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Abstract

Estimators of biological age (BA) – defined as the hypothetical underlying age of an organism – have attracted more and more attention in the last years, especially after the advent of new algorithms based on machine learning and genetic markers. While different aging clocks reportedly predict mortality in the general population, very little is known on their overlap. Here we review the evidence reported so far to support the existence of a partial overlap among different BA acceleration estimators, both from an epidemiological and a genetic perspective. On the epidemiological side, we review evidence supporting shared and independent influence on mortality risk of different aging clocks - including telomere length, brain, blood and epigenetic aging – and provide an overview of how an important exposure like diet may affect the different aging systems. On the genetic side, we apply linkage disequilibrium score regression analyses to support the existence of partly shared genomic overlap among these aging clocks. Through multivariate analysis of published genetic associations with these clocks, we also identified the most associated variants, genes, and pathways, which may affect common mechanisms underlying biological aging of different systems within the body. Based on our analyses, the most implicated pathways were involved in inflammation, lipid and carbohydrate metabolism, suggesting them as potential molecular targets for future anti-aging interventions. Overall, this review is meant as a contribution to the knowledge on the overlap of aging clocks, trying to clarify their shared biological basis and epidemiological implications.

1. Introduction

As the global population ages and average life expectancy increases, research on healthy aging has gained notable importance (Gialluisi et al., 2019). To this end, computing Biological Age (BA) – *i.e.* the actual underlying age of an organism – and its discrepancy with Chronological Age (Δage, a measure of BA acceleration; Figure 1), allows to define biological aging trajectories and may help identifying ways to modify these trajectories through a personalized approach. To reach this "precision healthy aging" goal, it is important to develop reliable BA estimators (James H. Cole et al., 2018), which have been reported as useful public health markers in diverse populations (see below). So far, many of these estimators were based on simple regression methods, where BA is a function of one or few bodily measures, e.g. circulating blood markers (Klemera and Doubal, 2006) or spirometry measures (Yamaguchi et al., 2012). More recently machine learning approaches for the estimation of BA have been developed (J. H. Cole et al., 2018; Polina Mamoshina et al., 2016; Evgeny Putin et al., 2016), which showed higher accuracy in predicting chronological age (Pearson's r>0.9). However, these algorithms are highly population-specific (Gialluisi et al., 2019; P Mamoshina et al., 2018). Moreover, although the resulting BA acceleration is significantly associated with the main determinants of disease like lifestyles (*e.g.* diet, smoking, drinking habits) and socioeconomic factors (education, household income, housing and occupational status), these explain less than 50% of the total variance in Δage, suggesting that genetic factors might influence interindividual variation in biological aging (Gialluisi et al., 2021). In spite of these recent developments, the overlap among the different BA markers developed so far is largely unexplored (X. Li et al., 2020),

as the underlying biology and genetic basis of BA acceleration. In particular, it is unclear whether the same genes or pathways underly variation in biological aging of different systems within the body, a hypothesis never investigated before. These open issues warrant further research on the reciprocal relationships among BA acceleration markers and on their combined influence on healthy aging, possibly analyzing additional estimators and clinical events and investigating their biological bases through multi-omic approaches.

The present review will focus on the epidemiological and biological overlap across different estimators of biological aging – *i.e.* parameters indicating the difference between biological and chronological age based on different sources of biomedical data – also known as aging clocks. First, we will provide a brief overview of the different clocks available and their properties as public health screening tools, then we will focus on their epidemiological overlap, especially on how they jointly predict mortality risk and how they relate to dietary patterns, one of the most important exposures affecting healthy aging. Given the relatively low number of studies, the few evidence collected so far and the heterogeneity of studies in terms of population setting, statistical analyses and BA acceleration markers tested, we opted for a narrative review approach, analyzing all the evidence in favor or against the existence of an overlap of the markers analyzed until June 2021.

Finally, through bioinformatic elaboration of genetic associations with published aging clocks, we will focus our attention on genes and molecular pathways underlying different aging clocks, trying to get biological insights into their common variance.

2. Aging clocks from biomedical data: an overview

To estimate biological aging, a number of methods have been developed based on different sources of biomedical and molecular data. These include organ-specific measures, such as spirometry (Yamaguchi et al., 2012), structural neuroimaging (Cole and Franke, 2017), electroencephalography (Sun et al., 2019), photographic images of the human skin (Bobrov et al., 2018), or blood biomarkers (Klemera and Doubal, 2006; P Mamoshina et al., 2018; E Putin et al., 2016), the latter conceived as markers of organismal BA. In addition to these instrumental data-based biomarkers, other parameters based on molecular data have been developed in the last few years (Jylhävä et al., 2017a).

Biological age estimates were mostly based on classical linear regression methods, in which age is a function of one or few bodily measures (Klemera and Doubal, 2006). However, supervised machine learning algorithms have been recently developed (Bobrov et al., 2018; J. H. Cole et al., 2017b; P Mamoshina et al., 2018; E Putin et al., 2016; Sun et al., 2019), showing very good accuracy in predicting chronological age (Gialluisi et al., 2019). These methods consist of a group of algorithms which, based on a number of input variables (or features), learn to predict a known (either categorical or continuous) outcome, usually called label. This is accomplished through a phase in which the algorithm strains to predict the label as accurately as possible in a training set, and a phase where the accuracy and generalizability of the model is tested in an independent dataset, the test set. The advantage of these algorithms is that they allow to model complex relationships of several features with the label, taking into account also non-linear relationships, at variance with classical statistical methods (Gialluisi et al., 2019). The most prominent example of such methods is represented

by Deep Neural Networks, algorithms which typically present an input layer, a variable number of hidden "decision" layers and an output layer (Ching et al., 2018). These algorithms are capable of capturing hidden underlying features and learning complex representations of highly multidimensional data (P Mamoshina et al., 2016), and automatically select features that are most relevant to predictions (Zhavoronkov and Mamoshina, 2019). This way, for each vector of input features provided (i.e. the blood test of a given subject), the algorithm is able to return an accurately predicted age value (Zhavoronkov et al., 2019).

2.1 Telomere length

Among all biological aging clocks developed so far, the first molecular marker to be discovered and deeply investigated to predict biological aging was telomere length (TL). Telomeres are nucleo-protein complexes located at the end of all eukaryotic chromosomes, which tend to shorten at each cell division within somatic cells (Harley et al., 1990). For this reason, TL is often considered an ageing biomarker (Zglinicki and Martin-Ruiz, 2005). Commonly measured in leukocytes, this has been associated with a number of environmental factors, including socio-economic status, smoking, oxidative and psychological stress (James H. Cole et al., 2018), as well as with an increased risk of clinical events and all-cause mortality (Cawthon et al., 2003; Wilbourn et al., 2018). Many of these associations however are not as robust (Sanders and Newman, 2013) and the correlation with chronological age remains quite modest as compared to other aging clocks (Pearson's $r = -0.3$) (Jylhävä et al., 2017b; Müezzinler et al., 2013). For these reasons, in the last decade

the focus of investigation in the field moved onto more accurate and powerful clocks (see below).

2.2 *Predictors of biological aging based on DNA methylation*

In 2013, two independent DNA methylation-based predictors were developed, also known as "DNAm age" or "epigenetic clocks" (Hannum et al., 2013; Horvath, 2013). DNA methylation is the addition of a methyl group to cytosine residues in cytosine-phosphate-guanine dinucleotides across the genome (known as CpG sites). These predictors are based on the assumption that cells undergo changes in DNA methylation patterns across the genome as subjects age (James H. Cole et al., 2018). These measures represent an important milestone in the field and have represented for years one of the most robust BA estimator available, showing high correlations (Person's r 0.96 for Horvath and 0.91 for Hannum clock) and small Mean Absolute Errors (MAE 3.6 and 4.9 years) with chronological age, along with high predictivity of incident mortality risk (Hannum et al., 2013; Horvath, 2013; Marioni et al., 2015). While similar in methodology - since both are based on penalized regression models aimed at predicting chronological age as accurately as possible starting from CpG sites - these two clocks are indeed only moderately correlated (Lu et al., 2018) and somewhat different, with only six overlapping CpG sites (Jylhävä et al., 2017a). Indeed, the Hannum's clock, based on 71 CpGs measured in peripheral blood cells, is strongly dependent on the composition of the blood sample, is thought to track aspects of immuno-senescence, and is also known as *extrinsic* epigenetic age acceleration. On the contrary, Horvath's clock, based on 353 CpGs from 51 different human tissues/cell types, is instead

independent of age-related changes in blood cell composition and is thought to tag an intrinsic cell aging process conserved across different cell types, hence it is defined as *intrinsic* epigenetic age acceleration (Gibson et al., 2019).

More recently, additional epigenetic clocks have been proposed, either incorporating white blood cell composition into the DNAm age metrics (Chen et al., 2016) or using different methods and CpG methylation data sources to estimate BA, *e.g*. incorporating information on morbidity and mortality risk (*e.g.,* smoking, plasma protein levels, white blood cell counts), and chronological age itself. The most prominent examples of these "second generation" DNAm age acceleration estimators are represented by GrimAge, a metric based on DNAm surrogate biomarkers for seven plasma proteins and smoking pack-years trained to best predict mortality (Lu et al., 2019), and by DNAmPhenoAge, a 513 CpG predictor trained on a measure that itself was trained on mortality, based on 42 circulating biomarkers and chronological age as input features (PhenoAge) (Levine et al., 2018). Both estimators further improved the prediction of mortality and of a variety of health-related metrics, morbidity and physical function (Chen et al., 2016; Levine et al., 2018; Lu et al., 2019).

