

Pre-adult Healthspan Interventions (PHI)

Accessible Enhancement of Innate Longevity & Fulfillment Potential
through Gentle Pre-Adult Interventions
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CONVENTIONS & NAVIGATION

Glossary-defined terms are identified by *green italics*. Hover the cursor on them for a brief definition. For the Glossary definition, press: Ctrl/Control + Click. To return from the Glossary, press: Alt/Option + Left-arrow.

In accordance with the Chicago Manual of Style¹, linked references are indicated in the body by underlined & superscripted blue footnote numbers (e.g.: ⁹⁹⁹), & in the footnotes by underlined blue text; accessed by hovering, then pressing: Ctrl/Control + Click. Footnoted comments are not blue or underlined.

ABSTRACT

The pre-adult exposome, beginning indefinitely before conception & extending with decreasing plasticity into early adulthood, substantially sets lifelong physical & neural structures within genetic constraints, affecting every aspect of healthspan. The PHI (Pre-adult Healthspan Interventions) program comprehensively identifies, validates, organizes & disseminates accessible ways & means to optimize worldwide pre-adult outcomes.

Many safe, beneficial, & accessible pre-adult interventions remain widely unknown or poorly utilized. Many more linger in the shadows for a variety of addressable reasons. Identification, characterization, centralized cataloging, & democratized implementation of exposome factors will enable significant enhancement of social harmony & individual fulfillment, including longevity, mental health, physical & cognitive capacity, & quality of life.

Benefits of proliferating PHI include reduced lifelong healthcare costs, improved social harmony & workforce productivity, & extended healthspan. Many PHI show near-immediate benefits that compound over time, not least through early establishment of excellent personal habits.

Though often lacking IP allure, hundreds of augmentive PHI can be kick-started by modest funding, & will yield huge distributed benefits. Global collaboration is essential, particularly from socialized health organizations (WHO, CDC, Child Health Foundation, etc.) to establish or incentivize:

¹ Felician University Library, <https://felician.libguides.com/ChicagoManualofStyle/footnotesandintext>

1. A curated, free, online, multilingual PHI compendium that includes expected effects, usage details, warnings, references, conflicting evidence, etc.
2. Testing of PHI safety, efficacy, optimization, synergies, & long-term outcomes, including genotype variations
3. Identification & qualification of suspected PHI from cultural, veterinary, aesthetics, sports, wound care, geroscience, & mental health practices
4. Increased younger & pregnant representation in health research
5. Global marketing of augmentive PHI

Amazing hi-tech interventions must continue being pursued, but inexpensive, accessible approaches offer excellent ROI & should be prioritized.

FOREWORD

Pre-adult augmentation of natural developmental outcomes typically yields correspondingly augmented adult physical & neural capacities, including longevity. Additional augmentation beyond as-found status is expected to be more successful when built upon a superior foundation, so proactive optimization will be desirable for the foreseeable future.

Early exposomes (environmental circumstances) play critical roles in health & development², influencing life-long well-being & capacity for contribution. The two years after conception are well-known to be a highly plastic period for establishing physical, cognitive, emotional & social foundations for later life^{3 4}, but as we shall see, longevity is also on that list, & the plastic period extends indefinitely into preconception & forward to early adulthood.

Hundreds of low-cost *PHI* have been variably qualified in the field or by clinical study, both positive (eat parsley) & negative (don't smoke). Some are soundly proven to be safe & effective. Many others are time-tested &/or partially qualified by modern methods, but even widely-accepted interventions usually lack precise dose-response data & personalization considerations. Uncounted others are only locally known, & lack even tentative safety qualification, or are merely plausible candidates.

As a program, *PHI* aims to maximize & balance everyone's innate physical & neural capacities. Basic health & survival during pregnancy & childhood are primary foci of WHO/UNICEF^{5 6 7}, CDC^{8 9} & other institutions, but optimization

² Edited by Bundy, ...Patton, et al, 2017. "Childhood and Adolescent Health and Development, 3rd Edition" <https://www.ncbi.nlm.nih.gov/books/NBK525240/>

³ Walker, ...Grantham-McGregor, et al, 2011. "Early Childhood Stimulation Benefits Adult Competence and Reduces Violent Behavior" <https://publications.aap.org/pediatrics/article-abstract/127/5/849/64930>

⁴ Gluckman, ...West-Eberhard, et al, 2009. "Towards a new developmental synthesis: adaptive developmental plasticity and human disease" <https://pubmed.ncbi.nlm.nih.gov/19427960/>

⁵ (WHO/UNICEF), 2020. "Survive and thrive - Transforming care for every small and sick newborn", <https://data.unicef.org/resources/survive-and-thrive-transforming-care-for-every-small-and-sick-newborn/>

⁶ (WHO), 2023. "Maternal Mortality", <https://www.who.int/news-room/fact-sheets/detail/maternal-mortality>

& longevity considerations are rare. Cognitive & physical optimization are the platforms upon which personal development can be most successful & durable, & if broadly applied, is a key to collective advancement. Pharmaceuticals not found in nature, such as most vaccines, can be miraculous, but long-term effects are often uncertain & sometimes disastrous¹⁰. Likewise, recently developed exotics, such as stem cell therapy, can have amazing results, but are not available to most of the world if only because of treatment costs. Safe, naturally-sourced, nontraumatic, inclusive techniques are thus emphasized herein, as low-hanging fruit that should be harvested before reaching higher.

Multiplying personal fulfillment, worldwide *PHI* implementation will maximize collective potential. Global adoption of *PHI* will mitigate anthropogenic existential threats by massively building the best possible foundation for creative fulfillment, social contribution, physical & mental achievement, contentment & healthful longevity.

Notably, many *HAPLI* (health, aesthetic, performance, & longevity interventions) already proven for *adult, elder* & veterinary health have repurposing potential as *PHI* with an accelerated approval process.

This monograph introduces the vision, concepts, strategy, plan, & terminology for *PHI*, supported by rationales & examples needed to foster extraordinarily healthy, & long-lived humans innately better-equipped for contemporary & emerging opportunities & dangers. It aims to stimulate more thoughtful, fact-based child rearing, as well as creation of accessible & comprehensive resources as the cornerstone of a movement to foster better humans.

BACKGROUND

Pre-adulthood is a period of nurturing by the community, building upon—and limited by—inborn & fostered neuro-physical fitness. Optimizing that fitness is the focus of *PHI*, expanding upon studies sponsored by the World Bank: “Evidence of Impact of Interventions on Growth & Development during Early & Middle Childhood”¹¹, & “The Human Capital & Productivity Benefits of Early Childhood Nutritional Interventions”¹².

⁷ (UNICEF), “Maternal and Newborn Health” (includes links to other UNICEF material), <https://www.unicef.org/health/maternal-and-newborn-health>

⁸ Trost, ...Lee, et al, 2022. “Pregnancy-Related Deaths: Data from Maternal Mortality Review Committees in 36 US States, 2017–2019”, <https://www.cdc.gov/reproductivehealth/maternal-mortality/erase-mm/data-mmrc.html>

⁹ (CDC), 2022. “Four in 5 pregnancy-related deaths in the U.S. are preventable”, <https://www.cdc.gov/media/releases/2022/p0919-pregnancy-related-deaths.html>

¹⁰ Rabinowitz, 2024. “Postpartum psychiatric illness or a drug cascade gone wrong?” <https://www.thegoldreport.com/news/postpartum-psychiatric-illness-or-a-drug-cascade-gone-wrong>

¹¹ Alderman, ...Walker, et al, 2017. “Child and Adolescent Health and Development, 3rd Edition”, Chapter 7: “Evidence of Impact of Interventions on Growth and Development during Early and Middle Childhood”. <https://www.ncbi.nlm.nih.gov/books/NBK525234/#pt2.ch7.sec2>

¹² Nandi, ...Patton, et al, 2017. “Child and Adolescent Health and Development, 3rd Edition”, Chapter 7: “The Human Capital and Productivity Benefits of Early Childhood Nutritional Interventions”. https://elibrary.worldbank.org/doi/10.1596/978-1-4648-0423-6_ch27

Within & between species, wild evolution adapts to environmental challenges with unnumbered genetic reserves of heritable feature combinations made yet more flexible by occasional mutations, & ever reset by coincidental or age-related demise. Odd chance or cataclysms can wipe out characteristics better-adapted to an ever-fickle present, with consequences ranging from re-emergence in a cousin, to extinction.

Many imperfections in the evolutionary process can be mitigated by *pre-adult HAPLI*. Refinement & mass-implementation of inexpensive, known-good (if perhaps not optimized), time-tested *pre-adult* mitigations are the centerpiece of *PHI*. Atop longstanding parenting “tips & tricks”, enhancements observed in veterinary & post-pubescent *HAPLI* must be tested for potential repurposing as *pre-adult* developmental boosters. Coming generations can thus safely, significantly, & with broad inclusivity, be psycho-physically enhanced for building & managing a brilliant future.

Evolutionary pressures, physio-chemical limitations & happenstance have resulted in uncounted gene-based morphogenic compromises that do not serve today’s humanity. Human features can approach natural optimization by identifying, refining & applying extant interventions, & by deriving *pre-adult HAPLI* from other medical practices. The compromises of natural history have not dealt us the best possible feature-sets for tomorrow’s world, but we can assume superior control through *PHI*.

It is possible & often easy to durably upgrade physiology by well-timed modification of biochemical signals; e.g., a slight extension of in-utero development time¹³ can result in greater cognitive abilities (or reflect or cause serious problems¹⁴). Evolutionary tradeoffs landed at ~38 weeks gestation as the best compromise, but is that still true? A signaling tweak that slightly delays birth might yield significant returns for a lifetime. Many pregnancy hazards of olden times have been obviated: compromised maternal mobility is no longer an unsafe state; vaginal delivery of big babies used to pose a double mortal threat; acute puerperal sepsis is all but eliminated; & so on. Managed neoteny¹⁵ is a fine fit for the *PHI* approach.

Gestation & childhood are marked by high resilience & rapid growth, which decelerate through puberty, decline in *adulthood*, & unravel into compounding vulnerabilities & death in *elderhood*. Systemically & locally, genes & other coding are varyingly & variably expressed throughout life by signals from within & outside cells. Be it despite or because of those signals, dysfunctions increasingly go unrepaired, ending in mortal catastrophe. This

¹³ Ma, ...Li, et al, 2022. “Lower gestational age is associated with lower cortical volume and cognitive and educational performance in adolescence”. <https://pubmed.ncbi.nlm.nih.gov/36329481/>

¹⁴ Galal, ...Smith, et al, 2022. “Postterm Pregnancy” <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3991404/ObGyn>

¹⁵ Skulachev, ...Sadovnichii, et al, 2017. “Neoteny, Prolongation of Youth: From Naked Mole Rats to ‘Naked Apes’ (Humans)”. <https://pubmed.ncbi.nlm.nih.gov/28202600/>

morphosis of cells, tissues, organs, & organism are fundamental to life's complex & shifting characteristics. Mysteries remain, but morphology is certainly influenced by genetic profile, & by *biological-age*-mediated genetic expression cued from several sources (e.g., *post-translational modification* of histones, & methylation changes to DNA segments, which evidently are at least partly orchestrated from the hypothalamus¹⁶). Much remains unknown, but therapies exist that promote well-being, & (minus the curious & important phenomena of *hormesis*) today's well-being portends tomorrow's.

