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Original Contribution

Socioeconomic Inequalities and Molecular Risk for Aging in Young Adulthood

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Diverse manifestations of biological aging often reflect disparities in socioeconomic status (SES). In this paper, we examine associations between indicators of SES and an mRNA-based aging signature during young adulthood, before clinical indications of aging are common. We use data from wave V (2016–2018) of the National Longitudinal Study of Adolescent to Adult Health, a nationally representative study of adults aged 33–43 years, with transcriptomic data from a subset of 2,491 participants. Biological aging is measured using 1) a composite transcriptomic aging signature previously identified by Peters et al.'s out-of-sample meta-analysis (*Nat Commun*. 2015;6:8570) and 2) 9 subsets that represent functional pathways of coexpressed genes. SES refers to income, education, occupation, subjective social status, and a composite measure combining these 4 dimensions. We examine hypothesized mechanisms through which SES could affect aging: body mass index, smoking, health insurance status, difficulty paying bills, and psychosocial stress. We find that SES—especially the composite measure and income—is associated with transcriptomic aging and immune, mitochondrial, ribosomal, lysosomal, and proteomal pathways. Counterfactual mediational models suggest that the mediators partially account for these associations. The results thus reveal that numerous biological pathways associated with aging are already linked to SES in young adulthood.

aging; biodemography; gene expression; life-span development; social epidemiology; social genomics; socioeconomic status

Abbreviations: Add Health, National Longitudinal Study of Adolescent to Adult Health; BMI, body mass index; SES, socioeconomic status.

The timing of the onset of age-related disease, functional decline, and death is strongly associated with chronological age. Significant differences in biological processes that underpin aging are observed within age-homogeneous groups, however, and may reflect socioeconomic status (SES), with lower-status groups showing more age-related biological change than higher-status groups. Such differences are worthy of study because the monitoring of biomarkers of aging holds the potential to promote healthy aging and postpone manifestations of age-related disease and death.

Several strategies for measuring biological senescence have been suggested, including, for example, DNA methylation clocks and phenotype-based aging measures based on cognitive performance and physical functioning (1–4). In this paper, we draw on transcriptomic data as one such strategy. Biological senescence is characterized by multisystem changes in health (5), and transcriptomic analysis is well-suited to describe activity in diverse molecular pathways. Many of these pathways—called "the hallmarks of aging"—are conserved across eukaryotes, including altered transcription of genes involved in mitochondrial proteins, protein synthesis, the immune system, growth factor signaling, DNA damage and repair, and mRNA processing (5–7).

Indeed, a well-powered meta-analysis of transcriptomic data from human whole blood revealed 8 modules of age-related, coexpressed genes that overlap appreciably with these pathways (8). The conservation of these transcriptomic changes from organisms such as yeast to humans suggests intrinsic cellular processes but, in the case of humans and some nonhuman primates, at least some genes in these

pathways are also responsive to social circumstances, including social status (9, 10).

This paper examines socioeconomic disparities in aging as indicated by mRNA abundance levels in whole blood, drawing on a nationally representative sample of US young adults who have been followed for over 2 decades, the National Longitudinal Study of Adolescent to Adult Health (Add Health) (11). We focus on a transcriptomics-based aging gene set (1,497 genes) that was identified in an out-of-sample meta-analysis conducted by Peters et al. (8). Because the study is well-powered and includes diverse populations, the resulting gene set is relatively comprehensive and generalizable.

Decades of research have established that low SES—typically defined in terms of education, occupation, and income—predicts elevated morbidity and mortality (12–14). Given that age-dependent declines in physiological function are often risk factors for major diseases, SES disparities in these morbidities may also be observed with respect to aging. Moreover, changes in protein-protein networks associated with longevity are frequently and expectedly associated with diseases of aging, many of which are predicted by SES (15). By extension, the transcriptomic basis for longevity networks may also be predicted, in part, by SES.

Observed associations between SES and age-related diseases likely reflect diverse mechanisms that promote wear and tear, which should be observed at the transcriptomic level. Low SES predicts exposures to psychosocial and environmental stressors and the efficacy of strategies for neutralizing such exposures (16–19). Further, many health-related risk factors (e.g., smoking, body mass index (BMI; weight (kg)/height $(m)^2$)) are associated with low SES and represent notable sources of physiological stressors (20, 21). Our work advances the understanding of how social exposure is embodied to create inequalities in health and mortality later in life using an innovative perspective (22).

