HHS Public Access

Author manuscript

Biodemography Soc Biol. Author manuscript; available in PMC 2024 November 27.

Published in final edited form as:

Biodemography Soc Biol. 2023 ; 68(4): 115–148. doi:10.1080/19485565.2023.2260742.

How does Loneliness "Get Under the Skin" to become Biologically Embedded?

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Abstract

Loneliness is linked to declining physical health across cardiovascular, inflammatory, metabolic, and cognitive domains. As a result, loneliness is increasingly being recognized as a public health threat, though the mechanisms that have been studied do not yet explain all loneliness-related health risk. Potential mechanisms include loneliness having 1.) direct, causal impacts on health, possibly maintained by epigenetic modification, 2.) indirect effects mediated through health-limiting behaviors, and 3.) artifactual associations perhaps related to genetic overlap and reverse causation. In this scoping review, we examine the evidence surrounding each of these pathways, with a particular emphasis on emerging research on epigenetic effects, in order to evaluate how loneliness becomes biologically embedded. We conclude that there are significant gaps in our knowledge of how psychosocial stress may lead to physiological changes, so more work is needed to understand if, how, and when loneliness has a direct influence on health. Hypothalamic-pituitary adrenocortical axis disruptions that lead to changes in gene expression through methylation and the activity of transcription factor proteins are one promising area of research but are confounded by a number of unmeasured factors. Therefore, work is needed using causally informative designs, such as twin and family studies and intensively longitudinal diary studies.

1. Links between Loneliness and Health

Loneliness has sometimes been defined as the perception that one's social needs are not being met by one's relationships (Hawkley & Cacioppo, 2010) or the experience that results from inadequate meaningful connections, where 'inadequate' refers to the discrepancy between an individual's preferred and actual experience (Prohaska et al., 2020). By either definition, loneliness is an emotional experience usually measured with self-report scales. Loneliness has also been referred to as perceived social isolation, a definition that clarifies that lack of social contact and lack of satisfaction from one's social contact (regardless of its frequency) are distinct, separable constructs, if correlated. Despite its inherent subjectivity, loneliness is associated with a range of physical health measures, across cardiovascular (Valtorta et al., 2016; Hodgson et al., 2020), cognitive (Kuiper et al., 2015; Lara et al., 2019), metabolic (Shiovitz-Ezra & Parag, 2019; Whisman, 2010), inflammatory (Vingeliene et al., 2019; Smith et al., 2020), and other self-reported (e.g., physical frailty, subjective health; Gale et al., 2018; Richard et al., 2017; Nummela et al., 2011) domains. In fact, in

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one meta-analysis, individuals who were lonely had 26% greater odds of early mortality than non-lonely individuals, suggesting the impact of loneliness is comparable in magnitude to other well-established risk factors for mortality like harmful substance use, obesity, and low levels of physical activity (Holt-Lunstad et al., 2015). Links between loneliness and declining health appear robust across multiple domains, causing many, including the U.S. Surgeon General and the National Academies of Sciences (NAS), to consider loneliness a pressing public health epidemic (U.S. Department of Health and Human Services, 2023; O'Sullivan et al., 2022; NAS, 2020).

Why is loneliness linked to poor health? Is the relationship causal? Multiple mechanisms have been studied, but collectively they do not yet explain all loneliness-related health risk. Therefore, this scoping review was conducted by searching relevant online databases[1] to summarize the available evidence. One possible mechanism is that an emotional experience like loneliness may cause physiological signals that result in downstream health effects. The effects of the physiological signals could be transient or chronic, and sustained change may occur through epigenetic modification. Might loneliness directly cause signals that change the regulation of DNA transcription, and, subsequently, gene expression? Exploring this possibility is the primary concern of this review, and, to that end, we consider several additional pathways and plausible mediating confounders of the relationship between loneliness and health[2].

One such confounder is health-limiting behavior, such as harmful substance use, limited exercise, poor diet, and poor healthcare adherence. In addition to having a direct effect, it is plausible that loneliness may "get under the skin" by influencing behavior. Reverse causation is also plausible, wherein an individuals' declining health affects their social functioning and relationships. Additionally, some of the genetic influences on health and loneliness could be shared. There may be pleiotropic genetic forces that influence both the propensity to be lonely and the propensity to be physically unhealthy. Finally, the association could be truly artifactual, that is, the result of exogenous variables, like the common family environment or demographic factors like age or socioeconomic status. We propose that the broad theoretical mechanisms by which loneliness "gets under the skin" to become biologically embedded to affect health are 1.) a direct influence through biological signaling that may result in epigenetic changes, 2.) indirectly through health-limiting behaviors, and 3.) artifactually through shared genetic influences, reverse causation, or other confounders.

