing that it was a small, unblinded study with no placebo control arm. "If you have nine people," says Horvath, "and you get a statistically significant result, it means there's a strong effect." He and the company are now running a randomized and placebo-controlled phase II replication on a larger group of 85 people.

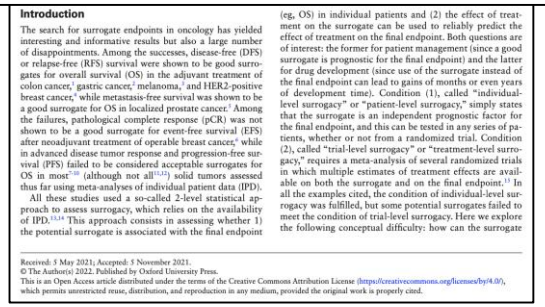
in the popular perception – that these things are really measuring biological ageing. We really need to understand how these things are working."

Horvath acknowledges this. "That's the weakness of these biomarkers," he says. "They come out of a machine-learning algorithm. They work beautifully in a mathematical sense, but biologists want more."

The US Food and Drug Administration does not currently recognize epigenetic-clock scores as surrogate end points for clinical trials. It wants their mechanistic basis to be better defined. And it wants an answer to the crucial question of whether a short-term decrease in someone's epigenetic-clock score definitively lowers their chances of developing age-related ill health.

Molecular horology

The DNA methylation that underpins epigenetic clocks is a reversible process that is catalysed by enzymes. It involves the addition of a tag known as a methyl group to parts of the genome in which cytosine bases are bound


Introduction

The search for surrogate endpoints in oncology has yielded interesting and informative results but also a large number of disappointments. Among the successes, disease-free (DFS) or relapse-free (RFS) survival were shown to be good surrogates for overall survival (OS) in the adjuvant treatment of colon cancer,[1] gastric cancer,[2] melanoma,[3] and HER2-positive breast cancer,[4] while metastasis-free survival was shown to be a good surrogate for OS in localized prostate cancer.[5] Among the failures, pathological complete response (pCR) was not shown to be a good surrogate for event-free survival (EFS) after neoadjuvant treatment of operable breast cancer,[6] while in advanced disease tumor response and progression-free survival (PFS) failed to be considered acceptable surrogates for OS in most[7–10] (although not all[11,12]) solid tumors assessed thus far using meta-analyses of individual patient data (IPD).

All these studies used a so-called 2-level statistical approach to assess surrogacy, which relies on the availability of IPD.[13,14] This approach consists in assessing whether 1) the potential surrogate is associated with the final endpoint (eg, OS) in individual patients and (2) the effect of treatment on the surrogate can be used to reliably predict the effect of treatment on the final endpoint. Both questions are of interest: the former for patient management (since a good surrogate is prognostic for the final endpoint) and the latter for drug development (since use of the surrogate instead of the final endpoint can lead to gains of months or even years of development time). Condition (1), called "individual-level surrogacy" or "patient-level surrogacy," simply states that the surrogate is an independent prognostic factor for the final endpoint, and this can be tested in any series of patients, whether or not from a randomized trial. Condition (2), called "trial-level surrogacy" or "treatment-level surrogacy," requires a meta-analysis of several randomized trials in which multiple estimates of treatment effects are available on both the surrogate and on the final endpoint.[15] In all the examples cited, the condition of individual-level surrogacy was fulfilled, but some potential surrogates failed to meet the condition of trial-level surrogacy. Here we explore the following conceptual difficulty: how can the surrogate

Received: 3 May 2021; Accepted: 5 November 2021.

