WHAT IS YOUR INTRINSIC AND EXTRINSIC EPIGENETIC AGE?

Immune Report

TruDiagnostic™

A Recap on TruAge™

Most people know that their body has an internal clock which can be measured via methylation specific epigenetic testing. We have reported this age output to you in our TruAge™ test! However, did you also know that we can break this down even further?

While biological age clocks are a good measure of the age of your body, we can look at the age of particular systems in your body as well. In this expanded report, we will discuss two metrics which give you more information above and beyond biological age. These are the intrinsic and extrinsic age of your body!

Our Clocks Tick in Different Ways, Thus Cell Type is Important!

If every cell in your body has the same DNA, how do your heart cells become heart cells and your hair cells become hair cells?

The answer is epigenetics! Epigenetics controls how a cell develops and functions by turning on and off certain genes. By selecting which genes are turned off and on, you can control your phenotype, or how your cells behave.

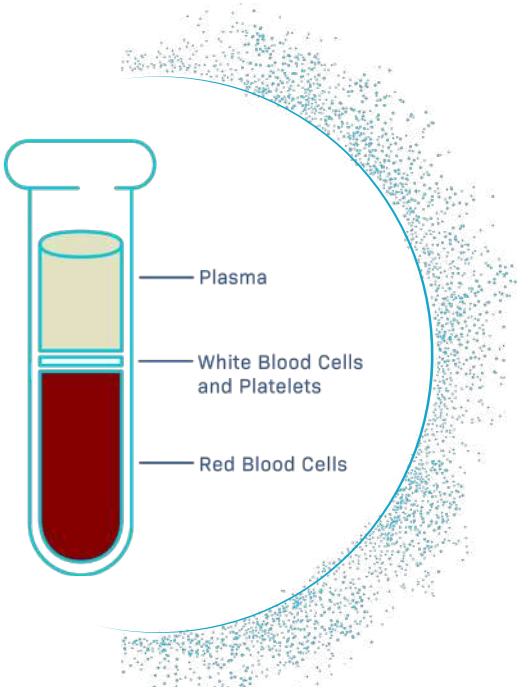
Thus, it makes sense that the epigenetic regulation of each cell would depend on what cell type it is. You wouldn't want your heart to make the proteins found in your bone and vice versa.

When we are measuring methylation (an epigenetic mechanism to turn off genes), we see that this is true and that all types of cells have different epigenetic signatures. Beyond that, if we measure biological aging of different tissues, we see them aging at different rates! In fact, our cerebellum and brain ages slower than the rest of the body. We also see that sometimes breast tissue in women can age faster than the rest of our body.

Therefore the rate of aging we calculate is dependent on what cell types we measure! So if we are using blood, what cells are we looking at?

What Cells are Found in Your Blood?

The average human adult has more than 5 liters (6 quarts) of blood in his or her body. Blood carries oxygen and nutrients to living cells and takes away their waste products. It also delivers immune cells to fight infections and contains platelets that can form a plug in a damaged blood vessel to prevent blood loss.



Thus, our blood has many different functions. In order to do a good job at a lot of different things, our blood contains many different parts:

