



Negative social ties as emerging risk factors for accelerated aging, inflammation, and multimorbidity

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Negative social ties, or “hasslers,” are pervasive yet understudied components of social networks that may accelerate biological aging and morbidity. Using ego-centric network data and DNA methylation-based biological aging clocks (i.e., DunedinPACE and age-accelerated GrimAge2) from saliva from a state representative probability sample in Indiana, we examine how negative social ties are associated with accelerated biological aging and a broad range of health outcomes, including inflammation and multimorbidity. Negative relationships are not rare within close relationships, as nearly 30% of individuals report having at least one hassler in their network. These hasslers tend to occupy peripheral network positions and are more likely to be connected through weak, uniplex ties. Importantly, exposure to negative social ties follows patterns of social and health vulnerability, with women, daily smokers, people in poorer health, and those with adverse childhood experiences more likely to report having hasslers in their networks. Having more hasslers is associated with accelerated biological aging in both rate and cumulative burden: Each additional hassler corresponds to approximately 1.5% faster pace of aging and roughly 9 mo older biological age. Moreover, not all hasslers exert the same influence; kin and nonkin hasslers show detrimental associations, whereas spouse hasslers do not. Finally, a greater number of hasslers is associated with multiple adverse health outcomes beyond epigenetic aging. These findings together highlight the critical role of negative social ties in biological aging as chronic stressors and the need for interventions that reduce harmful social exposures to promote healthier aging trajectories.

egocentric networks | negative ties | epigenetic aging | inflammation | multimorbidity

Aging is a universal biological process involving the gradual accumulation of unrepaired molecular damage, leading to progressive declines in physiological functions and increased vulnerability to disease (1, 2). Despite its universality, individuals vary substantially in their rates of biological aging, distinct from chronological aging, due to genetic predispositions, as well as environmental and social factors (3, 4). Advancements in epigenetic biomarkers, particularly DNA methylation (DNAm)-based epigenetic clocks, have now made it possible to quantify and study biological aging. Early epigenetic clocks primarily measure DNAm patterns correlated with chronological age; therefore, they are less suitable for health research, whereas newer, second-, and third-generation clocks, such as GrimAge and DunedinPACE, reflect aging phenotypes, health risks, and mortality outcomes (5, 6). Recent research demonstrates that accelerated biological aging, as indicated by these advanced DNAm clocks, robustly predicts critical health outcomes, including chronic conditions and mortality risk (7). With these critical tools, a crucial next step is to explore the factors that may accelerate or slow biological aging by linking molecular mechanisms with the broader social forces that shape the aging process.

Chronic stress is a well-established driver of biological aging, influencing epigenetic modifications that regulate gene expression and inflammation (8). While often conceptualized as sources of support that promote health and well-being (9–12), social relationships may also function as chronic stressors, contributing to increased allostatic load through repeated stress activation (13, 14). This dual nature of social ties—both protective and harmful—raises important questions about their role in biological aging and the pathogenesis of common morbidities. However, existing research relies on methods that capture only the positive dimensions of social relationships (e.g., social support), often overlooking negative or strained ties (15). As a result, there is comparatively little empirical insight into how the dark side of networks contributes to biological aging.

A growing body of research suggests that negative ties—relationships characterized by hostility, strain, or excessive burden, making one's life difficult—may be prevalent and have lasting health consequences (16–18). These negative ties, which we call “hasslers,”

Significance

Social relationships are fundamental to human health, yet research has focused primarily on their supportive dimensions. We investigate the role of “hasslers,” people in one's close social networks who create problems or make life more difficult, finding that these negative ties are not rare, disproportionately experienced by individuals facing greater social and health vulnerabilities, and consequential for aging. Each additional hassler is associated with faster biological aging, with especially pronounced effects when the hassler is a family member. These findings identify negative social ties as chronic stressors that shape aging trajectories and underscore the need for interventions that reduce harmful social exposures to promote healthier aging.

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may accelerate biological aging by mimicking the harmful effects of traditional chronic stressors, such as financial strain or workplace stress (19, 20), and contribute to increased inflammation, compromised immune function, and elevated risk for cardiovascular and other diseases (21). Several studies have demonstrated that conflict and hostility in the context of marital relationships are associated with accelerated epigenetic aging (22–24). However, it is unclear whether such stressful relationships outside of marriage have similar biological effects (10, 25, 26).

Simultaneously, it is crucial to recognize that what respondents describe as “hassling” does not uniformly represent relational toxicity (19, 20). As classic social theory reminds us, conflict and closeness often coexist within intimate ties. This dualistic argument has been articulated by Simmel (27): The greatest tensions frequently emerge within the most intimate relationships, precisely because their emotional security allows for friction without dissolution. In this light, some forms of hassling may reflect informal social control born out of love and concern, particularly within spousal or caregiving contexts. Yet, other forms of hassling may operate as chronic stressors, producing role strain and emotional exhaustion, especially within kin networks where obligations are enduring and less easily renegotiated. In contrast, hassling from nonkin ties may be experienced as less consequential or easier to disengage from. Building on theories of social balance and role systems (27–29), this study examines how the meaning and consequences of hassling differ across relationship types with a focus on the implications of such interactions depending on their relational and structural contexts.

These gaps in the literature are due in large part to methodological limitations, such as insufficient data on biological indicators of aging and social networks. To address these gaps, our study draws on an age-heterogeneous, state-representative probability sample in Indiana (i.e., the Person-to-Person Study) that uniquely includes both biomarkers and extensive measures of positive and negative interactions within personal networks using an in-depth ego-centric network module. To assess biological aging, we estimate second- and third-generation epigenetic clocks (age-accelerated GrimAge2 and DunedinPACE) derived from high-quality saliva samples. We begin by documenting the prevalence of negative ties (or *hasslers*) and identifying which individuals are most likely to report them. We then evaluate how having such negative ties is associated with accelerated biological aging, with particular attention to heterogeneity across relationship types (i.e., partners, kins, nonkins). To explore mechanisms, we further investigate the relational characteristics that define these negative ties. In addition, we assess whether negative ties are linked to a wider range of health indicators beyond epigenetic aging and, finally, conduct a series of sensitivity analyses to evaluate the robustness of our findings.

Our main hypothesis is that the presence of hasslers in core networks is associated with faster biological aging and poorer health; however, such associations do not, on their own, establish a causal effect of negative social ties on aging processes. Several alternative mechanisms could also generate the observed patterns. One is reverse causation: Individuals experiencing accelerated biological aging may become more irritable, thereby eliciting more negative interactions. Another possibility is perceptual or reporting bias, whereby individuals with more negative affect interpret benign interpersonal exchanges as hassling. A third explanation involves confounding from both observed factors (e.g., adverse childhood experiences, occupational environments) and unobserved traits that jointly shape exposure to negative social ties and biological aging. To address these sources of endogeneity and selection, we implement multiple strategies. First, we adjust for the 3-y retrospective Charlson comorbidity index from the linked

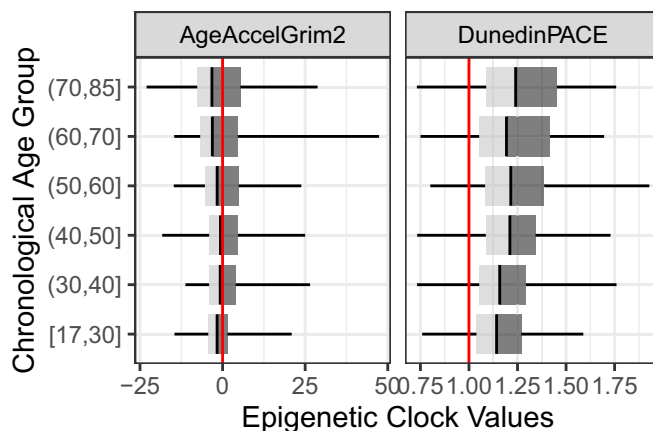


Fig. 1. Distribution of Age-Accelerated GrimAge2 and DunedinPACE across chronological age groups. This figure presents the distribution of Age-Accelerated GrimAge2 (Left) and DunedinPACE (Right) across different chronological age groups. Each box plot displays the median (black line), interquartile range (dark gray box), and overall data range (whiskers). The red vertical lines indicate the reference points: 0 for Age-Accelerated GrimAge2 (indicating no deviation from expected aging) and 1.00 for DunedinPACE (representing the population average pace of aging).

