KNOWING ALZ

Prevention | News | Resources

Can't-Miss Research from October

Chronic Inflammation

Inflammation can seem like a health and fitness fad, but its relationship to Alzheimer's is becoming clearer everyday. In this recent study, researchers found that "chronic low-grade inflammation was associated with an increased risk of Alzheimer's disease (AD) only in ApoE4 carriers". If you know you have the ApoE4 gene, you can work with your primary care doctor to get the C-reactive protein test used in the study to understand if you have chronic inflammation. Many of the common causes can be treated with lifestyle changes.
Further reading: If you don't know your ApoE4 status and would like to, there's a guide on page 4 of this newsletter. Also, here's an Alzheimer's inflammation connection explainer.

Herpes / Cold Sore Virus

"Herpes Causes Alzheimer's" makes for a clickable headline, but a more accurate headline would be "Cold Sore Virus Could Be a Cause of Alzheimer's". Cold sores are caused by a form of the Herpes virus called Herpes Simplex Virus 1 (HSV 1). Most people have this virus lying dormant inside them, and it can activate when the body is stressed (being ill, mentally stressed). A growing body of evidence outlined in this new study shows a correlation between HSV1 and Alzheimer's, likely due to repeated stress-induced activations of the virus leading to cell damage. The good news is that anti-virals could be a readily available means of combating these effects, with the study citing evidence from Taiwan that anti-herpes agents reduced Alzheimer's prevalence.
Further reading: An understandable explainer by the study author, another previous summary of the relationship between Herpes and Dementia.

Periodontitis

A new study, combined with previous evidence, suggests that poor oral health, specifically periodontitis, can cause inflammation and buildup of Amyloid Beta ($A\beta_{42}$) contributing to the development or progression of Alzheimer's. This is important for both prevention and caregiving, because poor oral health can increase as cognitive decline increases, due to a person's decreased awareness of daily tasks.

DNA + RNA Errors

Two studies found that genetic errors may be related to Alzheimer's. The first looked at the transcriptome (genes being actively expressed) of 450 brains in two aging cohorts, and found 21 genes associated with Alzheimer's. Researchers determined that splicing errors were the mechanism for three Alzheimer's risk factor genes. The second found non-inherited DNA errors in the brain cells of half of the 54 individuals they studied: "These spelling errors arise in our DNA as cells divide, and could explain why so many people develop diseases such as dementia when the individual has no family history"[1]. Although many subjects had Alzheimer's or Lewy Body

Movies / Videos

What They Had - "After her ailing mother wanders off during a blizzard, Bridget returns to her childhood home in Chicago…

On the Front Lines of Alzheimer's and Dementia - "We will meet those on the front lines, who will share with us what their cutting-edge research… has revealed." Watch

Watch Tau Infiltrate the Brain in Alzheimer's

Celebrities

Sandra Day O'Connor - made a "disclosure of a dementia diagnosis, the start of a journey that nine years ago robbed the life of her husband."

Politics

$425 Million increase for Alzheimer's Research funding - Appropriations have increased from $1.2 in 2015 to $3.1 billion in 2019 signaling congress' commitment to a cure.

