Social relationships and physiological determinants of longevity across the human life span

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Two decades of research indicate causal associations between social relationships and mortality, but important questions remain as to how social relationships affect health, when effects emerge, and how long they last. Drawing on data from four nationally representative longitudinal samples of the US population, we implemented an innovative life course design to assess the prospective association of both structural and functional dimensions of social relationships (social integration, social support, and social strain) with objectively measured biomarkers of physical health (C-reactive protein, systolic and diastolic blood pressure, waist circumference, and body mass index) within each life stage, including adolescence and young, middle, and late adulthood, and compare such associations across life stages. We found that a higher degree of social integration was associated with lower risk of physiological dysregulation in a dose–response manner in both early and later life. Conversely, lack of social connections was associated with vastly elevated risk in specific life stages. For example, social isolation increased the risk of inflammation by the same magnitude as physical inactivity in adolescence, and the effect of social isolation on hypertension exceeded that of clinical risk factors such as diabetes in old age. Analyses of multiple dimensions of social relationships within multiple samples across the life course produced consistent and robust associations with health. Physiological impacts of structural and functional dimensions of social relationships emerge uniquely in adolescence and midlife and persist into old age.

social relationships | physiological dysregulation | longevity | life course | biomarker

A defining characteristic of human society is that individual lives are intertwined through social relationships. Full social participation is such a fundamental human need that research since the 1900s has found the lack of social connections increases the odds of death by at least 50% (1, 2). When multidimensional assessments of social relationships were considered, the odds of mortality increased by 91% among the socially isolated (2). The magnitude of this effect is comparable to that of smoking and exceeds those of many other known risk factors of mortality, such as obesity or physical inactivity (2, 3). Although much evidence has accrued on the strong causal associations between social relationships and mortality as well as other health outcomes (4–7), important questions remain as to how social relationships affect health, when these effects emerge, and how long they last (8).

Studies of social, psychological, and behavioral mechanisms underlying the social relationship gradient in health have shed light on the first question (9–11). It is less clear, however, what biological mechanisms may be at play. Recent research on the biology of aging emphasizes the essential role of physiological stress response and regulation across multiple bodily systems in shaping longevity (12, 13). Although social relationship gradients in health and longevity (Fig. 1, path A) and physiological determinants of mortality (Fig. 1, path B) have been widely documented, these separate bodies of research have yet to be fully integrated. We have yet to determine whether social relationship differentials in longevity arise from a biological process in which social experiences "get under the skin" to alter physiological regulatory systems (Fig. 1, path C) (4).

Laboratory research on rats using experimental designs demonstrated that social isolation and hypervigilance increase the incidence of mammary tumors (14, 15) and compromise innate immune response to stress (16). In humans, deficits in social relationships such as social isolation or low social support can similarly lead to chronic activation of immune, neuroendocrine, and metabolic systems that lie in the pathways, leading to cardiovascular, neoplastic, and other common aging-related diseases (5, 8, 17, 18). Previous nonexperimental studies using observational data from human subjects tentatively support this proposition by documenting associations between social relationship measures such as social integration and support with biomarkers of inflammation (5, 8, 18), metabolic syndrome (18, 19), and cumulative dysregulation indicated by allostatic load (20). However, because these associations are largely based on cross-sectional data, they cannot be assumed to represent underlying causal relationships. Additional prospective longitudinal studies are needed to better address bias due to potential confounding factors and reverse causality, further explaining path C.