2.3 Biological age acceleration based on blood biomarkers

In a pioneering study in the field of machine learning applied to aging markers, Putin and colleagues used anonymized blood biochemistry records from 62,419 subjects from the general Russian population to estimate BA through an ensemble of Deep Neural Networks based on 41 standardized blood markers and sex of subjects (Evgeny Putin et al., 2016). This showed the best performance in predicting BA, when compared to other algorithms, with a

standard coefficient of determination (R^2, the fraction of variance in chronological age explained by the model) of 0.83, a Pearson correlation of 0.91, and a MAE of 5.55 years (Evgeny Putin et al., 2016). Mamoshina and colleagues (Polina Mamoshina et al., 2018) exploited these models to train similar algorithms on population-specific datasets, using samples from three ethnically different populations, namely South Koreans (N=65,760), Eastern Europeans (N=55,920) and Canadians (N=20,699). Algorithms were trained within each population and tested on independent test sets of the three populations available, using sex and 19 blood markers. These models showed good predictivity of chronological age when they were trained and tested on the same population (R^2 0.49-0.69, and MAE 5.59- 6.36 years). However, accuracy dropped when the models were tested on a population other than that of the training set, suggesting a high population-specificity (Polina Mamoshina et al., 2018). The aging acceleration (Δage) resulting from the above-mentioned BA estimate was associated with incident all-cause mortality in two North-American cohorts (Polina Mamoshina et al., 2018). This finding was replicated with a similar blood aging marker in an Italian population cohort, the Moli-sani study (N=4,772). Associations were observed not only with mortality, but also with hospitalization risk, for all and specific causes, as well as with measures of mental and physical wellbeing (Gialluisi et al., 2021). Deep learning architectures were recently proposed to estimate inflammatory age (iAGE), based on 50 circulating cytokines, chemokines and growth factors. In centenarians, iAge was on average 40 years lower than their corresponding chronological age, and was significantly associated with both multi-morbidity and immune-senescence (Sayed et al., 2021).

Proportional hazards mortality models have also been increasingly used in BA estimation. As a good aging clock should first estimate mortality risk as accurately as possible (Pyrkov and Fedichev, 2019), different clocks have been developed to maximize the accuracy of these estimation. Prominent examples in the field include MORTAL-bioage, based on the prediction of mortality risk by blood markers and chronological age through Cox models, and re-calibration of the risk in years (Pyrkov and Fedichev, 2019), and Phenotypic Age (or PhenoAge), based on modelling mortality through the application of Gompertz models to blood markers and age (Liu et al., 2018). The latter prediction was then used to train the DNAmPhenoAge (Levine et al., 2018) (see above). Thus, training biological aging prediction using biological rather than chronological age as a label, could further improve the efficacy of aging clocks as public health markers (Levine et al., 2018).

2.4 Brain-predicted age acceleration

Another accurate BA estimation method is based on the use of brain imaging features, either coming from structural Magnetic Resonance Imaging (MRI)(J. H. Cole et al., 2017b; James H. Cole et al., 2018) or from multimodal neuroimaging sources (Cole, 2020).

The most prominent example in the field is represented by brainPAD, a predicted brain aging clock where the BA measure was derived through Gaussian Process Regression applied to gray and white matter structural features (J. H. Cole et al., 2018, 2017c). This measure significantly predicted mortality in the aging Lothian Birth Cohort 1936 (mean (SD) age 73 (1) years), with a predictive capacity higher than other "molecular" clocks, like telomere and Horvath's epigenetic clock (J. H. Cole et al., 2018). This measure was robust to

the type of MRI scanner used (with high intraclass correlation between 1.5 T and 3T), as well as to the use of raw– rather than segmented – neuroimaging data, showing comparable accuracy (J. H. Cole et al., 2017b). More recently, a multi-modal estimation algorithm based on Lasso regression including T1-weigthed structural MRI, T2- fluid-attenuated inversion recovery (FLAIR), susceptibility-weighted imaging (SWI), diffusion-MRI, task functional MRI, and resting-state functional MRI, revealed an even better accuracy in the prediction of brain age (Pearson's r = 0.78 and MAE = 3.55 years) (Cole, 2020).

Overall, the above-mentioned evidence supports BA acceleration as a robust marker of public health, which may be used to screen health status and mortality risk in populations, through the use of different health records. However, the main hindrance to a wide use of some of these estimators like epigenetic clocks and brainPAD is represented by the costs implied to get their source data. Indeed, the costs of genome-wide methylation arrays and neuroimaging scans are yet too high for a potential spread application in public health. Last, but not least, a number of other molecular markers have been developed to predict aging in the field, including those based on protein glycosylation, lipidomic, transcriptomic, metabolomic and proteomic data (James H. Cole et al., 2018; Jylhävä et al., 2017b). However, these markers showed a worse performance than the predictors mentioned above and have not been tested for overlap with other aging clocks, thus, they will not be further discussed.

3. Epidemiological overlap of aging clocks

3.1 Nutrition as a modulator of Biological Age: common pathways across different metrics/biomarkers

The identification of the most powerful and common determinants of biological age is also necessary to develop and validate interventions that could slow down or counteract the aging process and its associated pathologies. A potential strategy to impact on aging is to intervene on lifestyle factors, such as diet or physical activity. Nutrition represents one of the most promising approaches to prolong healthspan and achieve longevity (Ekmekcioglu, 2020). A growing amount of data reveals that nutritional interventions such as calorie restriction (CR), intermittent fasting (IF) and Mediterranean Diet (MedDiet) can influence the health status of subjects (Dato et al., 2016; Heiss et al., 2018; Longo et al., 2015; Shlisky et al., 2017; Wahl et al., 2016; Xia et al., 2017), thus affecting biological age.

3.1.1 Mediterranean Diet

MedDiet is rich in plant-based foods such as vegetables, fruits, olive oil, legumes, grains, nuts, seeds and also comprises a high intake of fish and a moderate intake of red wine around meal times. Conversely, red meat, high-fat dairy products, and highly processed foods are consumed infrequently (Bach-Faig et al., 2011). This dietary pattern contains an abundance of bioactive compounds, including a range of vitamins and minerals, polyphenols, fibers, nitrate and mono-unsaturated and poly-unsaturated fatty acids (Tosti et al., 2018), many of which have been shown, individually or in combination, to elicit beneficial effects (Hernández and Rentero, 2018; Martucci et al., 2017) on cardiovascular risk (Estruch et al., 2018, 2006), blood pressure (Jennings et al., 2019; Mitjavila et al., 2013), cancer (Ostan et al., 2015), cognitive function (Marseglia et al., 2018), inflammation (Martínez-González et al., 2015; Santoro et al., 2020) or frailty status (Kojima et al., 2018), also mediated

by the gut microbiota (Ghosh et al., 2020). A recent systematic review and meta-analysis supported a strong association of high adherence to MedDiet with better physical performance (walking speed) and global cognitive function, as well as with a lower longitudinal decline of the latter in dementia-free adults (Coelho-Júnior et al., 2021). Overall, MedDiet is considered to be one of the most recognized diets for disease prevention and healthy aging (Soltani et al., 2019; Trichopoulou et al., 2005), partially due to its demonstrated anti-inflammatory and antioxidative properties which may impact on several hallmarks of aging (Crous-Bou et al., 2019; Esposito et al., 2021; Shannon et al., 2021). Telomeric DNA is highly susceptible to oxidative damage and dietary habits may have an impact on telomere attrition rates through the mediation of oxidative stress and chronic inflammation. Although contrasting data are present (Davinelli et al., 2019; Meinilä et al., 2019), the majority of the studies investigating the relationship between MedDiet and both leukocytes TL and telomerase activity reported a positive association (Boccardi et al., 2013; Crous-Bou et al., 2014; García-Calzón et al., 2015; Gu et al., 2015; Shivappa et al., 2017). An observational study of 217 old people from the South of Italy reported that individuals with high adherence to MedDiet had longer telomeres and higher telomerase activity compared with those with medium or low MedDiet adherence (Boccardi et al., 2013). Higher plasma concentrations of monounsaturated fatty acids were associated with greater leukocyte TL in those carrying the CC variant of the telomerase gene (*TERC*) polymorphism rs12696304 (Gomez-Delgado et al., 2018). In the Prevención con Dieta Mediterránea (PREDIMED) Study of middle-aged people at higher cardiovascular risk, 5 years intervention with a MedDiet supplemented with additional nuts was associated with greater risk of telomere shortening

when compared with the low-fat control diet. However, intervention with MedDiet plus additional extra-virgin olive oil did not influence telomere length when compared with the low-fat control diet (García-Calzón et al., 2016). Interestingly, a recent meta-analysis reported a positive association between adherence to MedDiet and TL in the whole sample set and in women only (Canudas et al., 2020). Similarly, another study observed longer telomeres in women with greater adherence to MedDiet (Crous-Bou et al., 2014) and in another analysis of the PREDIMED cohort, higher adherence to MedDiet at baseline was linked with higher TL only in female participants (García-Calzón et al., 2016).

Nutrition influences the ageing trajectory and the risk of all common age-related diseases also by epigenetic processes (Park et al., 2017). Whole genome DNA hypomethylation occurs during ageing and is associated with an increased risk of several cancers and cardiovascular events (Muka et al., 2016), possibly as a consequence of greater genomic instability (Cardelli, 2018). Nutritional interventions, known as "epigenetic diets", also represent a promising approach to positively counteract the epigenetic changes associated with ageing and promote the health for older adults (Bacalini et al., 2014). MedDiet might constitute a palatable and readily available epigenetic diet.

A study reported that young healthy women with a low consumption of fruit (low MedDiet adherence) had 3.7 times increase of genome hypomethylation in blood leukocytes than women with a higher consumption. A similar effect was seen in those women with lower folate intake (Agodi et al., 2015). In the PREDIMED study, Arpon et al. (Arpón et al., 2016) observed that the methylation status in peripheral blood mononuclear cells of eight genes

related to inflammation and immunocompetence, including *EEF2*, *COL18A1*, *IL4I1*, *LEPR*, *PLAGL1*, *IFRD1*, *MAP-KAPK2* and *PPARGC1B*, correlated with adherence to MedDiet.

DNAm age, the pattern of DNA methylation used to calculate the epigenetic clock, is influenced by lifestyle factors, including diet (Quach et al., 2017). A pilot study conducted within the NU-AGE project (Berendsen et al., 2014; Santoro et al., 2014), used Horvath's Clock to estimate DNAm age before and after intervention with a MedDiet for 1 year in old Italian and Polish participants (65–79 years). Results suggested that MedDiet intervention may promote epigenetic rejuvenation in elders but the effect is dependent on several individual-specific factors including sex and country of origin (Gensous et al., 2020). DNAmPhenoAge is also modulated by dietary habits, with a higher consumption of fruits and vegetables being associated with lower values of epigenetic age (Levine et al., 2018).