EHR data to reduce concerns about reverse causation, and we further examine whether the number of hasslers is significantly associated with self-reported health in a follow-up survey even after controlling for baseline health. Second, we incorporate occupation and psychosocial covariates to account for shared vulnerabilities and potential perceptual biases in reporting negative social interactions. Finally, we conduct sensitivity analyses to assess the magnitude of unobserved confounding required to explain away the estimated associations.

Results

SI Appendix, Table S1 provides summary statistics for demographic characteristics and the key variables in our analytic sample ($N = 2,345$). Participants range widely in their chronological age, from 18 to 103 y (mean = 46.24, SD = 18.09), allowing us to explore epigenetic aging across a broad age span. We employ two complementary epigenetic aging measures: age-accelerated GrimAge2 (AgeAccelGrim2), which captures cumulative biological aging relative to chronological age, and DunedinPACE (PACE), which captures the rate of biological aging. Fig. 1 illustrates that both AgeAccelGrim2 and PACE exhibit substantial variability across all chronological age groups. On average, older adults tend to display faster aging rates (PACE), but we also see individuals in younger age groups who show high epigenetic age acceleration (AgeAccelGrim2), indicating that some are aging faster biologically relative to what would be expected given their chronological age in the study population.

How Many Hasslers Are Present in Ego Networks? We define hasslers as network members whom respondents reported as “often” hassling them, causing them problems, or making life difficult, rather than selecting “never,” “rarely,” or “occasionally.” *SI Appendix, Table S2* presents the distribution of network size and the prevalence of hasslers within these networks. The average network size was 5.07 (SD = 2.46), with a maximum size of 25. Social isolation was rare, with only 1.3% of respondents reporting no network members, while 8.6% listed more than 10 names. On average, respondents identified 8.1% of their network members as hasslers. The overall proportion of hasslers remained relatively stable across different network sizes, although it tended to be higher

among individuals with three or more members in their networks. *SI Appendix, Table S3* reports the distribution of hasslers. The mean size of the hassler network was 0.43 (SD = 0.85). Among the full sample (N = 2,685), 28.8% reported having at least one hassler in their network, and about 10% indicated having two hasslers or more. These findings suggest that persistently negative ties are not rare among personal ties.

Who Is More Likely to Have Hasslers in Their Ego Networks?

To investigate how demographic, occupational, psychosocial, and health-related characteristics predict exposure to negative social ties, we estimated survey-weighted zero-inflated Poisson regression models, which enable us to identify predictors of both having zero hasslers in one's network (Panel A) and the expected number of hasslers (Panel B) simultaneously. *Fig. 2* presents the average marginal effects from these models (*SI Appendix, Table S4*). Women had a significantly lower probability of having zero hasslers than men ($P < 0.05$) and, correspondingly, had higher expected counts of hasslers ($P < 0.1$). Education, age, race, marital status, health insurance status, and life-time multiple morbidity showed

insignificant associations in the multivariate models at $P < 0.05$. There are no significant differences across different occupation categories, although unemployed respondents in general tended to have more hasslers than those who were employed.

Psychosocial factors emerged as important predictors of hassler presence. The result from ACEs suggests that individuals with more adverse childhood experiences were more likely to have hasslers in their networks. A larger network size was associated with both a lower probability of having zero hasslers and a higher expected number of hasslers. Notably, respondents who felt that others depended on them were more likely to report a greater number of hasslers, whereas those who viewed themselves as important to others tended to exhibit the opposite pattern. In addition, health factors and behaviors predicted exposure to hasslers. Better self-reported health was associated with both a higher likelihood of having zero hasslers and lower expected hassler counts. Daily smokers, compared with never smokers, showed a lower probability of having zero hasslers and higher expected counts. These results suggest that hassler exposure is not random but clustered around individuals with greater psychosocial and

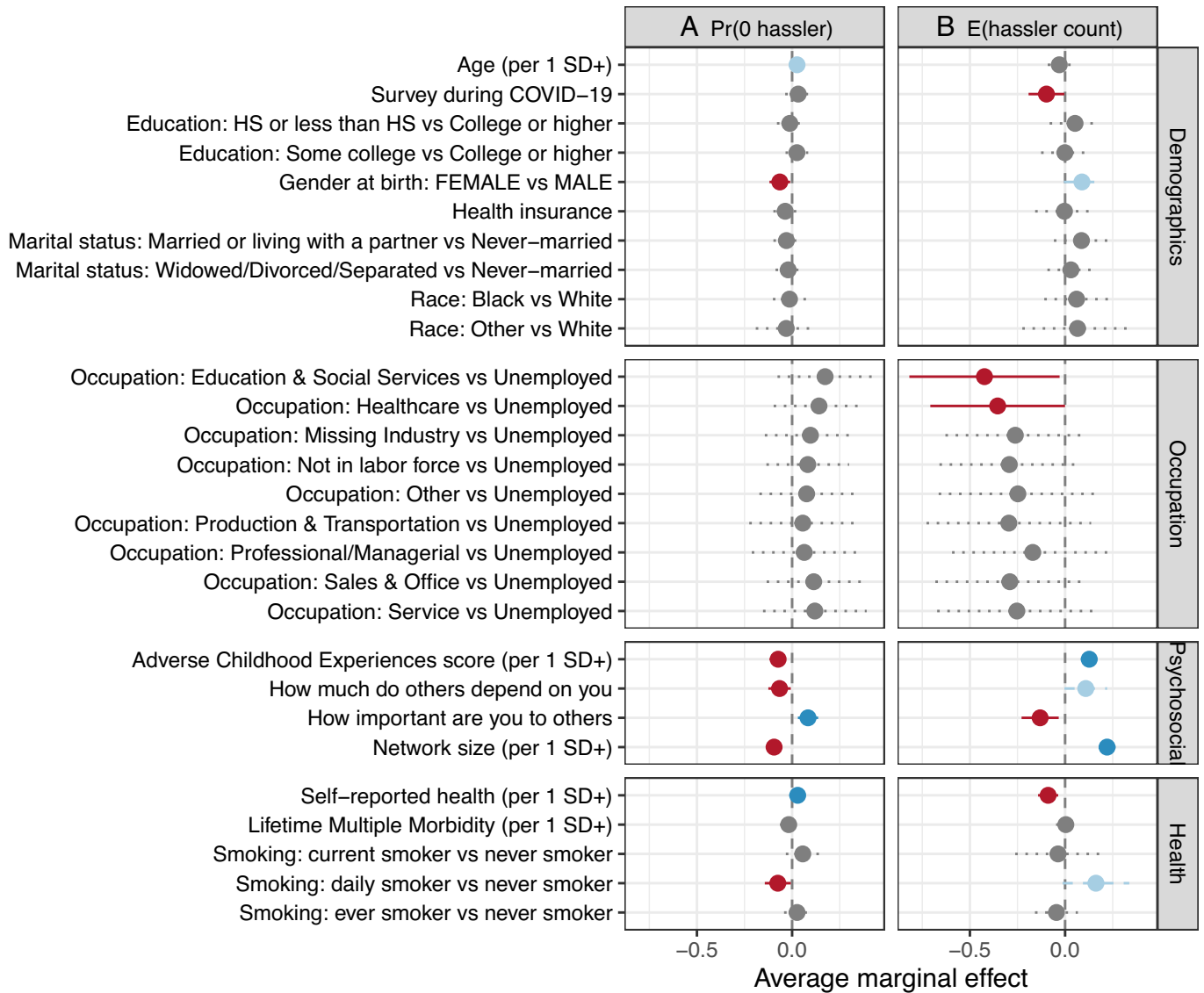


Fig. 2. Determinants of Hasslers in Ego Networks from Zero-Inflated Poisson Models. Average marginal effects from zero-inflated Poisson regression models predicting the probability of having zero hasslers (Panel A), and the expected count of hasslers (Panel B) in respondents' ego networks. Estimates are adjusted using survey weights and reflect changes in the outcome associated with a one-SD increase in continuous predictors or contrasts between categorical groups, with 95% CI. Please see *SI Appendix, Table S4*.

health vulnerabilities, underscoring the importance of examining whether such network strain contributes to accelerated biological aging.