2. Direct Influence of Loneliness on Health

A. Physiology: HPA Axis, Inflammation, Metabolism, Repair, and Brain Functioning

Discussing the possibility of loneliness having a direct effect on health, Hawkley and Cacioppo (2010) posit that feeling socially connected is tantamount to feeling safe, and, therefore, the experience of loneliness sets off hypervigilant physiological responses to

[1]The primary databases used for the search were PubMed, Google Scholar, and PsycNet. The literature search was conducted between January and May 2023, but given the broad scope of the topic, there is a possibility that the search was not exhaustive.
[2]When considering epigenetics, transcriptomics, and telomeres, literature was reviewed on both loneliness and related constructs (e.g., relational support) while, when evaluating other pathways, the review focuses primarily on loneliness.

(social) environmental threats. Indeed, lonely individuals are more susceptible to perceiving common events as stressful (Cacioppo, 1994). Theoretically, hypervigilant stress responses, especially when chronically occurring, can influence health, possibly through dysregulating the hypothalamic-pituitary adrenocortical (HPA) axis. The HPA axis consists of a system of endocrine pathways involved in maintaining homeostasis, which has been observed to be responsive to environmental stressors (Xiong & Zhang, 2013). Psychological stress can be detected by the limbic system which prompts the production of glucocorticoids (e.g., cortisol), adrenaline, and noradrenaline through the HPA axis (Eachus & Cunliffe, 2018). If those stresses and the corresponding HPA axis disruptions are chronic, receptor cells can develop an insensitivity towards these signals (referred to as glucocorticoid resistance), ultimately leading to greater susceptibility to inflammation and a number of associated adverse health conditions (Hawkley et al., 2007; Xiong & Zhang, 2013). It is also plausible that chronic loneliness could cause blunted (hypovigilant), rather than heightened (hypervigilant), physiological responses, which would theoretically also lead to greater inflammation. Indeed, blunted stress reactions have similarly been linked to negative health outcomes, perhaps reflecting difficulty in motivational and reward related sensitivity (Carroll et al., 2017). In either case, loneliness could have a role in compromising health by causing atypical stress responses, whether hypervigilant (leading to insensitivity) or hypovigilant.

Variability in cortisol levels is a common way HPA axis functioning has been studied to date. Cortisol output usually follows a diurnal rhythm with levels being high upon waking, increasing for the next 30 to 45 minutes (deemed the cortisol awakening response), then declining through the rest of the day until levels are lowest in the evening (Miller et al., 2007; Vreeburg et al., 2009). As a result, cortisol is studied not just in terms of average level, but also in terms of changes throughout the day. Variability in the cortisol awakening response is not clearly linked to physical health, with results varying across samples and health conditions (Steptoe & Serwinski, 2016). However, meta-analytic evidence suggests that a flatter slope of cortisol levels from morning to evening (i.e., a smaller decrease through the day), referred to as the diurnal cortisol rhythm, is consistently associated with a range of poor health outcomes (average effect size $r = 0.15$ across domains), especially in the domain of inflammatory and immune outcomes ($r = 0.29$; Adam et al., 2017).

Dysregulated HPA axis and inflammatory pathways are thought to be features of chronic depressive conditions (Pariante & Lightman, 2008; Stetler & Miller, 2011) and post-traumatic stress disorder (Yehuda, 2009; Boks et al., 2016). In addition, chronic social isolation has been linked to high HPA axis activation across numerous species in animal studies (for a review see Cacioppo et al., 2015). Links between HPA axis functioning and loneliness in humans are more tenuous. In an early study, Kiecolt-Glaser et al. (1984) found that mean concentrations of urinary cortisol were associated with higher loneliness. In recent years, to allow for more accurate modelling of the overall daily secretion of cortisol (defined as the area under the curve with reference to the ground [AUC_G]), salivary cortisol levels tend to be collected on multiple occasions in a given day (Pruessner et al., 2003). Consistent with the Kiecolt-Glaser et al. (1984) finding, a larger AUC_G has been linked to higher mean loneliness levels across university and other young adult samples (Pressman et al., 2005; Lai et al., 2018; Lai et al., 2019), with some similar evidence in older adult samples as well (Steptoe et al., 2004), though, null evidence (Montoliu et al., 2019) and significant negative

associations (Schutter et al., 2017) have also been observed with older adults, suggesting possible age-related differences. Methodological considerations (e.g., variation in the choice of modelled covariates) may also help explain the differences. One plausible interpretation is that loneliness initially elicits hypervigilant cortisol responses, but, when chronic, no longer has the same effect.