Examining how social and biological processes unfold and interact as individuals age is a critical step in advancing scientific explanations of the emergence and progression of diseases. A life course perspective, represented by the horizontal arrow D as a developmental trajectory, has not been fully brought to bear on this question. This perspective may offer considerable leverage by linking physical risks to social exposures that occur over time across multiple developmental stages from early to late life. The vast majority of biosocial research to date on this association has

Significance

Although much evidence has accrued in research over the past 20 years on the strong causal associations between social relationships and health and longevity, important gaps remain in our understanding of the mechanisms, timing, and duration of these associations. This study integrates social and biological disciplinary perspectives and research to examine how social relationships "get under the skin" to affect physiological well-being as individuals age. By combining data from and harmonizing measurement across four large nationally representative, population-based, contemporary surveys using an innovative longitudinal life course design, this study provides previously unidentified evidence on the biological and life course mechanisms linking social relationship patterns with health. As such, our findings advance explanations of the emergence and progression of diseases across the human life span.

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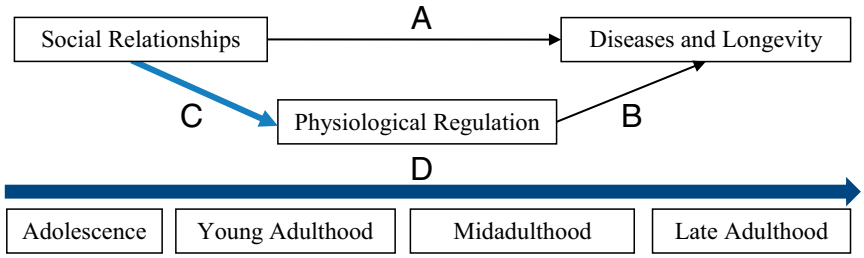

Fig. 1. A life course model of social relationship gradient in physical health: Mechanism and process. Empirical tests of the link represented in path C were applied in each stage of the life course trajectory D.

focused on older adults for whom morbidity and mortality rates are high (8, 21, 22). However, early life social experiences may be biologically embedded at that time, shown by an increasing body of research linking childhood disadvantage and maltreatment to increased likelihood of exaggerated biological stress response and, in turn, higher risks of inflammation and cardiovascular disease throughout adulthood (23–26).

Relationship deficits—such as social isolation, lack of support, or high strain—are alternative forms of social adversity that can create chronic stress by continuous exposure to chains of risk that accumulate over the life course (27, 28). Individuals who experienced early adversity are subject to multiple and longer durations of stress exposures and more prone to inflammatory and stress-related diseases as they age. At the same time, the emergence of chronic diseases usually takes many decades due to the long latency after the initial risk exposures (29). Therefore, extensive longitudinal data and analyses are imperative to understanding how the connection of social relationships and longevity unfolds over the human life span. Little empirical research exists that depicts this lifelong process partly because data that extend sufficiently over long periods of the life course, as depicted in trajectory D, are exceedingly rare.

This study addresses the aforementioned questions, integrates previous research on social relationships and health across disciplines, and tests a new longitudinal model of how social relationships matter for physiological health across the human life span. We make three unique contributions that shed new light on path C across trajectory D. First, using data from an array of nationally representative longitudinal samples of the US population, we implement an innovative life course design that begins at the earliest developmental stage (adolescence) in which physiological consequences of key social relationship patterns begin to manifest and traces subsequent life stages (young, middle, late adulthood) to depict the life-long process of stress response cascades that such relationship patterns initiate. The data come from The National Longitudinal Study of Adolescent to Adult Health (Add Health) to capture adolescence and young adulthood, the National Survey of Midlife Development in the United States (MIDUS) for middle adulthood, and both the Health and Retirement Study (HRS) and the National Social Life, Health, and Aging Project (NSHAP) for late adulthood. The use of multiple large, population-based samples in an integrative design allows us to assess linkages between social relationships and health for each life stage. It also offers an unprecedented fuller view of age variations in such linkages than any previous study of a particular sample or single life stage alone. Second, this study uses comprehensive and refined measurements of social relationships that encompass two primary dimensions that may differentially influence physical health at different stages of the life course. It assesses measures of social integration to capture the structural–quantitative dimension and measures of social support and strain to capture the functional–qualitative dimension, using age-appropriate conceptualizations of these domains for each life stage. Third, the study examines multiple objectively measured biomarkers or endophenotypes including inflammation (C-reactive protein, CRP), cardiovascular function (hypertension), and energy metabolism (overall obesity and abdominal obesity) to capture key physiological mechanisms underlying common diseases of aging and longevity (12).

