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 cross-sectional data from over 4,500 participants in the Women's Health Initiative (WHI) and the Invecchiare nel Chianti (InCHIANTI) study, the authors analyze two types of **epigenetic age acceleration**: Intrinsic (**IEAA**) and Extrinsic (**EEAA**). The study finds that slower **epigenetic aging** is significantly associated with a diet rich in fish and vegetables, moderate alcohol consumption, higher education, and physical activity, while faster aging is linked to obesity and metabolic syndrome.

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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 an 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

Numerous lifestyle factors are linked to health, including diet, physical activity, moderate alcohol consumption, and education. Diet is a modifiable behavior that can mitigate chronic disease risk, with components like whole grains, fish, fruits, and vegetables helping to reduce systemic inflammation. However, despite strong evidence connecting these factors to health outcomes, it remains unclear if they directly influence aging on a molecular level.

A promising tool for this investigation is the "

epigenetic clock". This biomarker uses

DNA methylation (DNAm) levels at specific sites in the genome to produce a highly accurate estimate of age. This "

DNAm age" has been shown to be a powerful predictor of all-cause mortality, frailty, and cognitive decline, suggesting it captures aspects of biological, not just chronological, age. While the

epigenetic clock has been applied to study numerous conditions like Alzheimer's, obesity, and lifetime stress, little is known about its relationship with common 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

This study uses two distinct measures of **epigenetic age acceleration**:

- **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 that is 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 before adjusting for chronological age. It is interpreted as a measure of immune system aging.

A positive value for either measure indicates accelerated

epigenetic aging—that an individual's blood is biologically older than expected for their chronological age.

Key Associations with Epigenetic Age Acceleration

In the primary analysis of 4,173 women from the WHI, numerous lifestyle and metabolic factors were correlated with 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, **metabolic syndrome** was a key factor. Higher

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

Longitudinal data from a subset of participants also revealed that an

increase in BMI over a 3-year period was significantly associated with an **increase in both EEAA and IEAA**.

Metformin and Epigenetic Aging

Given the link between epigenetic aging and markers of diabetes, the study investigated the effect of

metformin. In this observational analysis, women currently taking

metformin did not show slower epigenetic aging compared to those who never took it or would take it in the future. The authors note this null result could 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 dietary results are consistent with current guidelines, reflecting the health benefits of higher intake of fish, poultry, and fruits and vegetables.

The weak correlations observed likely reflect that a large proportion of variance in aging rates (around 40%) is explained by genetic factors. Still, education, physical activity, and low BMI were all associated with slower extrinsic aging.

EEAA, Inflammation, and Metabolic Functioning

EEAA incorporates aspects of immune system aging and was associated with numerous cardiometabolic biomarkers and dietary factors known to have anti-inflammatory effects.

- **Fish Intake:** The negative association between fish consumption and **EEAA** is consistent with studies showing fish is protective against age-related diseases. This may be mediated by the anti-inflammatory properties of omega-3 fatty acids. The fact that **CRP**—a marker of inflammation—was the most significant biomarker of **EEAA** supports this hypothesis.
- **Alcohol Consumption:** Moderate alcohol intake was negatively associated with **EEAA**, which is consistent with prospective studies identifying it as a protective factor against all-cause mortality. The effect appears to be driven by wine consumption and may be related to the anti-inflammatory effects of light alcohol use.
- **Fruits and Vegetables:** While self-reported intake had a weak association, blood **carotenoid levels**—a more objective measure—were significantly associated with lower **EEAA**.

Intrinsic Epigenetic Aging (IEAA) and Metabolic Health

IEAA showed fewer associations, consistent with the hypothesis that it reflects a more stable, cell-intrinsic aging process that is under stronger genetic control. However, it was still positively associated with BMI and the number of metabolic syndrome characteristics, suggesting a role in tracking metabolic aging. The negative association with poultry intake was significant but the mechanism is unclear. The association between BMI and blood

IEAA is much weaker than what has been observed in liver tissue, suggesting that the link between risk factors and aging may be tissue-specific.

CONCLUSIONS

This large study provides evidence that diet and lifestyle have a weak but statistically significant effect on

epigenetic aging rates in blood.

- **EEAA**, as a measure of immune system aging, appears closely linked to metabolic health and is sensitive to variations in diet, alcohol use, exercise, and education.
- **IEAA**, representing 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.