A deep learning blood based biomarker of biological aging recently showed negative associations with both high adherence to MedDiet (Gialluisi et al., 2021) and with dietary content of polyphenols (Esposito et al., 2021). Moreover, high adherence to MedDiet diet showed significant improvements in global cognition and episodic memory compared to those older adults with lower adherence, suggesting that MedDiet could slow down age-related cognitive decline (Marseglia et al., 2018). Nutritional epidemiology has suggested a protective role of healthy diets and of several candidate nutrients for brain aging outcomes. Existing evidence suggests that some nutrients or food ingredients, in particular specific vitamins, flavonoids and long chain ω-3 fatty acids have a potential to beneficially affect cognitive function (Flanagan et al., 2020) by slowing down neuroinflammation and oxidative stress.

Overall, the available evidence suggests that higher adherence to a MedDiet pattern may improve cognitive function and reduce blood aging, telomere attrition and changes in epigenetic markers and molecules, although the latter beneficial effects may be confined to specific population sub-groups.

3.1.2 Calorie Restriction

The reduction of caloric intake (by 10% to 40%) without causing malnutrition – also known as caloric restriction - has proven to be by far the most effective intervention that can extend the maximum lifespan in a wide range of organisms including yeast, nematodes, flies, and rodents (Liang et al., 2018). Interestingly, observations also demonstrated an effect on healthspan overlapping with a significant decrease in age-related diseases such as cardiovascular events, diabetes, neurodegenerative diseases and cancers (Balasubramanian et al., 2017; Colman et al., 2009; Fontana et al., 2010; Mattison et al., 2012). Centenarians, who represent the best model to study successful aging, share several health benefits with adults undergoing CR (Franceschi et al., 2018c). The beneficial effects of CR occur through a wide range of molecular mechanisms, largely overlapping with aging hallmarks, among which inflammation, oxidative stress and epigenetic factors have recently gained interest (Gensous et al., 2019). Although some studies exist on CR in humans such as the CALERIE study (Das et al., 2017), most of the studies regard animal models. In a rat model of diabetes, CR-treated rats compared with high-fat-diet rats increased telomerase activity without changes of telomere length and enhanced autophagy in heart tissue (Makino and Maeda, 2021)(Makino et al., 2015). In humans no clear evidence emerged that CR, as currently practiced in

humans, delays immune aging related to TL or T-cell immunosenescent markers (Tomiyama et al., 2017).

Epigenetic data on the effects of pure CR in humans are limited, as this intervention is difficult to implement in the long-run in humans. Two studies reported the results of epigenomic responses to a hypocaloric diet intervention, but no study has specifically evaluated the impact of CR on DNA methylation signatures of aging in humans (Bouchard et al., 2010; Milagro et al., 2011). A significant overlap between the genes that showed altered expression in response to CR and those whose methylation varies during aging has been reported (Ions et al., 2013).

Collectively, several studies reported that CR is protective against age-related DNA methylation changes in mammals in different tissues and organs like kidney (Kim et al., 2016), blood (Maegawa et al., 2017; Sziráki et al., 2018), liver (J. J. Cole et al., 2017; Hahn et al., 2017), hippocampus (Hadad et al., 2018), and cerebellum (Lardenoije et al., 2015).

Recently, according to age and tissue type it has been found that CR is responsible for a prevalent increase in DNA methylation levels of genes involved in the mitochondrial biogenesis (*Polg*, *Polg2*, *Tfam*, *Fis1*, and *Opa1*). Particularly, this increase was more pronounced when this diet was administered during adulthood and at old age (D'Aquila et al., 2020).

The remodeling of DNA methylation patterns associated with CR can target genomic regions associated with the development of age-related diseases. For example, in the kidney of old rats, CR was able to attenuate age-dependent methylation alterations in the promoters

of genes that are associated with inflammation, cancer, or diabetes (Kim et al., 2016), while in mouse liver, CR had a specific impact on genes involved in lipid metabolism-related pathways, resulting in the regulation of the lipid profile (with an attenuation of the age-associated increase in liver triglyceride content) (Hahn et al., 2017).

Important work has been recently carried out in animal models regarding the effect of CR on epigenetic clocks (Gensous et al., 2019; Xia et al., 2021). Animals treated with CR were significantly epigenetically younger than their untreated counterparts (Maegawa et al., 2017; Petkovich et al., 2017; Thompson et al., 2018; Wang et al., 2017) with only one exception (Meer et al., 2018).

Notably, disruption of brain energy metabolism with reduced glucose consumption, increased central insulin resistance, and impaired mitochondrial function have been linked to the mechanisms leading to neuroinflammatory and age-related neurodegenerative diseases (Cunnane et al., 2020; Zilberter and Zilberter, 2017). CR is also able to improve cognitive function in older people by counteracting inflammation (Fontana et al., 2021).

3.1.3 Intermitted Fasting

IF is a dietary pattern alternating between fasting and non-fasting periods. Specifically, the IF diet in a particular mouse strain extended both mean and maximal lifespans (Chung et al., 2013). Furthermore, IF lowered the occurrence of diabetes and levels of fasting glucose and insulin (Hsieh et al., 2005). These effects of IF are similar to those observed with CR (Chung et al., 2020). The beneficial results of IF on different cancers are also explained by

many research groups (Descamps et al., 2005). The observations in animals indicate that, owing to dietary intake reduction, IF could effectively regulate the number of risk factors and thereby prevent chronic diseases. Such modulatory effects of IF are similar to those of CR. Implementation of IF in humans has been proposed to prevent major risk factors for age-associated diseases (Varady and Hellerstein, 2007). To our knowledge, no study has evaluated the impact of intermittent fasting on telomere length and epigenetic signatures of aging.

There is a need of gaining insights into the precise molecular mechanisms of action of healthy dietary patterns as anti-aging strategies. It should be kept in mind that, in humans, nutritional interventions are context-dependent, relying on specific populations, gender or genetic factors. While some interventions can have beneficial effects in certain individuals, they could, at the same time, be detrimental in other groups. However, even if such heterogeneity exists the impact of nutrition on the different biological metrics seems to act by lowering levels of inflammation and oxidative stress and improving immune lipid and glucose metabolism by modulating the nutrient sensing pathways, autophagy and mitochondrial biogenesis (Figure 2).

3.2 Shared influence of biological aging on mortality

A handful of studies have been focused on the comparison of different BA markers, mostly analyzing few molecular and functional markers and reporting partial overlap in their influence on mortality risk and low to moderate reciprocal correlations, only partly

dependent on their shared variance with chronological age (J. H. Cole et al., 2018; Gao et al., 2019; Gialluisi et al., 2019; Kim et al., 2017; X. Li et al., 2020; Marioni et al., 2016; Murabito et al., 2018; Zhang et al., 2018). Marioni and colleagues (Marioni et al., 2016) were the first to investigate telomere length and epigenetic (Hannum) age acceleration jointly in the Lothian Birth Cohorts 1921 and 1936 (combined N>1,300). They observed weak, non-significant correlations between the two measures, which explained largely independent and complementary fractions of variance in chronological age in a combined cohort analysis (2.8% for telomere length, 34.5% for Hannum clock and 37.9% in joint models). The authors reported one SD increase in baseline Hannum age and TL were associated with a 25% increase and a 11% decrease in mortality risk, respectively, with the two estimators showing again independent influences (Marioni et al., 2016).

Kim et al. (Kim et al., 2017) found a frailty index based on 34 common health and functional impairment variables to outperform (Horvath) DNAm age acceleration in survival models predicting mortality risk in the Louisiana Healthy Aging Study cohort from US (N=262; 60-103 years). In particular, the association of the latter with mortality did not hold after adjustment for chronological age and leukocyte cell fractions. Moreover, when frailty and the DNAm age accelerator were included in the same model, only the former remained significant. This discrepancy was explained by the fact that frailty index assesses biological factors with a large effect on survival, whereas DNAmAge typically shows small effect sizes requiring larger samples to be detected (Kim et al., 2017). Zhang et al. (Zhang et al., 2018) developed a methylation-based mortality score based on aberrant methylation of 10 CpG sites in a Lasso regression model (MRscore), which was compared with the same frailty

index and DNAm age accelerator computed above, in >2,300 community-dwelling German adults (50-75 years) over 14 years of follow-up. They observed that both the methylation-based estimators were independently associated with frailty index, and all were associated with incident death risk. However, when the three indicators were included simultaneously in survival models, only associations of MRscore and frailty index persisted, with a 91% and 37% increase of mortality risk per SD increase, respectively. MRscore was further compared with telomere length and two other epigenetic clocks – DNAmPhenoAge and Horvath's age acceleration - in 534 males aged 55–85 years from the US Normative Aging Study (Gao et al., 2019). MRscore was associated with incident all-cause, cardiovascular and cancer mortality, outperforming TL, DNAmPhenoAge and Horvath's age acceleration. Interestingly, DNAmPhenoAge acceleration was the only aging biomarker that showed independent associations with all-cause and cardiovascular mortality along with MRscore, although with a lower accuracy (Gao et al., 2019).

Murabito and colleagues (Murabito et al., 2018) compared clinical, inflammatory, and DNAm age acceleration estimators in consecutive assessment of the Framingham Offspring cohort from US (from mean age 45±10 to 67±9 years). Specifically, they compared the Klemera-Dubal biological aging estimator based on different blood biomarkers (Klemera and Doubal, 2006), an inflammatory index based on circulating levels of acute phase reactants (chemokines, cytokines, selectins, and cell adhesion molecules), an *extrinsic* and an *intrinsic* alternative DNAm age acceleration. Increased blood, inflammatory, and extrinsic DNAm age acceleration were all independently associated with a 3-5% increase in the incident risk of all-cause mortality, while only blood and inflammatory indices were

associated with increased cardiovascular risk and only the former with increased cancer risk, in multivariable models. This supported a notable complementarity in predicting mortality and age-related disease risk for most of the clocks analyzed (Murabito et al., 2018).

In the Lothian Birth Cohort (N=669), Cole et al (J. H. Cole et al., 2018) reported brain age acceleration to predict mortality independently from DNAm (Horvath's) age acceleration, but not from telomere length, in a multivariable survival analysis including the three estimators. Specifically, one year increase in Δage was associated with a 6% and 7% increase in all-cause mortality for brain and DNAm age, respectively, with the model combining the two clocks showing a better accuracy than the single-clock models (J. H. Cole et al., 2018).