Indeed, SES predicts DNA methylation (23–25) and transcriptomic profiles indicative of health in adulthood (26, 27). The most consistent finding across such studies is that indicators of SES are associated with the chronic up-regulation of proinflammatory genes (28), and the dysregulation of immunity is a key finding in many aging signatures (7). Less consistently reported but also related to aging is down-regulation of genes associated with cell cycle and intracellular signaling (in the mitogen-activated protein kinase (MAPK) pathway). However, connections between SES and transcriptomics-based aging signatures are less studied (29, 30), especially among young adults. In a sample of respondents from Ireland, Australia, and Italy, education and income were associated with "intrinsic accelerated aging" (defined as the residuals from the regression of an epigenetic clock on chronological age and blood cell composition) (24). In a sample of African Americans in the United States, early adversity was associated with the Peters aging signature in young adulthood (31). Yet, to our knowledge, no published research has examined connections between SES and transcriptomic aging in a representative sample of the US population. Add Health includes standard measures of SES (income, education, and occupation and, additionally, subjective status), allowing us to examine how they are related to transcriptomic aging in early midlife.

This work examines not only SES gradients in aging but also possible mediating mechanisms using counterfactual models. BMI and smoking reflect strong SES-based gradients (32, 33) and are associated with gene expression profiles related to many common morbidities (21, 34, 35). Socially based stressors are also distributed in the population by SES and have well-documented deleterious effects on molecular risk for many stress-related symptoms and conditions (9, 28, 34, 35). Add Health includes measures of perceived stress and material hardship (lack of health insurance and difficulty paying bills), which are common stressors in the United States.

Findings reveal that all aspects of SES (especially the SES composite measure and income) in adulthood predict the aging composite measure and several functional pathways that play key roles in senescence; these associations may be explained, in part, by the proposed mediators.

METHODS

Sample

Data come from wave V (2016–2018) of Add Health, a nationally representative sample of adults aged 33–43 years (average age = 38 years) in 2016–2017. At wave V, mRNA data were collected and analyzed from a random subsample of respondents of which we were able to analyze sample 1 and sample 2 (n = 2,491). Web Appendix 1 (available at https://doi.org/10.1093/aje/kwad155) describes the protocol for the mRNA data, and Web Appendix 2 describes preprocessing steps for the mRNA data. This unique data set constitutes the largest nationally representative study of young adults with blood transcriptomic data that is currently available, to our knowledge. Web Table 1 shows a comparison between wave V and the wave V mRNA samples. Because of a relatively large sample size, statistically significant differences are observed but, substantively, the samples differ notably only in terms of SES (driven by education and, to a lesser extent, occupation) and race/ethnicity. The derivation of the analytical sample is depicted in Web Figure 1.

Aging signature

To measure age-related gene expression, we started with the 1,497 genes identified by Peters et al. (8) as differentially expressed by chronological age in a whole-blood meta-analysis. These authors also performed gene-set enrichment analyses, revealing some of the complex biological processes associated with aging: dysregulation of metabolic function, DNA damage accumulation, ribosomal biology, immunological function, and mitochondrial degeneration. We eliminated genes with zero counts, insufficient variation, or lack of Human Genome Organization (HUGO) identification, following standard practice in gene expression data preprocessing (36). Further details can be found in Web Appendix 2. Our gene set contains 1,048 genes

of the 1,497 aging genes originally identified by Peters et al. (8). We henceforth refer to this set of 1,048 as the aging composite signature. The analyses also refer to the 9 subsets of this composite aging signature identified by Peters et al. (8) using pathway analysis for coexpressed genes: DNA replication, RNA metabolism, mitochondrial function, ribosomal activity, immune-related genes, actin regulation, fatty acid metabolism, innate/adaptive immunity, and lysosome metabolism. That is, signatures were also created based on whether each of the 1,048 genes belonged to one of these 9 subsets. The 9 functionally defined gene sets identified by Peters et al. (8) do not, however, exhaust the full aging composite measure. They account for 230 out of 1,048 genes in all, leaving 818 of 1,048 genes, the functions of which presently remain unclear (designated the "aging complement set").

Measurement of SES at wave V

SES was operationalized by education, income, subjective social status, occupation, and a composite measure of the different indicators. Education is the number of years of completed education; income is the gross household income (log-transformed); occupation is measured as a socioeconomic index score for a young adult's current job (37, 38); and subjective status in young adulthood was assessed with the MacArthur Scale of Subjective Social Status, which asks respondents to rank themselves on a 10-rung ladder that represents money, education, and prestige in the US population (39). The SES composite represents the sum of the standardized indicators (see details in Web Appendix 3).

Measurement of mediators at wave V

Our candidate mediators, measured contemporaneously with the mRNA, include health behaviors and select measures of stress: BMI, current smoking status, a shortened version of Cohen's scale of perceived stress (40), lack of health insurance, and difficulty paying bills. Web Figure 2 shows correlations among the hypothesized mediators.