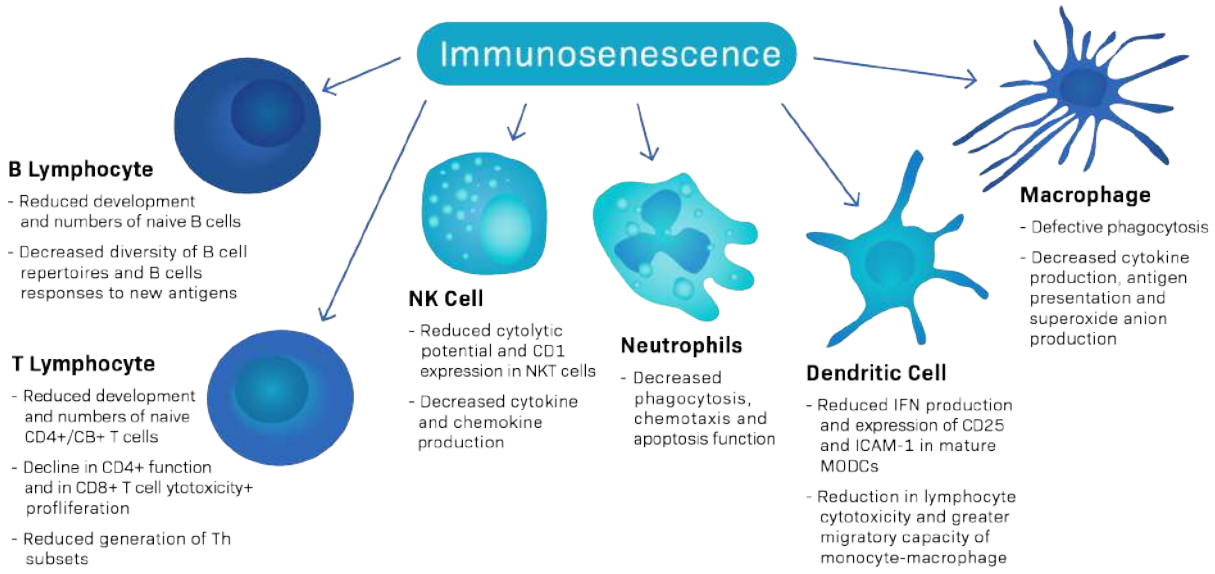
- One of the most important constituents of blood are the red blood cells. These cells contain hemoglobin and work to carry oxygen all throughout the body.

- The straw-colored fluid that forms the top layer is called plasma and forms about 60% of blood. Plasma is mainly water, but it also contains many important substances such as proteins (albumin, clotting factors, antibodies, enzymes, and hormones), sugars (glucose), and fat particles.

- Platelets are the cells which help your blood clot. They are irregularly shaped fragments of cells that circulate in the blood until they are either activated to form a blood clot or are removed by the spleen. They are in the blood so that if we get a tiny cut we don't bleed out.

- White Blood Cells (WBCs) are the cells of your immune system which help fight infections. WBCs come in many different shapes and sizes. Some cells have nuclei with multiple lobes, whereas others contain one large, round nucleus. Some contain packets of granules in their cytoplasm, known as granulocytes.

The interesting part about WBCs is that the amounts of these cells greatly change with age as shown in the graphic below!



Ever wonder why older people are more likely to have negative outcomes with things like COVID-19 and the regular flu? It is because the cells needed to mount an effective response tend to decrease in the blood as we age. **This is called Immunosenescence.**

Immunosenescence: How it relates to Health, Aging, and Biological Age

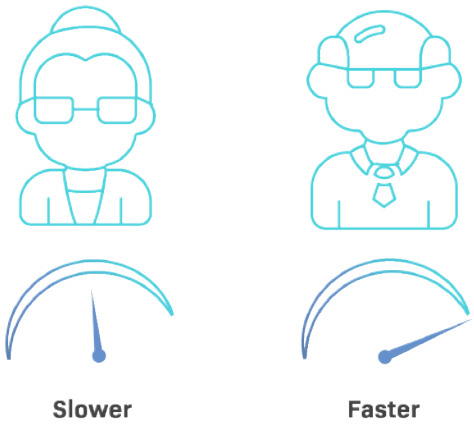
In humans, as well as in many other species, it is known that the immune system declines with age. This is known as immunosenescence. The process of immunosenescence leads to a higher incidence of infections, cancer and autoimmune diseases in the population. [Pawelec 1999]

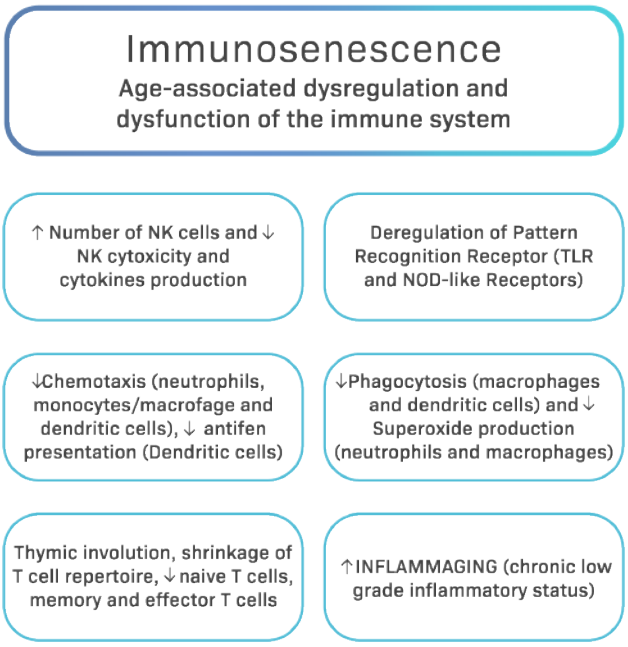
As you can see in the picture, it also changes the amount of immune cells in our blood. As we age we have fewer Naive T Cells, Natural Killer Cells, Macrophages, Dendritic cells and others.

