Declining autozygosity over time: An exploration in over 1 million individuals from three diverse cohorts

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This study found that genome-wide autozygosity is decreasing over generational time in three large cohorts of diverse genetic ancestries, though the rate of this decline varies by country and ancestry. This trend is most likely attributable to increases in urbanization and panmixia.

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REPORT

Declining autozygosity over time: An exploration in over 1 million individuals from three diverse cohorts

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Summary

Previous studies have hypothesized that autozygosity is decreasing over generational time. However, these studies were limited to relatively small samples (n < 11,000) lacking in diversity, which may limit the generalizability of their findings. We present data that partially support this hypothesis from three large cohorts of diverse ancestries, two from the US (All of Us, n = 82,474; the Million Veteran Program, n = 622,497) and one from the UK (UK Biobank, n = 380,899). Our results from a mixed-effect meta-analysis demonstrate an overall trend of decreasing autozygosity over generational time (meta-analyzed slope = −0.029, SE = 0.009, p = 6.03e−4). On the basis of our estimates, we would predict F_{ROH} to decline 0.29% for every 20-year increase in birth year. We determined that a model including an ancestry-by-country interaction term fit the data best, indicating that ancestry differences in this trend differ by country. We found further evidence to suggest a difference between the US and UK cohorts by meta-analyzing within country, observing a significant negative estimate in the US cohorts (meta-analyzed slope = −0.058, SE = 0.015, p = 1.50e−4) but a non-significant estimate in the UK (meta-analyzed slope = −0.001, SE = 0.008, p = 0.945). The association between autozygosity and birth year was substantially attenuated when accounting for educational attainment and income (meta-analyzed slope = −0.011, SE = 0.008, p = 0.167), suggesting they may partially account for decreasing autozygosity over time. Overall, we demonstrate decreasing autozygosity over time in a large, modern sample and speculate that this trend can be attributed to increases in urbanization and panmixia and differences in sociodemographic processes lead to country-specific differences in the rate of decline.

There has been great interest in using measures of autozygosity—the proportion of the genome contained in runs of homozygosity (ROHs) that are identical by descent (i.e., inherited from a common ancestor shared by both parents)—to examine evolutionary hypotheses about complex traits in humans[1–3] and to quantify the extent to which inbreeding depression impacts health and disease.[3–5] While longer and more frequent ROHs are found in samples with inbreeding between closer relatives, ROHs are ubiquitously found in samples across the world, even in seemingly outbred populations. By examining the proportion of the genome contained in ROHs (F_{ROH}) alongside other estimates of inbreeding (e.g., F_{UNI}, the correlation between uniting gametes[6]), studies have shown how demographic history can influence the distribution of these different measures of inbreeding.[3,7]

In a previous study[8] using a sample of adolescents (from the Adolescent Brain Cognitive Development Study [ABCD Study],[9] born between 2006 and 2007), we found an unexpectedly low mean level of autozygosity relative to previous autozygosity reports (mean F_{ROH} = 0.0005[8] compared to 0.0016–0.007[10–12]) while the variance of F_{ROH} was similar to other studies. These prior studies analyzed samples of individuals with European genetic ancestry across the United States and Europe, all of whom were born at least 10 years earlier than the adolescents studied in Colbert et al. (2022).[8] In researching this finding, we came across a study from Nalls et al. (2009),[13] who found that in a sample of 809 North Americans of European descent aged 19–99 years old, autozygosity steadily declined over time at a rate of 0.12% decrease in F_{ROH} for every 20-year increase in individuals' birth year. Aside from Nalls et al. (2009), there seem to be few mentions of this phenomenon in modern samples, except for a study that measured ancestry-based assortative mating to conclude that endogamy was decreasing over successive generations, which can be assumed to confer lower levels of F_{ROH}.[14] Very recently, another study replicated our findings, showing that autozygosity increases with age in UKB individuals with European genetic ancestry and, conversely, autozygosity decreases with age in British Pakistani individuals in the Genes and Health cohort.[15] There are also interesting analyses of ancient DNA samples that found decreasing F_{ROH} over thousands of years during