Covariates

Based on a literature review, we constructed a causal diagram to assess which variables might confound the relationship between mRNA aging signature and SES (see Web Figure 3). As controls, we include birth year, biological sex (male or female), self-designated race/ethnicity, region of residence, pregnancy status, an indicator variable for illnesses in the 4 weeks before interview, any illness in the 2 weeks before data collection, smoking status at the time of blood draw, an indicator for normal kit condition, an indicator for normal tube conditions, number of hours spent fasting before the blood draw, month of collection, and time of day in 2-hour intervals. Two mRNA technical controls were also included: assay batch and sample RNA profile quality. Finally, we include cell composition estimated using CIBERSORT32 (41). Descriptive statistics on the distribution of variables are reported in Web Table 1.

Statistical analysis

We began by testing the omnibus null hypothesis that SES is not associated with any gene in the composite aging signature and performed the same test for each of the functional subsets identified by Peters et al. (8) and the aging complement (i.e., the set of aging composite genes that lacked any defined functional subset). A series of linear models assesses differential expression of RNA-seq abundance data using the *limma* package in R (42). We then extract the minimum P value for each gene set, and we count the number of genes that are significant. The P value tests the hypothesis that there is at least 1 gene that is significant in each gene set. To correct for multiple comparisons across these partially overlapping (and therefore not statistically independent) gene subsets, we applied a whole-genome correction to each gene in our composite aging signature (and therefore its 9 interesting subsets). This approach corrects for type I error within and across the gene sets, and the correction was derived from a whole-genome linear regression for the association of SES with each gene with full controls. The P value of the omnibus test thus represents the multiplicity-corrected P value for the most significant gene but also the test of the omnibus hypothesis for the whole gene set (for more detail on this approach, see Dickhaus (43) and Futschik et al. (44)).

The omnibus test can be viewed as testing the "total effect" of SES on each gene set. For any gene set demonstrating this "total effect" of SES, we therefore asked whether this association was potentially mediated. For each gene in a SES-associated gene set, we estimated a univariate mediation model, using the R package *mediation* (45). This yielded a list of P values testing the mediation hypothesis for each gene in isolation. The mediational omnibus null hypothesis is thus that no gene with a demonstrated "total effect" of SES is attributable, in part, to the hypothesized mediators. The same correction for multiplicity applies to the direct effects (i.e., the component of the total effect *not* mediated by our hypothesized mediators). For each of the mediators, we report results from the omnibus tests of the average causal mediated effect. The data do not allow for an identification strategy, however, such that these results should be construed as multivariate descriptions and hypothesis-generating; causal language is avoided.

RESULTS

Figure 1 presents the results for the omnibus test for a total association of SES with each gene set. The statistical significance is shown for the minimum corrected P value within each signature (the correction is genomewide). The total association of SES with the aging composite signature is given in the bottom row, where different columns show different SES indicators. Figure 1 also shows the total association of SES with each aging-related functional gene subset identified by Peters et al. (8), together with its complement set (aging-related genes that were not included in any functional subset). Notable in this figure is the association of the composite SES and all individual indicators of SES with genes in the composite aging set (43 significant, unique genes with a minimum adjusted P value less than 0.0001