Results

Our results indicate that social integration is related to better physiological functioning and lower risks of physical disorders in a dose–response fashion across life stage samples. Fig. 2 illustrates that individuals with a higher degree of social connectedness at prior points in time have lower predicted values of all four markers. Descriptive statistics on biomarkers, sample characteristics, and covariates are shown in Tables S1–S3, respectively. Adjusting for age, sex, and race, the negative associations of social integration with poor physical functioning were statistically significant for log-transformed CRP [log(CRP)] and systolic blood pressure (BP) in all three life stages shown, including adolescence and young and late adulthood. Additional analyses with diastolic BP revealed qualitatively similar results, so we presented results of systolic BP because of its clinical relevance for subsequent vascular and other chronic disease events and mortality as individuals age (30). Social integration gradients in waist circumference (WC) and body mass index (BMI) were also evident across samples, but the associations were significant only in adolescence. The association between social integration index and BMI estimated in the late adulthood HRS sample was in the opposite direction as expected but did not reach statistical significance to warrant substantive explanations. The results from the NSHAP analyses were similar to those from the HRS and were thus omitted from Fig. 2. We focused instead on the longitudinal change model results from NSHAP below.

In addition to lower risks of poor functioning, more socially integrated individuals also had lower odds of deleterious physical outcomes that are of clinical significance. Table 1 shows that in the basic models adjusting for age, sex, and race, a higher social integration index score was related to a 25% [Odds Ratio (OR) = 0.74, 95% confidence interval (CI) = 0.57–0.97, $P = 0.031$] and 14% (OR = 0.86, 95% CI = 0.78–0.94, $P = 0.001$) lower odds of elevated inflammation in adolescence and young adulthood (Add Health) and late adulthood (HRS), respectively. The estimated OR for the NSHAP sample at baseline also shows a negative association resulting in a 40% (OR = 0.59, 95% CI = 0.37–0.95, $P = 0.029$) lower odds of inflammation. Adjusting for covariates reduced some but not all of these associations, indicating that the physiological effects of social integration are partially mediated by socioeconomic status, health risk behavior (i.e., smoking, physical activity, obesity), and prior chronic disease. To put the magnitude of the effects in perspective, additional analyses revealed that social isolation raised the odds of high inflammation (OR = 1.27, $P = 0.05$) to a comparable degree with physical inactivity (OR = 1.21, $P = 0.05$) (Add Health analyses).

The results for other biomarkers show large age variations in their associations with the social integration index. The protective effects of social integration were particularly large in adolescence (OR = 0.52, 95% CI = 0.39–0.68, $P = 0.000$) against abdominal obesity and particularly salient in old age

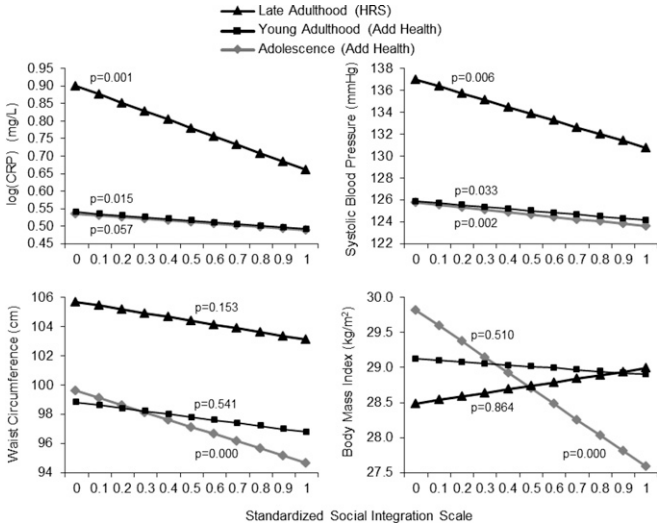

Fig. 2. Prospective associations of social integration with biomarkers of physiological functioning over the life course. Results based on ordinary least squares (OLS) models of biomarkers at follow-up regressed on baseline social integration, adjusting for age, sex, and race. HRS and NSHAP findings are similar, so we present the larger HRS sample results.