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the Holocene[7] and a noticeable decline in the abundance of short ROH segments shortly following the Neolithic transition.[16] We hypothesized that the relatively low level of autozygosity in the young ABCD Study sample might be reflective of secular trends of decreasing autozygosity over generational time in the modern era. In the previous study, we tested this by conducting a brief assessment of an independent cohort, the Collaborative Study on the Genetics of Alcoholism (COGA),[17–19] and observed a small but highly significant decrease in F_{ROH} with increasing individuals' birth year (standardized beta = −0.06, SE = 0.01, p = 2.5e−9).[8] On the basis of this finding, we would predict a 0.001 decrease in F_{ROH} over a period of 100 years. However, this trend has so far primarily been examined in relatively small (n < 11,000) North American cohorts comprised mostly of individuals of European and African descent. Thus, it is unclear to what extent this association between F_{ROH} and individuals' birth year generalizes across different and more diverse samples.

In the current report, we sought to address these gaps in the literature by using data from three large cohorts, two from the US (All of Us [AoU], n = 82,474; Million Veteran Program [MVP], n = 622,497) and one from the UK (UK Biobank [UKB], n = 380,899), which include individuals of six ancestry groups determined by genetic principal components (PCs), broadly defined as African ancestry (AFR) (n = 141,469), admixed American ancestry (AMR) (n = 69,365), Central South Asian ancestry (CSA) (n = 9,906), East Asian ancestry (EAS) (n = 15,241), European ancestry (EUR) (n = 847,425), and Middle Eastern ancestry (MID) (n = 2,464).

As allele frequencies can differ across genetic ancestry groups, we performed quality control, ROH calling, and F_{ROH} regressions separately in each genetic ancestry subset of the cohorts before meta-analyzing to increase sample size and statistical power. Thus, initial association tests were conducted in unrelated individuals in each ancestry subset of each cohort with a linear fixed-effect regression model, which tested for the effect of individuals' birth year on F_{ROH}, controlling for age, sex, and the first ten within-ancestry genetic PCs as well as genotyping batch and assessment center in the UK Biobank (Table S1). We also performed two additional tests in the UK Biobank in which we either excluded (0 PCs) or covaried for additional PCs (20 total PCs) in our primary models. Neither of these changes substantially altered our results (Table S2). In this report, we avoid comparing the F_{ROH}∼birth year relationships between genetic ancestries because sample sizes in some genetic ancestry subsets are too small to draw substantive conclusions (but individual within-ancestry estimates of the F_{ROH}∼birth year association are presented in Figure 1B). Using the effect sizes from the ancestry- and cohort-specific models, we performed two separate meta-analyses. First, we meta-analyzed across all cohorts and genetic ancestry groups by using a mixed-effect meta-analysis model. We first tested a model with main effects only (ancestry and country as fixed effects, cohort as a random effect); when we then tested a model with an interaction term between ancestry group and country, this model fit significantly better than the main-effects-only model (chi-square difference = 27.156, p = 5.32e−5). Given this finding, we decided to also examine country-specific estimates; thus, we also present a mixed-effect meta-analysis (controlling for genetic ancestry group as a fixed effect and cohort as a random effect) of the two US cohorts and a fixed-effect meta-analysis of the UK cohort (since there was only one UK cohort, we did not need to include cohort as a random effect) to calculate and compare country-specific estimates. In this report, we present the meta-analyzed slope (beta_M) from our meta-analysis models; this represents the effect of individuals' birth year on F_{ROH} on average across ancestry groups, countries, and cohorts. We applied a Bonferroni correction to correct for six total tests: two models (main model, model correcting for educational attainment and income) meta-analyzed three ways (across all cohorts, only in US samples, only in UK samples), resulting in a significance threshold of p = 0.0083. We note that this threshold is somewhat conservative given the substantial overlap amongst the tests.

