Aging Trajectories in Different Body Systems Share Common Environmental Etiology: The Healthy Aging Twin Study (HATS)

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Little is known about the extent to which aging trajectories of different body systems share common sources of variance. We here present a large twin study investigating the trajectories of change in five systems: cardiovascular, respiratory, skeletal, morphometric, and metabolic. Longitudinal clinical data were collected on 3,508 female twins in the TwinsUK registry (complete pairs: 740 monozygotic (MZ), 986 dizygotic (DZ), mean age at entry 48.9 ± 10.4, range 18–75 years; mean follow-up 10.2 ± 2.8 years, range 4–17.8 years). Panel data on multiple age-related variables were used to estimate biological ages for each individual at each time point, in linear mixed effects models. A weighted average approach was used to combine variables within predefined body system groups. Aging trajectories for each system in each individual were then constructed using linear modeling. Multivariate structural equation modeling of these aging trajectories showed low genetic effects (heritability), ranging from 2% in metabolic aging to 22% in cardiovascular aging. However, we found a significant effect of shared environmental factors on the variations in aging trajectories in cardiovascular (54%), skeletal (34%), morphometric (53%), and metabolic systems (53%). The remainder was due to environmental factors unique to each individual plus error. Multivariate Cholesky decomposition showed that among aging trajectories for various body systems there were significant and substantial correlations between the unique environmental latent factors as well as shared environmental factors. However, there was no evidence for a single common factor for aging. This study, the first of its kind in aging, suggests that diverse organ systems share non-genetic sources of variance for aging trajectories. Confirmatory studies are needed using population-based twin cohorts and alternative methods of handling missing data.

Keywords: aging, longitudinal studies, multi-morbidities, twin studies, multi-system changes

An important question facing researchers in the field of aging is to what extent the causes of age-related decline in one trait are shared with other aging phenotypes. Clinicians observe that not all body systems change at the same rate within an individual. Numerous studies have shown a wide variation in heritability of age-related phenotypes (Steves et al., 2012), but little is known about the extent of shared genetic effects on different systems. Similarly, the degree to which environmental factors impact upon aging trends in various body systems is unknown.

Twin studies can investigate the causes of variation in a population (van Dongen et al., 2012). Identical (MZ) twins share virtually all of their variable DNA sequence, while non-identical (DZ) twins share on average only half of their segregating genes. Classical twin studies compare the variability in MZ pairs compared with DZ pairs and estimate the extent attributable to genetic factors (the heritability) and to environmental factors either shared by the twin pair or unique to each twin. A wide distribution of heritability estimates for age-related disorders ranging between 35% and...
80% in knee osteoarthritis, age-related macular degeneration, nuclear cataract, falls, frailty, and Alzheimer’s disease (Dato et al., 2012; Gatz et al., 2006; Hammond et al., 2000; Hammond et al., 2002; Lichtenstein et al., 2000; Michaelsson et al., 2005; Pajala et al., 2006; Spector et al., 1996) has been reported. Although few studies have examined the relative influence of genes and environment on longitudinal change, the genetic epidemiology of an aging trait examined cross-sectionally does not necessarily predict what is seen over time in the same individual: for some traits such as respiratory function and blood pressure, there is evidence for shared sources of variance underpinning both the cross-sectional measures as well as the trajectory of change. However, for some other traits (grip strength and wellbeing; Finkel et al., 2003) and cognitive function (McGue & Christensen, 2002), the role of genetic factors appears to be much reduced for the slope of change in older age.

Twin studies can also estimate the relative importance of genetic and environmental factors that are shared between aging traits. This can be achieved by comparison of twin-pair cross-trait covariance for continuous traits, or concordance between hypertension, migraine, Raynaud’s phenomenon, and coronary artery disease (Williams et al., 2004). It has been shown that shared genetic factors explain associations between hypertension, migraine, Raynaud’s phenomenon, and coronary artery disease (Williams et al., 2004). Also, there is evidence for shared sources of variance underpinning both physical functioning and cognitive function in older adults (Johnson et al., 2009). However, to our knowledge, no twin study has reported the extent of shared sources of influence for intra-individual changes over time for various age-related traits. We aimed in this study to determine the extent of sharing of genetic versus environmental sources of variation in changes in various body systems over time within a healthy aging twin population.

Methods

Details about the study population (TwinsUK), follow-up visits, and laboratory and clinical measures related to different aging systems are described in Supplementary Methods (available on the Cambridge University Press website). The TwinsUK study has prospectively following a large cohort of UK twins for >20 years (Moayyeri et al., 2013). For this study, we investigated longitudinal changes in five body systems in female twins with at least two clinical visits. These included cardiovascular, respiratory, skeletal, morphometric, and metabolic systems (Supplementary Table 1). For each system, we examined the available data on measures of health and their association with age. All measures significantly associated with age were entered into the prediction models and are shown in Table 1.