This means, when we process the DNA of your blood as you age, the DNA markers also change. Thus, it can affect our reading of biological age!

We can control for this change though. If we don't control for it in our interpretation, we get a measurement of extrinsic epigenetic age. This is a surrogate marker for the age of our immune system.

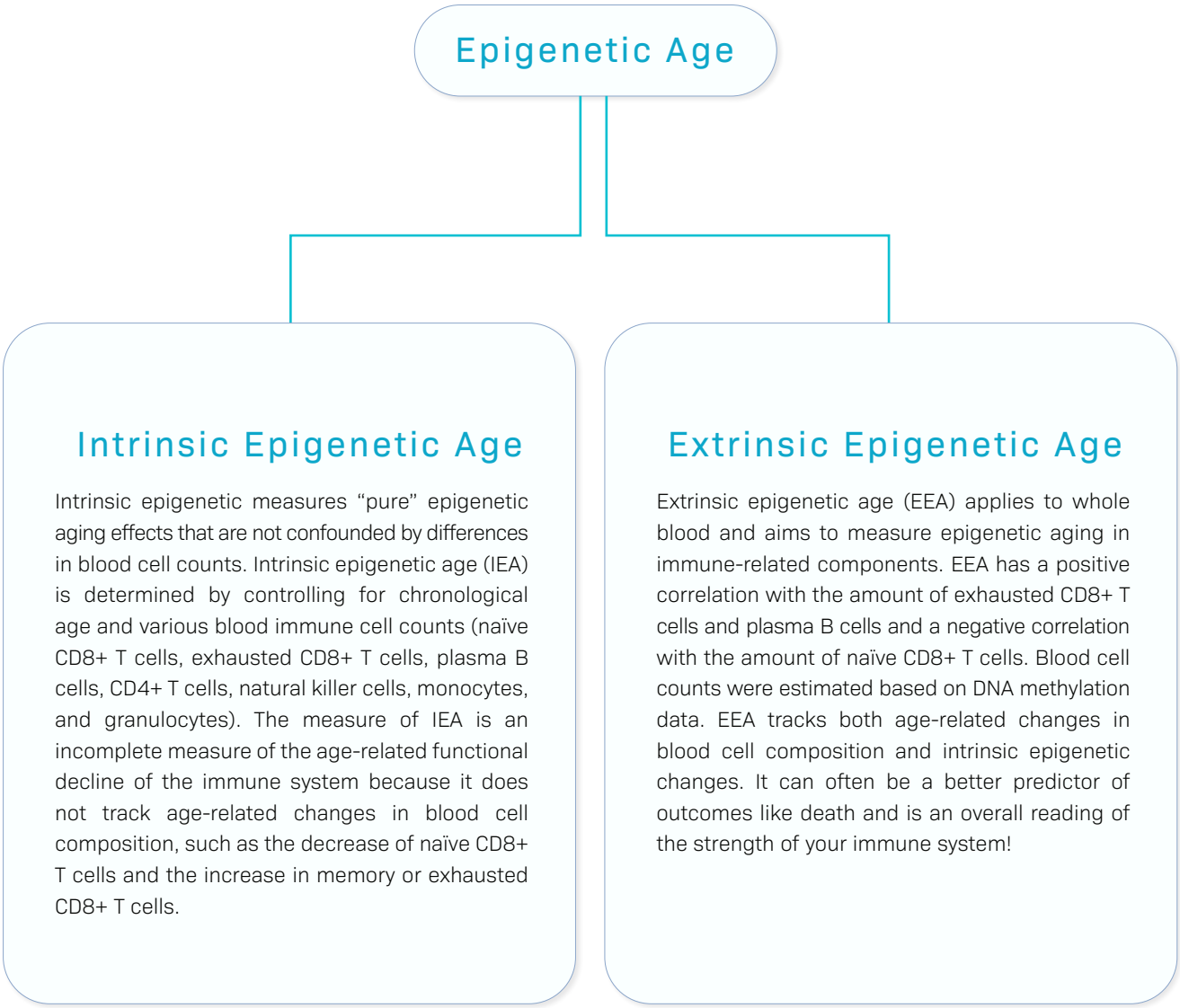
If we do control for this, we get the intrinsic epigenetic age. Which is the age of our cells without taking immune sets into account!