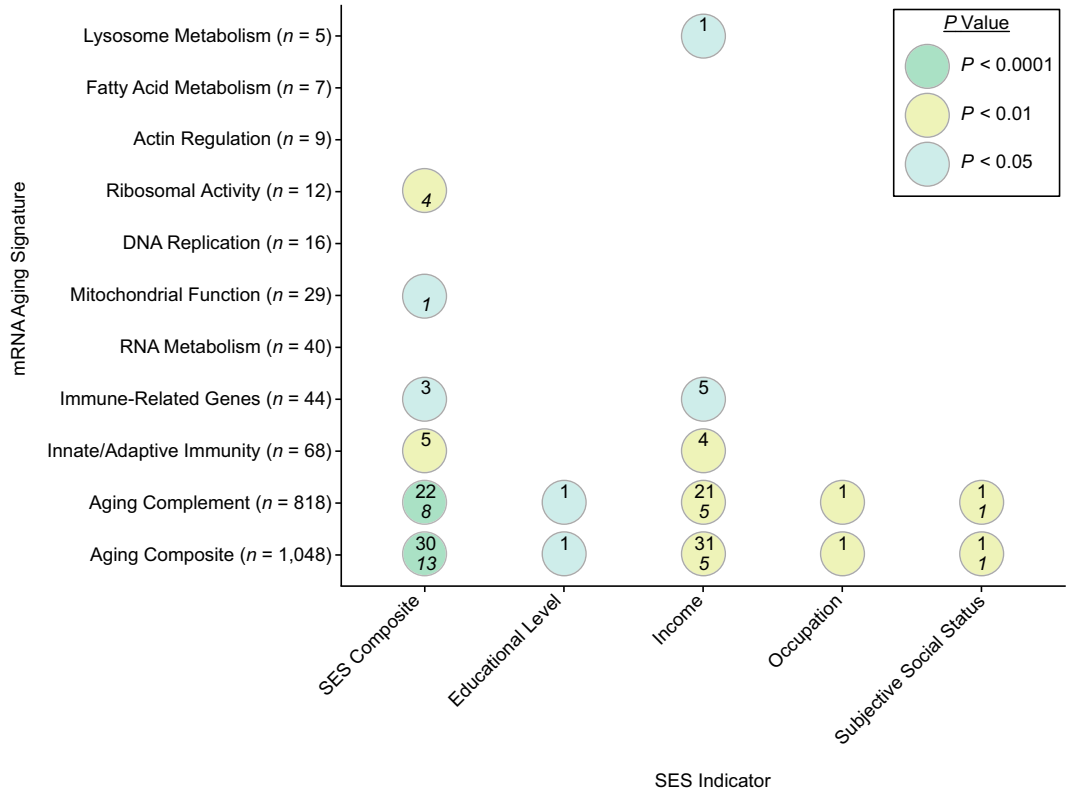

Figure 1. Associations between socioeconomic status (SES) and the composite aging signature (bottom row) and its functional subclusters (the number of genes included in each cluster is indicated in parentheses), National Longitudinal Study of Adolescent to Adult Health, 2016–2018. Circle size corresponds to omnibus statistical significance (*P* value on the $-\log_{10}$ scale) for the association between SES and each a priori gene set, corrected for multiple comparisons. Numbers within circles indicate the frequency of significantly up-regulated (top ones) and significantly down-regulated (italic bottom ones) genes, including the "aging complement" set of aging-associated genes with no attributed biological function. The detailed list of genes is presented in Web Table 5.

for the SES composite and 36 with a *P* value less than 0.01 for income) and its complement subset (30 significant genes with a minimum *P* value less than 0.0001 for the SES composite and 26 with a *P* value less than 0.01 for income). The SES composite and income are also associated with the immune subset and the innate/adaptive immunity subset, and the SES composite is additionally related to the mitochondrial and ribosomal subsets and income with the lysosome metabolism subset. These results thus provide initial evidence that molecular risk for aging is graded by SES, particularly for associations involving the aging and SES composite measures, immunity, and income. We observe SES grading both with the omnibus test (reflecting the minimum *P* value within a set) and in terms of the number of significant genes, although a relatively small subset of the 1,048 genes accounts for all total effects.

Figure 2 depicts the omnibus tests for mediation (average causal mediated effects) among gene sets demonstrating a total SES association (i.e., as indicated by Figure 1) for the 5 different mediators. In the figure, we report the *minimum P value per signature* associated with each mediator and the median of the proportion mediated across genes. Mediation was supported for almost all hypothesized mediators across different SES indicators in the overall aging set. The SES composite and income associations were most frequently mediated by BMI for both the overall aging set and different gene subsets. Similarly, smoking partially mediated the association of subjective social status and the aging composite. Moreover, other stressors also significantly mediated the SES composite, education, occupation, and subjective social status. In particular, BMI has a prominent mediating role for all SES indicators except education. Similarly, perceived stress mediates the association for all SES indicators and the aging composite. Finally, smoking is a significant mediator for the SES composite, subjective social status, and education. Direct effects—the component of the total effect *not* mediated by our hypothesized mediators—are shown in Web Figure 4, suggesting that the mediators do not fully mediate the associations between SES and aging. These results suggest that the hypothesized mediators are plausible candidates for further investigation but that additional mechanisms are also implicated.

We then sought to identify the function of the 818 genes in the complement set via a gene-set enrichment analysis. In particular, we identified Reactome (46) physiological functions that are SES-dependent via a whole-genome