Benefits can arise by reducing the high incidence of metabolic, genetic & proteomic damage of *pre-adulthood*, which stunts repair & accelerates *senescence*. Additionally, super-efficient hormetic repair can leave tissue in better shape than it had before the assault. Benefits can also be realized by addressing deficiencies not attributable to assertive damage, but rather due to innate or pre-existing deficiencies in the genome, epigenome, or environment of the bairn &/or caregivers. Optimization of repair & growth mechanisms, environments, & dwell-time during appropriate developmental periods (e.g., neurocognitive enhancement related to healthy gestation extension, mentioned above) can establish a better organism &/or reduce remedial needs. Presumed aging factors might, however, result in surprising outcomes, as illustrated in mixed findings concerning effects of childhood health & familial adversities on epigenetic age^{17 18}, hinting at sources of yet further optimization.

Sub-optimal foetal & pediatric development can often be improved by simple domestic behaviors, including obvious, if incompletely characterized *pre-adult HAPLI*, such as diet^{19 20}, exercise²¹, sleep²², good hydration²³ & supplementation^{24 25 26}. Evidently, many other common parental & communal pre-natal & child-rearing traditions are beneficial, like massage^{27 28}, yoga²⁹, meditation^{30 31 32}, & shared work, play, religious, pedagogical, sports & artistic

¹⁶ Mitteldorf, 2022. "Is there a master timekeeper, upstream of the methylation clock?" <https://joshmitteldorf.scienceblog.com/2022/06/20/is-there-a-master-timekeeper-upstream-of-the-methylation-clock/>

¹⁷ Schmitz, ...Seeman, et al, 2023. "Associations of Early-Life Adversity With Later-Life Epigenetic Aging Profiles in the Multi-Ethnic Study of Atherosclerosis". <https://academic.oup.com/aje/advance-article-abstract/doi/10.1093/aje/kwad172/7241428>

¹⁸ Larkina & Smith, 2022. "Investigating Links between Childhood Health and Family Life, and Accelerated Biological Aging" https://academic.oup.com/innovateage/article/6/Supplement_1/448/6938377

¹⁹ Diuof, ...Heude, et al, 2012. "Specific role of maternal weight change in the first trimester on birth size" <https://onlinelibrary.wiley.com/doi/epdf/10.1111/j.1740-8709.2012.00423.x>

²⁰ Suha, 2020. "The Importance of Nutrition for Development in Early Childhood" <https://scholarworks.lib.csusb.edu/cgi/viewcontent.cgi?article=2272&context=etd>

²¹ Moyer, Reoyo, May, 2016. "The Influence of Prenatal Exercise on Offspring Health: A Review". <https://pubmed.ncbi.nlm.nih.gov/27777506/>

²² Finkelstein, Shiener, Wainstock, 2021. "The association between sleep disturbances and adverse perinatal outcome: a prospective study", [https://www.ajog.org/article/S0002-9378\(21\)01785-3/fulltext](https://www.ajog.org/article/S0002-9378(21)01785-3/fulltext)

²³ Song, ...Ma, et al, 2023. "A Study of the Fluid Intake, Hydration Status, and Health Effects among Pregnant Women in Their Second Trimester in China: A Cross-Sectional Study". <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10096982/>

²⁴ Goh, ...Koren, et al, 2006. "Prenatal multivitamin supplementation and rates of congenital anomalies: a meta-analysis". <https://pubmed.ncbi.nlm.nih.gov/17022907/>

²⁵ Roberts, ...Mendez, et al, 2022. "The Effects of Nutritional Interventions on the Cognitive Development of Preschool-Age Children: A Systematic Review". <https://www.mdpi.com/2072-6643/14/3/532>

²⁶ Masterjohn, 2013. "Vitamins for Fetal Development: Conception to Birth". <https://www.westonaprice.org/health-topics/vitamins-for-fetal-development-conception-to-birth/#gsc.gsc.tab=0>

²⁷ Mueller & Grunwald, 2021. "Effects, Side Effects and Contraindications of Relaxation Massage during Pregnancy: A Systematic Review of Randomized Controlled Trials". <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8396946/>

²⁸ Ireland & Olsen. "Massage therapy and therapeutic touch in children: state of the science". <https://www.ncbi.nlm.nih.gov/books/NBK68280/>

²⁹ Mohammed, ...Saini, et al, 2019. "Biological markers for the effects of yoga as a complementary and alternative medicine" <https://pubmed.ncbi.nlm.nih.gov/30735481/>

³⁰ Massa, ...Babbar, et al, 2022. "A Randomized Control Trial of Meditation for Mothers Pumping Breastmilk for Preterm Infants" <https://pubmed.ncbi.nlm.nih.gov/35240703/>

³¹ Wanlapa, ...Thawatchai, et al, 2011. "Meditation for preterm birth prevention: a randomized controlled trial in Udonthani, Thailand" <https://myjournal.mohe.gov.my/public/article-view.php?id=65752>

activities. Sometimes “at-home” behavior is not actually at home, revealing a need to reevaluate popular assumptions. A large European study found that, of many factors tested, children’s day care (as opposed to home care) is the best way to prevent serious lung damage in both male & female children³³. No explanation is offered. Is it the smoke-free environment, organized exercise, socio-economic status of typical enrollees, immunities gained from constant exposure to other kids, or even psycho-epigenetic effects of early socialization? Is this favorable finding trounced by adverse outcomes outside the pulmonary system?

An exemplary *pre-adult HAPLI* is folate supplementation that corrects a formerly-widespread prenatal deficiency³⁴ that can result in heart-wrenching birth defects. It was discovered & championed by Smithells & Hibbard in the 1960s, when many healthcare professionals scoffed at nutritional supplementation for apparently-healthy people. Eschewing tobacco³⁵ & alcohol³⁶ consumption during pregnancy improves lifelong cognitive & physical health of the child, & is now universally expected behavior, thanks to research, legal changes & educational campaigns. Few afflictions reduce healthspan more definitively than SIDS (sudden infant death syndrome), & although its etiology is not fully understood, simple preventive measures have been identified^{37 38}.

Innumerable poorly-characterized & synergistically-combined *HAPLI* against gestational^{39 40} & pediatric⁴¹ afflictions wait in the wings. From avocado^{42 43} to zucchini⁴⁴, fresh fruit & vegetables tend to be a life-long plus, starting with fertility enhancement, but even completed studies necessarily limit experimental parameters, such as cultivar, timing & quantity variables, & differences between individuals. Vitamin D ^{45 46} studies exemplify the problem. Though a crucial health factor⁴⁷ with a long history of study, reported mechanisms are often vague, illogical or contentious. It arguably should be present (with cofactors) at levels well above prevailing practices,

³² Davidson, ...Sheridan, et al, 2003. “Alterations in brain and immune function produced by mindfulness meditation” <https://pubmed.ncbi.nlm.nih.gov/12883106/>

³³ Svanes, ...Wjst, et al, 2010. “Early life origins of chronic obstructive pulmonary disease” https://thorax.bmj.com/content/thoraxjnl/suppl/2011/10/21/thx.2008.112136.DC2/Thorax_Appendix_112136.pdf

³⁴ Wald, 2011. “Commentary: A brief history of folic acid in the prevention of neural tube defects”, <https://academic.oup.com/ije/article/40/5/1154/660590?login=false>

³⁵ “Smoking During Pregnancy”, https://www.cdc.gov/tobacco/basic_information/health_effects/pregnancy/index.htm

³⁶ “Alcohol Use During Pregnancy”, <https://www.cdc.gov/ncbddd/fasd/alcohol-use.html>

³⁷ Goldwater, 2022. “Sudden Infant Death Syndrome (SIDS) Research: Dogma disguised as science”, <https://doi.org/10.20935/AL5663>

³⁸ Stecko, ...Fabian-Danielewska, et al, 2019. “Sudden Infant Death Syndrome - risk factors and prevention”, <https://zenodo.org/records/3243811>

³⁹ “What are some common complications of pregnancy”, <https://www.nichd.nih.gov/health/topics/pregnancy/conditioninfo/complications>

⁴⁰ “Drug Use and Pregnancy”, <https://www.webmd.com/baby/drug-use-and-pregnancy>

⁴¹ “Conditions”, <https://www.healthychildren.org/english/health-issues/conditions/Pages/default.aspx>

⁴² Comerford, ...Atkinson, et al, 2016. “The Role of Avocados in Maternal Diets during the Periconceptional Period, Pregnancy, and Lactation”, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4882725/>

⁴³ Cheng, ...Hantunen, et al, 2025. “Avocado consumption during pregnancy linked to lower child food allergy risk”, <https://www.nature.com/articles/s41390-025-03968-4>

⁴⁴ Arifin, 2018. “Amazing Benefits of Zucchini during Pregnancy”, <https://drhealthbenefits.com/food-beverages/vegetables/benefits-of-zucchini-during-pregnancy>

⁴⁵ Hollis & Wagner, 2022. “Substantial Vitamin D Supplementation Is Required during the Prenatal Period to Improve Birth Outcomes”

https://www.researchgate.net/publication/358773273_Substantial_Vitamin_D_Supplementation_Is_Required_during_the_Prenatal_Period_to_Improve_Birth_Outcomes

⁴⁶ Kozhevnikova, ...Jethwa, et al., 2025. “The anti-inflammatory effects of vitamin D on offspring brain development during pregnancy: critical review”. *Academia Nutrition and*

Dietetics, 2(1). <https://doi.org/10.20935/AcadNutr7573>. See also the references within the paper.

⁴⁷ Spacone, 2022. “Vitamin D deficiency and Acute Respiratory Infections” <https://doi.org/10.20935/AL4732>

& is best obtained (coincident with other health factors) by frequent exposures to early sunlight without sunscreen (which blocks UVB light responsible for its innate production), but infrequent, intense, high-temperature exposure should be eschewed⁴⁸. Latitude, elevation, exposure area, time of day, & skin color affect outcomes. Gestational^{49 50} & pediatric⁵¹ *HAPLI* are often poorly optimized for integrated results. Biology is complicated!

PHI advocacy cannot overlook dietetic carbohydrates. Especially in refined, concentrated forms, the sensual appeal, ubiquity (including 'generous' addition to processed foods) & commercial promotion of sweet, instantly-gratifying hexoses (glucose, fructose, etc.), dihexoses (especially sucrose) & many edible starches have resulted in an epidemic of preventable diseases that impede or damage human development & degrade health. Excessive consumption of concentrated, easily-digested carbohydrates is associated with a rogues' gallery of pregnancy complications^{52 53} (gestational diabetes mellitus, preeclampsia, preterm birth...), & childhood-cum-adult maladies^{54 55} (dental caries, obesity, ADHD, cardiovascular disease...) that linger & fester throughout life. There is a particularly illustrative relationship between dental health, which is largely established in *pre-adulthood*, & seemingly-unrelated morbidity & mortality later in life^{56 57 58 59}. A related concern is public water fluoridation, which continues to be controversial, based today upon many studies⁶⁰ that implicate the practice with several adverse effects that arguably outstrip its protective effects against dental caries. Consumption of fluoridated water during pregnancy and childhood might best be reduced in *pre-adulthood*, with a corresponding extra attention to dental care and causative dietary practices, especially consumption of table sugar.