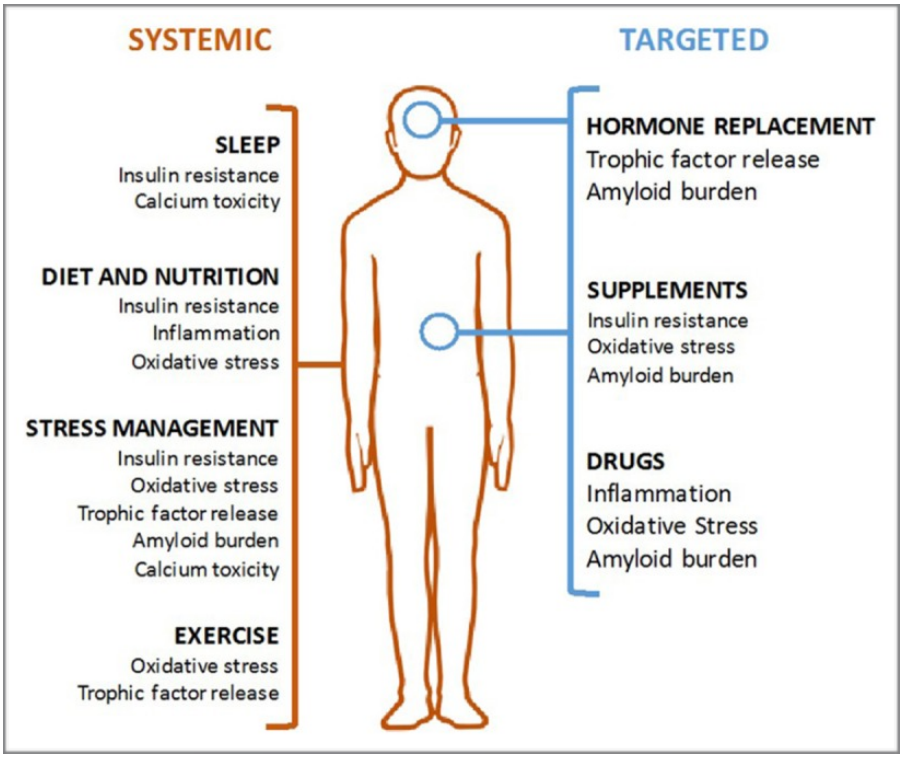
dementia, the results cannot be used for treatment or diagnosis, but both studies provide promising avenues for future research on the genetic components of dementia.
Further reading: Another new study on epigenetics and a decent article on it.

CRISPR Biomarker

AD genetics research has taken a big step forward in 2018. A recent study used CRISPR, a precise gene-editing system, to discover another AD biomarker. The researcher removed a gene to find out how neurons function in the absence of the STIM1 (you don't need to know what that is) protein. Researchers were '"able to simulate what occurs in [neurons] without this protein, and [they] observed alterations very similar to those seen in tissues with Alzheimer's"[1]. Up to now, the effects of a deficiency in this Alzheimer's-related protein were not known, and so this research gives us a new biomarker for AD — in other words, an indicator of the progression of the neurodegenerative process. Additionally, the absence of the STIM1 protein caused a lack of control over calcium transport in the neurons, which "supports a role for Ca^{2+} transport and signaling dysregulation in AD"[2] (a complicated topic covered in an upcoming Deep Dive). With more research, STIM1 protein could be used as another biomarker to measure the progression of AD.

Deep Dive: Alzheimer's Prevention Research Review

Preventing Alzheimer's might seem too good to be true, but there is a solid body of evidence that risk reduction and prevention can be achieved through lifestyle changes . Earlier this year, Richard Isaacson, the founder of the first Alzheimer's prevention clinic in the USA, and a team of researchers published a review aggregating 150 studies into 6 Alzheimer's disease mechanisms and the related lifestyle factors. This is a huge step forward for science-backed prevention strategies. What follows is a high level overview of that paper titled "*Mechanisms of Risk Reduction in the Clinical Practice of Alzheimer's Disease Prevention*", which was written with a research or healthcare professional audience in mind. It's important to have a basic understanding of the mechanisms that contribute to developing Alzheimer's and what you can do to stop these processes or compensate for their effects. This understanding will help ground any lifestyle changes in a cause-effect relationship and will give you a starting point for discussing changes with your doctor. Having looked into many prevention programs and methodologies, this study is the gold-standard in science-backed clinically-based prevention strategies. Not every primary care doctor will be well-versed in research on preventing cognitive decline, but most will be receptive to working with you on a plan if you come in with an idea of what you want to achieve and why. In that spirit, the next several newsletters will try to provide a genuine understanding of the 6 disease mechanisms (1-2 per newsletter) and what you can do about them.