Focused Clinical Trials and Broader Publicly-Subsidized Societal Interventions

ARTICLES
https://doi.org/10.1038/s41591-022-01973-2
nature medicine

OPEN

The Burden of Proof studies: assessing the evidence of risk

Peng Zheng[1,2], Ashkan Afshin[1,2], Stan Biryukov[1], Catherine Bisignano[1], Michael Brauer[1,2,3], Dana Bryazka[1], Katrin Burkart[1,2], Kelly M. Cercy[1], Leslie Cornaby[1], Xiaochen Dai[1,2], M. Ashworth Dirac[1,2], Kara Estep[1], Kairsten A. Fay[1], Rachel Feldman[1], Alize J. Ferrari[1,2,4,5], Emmanuela Gakidou[1,2], Gabriela Fernanda Gil[1], Max Griswold[1], Simon I. Hay[1,2], Jiawei He[1], Caleb M. S. Irvine[1], Nicholas J. Kassebaum[1,2,6], Kate E. LeGrand[1], Haley Lescinsky[1], Stephen S. Lim[1,2], Justin Lo[1], Erin C. Mullany[1], Kanyin Liane Ong[1], Puja C. Rao[1], Christian Razo[1], Marissa B. Reitsma[1], Gregory A. Roth[1,2,7], Damian F. Santomauro[1,2,4,5], Reed J. D. Sorensen[1], Vinay Srinivasan[1], Jeffrey D. Stanaway[1,2], Stein Emil Vollset[1,2], Theo Vos[1,2], Nelson Wang[8], Catherine A. Welgan[1], Sarah S. Wozniak[1], Aleksandr Y. Aravkin[1,2,9,10] and Christopher J. L. Murray[1,2,10]

Exposure to risks throughout life results in a wide variety of outcomes. Objectively judging the relative impact of these risks on personal and population health is fundamental to individual survival and societal prosperity. Existing mechanisms to quantify and rank the magnitude of these myriad effects and the uncertainty in their estimation are largely subjective, leaving room for interpretation that can fuel academic controversy and add to confusion when communicating risk. We present a new suite of meta-analyses—termed the Burden of Proof studies—designed specifically to help evaluate these methodological issues objectively and quantitatively. Through this data-driven approach that complements existing systems, including GRADE and Cochrane Reviews, we aim to aggregate evidence across multiple studies and enable a quantitative comparison of risk–outcome pairs. We introduce the burden of proof risk function (BPRF), which estimates the level of risk closest to the null hypothesis that is consistent with available data. Here we illustrate the BPRF methodology for the evaluation of four exemplar risk–outcome pairs: smoking and lung cancer, systolic blood pressure and ischemic heart disease, vegetable consumption and ischemic heart disease, and unprocessed red meat consumption and ischemic heart disease. The strength of evidence for each relationship is assessed by computing and summarizing the BPRF, and then translating the summary to a simple star rating. The Burden of Proof methodology provides a consistent way to understand, evaluate and summarize evidence of risk across different risk–outcome pairs, and informs risk analysis conducted as part of the Global Burden of Diseases, Injuries, and Risk Factors Study.

Exposure to different risk factors plays an important role in the likelihood of an individual developing or experiencing more severe outcomes from certain diseases, such as high blood pressure increasing the risk of heart disease or not having access to a safe water source increasing the risk of diarrheal diseases[1]. Understanding and quantifying the relationship between risk factor exposure and the risk of a subsequent outcome is therefore essential to set priorities for public policy, to guide public health practices, to help clinicians advise their patients and to inform personal health choices. Consequently, information on risk–outcome relationships can be used in the formulation of many types of public policies, including national recommendations on diet, occupational health rules, regulations on behavior such as smoking in public places, and guidance on appropriate levels of taxes and subsidies. As new evidence is continuously being produced and published, the systematic and comparable assessment of risk functions is a dynamic challenge. Up-to-date assessments of risk–outcome relationships are essential to, and a core component of, the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) comparative risk assessment (CRA)[2–7], which aims to help decision-makers understand the magnitude of different health problems.

Evidence on risk–outcome relationships comes from many types of studies, including randomized controlled trials (RCTs), cohort studies, case-control studies, cross-sectional analyses, ecological studies and animal studies. Each study type has characteristic strengths and weaknesses. For example, RCTs are the most robust method for dealing with confounding but are often conducted with strict inclusion and exclusion criteria, meaning that trial participants

[1]Institute for Health Metrics and Evaluation, University of Washington, Seattle, WA, USA. [2]Department of Health Metrics Sciences, School of Medicine, University of Washington, Seattle, WA, USA. [3]School of Population and Public Health, University of British Columbia, Vancouver, British Columbia, Canada. [4]School of Public Health, The University of Queensland, Brisbane, Queensland, Australia. [5]Queensland Centre for Mental Health Research, Wacol, Queensland, Australia. [6]Department of Anesthesiology & Pain Medicine, University of Washington, Seattle, WA, USA. [7]Division of Cardiology, University of Washington, Seattle, WA, USA. [8]The George Institute for Global Health, The University of New South Wales, Sydney, New South Wales, Australia. [9]Department of Applied Mathematics, University of Washington, Seattle, WA, USA. [10]These authors contributed equally: Aleksandr Y. Aravkin, Christopher J. L. Murray. ✉e-mail: cjlm@uw.edu

The international journal of science / 13 October 2022
nature

Studies linking diet with health must get a whole lot better

A research-rating system has identified gaps in studies that assess the connection between diet and various health risks.