Superior systemic features & capabilities can be fostered by applying, at curated points in youth, *HAPLI* variations usually associated with *adults* & *elders*. Among those proven for *pre-adults* are improved physique & delay of systemic *senescence* by weight control⁶¹, vaccinations⁶², & child safety seats⁶³

⁴⁸ Grassroots Health, 2020. "Sun Burns, Not Sun Exposure, are Associated with Increased Risk for Melanoma" <https://www.grassrootshhealth.net/blog/sun-burns-not-sun-exposure-associated-increased-risk-melanoma/>

⁴⁹ "What are some common complications of pregnancy", <https://www.nichd.nih.gov/health/topics/pregnancy/conditioninfo/complications>

⁵⁰ "Drug Use and Pregnancy", <https://www.webmd.com/baby/drug-use-and-pregnancy>

⁵¹ "Conditions", <https://www.healthychildren.org/english/health-issues/conditions/Pages/default.aspx>

⁵² Casas, Barquero, Estruch, 2020. "Impact of Sugary Food Consumption on Pregnancy: A Review", <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7700555/>

⁵³ Negrato, ...Zajdenverg, et al, 2022. "Glycemic and nonglycemic mechanisms of congenital malformations in hyperglycemic pregnancies: a narrative review". <https://pubmed.ncbi.nlm.nih.gov/36191262/>

⁵⁴ Vos, ...Johnson, et al, 2017. "Added Sugars and Cardiovascular Disease Risk in Children: A Scientific Statement from the American Heart Association", <https://pubmed.ncbi.nlm.nih.gov/27550974/>

⁵⁵ Gracner, Boone & Gertler, 2024. "Exposure to sugar rationing in the first 1000 days of life protected against chronic disease", <https://www.science.org/doi/10.1126/science.adn5421>

⁵⁶ (Mayo Clinic Staff), 2004. "Oral health: A window to your overall health", <https://www.mayoclinic.org/healthy-lifestyle/adult-health/in-depth/dental/art-20047475>

⁵⁷ Ross, 2022. "How Your Oral Health Affects Your Overall Health", <https://health.clevelandclinic.org/oral-health-body-connection>

⁵⁸ Gurarie & Luong, 2023. "Your Mouth Has a Lot to Say About Your Overall Health", <https://www.verywellhealth.com/importance-of-dental-hygiene-5235243>

⁵⁹ Christensen (AHA), 2021. How oral health may affect your heart, brain and risk of death <https://www.heart.org/en/news/2021/03/19/how-oral-health-may-affect-your-heart-brain-and-risk-of-death>

⁶⁰ B. Johnson, 2025. "Fluoride: Friend or Foe?", https://blueprint.bryanjohnson.com/blogs/news/fluoride-friend-or-foe?utm_source=Klaviyo&utm_medium=campaign&utm_campaign=Fluoride%20%28blog%20email%29&utm_klaviyo_id=01H9NZKCFAYH6TG3XKD4EA5GHY&_kx=TX7z5IFbnwVq4i7EHrphR7SN5FXHci5YsA2i1ecEiuU.UDtiqu

⁶¹ "Pediatric Weight Management", <https://www.andeal.org/topic.cfm?menu=5296>

. Many plausible *PHI* await development in the large pool of *HAPLI* that are salutary when applied to post-pubescent &/or other mammals (e.g., this study⁶⁴ with mice). Obvious targets include adaptations of *GRAS* interventions proven effective for athletes, public figures, health & longevity enthusiasts, but unproven for *pre-adults* (e.g., 'nutraceuticals'; anti-diabetic measures⁶⁵; peptides made impractical⁶⁶ by delays in translating them into tested accessible forms: advanced exercise routines: hypoxic/hyperoxia

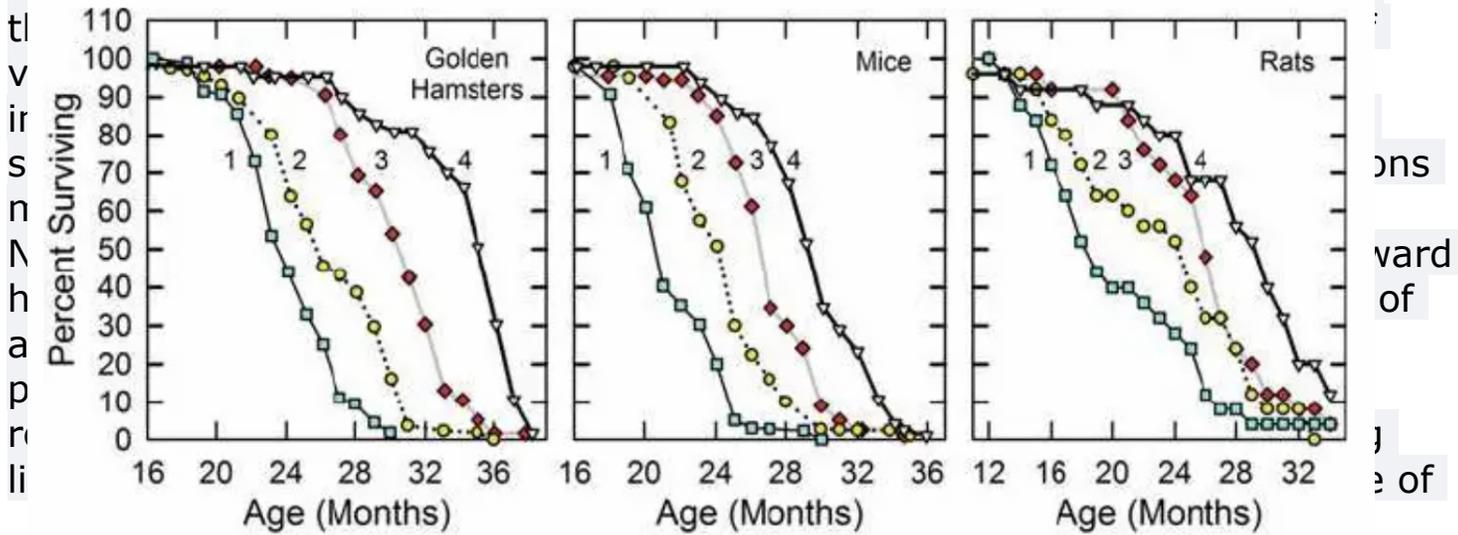


Fig. 6.4 Differing and interacting effects of different developmental states on life extension by calorie restriction (CR) in three animal species. 1: ad libitum feeding throughout life. 2: 50% CR throughout life. 3: 50% CR only during the second 12 months of life. 4: 50% CR only during the first 12 months of life. In every case, restriction during early development extended life more than restriction later in life even though the total time of restriction was the same in both cases. Redrawn from Deyl et al. (1975)

Aging”).

A shockingly-great porcine *PHI* was demonstrated in a recent trial. Substantial morphogenic enhancement was effected by ‘repurposing’ AKG (alpha-ketoglutarate) & HMB (β -hydroxy- β -methylbutyrate) – both readily-

⁶² "Vaccine Education Center", <https://www.chop.edu/centers-programs/vaccine-education-center>
⁶³ Elliot, ...Durbin, et al, 2006. "Effectiveness of Child Safety Seats vs Seat Belts in Reducing Risk for Death in Children in Passenger Vehicle Crashes", <https://jamaneetwork.com/journals/jamapediatrics/fullarticle/205063>
⁶⁴ Zhu, ...Yuan, et al, 2022. "Metformin treatment of juvenile mice alters aging-related developmental and metabolic phenotypes", <https://www.sciencedirect.com/science/article/abs/pii/S004763742100169X?via%3Dihub>
⁶⁵ Daniels, 2009. "L-carnitine supplementation may prevent pregnancy-related declines", <https://www.nutraingredients.com/Article/2009/07/29/L-carnitine-supplementation-may-prevent-pregnancy-related-declines>
⁶⁶ Gleeson, Fein & Whitehead, 2021. "Oral delivery of peptide therapeutics in infants: Challenges and opportunities" <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8178217/>
⁶⁷ Giuliano & Buss, "YGE Younging 1.0 Part 5: Practical Initiation of Younging 1.0 Via Hypoxic Interventions", <https://www.anti-agingfirewalls.com/2021/08/01/yge-younging-1-0-part-5-practical-initiation-of-younging-1-0-via-hypoxic-interventions/>
⁶⁸ El-Mouseh, ...Zenclussen, et al, 2012. "Exploring the potential of low doses carbon monoxide as therapy in pregnancy complications" <https://medicalgasresearch.biomedcentral.com/articles/10.1186/2045-9912-2-4>
⁶⁹ Venditti, ...Smith, et al, 2011. "Effects of chronic carbon monoxide exposure on fetal growth and development in mice", <https://bmcpregnancychildbirth.biomedcentral.com/articles/10.1186/1471-2393-11-101>
⁷⁰ Dickson, ...Smith, et al, 2020. "Carbon monoxide increases utero-placental angiogenesis without impacting pregnancy specific adaptations in mice", <https://rbej.biomedcentral.com/articles/10.1186/s12958-020-00594-z>
⁷¹ "Supported Interventions" <https://www.nia.nih.gov/research/dab/interventions-testing-program-itp/supported-interventions>
⁷² Summarized by Fahy, 2010, Fig. 6.4, "Precedents for the Biological Control of Aging: Experimental Postponement, Prevention, and Reversal of Aging Processes", The Future of Aging, 127-223, https://www.academia.edu/7762051/Precedents_for_the_Biological_Control_of_Aging_Experimental_Postponement_Prevention_and_Reversal_of_Aging_Processes?email_work_card=abstract-read-more. Originally from: Deyl, Juricova, Stuchlikova, 1975, "The Effect of Nutritional Regimes Upon Collagen Concentration and Survival of Rats", https://link.springer.com/chapter/10.1007/978-1-4757-0731-1_31

accessible & *GRAS* – for application very early in life⁷³. AKG is used by bodybuilders for metabolic cycle enhancement, & by longevicists for management of the inflammatory reflex⁷⁴, because it stimulates the cholinergic anti-inflammatory pathway, as promoted in the "Younging"⁷⁵ rejuvenation approach. HMB is widely used by bodybuilders & wound-care specialists to speed tissue repair. Startling results were achieved by simply adding AKG &/or HMB to the feed of expectant sows. Piglet development was enhanced at birth & throughout their (deliberately-truncated) lives, in all of numerous measured parameters (e.g., ~20% non-pathological increase in birth weight). The report cites similar studies & remarkable outcomes when the same supplements are fed to poultry. Notably, human birth weight⁷⁶ is positively correlated to brain tissue volume & cognitive performance in *elderhood*, whereas premature birth⁷⁷ & atypical gestational brain development is associated with lifelong abnormalities⁷⁸ resulting in learning & mental health⁷⁹ impairments. Above-average stature is often associated with shorter lifespan, but this depends upon the underpinnings for increased growth^{80 81}. An oft-observed example with plants is precariously increased height based upon competition for sunlight. We cannot know if the pigs' treatment-induced stature increase would be a longevity liability if it translated to humans. Studies of porcine amino acid metabolism⁸², including 'nonessential' glycine⁸³, reveals common *GRAS* factors that are usually non-optimum across a range of mammals (including humans) during developmental periods, significantly affecting adult outcomes^{84 85}. Targeted supplementation with amino acids for pregnant pigs & humans is desirable⁸⁶, & childhood protein intake clearly affects health & longevity factors⁸⁷. Taurine (also 'nonessential') is getting a lot of publicity lately, yet a recent summary⁸⁸ with 30 intriguing references does not include a single word exploring *pre-adult* application. One study⁸⁹ revealed health & longevity