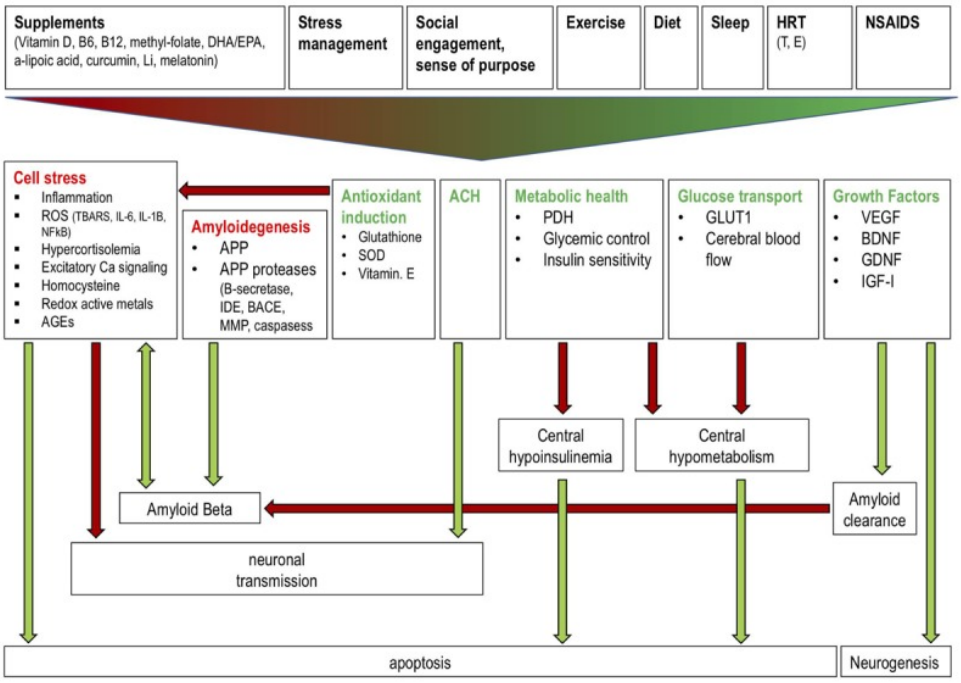


Mechanisms of Risk Reduction in the Clinical Practice of Alzheimer's

6 Disease Mechanisms: An Overview

I won't be going into a lot of detail on the mechanisms for now. I believe it is more useful to start with an overall understanding by humanizing each factor. Future Deep Dives will discuss each mechanism in an in-depth fashion, so that you can understand exactly the inputs and outputs of each lifestyle factor.

- **Glucose Metabolism and Insulin Resistance**: Essentially, the system to deliver energy to cells, store glucose as fat, and maintain healthy blood sugar levels is not at its best. A simple but incomplete way to start thinking of this mechanism is to imagine a scale with being completely healthy on one end and having diabetes on the other. Having poor glucose metabolism and high insulin resistance means being closer to the diabetes end of that scale.
- **Inflammation**: The body's natural reaction meant to combat foreign invaders (bacteria, viruses) or harmful particles (chemicals, heavy metals) can be unhealthy when the inflammation is chronic. For example, persistent pollution can cause a long-term inflammatory response, and your healthy cells become collateral damage in your body's efforts to rid itself of the pollution.
- **Oxidative Stress**: This one is not very intuitive, but it's why you see products touting antioxidants. Oxidative Stress occurs when your body has more free radicals than it can clear away with antioxidants (both produced by the body and consumed). Free radicals are naturally produced during energy transport and processing, and through unhealthy means like inflammation. The most relatable free radical is hydrogen peroxide (H_2O_2). As you know, a common use of hydrogen peroxide is to clean injuries by sterilizing the wound, aka killing the bacteria, so it's easy to understand that having hydrogen peroxide in your body could cause damage. To prevent this damage, our bodies naturally produce antioxidants that remove H_2O_2 and other free radicals. However, when too many free radicals are produced through unhealthy means like inflammation, healthy cells get damaged. For more, watch this video explainer: Oxygen free radicals & cellular injury - causes, symptoms & pathology.