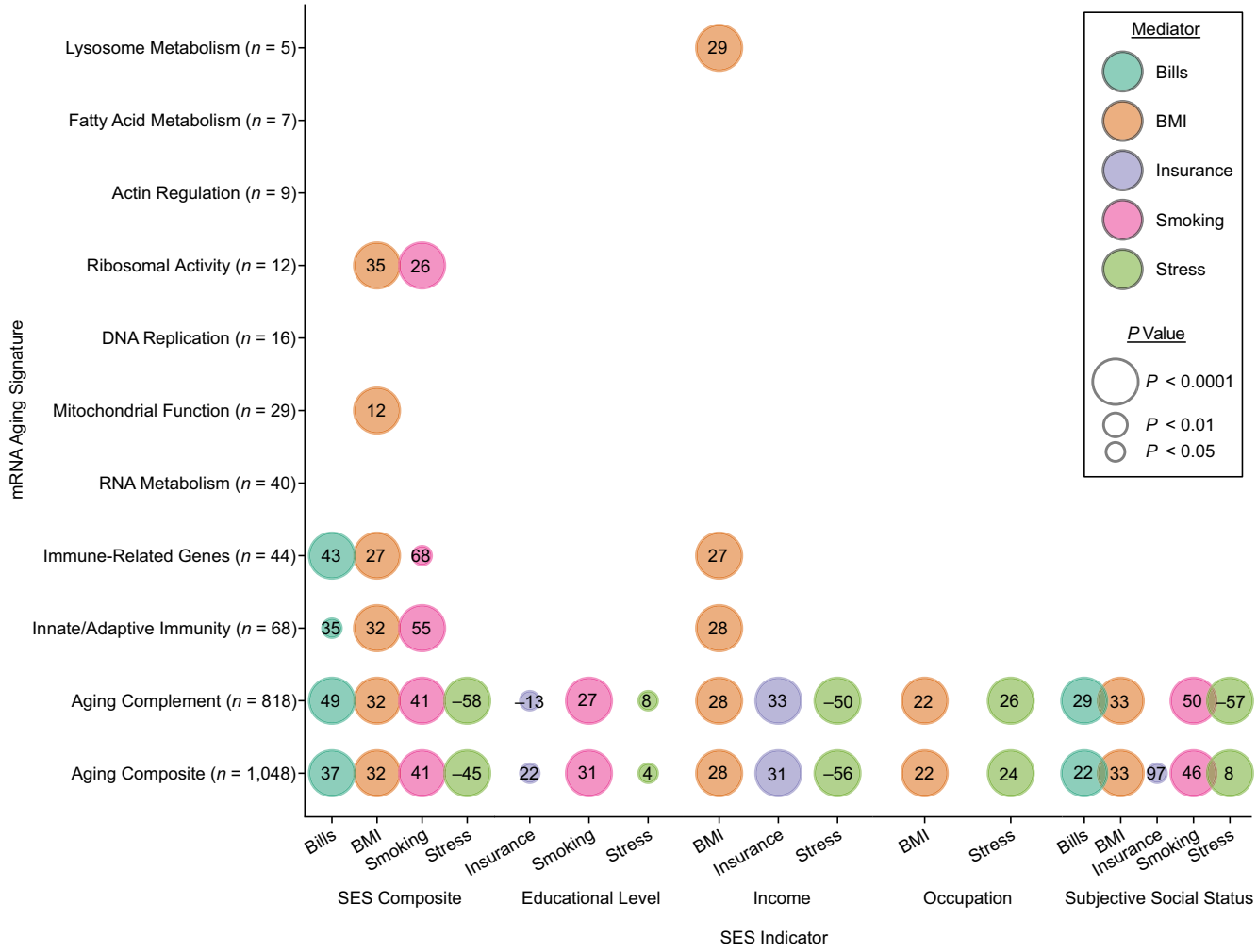

Figure 2. Decomposition of the demonstrated total effects in Figure 1, depicting minimum *P* values for the average causal mediated effects within each of the gene sets, National Longitudinal Study of Adolescent to Adult Health, 2016–2018. The *P* values are corrected for multiplicity and depicted on the $-\log_{10}$ scale. The figure shows the median of the proportion mediated across genes reported for each of the mediators (a negative proportion mediated suggests suppression). Web Table 6 shows the number of genes significant for each treatment, gene set, and mediator combination for the average causal mediated effects and for the total average direct effect. BMI, body mass index; SES, socioeconomic status.

screen and measured their overlap with our 818 aging genes. Figure 3 shows the SES-dependent physiological pathways identified by Reactome which overlap with the complement gene set. Immune and stress response emerge as relevant pathways (47).

Figure 4 relates the Reactome pathways presented in Figure 3 with the previously established hallmarks of aging (48) for each of the socioeconomic indicators. Most of the enriched pathways associated with every socioeconomic indicator can be linked to a loss of proteostasis. These include pathways in the gene translational control and RNA processing and decay pathways. Pathways in cellular energetics and infectious diseases are associated with mitochondrial dysfunction and cellular senescence hallmarks of aging, respectively, and are also observed for every SES indicator. Web Table 2 shows the detailed pathways for each of the SES indicators. The complement set is thus predicted by SES and its indicators and reflects molecular risks associated with aging.

We performed supplementary analyses to better describe heterogeneity in gene-specific associations within and across age-related gene sets. The results remained robust with the inclusion of early life circumstances, such as parental socioeconomic conditions (income and education) and adverse childhood conditions. Similar conclusions are also reached when all of the mediators together are used in mediation analysis (see Web Table 3). Moreover, we calculated expectation values (e-values) to test the sensitivity of an observed association to an unmeasured confounder (49). E-values were calculated for associations reported in Figures 1 and 2 and suggest that, generally, relationships involving occupational status are likely sensitive to unmeasured confounders (see Web Table 4). Finally, Web Figure 5 shows inferred cell type composition by SES.