The Difference Between Intrinsic and Extrinsic Epigenetic Aging:

So if we break down epigenetic age, it can be split into two important categories: ***intrinsic*** and ***extrinsic*** epigenetic age.

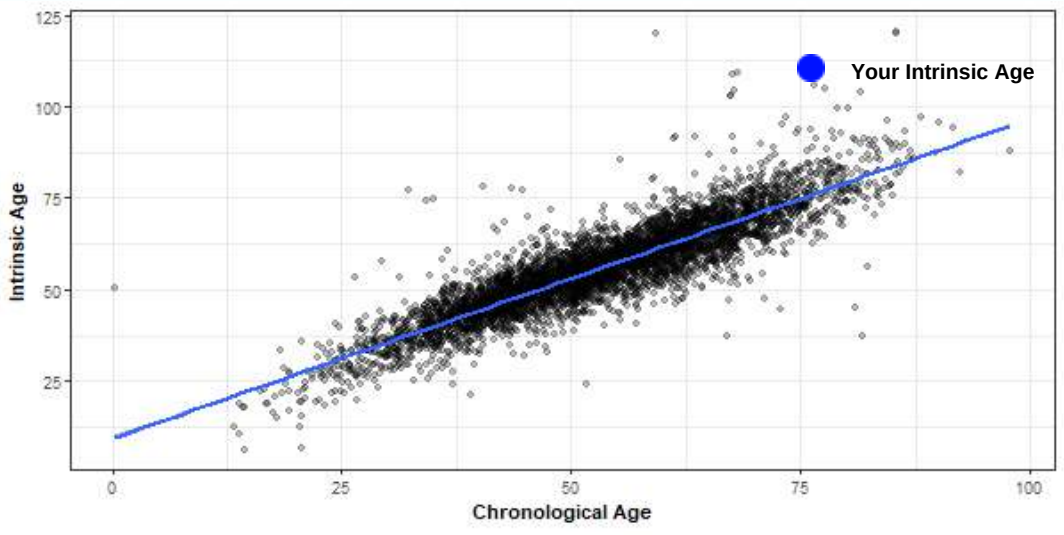


Therefore, we have two markers of epigenetic biological age which can tell us two very different things. One is aging with relationship to the immune system, and the other is the intrinsic basic fundamental process of cellular aging.

YOUR INTRINSIC
Epigenetic Age

Your measurement of Intrinsic Epigenetic Age is 47.49 years

You versus the population:



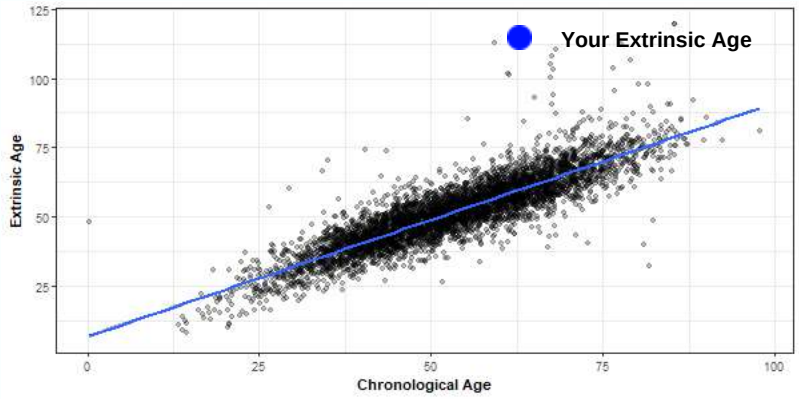
YOUR EXTRINSIC
Epigenetic Age

Your measurement of Extrinsic Epigenetic Age is 45.50 years

Test	Meaning	Normal Range Values	Your Percentage as Calculated using Lymphocyte Deconvolution
Lymphs %	Percentage of Lymphocytes:	20% to 40%	42.67%
	B		7.48%
	CD4T		14.40%
	CD8T		11.77%
	NK		9.03%
Neutro%	Percentage of Neutrophils	40% to 60%	49.26%
Monos.%	Percentage of Monocytes	2% to 8%	8.06%
Eosino%	Percentage of Eosinophils	1% to 4%	0.00%
CD4/CD8 Ratio			1.22