against hypertension. In the basic model, the OR estimated for the HRS sample shows a significant 13% lower odds of hypertension (OR = 0.87, 95% CI = 0.78–0.89, $P = 0.013$) at follow-up for those with a higher mean social integration level earlier in time. The corresponding estimates for the NSHAP sample from the longitudinal residual change model show a 54% reduction in the odds of developing hypertension (OR = 0.46, 95% CI = 0.25–0.85, $P = 0.014$) over time for those with a higher baseline social integration score.

In both studies, these associations remained robust after adjusting for all of the other covariates in the full models. We note that with an interval of 6 y in the elderly NSHAP sample who already had a high prevalence of hypertension at baseline, a change in risk of this size was substantial. Specifically, the effect of social isolation (OR = 2.42, $P = 0.007$) on hypertension risk exceeded the effect of diabetes (OR = 1.49, $P = 0.059$), a well-known risk factor for hypertension at older ages. The associations of social integration with overall obesity are significant in both early and late life. The OR estimates indicate strong protective effects of social connectedness against obesity in adolescence in the basic model and also at old age in the change models estimated for the NSHAP sample.

We did not find any significant results regarding the social integration–biomarker associations in the MIDUS sample, which may be due to empirical and substantive factors. Compared with other studies, the MIDUS sample with biomarkers is more homogeneous, consisting of mostly white respondents with higher levels of educational attainment and household income. However, supplemental analyses restricted to only white respondents with the other three studies did not change their results. [To further examine whether the associations between integration and biomarkers in the MIDUS sample were generalizable, we conducted parallel analyses using a middle-aged subsample (age 34–74) of the National Health and Nutrition Examination Survey (NHANES 1999–2006) (31). Consistent with the MIDUS results, higher social integration among middle-aged NHANES respondents was not protective against physiological risks.] Therefore, the racial and socioeconomic (SES) composition of the MIDUS sample is unlikely to account for its lack of consistency with the other samples. Further scrutiny of the MIDUS data revealed that ~80% of the sample reported weekly family and friend contact, indicating

Table 1. Estimated ORs of the linkages between social integration and biomarkers of physiological dysregulation across the life course (95% confidence intervals)

		Adolescence	Young adulthood	Young to midadulthood	Late adulthood	
Biomarker outcomes[a]	Model	Add Health; age 12–18	Add Health; age 24–32	MIDUS; age 25–64	HRS; age 50–98	NSHAP[b]; age 57–91
Inflammation	Basic[c]	0.74*	0.76*	1.03	0.86**	0.59*
		(0.57, 0.97)	(0.61, 0.96)	(0.53, 1.98)	(0.78, 0.94)	(0.37, 0.95)
	Full[d]	0.99	0.79[†]	1.07	0.89*	0.77
		(0.76, 1.29)	(0.62, 1.00)	(0.55, 2.10)	(0.81, 0.98)	(0.48, 1.23)
	N	6,747	6,747	863	4,323	1,153
Hypertension	Basic[c]	0.90	1.12	1.74	0.87*	0.46**
		(0.65, 1.24)	(0.80, 1.57)	(0.81, 3.76)	(0.78, 0.89)	(0.25, 0.85)
	Full[d]	1.09	1.16	1.69	0.89*	0.41**
		(0.78, 1.52)	(0.83, 1.63)	(0.73, 3.93)	(0.80, 0.99)	(0.22, 0.76)
	N	7,561	7,561	863	4,323	1,433
Abdominal Obesity	Basic[c]	0.52***	0.81**	1.28	0.96	0.71
		(0.39, 0.68)	(0.63, 1.03)	(0.62, 2.65)	(0.86, 1.07)	(0.29, 1.79)
	Full[d]	0.75	0.68[†]	0.81	1.01	0.91
		(0.49, 1.13)	(0.44, 1.04)	(0.26, 2.53)	(0.90, 1.14)	(0.38, 2.20)
	N	7,889	7,889	863	4,323	1,423
Overall Obesity	Basic[c]	0.59***	0.97	1.50	1.03	0.34*
		(0.44, 0.78)	(0.75, 1.26)	(0.72, 3.12)	(0.93, 1.14)	(0.13, 0.86)
	Full[d]	0.66**	1.07	1.70	1.09	0.44[†]
		(0.49, 0.88)	(0.82, 1.40)	(0.79, 3.65)	(0.97, 1.22)	(0.19, 1.00)
	N	7,889	7,889	863	4,323	1,388