Mechanisms of Risk Reduction in the Clinical Practice of Alzheimer's Disease

- **Trophic Factors**: "The helper molecules that allow a neuron to develop and maintain connections with its neighbors... Without trophic factors, a nerve cell may die. Trophic factors maintain the connections that are retained as development and learning take place." -ALS Association. Trophic factors play an important role in early development when our brains create an excess of connections and then later go through a period of pruning to keep only the most important connections. As a result, maintaining trophic factor levels is important to maintaining brain health and preventing neurons from dying.
- **Amyloid Burden**: Often considered the main culprit in Alzheimer's, amyloid build up causes the plaques that define Alzheimer's disease, and the effects of the excess amyloid are believed to directly and indirectly contribute to cell death. Reducing amyloid burden and related subjects have been the focus of the bulk of research into Alzheimer's treatments over the past 25 years.
- **Calcium Toxicity**: Buildup of calcium due to excess vitamin D or sleep deprivation can diminish the ability of neurons to manage the flow of molecules within themselves, leading to cell death.

Prevention: What can you do?

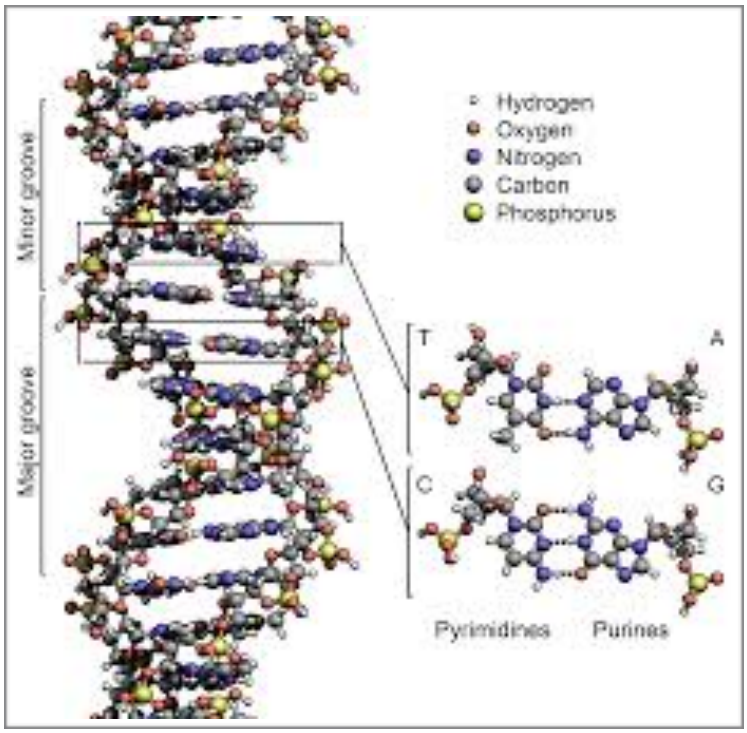
Keep in mind that a cornerstone of risk reduction and prevention is tailoring the regimen to the individual, so these are simply general prevention guidelines pulled out of the study to get you thinking about next steps.

1. **Exercise** - Regular exercise is important (at least 3 sessions per week), resistance weight training and aerobic exercise are recommended.
2. **Diet** - High-fat, low-carbohydrate ketogenic diet or moderate-fat, low-carbohydrate Mediterranean diet are recommended.
    1. The study suggests “carbohydrate-restricted diets, with Mediterranean diets being particularly useful for older individuals or those with existing insulin resistance"*.
    2. For inflammation reduction, “the most potent dietary inducers of this systemic inflammatory response appear to be refined starches (e.g., white flour and its derivatives), refined sugar (e.g., sucrose and high-fructose corn syrup), artificial *trans*-fats, and saturated fats in the presence of high carbohydrate intake."*
3. **Sleep** - “7-8 h beginning at 11 pm”* is the suggested amount.
4. **Social Engagement** - "Greater social engagement has been associated epidemiologically with reduced risk of AD.”*
5. **Stress Management** - Cognitive behavioral therapy, mindfulness training/meditation are research-supported options.
6. **Hormone Replacement Therapy, NSAID, Supplements** - These really need to be doctor recommendations or at least discussions, because they have different risks and rewards for everyone.