This is a functional measurement of your immune system! This measures and predicts many of the cells which change as our immune system declines. If you have more of these cells, it means your immune system looks younger and can be more effective at protecting you from viruses, bacteria, cancer, and general inflammaging.

You versus the population:



Disclaimer: The Cell Estimation algorithm is based on a reference-free protocol that uses only your epigenetic profile to calculate the values. This makes the algorithm extremely sensitive to any changes in the methylation values of your DNA. Therefore, the number generated in this report may not be a true reflection of your immune cell counts and you might see some abnormal values as this continues to improve.

What Might have Played into my Score?

The Two Main Studies:

Two studies have been done which have looked at correlations between these rates of aging. These are able to give us insights into the behaviors which are correlated with better extrinsic aging rates (and therefore less mortality and better immune systems).

One is the ***Bogalusa study*** and the other is the ***Women's Health Initiative Study*** (WHI). We have included tables of their associations below and summarized many results in the text below as well.

Bogalusa Study Multivariate model that regresses epigenetic age acceleration on participant characteristics in the Bogalusa Study. Coefficients and p values from regressing measures of intrinsic and extrinsic epigenetic age acceleration on participant characteristics from dataset 1.

Multivariate linear regression		Intrinsic EAA			Extrinsic EAA		
		Estimate (SE)	Z	*p*	Estimate (SE)	Z	*p*
Race	Caucasian vs. African American	-0.013 (0.316)	-0.04	0.97	0.843 (0.316)	2.67	0.0076
Gender	Female vs. Male	-0.622 (0.278)	-2.24	0.025	-0.718 (0.277)	-2.60	0.0093
Education	Grade 8-9 vs. < Grade 8	1.583 (1.468)	1.08	0.28	2.177 (1.465)	1.49	0.14
	Grade 10-12 vs. < Grade 8	1.285 (1.27)	1.01	0.31	2.267 (1.267)	1.79	0.074
	Vocat/Tech vs. < Grade 8	0.307 (1.299)	0.24	0.81	1.921 (1.295)	1.48	0.14
	College vs. < Grade 8	0.85 (1.281)	0.66	0.51	2.375 (1.277)	1.86	0.062
	Graduate vs. < Grade 8	0.147 (1.336)	0.11	0.91	1.53 (1.332)	1.15	0.25
Diabetes (II)		0.173 (0.485)	0.36	0.72	0.012 (0.483)	0.03	0.98
Hypertension		0.539 (0.291)	1.86	0.064	1.247 (0.29)	4.30	$1.7x10^{-5}$
R-squared		0.025			0.043		

WHI Study Multivariate model that regresses epigenetic age acceleration on participant characteristics in the WHI Study. Coefficients and p values from regressing measures of intrinsic and extrinsic epigenetic age acceleration on participant characteristics from dataset 2.