More recently, Li et al reported the most comprehensive study on the epidemiological overlap of different aging clocks, analyzing nine BA acceleration composite markers in a Swedish population-based cohort (N=845) and examining longitudinal trajectories, correlations, and associations with incident death risk over a 20 years follow-up (X. Li et al., 2020). Methods assessed included telomere length; a physiological age marker using a set of blood and urine biomarkers and physical examination data; a latent score of cognitive function including crystallized and fluid intelligence, memory, and perceptual speed abilities; a functional aging index based on sensory abilities, muscle strength, walking speed time and lung function; a frailty index based on self-reported health symptoms, diseases, disability, mood, and activities in daily living; and four types of epigenetic clock (Horvath, Hannum, DNAmPhenoAge, and GrimAge). All aging clocks except for TL were associated with mortality risk, independently of chronological age, with the strongest associations being reported for GrimAge and frailty index. In a multivariable survival model including

all the clocks tested, Horvath DNAmAge, DNAmGrimAge, and frailty index remained significantly predictive of all-cause mortality (X. Li et al., 2020). Interestingly, molecular and functional estimators were only weakly correlated, with TL showing the least correlation with all other aging biomarkers, in line with previous evidence from a cohort of ~1,000 middle-aged adults from the Dunedin Study (Belsky et al., 2018b). This further suggests that these markers tap into different domains of the aging process.

Overall, the evidence reported in this paragraph indicates that combining estimators based on different biomedical sources may help improve their efficacy as public health markers in the general population, through exploiting their complementarity in tagging different biological aging domains. However, these studies were mostly focused on few types of aging indices, comparing molecular and functional measures. When more types of clocks were available, these were compared within relatively low samples (usually ranging between ~200 and ~1,000 subjects). Moreover, the reviewed studies often analyzed all-cause mortality as an outcome, largely neglecting specific causes of deaths and other measures of interest in the healthy aging process, which is far to be defined as a simple predictor of mortality and longevity (X. Li et al., 2020).

4. Shared genetic underpinnings of aging clocks

Very little is known on the genomic and biological overlap among different BA acceleration parameters. Moderate to high heritability has been reported for both longevity (Giuliani et al., 2018) – a trait strictly related to biological aging – and BA acceleration based on telomere

length (0.44-0.86)(Broer et al., 2013; Njajou et al., 2007), DNA methylation (0.34-0.55) and brain features (≥0.5)(J. H. Cole et al., 2017b). Also, cross-time phenotypic correlations between epigenetic clocks at different time points is largely mediated by genetic factors (Jylhävä et al., 2019), in line with the evidence suggesting partial genetic basis for blood-based biological aging (Gialluisi et al., 2021). Still, only few studies attempted to identify genetic variants and genes influencing the aging clocks developed so far. Genome Wide Association Scans (GWAS) detected significant associations of common genetic variants with TL (C. Li et al., 2020), DNAm age (Gibson et al., 2019; Lu et al., 2018; Van Dongen et al., 2016) and brainPAD (B.A. Jonsson et al., 2019; Kaufmann et al., 2019), revealing further insights into their underlying biology. They provided genetic links between TL and DNAm age acceleration (Lu et al., 2018), supported strong genetic correlations of the latter with longevity and lifestyle/socioeconomic factors (Mccartney et al., 2020), and revealed a significant overlap between brainPAD in healthy individuals and polygenic risk of several neuropsychiatric and neurodegenerative disorders (Kaufmann et al., 2019). These findings make the search for shared genetic underpinnings of BA acceleration estimators very promising, even through "classical" tools like GWAS studies, as suggested elsewhere (Giuliani et al., 2018).

4.1 Previous GWAS on aging clocks

Different BA estimators – mostly based on molecular data – have been tested for association with Single Nucleotide Polymorphisms (SNPs) and small insertions/deletions (indels) throughout the genome, revealing genes robustly implicated in biological aging by

independent GWAS studies (Codd et al., 2013, 2010; Gibson et al., 2019; B. A. Jonsson et al., 2019; Kaufmann et al., 2019; Kuo et al., 2020b; Levy et al., 2010; C. Li et al., 2020; Lu et al., 2018; Mangino et al., 2012; Mccartney et al., 2020; Pooley et al., 2013; Prescott et al., 2011). The first and most investigated estimator in this sense was telomere length, for which robust associations have been reported at different genes like those involved in contrasting attrition and preserving telomeres. These include *TERC* (encoding telomerase RNA component, the RNA subunit of telomerase; 3q26.2), *TERT* (telomerase reverse transcriptase; 5p15.33), *OFBC1* (oligonucleotide/oligosaccharide-binding fold containing 1, a component of the telomere-binding complex implicated in telomere length regulation; 10q24.3), *NAF1* (nuclear assembly factor 1, required for assembly of H/ACA box small nucleolar RNA, which TERC belongs to; 4q32.2) and *RTEL1* (regulator of telomere elongation helicase 1; 20q13.3), among others (Codd et al., 2013, 2010; Levy et al., 2010; C. Li et al., 2020; Mangino et al., 2012; Mccartney et al., 2020; Pooley et al., 2013; Prescott et al., 2011).

Some of the above mentioned genes were later found associated with Horvath DNAm age, such as *TERT* and *OBFC1* (Lu et al., 2018). Prominently, variants lying within *TERT* showed genome-wide significant associations, although the direction of effect was not concordant with those previously observed with TL. This controversial pleiotropy was attenuated at the phenotypic level, where no associations between TL and Horvath's clock had been detected, suggesting a prominent influence of environmental factors on their reciprocal relationship (Lu et al., 2018). A larger study stemming from this later investigated both Horvath and Hannum DNAm age acceleration in ~13,500 individuals of European ancestry, revealing further genes implicated in epigenetic aging, involved in metabolism (e.g. *NHLRC1*, *TPMT*),

immune system pathways (e.g. *TRIM46, TRIM59, EDARADD*), or both (*UBE2D3, MANBA*), or regulating other important aspects like neuroprotection (*MTRNR2L7*), autophagy (*FAIM, TERT*) and lifespan (*CISD2*) (Gibson et al., 2019). Interestingly, no genome-wide significant variants or genes were found to overlap between the two epigenetic clocks tested, supporting the hypothesis that they represent different aspects of ageing, in line with moderate phenotypic correlations previously reported (Gibson et al., 2019). More recently, McCartney and colleagues investigated four different epigenetic clocks, which included both first – Hannum's and Horvath's DNAm age acceleration – and second generation clocks – DNAmPhenoAge and GrimAge (Mccartney et al., 2020). They identified more than 100 novel genome-wide significant associations, in a multi-ethnic dataset (N > 41,000). Novel shared loci included some genes previously implicated in epigenetic and telomere aging like *TERT*, *TRIM59* and *EDARADD*, as well as new interesting candidates like *TET2* (tet methylcytosine dioxygenase 2; 4q24), whose product catalyzes the conversion of 5-methylcytosine to 5-hydroxymethylcytosine at CpGs. Interestingly, cross-clock genetic correlation (indicating the SNP-based coheritability of the different clocks) were in the range [0.3-0.6], in line with that previously observed between Hannum and Horvath clocks (0.6) by Gibson et al (Gibson et al., 2019). Similar estimates (0.4) were obtained when comparing two partly related biological aging predictors based on blood chemistry/cellular markers, chronological age and other clinical variables, namely PhenoAge and BloodAge accelerations, which were tested in an independent GWAS on ~380,000 European-descent participants from the UK Biobank (Kuo et al., 2020b). Authors identified the strongest signals at two major protein-coding SNPs in *APOE* (apolipoprotein E, 19q13.32), a gene

known to be implicated in age-related disorders like cardiovascular disease and late-onset Alzheimer's disease. However, while BloodAge acceleration was associated positively with the APOE-e4 risk allele (rs429358) and negatively associated with the APOE-e2 protective allele (rs7412) - in line with expectations – these variants showed opposite effects on PhenoAge acceleration. A pathway enrichment analysis of all the genes identified revealed a link of BloodAge acceleration with lipid-related pathways, consistent with the role of APOE in transporting extracellular cholesterol and with the influence of the e2 allele on decreasing its circulating levels (Kuo et al., 2020a; Martínez-Magaña et al., 2019). Genes associated with PhenoAge acceleration showed enrichment for immune system, cell function, and carbohydrate homeostasis pathways (Kuo et al., 2020b). Overall, this evidence may be interpreted as a possible indication that the two measures, although based on partly overlapping markers, may capture different aging domains. Of interest, *APOE* was not among the top associated loci in a GWAS of brainPAD in the UK Biobank (N~17,000), which instead revealed two significant hits: one near *KCNK2* (potassium channel, subfamily K, member 2; 1q41) and another one tagging a well-known inversion spanning over a ~1 Mb region covering the *MAPT* gene (microtubule-associated protein tau; 17q21.31) (B. A. Jonsson et al., 2019). Of note, the tau protein has been previously involved in the etiology of Parkinson disease and of different forms of dementia, and this association correlated with reduced white matter surface area, a known structural feature of brain aging and neurodegeneration (B. A. Jonsson et al., 2019). In a larger study using structural MRI data from 20,170 adult healthy individuals of European ancestry from the UK Biobank, Kaufmann and colleagues (Kaufmann et al., 2019) further clarified the genetic

underpinnings of brain aging, identifying a novel associated locus at *MOBP* (myelin-associated oligodendrocyte basic protein; 3p22.1). Moreover, they detected substantial pleiotropic influences of different genes on regional/global brain aging and common brain disorders such as major depression, autism spectrum, bipolar and attention deficit hyperactivity disorder, multiple sclerosis, dementia and schizophrenia (Kaufmann et al., 2019). However, no genetic overlap with other aging clocks was computed, nor enrichment of association with molecular pathways or functional genomic elements was tested.

4.2 Cross-clock genomic overlap through LD-score regression

For the purpose of this review, we assessed here genetic overlap across all the biological aging clocks tested so far at the genomic level, namely telomere length (Codd et al., 2013), epigenetic age acceleration (Hannum, Horvath, GrimAge and DNAmPhenoAge) (Mccartney et al., 2020), blood-based markers like PhenoAge and Blood(Bio)Age (Kuo et al., 2020b), and brainPAD (Kaufmann et al., 2019). To do so, we used the relevant GWAS summary statistics coming from the largest datasets publicly available without restrictions (see URLs).