***$P < 0.001$, **$P < 0.01$, *$P < 0.05$, [†]$P < 0.1$ (two-tailed test).

[a]Measures and cut points used for each marker in Table S1.

[b]Results for inflammation are based on data at wave 1 only; results for the other three markers are based on data at waves 1 and 2 and longitudinal residual change models.

[c]Adjusted for age, sex, and race.

[d]Adjusted for the full set of covariates in Table S3 for each dataset.

higher overall reports of integration than the other-aged samples. We therefore used a more stringent cutoff for the frequency of social contact in the MIDUS analysis, but these results continue to show that the degree of social embeddedness has less variation in midlife such that the sheer number of social connections does not differentiate individuals in terms of physical health risks.

We next addressed whether the quality of social relationships matters for health, given the quality of relationships is not informed by a count of social ties and interactions. Social support and strain measures are summarized in Table S2. In general, we found that perceived social support and strain measures are related to physiological indicators differently from social integration in that associations are more modest, nonlinear, and particularly salient for midadulthood. Most respondents in study samples with available information on quality of social relationships reported adequate levels of social support and little strain. Even though variations in the quality of relationships are small, those who perceived more support or strain are different from others in both physical functioning and clinical risk factors. Models including both social integration and social support and strain show similar results from those including them separately, suggesting largely independent associations of each social relationship dimension with biomarkers. The results reported below thus relate to models of social support and social strain without the inclusion of social integration.

Fig. 3 illustrated that adjusting for age, sex, and race, those with high (top quartile) social support at the baseline show significantly lower mean values of three markers assessed at the follow-ups than those with lower social support, including systolic BP at old age ($P = 0.038$), WC at young to middle age ($P = 0.099$) and old age ($P = 0.031$), and BMI at young to middle age ($P = 0.003$). Compared with those with low strain, those with high (top quartile) strain at the baseline exhibited significantly higher mean values of CRP at the follow-up in midadulthood and higher mean values of WC and BMI at the follow-up in both mid- and late adulthood. Results from the HRS analyses were similar to the results of the NSHAP analyses and are not shown.

The results for binary outcomes based on clinical thresholds are summarized in Table S4. In these models, continuous measures of social support and social strain yielded superior model fit than the dichotomous measures. Higher social support was associated with lower odds of abdominal and overall obesity in young to midadulthood (MIDUS sample only). Such effects were moderate in size and mostly eliminated or explained away by the adjustment of additional covariates. Higher social strain was predictive of mildly increased odds of inflammatory response and abdominal obesity in young to midadulthood and more substantial increases in the odds of overall obesity in both mid- and late adulthood that persisted after the adjustment of the full set of covariates.

Discussion

By combining data from four large nationally representative, population-based, contemporary studies using an innovative longitudinal life course design, this study has provided previously unidentified causal evidence on the mechanisms linking social relationship patterns with health and longevity across the human life span. Although the links represented in Fig. 1 have been found to be strong in past social research that focused on path A, as well as biological research that focused on path B, our study provided evidence that connects paths A and B through path C and, for the first time to our knowledge, documented the life course process in which these paths unfold as depicted in trajectory D.