Associations between loneliness and both the cortisol awakening response and diurnal cortisol rhythms have been inconsistent across samples. Some evidence suggests that higher loneliness levels (Steptoe et al., 2004) and prior day increases in loneliness (Adam et al., 2006; Doane & Adam, 2010) are associated with a larger increase in cortisol upon awakening (relative to the awakening response of a non-lonely individual or, within-person, a non-lonely previous day). However, in other samples, greater mean loneliness levels were associated with a smaller (Schutter et al., 2017; Lai et al., 2018; Jopling et al., 2021), or not significantly different (Doane et al., 2013; Montoliu et al., 2019; Drake et al., 2016) awakening response. Associations between the cortisol awakening response and other psychosocial factors are similarly mixed across domains and somewhat inconsistent (Chida & Steptoe, 2009). In the Youth Emotion Project sample, diurnal cortisol rhythm has been observed to be flatter in individuals higher in loneliness (Doane & Adam, 2010; Doane et al., 2013), though in at least two separate young adult samples, loneliness has been linked with greater slopes (Drake et al., 2016; Lai et al., 2018; Lai et al., 2019). In sum, loneliness appears to be consistently linked with greater total cortisol secretion in young adults, but it is unclear if this generalizes across age ranges or is linked to changes in the daily patterning of the secretion.

Beyond the HPA axis, loneliness has been hypothesized to signal metabolic responses in the autonomic nervous system or immunological responses like the secretion of inflammatory cytokines, growth factors, or antibodies. In response to acute lab-based stressors, individuals higher in loneliness, on average, had elevated total peripheral resistances (i.e., force exerted by circulating blood) and diastolic and systolic blood pressures, as well as blunted heart rates, cardiac outputs, and heart rate variabilities relative to non-lonely individuals, perhaps suggesting an effect on the autonomic nervous system's regulation of cardiovascular activity (Cacioppo et al., 2002; Ong et al., 2012; Nausheen et al., 2007; O'Donovan & Hughes, 2007; Norman et al., 2011). In addition, loneliness has been linked to elevated inflammatory cytokine responses to acute stress, including several interleukin proteins (e.g., IL-6, IL-1Ra, IL-1β) and tumor necrosis factor-alpha (TNF-α), as well as elevated fibrinogen (a protein in blood plasma that exhibits changes in serum concentration during inflammation) and decreased levels of natural killer lymphocyte cells (Steptoe et al., 2004; Hackett et al., 2012; Jaremka et al., 2013). Brown et al. (2018) meta-analyzed studies on loneliness and reactivity to acute stressors, finding that, though publication bias is possible, the majority (10 of 12) of published empirical studies reported significant associations between loneliness and stress reactivity, when including both elevated (7 of 10) or blunted (3 of 10) physiological responses to acute stress.

Loneliness may elicit additional physiological responses related to immunity and repair. The cross-sectional literature largely corroborates the controlled associations observed between loneliness and cardiovascular functioning, inflammatory cytokines, fibrinogen, and

immune cell activity and extends to include associations with markers of lipid metabolism and glycemic control, growth factors, antibody responses to viruses, immunoglobulins, additional blood protein markers (e.g., c-reactive protein, ferritin) and, as previously reviewed, cortisol (for a comprehensive review, see Pourriyahi et al., 2021). In addition, loneliness and psychological stress have been linked to physiological repair and restorative process, such as slower recovery from wounds (Hawkley & Cacioppo, 2003) and decreased natural killer cell activity which are protective against cancer (Kiecolt-Glaser et al., 1984).

In addition, social isolation has significant effects on brain structure and processes in adult social animals (Cacioppo et al., 2014). Studies with mice have shown that isolation decreases anti-neuroinflammatory responses and survival rate, while increases infarct sizes and oxidative stress following the induction of stroke (Karelina et al., 2009; Karelina et al., 2011). Studies with insects (e.g., Maleszka et al., 2009; Burrows et al., 2011) and other rodents (e.g., Bhide & Bedi, 1984; Garrido et al., 2013) have shown reductions in brain size when the animal is isolated. These and other observed effects of social isolation on brain morphology led to the hypothesis that social isolation affects neurogenesis, especially the rate of new cell proliferation in the adult brain (van Praag et al., 2000). How exactly the human brain responds to perceived social isolation remains unclear, but significant evidence has accumulated that indicates social species' brains adapt (in structure and in activity) to the differing functional demands of interconnected versus isolated living (Cacioppo et al., 2014).