The overlap was computed as genetic correlations through LD score regression, a method that allows to compute SNP-based co-heritability for a given pair of traits as the ratio between their genetic covariance and the squared root of the product of their heritabilities, taking into account SNPs' LD in 1 cM bins genome-wide (Bulik-Sullivan et al., 2015). Correlations were deemed significant when they survived Bonferroni correction for testing

of eight different aging markers (for a total of 56 pairwise comparisons, excluding those of each clock with itself, $\alpha = 9 \times 10^{-4}$).

Beyond low to moderate positive correlations among DNAm age accelerations – in line with previous evidence (Gibson et al., 2019; Mccartney et al., 2020) - this analysis revealed for the first time additional significant genetic correlations – e.g. for DNAm clocks with both blood ages and TL ($p < 9 \times 10^{-4}$). Indeed, DNAmPhenoAge was positively correlated with both Blood and PhenoAge acceleration, while GrimAge was significantly correlated only with the latter. On the other hand, TL showed significant negative correlations with both GrimAge and Hannum epigenetic clocks, and brainPAD did not show any significant genomic overlap (Figure 3). Overall, this patchy correlation pattern suggests the existence of partly different genetic underpinnings for the diverse clocks, in line with previous epidemiological and – to a lesser extent - genetic evidence.

4.3 Single variants, genes and molecular pathways underlying biological aging

To identify pleiotropic variants influencing more than one biological aging domain among those tested so far, we performed a multivariate genetic association analysis on 2,076,998 variants tested in all the analyzed studies (Codd et al., 2013; Kaufmann et al., 2019; Kuo et al., 2020b; Mccartney et al., 2020). This analysis was carried out through TATES (van der Sluis et al., 2013), combining the univariate association P-values of the single aging markers while taking into account their cross-clock genetic correlations, which were taken as proxies of phenotypic correlations due to the lack of a comprehensive analysis testing all the

markers. This revealed 2,322 genome-wide significant multivariate associations ($p < 5\times10^{-8}$; Figure 3a), mostly driven by the results of univariate GWAS and not always concordant across all clocks tested (Table S1), in keeping with previous evidence (see above). We report in Table 1 those variants predicted to have a HIGH or MODERATE impact on gene function, as classified by Ensembl Variant Effect Predictor (VEP) v103 (McLaren et al., 2016). Interestingly, among those SNPs with HIGH functional impact, two variants were stop-gain. rs857725 is located within *SPTA1* (1q23.1, spectrin, alpha, erythrocytic 1), encoding a component of the erythrocyte plasma membrane, and has been previously associated with hemoglobin concentration (Chen et al., 2020). This SNP is in high LD with another variant, rs2779116, associated with glycated hemoglobin levels, a clinical marker of diabetes (Wojcik et al., 2019). rs2228671, within *LDLR* (19p13.12; low density lipoprotein receptor), was previously associated with both total and LDL-cholesterol circulating levels (Aulchenko et al., 2009). Interestingly, the loss of this gene favors the development of hypercholesterolemia and ApoE/LDLR$^{-/-}$ mice – an animal model of atherosclerosis – present several biochemical changes, including the decrease in phospholipid composition of erythrocyte membranes and alterations in the secondary structure of hemoglobin (Dybas et al., 2020). Another HIGH impact multivariate association was found at rs650692, within *EDARADD* (1q42.3; EDAR-associated death domain), a gene previously associated with epigenetic age acceleration, implicated in innate immunity and cytokine signaling (Gibson et al., 2019).

To have further biological insights into the underlying biology of common variance of different aging biomarkers, multivariate associations underwent gene and pathway enrichment tests through MAGMA v1.08 (de Leeuw et al., 2015) within the FUMA platform

(Watanabe et al., 2017). The analysis of 18,859 genes which the variants were annotated to (within a ±10 kb interval) revealed 252 genes with significant enrichment of associations surviving correction for multiple testing ($p < 2.7\times10^{-6}$, Figure 3b; Table S2). The most significantly enriched genes included *TOMM40* (translocase of outer mitochondrial membrane 40 homolog), *NHLRC1* (NHL repeat containing 1; 6p22.3), *TMEM258* (transmembrane protein 258; 11q12.2) and *APOE* (19q13.32). These genes are involved in known aging-related processes and diseases, like white matter integrity, Alzheimer's disease (*APOE* and *TOMM40*) (Lyall et al., 2014; Roses et al., 2016), dementia in the context of a neurodegenerative epilepsy (*NHLRC1*) (Nitschke et al., 2018) and intestinal inflammation (*TMEM258*)(Graham et al., 2017).

To have a more network-oriented view, we submitted the list of genes with a statistically significant enrichment to the STRING v11.0 platform, a database of known and predicted protein-protein interactions (Szklarczyk et al., 2019). The resulting network showed a significant excess of interactions (enrichment $p = 1.1\times10^{-16}$; 240 nodes, 166 edges vs 81 expected, average node degree 1.38 and average local clustering coefficient 0.39), suggesting the gene products are highly likely to be linked in molecular networks (Figure 5). Moreover, they highlighted some local networks of interests, such as the one among the apolipoproteins APOE, APOC1 and APOA5, which play an essential role in triglyceride and cholesterol transport and metabolism (Dominiczak and Caslake, 2011), as well as in cardiovascular risk (Zhou et al., 2018). Similarly, the interaction among *CRP* (C-reactive protein), *TNF* (tumor necrosis factor) and *SELP* (P-selectin, a marker of platelet activation), along with *IL6R* (interleukin-6 receptor), underlines the importance of low-grade

inflammation in the aging process, a phenomenon better known as "inflammaging" (Franceschi et al., 2018a). Other genes of interest in the network are represented by *LEPR* (leptin receptor), involved in regulating appetite/food intake, inflammation and fat metabolism (Klok et al., 2007), and by *ZBTB12*, which was previously associated with inflammation, platelet activation and cardiovascular risk (Noro et al., 2019).

A competitive gene-set enrichment analysis, testing 9,996 Gene Ontology terms and 5,500 curated (KEGG, Reactome and BioCarta) pathways, revealed 15,485 gene sets annotated with at least two enriched genes, five of which revealed significant enrichments surviving Bonferroni correction ($p < 3.2\times10^{-6}$; Table S3). These included the GO terms *triglyceride rich lipoprotein particle clearance, transdifferentiation, negative regulation of biosynthetic process, response to carbohydrate* and *positive regulation of gene expression* (Table S4a-e). These findings represent further links with some important characteristics of the aging process, especially with lipid and carbohydrate homeostasis. Indeed, plasma glucose levels tend to increase with age, which can trigger irreversible glycosylation of proteins, a peculiar phenomenon of biological aging (Franceschi et al., 2018b). Similarly, changes in circulating lipid profiles (Johnson and Stolzing, 2019) are associated with aging and longevity (Franceschi et al., 2018b), and markers like triglycerides, HDL and LDL cholesterol were among the most important features in blood-based biological aging algorithms developed in diverse ethnicities, along with glucose (Gialluisi et al., 2021; Polina Mamoshina et al., 2018) and glycated haemoglobin (Belsky et al., 2018a). Prominently, lipids represent important players in different aging-related processes, including inflammaging (Franceschi et al., 2018b). Specific sphingolipid and phospholipid blood profiles have also been reported to change

with age and are associated with exceptional human longevity (Johnson and Stolzing, 2019). Moreover, defects in sphingolipid metabolism seem to play a role in neurodegenerative processes and were suggested as promising targets for their treatment (Di Pardo and Maglione, 2018).

5. Conclusions

We reviewed evidence of a significant but partial overlap across different markers of biological aging, both at the epidemiological and at the genetic level. While epidemiological evidence supports quite consistently the existence of different aging domains within the human body, connected in a sort of aging network (Whitwell et al., 2020), it also warrants further investigations to clarify the degree of overlap with additional aging clocks in predicting mortality risk, stemming from diverse sources of biomedical data. On the genetic side, the field is still in a rather embryonic phase and the genetic overlap across diverse clocks has been under-investigated. Here we attempted to fill in this gap of knowledge by testing and reporting novel genetic correlations and multivariate single-variant associations across different aging clocks. These allowed to identify genes and pathways enriched for associations with biological aging estimators tested in GWAS so far, providing support to the existence of a complex molecular network underlying common variation in BA clocks. Findings reported here suggest immune-metabolic health - in particular inflammation, lipid and carbohydrate metabolism - as the most promising molecular targets for successful anti-aging interventions in the future. Such interventions should be ideally aimed at slowing down biological aging before the onset of age-related diseases, through promoting a healthy

diet, physical activity and any other prevention strategy which allows to reduce the pace of aging in one or more body domain. Also, the importance of genetics as underlined in this review – mostly based on common variants with typically low effect sizes - and the current lack of power to detect rare variants heavily affecting longevity (Garagnani et al., 2021) suggest the need for a personalized approach to building aging maps, as also supported by evidence that even known "successful" interventions like MedDiet do not reduce epigenetic aging uniformly in all individuals (Gensous et al., 2020). In this perspective, the use of novel machine learning techniques combining, genetic, lifestyle, socioeconomic, gender and any other "exposomic" information may help building targeted anti-aging strategies for each individual.

Take-home message box: dietary patterns and biological aging

- Nutritional interventions like calorie restriction (CR), intermittent fasting (IF) and Mediterranean Diet (MedDiet) can influence health status and the pace of biological aging.
- A higher adherence to a MedDiet pattern has been associated with reduced telomere attrition, blood and epigenetic ageing, as well as improved walking speed and cognition.
- In particular, the intake of fruits, vegetables, and polyphenols has reported beneficial associations with reduced biological ageing.
- CR represents an effective intervention to extend lifespan and slow down biological aging in a wide range of organisms, although robust evidence in humans is still lacking.

- IF showed effects similar to CR in animal models, acting through the same pathways, namely lowering inflammation and oxidative stress levels and improving lipid and glucose metabolism.
- Further research is needed in humans to clarify the effect of CR and IF, and to understand why generally healthy interventions like MedDiet show heterogeneous effects. In this perspective, a personalized nutrition approach taking into account population, gender and genetic factors is warranted.