Our study strengthened support for causal linkages between social relationships and physical functioning embodied in path C by improving both the measurement and analyses of these

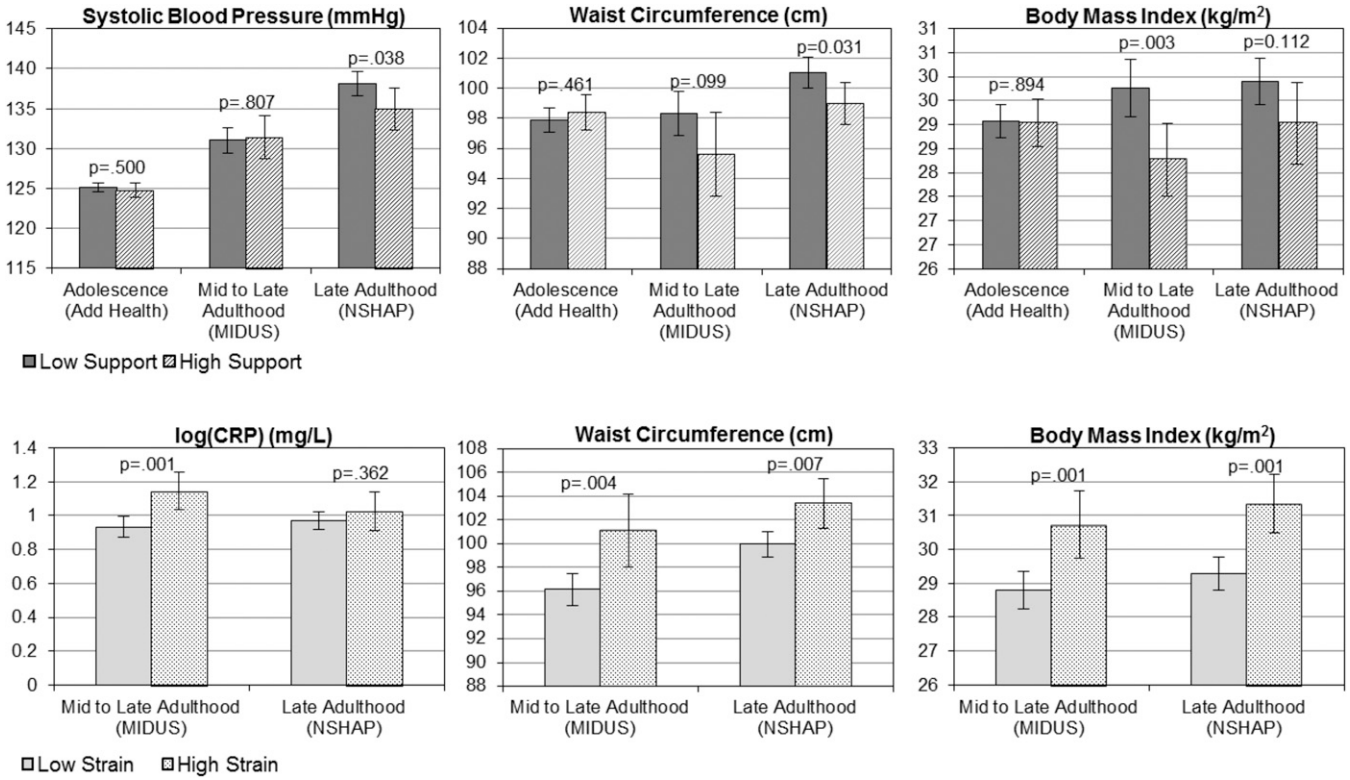

Fig. 3. Prospective associations of social support and strain with biomarkers of physiological functioning over the life course. OLS models of biomarkers at follow-up regressed on baseline dichotomous measures of social support and social strain, adjusting for age, sex, and race. HRS and NSHAP findings are similar, so we present the larger HRS sample results.