Does eating red meat reduce lifespan? Some researchers certainly think so. Work such as the Global Burden of Diseases, Injuries, and Risk Factors Study[1] has led the World Health Organization and the US Department of Agriculture to advise that people limit consumption of unprocessed red meat, to protect themselves from diseases such as type 2 diabetes and various cancers.

Other researchers are less sure. Targets for red-meat consumption, set by public-health officials and expert panels, vary widely, with some advising that people eat no more than 14 grams per day and others not stating a recommended limit. This sends a confusing message, which in itself is not good for public health.

It's not just red meat: the evidence base surrounding much nutritional and wider health advice is similarly disputed. Now, a new approach could help health policymakers to better evaluate the quality of studies assessing potential health risks. A team at the Institute for Health Metrics and Evaluation (IHME) at the University of Washington in Seattle has created a star-based metric that rates the quality of the evidence for a link between a given behaviour — such as eating red meat or smoking — and a particular health outcome[2]. A five-star score means that the link is clearly established; one star means that either there's no association between the two factors or that the evidence is too weak to draw a firm conclusion.

What the researchers call 'burden of proof' analysis does not, of itself, clear up vexing issues such as the risks of red meat or the benefits of vegetables. But as a judgement on the quality of available research, it can help to flag, to research funders, areas in which better evidence is needed for firmer conclusions.

How is the star rating constructed? What are its parameters — and can the methodology itself be considered to be rigorous research? The IHME team did several things to try to quantify the effects of various biases in the studies being assessed. An epidemiological study, for example, might be biased in different ways to a study testing the outcomes of health interventions. The researchers also did away with what can be a common source of bias in research, namely, the assumption that health risks increase exponentially with the parameter being studied, for example blood pressure or consumption of unprocessed red meat. And they attempted to account for the bias that can arise when sample sizes are small.

> "Studies assessing diet and its health outcomes get notably lower star-ratings."

Applying this framework to studies assessing a total of 180 questions, produced results that are mostly unsurprising. Studies assessing an association between smoking and a variety of cancers, for example, earn a five-star rating[3]. Similarly, high systolic blood pressure — the force exerted by the heart to pump blood — has a five-star association with the narrowing of the blood vessels called ischaemic heart disease[4].

Studies assessing diet and its health outcomes get notably lower star-ratings. The IHME's analysis, for example, finds only weak evidence of an association between eating unprocessed red meat and outcomes such as colorectal cancer, type 2 diabetes and ischaemic heart disease[5]. It finds no relationship in studies that explore whether eating unprocessed red meat leads to two kinds of strokes. There is stronger, but not overwhelming, evidence that eating vegetables reduces the risk of strokes and ischaemic heart disease[6].

In some cases, the lower star-ratings could be due to effect size: for example, any health risks from red-meat consumption are likely to be small relative to the huge toll that smoking takes on the body. Above all, the lower-rated findings demonstrate that studies in these areas need to get better if they are to yield convincing results.

Teasing out the effect of a single dietary component from those of the complex variety of exposures over a person's lifetime is difficult. It would need larger studies, with a diverse pool of participants and strict control over their daily diet. Such studies will entail collaboration between research groups with different expertise, and access to participants in different environmental settings — a move that funders must encourage. This is an undertaking worth prioritizing. A small risk for an individual does not mean a small impact on public health: a low-risk behaviour can have a large population-level impact if it is very common.

The literature in the field of responsible research and innovation highlights how metrics in science must always be interrogated for robustness and rigour. There needs to be wide consultation and, as much as possible, the unintended consequences of using metrics must be anticipated, as initiatives such as the San Francisco Declaration on Research Assessment and the Leiden Manifesto show. This work must come sooner rather than later.

We have evidence that underpowered clinical studies, lacking necessary controls to make sense of the data, are not helping. If funders do not target their efforts at producing quality data, the public will remain confused, weary, distrustful and deprived of the information they need to make informed health and lifestyle choices.

1. GBD 2019 Risk Factors Collaborators *Lancet* **396**, 1223–1249 (2020).
2. Zheng, P. *et al. Nature Med.* https://doi.org/10.1038/s41591-022-01973-2 (2022).
3. Dai, X. *et al. Nature Med.* https://doi.org/10.1038/s41591-022-01978-x (2022).
4. Rizzi, C. *et al. Nature Med.* https://doi.org/10.1038/s41591-022-01974-1 (2022).
5. Lescinsky, H. *et al. Nature Med.* https://doi.org/10.1038/s41591-022-01968-z (2022).
6. Stanaway, J. D. *et al. Nature Med.* https://doi.org/10.1038/s41591-022-01970-5 (2022).