To What Extent Does Exposure to Hasslers through Ego Networks Predict Accelerated Biological Aging? We examine associations between having hasslers and accelerated biological aging (AgeAccelGrim2) and the rate of aging (PACE) by estimating a series of OLS regression models (Models 1 to 6 in Table 1, also see SI Appendix, Table S5 for the full regression coefficients) while controlling for demographic confounders (i.e., age, gender, education, marital status, and related technical background variables). Models 1 and 4 focus on the count of hasslers in networks. Individuals reporting more hasslers exhibit meaningful differences in both the rate and acceleration of biological aging. For PACE, each additional hassler is associated with a 0.015 unit increase (Model 1), corresponding to a 1.5% faster pace of aging. This means that rather than aging 1.00 biological year per calendar year, individuals with one more hassler age approximately 1.015 biological years annually. Although this yearly increase is modest, it accumulates over time: Over a 10-y period, this faster rate results in about 1.8 extra months of biological aging for those with an additional hassler. For AgeAccelGrim2, which measures accelerated biological relative to chronological age, each additional hassler is associated with a 9-mo increase (Model 4), indicating that individuals with one more hassler are, on average, about 9 to 10 mo ($0.784 \times 12 \text{ mo} = 9.4$) biologically older at the time of measurement than their peers of the same chronological age. To gauge the magnitude of these associations, we standardized both the independent and dependent variables in the regression models. The results indicate small but detectable associations: A one-SD increase in the number of hasslers corresponds to a 0.065 SD increase in PACE and a 0.087 SD increase in AgeAccelGrim2. When benchmarked against the established effects of smoking—a

major behavioral aging risk factor—these effect sizes correspond to approximately 17% of the PACE difference and 13% of the AgeAccelGrim2 difference between nonsmokers and smokers (0.383 SD for PACE; 0.659 SD for AgeAccelGrim2).

We next consider the presence of any hasslers in Models 2 and 5, which show that the presence of hasslers is linked to elevated aging scores (a 2.6% faster pace of aging and 15 mo of accelerated biological aging). Finally, Models 3 and 6 explore potential non-linear associations by estimating separate indicators for the number of hasslers. The results for PACE (Model 3) show that only individuals reporting two hasslers exhibit a statistically significant increase in biological aging, whereas higher counts display positive but imprecisely estimated effects. For AgeAccelGrim2 (Model 6), the association increases in magnitude as the number of hasslers rises, with particularly pronounced effects for those reporting two or more hasslers. Although the pattern is not perfectly monotonic, the results suggest that greater exposure corresponds to larger increases in epigenetic aging. SI Appendix, Table S6 reports three alternative operationalizations of negative ties (i.e., the relative number of hasslers, categorical measures of the proportion of hasslers, and the mean frequency of hassling) and shows that the associations are robust across all measurement strategies.

Which Kinds of Negative Social Ties Matter Most for Accelerated Biological Aging, and Why? Yet, not all hasslers might be the same; the meaning of a hassler who is also a spouse might be different from the meaning of hasslers who are kin or nonkin. SI Appendix, Fig. S1 shows the total number of hasslers by relationship type and the proportion of hasslers in each relationship category. Hassler prevalence varied considerably across relationship types. Among partner/spouse relationships, approximately 8.5% of spouses and 8.7% of partners were classified as hasslers. Within kin relationships, parents (9.8%) and children (9.7%) showed the highest proportions of hasslers, while grandparents (5.2%) and

Table 1. Associations between exposure to hasslers and epigenetic aging clocks

	PACE			AgeAccelGrim2		
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Number of hasslers	0.0152** (0.00384)			0.784** (0.189)		
Presence of any hassler		0.0258** (0.00709)			1.237** (0.296)	
Number of Hasslers (ref = 0)						
1			0.0108 (0.00782)			0.679* (0.290)
2			0.0682** (0.0157)			2.324** (0.369)
3			0.0426 (0.0331)			1.774+ (0.950)
4			0.0966+ (0.0534)			4.570** (1.144)
5+			−0.0131 (0.0223)			2.642 (1.900)
Observations	2,345	2,345	2,345	2,345	2,345	2,345
Controls						
Individual controls	V	V	V	V	V	V
Network size dummies	V	V	V	V	V	V

Note. Coefficients represent the average marginal effects of exposure to hasslers on biological aging outcomes, with SE in parentheses. Individual controls include batch effects, leukocyte cell composition, age, gender, race/ethnicity, education, and marital status. Network size dummies account for differences in social network size, ensuring that the relative impact of negative ties is not confounded by absolute network size. Statistical significance is denoted as follows: + $P < 0.10$, * $P < 0.05$, ** $P < 0.01$ (two-tailed tests).

Table 2. Associations between spouse, kin, and nonkin hasslers and epigenetic aging clocks

	PACE		AgeAccelGrim2	
	Model 1	Model 2	Model 3	Model 4
Presence of any spouse hassler	0.00900 (0.0174)		0.796 (0.648)	
Presence of any kin hassler	0.0256** (0.00836)		1.100** (0.367)	
Presence of any nonkin hassler	0.0150 (0.00910)		0.833* (0.318)	
Standardized number of spouse hasslers		0.00253 (0.00372)		0.165 (0.122)
Standardized number of kin hasslers		0.00647* (0.00288)		0.342* (0.136)
Standardized number of nonkin hasslers		0.00519+ (0.00309)		0.365* (0.143)
Observations	2,346	2,346	2,346	2,346

Note. Coefficients represent the average marginal effects of exposure to hasslers across different relationship types on biological aging outcomes, with SE in parentheses. Individual controls include batch effects, leukocyte cell composition, age, gender, race/ethnicity, education, and marital status. Network size dummies are included to account for variation in social network size, ensuring that the effects of negative ties are not confounded by absolute network size. Statistical significance is denoted as follows: * $P < 0.05$, ** $P < 0.01$ (two-tailed tests).

grandchildren (5.8%) had the lowest. Sibling and other kinship relationships fell in the middle range (both 7.5%). Nonkin relationships showed the wide variations in hassler prevalence. The “other” category had an exceptionally high proportion (40.5%) of hasslers, though this likely reflects a small group of heterogeneous relationships. Coworkers (11.3%) and roommates (10.4%) had notably higher hassler proportions compared to other nonkin ties. Friends, despite being a common relationship type, had a relatively low proportion (3.5%) of hasslers, as did church members (3.4%) and healthcare providers (4.1%). Neighbors showed a moderate proportion (6.5%). The substantial variation in hassler prevalence across relationship types implies that ties that involve obligation, shared space, or interdependence (e.g., parents, children, coworkers, roommates) appear more likely to produce hasslers, whereas voluntary and self-selected ties (e.g., friends, church members, healthcare providers) tend to generate fewer.

Given this substantial variation across relationship types, the next step is to determine whether the biological consequences of hasslers are equally heterogeneous. Table 2 presents the associations between spouse, kin, and nonkin hasslers and two epigenetic aging measures. The biological impact of hasslers varied substantially by relationship type. For PACE, kin hasslers showed the strongest associations with the accelerated pace of aging. The presence of any kin hassler was associated with a 0.0256 unit increase in PACE ($P < 0.01$), and each SD increase in the number of kin hasslers was associated with a 0.00647 unit increase ($P < 0.05$). In contrast, spouse hasslers and nonkin hasslers showed no significant associations with PACE, though coefficients were positive. For AgeAccelGrim2, both kin and nonkin hasslers showed significant associations: The presence of any kin hassler was associated with a 1.1 y increase in AgeAccelGrim2 ($P < 0.01$), while the presence of any nonkin hassler was associated with a 0.833 y increase ($P < 0.05$). When examining the standardized number of hasslers, both kin (0.342, $P < 0.05$) and nonkin hasslers (0.365, $P < 0.05$) showed similar magnitudes of associations. Spouse hasslers again showed no significant associations with AgeAccelGrim2, despite positive point estimates.