In the primary meta-analysis across all ancestry groups and cohorts, individuals' birth year was negatively associated with F_{ROH} on average (beta_M = −0.029, SE = 0.009, p = 6.03e−4; Figure 1A, Table S1). This effect equates to a 0.29% (SE = 0.12) decline in F_{ROH} for every 20 years increase in individuals' birth year; this estimate is larger in magnitude than the 0.12% (SE = 0.04) decrease in F_{ROH} per 20 years previously observed by Nalls et al. (2009). In the supplemental text, we also present an analysis of the association between birth year and an alternative measure of inbreeding, F_{UNI}; overall, we observe weaker associations but consistent direction of effects (Table S3). We performed post-hoc analyses estimating the associations between birth year and number of ROH segments (NSEG) and average length of ROH segments (KB AVG) to determine whether the association may be driven by a decrease in number or length of ROHs. Estimates of the association between these measures and birth year in the CSA ancestry group were noticeable outliers, so we also performed these meta-analyses excluding individuals with CSA genetic ancestry. Higher rates of consanguinity have previously been reported for individuals of CSA genetic ancestry in the UK Biobank[15] and other UK-based cohorts of CSA genetic ancestry. Results from the overall meta-analysis (Table S4) were non-significant (NSEG: beta_M = −0.026, SE = 0.029, p = 0.372; KB AVG: beta_M = −10.891, SE = 10.361, p = 0.293). Effect sizes increased when we excluded the CSA ancestry groups from the meta-analysis, and stronger effects were observed for number of ROH segments than for ROH lengths (NSEG: beta_M = −0.080, SE = 0.031, p = 0.009; KB AVG: beta_M = −26.467, SE = 11.212, p = 0.018), but did not pass our multiple testing correction threshold for significance (alpha = 0.0083). In the meta-analysis of US-only cohorts (excluding CSA ancestry groups), the association between birth year and number of ROH segments was

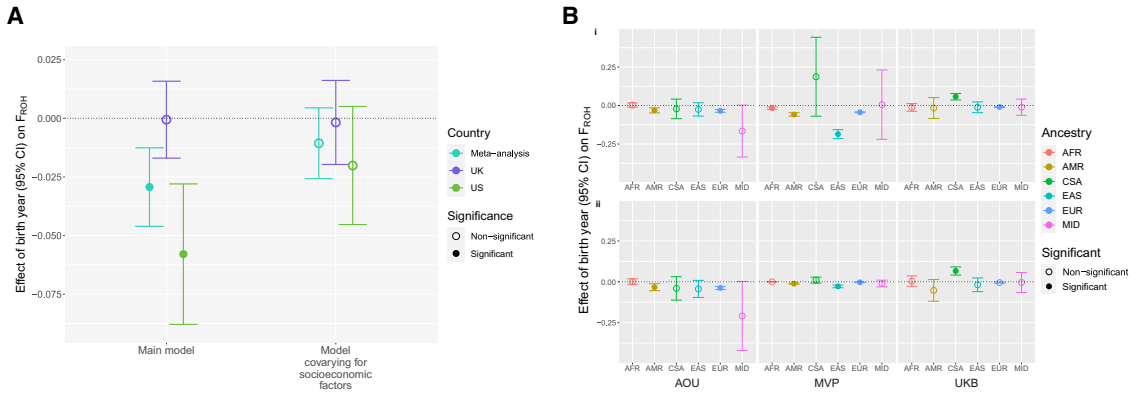

Figure 1. Effect of birth year on F_{ROH}

(A) Effect of birth year on F_{ROH} in each meta-analysis and model type. Points represent meta-analyzed slope values and bars represent 95% confidence intervals. Significance was determined with a conservative Bonferroni correction for six tests (three types of meta-analysis [UK, US, and overall] and two possible models [main model, model controlling for socioeconomic factors]), resulting in a p value threshold of 0.0083.

(B) Effect of birth year on F_{ROH} in each ancestry and cohort. Points represent betas and bars represent 95% confidence intervals. Effects in the main model are shown in (Bi), effects when controlling for educational attainment and income are shown in (Bii). Significance was determined with the previously mentioned threshold of p = 0.0083. AFR, African genetic ancestry; AMR, admixed American genetic ancestry; CSA, Central South Asian genetic ancestry; EAS, East Asian genetic ancestry; EUR, European genetic ancestry; MID, Middle Eastern genetic ancestry.

statistically significant (beta_M = −0.131, SE = 0.044, p = 0.003).