For estimation of ‘aging trajectories’ in each body system, we used mixed-effects regression models with two steps:

1. mixed-effects random-coefficient models, using chronological age as the dependent variable and an age-related trait as the predictor, were constructed separately for each trait using all the available data from various clinical visits for all participants. Models were adjusted for body mass index (BMI), except morphometric models (fat, lean and bone mass) which were adjusted for height. The predictor trait in each model was also considered as the random coefficient to allow different associations for each individual;

2. based on the fitted models, a measure of trait-specific ‘biological age’ was predicted for each individual in each visit with a trait measurement. Predictions were done using mixed-effects fitted values, which are equal to the fixed-portion linear predictors plus contributions based on predicted random effects;

3. to produce a single measure of biological age in each body system, we used a weighted averaging approach (Supplementary Table 1). The major domains of each system were considered as units of weight. Estimates of the biological age for each clinical measure within each domain were scaled according to the number of non-missing components for each individual (e.g., in the case of blood pressure, for those with full data, a scalar of 0.5 was applied to each component, systolic and diastolic blood pressure; for those lacking full data, the scalar was 1/n, where n is the number of present components). Participants who had available data above prespecified thresholds for each body system were included (≥2 domains for skeletal and metabolic systems and ≥3 for other systems). This method enabled estimation of aging trajectories in participants with missing data in some clinical measures, thereby allowing their inclusion in the modeling;

4. for this stage, only participants with at least two measures of ‘biological age’ in each body system separated for ≥4 years were included. Longitudinal slope of change was estimated separately for each individual by regressing ‘biological age’ over duration of follow-up. The slope of these models was the trajectory of predicted biological ages for each body system for each individual (aging trajectory). A slope of 1 indicated that the rate of change in biological age was equal to change in chronological age between visits. However, a slope of <1 indicated changes lower than expected (slow aging) and a slope of >1 marked changes higher than expected (fast aging). Supplementary Figure 1 illustrates these slopes for a single participant. Average ‘aging trajectories’ modeled in our study are less than predicted (i.e., <1, Supplementary Table 4). This frequently observed phenomenon may be explained by ‘cohort effects’. Aging trajectories, adjusted using the residual approach for chronological age, were used for structural equation modeling, which divides the observed phenotypic...
### TABLE 1

#### Age-Related Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Body system/measure</th>
<th>Monozygotic twins</th>
<th>Dizygotic twins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (individuals)</td>
<td>N (twin pairs)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1,509</td>
<td>740</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>1,509</td>
<td>740</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>1,389</td>
<td>683</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>1,389</td>
<td>683</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>1,396</td>
<td>687</td>
</tr>
<tr>
<td>High-density lipoprotein</td>
<td>1,396</td>
<td>687</td>
</tr>
<tr>
<td>Low-density lipoprotein</td>
<td>1,395</td>
<td>686</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1,396</td>
<td>687</td>
</tr>
<tr>
<td>PR interval (mSec)</td>
<td>1,097</td>
<td>536</td>
</tr>
<tr>
<td>QT interval (mSec)</td>
<td>1,116</td>
<td>546</td>
</tr>
<tr>
<td>Fibrinogen (gr/L)</td>
<td>555</td>
<td>274</td>
</tr>
<tr>
<td>Adiponectin (µg/mL)</td>
<td>420</td>
<td>204</td>
</tr>
<tr>
<td>Homocysteine (µmol/L)</td>
<td>632</td>
<td>312</td>
</tr>
<tr>
<td>Fetal weight (gr)</td>
<td>45.8</td>
<td>28.2</td>
</tr>
<tr>
<td>Total body fat mass (gr)</td>
<td>1,347</td>
<td>656</td>
</tr>
<tr>
<td>Bone mineral content (gr)</td>
<td>1,316</td>
<td>639</td>
</tr>
<tr>
<td>Grip strength (kg)</td>
<td>1,241</td>
<td>602</td>
</tr>
<tr>
<td>Femoral neck BMD (mg/cm²)</td>
<td>1,338</td>
<td>652</td>
</tr>
<tr>
<td>Total hip BMD (mg/cm²)</td>
<td>1,338</td>
<td>652</td>
</tr>
<tr>
<td>Lumbar spine BMD (mg/cm²)</td>
<td>1,341</td>
<td>655</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>863</td>
<td>413</td>
</tr>
</tbody>
</table>

Note: BMI: body mass index; BMD: bone mineral density; BUA: broadband ultrasound attenuation; VOS: velocity of sound; DHEAS: dehydroepiandrosterone sulphate; eGFR: estimated glomerular filtration rate. Values are mean (standard deviation).
Results

The characteristics of study population and the distribution of various clinical measures in the first and last visits are summarized in Table 1. In total, 3,508 twins had predicted biological age in at least one body system separated for >4 years. The mean duration of follow-up for the whole study population was 10.2 ± 2.8 years (range 4–17.8 years) and 43% of twins were MZ (identical). Pairwise correlations in MZ and DZ twins for all aging-related variables are presented in Table 2, and four-by-four correlation tables in the twins at the first and last visits are shown in Supplementary Table 6. These show increased cross-twin, cross-time correlation in identical compared to fraternal twins in several clinical traits, suggesting longitudinal genetic influence. We were able to estimate aging trajectories in the cardiovascular system for 3,349 twins, respiratory for 2,498 twins, morphometric for 3,268, skeletal for 3,232, and metabolic system for 2,593 twins.

