DOCUMENT SUMMARY This research paper from the journal *AGING* investigates the relationship between various lifestyle factors and the **epigenetic clock**, a molecular biomarker of aging. Using data from over 4,500 participants, the study analyzes two types of **epigenetic age acceleration**: Intrinsic (**IEAA**) and Extrinsic (**EEAA**). The authors find that slower **epigenetic aging** is significantly associated with a diet rich in fish and vegetables, moderate alcohol consumption, higher education, and physical activity. Conversely, faster aging is linked to obesity and metabolic syndrome, with longitudinal data showing that an increase in BMI over time accelerates both aging measures.

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METADATA Category: RESEARCH Type: report Relevance: Supporting Update Frequency: Static Tags: #epigenetic_clock #aging #dna_methylation #lifestyle_factors #diet #nutrition #exercise #alcohol #obesity #metabolic_syndrome #EEAA #IEAA Related Docs: `wattacheril_2023_research_review_epigenomics_environmental_influences_disease.md`. This paper provides a practical application of epigenomic measurement and can be linked to content on nutrition, exercise, and the management of metabolic conditions. Supersedes: N/A

FORMATTED CONTENT

ABSTRACT

Behavioral and lifestyle factors have been shown to relate to a number of health-related outcomes, yet there is a need for studies that examine their relationship to molecular aging rates. Toward this end, we use recent

epigenetic biomarkers of age that have previously been shown to predict all-cause mortality, chronic conditions and age-related functional decline. We analyze cross-sectional data from 4,173 postmenopausal female participants from the Women's Health Initiative, as well as 402 male and female participants from the Italian cohort study, Invecchiare nel Chianti.

Extrinsic epigenetic age acceleration (EEAA) exhibits significant associations with fish intake, moderate alcohol consumption, education, BMI, and blood carotenoid levels—an indicator of fruit and vegetable consumption, whereas **intrinsic epigenetic age acceleration (IEAA)** is associated with poultry intake and BMI. Both

EEAA and **IEAA** were also found to relate to indicators of metabolic syndrome, which appear to mediate their associations with BMI. Metformin—the first-line medication for the treatment of type 2 diabetes—does not delay

epigenetic aging in this observational study. Finally, longitudinal data suggests that an increase in BMI is associated with increase in both

EEAA and **IEAA**. Overall, the

epigenetic age analysis of blood confirms the conventional wisdom regarding the benefits of eating a high plant diet with lean meats, moderate alcohol consumption, physical activity, and education, as well as the health risks of obesity and metabolic syndrome.

INTRODUCTION

While lifestyle factors like diet, physical activity, and education are strongly linked to health outcomes, it is unclear whether they directly influence aging on a molecular level. A promising biomarker for investigating this is the "

epigenetic clock". This tool uses

DNA methylation (DNAm) levels at hundreds of specific sites (CpGs) in the genome to produce a highly accurate estimate of age, referred to as "**DNAm age**".

Crucially, this

epigenetic age appears to be a biomarker of *biological* age, as it has been found to be predictive of all-cause mortality, frailty, cancer, and cognitive decline. However, little is known about the relationship between epigenetic aging rates and lifestyle factors. This study investigates these relationships using blood

DNA methylation data from two large cohorts: the Women's Health Initiative (WHI) and the Invecchiare nel Chianti (InCHIANTI) study.

RESULTS

Two Measures of Epigenetic Age Acceleration

The study uses two distinct measures of

epigenetic age acceleration, which is the epigenetic age left unexplained by chronological age.

- **Intrinsic Epigenetic Age Acceleration (IEAA):** This measure is adjusted for both chronological age and blood cell composition. It is interpreted as a measure of "cell-intrinsic" aging, independent of changes in the immune system.
- **Extrinsic Epigenetic Age Acceleration (EEAA):** This measure integrates known age-related changes in blood cell counts into the age estimate. It is interpreted as a measure of immune system aging.

For both measures, a positive value indicates accelerated

epigenetic aging—the individual's blood is biologically older than expected.

Key Associations with Epigenetic Age Acceleration

In an analysis of over 4,000 women, the study found significant correlations between lifestyle factors and the two aging measures.