To further understand these heterogeneities, we assess relational characteristics of hasslers by examining network members’ tie strength, their degree centrality in ego’s network (i.e., how connected the alter is to other network members), and tie multiplexity (i.e., the extent to which ego has connections to network members

through multiple relationship types across five different social support and exchange dimensions). Fig. 3 presents survey-weighted comparisons of these network metrics between hasslers and nonhasslers across partner, kin, and nonkin relationship categories. Tie strength patterns revealed a consistent finding across all relationship types: Hasslers maintained significantly weaker ties with egos than nonhasslers did. For alters’ network positions, nonhasslers held significantly more central positions within ego networks relative to hasslers, though the centrality of hasslers and nonhasslers did not differ significantly within kin ties. When it comes to tie multiplexity, nonkin and kin hasslers had fewer multiplex ties than their nonhassler counterparts, indicating more unidimensional connections. Spouse hasslers showed a slight reduction in multiplexity relative to spouse nonhasslers, but the difference was not significant.

These network patterns help explain why different types of hasslers show distinct associations with biological aging. Kin hasslers, who are more embedded and harder to avoid, exhibit the strongest and most consistent links to accelerated aging, especially for PACE, likely because their conflicts are both enduring and structurally inescapable. Nonkin hasslers, though weakly tied and peripheral, still predict faster aging on the more mortality-sensitive AgeAccelGrim2 clock, suggesting that even superficial strain may impose cumulative physiological burdens. Spouse hasslers show no significant associations, possibly because spousal ties mix negative and positive exchanges.

Does the Negative Association of Hasslers with Health Extend beyond Biological Aging? Next, we assess whether the negative associations of hasslers are specific to biological aging or whether they extend across a broad set of health outcomes. We standardized all outcomes to clarify the relative magnitude of associations between hasslers and different aspects of health. Fig. 4 and see also SI Appendix, Table S7 for the unstandardized average marginal effects and SI Appendix, Tables S8 and S9 for full regression coefficients shows that the number of hasslers in one’s network is consistently associated with worse health across multiple domains. The strongest associations are observed for mental health outcomes. Each additional hassler is associated with a 0.28 SD increase in depression severity and a 0.25 SD increase in anxiety severity, followed closely by poorer self-rated mental health (0.22 SD). Associations with physical health and adiposity-related

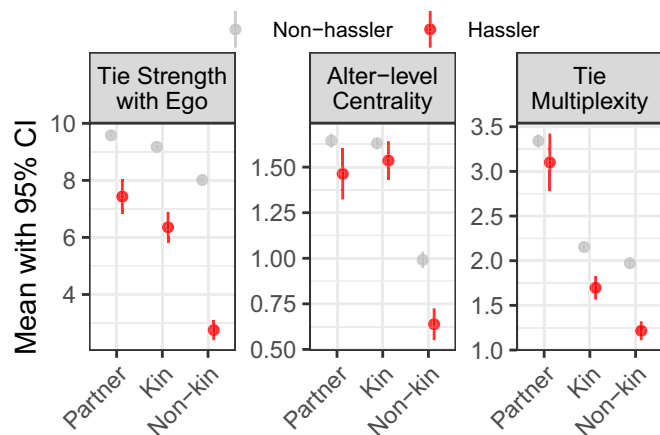


Fig. 3. Differences in tie strength, alter-level centrality, and multiplexity between hasslers and nonhasslers across relationship categories. Mean values (with 83% CI) of three alter-level characteristics for partners, kin, and nonkin, shown separately for hasslers and nonhasslers. Tie strength is measured on a 1 to 10 scale, indicating the perceived strength of ego-alter relationships. Alter-level centrality reflects each alter's average perceived closeness to all other alters in the ego network (0 = "don't know each other," 1 = "not very close," 2 = "sort of close," 3 = "very close"). Multiplexity is measured as the count (0 to 5) of relationship roles the alter occupies, including confidante, health discussant, health regulator, regular companion, and hassler. Across all relationship categories, hasslers tend to exhibit weaker ties to ego, lower centrality, and reduced multiplexity compared with nonhasslers, with the largest differences observed among nonkin alters.

outcomes are more modest but remain statistically significant. Additional hasslers are associated with higher BMI (0.14 SD), poorer general health (0.13 SD), poorer physical health (0.13 SD), and a higher waist-to-hip ratio (0.12 SD). Importantly, associations with biological aging measures are comparable in magnitude to several established health indicators. Each additional hassler is associated with faster GrimAge2 acceleration (0.10 SD) and faster DunedinPACE (0.08 SD), effect sizes similar to those observed for multimorbidity (0.09 SD) and larger than those for inflammation (0.03 SD). It is important to note that the number of hasslers does not significantly affect height, which serves as a useful control because height is a stable biological trait unlikely to be influenced by social relationships in adulthood; thus, the absence of a significant association for height strengthens confidence that the observed associations with other health outcomes reflect genuine associations rather than methodological artifacts. These results underscore the broad and multifaceted impact of relational stressors on health trajectories.

To What Extent Is the Association Explained by Confounding, Selection, or Reverse Causality? To evaluate the robustness of our findings, we conducted a series of sensitivity analyses that incorporated potential confounders of the relationship between negative social ties and biological aging. *SI Appendix, Table S10* reports the average marginal effects of the number of hasslers on PACE (Models 1 to 8) and AgeAccelGrim2 (Models 9 to 16) as successive sets of controls are added to the baseline models (Models 1 and 9). In the PACE models, the number of hasslers remained significantly associated with faster biological aging after adjusting for insurance status and the timing of the COVID-19 pandemic. The association was attenuated but remained significant after further adjustment for the presurvey Charlson comorbidity index (Model 3) and the lifetime multimorbidity index (Model 4), providing evidence against the health selection hypothesis. In Model 5, we accounted for two measures of affective orientation toward others to assess whether reports of hasslers primarily reflected respondents' own dispositional tendencies rather than

characteristics of their network alters. These controls did not meaningfully alter the magnitude or significance of the association, suggesting that the results are not artifacts of negative self- or other perception. We next examined whether occupational and industry differences might confound the observed association, given that certain types of work expose individuals to heightened interpersonal strain and physiological stress. Model 6 shows that adjusting for occupation and industry did not alter the estimated effect of hasslers on biological aging. In Models 7 and 8, the associations attenuated but remained significant after adding controls for smoking (0.0109, $P < 0.01$) and adverse childhood experiences (0.0118, $P < 0.01$), respectively. Parallel patterns emerged in the AgeAccelGrim2 models. The initial association (0.784, $P < 0.01$) decreased to 0.496 ($P < 0.01$) after adjusting for smoking, suggesting partial mediation. Overall, the results show that although behaviors such as smoking explain part of the link, the association between negative social ties and accelerated aging remains strong, indicating an independent and enduring effect of social stress.

Using longitudinal follow-up data collected between June and September 2022, we examined whether reverse causality could account for the associations observed at baseline. As shown in *SI Appendix, Table S11*, baseline reports of hasslers significantly predicted worse follow-up health across all domains. Specifically, individuals with more hasslers reported poorer general health (Model 1: 0.145, $P < 0.01$), worse mental health (Model 3: 0.157, $P < 0.01$), and poorer physical health (Model 5: 0.229, $P < 0.01$). Importantly, although these associations were attenuated after adjusting for the corresponding baseline levels of each outcome, they remained statistically significant and substantively meaningful. Net of baseline health, the number of hasslers at baseline continued to predict declines in general health (Model 2: 0.106, $P < 0.1$), mental health (Model 4: 0.0859, $P < 0.05$), and physical health (Model 6: 0.131, $P < 0.05$) in the follow-up period. This pattern supports temporal ordering from exposure to hasslers to subsequent health deterioration, offering strong evidence against reverse causality and reinforcing the interpretation that negative social ties may adversely shape later health.