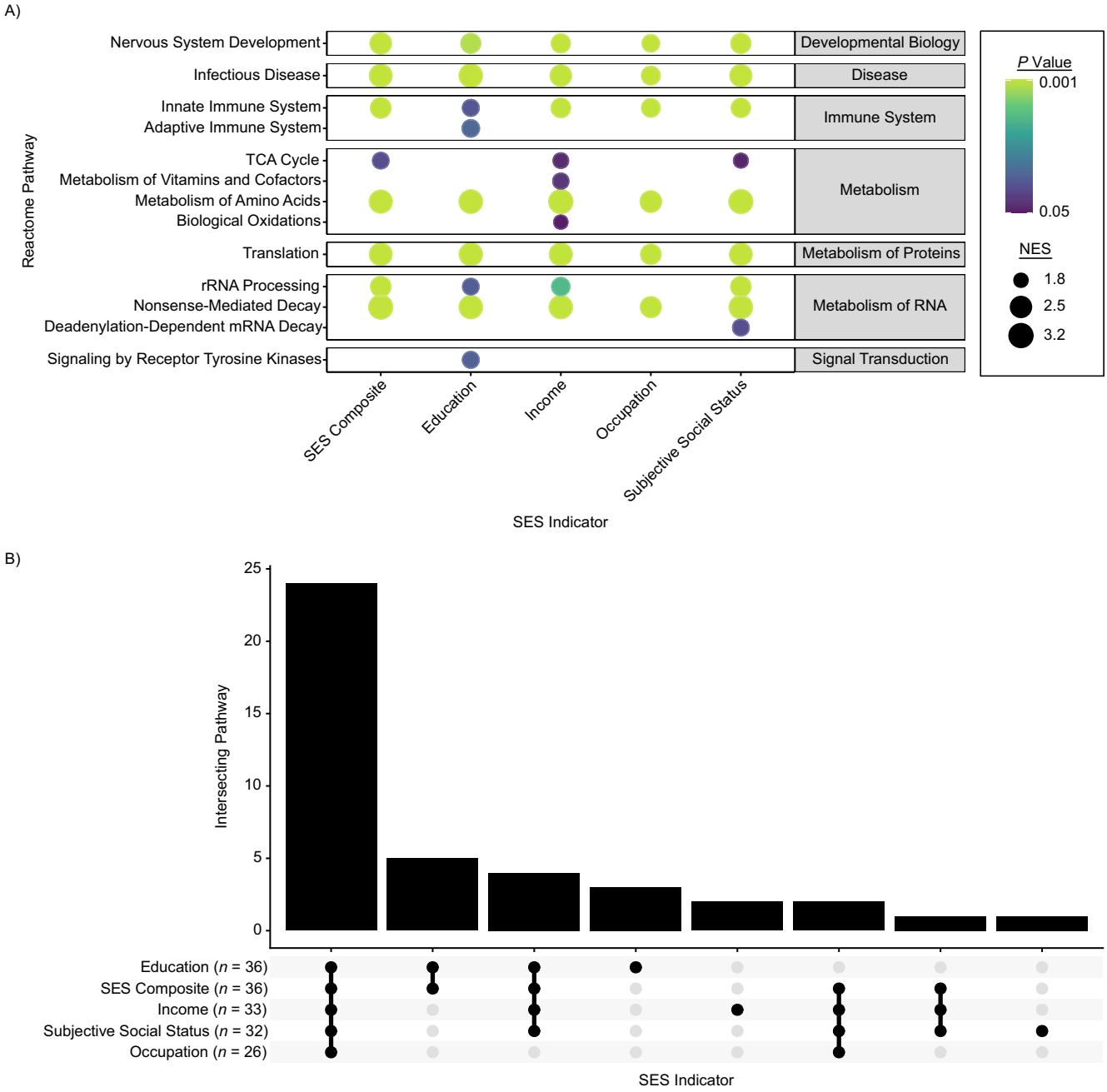

Figure 3. High-level summary of the socioeconomic status (SES)-dependent physiological roles of the 818 aging genes in the complement set, National Longitudinal Study of Adolescent to Adult Health, 2016–2018. Panel A represents the significantly enriched Reactome pathways (with parent nodes reported to the right and child nodes reported to the left). The size of each circle signifies the degree of enrichment, as indicated by a normalized enrichment score (NES), and the color of the circle indicates statistical significance (false discovery rate–adjusted *P* value). Panel B shows the number of Reactome pathways enriched by the differentially expressed genes within the aging complement set, by SES indicator. TCA, tricarboxylic acid.