With associations across stress and immune responses, metabolic processes, physiological repair, and brain structure, there are many possible pathways by which loneliness may have a direct influence on health, albeit such theories are largely based on cross-sectional, correlational research. Given the wide array of immune and metabolic correlates in particular, Pourriyahi et al. (2021) argue that loneliness is not just a psychosocial phenomenon, but rather involves a complex system of physiological alterations and therefore should be considered an "immunometabolic syndrome". Loneliness is relatively "trait-like" over time, that is, like personality traits, the rank order of loneliness between individuals tends to be highly stable (Mund et al., 2020), suggesting that some individuals experience a relatively higher degree of cumulative loneliness through the lifespan. Those individuals would be more likely to experience a significantly greater accumulation of atypical stress and immune responses. In the case of HPA axis disruptions, this would likely be associated with greater susceptibility to inflammation and associated conditions. Though the immune and metabolic correlates are, indeed, wide-ranging (though not always consistent across studies), and experimental research indicates that lonely individuals do not respond to stress in the same manner as non-lonely individuals, the etiology of the associations is largely unknown and potentially confounded by a number of factors. As a result, it is not possible to conclude if loneliness causes this theorized cascade of immune and metabolic responses thought to underlie adverse health outcomes.

B. Transcriptomics, Epigenetics, and Telomeres

Poor health may result from an accumulation of "events" involving atypical stress and immune responses signaled by loneliness, though, it has been theorized that psychosocial

stressors are more likely to have a lasting effect on health if they become “biologically embedded” in the form of epigenetic changes that endure even after the stress “signal” is no longer actively evoking a response (Pariante & Lightman, 2008). For instance, transcription factor proteins and methyl groups can bind to the upstream promoter end of a gene in order to initiate or prevent the transcription of that sequence of DNA into RNA, and, as a result, the subsequent translation of the RNA into functional protein products. In this manner, transcription factors and methyl groups can create epigenetic changes by regulating gene expression, in that they allow for variability in gene products that do not result from differences in gene sequence.

a. CTRA—Cortisol is thought to be involved in the regulation of many physiological processes through its influence on gene expression (Yamamoto, 1985). For instance, cortisol activates the glucocorticoid receptor protein, which, in turn, inhibits transcription factors (e.g, nuclear factor κB) involved in pro-inflammatory signaling pathways (Rhen & Cidlowski, 2005). Given that cortisol prevents the transcription of genes associated with inflammatory responses, it is somewhat paradoxical that psychosocial stressors like loneliness and depressive disorders are associated with both increased cortisol and increased inflammatory process. Glucocorticoid resistance refers to glucocorticoid receptors developing an insensitivity to the anti-inflammatory signal sent by circulating cortisol, in effect allowing inflammatory processes to continue relatively unchecked. Indeed, there is in vitro and cross-sectional evidence consistent with humans developing an insensitivity to glucocorticoids following chronic stress (Miller et al., 2002; Pace et al., 2007).

Cole et al. (2007) studied RNA expression profiles in chronically lonely versus socially connected adults in order understand the transcriptional pathways underlying glucocorticoid resistance, and, more broadly, social environmental influences on gene expression. They found significant differences in the RNA profiles of the two groups, consistent with glucocorticoid resistance having developed in the lonely group. Specifically, in the RNA profiles of the lonely group, there was a relative under-expression of genes with anti-inflammatory glucocorticoid response elements (despite comparable cortisol levels across groups) and an over-expression of pro-inflammatory genes (e.g., in the nuclear factor κB transcription factor pathway). Cole et al. (2007) interpreted this finding as consistent with adverse social conditions causing the desensitization of the glucocorticoid receptor, allowing for NF–κB activity to increase, thus promoting greater inflammation (and the observed difference in inflammatory gene expression).

Future work corroborated the finding social adversity was associated with increased expression of genes linked to inflammatory responses and decreased expression of genes linked to Type I interferon antiviral/immune responses across experimental animal model paradigms (e.g., Cole et al., 2012; Tung et al., 2012; Powell et al., 2013; Cole et al., 2015) and in observational human research, including such adversities as chronic stress (Miller et al., 2008, 2014), poverty (Miller et al., 2009), bereavement (O’Connor et al., 2014), and PTSD (O’Donovan et al., 2011). These results largely stem from peripheral tissue samples (e.g., blood), though recent evidence has validated that associations between loneliness and gene expression patterns extend to other cell types, such as that of the post-mortem dorsolateral prefrontal cortex (Canli et al., 2018) and the nucleus accumbens (Canli et al.,

2016). Given these consistent patterns across multiple types of social adversity, Cole (2014, 2019) deemed the effect the Conserved Transcription Response to Adversity (CTRA), and subsequently CTRA has been associated with increased risk or severity of multiple adverse physical health outcomes (Antoni et al., 2016; Simons et al., 2017).