To address the possibility that our findings reflect the unique social conditions of data collection during the COVID-19 pandemic, particularly elevated partner conflict among cohabiting respondents, we tested whether the association between hasslers and biological aging differed by marital status and by the COVID versus non-COVID period. There is little support for a "pandemic marital-strain" explanation: The hassler–aging association is not confined to married or partnered respondents, and the COVID-period contrasts do not show a consistent pattern of amplification among the married/partnered group (*SI Appendix, Table S12*). We also examined gender heterogeneity, given the possibility that men may be more likely than women to label spousal behavior as hassling. Gender-stratified analyses offer no evidence that the association is driven primarily by men (*SI Appendix, Table S13*). Together, these supplementary checks reduce concern that our main results are an artifact of pandemic-era cohabitation dynamics or male-specific reporting tendencies.

To evaluate the robustness of the associations to potential unmeasured confounding, we conducted sensitivity analyses using the *konfound* tool (30). For PACE (*SI Appendix, Table S14*), the Robustness of Inference to Replacement (RIR) statistic indicated that 48.3% of the sample (1,132 cases) would need to be replaced by counterfactual cases with null effects to fully eliminate the association. The Impact Threshold for a Confounding Variable (ITCV) was 0.039, corresponding to required confounder–outcome and confounder–predictor correlations of 0.198. These values

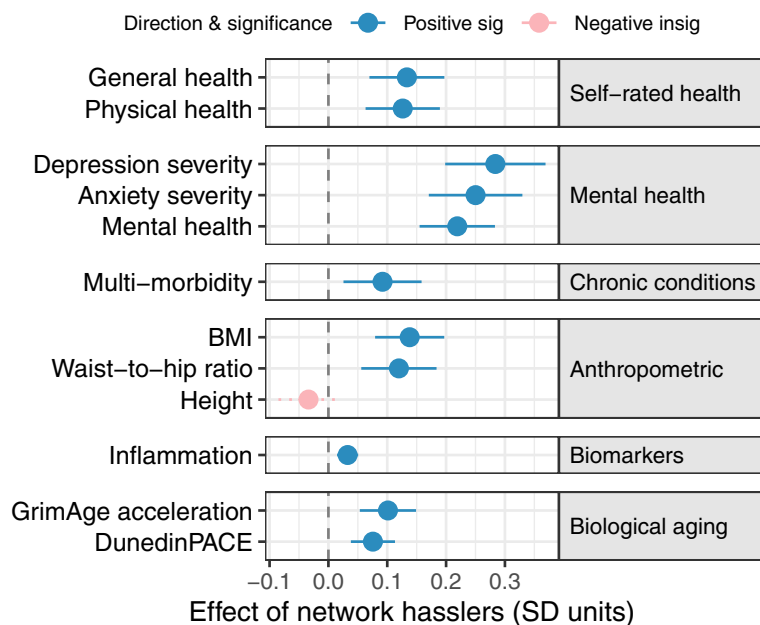


Fig. 4. Associations between the number of hasslers and other health outcomes. Average marginal effects from survey-weighted regression models examining associations between the number of hasslers and various health outcomes (standardized to SD units). Estimates with 95% CI reflect the change in each outcome (in SD units) associated with an additional hassler in ego networks, adjusted for batch effects, leukocyte cell composition, age, race, gender, education, marital status, and network size. Outcomes are grouped by domain: self-rated health, mental health, chronic conditions, anthropometric measures, biomarkers, and biological aging. Please see [SI Appendix, Table S7](#) for the unstandardized average marginal effects.

indicate that an unmeasured confounder would need to be stronger than nearly all observed covariates to overturn the effect; only leukocyte composition exhibits a comparable ITCV (0.034), and none of the sociodemographic controls come close. For AgeAccelGrim2, the RIR was similarly high—43.1% of the sample (1,010 cases)—and the ITCV was 0.032, implying threshold correlations of 0.179 with both the predictor and the outcome. Again, the required strength of an omitted confounder exceeds that of all observed covariates except for leukocyte composition (0.037). These patterns demonstrate that the associations between the number of hasslers and both epigenetic aging measures are highly robust to omitted-variable bias.

Discussion

Negative social ties have long been understood as a persistent element of human social life (15, 27, 28). Sociological and psychological research shows that these negative ties take many forms, from everyday irritations and criticism to exclusion, hostility, denunciations, and even violence across a wide range of settings (19, 20, 31–33). Some negative ties dissolve when they destabilize broader network balance (34), some are leveraged to clarify status ambiguity or strengthen group cohesion (35), and others persist because of their ambivalent mix of support and strain (19, 20, 36). In everyday life, many individuals routinely encounter people who create problems or make life more difficult—who we refer to as *hasslers*. Their familiarity often leads people to normalize and endure them, which has resulted in surprisingly little attention to their long-term health implications. While supportive ties are well known to buffer age-related physiological decline (12, 37–39), the absence of supportive ties is not equivalent to the presence of negative ones. By integrating comprehensive ego-centric network data with DNAm-based measures of biological age, this study provides evidence that negative social relationships operate as potent, chronic stressors capable of shaping epigenetic and physiological risk profiles across adulthood.

Prior work has documented that adverse social experiences ranging from loneliness to marital conflict can elevate allostatic load, increase inflammation, and shorten telomeres (14, 40–42). Recent research using data on older adults from the Health and Retirement Study shows that both loneliness and social isolation,

including the absence of friendships and marital relationships, are associated with epigenetic clocks measuring mortality risk and accelerated aging across multiple organ systems (37, 39, 43, 44). However, few population-based studies have isolated the specific impacts of negative ties within networks of close relationships on biologically measured aging outcomes. Our data address this gap by linking directly measured negative ties to two state-of-the-art epigenetic clocks that capture both accelerated aging and the pace of aging. We find that respondents with more hasslers exhibit significantly greater epigenetic age acceleration, which is robust even after accounting for affective orientation, occupation, adverse childhood experiences, smoking, and prior comorbidity in addition to demographic characteristics and network size. These results suggest that the hasslers in one's social environment may constitute an overlooked but consequential biological risk factor.

We find that each additional hassler is associated with approximately 1.5% faster biological aging and roughly 9 mo of additional biological age among individuals of the same chronological age. In standardized terms, these associations are small, consistent with effect sizes below conventional thresholds for small correlations. However, biological aging is a cumulative process, and even modest differences in annual pace can translate into meaningful divergence in biological age over time. When benchmarked against smoking, a well-established behavioral risk factor, the hassler association corresponds to approximately 13 to 17% of the estimated smoking-related difference in these aging measures. This is not a negligible impact, although it should be interpreted with caution and not taken as causal, as we discuss in the limitations below.

Our analyses show clearly that not all hasslers are the same. The nature of relationships and the network context substantially condition both the exposure to hasslers and their biological consequences. Ties characterized by obligation, shared space, or structural interdependence, such as parents, children, coworkers, or roommates, are more likely to be hasslers than voluntary, self-selected ties such as friends, church members, and neighbors. This heterogeneity extends to biology: Kin hasslers are the most robust predictors of accelerated aging, while nonkin hasslers matter primarily for the mortality-sensitive AgeAccelGrim2 clock. In contrast, spouse hasslers show no significant associations with either measure. This pattern complicates existing work that emphasizes marital strain as a key driver of aging (22–24); our

results suggest that spousal negativity may be buffered by the ambivalent mix of support and obligation within intimate partnerships, whereas kin conflicts, which are often emotionally salient yet hard to abandon, leave a clear imprint on aging.