We found divergent effects in the within-country meta-analyses, observing a significant and strong negative effect of individuals' birth year on F_{ROH} in the US cohorts (beta_M = −0.058, SE = 0.015, p = 1.50e−4) but a non-significant effect in the UK cohort (beta_M = −0.001, SE = 0.008, p = 0.945). We note that a significant negative association was observed in the UKB sample of European descent (beta = −0.010, SE = 0.002, p = 6.11e−9); still, the effect was much weaker than in the genetically defined European ancestry subsets of the AoU (beta = −0.035, SE = 0.005, p = 2.22e−13) and MVP (beta = −0.044, SE = 0.001, p = 2.65e−195) cohorts (Figure 1B). This may reflect differences across the US and UK in terms of the rate of urbanization and/or demographic changes. While the percent of the population living in urban areas has surged 29% over the last 70 years in the US, urbanization in the UK has only increased by 6.2%,[20] potentially contributing to the weaker changes in autozygosity in the UK cohort. Another possible reason for this difference is migration patterns; consistent immigration to the US from many different countries over the 20th century has facilitated more diverse and frequent admixture in Americans,[21] leading to a more rapid decline in average autozygosity compared to the UK where immigration rates are lower.[22] Furthermore, the physical isolation of Britain from the rest of Europe has presented challenges to migration historically,[23] providing an explanation for the more stable rate of autozygosity in this population. We also acknowledge that the UK Biobank, compared to the two US cohorts, is much more limited in the birth year span of its cohort. Individuals in the UK Biobank were born between 1936 and 1970, while individuals in the MVP and AoU cohorts had birth years ranging from 1904 to 1999 and 1915 to 2003, respectively. It is possible that the decline in autozygosity observed in the US cohorts may only become identifiable over many generations, as shorter periods of time may reflect short-term trends in response to historical and sociocultural changes. However, when we restricted the age range in the genetically defined European subset of the AoU cohort to match the birth years of the UKB (1936–1970), the effect, while slightly attenuated, was still larger in the AoU cohort (beta = −0.028, SE = 0.006, p = 1.13e−6) than in the UKB cohort.

Previous studies have demonstrated strong relationships between educational attainment, social mobility, and autozygosity; greater educational attainment correlates with more mobility,[24] and greater mobility in the parental generation mediates observed relationships between their educational attainment and their child's autozygosity.[12] To investigate whether differences in educational attainment and other socioeconomic factors such as income might be responsible for the observed decline in autozygosity over time, we tested an additional model in which birth year, educational attainment, and income simultaneously predicted F_{ROH} (while controlling for the same covariates as above, see supplemental material and methods). After meta-analyzing across cohorts and genetic ancestry groups, the effect of birth year on F_{ROH} was attenuated when educational attainment and income were included in the model (beta_M = −0.011, SE = 0.008, p = 0.167; Figure 1A). We subsequently meta-analyzed within countries and found that educational attainment and income substantially weakened the effect in the US cohorts (beta_M = −0.020, SE = 0.013, p = 0.117) (Figure 1A). In the UK, where the association between F_{ROH} and birth year was already close to null when averaged across ancestry groups, controlling for educational attainment and income had no notable effect