Multivariate linear regression		Intrinsic EAA		Extrinsic EAA	
		Estimate (SE)	*p*	Estimate (SE)	*p*
Race/Ethnicity	Hispanic vs. African American	-0.94 (0.35)	0.007	3.363 (0.439)	$<10^{-15}$
	White vs. African American	0.71 (0.295)	0.016	1.94 (0.37)	$1.6x10^{-7}$
HDL-cholesterol		0.006 (0.01)	0.558	-0.003 (0.013)	0.799
Triglyceride		0.003 (0.002)	0.059	0.004 (0.002)	0.04
Insulin		0 (0.001)	0.664	0.001 (0.001)	0.337
Glucose		0.003 (0.004)	0.486	0.007 (0.005)	0.112
CRP		0.023 (0.018)	0.215	0.052 (0.023)	0.023
Creatinine		0.703 (0.594)	0.237	1.985 (0.745)	0.008
BMI		0.035 (0.021)	0.103	0.045 (0.027)	.093
Education	High School (HS) vs. no HS	0.357 (0.426)	0.403	-0.784 (0.534)	0.142
	Some College vs. no HS	0.469 (0.381)	0.219	-1.172 (0.478)	0.014
	College vs. no HS	0.486 (0.519)	0.349	-2.253 (0.65)	0.001
	Grad School vs. no HS	0.36 (0.424)	0.396	-1.648 (0.531)	0.002
Alcohol	Past Drinker vs. Never	1.668 (1.1)	0.13	-0.598 (1.379)	0.665
	Light Drinker vs. Never	-0.101 (0.536)	0.85	-0.751 (0.672)	0.264
	Moderate vs. Never	-0.416 (0.748)	0.578	-0.401 (0.937)	0.669
	Heavy vs. Never	-0.354 (0.88)	0.687	-0.833 (1.103)	0.45
Smoking	Former vs. Current	-0.573 (1.039)	0.581	-0.104 (1.302)	0.936
	Never vs. Current	-0.376 (1.039)	0.718	-0.122 (1.303)	0.925
Diabetes		0.216 (0.43)	0.616	-0.061 (0.539)	0.909
Hypertension		0.364 (0.241)	0.131	0.262 (0.302)	0.386
R-squared		0.029		0.069	

Contributing Factors

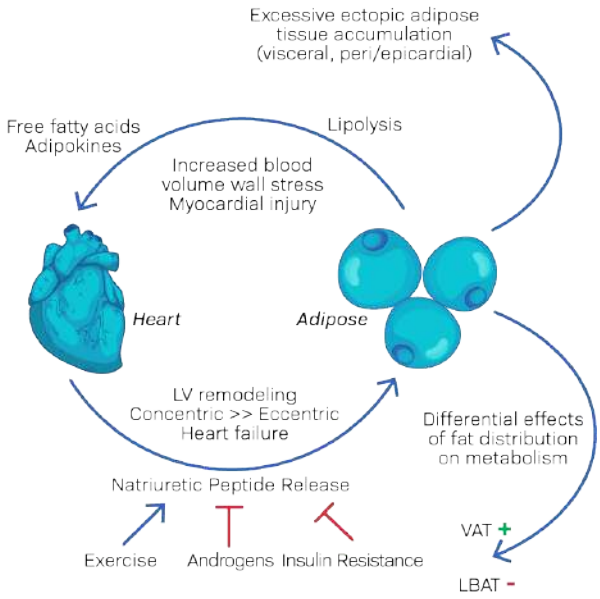
Cardiometabolic Disease, Metabolic Syndrome, and BMI:

The health of your metabolic system and your cardiovascular system are intimately related. In fact, because these account for a large proportion of all disease risk, it is no wonder that these metrics can have effects on aging.

Cardiometabolic disease can also affect your extrinsic aging rate! Epigenetic age acceleration (EAA) is linked more closely with risk factors for cardiometabolic disease than intrinsic aging according to one study.

Extrinsic epigenetic age acceleration (EEAA) was generally higher in individuals with higher triglyceride levels, higher C-Reactive protein, and higher creatinine.

Neither intrinsic nor extrinsic aging rates of blood tissue are predictive of incident coronary heart disease (CHD) in the Women's Health Initiative study (WHI) even though EEAA is weakly associated with several cardiometabolic risk factors of CHD (such as hypertension, triglycerides, and CRP). [Horvath 2016]



Dietary Intake

EEAA exhibits significant associations with fish intake, moderate alcohol consumption, and blood carotenoid levels (p=1x10-5), an indicator of fruit and vegetable consumption. [Quach 2017]

Race/Ethnicity

Race, ethnicity, and their underlying genetic features also have a significant effect on extrinsic epigenetic aging. One study looked at race and found the following correlations below.

Hispanics and Tsimane have a higher EEAA than Caucasian:

Hispanics have a significantly older extrinsic epigenetic age than Caucasians and fewer naïve CD4+ T cells, based on cytometric data from several studies. This pattern of fewer naïve CD4+ T cells is even more pronounced for Tsimane, who experience repeated acute infections and elevated, often chronic, inflammatory loads.