⁷³ Tataru, ...Studzinski et al, 2012. "Effects of combined maternal administration with alpha-ketoglutarate (AKG) and β-hydroxy-β-methylbutyrate (HMB) on prenatal programming of skeletal properties in the offspring" <https://nutritionandmetabolism.biomedcentral.com/articles/10.1186/1743-7075-9-39>

⁷⁴ Pavlov & Tracey, 2012. "The Vagus Nerve and the Inflammatory Reflex – Linking Immunity and Metabolism" <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4082307/>

⁷⁵ Giuliano & Buss, 2020. "YGA Introduction to the YOUNGING Series – Emerging Aging Reversal Strategies and Treatments" <https://www.anti-agingfirewalls.com/2020/09/02/introduction-to-the-younging-series-emerging-aging-reversal-strategies-and-treatments/>

⁷⁶ Wheeler, ...Cox et al, 2021. "Birth weight is associated with brain tissue volume seven decades later but not with MRI markers of brain ageing" <https://www.sciencedirect.com/science/article/pii/S2213158221002205?via%3Dihub>

⁷⁷ Volpe, 2009. "Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances" <https://jamanetwork.com/journals/jamapsychiatry/fullarticle/1171951>

⁷⁸ Nosarti, ...Murray et al, 2012. "Preterm birth and psychiatric disorders in young adult life" <https://jamanetwork.com/journals/jamapsychiatry/fullarticle/1171951>

⁷⁹ Paus, ...Giedd et al, 2008. "Why do many psychiatric disorders emerge during adolescence?" <https://www.nature.com/articles/nrn2513>

⁸⁰ Hou, 2024. "Energetic cost of biosynthesis is a missing link between growth and longevity in mammals" <https://www.pnas.org/doi/abs/10.1073/pnas.2315921121>

⁸¹ Conover, ...Mason, et al, 2010. "Longevity is not influenced by prenatal programming of body size" <https://onlinelibrary.wiley.com/doi/10.1111/j.1474-9726.2010.00589.x>

⁸² Wu, ...Wang, et al, 2017. "Functional amino acids in the development of the pig placenta" <https://onlinelibrary.wiley.com/doi/full/10.1002/mrd.22809>

⁸³ Tan, ...Yin, et al, 2022. "A review of the amino acid metabolism in placental function response to fetal loss and low birth weight in pigs" <https://jasbsci.biomedcentral.com/articles/10.1186/s40104-022-00676-5>

⁸⁴ Prather, ...Green, et al, 2010. "Transcriptional, Post-Transcriptional and Epigenetic Control of Porcine Oocyte Maturation and Embryogenesis" <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2842954/>

⁸⁵ Furuta, ...Ghosh, et al, 2021. "Changes of Plasma Amino Acid Profiles in Infants with a Nutrient-Fortified Complementary Food Supplement: Evidence from a 12-Month Single-Blind Cluster-Randomized Controlled Trial" <https://www.frontiersin.org/articles/10.3389/fnut.2021.606002/full>

⁸⁶ Jung, Choi, 2019. "Relation of Taurine Intake During Pregnancy and Newborns' Growth" <https://pubmed.ncbi.nlm.nih.gov/31468407/>

⁸⁷ Garcia-Iborra, ...Ramirez, et al, 2023. "Optimal Protein Intake in Healthy Children and Adolescents: Evaluating Current Evidence" <https://www.mdpi.com/2072-6643/15/7/1683>

⁸⁸ Williams & Gonzalez, 2023. "Remarkable Rejuvenation Effects of Taurine" <https://www.lifeextension.com/magazine/2023/7/longevity-effects-of-aurine>

⁸⁹ Shindyapina, ...Gladyshev, et al. "Rapamycin treatment during development extends lifespan and healthspan" <https://www.biorxiv.org/content/10.1101/2022.02.18.481092v1>

enhancements attributable to rapamycin (sirolimus) infusions in juvenile mice, & another⁹⁰ found that rapamycin increases egg viability by promoting DNA damage repair, & there are many more. At the same time, pediatric rapamycin medical therapy has resulted in dosage-sensitive adverse effects for children⁹¹. Optimization of today's recommendations for the *pre-adult* period has a long way to go.

There will be simple therapies composed of derived, combined, suspected & still-undiscovered interventions, as exemplified⁹² by improved murine biometrics & lifespans with a single early-life induction of the SKOM "Yamanaka factors". Combining individual *PHI* might result in wonderful synergies, or be deadly, but we can't know without testing. This tier also includes potential *pre-adult HAPLI* that are prohibitive due to cost, risk, uncertain effectiveness, intrusiveness, or complexity. Advancement of genetic, stem cell, & other high-end interventions must continue, but the vast array of low-cost, negligible-risk interventions available for immediate or near-horizon mass deployment merit priority. Their optimization & broad integration can be expected to upgrade average *pre-adult* development sooner, better & more cheaply than other near-term approaches, & merit predominant public investment.

In summary, atop refinement & wide adoption of known-effective *pre-adult* interventions, qualification for *pre-adults* of proven & emerging post-pubescent & veterinary interventions promises broad human enhancement. Better early development enables increased productivity & joie de vivre, redoubled by establishment of favorable lifestyle habits that many *PHI* include. Mounting social & ecological challenges demand better humans; *PHI* is compassionate, possible, necessary, economical & urgent.

THE VISION

Pre-adult HAPLI was accumulating before recorded history, but optimized implementation is far from complete. Sports, cognitive, veterinary, psychological, aesthetic & geriatric medicine raise expectations for further boosting of healthy longevity during *pre-adulthood*. *PHI* science can advance to higher heights by incentivizing:

- 1) Refinement of known, accessible *PHI*
- 2) Identification of veterinary & post-pubescent human *HAPLI* with *pre-adult* therapeutic potential, & aggressive qualification of them as *PHI*

⁹⁰ Yang, ...Jin, et al, 2022. "Rapamycin improves the quality and developmental competence of mice oocytes by promoting DNA damage repair during in vitro maturation" <https://pubmed.ncbi.nlm.nih.gov/35436937/>

⁹¹ Zhang, ...Ji, et al, 2022. "Safety Evaluation of Oral Sirolimus in the Treatment of Childhood Diseases: A Systematic Review" <https://www.mdpi.com/2227-9067/9/9/1295>

⁹² Alle, ...Lemaitre, et al (2022). "A single short reprogramming early in life initiates and propagates an epigenetically related mechanism improving fitness and promoting an increased healthy lifespan", <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9649606/>

3) Routine inclusion of both control & treated *pre-adult* subjects in laboratory testing of prospective *HAPLI*

Recent developments^{93 94} go beyond restoring characteristics associated with an individual's current *conceptual-age*, & these interventions can now be quickly & objectively evaluated with biometrics-based 'clocks'^{95 96}. Examples include regrowth of the involuted thymus⁹⁷ (which also resulted in broad reversal of *BA* according to multiple biomarkers), & ovarian rejuvenation⁹⁸ for extended fertility & hormonal balance. Additional breakthroughs are needed to approach & perhaps exceed *IMP-a*-level disease resistance, & resilience from damage. Today's widely-accepted longevity record is 122 years, but *PHI* will increase that, & add to its quality.

Knowledge without implementation is already an unacceptable norm. Completion of the *PHI* program requires popularization, requiring something like the following actions:

1. Establish clinics focused on *PHI* implementation with outcome tracking
2. Curate a free, accessible, multilingual *PHI* compendium
3. Vigorously marketing, including incentivization of *PHI*

The near future includes better *HAPLI* for older *adults*, ameliorating the avalanche of compounded infirmities of *elderhood* (additionally, interventions against obdurate age-associated diseases – lost teeth⁹⁹ & limbs, fused vertebrae, etc. – are progressing). Latter-stage *HAPLI* has great value, but delay & reversal of *BA* works best when initiated before the winter storms of natural life. *PHI* enhances natural resistance to that onslaught. The urgency of addressing degenerative diseases of *elders* has disgraced us by effectively inhibiting development of *PHI* against preventable (& often irreversible) degeneration of our children. Grand improvement of the human condition via *PHI* impatiently awaits our attention.

FUTURE HUMANS

Dreams aside, healthspan can be augmented right now by risk-free optimization & popularization of existing prenatal & pediatric interventions. Proven & emerging *PHI* includes a long list of safe & highly-accessible

⁹³ Horvath, ...Katcher, et al, 2020. "Reversing age: dual species measurement of epigenetic age with a single clock", <https://www.biorxiv.org/content/10.1101/2020.05.07.082917v1>

⁹⁴ Horvath, ...Katcher, et al, 2023. "Reversal of Biological Age in Multiple Rat Organs by Young Porcine Plasma Fraction",

<https://www.biorxiv.org/content/10.1101/2023.08.06.552148v1.full.pdf>

⁹⁵ Belsky, ...Caspi, et al, 2016, "Eleven Telomere, Epigenetic Clock, and Biomarker-Composite Quantifications of Biological Aging: Do they Measure the Same Thing?",

<https://academic.oup.com/aje/article/187/6/1220/4622080?login=false>

⁹⁶ Meyer & Schumacher, 2024. "Aging clocks based on accumulating stochastic variation" <https://www.nature.com/articles/s43587-024-00619-x>

⁹⁷ Fahy, ...Horvath, et al, 2019. "Reversal of epigenetic aging and immunosenescent trends in humans", <https://onlinelibrary.wiley.com/doi/full/10.1111/ace1.13028>

⁹⁸ Sfakianoudis, ...Pantos, et al, 2020. "Reactivating Ovarian Function through Autologous Platelet-Rich Plasma Intraovarian Infusion: Pilot Data on Premature Ovarian Insufficiency, Perimenopausal, Menopausal, and Poor Responder Women", <https://www.mdpi.com/2077-0383/9/6/1809>

⁹⁹ Takahashi, ...Murashima-Suginami, et al, 2024. "Development of a new antibody drug to treat congenital tooth agenesis" <https://pubmed.ncbi.nlm.nih.gov/39389160/>

lifestyle factor optimizations, supplements, & medical procedures that enhance systemic & organ-specific development.

Qualification, optimization, & implementation of veterinary & post-pubescent *HAPLI* to *pre-adults* can almost certainly extend high-functioning natural healthspan; improving innate neural & physical features & spawning a human family that is more perceptive, productive, robust, happy, & intelligent, & thus makes better decisions.

The experiments of Tatara, Lamaitre, Gladyshev, & many others show that *PHI* has exceptional promise, but human usage requires exacting characterization of safety, efficacy, & dosing attributes (including individualized factors). With all that in hand, we envision managed incubation of features that broadly improve innate individual capacity & performance. Optimizing *pre-adult* growth environment for organ development will improve dexterity, verbal, musical & scholastic potential, & globally improve healthspan & fulfillment prospects. Imagine if Tatara's AKG/HMB intervention (as above, with pigs) yields similar 20% developmental enhancement for humans! Cocktails of multiple, strategically-administered *PHI* portend compounded benefits, as suggested in numerous publications, such as an intriguing Taiji-reprogram¹⁰⁰ proposal.