Take-home message box: epidemiological overlap of different aging clocks

- The studies which jointly analyzed different biological aging markers generally revealed low to moderate reciprocal correlations, suggesting these markers may tap into different domains of the aging process.
- These studies also identified a partial overlap and a certain complementarity in predicting mortality, for all and specific causes, across different ethnicities.
- In particular, different types of epigenetic aging markers showed influences on mortality independent from other functional markers based on frailty indices, and from aging clocks based on blood/inflammatory markers and brain neuroimaging data.
- Even different types of epigenetic clocks showed independent influences on mortality, while telomere length generally showed non-significant associations when modelled together with other biological aging markers.
- Evidence collected so far suggest that combining estimators based on different biomedical sources may help improve their efficacy as public health markers in the general population, through exploiting their complementarity in tagging different biological aging domains.

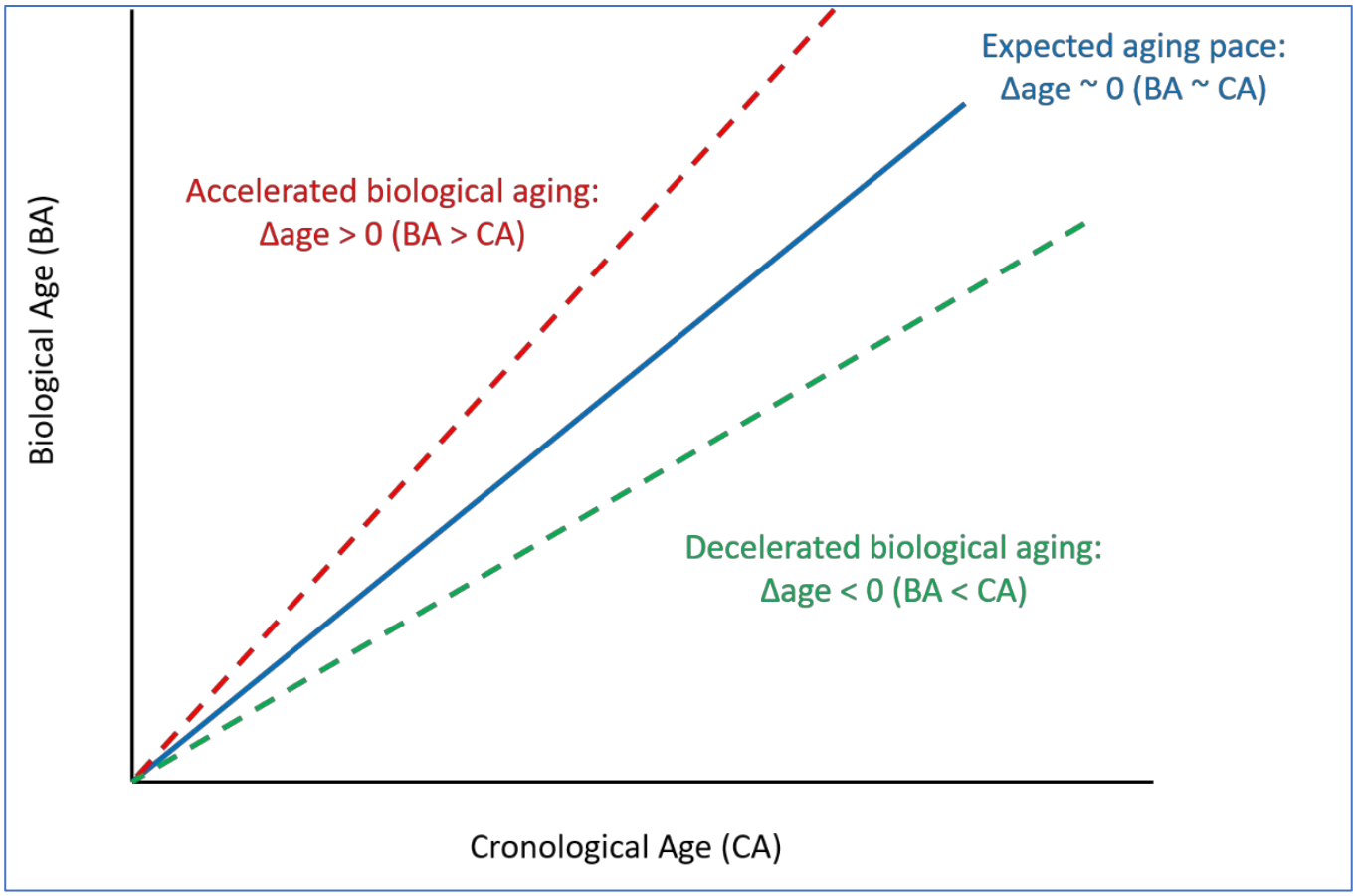
- Further studies analyzing diverse types of clocks – including both molecular and functional indices – in larger populations are needed. These should also aim at testing clinical outcomes other than mortality, like hospitalizations, and other measures of interest in the healthy aging process (e.g. quality of life).

Take-home message box: shared genetic basis of aging clocks

- Both longevity and aging clocks show moderate to high heritability, and additional epidemiological evidence suggests the existence of a genetic influence on biological aging.
- Genome Wide Association Studies (GWAS) mostly identified common genetic variants (SNPs) influencing biological aging and revealed substantial genomic overlap with longevity, lifestyle/socioeconomic factors, and age-related (e.g. neurodegenerative) disorders.
- Genes most robustly associated with aging clocks are involved in telomere elongation/preservation, metabolism, immunity, neuroprotection and autophagy.
- A post-hoc analysis of GWAS summary statistics revealed a patchy correlation pattern across the diverse clocks, suggesting the existence of partly independent heritabilities.
- Significant multivariate associations with the different aging clocks were identified, at variants with high predicted impact on protein function, e.g. in genes involved in glycated hemoglobin (*SPTA1*) and LDL cholesterol levels (*LDLR*), as well as in innate immunity and cytokine signaling (*EDARADD*).
- Genes implicated in known aging-related processes and diseases, like white matter integrity, Alzheimer's disease/dementia and neurodegeneration (*APOE*, *TOMM40* and *NHLRC1*) showed the strongest enrichment of associations with aging clocks.

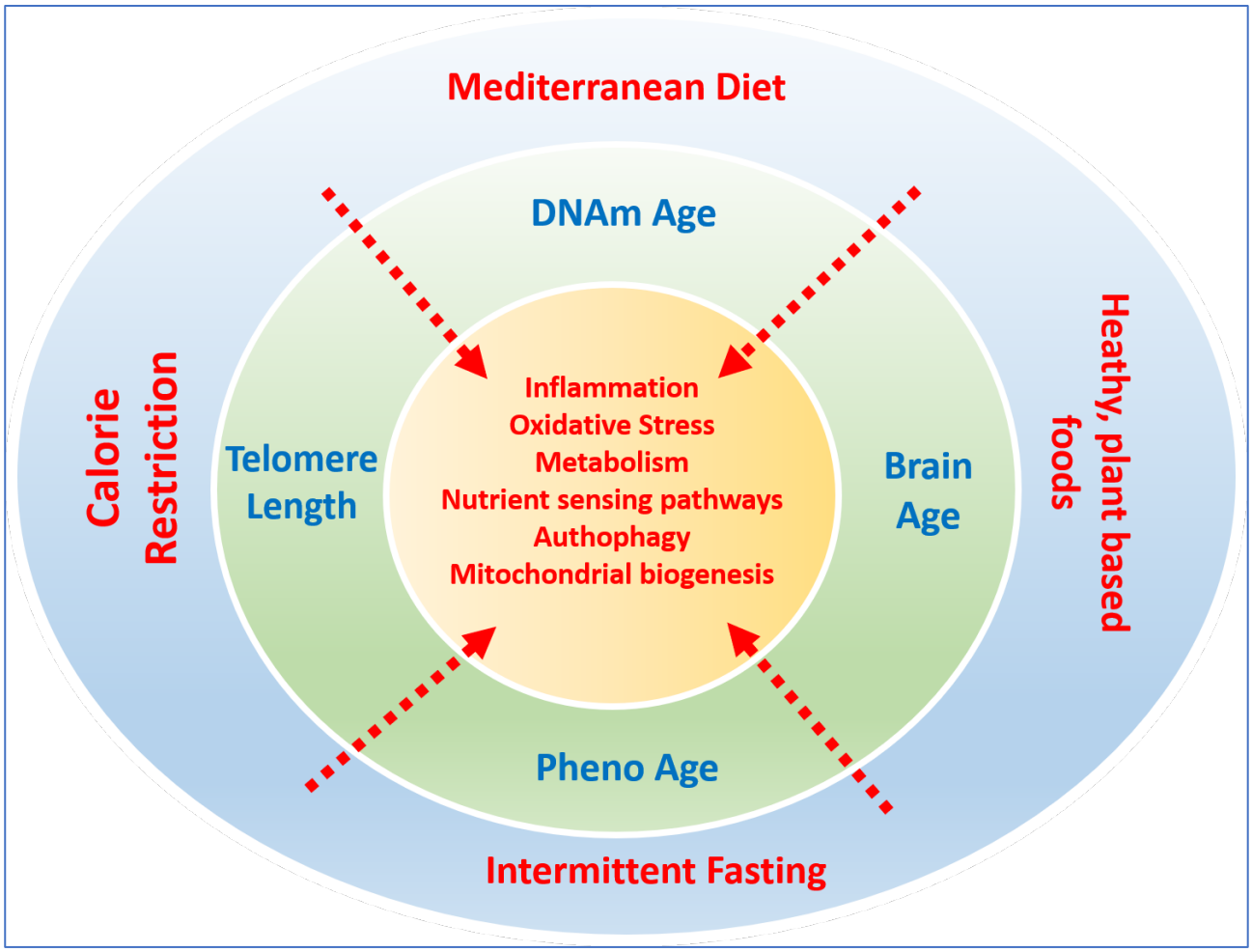
- A network-based analysis of associations with aging clocks supported non-random interactions among the enriched genes, suggesting they are likely to be linked in molecular networks. Among these, the local network of the apolipoproteins APOE, APOC1 and APOA5 suggests the importance of triglyceride and cholesterol transport and metabolism in biological aging, while the interaction among CRP (C-reactive protein), TNF (tumor necrosis factor), SELP (P-selectin, a marker of platelet activation), and IL6R (interleukin-6 receptor), further supports the prominence of inflammation in the aging process (inflammaging).
- Pathway-based enrichments corroborated evidence collected at the network level, providing further links with lipid and carbohydrate homeostasis.