on the F_{ROH}~birth year relationship (beta_M = −0.002, SE = 0.009, p = 0.848). We speculate that generations have become increasingly more educated over time, and this has changed patterns in mobility; perhaps these patterns of increased geographic mobility, acting in concert with assortative mating on socioeconomic status, have partially contributed to the observed decrease in autozygosity over time. As mentioned above, studies including both parental and offspring educational attainment in ROH analyses[8,12] have shown that individuals with higher educational attainment are more likely to migrate a greater distance from their hometown, leading to their mating with an individual more genetically different from them and possibly confounding the relationship between F_{ROH} and educational attainment. While the datasets used in this study do not have parental phenotypes available, we aimed to approximate these parental phenotypes by using educational attainment polygenic scores (PGSs) of the study participants as an estimate of the parental average for educational attainment, as has been done previously.[25] Due to the characteristics of the cohorts included in our study and the limited availability of educational attainment genome-wide association studies (GWASs) in individuals of non-European genetic ancestry, we restricted the analysis to individuals of genetically defined European ancestry in the UKB cohort. Covarying for educational attainment PGSs did not affect the relationship between F_{ROH} and birth year in this subset (beta = −0.010, SE = 0.002, p = 6.77e−9, partial R^2 for birth year = 0.0093% in both models), suggesting that parental educational attainment may not be contributing to this association. However, interpretation of these results is limited, considering that actual measures of parental educational attainment were unavailable, and the analysis was restricted to individuals in the UKB with European genetic ancestry. Additionally, to test whether levels of education and income have increased over generations, we regressed educational attainment and income on birth year and indeed observed a significant increase in educational attainment over time (beta_M = 0.102, SE = 0.034, p = 0.003; Table S5), while the change in income was not significant (beta_M = −0.081, SE = 0.116, p = 0.487). Within-country meta-analyses revealed a much stronger positive relationship between educational attainment and birth year in the UK (beta_M = 0.136, SE = 0.009, p = 1.04e−56) than in the US (beta_M = 0.069, SE = 0.068, p = 0.309). Furthermore, this null result in the US meta-analysis seemed to be driven by conflicting ancestry-specific results in the AoU cohort: the two largest ancestry groups show significant *negative* relationships between educational attainment and birth year, and the third-largest ancestry group demonstrates a significant association in the expected, positive direction (Table S1). Results did not change when we restricted the age range in AoU to match the birth years of the UK Biobank (1936–1970).

Like Nalls et al. (2009), we consider that the overall pattern of decreasing autozygosity may be associated with population growth, urbanization, and increased mobility. Population sizes have increased both in the US and worldwide[26] and previous analyses have noted that rapid growth in population size or large effective population size is associated with a decrease in autozygosity.[3,7,27] For example, a study from Ceballos et al. (2021)[7] found a decrease in F_{ROH} over thousands of years during the Holocene, most likely in response to population growth arising from the development of agriculture at the time. Population expansion, therefore, appears to contribute to decreases in autozygosity over both short and long time periods as well as in both modern and ancient samples. In addition to modern population growth, the flocking of individuals from many small, isolated rural areas to densely populated cities breaks down previous geographic and population barriers to panmixia, in turn reducing endogamy and increasing the likelihood that individuals mate with those who are more genetically different from themselves.[24,28] Our results also suggest that socioeconomic factors, especially educational attainment, at least partially explain the F_{ROH}~birth year relationship. We found that educational attainment is higher on average in more recent generations, although this relationship was stronger in the UK Biobank and the MVP cohorts than in AoU, where results were mixed. One previous study found that those with higher educational attainment were more likely to move large distances away from their birthplace and subsequently mate with an individual who was less closely related to them but who also shared a similarly high level of educational attainment. As a result, offspring of these individuals were more outbred (had low levels of autozygosity) and would have inherited genes associated with greater educational attainment.[12] As individuals became increasingly more educated, this pattern of migration and mating may have become more common, leading to overall declines in average autozygosity. It may also be that increased globalization and mobility are reflected in higher levels of educational attainment,[29,30] which then are associated with lower autozygosity on average in the countries we have studied. Still, the relationships between socioeconomic factors and birth year were not as definite in the US cohorts as in the UK Biobank, and further studies are needed to clarify the role of these factors in the observed decline in autozygosity.

Nalls et al. (2009) also hypothesized that decreasing autozygosity should correlate with decreasing rates of rare recessive genetic diseases, while Campbell et al. (2009)[31] estimated that this effect measured by Nalls et al. (2009) has prevented 1% of the annual births that would be affected with an autosomal-recessive disorder. We might also expect slight changes in complex traits that are partly influenced by recessive variants, such as cognitive abilities.[3] We used our estimated rates of declining autozygosity and estimates of associations between F_{ROH} and complex traits from published literature[3] to predict estimated changes in several traits. For example, on the basis of our findings in the European-ancestry subset of the AoU sample and published associations in Clark et al. (2019), we predict a 0.004 standard deviation increase in cognitive *g*,

a 0.019-kg increase in grip strength, a 0.019-cm increase in height, and a 0.0095-year increase in educational attainment over a 100-year period as a result of decreases in autozygosity. Of course, these are only illustrative predictions, but we expect that while declining autozygosity might have small effects on complex traits, such as those estimated here, this decline may show more appreciable effects on traits and diseases that are more strongly influenced by rare, recessive genetic variants. However, we note that over short periods of time (e.g., 100 years) cultural changes may ultimately have a larger impact on phenotypic outcomes than genetic changes.[24]