Nootropics¹⁰¹ & other psychotropics¹⁰² are a broad class of food & pharma/nutraceuticals used to enhance or alter cognitive features; ranging from spinach to sleeping pills, alcohol & LSD. Many such substances lurk in dark corners (not least, illegality), & careful dose-response research is hard to find, so skepticism about popular opinions is appropriate. Effects during *pre-adulthood* are usually reported to be mostly-adverse or furrowed-brow-uncertain (e.g., caffeine¹⁰³, 'recreational' drugs¹⁰⁴, green tea^{105 106}, vinpocetine¹⁰⁷). By contrast, blueberries, spinach, cocoa, salmon, eggs – all reported to have mild psychotropic effects, & containing thousands of chemicals (doubtless including toxins) – are generally¹⁰⁸ smiled upon without skeptical research, as positive factors during *pre-adulthood*, barring unusually high consumption. *Pre-adult* psychotropic research is hard to find, so dangers & benefits remain speculative.

¹⁰⁰ Wang, ...Wang, et al, 2021. "Taiji-reprogram: a framework to uncover cell-type specific regulators and predict cellular reprogramming cocktails". <https://academic.oup.com/nargab/article/3/4/lqab100/6423166>

¹⁰¹ "Nootropic", Wikipedia Encyclopedia: <https://en.wikipedia.org/wiki/Nootropic>

¹⁰² "Psychoactive drug", Wikipedia Encyclopedia: https://en.wikipedia.org/wiki/Psychoactive_drug

¹⁰³ James, 2020. "Maternal caffeine consumption and pregnancy outcomes: a narrative review with implications for advice to mothers and mothers-to-be". <https://ebm.bmj.com/content/26/3/114>

¹⁰⁴ Scott & Lust, 2010. "Illicit substance use in pregnancy – a review". <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4989592/>

¹⁰⁵ El-Borm & El-Gaber, 2021. "Effect of prenatal exposure of green tea extract on the developing central nervous system of rat fetuses; histological, immune-histochemical and ultrastructural studies". <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8324952/>

¹⁰⁶ Younes, ...Wright, et al, 2018. "Scientific opinion on the safety of green tea catechins". <https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2018.5239>

¹⁰⁷ Catlin, ...McIntyre, et al, 2018. "Embryo-fetal development studies with the dietary supplement vinpocetine in the rat and rabbit". <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5980693/>

¹⁰⁸ L. Fields, 2015. "Good eats: 6 perfect foods for your pregnancy". <https://www.pregnancymagazine.com/pregnancy/pregnancy-health/6-foods-for-pregnancy>

Medicinal characteristics attributed to herbs & spices are usually rooted in ancient practices, but poorly validated by modern methods. Notwithstanding uncontrolled concentrations, fuzzy distinction from vegetables, & complex chemistry, herbal potions can be dangerous. It is thus usually difficult to advise for or against them in the sensitive *pre-adult* period. Ginseng^{109 110} ginkgo biloba, & cinnamon^{111 112} typify the promises, risks, uncertainties, & need for further investigation. For example, ginkgo biloba is administered¹¹³ to treat asymmetrical intra-uterine growth restriction (affecting >20%¹¹⁴ of worldwide pregnancies), significantly increasing blood flow to the foetus, & resulting in >11% greater growth after six weeks of treatment on 29-week-old treated foeti, versus controls. Would this treatment improve outcomes if administered to "normal" foeti? ...If doubled or started earlier? ...If continued beyond six weeks &/or during childhood? ...If the dosage were personalized & optimized? ...In combined interventions? Other findings¹¹⁵ give us pause: ginkgo fed to pregnant mice (albeit, at seemingly high dosages of 78 & 100 mg/kg/day) resulted in liver pathology, but a different murine study¹¹⁶ says this herb has no effect at all. A primitive state of the art rightly inclines health-care providers to err on the side of caution, & advise avoidance of most herbal interventions. Extraordinary providers & parents must typically depend upon themselves for even a superficial & partial understanding.

Aromatherapy evidently can have at least small effects on the outcomes of *pre-adulthood*^{117 118}, but strong data & long-term outcomes are not easy to find. Some essential oils are not recommended for children & during pregnancy, & long-term inhalation of oil is an obvious red flag.

There are many biologically active substances (e.g., carbon monoxide & peptides¹¹⁹) that will or might enhance *pre-adult* development, which cannot be successfully taken orally, but can enter the lungs & blood stream when inhaled, or even directly into the brain when nasally administered into the sinuses. Such substances sometimes must be administered hypodermically, at a slightly higher level of bodily invasion & inaccessibility. Claims & possibilities must be sorted through to optimize a personal *PHI* program.

¹⁰⁹ Seely, ...Koren, et al, 2018. "Safety and efficacy of Panax Ginseng During Pregnancy and Lactation". <https://www.jptcp.com/index.php/jptcp/article/view/188/148>

¹¹⁰ Bhardwaj, 2020. "Ginseng is a complete NO-NO for pregnant women, confirms a top dietician. Here's why". <https://www.healthshots.com/preventive-care/reproductive-care/side-effects-of-ginseng-heres-why-pregnant-women-must-avoid-this-herb/>

¹¹¹ Rao & Gan, 2014. "Cinnamon: A Multifaceted Medicinal Plant". <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4003790/>

¹¹² Waggot & Gordon. "Is Cinnamon Safe During Pregnancy? Is It Good or Bad?". <https://www.pregnancyfoodchecker.com/is-cinnamon-safe-during-pregnancy/>

¹¹³ El Aal, ...Fahmy, et al, 2017. "Effects of oral ginkgo biloba extract on pregnancy complicated by asymmetrically intrauterine growth restriction: a double-blinded randomized placebo-controlled trial" https://www.academia.edu/51383554/Effects_of_oral_ginkgo_biloba_extract_on_pregnancy_complicated_by_asymmetrically_intrauterine_growth_restriction_a_double_blinded_randomized_placebo_controlled_trial

¹¹⁴ Saleem, ...Qadir, et al, 2011. "Intrauterine growth retardation - small events, big consequences" <https://ncbi.nlm.nih.gov/pmc/articles/PMC3177763/>

¹¹⁵ Zehra, ...Lone, et al, 2010. "Ginkgo biloba Effects on Mice Fetal Liver". Intl. Journal of Morphology, 28(3), 765-770. <https://dx.doi.org/10.4067/S0717-95022010000300017>

¹¹⁶ Fernandes, ...Peters, et al, 2010. "Effects of Ginkgo biloba extract on the embryo-fetal development in Wistar rats" <https://pubmed.ncbi.nlm.nih.gov/20437472/>

¹¹⁷ Freeman, ...Kansagara, et al, 2019. "Aromatherapy and Essential Oils: A Map of the Evidence". <https://www.hsrd.research.va.gov/publications/esp/aromatherapy.pdf>

¹¹⁸ Children's Hospital of Philadelphia, 2018. "How Aromatherapy Can Help Children" <https://www.chop.edu/news/health-tip/how-aromatherapy-can-help-children>

¹¹⁹ Pharmapproach, 2022. "Nasal Route of Drug Administration: Advantages and Disadvantages". <https://www.pharmapproach.com/nasal-route-of-drug-administration-advantages-and-disadvantages/>

Sexual activity, especially orgasm, appears to be a net benefit to the fetus during pregnancy, with some caveats¹²⁰. During most of *pre-adult* life, optimization of sexual activity is stymied by taboos, myths, cultural expectations, restrictive laws, & known dangers. Early sexual encounters are not yet ripe for evaluation, but will someday be engineered to result in better adult fitness, both psychologically & physically^{121 122 123}.

Other classes of possibly-favorable *PHI* includes simple post-prandial strolls, PEMF therapies, photobiomodulation¹²⁴, fasting modalities, hypo/hyper-oxygenation & other bioactive gas manipulation, prayer, socialization, naps, chanting, specific exercise routines, etc. Troves of data often exist, & AI apps offer quick access to obscure information sources. Ideally, this essay will evolve into a comprehensive, well-organized reference book, as well.

IMPLEMENTATION

Impressive socio-economic returns, played against modest (or even reduced) short-term expenses, suggest that a *PHI* program merits charitable support & government-subsidized advocacy, research & education, in coordination with public-health advocates involved in gestational, pediatric & parental affairs. Risk analysis clearly points to immediate action:

- 1) Establish pilot obstetrics/pediatrics clinics where proven *PHI* interventions & known hazards are taught & incentivized, & modern biometric tracking are applied, such as epigenetic age evaluation to quantify intervention-associated aging rates.
- 2) Bolster social tracking of *pre-adult* behavior & performance metrics.
- 3) Test existing geroscience, sports, wound-care, aesthetics & veterinary medicine for pre-adult enhancement of adult outcomes
- 4) Incentivize geroscience, sports, wound-care, aesthetics & veterinary research to include pregnant & juvenile subjects, & to deliver detailed lifespan & biometrics data
- 5) Create, curate, & heavily publicize an accessible, multi-lingual, fully-referenced, comprehensive online compendium of *PHI*, including dissenting, legendary, & speculative perspectives with appropriate commentary. This compendium must be overseen by a diverse board of directors, including representatives of national & international health agencies (WHO, CCDC, CDC, ECDC, Rospotrebnadzor, NCGM, etc.), as well as related academic & professional organizations (e.g., DONA,

¹²⁰ El Gharib, 2018. "Orgasm During Pregnancy". <https://scientiaricerca.com/srgype/pdf/SRGYPE-02-00036.pdf>

¹²¹ Brito & Nichols, 2023. "Are there side effects to masturbation?". <https://www.medicalnewstoday.com/articles/320265>

¹²² Parenting Healthy Babies, 2018. "14 Side Effects of Masturbation in Teens". <https://parentinghealthybabies.com/masturbation-teens-side-effects/>

¹²³ Sabia & Rees, 2008. "The effect of adolescent virginity status on psychological well-being".

<https://www.sciencedirect.com/science/article/abs/pii/S0167629608000593?via%3Dihub>

¹²⁴ Calderhead & Tanaka, 2017. "Photobiological Basics and Clinical Indications of Phototherapy for Skin Rejuvenation" <https://www.intechopen.com/chapters/54924>

ACVNM, SPN, SCCAP, AAP, FIGO, AHG, RCOG, AACAP, AMTA, ICDA, AWMNH...).

ECONOMICS

PHI implementation costs can be estimated, but benefits are largely incalculable. What is the value of pain, happiness, preventable developmental challenges, foreshortened productive lifespan, or the prospect of actively contributing to the development of your great-grandchildren? Detailed economic considerations have not yet been initiated, but interventions advanced herein deliberately focus on financial accessibility. Many are cheaper than the adverse alternatives (nobody goes broke by not buying liquor), depending more on consciousness & dedication than income level. Even impoverished people can do a lot, with despair & ignorance primary impediments to significant participation. Good research is expensive, but scores of neglected *PHI* have enough supporting data to merit mass implementation. Smart marketing will have a domino effect in *PHI* qualification & advancement.