Our network analyses help explain why. Kin hasslers tend to occupy still central positions within egos' networks, but crucially, they tend to be *weaker in tie strength* and *less multiplex* than nonhassling kin ties, suggesting that these relationships are marked by obligation and structural embeddedness, but with reduced strength and fewer overlapping exchanges. While both embeddedness and multiplexity are usually protective because they offer support, monitoring, and multiple channels of reciprocity (45, 46), when a tie is embedded *without* strong or multiplex connections—and it is *negative*—, the same structural features can trap individuals in repeated contacts with limited compensatory mechanisms. In other words, embeddedness that typically signals social protection can become a pathway for chronic stress when it is anchored in hasslers, turning “good structure” into biological risk.

Crucially, the detrimental influence of negative ties extends beyond epigenetic aging alone. When analyzing additional indicators—self-reported health, psychiatric symptoms, epigenetic inflammation score, waist-to-hip ratio, and BMI—those reporting a higher number of hasslers showed systematically worse health profiles across the board. Such convergence across molecular, anthropometric, clinical, and subjective outcomes strongly supports the idea that negative social relationships exact a broad physiological toll (18, 25). These findings reinforce the concept of *allostatic load*, the cumulative “wear and tear” emerging from repeated physiological attempts to adapt to stress (14, 47). Although positive social integration can reduce allostatic load, our study demonstrates the inverse: Frequent exposure to hasslers may chronically activate stress-sensitive systems, fueling systemic inflammation, epigenetic dysregulation, and metabolic strain. These findings extend the literature by highlighting that negative social relationships are directly implicated in the same downstream physiological processes previously ascribed to major psychosocial and environmental stressors.

Negative social interactions could contribute to faster biological aging by putting chronic strain on the body's hypothalamic–pituitary–adrenal (HPA) axis. When people experience frequent interpersonal tension, their bodies respond by activating stress-related systems, which trigger the release of hormones like cortisol and adrenaline (48). While these hormones help the body respond to immediate challenges, prolonged activation can take a toll on mental health, increasing feelings of anxiety and depression (49). At the same time, chronic social stress can fuel inflammation in the body. When stress is persistent, it activates molecular pathways that increase the production of inflammatory proteins, and over time, this repeated immune activation leads to higher levels of epigenetic inflammation scores. Our findings on the significant associations between the number of hasslers in close social ties and both mental health and inflammation markers provide indirect evidence to support these mechanisms.

Our findings reveal that exposure to negative social ties is not evenly distributed, but it is instead patterned along lines of psychosocial and health vulnerability. In particular, women, daily smokers, those in poorer health, and those with greater histories of adverse childhood experiences (ACEs) were all more likely to have (more) hasslers in their networks. These inequalities have important implications for understanding how social environments may compound disadvantage across the life course (50, 51). Individuals with greater psychosocial adversity, such as those with higher ACEs, appear not only to carry early-life scars but to

inhabit adult relational contexts where difficult, demanding, or conflict-prone ties are more common. Poorer health and health-behavior risks show a similar pattern: Those already at elevated physiological risk are simultaneously embedded in social networks that may amplify stress exposure. These patterns reflect a form of “relational inequality,” in which unequal exposure to negative relationships becomes a mechanism through which broader health disparities are reproduced (52).

Several limitations merit attention. First, because our analyses are cross-sectional, we cannot establish a definitive causal pathway between negative ties and biological aging; longitudinal or quasi-experimental designs are needed to clarify how hasslers emerge and whether they prospectively accelerate aging. We took multiple steps to assess alternative explanations, including adjustment for a) self-perceptual bias (i.e., the possibility that reporting hasslers reflects respondents' dispositions rather than objective network features), b) occupational context that might jointly increase exposure to negative interactions and independently influence aging via job stress, schedules, or economic precarity, c) adverse childhood experiences, d) health selection using prior comorbidity and longitudinal data on self-reported health, and e) smoking behavior. These checks increase confidence in the robustness of our associations, but they should not constitute causal estimates.

Second, hasslers are measured via respondents' self-reports and therefore may be influenced by stable personality traits, or broader appraisal tendencies that shape how social interactions are perceived and recalled. We partially address this concern by adjusting for respondents' affective orientation toward others, but these controls cannot fully capture underlying dispositional or psychological factors. Future studies that incorporate independent alter-reports or validated assessments of personality would further strengthen causal inference. Third, our results may be affected by mortality selection. Individuals with poorer health, lower support, or chronic stress are more likely to die before data collection, yielding an analytic sample that may be healthier and more socially advantaged than the population at risk. If the highest-risk individuals are disproportionately missing, our estimates likely understate the true impact of negative ties. However, age-specific analyses indicate that associations are significant among young adults (18–30) for PACE and broadly similar across age groups for AgeAccelGrim2 (*SI Appendix, Table S15*), which suggests that mortality selection alone is unlikely to account for the findings. Nevertheless, because we cannot directly model mortality selection, these limitations continue to caution against causal interpretation.

Finally, while we conceptualize hassling as one dimension of negative interaction within ego networks, our survey includes only a single explicit indicator of negative relational behavior. We therefore cannot assess whether hassling co-occurs with other forms of negative ties—such as hostility, coercion, chronic criticism, or gaslighting—or whether different negative-tie subtypes have distinct biological consequences. Given longstanding arguments that negative exchanges take multiple forms within networks, future work would benefit from richer measurement of negative ties. Such data would allow researchers to differentiate various kinds of relational strain, test whether hasslers represent a unique subtype or a broader negative-tie pattern, and more precisely locate hassling within the interpersonal processes that shape health and aging.

Taken together, our findings indicate that negative social relationships may function as powerful chronic stressors, accelerating age-related biological processes through multiple, interlinked pathways. By systematically mapping these relationships onto advanced epigenetic measures and additional health markers, this study highlights that the “dark side” of social connections can wear

down physiological resilience and hasten aging and the development of multiple morbidities. Future strategies to mitigate relationship strain, alongside bolstering positive support, could represent a crucial avenue to promote healthier aging and reduce the burden of age-related disease. Rather than focusing solely on loneliness or isolation, these results underscore the need to recognize and address the multifaceted nature of social adversity in shaping our biological and aging trajectories.

Data and Methods

This study utilizes data from the Person-to-Person Health Interview Study (P2P), a statewide omnibus health survey conducted in Indiana (53). The P2P provides representative estimates for Indiana's adult population (aged 18 y and older) on various health, social, and behavioral measures. Employing a stratified probability sampling design similar to the General Social Survey, the study drew participants from household addresses in both rural and urban counties across Indiana. Sampling was executed by the National Opinion Research Center at the University of Chicago, with intentional oversampling in two economically disadvantaged rural counties. Trained interviewers administered structured surveys using standardized protocols and collected anthropometric measurements. At the end of each interview, participants were invited to provide saliva samples for epigenetic analysis. DNA extraction and quality assessment occurred within 6 wk of collection at the Indiana University Genetics Biobank using the Chemagic 360 magnetic bead-based high-throughput extraction system. Data collection spanned from October 2018 to July 2021, with 2,685 individuals participating (overall response rate of approximately 30%). Of these, 87.4% ($N = 2,347$) consented to saliva collection. An additional 10 respondents were excluded due to missing data on key control variables, predictors, or outcomes. The final analytic sample included 2,345 participants for analyses predicting biological aging clocks, though the exact sample size varied slightly across regression models depending on the specific control variables and outcome measures included. For a subset of the analytic sample ($N = 1,271$), we conducted a follow-up survey between June and September 2022 that collected self-reported health measures, although longitudinal epigenetic aging clocks were not available for this wave. The Institutional Review Board at Indiana University approved all study procedures. Informed consent was obtained from each participant, and the confidentiality of data was rigorously maintained throughout the study. The full survey codebook is available at the project website (<https://irsay.iu.edu/tools-resources/data-resources/p2p-health-interview-study/>).