African Americans have lower EEAA than Caucasian:

African Americans have lower EEAA than Caucasians in the WHI and in the Bogalusa Study. In fact, one study found that African Americans have indications of a significantly younger immune system age than Caucasians (p = 0.0076) after controlling for gender, educational level, diabetes status, and hypertension.

In the Bogalusa study, we find three significant predictors of EEAA: race/ethnicity, hypertension, and gender (p = 0.0093, Table 5). A marginal analysis in the Bogalusa study identifies a significant association between EEAA and hypertension (p = 8.0 × 10−5, Additional file 5G–I), type II diabetes status in Caucasians (p = 0.0085, Additional file 6H), but not in African Americans (Additional file 6I). [Horvath 2016]

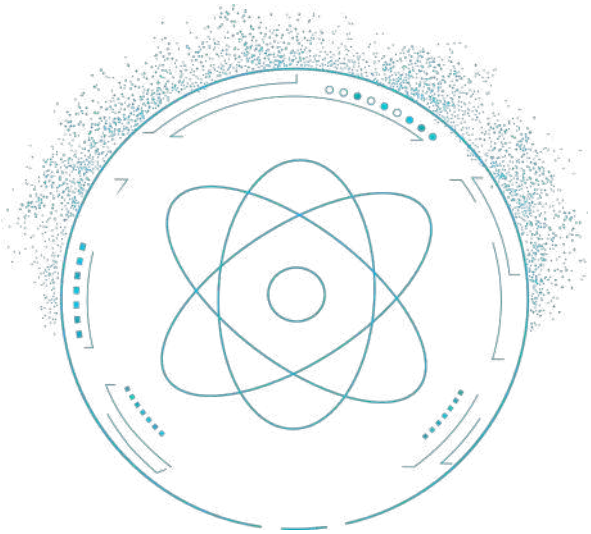
Contributing Factors

Education

Often, education is linked to changes in aging because it is correlated to other lifestyle metrics.

In the WHI study, Extrinsic epigenetic age was lower with higher levels of education in all ethnic groups. For each racial/ethnic group, we find that women who did not finish high school exhibit the highest levels of EEAA.

However, contrary to the findings in the WHI, no significant association can be observed between EEAA and educational level in other studies. It might be too early to tell how this is correlated to Extrinsic epigenetic aging.



Mood Stabilizers

Are you currently taking mood stabilizers? Compared with controls, there was a decrease in EEAA and IEAA in patients with Bipolar Disorder (BD). Further, there was a significant decrease in EEAA and IEAA in patients with BD taking medication combinations of mood stabilizers (including lithium carbonate, sodium valproate, and carbamazepine) than in those taking no medication/monotherapy. [Okazaki 2020]

Smoking

Nominally significant genetic correlations between EEAA and lifestyle factors including smoking behaviors and education support the hypothesis that Hannum-based epigenetic ageing is sensitive to variations in environment.

What are my concerns if my reading is high?

Your Immune System

Since extrinsic epigenetic age is also able to predict the amount of some of your immune values, it is also considered a surrogate marker of the immune system. As a result, a low score here might mean that your immune system isn't doing the things that it should.

When the immune system isn't functioning correctly, your risk of some diseases and disease complications increase. Some of these things include higher cancer risk, higher inflammation (often called inflammaging), higher burdens of senescence, higher risk of autoimmune disease and much more. If you are worried about your score in this regard, please contact your physician to learn more.

Your Longevity

Unfortunately, higher extrinsic epigenetic aging is also correlated with shorter lifespans. Chen et al. (18) included 2,734 deaths in a study and showed that higher extrinsic epigenetic age correlated to a higher hazard ratio for death.