SUMMARY

Virtually every part of everyone's physiology could have been improved with a superior developmental environment. It varies by person, but invariably there are missed interventions that would have made each of us more fit for life's challenges & opportunities. As negative examples, congenital defects are usually carried for life, & emotional damage in youth accelerates epigenetic aging¹²⁵, typically subtracting from personal healthspan, & beyond. Overwhelming evidence says that humanity can enter adulthood with critically improved neural & physical potential for a productive, long & joyous life by an aggressive *PHI* program to identify, refine & implement developmental enhancements.

Existing & pending interventions oriented toward *adult*, *elder* & veterinary health suggest – but rarely mention (e.g., here^{126 127}) – untapped potential for improving outcomes of *pre-adulthood*, & usually exclude pregnant or juvenile subjects. Such interventions, repurposed for *pre-adults*, hold high promise for adding to proven & accessible *pre-adult* enhancement interventions. ...Which typically are quixotically unknown or disregarded. A *PHI* program will identify & optimize these interventions (initially & especially those that are broadly accessible) through propaganda campaigns, an

¹²⁵ Kim, ...Hou, et al, 2023. "Association of Adverse Childhood Experiences With Accelerated Epigenetic Aging in Midlife"

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10261996/?_kx=oqY_SdY3ARz4ZBnWnci5DqWCwI01sW_AGsMDS4D68Zc%3D.XgUmH2

¹²⁶ Verburgh, 2014. "Nutrigerontology: why we need a new scientific discipline to develop diets and guidelines to reduce the risk of aging-related diseases"

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4326913/>

¹²⁷ Longo, ...Fontana, et al, 2015. "Interventions to Slow Aging in Humans: Are We Ready?" <https://onlinelibrary.wiley.com/doi/full/10.1111/accel.12338>

accessible compendium, & generous incentivization for characterization & adoption. Adding to obvious humanitarian justifications for *PHI*, existential threats have arisen that will be ameliorated by a smarter, happier, longer-lived populace.

Virtually every part of everyone's physiology could have been improved with a superior developmental environment. We all bear scars of missed early interventions that would have made of us more fit for life's challenges & opportunities, had they been applied. As negative examples, congenital defects are usually carried for life, & emotional damage in youth accelerates epigenetic aging¹²⁸, probably subtracting from longevity, among other salient metrics. Overwhelming evidence says that humanity can enter adulthood with critically improved neural & physical potential for a productive, long & joyous life through an aggressive *PHI* program to identify, refine & implement developmental enhancements.

Innate human capacity is limited by evolved genetics & genomic expression, moderated by biological damage & enhancement integrated along the way. Evolution is always a compromise that lags environment, & cannot deliver the sweet spot for any feature needed today. *PHI* derived from post-pubescent & animal *HAPLI* offer inclusive fast-lanes to broadly minimize damage & maximize humane developmental enhancement, efficiently upgrading & prolonging healthspan. The list is long & wide, from promoting desirable growth, to inhibiting deleterious *senescence*, irreversibly enhancing or limiting *pre-adult* development.

Firstly, we must gather, qualify, post, & vigorously present known *PHI*. Optimization & personalized-medicine trials must be completed. An internet search on almost every health-related topic (e.g., 'durian consumption during infancy') will reveal something (often unproven) about *PHI* applicability. *Pre-adult* behavior & circumstances, compared to later performance metrics, merit fresh review & better tracking, to discover & quantify developmental factors affecting social outcomes. Known & likely adverse behaviors must be included, as should common behaviors for which no research is available. Public policy must provide thorough & generously-incentivized education on *PHI* for expectant parents. This is not a wasteful handout; but rather a wise social investment to reduce healthcare expenses, & increase productivity, pro-social behavior, national wealth, joy & healthspan.

Secondly, there are many *HAPLI* that are accessible, socially palatable, & safe in veterinary, *adult* & *elder* applications, that perhaps can be repurposed as

¹²⁸ Kim, ...Hou, et al, 2023. "Association of Adverse Childhood Experiences With Accelerated Epigenetic Aging in Midlife"
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10261996/?_kx=oqY_SdY3ARz4ZBnWnci5DqWCwI01sW_AGsMDS4D68Zc%3D.XgUmH2

PHI with minimal experimentation, risk & regulatory hurdles. *GRAS* factors, like super-foods (e.g., watercress), some nutraceuticals, exercise & hygienic sleep habits, are believed to slow *BA* or enhance healthful growth. Agreeable interventions could be swiftly applied upon validation, spawning 'uberKinder' not limited by race, gender, etc.

Finally, there are novel & combined interventions that are not ready for usage, or still to be discovered.

PHI is not just a 'nice-to-have'. Maximizing *PHI* is *objectively* a pressing priority as a long-term, inexpensive, high-ROI, low-risk solution to global challenges that require a population innately better-equipped to overcome them. Promoting *PHI* is a humanitarian imperative for gently & inclusively augmenting the human condition. As a happy example, The Economist of London has lately advanced public awareness of bright possibilities for improved stature & innate intelligence through early, accessible interventions^{129,130}. *PHI* needs more public exposure, & coordination of political & medical leadership to massively implement *pre-adult* augmentations, & to identify, characterize & broadly implement tentative *HAPLI* to create a smarter, happier, more united & productive humanity.

ACKNOWLEDGEMENTS

PHI was inspired by Conboy Lab plasma research¹³¹, which presciently included treated & untreated, young & old mice. Unexpected physiological enhancement of treated young mice was observed, pointing to similar possibilities for other interventions.

Consultation & editing by Nancy Miceli, Boris Djordjevic, Zack Varkaris, Aubrey de Grey, Ted Coombs, Albert Donnay & others have improved this paper, but they bear no responsibility for its content.

GLOSSARY:

Age (& aging): As an unmodified noun or verb describing an organism, 'age' is ambiguous, causing misunderstandings that have contributed to profound suffering & early deaths. Most people think of their 'age' as a measure of time passed since birth (i.e., the end of the 2nd phase of the expulsion stage of parturition); herein called '**temporal age**' that happens as the calendar turns & ends upon legal death (varies by jurisdiction, usually either permanent cessation of cardiopulmonary or brain activity). Biologists typically think of 'age/aging'

¹²⁹ The Economist, 2024. "How to raise the world's IQ" <https://www.economist.com/leaders/2024/07/11/how-to-raise-the-worlds-iq> &

¹³⁰ The Economist, 2024. "Cheap fixes could help 450m people stand taller and think quicker" <https://www.economist.com/graphic-detail/2024/08/08/cheap-fixes-could-help-450m-people-stand-taller-and-think-quicker>

¹³¹ Medipour, ...Conboy, et al, 2020. "Rejuvenation of three germ layers tissues by exchanging old blood plasma with saline-albumin" [Results include 44% ($p=0.009$) minimal Feret diameters (indicative of repaired muscle patency), and 42% ($p=0.201$) improvements in neural proliferation]. <https://www.aging-us.com/article/103418>

differently; implicitly or explicitly using modifiers to communicate intended meanings. ...Or not, adding to the confusion. Herein, invented &/or clarified versions of traditional definitions are specified. '*Conceptual-age*' (CA) begins at conception & follows the calendar; '*biological age*' begins during gastrulation¹³² ('ground zero' of epigenetic age – in the third week of CA), & is influenced by circumstances, lifestyle, as well as passage of time.

This monograph speaks to human development, but conceptually applies to most mammals. For other creatures, defining 'age' is often complicated by biological mechanisms outside the present scope.

Biological age (BA; aka 'phenotypic age') describes the CA phenotype that characterizes the subject, irrespective of actual CA. For humans, BA is zeroed during gastrulation, but confusingly is popularly zeroed at birth (parturition), ~266 days¹³³ after conception. BA is calculated for organs as well as the organism, from variably weighted & proprietary amalgamations of biomarkers & behavioral characteristics; epigenetic modifications, morbidities, telomere lengths, functional limits, senescent cell density in uninjured tissue, glucose or proteins in urine, etc. These summations change somewhat predictably over time, from gastrulation to extreme old age.

BA tests compare weighted biomarker readings to the same factors when averaged for many people, relative to their CA (or historically demonstrated remaining lifespans). Test results vary within an organism, depending upon the tissue examined, but even with identical tissue, equipment & techniques, small non-uniformities are typical. Still, BA measurement has become surprisingly accurate, & keeps improving¹³⁴. Epigenetic methylation data, e.g., now yields correct *temporal age* within <15 months, simplifying longevity intervention evaluation, but several months of variation can be expected within samples taken at the same time, & more so if taken at different times of the day. Recent studies¹³⁵ have revealed a new, well-grounded noise barometer that reveals epigenetic pressure of aging & disease.

Conceptual/Gestational/Fertilization age (CA/GA/FA): FA (applies during pregnancy) is time passed since embryogenesis. CA is FA, extended beyond birth (for full-term birth, *temporal age* plus ~266 days). CA is traditionally identical to FA, but herein continues throughout life. GA is like FA, but counted from the first day of the last pre-pregnancy menstrual period; ~14 days before conception.

Epigenetics: refers to genome alterations (typically, covalent bonds to radicals, e.g. a methyl group) that don't involve mutation of nucleotides or histones, but sometimes influence gene expression.

¹³² Kerepesi, ...Gladyshev, et al, 2021. "Epigenetic clocks reveal a rejuvenation event during embryogenesis followed by aging". <https://www.aging-us.com/article/103418>

¹³³ "Baby Due Date". <https://www.betterhealth.vic.gov.au/health/healthyiving/baby-due-date>

¹³⁴ Higgins-Chen, ...Levine, et al, 2021. "A computational solution for bolstering reliability of epigenetic clocks: Implications for clinical trials and longitudinal tracking". <https://doi.org/10.1101/2021.04.16.440205>

¹³⁵ Mei, ...Conboy, et al, 2023. "Fail-tests of DNA methylation clocks, and development of a noise barometer for measuring epigenetic pressure of aging and disease". <https://www.aging-us.com/article/205046/text>

GRAS: 'generally regarded as safe' is an FDA designation that a substance is considered safe to eat, but also often applies to ingestion by other means.

HAPLI: 'health [includes mental, physical, & emotional], aesthetic, performance, & longevity interventions'

Hormesis: a dose-response phenomenon, usually applied to nominally-toxic factors, where a favorable outcome occurs at a low dose. Mild injury can stimulate repair/regeneration that outstrips its damage; e.g., inoculation by weakened pathogens can stimulate a strong & lasting immune response; a bit of mental, emotional & physical stress can strengthen affected bodily systems. Sometimes, as with carbon monoxide, a very small dose is actually necessary for life, with a multi-factorial sweet spot very close, but not equal to zero.

Lifespan & healthspan: Individual lifespan traditionally refers to the time between legally-defined birth & death. Herein, 'natural lifespan' is how long an individual would live in a nominally safe environment, were it not for declining resilience with age. Accidental death, homicide, suicide, & death due to pathogens & injuries that would be overcome, were it not for age-related weaknesses, confound precise definition of natural lifespan. Most 'natural' deaths are attributable to both age-related & other factors. A typical safe, clean environment is not enough to result in a 'natural maximum lifespan' (NML – see below), because at this moment environments are never optimized for longevity. Species-average lifespan variably includes accidental or induced death. 'Healthspan' though somewhat subjective, is of greater interest, defining the part of life not seriously encumbered by debilities; both physical & psychoneurological. ...But how is integrated health to be quantified? "Health" status is expected to be related conceptual age, & even then, it is not well-defined. Naturally-possible maximum healthspan includes what *could* be, limited by genetically-possible physical limits (such as elastin degradation) & optimized simple interventions.