Models using SEM showed low heritabilities for aging trajectories in all five body systems. As shown in Table 3 and Supplementary Figure 2, the genetic component of the variances ranged from 2% (95% CI 0–12) in metabolic...
Aging to 11% (95% CI 1–21) in cardiovascular aging. However, there was a significant effect of environmental factors shared between twins. This component explained 54 (45–62)% of the variance in cardiovascular aging, 53 (44–61)% in morphometric, 34 (23–42)% in skeletal, 53 (44–58)% in metabolic, and 12 (1–21)% in respiratory aging. The remainder of the variance was due to environmental factors unique to each individual (Supplementary Figure 2).

Using a multivariate model, we investigated the correlation between variance components for aging trajectories in five body systems (Figure 1). The correlations between genetic components were negligible and not significant, so not reported. However, there were significant and substantial correlations between the unique environmental latent factors between all body systems (except metabolic–morphometric correlations), ranging from 0.11 (95% CI 0.03–0.20) between respiratory and metabolic systems to 0.57 (95% CI 0.52–0.62) in skeletal and cardiovascular systems (Supplementary Table 2, bottom-left). Moreover, some pairs of body systems showed significant correlations in the shared environmental component (Supplementary Table 2, top-right). These included cardiovascular — respiratory (correlation coefficient [CC] = 57 [28–92]%), respiratory — skeletal, CC = 58 [18–94]% and skeletal — morphometric systems (CC = 39 [24–53]%).

As in genetic common factors were unlikely to explain these data: despite having fewer parameters in the model, and therefore more degrees of freedom, the common factor solution had a higher Akaike Information Criterion (AIC; ΔAIC = 146). Full statistics are provided in Supplementary Table 3. More details about the process of estimation of ‘aging trajectories’ and comparison between MZ and DZ twins are summarized in Supplementary Table 4.

**Discussion**

To our knowledge, this is the first study investigating the extent to which aging trajectories of different body systems share common sources of variance. We found that diverse systems showing age-related changes shared common sources, but these were primarily non-genetic. Examination of the fit statistics revealed that a single common factor solution was very unlikely to be plausible — that is, that
different dyads of organ systems shared sources of variance, but this was not due to a single underlying aging factor.

In common with convention, in our study, ‘common environment’ or ‘C’ measures the contribution of environmental influences that act to make members of twin pairs similar. Somewhat surprisingly, in this study, latent factors related to such common environment played a major role in determination of variance in aging trajectories, and moreover showed significant correlations between various body systems. Published twin studies of change in aging, until very recently, have not shown significant effects of shared environment, and few cross-sectional studies reveal an effect of C (Steves et al., 2012). This may be in part due to lack of power to detect C, and in this respect the size of the current study is a significant advantage. Recently, however, the Swedish Twin Study of Aging (SATSA) have also reported similar findings using latent growth curve modeling: ‘increasing variance in the functional ability factors (with age) resulted largely from increases in environmental components of variance, including correlated and shared rearing environmental variance’ (Finkel et al., 2014, pp. 713–714).

In this study, up to 50% of variation in trajectories of cardiovascular and morphometric aging was attributed to common environmental latent factors. It is important to note the nature of phenotyping in this cohort: twins visit on the same day and therefore may experience similar patterns of missingness, and possible inadvertent changes in protocol over time. Measurement errors could be correlated between twins due to the shared visit. While twin visits are run in parallel and the same research assistant or nurse does not perform the test for both twins, other factors unique to the day may be shared, including equipment calibration and environmental factors. In addition, TwinsUK operates a rolling recruitment for visits and the numbers of visits and time intervals between them are largely shared by twin pairs. These factors may serve to inflate C. Therefore, confirmatory studies in other cohorts using different methodology are highly advisable. In cohorts where there is a scheduled follow-up visit, a different approach to data analysis — for example, using FIML or Bayesian analysis — may be possible, which could test whether the results presented here are significantly biased by the methodology adopted.