Figure 1. Biological aging.



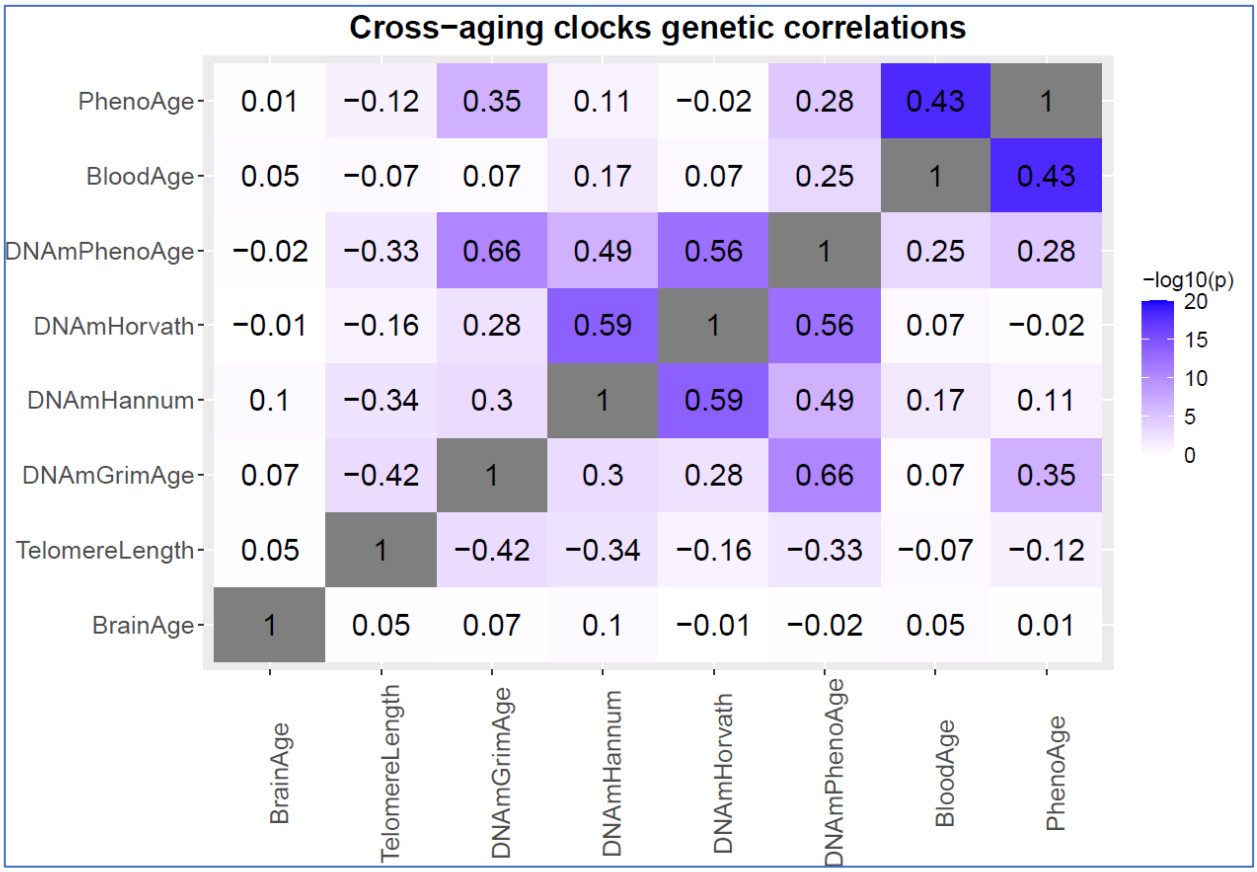
Biological aging can be quantified through computing the difference between Biological and Chronological Age (ΔAge = BA – CA). ΔAge > 0 suggests accelerated biological aging of an organism compared to its chronological age, while Δage < 0 indicates decelerated biological aging. A typical example of decelerated biological aging is represented by centenarians (Horvath et al., 2015b), while an accelerated biological aging was observed in Down Syndrome patients, compared to controls (J. H. Cole et al., 2017a; Horvath et al., 2015a).

Figure 2. Main healthy nutritional dietary patterns affecting biological aging.



These dietary patterns influence biological aging by modulating common pathways related to inflammation, oxidative stress and metabolism.

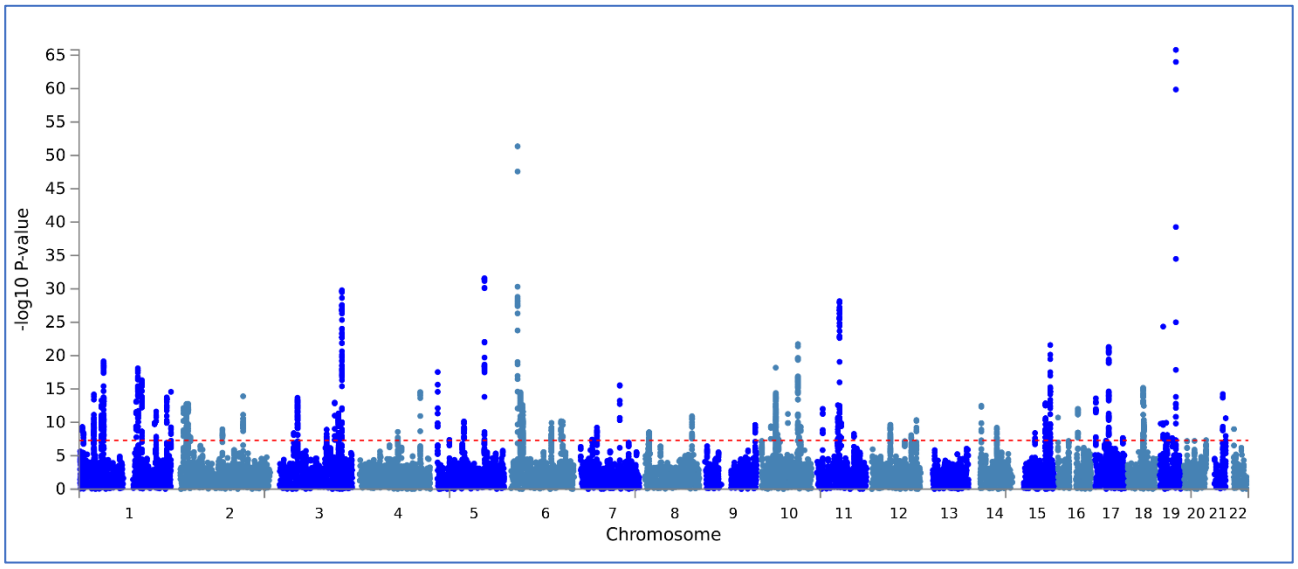
Figure 3. Genetic correlation matrix of the different aging clocks.



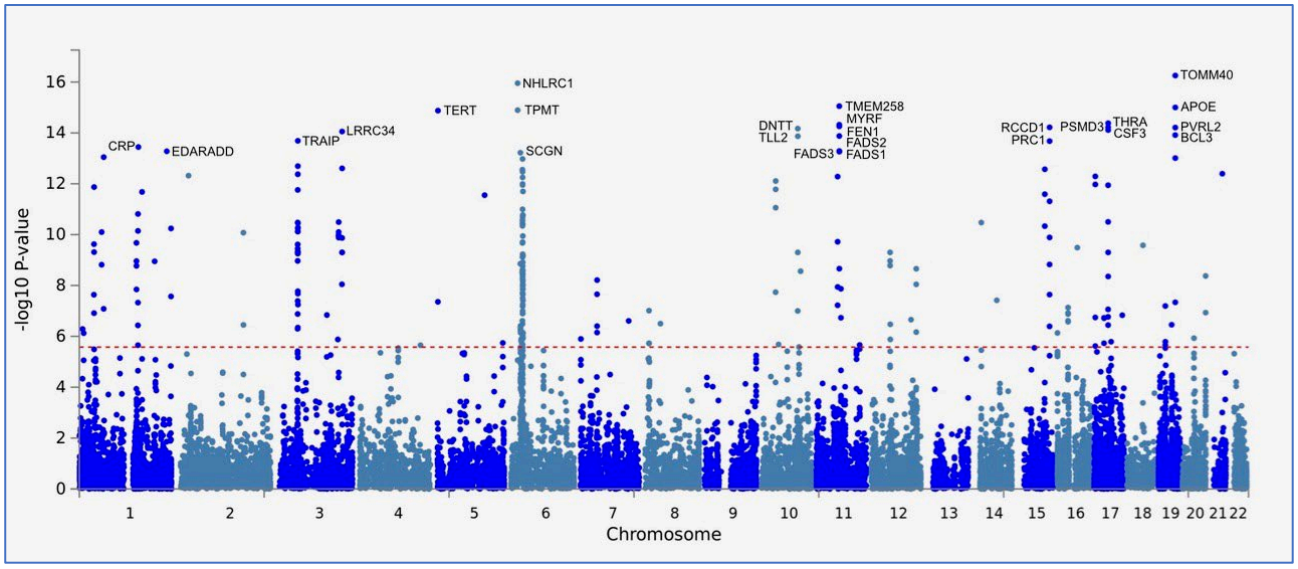
Reciprocal genetic correlations (r_g) as computed in LDSC (Bulik-Sullivan et al., 2015) are reported, for each pairwise comparison among the aging clocks analyzed. Squares in the matrix are colored differently based on the level of significance of r_g.