Percent-age (P-a), innate minimum percent-age (IMP-a), & natural maximum lifespan (NML): Percent-age expresses the percentage of lifespan that has transpired to date, for a specific organ, tissue, or (as discussed here) organism. In typical life circumstances, a person's P-a will be a non-straight line (see FIGURE 1), from 0% (i.e., CA = 0), to their 100% natural (i.e., death by non-accidental means) lifespan. Extraordinary measures can extend P-a beyond 100% (e.g., liver transplant extends P-a to 102.4% in the example).

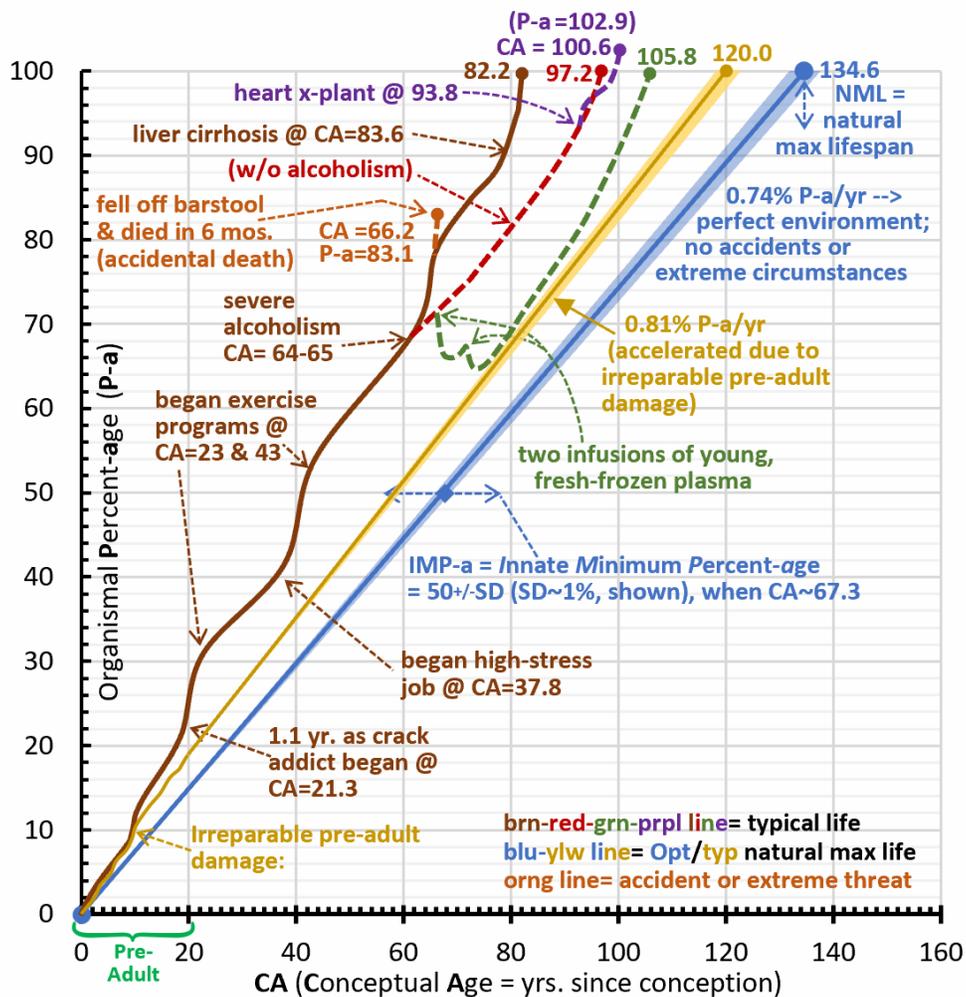


FIGURE 1: IMP-a, P-a, NML & aging path examples

Full life (conception to death) of someone whose NML=134.6 yrs. The blue line defines IMP-a. Curvy lines illustrate sample life paths, including events that affected BA rate; thus, CA & P-a at death.

Heart transplant, exercise, & yFFP infusion are sample HAPLI that affect lifespan. Adverse actions & accidental death are also illustrated. P-a reversal by yFFP infusion is illustrated by a green line.

Natural lifespan appears to be limited. Even legends rarely claim 1000-year lifespans. Lacking irreparable accidents (variably including infections; made complex by hormesis & BA-related loss of resilience & immunity) or heroic measures (e.g., organ transplant), genetics & compounding stochastic, metabolic, & telomere damage intermingle to determine an individual's **natural maximum lifespan** (NML = 134.6 yrs. in Fig. 1, within a narrow distribution → illustrated standard deviation is 1%). NML is an ideal; requiring perfect environments at every moment. NML exceeds any actual natural lifespan claim, since nobody has ever done everything right. Within natural means, *BA* cannot be made less than

IMP-a (i.e., the lowest possible P-a at current CA), multiplied by NML. **NML** defines the highest possible CA in accident-free, undisturbed nature.

Phases of Natural Life: A typical natural lifetime without severe accidents can be divided into phases, loosely defined by interacting, overlapping biological & social functions. Many life-phase categorizations have been put forward, based upon measurements of chemistry, psychology, physiology, & physical, social, &/or cognitive function. Rapid early development transitions into relatively stable & high-function young adulthood; then to minor physical impairment complemented by cognitive maturity; then to obvious physical degeneration but seasoned judgement; finally, to increasingly profound & chronic physical & cognitive morbidities, ending in death. These phases (which vary between & within individuals, & are influenced by circumstances, lifestyle & medical interventions) are quintiled, & based below upon 100% P-a of a 150 year NML (P-a spans would typically be reduced in a typical imperfect life):

Pre-adult: The foundational period, including intertwined subphases of parental preparation, conception, incubation, infancy, toddlerhood, childhood, & through adolescence. Characterized by rapid change & high plasticity that profoundly influences adult outcomes. Parental preparation is a pre-conception "nest building" period of several months, where parental fitness for childbearing is optimized. After conception, pre-adulthood typically spans percent-age (P-a) of approximately -1 to 20%, estimate for an optimized NML, -1 to ~13% (est.).

Reproductive Adulthood: a phase of peak physical capabilities (including reproduction), with typical P-a span = 20-40%; estimate with optimized NML, 13-40%.

Post-Reproductive Adulthood: a phase typified by child rearing, fading fecundity, & high productivity, & increasing but tolerable senescence; typical P-a is 40-60%; estimate with optimized NML, 40-75%.

Ambulatory Elderhood: a phase of obviously reduced physical fitness & resilience, & emerging chronic diseases, but also marked by seasoned guidance of younger community members; typical P-a: 60-80%; Estimate with optimized NML, 75-95% .

Geriatric Elderhood: The high-senescence phase of life, defined by fading contribution to the community, one or more advanced physical & cognitive disabilities, then death; typical P-a: 80-100%; with optimized NML, 95-100%.

Phases can be subdivided (especially 'Pre-adult'), but the above provides adequate definitions for purposes herein.

PHI: 'Pre-adult Healthspan Interventions' A program to increase health & healthy lifespan through early interventions in the formative period of life, beginning a few months prior to conception, through gestation, infancy, childhood, & adolescence.

Post-translational Modification (PTM; a.k.a. radicalation): refers to the covalent bonding by various radicals to proteins. Herein, PTM of histones (e.g., methylation, acetylation, phosphorylation, SUMOylation, etc.) is of particular

interest, as it variably affects expression potential of the DNA segment that wraps around a histone core, especially in the region proximate to the PTM. DNA may undergo epigenetic changes (especially methylation & acetylation) of its nucleobases, affecting translation by that segment, but these are not considered PTMs.

Senescence: A spectrum¹³⁶ of physiological deteriorations for an organism, organ, tissue or cell, with ambiguous implications, unless modified as below:

- 1) healthful clearing of unneeded members (**salutary senescence**)
- 2) degeneration into reduced or lost function (**dysfunctional senescence**)
- 3) non-passive degeneration into dysfunction that also promotes degeneration of healthy members of the community (**pathogenic senescence**)

In wild nature, adversely senescing tissue early in life is typically repaired or replaced efficiently. As repair mechanisms fade & damage accumulates, pathological senescence waxes worse & more widespread. BA-related adverse organismal senescing starts with increasing attrition of healthy cells, compounding into organ & tissue morbidities, & finally into organismal mortality. For individual somatic cells, 'senescence' refers to a state of failure to fulfill normal function, sometimes combined with failure to apoptose, & deterioration into a 'SASP' (senescence associated secretory phenotype). SASP cells are in a pathogenic 'zombie' state, generating proinflammatory & matrix-degrading molecules (among others). Other biological kingdoms exhibit variants on senescence, with some reported able to reverse senescence over time.

ADDITIONAL MATERIAL

EXAMPLE:
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Cognition:

General health:

Alam, Tan, 2025. "Effects of prenatal carotenoid supplementation on maternal and infant health outcomes: a scoping review". *Academia Nutrition and Dietetics*, 2(2). <https://doi.org/10.20935/AcadNutr7763>

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¹³⁶ Wallis, Mizen, Bishop, 2021. "The bright and dark side of extracellular vesicles in the senescence-associated secretory phenotype". <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7347005/>

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Physical features:

Tartrazine & ADHD

Add material on epigenetic changes and other biometrics

<https://www.parents.com/>

<https://www.thebump.com/>

[Type 2 diabetes: Red light therapy could help lower blood sugar levels \(medicalnewstoday.com\)](https://www.medicalnewstoday.com) Note: PBM effects are dose, wavelength and intensity dependent. PBM has not been well-tested for fetal and childhood applications, and is not proven to be safe or effective. Generally, within safe ranges of intensity and dosage, PBM can be therapeutic. Red and near-infrared PBM primarily accelerates tissue repair by modulating cellular energy, redox signaling, and inflammation. Blue/green PBM penetrates less, and does not significantly affect mitochondrial behavior, but offers some useful inflammatory and anti-microbial effects.

1) Hamblin, M. R. (2017). *Mechanisms and applications of the anti-inflammatory effects of photobiomodulation*. **AIMS Biophysics**, 4(3), 337–361. <https://doi.org/10.3934/biophy.2017.3.337>. Considered a backbone of PBM therapy. Explains how PBM works biologically, including dose, wavelength, and effects on tissue, such as mechanistic depth, mitochondrial signaling (cytochrome c oxidase, ROS, NO), hormesis and biphasic dose response, and relationships between inflammation, healing, neurology, and aging.

2)

light are known to enhance mitochondrial function, vasodilation, and nitric oxide (NO) release (enhanced generally by red light is known to

<https://bjsm.bmj.com/content/early/2024/02/05/bjsports-2023-107663> Physical fitness in male adolescents and atherosclerosis in middle age: a population-based cohort study

<https://www.heart.org/en/news/2021/03/19/how-oral-health-may-affect-your-heart-brain-and-risk-of-death>

Autoimmunity, T1 diabetes, etc., in turn, are associated with premature ovarian failure, which typically accelerates other age-related diseases. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5327623/>

<https://www.nature.com/articles/s43587-023-00560-5> CAR-T treated 3-4 mo-old mice (9-13 y-old human equivalent) had significantly less metabolic dysfunction in adulthood (sacrificed – no lifespan data provided). “Perhaps the most striking observation of the current work was the ability of uPAR CAR T cells to act prophylactically to blunt age-induced and diet-induced metabolic decline.”

intermittent hypoxia, hyperbaric, pEMF???