All quotes and images are from the study “Mechanisms of Risk Reduction in the Clinical Practice of Alzheimer’s Disease Prevention" Original study from Frontiers in Aging Neuroscience are provided here courtesy of Frontiers Media SA. Copyright © 2018 Schelke, Attia, Palenchar, Kaplan, Mureb, Ganzer, Scheyer, Rahman, Kachko, Krikorian, Mosconi and Isaacson.

Guide: At-Home Genetic Testing

The relationship between your genes and your chances of getting Alzheimer's disease is not straightforward or simple, but if you have Alzheimer’s in the family, there are useful things that you can learn from your own genetics. First, there are two important categories of Alzheimer’s disease (AD) when talking about genetic risk factors: early-onset familial Alzheimer's Disease (eFAD) and late-onset Alzheimer’s Disease. eFAD "is caused by a mutation in a single gene, and a single copy of the mutant gene, inherited from one parent, will cause the disease."* Late-onset AD genetics are complex and there are likely many genetic factors that both reduce and increase disease risk. ApoE is the most understood AD genetic risk factor with each copy (0, 1 or 2) of the e4 allele increasing disease risk. Before considering testing, I recommend that you thoroughly understand ApoE, what having the e4 allele would mean for your disease risk, and what a positive result might mean for you. If you can't recite a few ApoE related stats and explain the broad strokes, stop reading this guide and read these articles from the National Institute of Health and APOE4.info.



Now that you're up to speed on ApoE, let's talk about "Direct to Consumer Testing.” The most common product is 23andMe. Start by reading this article from the NIH. I know it seems like a lot of background information, but the ease of 23andMe can undermine the gravity of the

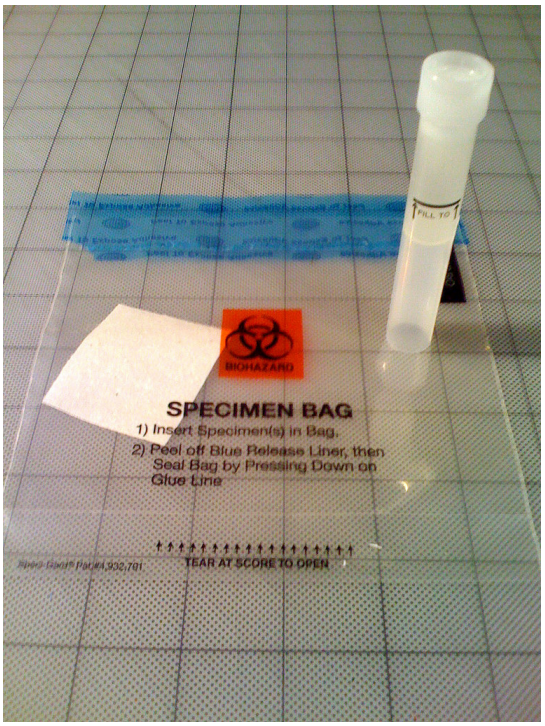
information it provides. Some people already have a good grounding in risk factors and the results will come as useful information. For others, the information will be stressful, and for a non-expert, easily misinterpreted. In case you missed it, I'm trying to convey that testing isn't for everyone. For good measure, here's three more resources and a cautionary tale: Alzheimer's Disease Genetics Fact Sheet, Alzheimer Association Genetic Testing Guide, Alzheimer's Society Guide to Dementia and genes, cautionary tale.

If you're like me, you want as much information as possible to make the best decisions over your lifetime. Three of my grandparents had dementia, so I want to better understand my risk factors. There's no surefire way of preventing dementia, but that doesn't mean there's nothing to be done. On 23andMe, here's an example of the report you'll receive after your testing.