Factors Associated with Slower Extrinsic Aging (Lower EEAA):

- Greater intake of
  fish
- **Moderate alcohol consumption**

- Higher **education** level
- Higher plasma levels of **carotenoids** (a marker for fruit and vegetable intake)
- More **exercise**
- Lower **BMI** and waist-to-hip ratio
- Lower levels of C-reactive protein (**CRP**), insulin, glucose, and triglycerides
- Higher levels of HDL cholesterol

Factors Associated with Slower Intrinsic Aging (Lower IEAA):

- Greater intake of **poultry**
- Lower **BMI**
- Lower levels of **CRP**, insulin, glucose, and triglycerides

Notably, both

EEAA and **IEAA** were positively associated with the number of symptoms of **metabolic syndrome**. The inclusion of metabolic biomarkers in statistical models significantly diminished the effect of BMI, suggesting that inflammation and metabolic dysregulation may partly explain the link between obesity and accelerated epigenetic aging.

A longitudinal analysis of participants with repeat measurements revealed that an

increase in BMI over time was significantly associated with an **increase in both EEAA and IEAA**.

Pictorial Summary of Main Findings

(Textual summary of Figure 4 from the source document)

- **Extrinsic Epigenetic Age (Immune System Aging):**
  - **Anti-Aging Factors (↓ EEAA):** Fish, Fruits & vegetables, Moderate alcohol, Education & income, Exercise.
  - **Pro-Aging Factors (↑ EEAA):** Insulin & glucose, C-reactive protein, BMI & Waist-to-hip ratio, Triglycerides, Systolic blood pressure, Low HDL cholesterol.
- **Intrinsic Epigenetic Age (Cell-Intrinsic Aging):**
  - **Anti-Aging Factors (↓ IEAA):** Poultry.
  - **Pro-Aging Factors (↑ IEAA):** Insulin & glucose, C-reactive protein, BMI & Waist-to-hip ratio, Triglycerides, Systolic blood pressure, Low HDL cholesterol.

Metformin and Epigenetic Aging

The study investigated the effect of

metformin, a widely used medication for type 2 diabetes. In this observational analysis, women currently taking

metformin did not show slower epigenetic aging compared to those who never took it. The authors note this null result may be due to the limitations of an observational study or lack of statistical power.

DISCUSSION

> To our knowledge, this is the first study to examine associations between lifestyle factors and measures of
>
> **epigenetic age acceleration** in blood. The results are consistent with current dietary guidelines, reflecting benefits associated with higher intake of fish, poultry, and fruits and vegetables.

The weak correlations likely reflect that a significant portion of aging variance (around 40%) is due to genetic factors. Still, education, physical activity, and low BMI were associated with slower extrinsic aging.

EEAA (Immune System Aging), which incorporates changes in blood cell counts, was associated with cardiometabolic biomarkers and dietary factors known for their anti-inflammatory effects.

- The benefit of **fish intake** may be mediated by the anti-inflammatory properties of omega-3 fatty acids. This is supported by the finding that **CRP** (a marker of inflammation) was a highly significant explanatory biomarker of **EEAA**.
- **Moderate alcohol consumption**, particularly wine, was also negatively associated with **EEAA**, which may relate to the anti-inflammatory effects of light drinking.
- **Blood carotenoid levels**, a quantitative surrogate for fruit and vegetable intake, were significantly associated with lower **EEAA**, likely reflecting the anti-inflammatory and cardiometabolic benefits of these foods.

IEAA (Cell-Intrinsic Aging) showed fewer associations, consistent with the hypothesis that it reflects a more stable process under stronger genetic control. However, it was still positively associated with BMI and metabolic syndrome characteristics, suggesting it tracks metabolic aging.

CONCLUSIONS

The study's large sample size provides sufficient power for its main conclusion: diet and lifestyle have a weak but detectable effect on

epigenetic aging rates in blood.

- **EEAA** (immune system aging) appears closely linked to metabolic health and is sensitive to variations in environment and lifestyle.
- **IEAA** (cell-intrinsic aging) is more stable but is still associated with metabolic health and responds to changes in obesity over time.

Overall, our results are consistent with previous literature supporting the protective effects of fish, poultry and alcohol consumption, exercise, education, as well as the risk of obesity and dyslipidemia.