Born too soon and vulnerable: the disproportionate burden of RSV among preterm babies in LMICs

[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(24\)00254-X/abstract?dgcid=raven_jbs_etoc_email](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(24)00254-X/abstract?dgcid=raven_jbs_etoc_email)

Any use for BDNF? <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4697050/>

<https://www.sciencedirect.com/science/article/abs/pii/S0041008X80904263> Temporary **and lasting cardiac effects of pre- and postnatal exposure to carbon monoxide**

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AUTISM – to be added to the essay (from ChatGPT 5.2):

Multiple prenatal (pregnancy-period) factors have been associated with altered autism spectrum disorder (ASD) risk, though it is essential to emphasize up front that **association ≠ causation**, effects

are generally **modest**, and **most exposed pregnancies do not result in ASD**. ASD arises from **polygenic susceptibility interacting with prenatal biology**, rather than a single cause.

Below is a **structured, evidence-weighted overview**, followed by **mechanistic interpretation, risk-reduction framing**, and **traditional/cultural practices with safety notes**, as you prefer for health topics.

1. Maternal Immune Activation (MIA) — Strongest and most replicated

Associations

- Maternal infections (especially **viral**) during pregnancy
- Elevated inflammatory markers (IL-6, CRP)
- Autoimmune disease activity during gestation

Proposed mechanism

- Cytokines (notably **IL-6**) cross or signal across the placenta
- Alter fetal brain development (microglial priming, synapse formation)

Evidence

- Large epidemiologic cohorts
- Strong animal model concordance

Key references

- Brown AS et al., *Am J Psychiatry* (2014)
- Estes ML & McAllister AK, *Trends Neurosci* (2016)
- Knuesel I et al., *Mol Psychiatry* (2014)

2. Maternal Fever (independent of infection) — Moderate

Associations

- Fever during pregnancy linked to higher ASD risk
- **Antipyretic treatment (acetaminophen)** appears to reduce this risk when fever is treated

Mechanism

- Hyperthermia and inflammatory signaling during neurodevelopmental windows

References

- Zerbo O et al., *Pediatrics* (2017)
- Hornig M et al., *Mol Psychiatry* (2018)

3. Certain Medications During Pregnancy — Drug-specific

Higher-confidence associations

- **Valproate** (antiepileptic): high, dose-dependent risk
- **Thalidomide** (historical): very high risk

Mixed or debated

- **SSRIs**: modest association; confounding by maternal psychiatric illness remains significant
- **Acetaminophen**: association reported, but causality remains debated

References

- Christensen J et al., *JAMA* (2013)
- Hviid A et al., *JAMA* (2013)
- Liew Z et al., *Am J Epidemiol* (2019)

4. Maternal Metabolic Conditions — Moderate

Associations

- Gestational diabetes
- Pre-pregnancy obesity
- Severe insulin resistance

Mechanisms

- Chronic low-grade inflammation
- Altered placental nutrient signaling
- Fetal hyperinsulinemia

References

- Krakowiak P et al., *Pediatrics* (2012)
- Li M et al., *Mol Psychiatry* (2016)

5. Nutritional Factors — Protective and risk-modifying Protective

- **Adequate folate intake** (especially periconceptual)
- **Balanced iodine and iron status**

Potential risk

- Severe deficiencies
- Very high folate *with* B12 deficiency (rare, nuanced finding)

References

- Surén P et al., *JAMA* (2013)
- Schmidt RJ et al., *Epidemiology* (2012)

6. Environmental Exposures — Small but consistent signals

Associated exposures

- Air pollution (PM2.5)
- Organophosphate pesticides
- Heavy metals (e.g., mercury, lead)
- Endocrine-disrupting chemicals (phthalates)

Mechanisms

- Oxidative stress
- Epigenetic modulation
- Hormone receptor interference

References

- Volk HE et al., *Arch Gen Psychiatry* (2011)
- Shelton JF et al., *Environ Health Perspect* (2014)

7. Advanced Parental Age — Well replicated

- Increased paternal age (de novo mutations)
- Advanced maternal age (chromosomal and placental factors)

References

- Sandin S et al., *JAMA* (2012)
- Kong A et al., *Nature* (2012)

8. Factors NOT Supported by Evidence

- Vaccines during pregnancy
- Ultrasound exposure (diagnostic levels)
- Modern obstetric monitoring
- Routine prenatal vitamins (when appropriately dosed)

These have been repeatedly examined and **not shown to increase ASD risk**.

Postnatal (after-birth) factors have been studied extensively in relation to **autism spectrum disorder (ASD)**. The current scientific consensus is that **ASD originates primarily prenatally**, but **postnatal factors can influence severity, functional outcomes, and comorbidities**, and—more controversially—may *unmask or amplify* vulnerabilities in genetically or prenatally primed individuals. Below is a **carefully evidence-graded overview**, with mechanisms, strength of evidence, and limits clearly stated.

Framing First (Important)

- **ASD is not “caused” after birth in most cases**
- Postnatal factors:
 - May **worsen symptoms**
 - May **alter developmental trajectory**
 - May **increase functional impairment**
- Effects are typically **conditional** on genetic and prenatal risk

1. Early-Life Infection & Immune Dysregulation

Evidence strength: Moderate

Associations

- Severe neonatal infections
- Recurrent early childhood infections
- Chronic immune activation (elevated cytokines)

Mechanisms

- Microglial priming during synaptic pruning windows
- Neuroinflammation affecting cortical circuit refinement

Notes

- Particularly relevant during **0–3 years**, when synaptic pruning is maximal
- Not specific to ASD (also linked to ADHD, schizophrenia risk)

Key refs

- Estes & McAllister, *Trends Neurosci* (2016)
- Bilbo & Schwarz, *Nat Rev Neurosci* (2009)

2. Gut Microbiome Disruption

Evidence strength: Moderate, rapidly evolving

Associations

- Antibiotic exposure (especially repeated/broad-spectrum)
- Cesarean birth with limited microbial seeding (context-dependent)
- Severe early GI dysbiosis

Mechanisms

- Gut–brain axis signaling (SCFAs, tryptophan metabolites)
- Immune modulation
- Vagus nerve signaling

Important caveat

- Dysbiosis likely **modifies symptom expression**, not core causation

Key refs

- Sharon et al., *Cell* (2019)
- Kang et al., *Microbiome* (2017)

3. Environmental Neurotoxic Exposures

Evidence strength: Low–Moderate

Associated exposures

- Lead (still relevant globally)
- Air pollution (PM2.5, NO₂)
- Organophosphate pesticides
- Flame retardants (PBDEs)

Mechanisms

- Oxidative stress
- Mitochondrial impairment
- Epigenetic modification

Note

- Effects are **small individually**, larger cumulatively

Key refs

- Volk et al., *Arch Gen Psychiatry* (2011)
- Grandjean & Landrigan, *Lancet Neurology* (2014)

4. Severe Early Psychosocial Stress

Evidence strength: Low for causation, moderate for symptom worsening

Examples

- Extreme neglect or deprivation
- Institutionalization
- Chronic caregiver stress

Mechanisms

- HPA-axis dysregulation

- Altered cortisol signaling
- Impaired social learning inputs

Distinction

- Can produce *autism-like features* (social withdrawal, language delay)
- Does **not** create classic ASD neurobiology

Key refs

- Rutter et al., *J Child Psychol Psychiatry* (2007)

5. Sleep Disruption

Evidence strength: Moderate for symptom exacerbation

Associations

- Chronic sleep deprivation
- Circadian rhythm disruption

Effects

- Worsened:
 - Irritability
 - Executive function
 - Social responsiveness

Mechanism

- Synaptic homeostasis failure
- Impaired glymphatic clearance

Key refs

- Cohen et al., *Pediatrics* (2014)

6. Nutritional Deficiencies or Imbalances

Evidence strength: Low–Moderate

Potential contributors

- Iron deficiency
- Iodine deficiency
- Omega-3 insufficiency
- Severe restrictive diets

Mechanisms

- Neurotransmitter synthesis disruption
- Myelination deficits
- Mitochondrial inefficiency

Important

- Deficiencies worsen cognition and behavior broadly—not ASD-specific

Key refs

- Schmidt et al., *Nutrients* (2015)

7. Sensory Overload & Environmental Mismatch

Evidence strength: Moderate for symptom severity

Examples

- Excessive noise
- Chaotic environments
- Inappropriate educational settings

Mechanism

- Heightened sensory reactivity → stress → behavioral dysregulation

This does **not cause ASD**, but strongly influences daily functioning.

8. Factors NOT Supported as Postnatal Causes

- Vaccines (extensively disproven)
- Routine antibiotics (when medically necessary)
- Standard infant formulas
- Typical screen exposure (excessive use may affect language, not ASD causation)

Key ref

- Taylor et al., *Vaccine* (2014)

9. Traditional & Cultural Perspectives (With Safety Notes)

(Included per your stated preference)

Common themes across cultures

- Protecting infants from illness
- Emphasis on regular sleep–wake cycles
- Digestive health
- Reduced stress environments

Examples

- **TCM**: focus on gut balance, avoidance of “heat” and inflammation
- **Ayurveda**: early-life routines (dinacharya), digestive support
- **African & Indigenous traditions**: communal caregiving, reduced sensory chaos

△ These practices may **support regulation and resilience**, but **do not prevent ASD**.

10. Integrative Interpretation

ASD severity after birth appears influenced by:

- **Neuroimmune tone**
- **Metabolic efficiency**
- **Environmental match to neurotype**
- **Cumulative stress load**

Postnatal factors are best understood as **modifiers**, not originators.

Key Takeaways

- ASD largely originates **before birth**
- Postnatal factors can:
 - Worsen symptoms
 - Affect developmental outcomes
 - Influence comorbidities
- Effects are **context-dependent and cumulative**
- No credible evidence supports abrupt postnatal “triggering” in isolation

References (Selected)

- Estes ML & McAllister AK. *Trends Neurosci.* 2016
- Sharon G et al. *Cell.* 2019
- Volk HE et al. *Arch Gen Psychiatry.* 2011
- Grandjean P, Landrigan PJ. *Lancet Neurol.* 2014
- Rutter M et al. *J Child Psychol Psychiatry.* 2007
- Taylor LE et al. *Vaccine.* 2014

If you would like, I can:

- Quantify **effect sizes** where known
- Map **critical postnatal windows (0–6 mo, 6–24 mo, 2–5 yr)**
- Integrate prenatal + postnatal factors into a **PHI risk-modulation framework**
- Discuss **protective postnatal interventions with evidence grading**

Just let me know how you want to proceed.

To add references:

- 1) *copy link address of the targeted reference*
- 2) Place cursor in location you want to insert reference
- 3) *Go to: “References”*
- 4) *select: “Insert Footnote” → superscript number will appear*
- 5) *highlight the footnote number*
- 6) *Go to: Insert*
- 7) *Select: Link*

- 8) In "Address" box, paste: copied address of reference
- 9) Click: "OK"
- 10) Go to numbered footnote, & insert: Author(s), date, "title" & link
- 11) Change footnote font to "Verdana" 6pt