DISCUSSION

This paper explores the association between an SES composite and its indicators and molecular risk for aging using mRNA abundance levels collected as part of a nationally representative sample of young adults in the United States. We found associations between all socioeconomic indicators and the aging composite measure. Some of the aging subsets—defined according to functional biological pathways—are only significant for the composite measure of SES and income. In general, the immune system, mitochondrial function, and ribosome metabolism are graded by

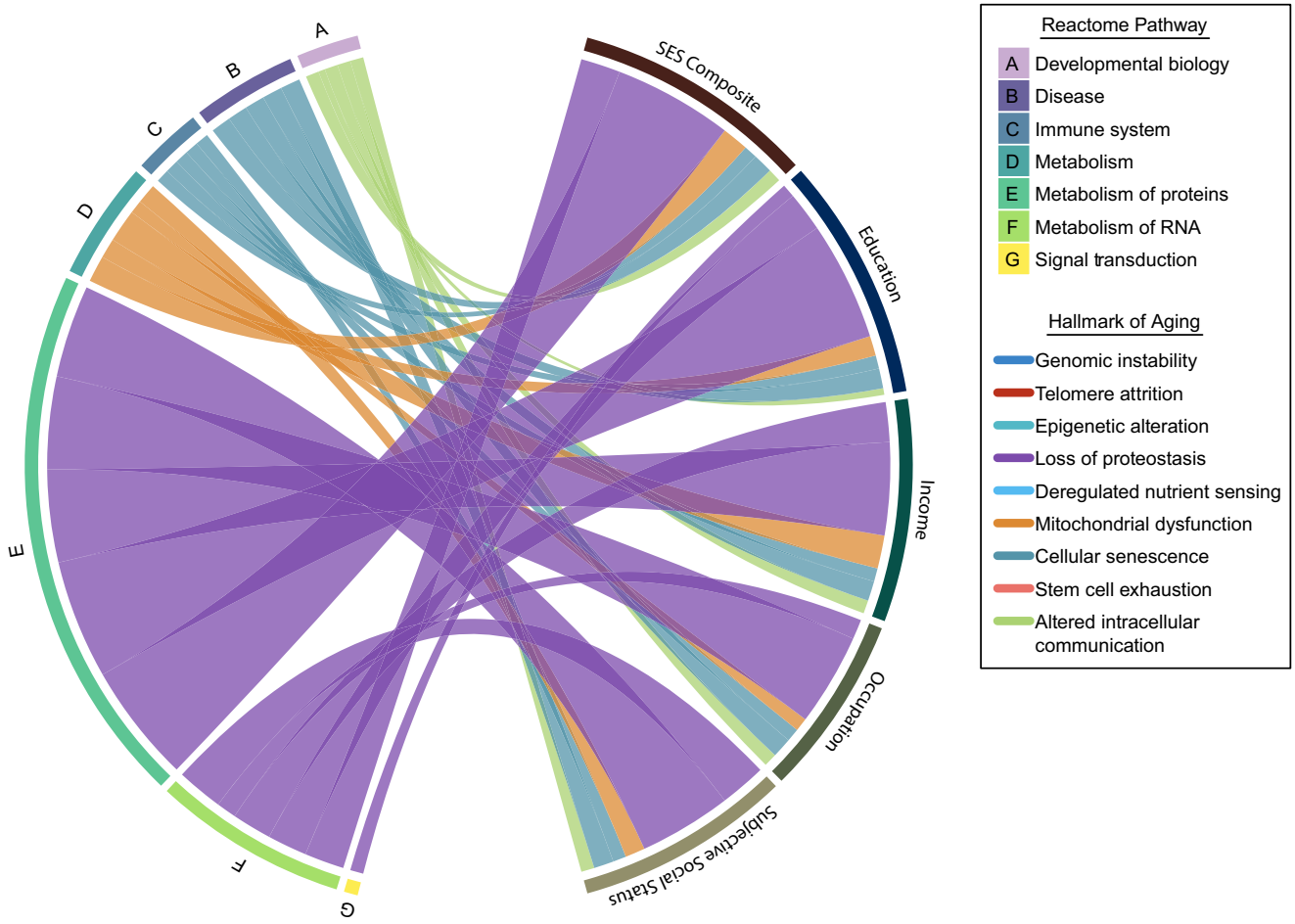

Figure 4. Biological pathways (identified by Reactome) enriched by genes differentially regulated by socioeconomic status (SES) indicators and their associations with the hallmarks of aging (50), National Longitudinal Study of Adolescent to Adult Health, 2016–2018. This chord diagram shows pathways classified into 7 classes enriched by every SES indicator for the aging complement. Pathways are shown for their predominant hallmark of aging.

SES. Moreover, the analyses aimed to understand possible mediational pathways linking socioeconomic circumstances in early adulthood to aging. Factors such as BMI and smoking showed a significant mediational effect for most of the SES associations. Stress and financial stress also emerged as potential mediators of several SES associations. Direct effects remained present even when controlling these mediational factors, suggesting the robustness of the findings to the inclusion of the mediators and the need for future research to identify additional mediating mechanisms. For example, modifiable health behaviors, such as diet, sleeping, and exercise, as well as environmental contextual factors (e.g., pollution and neighborhood disorganization) and psychological characteristics, warrant further exploration (50–52). Finally, we found that loss of proteostasis (53), mitochondrial disfunction, and cellular senescence are the hallmarks of aging which are most strongly associated with Reactome pathways related to SES, opening up new areas of research for quantification of multisystem physiological well-being.