linkages. First, our study engaged a more comprehensive set of measures of relationship characteristics across multiple social life domains that are specific to each life stage and harmonized across four nationally representative studies. We also examined the associations between these relationship indicators and biomarkers across multiple physiological systems also harmonized across studies. The common patterns that emerged from the study of multiple measures of both social exposures and biological outcomes strongly support the generality of the associations, indicating social integration protects health and promotes longevity. Second, the use of longitudinal data for lagged measures of social exposures in relation to subsequent measures of biomarkers in all study samples ensured the proper temporal order in causal relationships underlying the association. Although the lack of repeated longitudinal measures of biomarkers in three study samples precludes causal inference of the physiological impact of social relationships, the NSHAP study allowed us to model change in physiological function as an outcome using two waves of biomarker measurements and hence provided a more rigorous test of the causal effects of interest. Although we cannot eliminate the possibility that some prior condition affects both social relations and physiology, this limitation relates more to biomarker data measured at one point in time than those that include repeated biomarker measures over time. We cannot rule out the potential effect of mortality selection of older or frailer adults. The results are thus likely conservative regarding the full range of physiological effects of social relations. Furthermore, the results are not only consistent across studies included but also consistent with those obtained in previous research across diverse samples such as laboratory animals (14–16) and clinical populations (5) and study designs such as experiments (14–16) and mortality follow-ups (6–8). They provide robust and uniform support for the existence and causal nature of path C.

In addition, our study identified the multifaceted links of different dimensions of social relations to physical health. A measurement approach including more than one type of relationship measure may better represent the multiple pathways by which social relations affect health (2). By assessing both the structural and functional dimensions of social relationships, we found that particular network and support characteristics may have unique influences on health. Extending previous research, we found that the links between social embeddedness and better physical functioning, as well as lower clinically significant disease risks, are exceptionally strong across most biological markers examined. Greater perceived quality of network ties was also beneficial for some markers with more variation across the life course. We further assessed the quality of social relationships by distinguishing positive and negative functions of network connections. We found evidence for social strain as a more significant predictor of (worsening) physiological outcomes than commonly examined social support measures hypothesized to improve health. This suggests the importance of considering psychosocial distress that may arise from negative social exchanges in future investigations of social relationships and health links.

The longitudinal life course design that we used in trajectory D elucidates when and how social integration matters for health as the aging process unfolds. We found evidence for the early emergence and persistence of the path C linkage between social relationships and physical health over the life course. We did not include the childhood life stage in this study because we focus more on meaningful social connections beyond familial contexts. Embeddedness in social networks seems to be especially critical for health during the formative years of building social relationships in adolescence and in the later adult years when the maintenance of social connections are relevant. The robust findings that social integration during adolescence (and not during young adulthood) matters for young adult metabolic and cardiovascular healthy functioning suggest that these early relationship contexts and connections play a role in predisease pathways into adulthood. The young adult years are considered to be the healthy years of the life span, yet adolescent social connections differentiate health risks in young adults, long before symptoms or overt signs of disease emerge.

After the busy years of midlife, maintaining social connections in older adulthood plays a vital role in protecting health. Chronic conditions naturally increase during late adulthood as part of the aging process. However, socially embedded older adults experience fewer disease risks, and our results from the NSHAP analyses suggest a causal role of social connections in reducing hypertension and obesity in old age. The deleterious effect of social isolation, in particular, was estimated to exceed that of diabetes, a well-known clinical risk factor for many chronic diseases including hypertension. Our findings therefore point to two life stages when the development and maintenance of social relationships can be especially critical for reducing future health risks and, in turn, reducing the high cost and consequences of chronic disease for individuals, families, and society as a whole.