Thus, the high predictive significance of EEAA for all-cause mortality probably reflects the fact that it assesses multiple aspects of the biological age of the immune system including both changes in blood cell composition and cell-intrinsic epigenetic changes. It has been known for decades that poor T cell functioning is predictive of mortality. [Roberts 1974]

How to Positively Affect this Metric and What Could have Affected your Metric:

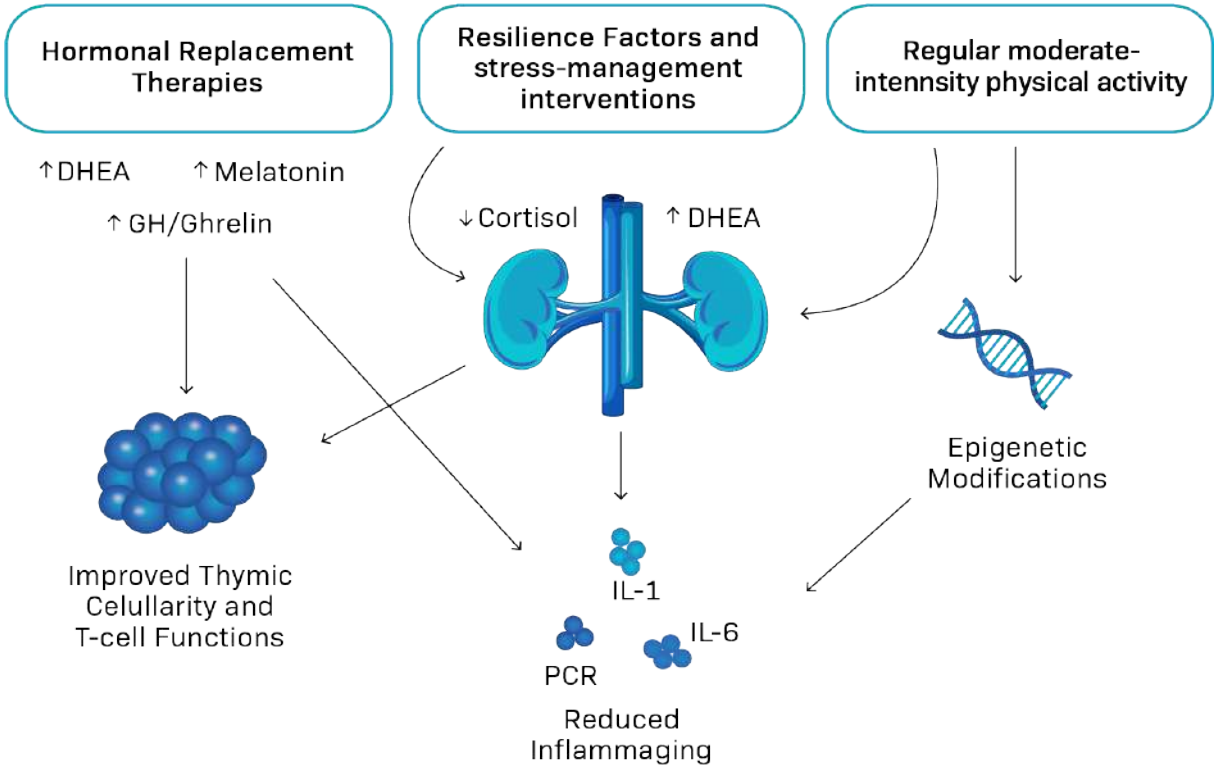
One of the best things about epigenetic measurements on aging is that they can be changed for better health. While research is still in its infancy on this topic. We are working to find the best interventions to change these metrics! So far, there is still some data on how to change this and many ways to speculate on these outcomes as well.

First, extrinsic epigenetic age acceleration (EEAA) exhibits significant associations with fish intake (p=0.02), moderate alcohol consumption (p=0.01), BMI (p=0.01), and blood carotenoid levels (p=1x10-5), an indicator of fruit and vegetable consumption, whereas intrinsic epigenetic age acceleration (IEAA) is associated with poultry intake (p=0.03) and BMI (p=0.05). [Quach 2017]

This means that moderate consumption of alcohol (only validated at 1 drink per week) could help reduce this metric. Fish intake is also correlated to lower values. Increasing your diet of both of these could help reduce this metric! Additionally, increasing your consumption of fruits and vegetables is also correlated with improvement.

Other interventions like reducing your BMI and body weight are also correlated with improved metrics.

It is plausible to believe that therapies which prevent or delay the immune system's decline over time might be helpful here as well. One validated intervention in this space revolves around regeneration of the thymus. The thymus is one of our most important immune organs and gets smaller as we age. DHEA, Melatonin, and GH related therapies have all shown improvement in regenerating the thymus and changing the immune cells in our body. Please talk to your doctor about therapies which can help increase the immune system!



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