Figure 4. Manhattan plot of **a)** multivariate single-variant associations with different aging clocks and **b)** relative gene-based enrichment analysis.

a)

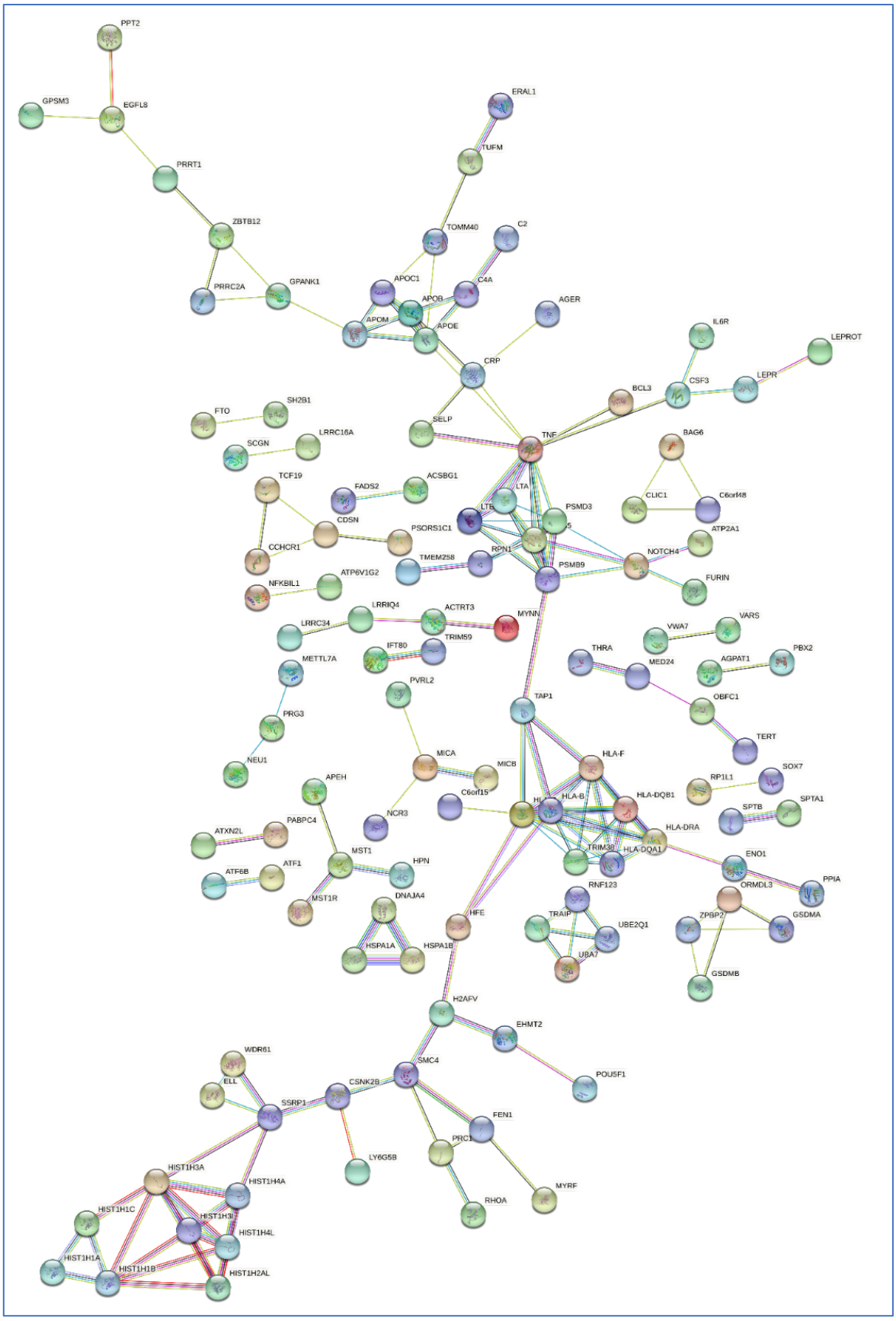


b)



Red dashed lines represent the statistical significance thresholds (α) for the two analyses, namely **a)** 5×10^{-8}; and **b)** 2.7×10^{-6}. In **b)**, the 25 most enriched genes are reported (see Figure S2 for a full list).

Figure 5. Interaction network of genes enriched for associations with aging clocks.



The reported network - including both direct (physical) and indirect (functional) associations – was based on the STRING v11.0 database (Szklarczyk et al., 2019). Only high-confidence interactions between proteins are reported (interaction score > 0.7), while

disconnected nodes in the network were hidden. Each node represents all the proteins produced by a single protein-coding gene locus, while edges represent protein-protein associations. Line color indicates the type of interaction evidence: light blue = from curated databases; purple = experimentally determined; green = gene neighborhood; red = gene fusions; blue = gene co-occurrence; yellow = text-mining; black = co-expression; violet = protein homology.

Table 1. Single-variant multivariate associations with aging clocks with a HIGH (H) and MODERATE (M) predicted impact on protein function.

Variant	Location	Allele	Consequence	IMPACT	Gene	Aminoacid change	Codon change	1000g EUR Allele Freq (%)	Multivariate P
rs857725	1:158607935-158607935	A	stop_gained	H	SPTA1	K/*	Aag/Tag	-	1.52E-17
rs650692	1:236514002-236514002	G	splice_acceptor_variant	H	EDARADD	-	-	35.38	8.21E-14
rs2228671	19:11210912-11210912	A	stop_gained	H	LDLR	C/*	tgC/tgA	-	3.69E-20
rs2305480	17:38062196-38062196	A	missense_variant	M	GSDMB	P/S	Cca/Tca	28.67	5.56E-09
rs174535	11:61551356-61551356	A	missense_variant	M	MYRF	S/R	agT/agA	-	7.08E-26
rs1041981	6:31540784-31540784	A	missense_variant	M	LTA	T/N	aCc/aAc	38.96	3.69E-12
rs3130618	6:31632134-31632134	A	missense_variant	M	GPANK1	R/L	cGa/cTa	13.34	9.39E-10
rs587404	1:39908506-39908506	A	missense_variant	M	MACF1	A/T	Gcc/Acc	34.41	2.53E-09
rs1265054	6:31079643-31079643	C	missense_variant	M	C6orf15	K/E	Aag/Gag	53.19	5.71E-09
rs1260326	2:27730940-27730940	C	missense_variant, splice_region_variant	M	GCKR	L/P	cTg/cCg	-	1.66E-08
rs1142345	6:18130918-18130918	C	missense_variant	M	TPMT	Y/C	tAt/tGt	3.91	4.45E-52
rs857685	1:158577109-158577109	C	missense_variant	M	OR10Z1	N/T	aAt/aCt	24.22	2.31E-18
rs3811444	1:248039451-248039451	T	missense_variant	M	TRIM58	T/M	aCg/aTg	22.74	2.67E-15
rs3197999	3:49721532-49721532	A	missense_variant	M	MST1	R/C	Cgc/Tgc	19.19	1.01E-13
rs2230590	3:49936102-49936102	A	missense_variant	M	MST1R	Q/L	cAa/cTa	-	2.24E-12
rs1062633	3:49924940-49924940	C	missense_variant	M	MST1R	R/G	Aga/Gga	41.91	2.82E-12
rs3130617	6:31627523-31627523	T	missense_variant	M	C6orf47	G/R	Ggg/Agg	81.57	3.61E-11
rs1046080	6:31595882-31595882	A	missense_variant	M	PRRC2A	T/K	aCa/aAa	81.55	7.23E-11
rs2296172	1:39835817-39835817	G	missense_variant	M	MACF1	M/V	Atg/Gtg	11.82	7.95E-11
rs2272593	6:31601344-31601344	C	missense_variant	M	PRRC2A	L/P	cTt/cCt	81.53	7.95E-11
rs1169288	12:121416650-121416650	C	missense_variant	M	HNF1A	I/L	Atc/Ctc	29.85	1.16E-09
rs1339847	1:248039294-248039294	A	missense_variant	M	TRIM58	V/I	Gtc/Atc	12.6	4.12E-09
rs3208856	19:45296806-45296806	G	missense_variant	M	CBLC	H/D	Cac/Gac	-	4.12E-09
rs3129941	6:32337686-32337686	G	missense_variant	M	C6orf10	C/R	Tgt/Cgt	-	7.95E-09
rs1801133	1:11856378-11856378	A	missense_variant	M	MTHFR	A/V	gCc/gTc	24.54	9.39E-09
rs855791	22:37462936-37462936	G	missense_variant	M	TMPRSS6	V/A	gTc/gCc	-	1.23E-08

rs2276038	11:57137424-57137424	A	missense_variant	M	P2RX3	A/E	gCg/gAg	-	1.37E-08
rs11073964	15:91543761-91543761	A	missense_variant	M	VPS33B	G/C	Ggt/Tgt	-	3.76E-13
rs1488689	17:3352294-3352294	G	missense_variant	M	SPATA22	I/T	aTa/aCa	26.7	1.64E-12
rs1488690	17:3352331-3352331	G	missense_variant	M	SPATA22	V/L	Gtg/Ctg	-	1.68E-12
rs1137100	1:66036441-66036441	G	missense_variant	M	LEPR	K/R	aAg/aGg	32.03	1.01E-11
rs4691896	4:164085425-164085425	A	missense_variant	M	NAF1	I/F	Att/Ttt	-	1.13E-11
rs3741367	11:66083129-66083129	C	missense_variant	M	CD248	H/R	cAt/cGt	29.21	1.34E-10
rs8176746	9:136131322-136131322	T	missense_variant	M	ABO	L/M	Ctg/Atg	15.28	3.25E-10
rs8176743	9:136131415-136131415	T	missense_variant	M	ABO	G/S	Ggc/Agc	15.3	4.7E-10
rs10876024	12:50747005-50747005	A	missense_variant	M	FAM186A	R/W	Agg/Tgg	-	7.01E-10
rs10876023	12:50746917-50746917	G	missense_variant	M	FAM186A	L/P	cTt/cCt	60.92	7.15E-10
rs7296291	12:50744119-50744119	A	missense_variant	M	FAM186A	H/Y	Cat/Tat	60.52	7.95E-10
rs12303082	12:50754563-50754563	G	missense_variant	M	FAM186A	K/Q	Aag/Cag	60.54	7.95E-10
rs1137101	1:66058513-66058513	G	missense_variant	M	LEPR	Q/R	cAg/cGg	58.43	6E-09

Variants were annotated through Ensembl VEP v103 (McLaren et al., 2016). Multivariate association p-value, as per TATES output, is reported. A full list of genome-wide significant multivariate associations is reported in Table S1, along with details of associations with each aging clock.

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Author contributions

AG and AT carried out post-hoc analyses of public data. AG and AS reviewed the literature and wrote the manuscript, with contributions from all the co-authors. LI, CF, CC, GdG and MBD contributed to critical revision of the manuscript, review of the literature and/or interpretation of the evidence reported in this review. All Authors approved the final version of the manuscript and take full responsibility for its content.

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Declaration of Competing Interest

The Authors declare no competing financial interests.