The paper contributes to the existing literature on health disparities and aging by examining gene expression in a diverse sample of young adults (54, 55). Indeed, the SES disparities in age-related morbidity and mortality which are found later in life are observed, in terms of age-related gene expression, in the early adult life course. Our work suggests new avenues for studying SES differences in aging by emphasizing molecular risk decades before studies of aging and biology typically commence (2, 56). Of particular interest are 1) how early in life such patterns begin to coalesce and 2) whether these associations indeed predict age-related morbidity and mortality in the coming years.

Moreover, young adulthood—the life stage that extends from completion of secondary schooling to the establishment of one's independent household and early career development in Western societies—may offer a telling vantage point for the study of between-person variability in aging. Young adulthood has been characterized as a period of relative health but increasing health risks (57), suggesting diverging health profiles in the population in the third and fourth decades of life. SES and biological indicators of aging are often examined later in life (32), such that young adulthood represents an understudied phase

of the life course. Nevertheless, some evidence suggests that SES during this period predicts later morbidity (58). In fact, molecular risk (as indicated by transcription profiles) for the most common chronic conditions of later adulthood, which are strongly age-graded, is evident in young adulthood and is predicted by SES (59). Additionally, some evidence suggests the emergence of a linear association between chronological age and up-regulated aging genes beginning in young adulthood, and a peak expression of down-regulated aging genes at ages 30–45 years (33).

The focus on RNA-seq provides insight into the mechanisms that are extrinsically transduced from social experiences, such as social status and myriad forms of correlated acute and chronic stressors (60). To date, most research on aging and gene expression has focused on epigenetic changes associated with aging, with an emphasis on DNA methylation (29). Such a focus is warranted given mounting evidence that senescence, as indicated by methylation patterns, is correlated with cancer, musculoskeletal disease, and major depressive disorder and predicts cardiovascular disease and mortality (61–63). The degree of overlap, however, among various biological measures of aging (1) and, specifically, between differentially expressed genes in transcriptomic clocks and methylation sites in epigenetic clocks, is apparently low (64), suggesting the need to examine diverse biological indicators of aging (7, 29). Thus, future research should examine associations between transcriptomic results and other measures of physiological aging, especially with the decrease in cost associated with the analysis of transcriptomic and proteonomic data.

Finally, the data reflect a wide range of life circumstances in the US population of young adults, including diversity of socioeconomic circumstances. Moreover, the sample is relatively large for transcriptomic research that uses social data. Statistical power may be especially problematic in gene expression studies of aging where some genes (e.g., those related to ribosomal production and biogenesis) are very highly expressed and important changes in expression may be reflected in relatively small fold-changes (7). Larger samples thus allow for the detection of differential expression of such genes.

Our study is not free of limitations. First, because the data were not derived from a randomized experiment, causal conclusions are not possible without strong, untestable assumptions (e.g., no measured or unmeasured confounders and no causal interrelationships among the mediators themselves). Moreover, the methodological tools that we exploited for mediational analysis were initially developed for univariate analysis. Because socioeconomic conditions are not exogenous, we cannot exclude the possibility of health selection or downward social mobility due to health problems. In order to examine these possibilities, it would be necessary to have longitudinal data on gene expression. Future research should focus on strengthening causal inference, as well as on collecting repeated measurements of mRNA abundance data. Second, the associations between SES and mRNA abundance levels are not uniformly up- and down-regulated within biological pathways. The results should thus be interpreted as indicators of dysregulation in aging-related gene activity. In some cases, the direction for single genes or biological pathways might be contrary to expectations or the expected direction may not be known. Future research should investigate the directionality of associations between indicators of SES and specific genes in the aging signature, especially with data covering different age groups. Third, data were originally collected in wave I from a representative sample of the US adolescent population that has been followed across 5 waves of interviews; we cannot exclude the possibility that the mRNA sample might have lost some of its representativeness due to attrition. However, as Web Table 1 shows, the differences between the mRNA and wave V samples do not seem to be substantively large.

Nevertheless, despite these limitations, this work provides a better understanding of the mechanisms leading to socioeconomic differences in biological senescence. The findings can be an effective tool for uncovering how to mitigate the SES gradient before it manifests in age-related chronic diseases and mortality in later adulthood. The gene expression data are especially useful for examining the association between SES and health because the transcriptome has been found to be responsive to environmental interventions. Our results thus emphasize how young adulthood is a life-course phase of importance for SES disparities in aging pathways (56, 65).

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The data set is available from the corresponding author.

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