I Recommend 23andMe, Here's Why:

- **FDA Regulated:** Regulations limit what 23andMe is allowed to extrapolate from your genetic data, but in this realm that is a plus. The reports they provide are scientifically rock-solid, and they go in-depth to explain to you what exactly the consequences are of each result. They sequence over 600,000 single nucleotide polymorphisms (SNPs, "snips"), but only a fraction have enough research backing for 23andMe to offer a report. However…
- **Downloadable Data:** You own your data, which means you can download it for analysis elsewhere. There is a whole industry of companies and software programs (listed below) built to provide different reports from the genetic data sequenced by 23andMe, Ancestry, or others. Regardless of who you choose, make sure you can download your data and make sure that these third party vendors think the data from your tester is reliable. In my research, it seems like 23andMe is the most dependable service without spending $500+.
- **Seemingly Trustworthy:** Watch DNA Testing and Privacy (Behind the scenes at the 23andMe Lab).
- **Other Testing Companies:** Ancestry, Helix, Genos, FamilyTreeDNA, DNA.land, Genes for Good, MyHeritage, LivingDNA

What to Expect in the Testing Process:



- You'll get a kit the mail with a saliva tube and return label. My recommendation is to fill the saliva tube, package it up, and send it back right away. You'll be waiting long enough in the other steps, so you'll want to get this done quickly.
- About 6-8 weeks later, results will be posted to your account.
- Read through to see the highlights of the report and your ApoE value quickly. You've already done the research and should know what exactly the result means for you. The whole report is a lot of information at once, so you shouldn't feel the need to dive too deep right away.
- Keep revisiting your report every couple of days for the next few weeks. Read the full reports of any important results, because you need all the provided context to have a proper perspective on risks.
- If you're curious to know more, download your raw data and head over to one of these services: Promethease, Dash Genomics, Found My Fitness for additional analysis 23andMe cannot legally provide given FDA regulations. This step is probably best done with a genetic counselor.
- Bonus: Answer as many survey questions as you have time for in 23andMe, because the more people that answer questions, the more everyone will gain for their reports.

Here's a good starting place if you want to know more about genetics.

KNOWING ALZ

About the Newsletter

Feedback and Questions are Greatly Appreciated

Please feel free to email me at steve@knowingalz.com or fill out this form with any questions or feedback you may have. My goal is to help make your experience learning about and dealing with Alzheimer's or other dementias easier, so let me know how I can do that better.

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The "Origin Story"

Having loved three grandparents with dementia, I know just caring for and about them can take up all the extra space in your life. It takes up time, mental space, and sometimes even physical space (I know some of you have a basement full of a loved one's things). Putting even more effort into dementia is just simply the last thing on your mind. It's because of this that even after a decade of having loved ones suffer from dementia, I knew very little about Alzheimer's or dementia beyond seeing its first-hand effects. After my third grandparent passed away with dementia, I threw myself into learning everything I could about the disease. All of a sudden, I was neck-deep in the thousands of resources out there. I was reading news that I barely understood and didn't know where to go to get good answers to my questions. Many hundreds of hours of research later, I'm still finding new things every day. The amount of resources and attention Alzheimer's Disease (AD) and dementia is getting is awesome, but it's also overwhelming. It's too late to help my grandparents, but I can still help my parents, myself and now you. My goal is simple: reduce the amount of time it takes to learn what you want to know about Alzheimer's and dementia.

Here's how:

- **News:** All the Alzheimer's- and dementia-related news is now gathered in one place. I've coded a program that aggregates news stories on Alzheimer's and dementia from across the web. I review the articles daily and post links to the best ones. Occasionally, I'll provide a summary or review of a study that I think didn't get good coverage. BUT, I think reading news on AD every day or every week isn't the best way to learn.
- **Monthly Newsletter:** There's a lot of news, but not a lot that you NEED to read. The newsletter gives you the top news items from the month, prioritizing prevention and caregiving research. It includes deep dives into broader topics around those news items, guides on important non-news topics, and anything else I think is interesting or worth knowing from the month. The purpose is to provide a single document with a lot of value in a short amount of time, without you having to do anything more than open your email. For the overachievers, it also has a lot of further reading suggestions. **Subscribe here if you haven't already.**
- **Questions Answered:** One of the biggest frustrations when trying to understand Alzheimer's is finding answers to your questions. The sheer number of resources out there means there are often many different answers to one question, or the answer is buried deep in a forum somewhere. Instead of wasting your time, fill out this form, and I'll help you find what you're looking for.