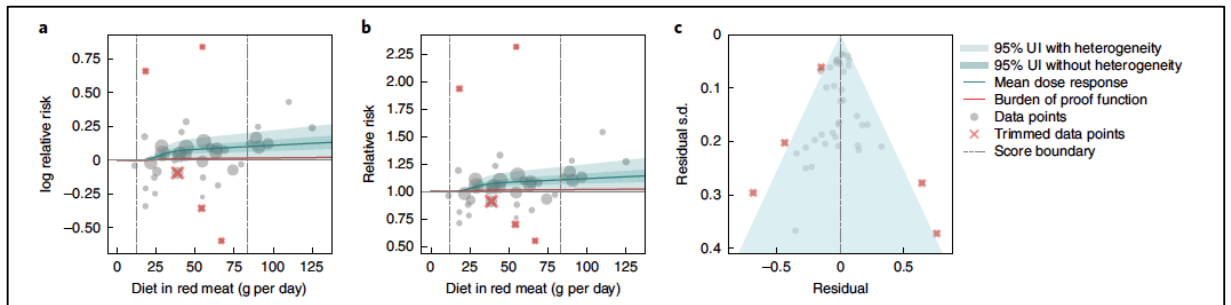


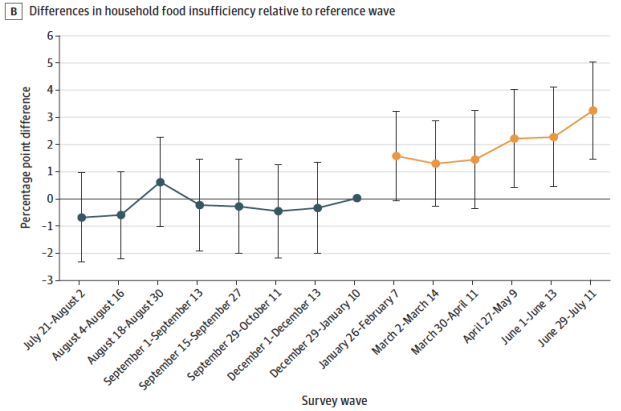
Fig. 4 | Unprocessed red meat consumption and ischemic heart disease. a, Log relative risk function for unprocessed red meat consumption and ischemic heart disease. **b**, Relative risk function for unprocessed red meat consumption and ischemic heart disease. **c**, A modified funnel plot for unprocessed red meat consumption and ischemic heart disease showing the residuals (relative to 0) on the *x* axis and the estimated standard deviation (s.d.) that includes reported s.d. and between-study heterogeneity on the *y* axis.