Importantly, we also note that these findings shed light on the consequences of overlooking sample composition—including range of birth years—when conducting comparisons of the effects of autozygosity across populations. Future studies that wish to analyze estimates of inbreeding, such as F_{ROH}, across populations should be aware that sample differences not only in geography or genetically defined ancestry groups but also in age can affect the mean level of F_{ROH}.

We note several limitations to the current study, the first being that our analyses only include samples from the US and UK. Given the differences observed between the US and UK cohorts, we would also expect changes in autozygosity over time to differ in cohorts from other countries in response to region-specific cultural practices (e.g., consanguinity) and demographic trends (e.g., migration rates). As biobanks in other countries continue to grow and include more diverse samples, we will be better able to assess how this pattern may differ from country to country. While we were able to include a diverse sample encompassing individuals from six different genetic ancestry clusters, a major limitation of our sample ($n = 1{,}085{,}870$) is that it still consisted mainly of individuals with European genetic ancestry ($n = 847{,}427$; 78.0%). Therefore, the overall generalizability of our findings across samples of non-European ancestry groups is limited. Furthermore, the degree of admixture in individuals in this study most likely varies amongst the different genetic ancestry groups and cohorts. For example, a majority of the individuals in the genetically defined American and African ancestry subsets of the UK Biobank are most likely admixed and share ancestry with the individuals in the European ancestry subset. On the other hand, individuals in the UK Biobank with less common patterns of admixture could not be grouped into sufficiently sized groups and were thus excluded by the PanUKB analysis team.[32] A study of ancestry diversity in the MVP cohort found that admixture is increasing over time and younger individuals demonstrate greater genetic heterogeneity,[33] suggesting that cross-ancestry mating may be a contributing factor to declining autozygosity and by excluding individuals with greater admixture we are most likely under-estimating the true decline in autozygosity over time. Finally, while we show that educational attainment and income partly drive the observed association, we were unable to investigate how other variables linked to assortative mating, such as religiosity, may also influence autozygosity.[34] Moreover, it is difficult to determine whether educational attainment is truly driving the F_{ROH}~birth year relationship or whether controlling for educational attainment may be inducing a collider bias that weakens the relationship given that F_{ROH} could be causing decreases in educational attainment[3,5,10] (i.e., inbreeding depression) and birth year may also be causing increases in educational attainment. In the UKB, we do find that educational attainment is somewhat negatively correlated with F_{ROH} ($r = -0.009$) and positively correlated with birth year ($r = 0.218$), suggesting that collider bias may be a concern. Our findings should be interpreted in light of this potential bias.

In summary, we demonstrate an overall trend of declining autozygosity over time on average across multiple ancestry groups and countries, with a stronger overall effect in the US than in the UK. Controlling for educational attainment and income substantially attenuates this relationship but does not fully explain the decline in autozygosity observed. We hypothesize that population growth combined with increased urbanization, globalization, and mobility are likely to be driving this trend. Future research should assess the relationship between autozygosity and individuals' birth year in better-powered samples of more diverse ancestry groups and ages in order to determine how autozygosity has changed across different time spans and regions.

Data and code availability

The UK Biobank data used in this study are available from the UK Biobank by applying for access via the Access Management System (https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access). Original All of Us Biobank data are available to registered and approved All of Us researchers (https://www.researchallofus.org/register/). Genetic data requires controlled tier access, which researchers can register for through their institutions. Data from the Million Veteran Program are only available to VA investigators and other approved partners. Code to analyze the UK Biobank data is available via GitHub: https://github.com/sarahcolbert/autozygosity_time_ukbb. For privacy reasons, we are unable to share the code used to analyze the AoU and MVP data, but the code is almost identical to the code used to analyze the UK Biobank data.

Supplemental information

Supplemental information can be found online at https://doi.org/10.1016/j.ajhg.2023.04.007.

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Declaration of interests

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