However, it is intriguing that we detected such a strong effect of C, due to the growing evidence from longitudinal aging studies of effects of factors generally shared by twins. Environments that may contribute to this include physical environments; for example, maternal, uterine, and early life factors implicated in the developmental origins of disease hypothesis (Barker et al., 2002). This hypothesis suggests that environmental factors, particularly nutrition, act in early life to program risk for cardiovascular and metabolic diseases in later adult life, leading to premature death. Many international observational and experimental studies have confirmed associations between early growth patterns and increased risk of hypertension, impaired glucose tolerance, type II diabetes, central obesity, and the metabolic syndrome in adult life (McMillen & Robinson, 2005). This study is consistent with an extension of this hypothesis to include trajectories in healthy aging. It is notable that twins may, throughout their lives, also share other common factors implicated in aging such as socio-economic status, dietary, and activity habits (Fisher et al., 2010; Rozin & Millman, 1987). These factors may also contribute to the correlations we observed between shared environmental components of aging in, for instance, cardiovascular and respiratory systems.

In these models, non-shared measurement error and unique environmental effects are not separated. However, reliabilities of the tests used are generally high and so this is unlikely to account for the magnitude of the ‘unique environmental’ term (‘E’). In our study, moreover, we found a significant correlation between all body systems with regard to this component. Since each aging trajectory has been estimated by contribution of multiple data-points from different measures, it is unlikely that the unique environmental correlations observed are due to measurement error.

Rather, factors that are not genetic but are likewise not due to shared family factors, appeared to determine the extent of aging in several body systems. In addition to early developmental differences and the body’s response to environmental factors in adulthood, accumulated ‘errors’ — for example, somatic gene mutation and epigenetic remodeling — continuing throughout life may have consequences for the ‘internal environment’ (Vogt et al., 2008). Such stochastic processes may play a role in the non-shared environmental sources of variation identified by this study (Steves et al., 2012).

This study has some limitations. In common with many other studies in this field, we had the problem of missing data. The methodology allowed use of as much of the data as possible, including multiple visits for some pairs. An alternative method, using full information maximum likelihood, would be a good alternative in datasets with waves of data, but was problematic in this dataset where twin pairs are seen at varying intervals and varying numbers of time points. Clearly, our findings need to be tested in other cohorts with scheduled data visits allowing alternative modeling, and also incorporating male participants in order to generalize to the whole population.

As a longitudinal volunteer cohort, there is a potential for healthy volunteer bias and attrition bias. As we have detailed previously, the female volunteers in this study represent a marginally higher socio-economic group with higher education compared to the UK general population (Steves et al., 2013). However, previous investigations in the TwinsUK cohort have shown that means and variances for various clinical traits are similar between female twins and female singletons from other population-based cohort studies (Andrew et al., 2001).
We did not observe any difference in age and clinical measure patterns between participants contributing to various numbers of aging systems in our models (Supplementary Table 5). The measures utilized to define aging trajectories were not exhaustive and were grouped into the five system categories a priori. Therefore, the starting point for this study was the clinical aging domains. Alternative data-driven modeling for all aging traits may also be informative on how seemingly diverse traits may change in concert, or in diversity. We assumed linearity of trajectories of change in aging traits, in order to avoid over-complexity of models.

Finally, this classical twin model relies on several assumptions: (1) MZ share 100% of their variable DNA. Recent evidence shows that MZ twins can be different from each other in copy number variation, post-zygotic mutations (Bruder et al., 2008), and differences in X-chromosome inactivation. These factors could lead to underestimation of heritability. (2) DZ twins and MZ twins share their ‘shared environment’ to an equal extent. Numerous studies have broadly upheld this assumption (e.g., in studies of wrongly labeled twins; Derks et al., 2006; Kendler et al., 1993; Scarf, 1968), and challenges are confined to subjective traits (Richardson & Norgate, 2005; Tishler & Carey, 2007). (3) there is no assortative mating on the traits of interest. We consider that as these traits involve primarily the post-reproductive period it is not likely that this is a major consideration. (4) there are no non-additive genetic effects. In practice, such effects are present only when dominance at a key locus exists, or between two loci interacting. Aging appears to be substantially polygenetic, and so violation of this assumption is unlikely.

In conclusion, we found that diverse body systems shared common sources of variance for female aging that were not genetic. There appeared to be an important contribution of shared environmental factors to aging in various systems, which may reflect the fetal origins hypothesis of aging, or lifelong shared dietary/activity habits, but confirmatory studies using alternative missing data handling in population-based cohorts are needed to ensure that this shared environmental term has not been artificially inflated. Unique environmental factors, which are a combination of stochastic events and environmental exposures in individuals, also made an important contribution to the aging trajectories observed. Importantly, these effects were significantly correlated between different systems. We would tentatively conclude that environmental factors may be dominant in explaining variance in aging trajectories. The path by which they lead to aging may be potentially identified and modified, thus justifying ongoing research for the prevention of aging.

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Supplementary Materials

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References