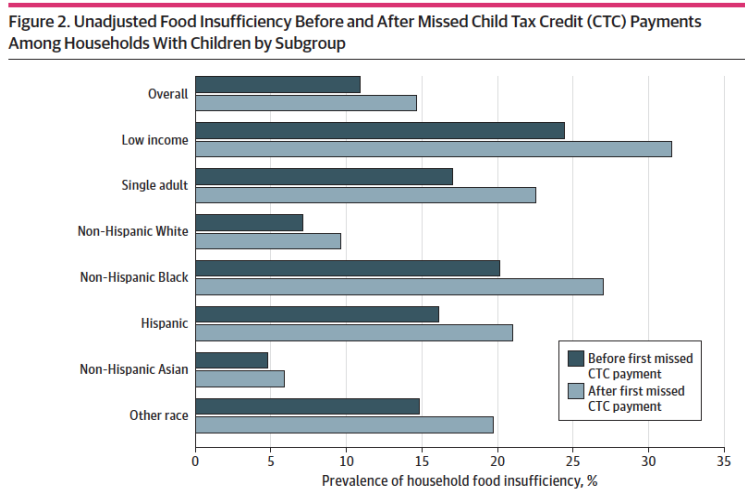
JAMA Network | Open

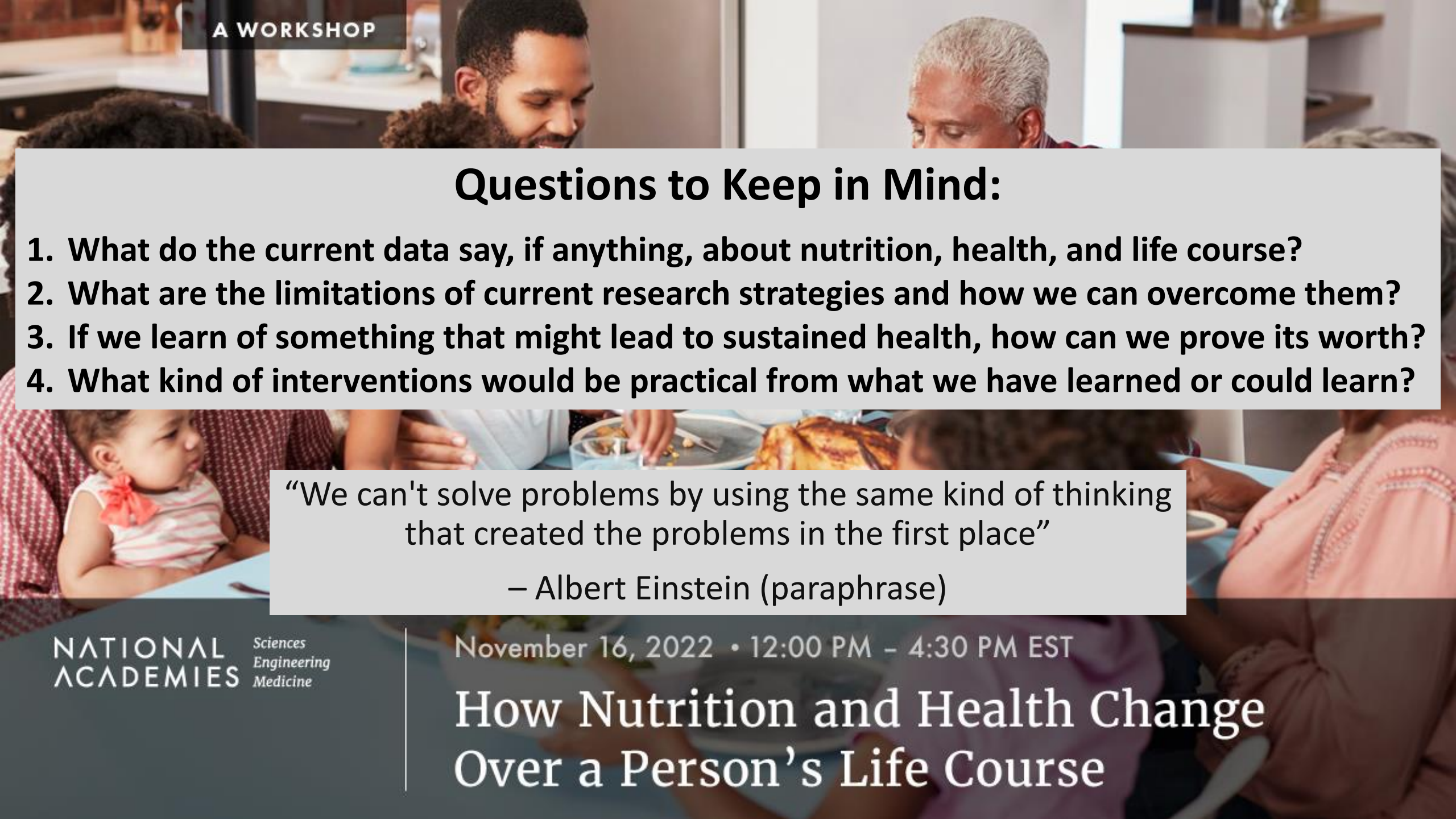
Original Investigation | Health Policy

Association of the Expiration of Child Tax Credit Advance Payments With Food Insufficiency in US Households

Allison Bovell-Ammon, MDiv; Nicole C. McCann, BA; Martha Mulugeta, MPH; Stephanie Ettinger de Cuba, PhD, MPH; Julia Raifman, ScD; Paul Shafer, PhD







Questions to Keep in Mind:

1. **What do the current data say, if anything, about nutrition, health, and life course?**
2. **What are the limitations of current research strategies and how we can overcome them?**
3. **If we learn of something that might lead to sustained health, how can we prove its worth?**
4. **What kind of interventions would be practical from what we have learned or could learn?**

"We can't solve problems by using the same kind of thinking that created the problems in the first place"

– Albert Einstein (paraphrase)

NATIONAL ACADEMIES Sciences Engineering Medicine

November 16, 2022 • 12:00 PM – 4:30 PM EST

How Nutrition and Health Change Over a Person's Life Course