Egocentric Network Module. A central aspect of the P2P survey is its ego-centric network module, which captures respondents' ("egos") significant social connections ("alters"). Participants were asked to complete a personal social network protocol following standard methods of egocentric network research (54). Initially, respondents were asked via "name generators" to list individuals with whom they have interacted over the past 6 mo. Here, the number of individual respondents who could be named was unrestricted, avoiding potential right censoring common in similar ego-centric network surveys. The survey employed five name generators from the PhenX Social Network Battery (55) to elicit different types of relationships: confidantes (people with whom respondents discussed personal problems), health discussants (individuals respondents discussed their health with or could rely on for help regarding physical or emotional issues), health regulators (those frequently discussing and influencing respondents' mental and physical health behaviors), regular companions (people respondents regularly spent free or leisure time with), and hasslers (individuals causing respondents stress or difficulty). Following the elicitation of names, respondents completed "name interpreter" questions that detailed each alter's characteristics and relationship attributes.

To identify negative ties, we ask each ego to assess each alter's potential for interpersonal stress or conflict in the following question: "How often has (alter) hassled you, caused problems, or made life difficult?" Here, we define "difficult ties" (i.e., hasslers) as alters whom respondents identified as often causing problems or difficulties, rather than occasionally, rarely, or never. We do not consider "occasional hassling" as hasslers since this likely captures normative, supportive informal social control and should not be interpreted as negative. Our primary measures in this study are the count of hasslers within each respondent's network.

We present results assuming zero hasslers when network size is zero, though the findings remain virtually unchanged if we drop these cases, as very few individuals ($N = 35$, 1.3%) report a network size of zero. To examine the heterogeneous influence of spouse, kin, and nonkin hasslers, we first classify all alters into three relationship categories: spouse (spouse or partner); kin (parent, sibling, child, grandparent, grandchild, or other relative); and nonkin (friend, coworker, neighbor, roommate, church member, health provider, or other). Because alters may occupy multiple relational roles across the network, we allow an alter to contribute to more than one category when appropriate. For each respondent, we then count the number of hasslers within each category. To assess robustness and comparability across relationship types, we examine both binary indicators of whether any spouse/kin/nonkin hassler is present and standardized counts of hasslers within each category.

To characterize the relational context of hassling ties, we examine several features of each alter who engages in hassling. First, we measure tie strength using respondents' ratings of how strong their relationship is with each alter on a 1 to 10 scale (10 = strongest). Second, we assess each alter's degree centrality within the ego network, capturing how connected that alter is to other network members. Degree centrality is computed from pairwise closeness ratings in which respondents indicate how close each pair of alters is to one another (0 = don't know each other, 1 = not very close, 2 = sort of close, 3 = very close). For each alter, we take the mean closeness score across all other alters. Finally, we measure tie multiplexity, defined as the number of distinct social support or exchange domains (out of five possible types) through which ego and alter are connected. This count reflects the extent to which the relationship spans multiple functional dimensions of social involvement.

Saliva Collection and Epigenetic Data Processing. DNA methylation (DNAm) was assessed from saliva samples using the Infinium Methylation EPIC BeadChip. To ensure unbiased results, samples were randomized across plates based on demographic variables (age, sex, and race/ethnicity), and 40 pairs of blinded duplicate samples were included. Data preprocessing and quality control were conducted using the *minfi* package in R, with probes and samples failing the detection P -value threshold excluded, along with samples demonstrating sex mismatches. This study focuses on two advanced DNAm clocks—age-accelerated GrimAge2 and DunedinPACE—both of which demonstrate superior predictive validity for morbidity and mortality compared to earlier-generation epigenetic clocks. Age-accelerated GrimAge2 (AgeAccelGrim2) and DunedinPACE (PACE) offer complementary insights into biological aging by capturing both cumulative biological aging and the current rate of physiological aging, respectively, providing a robust, multidimensional evaluation of aging processes and associated longevity risks.

GrimAge2 was developed using a two-stage procedure: First, plasma proteins and smoking pack-years were regressed on chronological age, sex, and CpG methylation levels to generate DNAm-derived biomarkers. These biomarkers were then used to predict time-to-death, adjusting for age, sex, and DNAm-smoking-pack-years (6). We use the age-adjusted version (i.e., age regressed out) of GrimAge2, which represents the residual difference between observed and predicted GrimAge2, with higher values indicating accelerated biological aging beyond what is expected for a given chronological age. Elevated AgeAccelGrim2 scores are associated with increased vulnerability to mortality and age-related diseases, making it a robust predictor of long-term health risks and physiological decline. In contrast, DunedinPACE quantifies the ongoing rate of biological aging rather than cumulative age acceleration. The creation of this measure also involved multiple phases (5). First, researchers tracked longitudinal changes in 19 biomarkers reflecting multiple organ systems, assessed at ages 26, 32, 38, and 45. They then used linear mixed-effects models to estimate the rate of change for each biomarker, which were combined to calculate individual pace of aging scores. These scores were scaled so that a value of 1.0 represents one biological year per chronological year (e.g., a score of 2.3 indicates aging at 2.3 biological years per chronological year). Finally, researchers applied elastic net regression to create an algorithm that predicts the 20-y pace of aging using a subset of DNAm markers measured at age 45. Thus, unlike GrimAge2, PACE provides a dynamic measure of aging speed, directly capturing the rate of cellular and physiological deterioration.

It is important to note that saliva contains both leukocytes and epithelial cells, which differ from the peripheral blood leukocyte mixtures used to develop the original GrimAge2 and DunedinPACE clocks. Because epithelial cells tend to exhibit methylation patterns associated with older or faster biological aging, saliva-based DNAm clocks can yield higher absolute levels than the blood-based

reference distributions. However, salivary methylation estimates have been widely used for both PACE (56) and GrimAge2 (57), and their rank-ordering and associations with exposures remain stable when applied to saliva, even if absolute levels differ due to cell-type composition (58), which is not surprising given that immune cells account for more than 80% of the DNA present in saliva (59). Nevertheless, comparisons of our sample's mean AgeAccelGrim2 or PACE values to the original reference populations should be interpreted cautiously. The mean AgeAccelGrim2 in our sample is -0.69 ($SD = 7.04$), indicating that participants, on average, closely match the GrimAge2 reference population for cumulative epigenetic aging, though considerable variation exists at the individual level (range: -22.99 to 47.36 y). By contrast, the mean PACE is 1.19 ($SD = 0.19$), above the benchmark rate of 1.0 established in the original Dunedin Study cohort, though it may be due to the nature of the saliva sample in our study.

Other Health Outcomes. *Self-rated general health* was measured by asking "Would you say that, overall, your health is..." with response options: 1) Poor, 2) Fair, 3) Good, 4) Very Good, 5) Excellent. *Self-rated physical health* was measured by asking "Would you say that, in general, your physical health is..." with response options: 1) Poor, 2) Fair, 3) Good, 4) Very Good, 5) Excellent. *Self-rated mental health* was measured by asking "Would you say that, in general, your mental health is..." with response options: 1) Poor, 2) Fair, 3) Good, 4) Very Good, 5) Excellent. *Depression and anxiety severity* (range = 0 to 100) were measured using the Computerized Adaptive Test-Mental Health (CAT-MH) (60, 61), an efficient computerized adaptive test based on multidimensional item response theory. The CAT-MH contains validated measures for diagnostic screening and continuous measurement of targeted mental health disorders and is superior to brief assessments used in other studies.

Multimorbidity (range = 0 to 9) was measured by summing the total number of affirmative responses to a set of question asking whether respondents had ever been diagnosed by a physician with the following conditions: arthritis, asthma, cancer, emphysema, stroke, myocardial infarction, coronary heart disease, kidney disease, obesity, and diabetes. Epigenetic inflammation score is a measure derived from a large-scale epigenome-wide association study (EWAS) of circulating C-reactive protein (CRP), a widely used biomarker of systemic inflammation, which identified and replicated DNAm signatures at 58 CpG sites across two large and ethnically diverse cohorts ($N > 12,000$). These methylation markers were robustly associated with CRP levels and showed enrichment in genes linked to immune response and cardiometabolic risk, independent of known genetic predictors. By leveraging these validated methylation sites, we construct a composite inflammation score that reflects chronic inflammatory processes at the molecular level (62).