The age variations we found for these associations also depend on relationship measures. Whereas the size of social networks was consistently important to physical health in both early and late adulthood, network size was not found to be significantly related to any biomarkers in midadulthood. Our additional analyses suggest that this is unlikely to be a methodological artifact. Several substantive explanations are possible. On one hand, adults in midlife are naturally embedded in multiple social networks associated with this life stage, including those at work, in the community, with children and other parents, and aging parents. Social integration is not a discriminating factor in midlife for most adults. On the other hand, these multiple social connections in midlife are potentially stressful in nature. Prior research shows that greater role conflict across multiple social domains and across generations is especially prevalent during this life stage (32). Therefore, the perceived quality of social relationships rather than the density of one's social network may better capture the link between social ties and health in midlife.

In fact, this conclusion is supported by our finding that social support and strain, which measured qualitative characteristics of social connections that are distinct from relationship quantity, mattered more for physical health in midadulthood and continued to have impacts in late adulthood. In adolescence, however, social integration was more pertinent to physical health than social support as perceived by individuals. This life course pattern of variation in the relative importance of social integration and support to physiological functioning was previously unknown and can have new practical import for policy intervention.

Our study sheds light on the biological mechanisms through which social relationships impact health across the human life span. Our findings suggest the early emergence and continuity of the physiological impacts of social relationships across the life course. They also suggest physiological vulnerabilities to social stress that may be specific to life course stages and relationship stressors. Disrupting various social relation deficits and physiological risk connections could directly arrest early progression toward chronic diseases and delay disease onset or lessen the disease burden in late life. The findings, therefore, provide a strong scientific basis for effective prevention and intervention that will lead to further improvement in life expectancy.

Materials and Methods

We used longitudinal data from four nationally representative studies to test path C and collectively cover all stages of the life course depicted in developmental trajectory D (Fig. 1). Refer to *Data Description* for details on data description.

The physical health biomarkers that we examine are continuous measures of CRP, systolic and diastolic BP, WC, and BMI, which represent important biological pathways underlying stress response that strongly predict future disease and

mortality (12). We also used categorical measures based on clinical cut points that indicate the corresponding disease outcomes including inflammation, hypertension, abdominal obesity, and obesity. Weighted descriptive statistics for each biomarker sample and dataset were reported in Table S1. For social relationship variables, we measured (*i*) social integration to capture the structural and quantitative components of relationships and (*ii*) social support and social strain to assess the quality of social connections in terms of the functions these connections served. Details on scale construction and descriptive statistics for relationship variables are included in Table S2.

We conducted multivariate regression analyses to examine the prospective associations between social relationship characteristics and biomarkers using the longitudinal design unique to each dataset. For three studies where biomarkers were assessed at the follow-up surveys only (Add Health, MIDUS, and HRS), we estimated models of biomarker outcomes in relation to social relationship measures assessed at prior points in time. Because the HRS included five waves of data on social integration (1998–2006), we estimated the latent growth curve models to most effectively summarize individual trajectories (19) (see Fig. S1 for HRS model specification). The NSHAP provided repeated measures of three other biomarkers at both baseline and the follow-up, including BP, WC, and BMI. Therefore, we used longitudinal residual change models to examine the effects of social relationships at wave I on changes in these biomarkers over time from wave I to wave II. This design offers a more rigorous test of potential causality, as it minimizes the risks of both reverse causality and spuriousness (e.g., that some other variable is affecting both biomarkers and social relationships). For each outcome variable, we estimated models in a stepwise fashion: (*i*) basic models of individual social relationship variables adjusting for age, sex, and race; (*ii*) models of all social relationship variables (when available for the samples) adjusting for age, sex, and race; and (*iii*) full models adjusting for all covariates that are strong risk factors for inflammation, metabolic, and cardiovascular dysregulation and may contribute to their associations with social relationships. See *Data, Measures, and Methods* for a detailed description of analytic approaches for each sample and Table S3 for covariates included in fully adjusted models.

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