For anthropometric measurement, trained interviewers measured participants' weight and height three times using a standardized protocol to ensure accuracy and reliability. Waist and hip circumferences were also measured three times using a flexible measuring tape at the narrowest part of the waist and the widest part of the hips, respectively. The final weight, height, waist, and hip values used in analyses were the averages of the three measurements. The waist-to-hip ratio was calculated as the average waist circumference divided by the average hip circumference. Body Mass Index (BMI) was computed as weight (kg) divided by height squared (m^2). These anthropometric indicators were used to assess overall body composition and central adiposity in subsequent analyses.

Controls. Consistent with standard practice for models regressing epigenetic clocks on predictors, we adjust for two technical covariates: batch effects and cell types (63, 64). We control for the following sociodemographic characteristics across all models: age, gender at birth (men/women), race and ethnicity (non-Hispanic White/non-Hispanic Black/Other race), educational attainment (less than high school education or high school diploma or equivalent/some college or technical school/bachelor's degree or higher), and marital status (never married/married or living with a partner/divorced or widowed or separated).

In the sensitivity analysis, we account for additional potential posttreatment confounders that might influence both social network characteristics and epigenetic aging to rigorously assess the robustness of our findings. First, the COVID-19 pandemic occurred while the P2P study was in the field, and data collection was suspended for 1 y during the height of the pandemic. The COVID-19 pandemic might have induced differences in social network patterns (65) and/or affected epigenetic aging (66). As such, we adjust for a variable indicating whether the data were collected before or after the pandemic. Second, we adjust for health

insurance status, which captures disparities in access to medical care and preventive services, as it may shape both biological aging and the structure of social relationships. Third, to account for underlying morbidity burden and reduce the risk of reverse health selection, we constructed a Charlson Comorbidity Index based on ICD-9/10 diagnoses recorded in the Indiana Network for Patient Care (INPC) electronic health record data (67). Using the comorbidity R package (68) and the original Charlson weighting scheme (69), we mapped all qualifying diagnoses occurring within the 3 y prior to respondents' interview dates. Diagnoses were identified by linking all encounter-level information 3 y prior to survey dates and applying an established severity hierarchy. We imputed zeros for patients who had at least one encounter but no qualifying diagnoses. Because individuals with limited healthcare contact may appear artificially "healthy," we also constructed an indicator for any encounter in the prior 3 y and adjusted for it in all regression models to mitigate ascertainment bias. Fourth, to capture their affective orientation toward others, we use two survey items—your importance to others ("How important are you to others?") and others' dependence on you ("How much do other people depend on you?")—from the mattering scale (70) and binarize them (coded 1 = "a lot," and 0 = "somewhat," "a little," or "not at all").

Fifth, we construct occupational categories using a multistep process that integrates structured industry checklists with open-ended occupational histories and harmonized coding schemes. In the survey, respondents indicated whether they had ever worked in any of a predefined set of industries (i.e., farming, automotive, construction, manufacturing, railroad, forestry, electrical, beauty services, welding, firefighting). For respondents whose primary occupation was not captured by these industry options, they list any occupations in which you worked five or more years in the open-ended response format, which trained research assistants code into standardized occupational categories using the SOC 2018 scheme. We then merged the coded open-ended occupations with the structured industry indicators to produce a unified combined occupation label that preserves the most specific available information. Then, to facilitate analysis, we grouped the combined occupation labels into ten broader occupational groups: 1) Professional/Managerial, 2) Healthcare, 3) Education and Social Services, 4) Service, 5) Sales and Office, 6) Production and Transportation, 7) Other (e.g., arts, entertainment, media, and military-specific occupations), 8) Not in labor force, 9) Unemployed, and 10) Missing Industry (respondents with employment but insufficient information to classify). Sixth, we adjust for smoking status (never smoker/ever smoker/current smoker/daily smoker) to determine whether the association between social network characteristics and epigenetic clocks is behavioral rather than biological. Finally, we measure childhood experiences (ACEs), as prior literature has consistently linked early-life adversity with accelerated biological aging trajectories, using the 12-item index, which assesses potentially traumatic events that occur in childhood (0 to 17 y), such as experiencing violence, abuse, or neglect, witnessing violence in the home, or substance abuse in the home (71) (Cronbach's $\alpha = 0.83$).

Analytic Strategy. Our analytic approach focuses on evaluating how negative social ties (hasslers) within individuals' social networks relate to accelerated biological aging, as measured by two DNAm-based epigenetic clocks: age-accelerated GrimAge2 (AgeAccelGrim2) and PACE. The primary independent variable is the count of hasslers reported by each respondent. We employ OLS regression models to estimate associations between negative social ties and our biological aging outcomes. Our initial models include basic sociodemographic covariates—age, gender, race/ethnicity, education, and marital status—to adjust for fundamental demographic confounding. We also introduce dummy variables indicating network size categories to account for the possibility that respondents with larger networks may report a higher absolute count of hasslers, clarifying the independent contribution of network negativity above and beyond network size itself.

To further assess the robustness and validity of our results, we conduct a series of sensitivity analyses. In doing so, we explore alternative specifications of negative ties to assess potential nonlinearities or threshold effects in several complementary ways: We construct a binary indicator for whether any hassler is present in a respondent's network; we categorize the number of hasslers using discrete dummy variables (0, 1, 2, 3, 4, 5+); we measure the proportion of network members who are hasslers and also create categorical versions of this measure (0, 1 to 24%, 25 to 49%, 50 to 99%, 100%). These analyses examine whether biological aging accelerates disproportionately when negative ties surpass a critical threshold within an individual's close relationships. In addition, we

capture overall intensity by computing the mean hassling frequency across all alters (coded 3 = often, 2 = occasionally, 1 = rarely, 0 = never).

To address potential selection and endogeneity concerns, we sequentially introduce additional controls that could confound the observed relationship between negative social ties and biological aging. Moreover, as a negative control outcome, we test the association between baseline hasslers and adult height, for which no association is expected. In addition, using a subset of samples we followed up longitudinally, we estimate lagged dependent variable (LDV) models for self-rated health, regressing follow-up self-rated health on baseline hasslers while adjusting for baseline self-rated health and covariates. To quantify how strong unmeasured confounding would need to be to overturn our findings, we use the *konfound* Stata package to compute two sensitivity indices (30): the Impact Threshold for a Confounding Variable (ITCV) and the Robustness of Inference to Replacement (RIR). The ITCV quantifies the smallest correlation that a single omitted confounder would need to have with both the exposure and the outcome, conditional on the set of observed covariates, to reduce our estimated effect below a chosen threshold. Notably, results are substantively identical when using the unconditional version. The RIR expresses the minimum proportion of cases in the sample that would have to be hypothetically replaced by cases showing no effect of the exposure in order to invalidate the inference. Finally, we expand our analyses to other health outcomes, including self-rated health, mental health symptoms (anxiety and depression severity scores), inflammation, and anthropometric indicators (waist-to-hip ratio, BMI). This comprehensive assessment evaluates whether negative social relationships exert broad-spectrum health impacts beyond biological aging itself, reflecting chronic stress-induced multisystem physiological dysregulation.

We interpret and report results as average marginal effects to facilitate intuitive understanding and direct comparison across models. To ensure the generalizability and representativeness of our findings to the adult population of Indiana, all analyses incorporate survey weights provided by NORC. These weights correct

for differential nonresponse rates and oversampling of specific demographic subgroups. Analyses are performed using Stata and R statistical software.

Data, Materials, and Software Availability. The underlying P2P data cannot be publicly shared at this time because they include sensitive individual-level information (e.g., biomarkers, detailed social relationship measures, and location-related variables) and is governed by an active Data Use Agreement that prohibits redistribution/public release. In the interim, data access is available to qualified researchers upon reasonable request and contingent on execution of an appropriate DUA and any required approvals. We are preparing the dataset for deposit in ICPSR by June 2026. All code/scripts are publicly available via Harvard Dataverse (DOI: [10.7910/DVN/XEUYCZ](https://doi.org/10.7910/DVN/XEUYCZ)) (72) and mirrored on GitHub (<https://github.com/letitbk/p2p-hassler-replication>) (73).

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