Variability in loneliness was involved in the original observation of CTRA patterning, and recent work validated the presence of a modest association (between self-reported loneliness and a composite CTRA score) and explored moderators. For instance, Kim et al. (2021) observed that, among caregivers of individuals with cancer, only loneliness uniquely predicted elevated CTRA gene expression in a model that also included demographic factors, caregiving stress, social support, and resilience factors such as meaning/purpose in caregiving. On the other hand, in an older adult community sample, Cole et al. (2015b) observed that controlling for eudaimonic well-being (i.e., sense of purpose in life) completely attenuated the observed bivariate association between CTRA and loneliness. Separately, Lee et al. (2021) observed that high levels of collectivism moderated the association, such that loneliness correlated with greater elevations in CTRA among participants with high levels of collectivism and was not associated in participants with lower levels of collectivism (i.e., high individualism). During the COVID-19 pandemic, in-person, but not online social connection was associated with reduced CTRA expression in young adults (Snodgrass et al., 2022). Further work that explicates individual differences in the association between loneliness and CTRA may prove valuable in targeting the health risks associated with loneliness.

Additional work is also needed to validate the proposed mechanistic pathways. While the presence of differences in RNA profiles have been replicated across adversities, the pathway from the perception of adversity to those differences in RNA profiles is uncertain. For instance, neuroimaging analyses aimed at linking differential central nervous system activity to CTRA pathways would be beneficial. In addition, the degree to which the RNA profiles are the result of differences in gene sequence (i.e., DNA) are unknown; twin and family studies or genome-wide association studies can help shed light on the origins of individual differences in the CTRA profile.

b. Methylation—The regulation of gene expression in the CTRA is proposed to be caused by the activity of transcription factor proteins. Methyl group molecules can similarly bind to the promoter of a gene to prevent its transcription, in effect regulating whether the gene becomes expressed in a functional protein product. DNA methylation of this kind is an essential part of normal development, which changes through the lifespan, generally corresponding to an individual's age and health. Methylation levels can be estimated (0%-100%) in thousands of regions of the genome called CpG islands. In older individuals, DNA is considerably less methylated throughout the genome and the correlation between neighboring CpG islands' methylation levels is smaller, suggesting marked differences in the regulation of gene expression in older adults and children (Heyn et al., 2012).

The strong associations between methylation and age were leveraged to develop the first "epigenetic clocks" in 2013. The methylation levels measured at specific CpG sites can be used as predictors of, for instance, chronological age in a linear regression. For a given

individual, a linear of combination of the corresponding beta weights (i.e., of methylation levels at specific CpG sites on age) can then be calculated as a measure of the individual's epigenetic age, that is, their estimated age as statistically predicted by their methylation levels. Using methylation levels from 51 healthy tissues and cell types across thousands of CpG islands as predictors of chronological age, Horvath (2013) developed an early measure of epigenetic age, and it correlated very strongly with chronological age ($r = 0.96$); for 50 percent of participants the difference between their epigenetic and chronological ages was less than 3.6 years (i.e., median prediction error).

Additional measures of epigenetic age have been developed in subsequent years, including the Hannum clock which similarly was trained to predict chronological age, but used measurements from a greater number of CpG sites than the Horvath clock, sampled strictly from blood cells (Hannum et al., 2013). Aimed at using methylation data to better predict future disease and mortality, "second-generation" algorithms were trained on indicators of health and aging beyond chronological age. For instance, a "phenotypic age" clock (referred to as "PhenoAge") was developed by using blood cell methylation levels to predict various clinical health markers (e.g., the C-reactive protein indicator of inflammation, metabolic glucose levels, white blood cell counts) and chronological age, resulting in an epigenetic clock that theoretically was a stronger proxy for biological or functional age (Levine et al., 2018). Similarly, the "GrimAge" clock was trained on various clinical makers in addition to chronological age, with a focus on plasma proteins that have previously been associated with mortality or morbidity (Lu et al., 2019). The "DunedinPACE" measure was trained on within-individual decline in indicators of organ-system integrity from members of the longitudinal Dunedin study (Belsky et al., 2022). Unlike the other "clocks", DunedinPACE is not a measure of biological age in years, rather it is calculated as a ratio of an individual's rate or pace of aging, that is, the number of "biological years" they are currently aging per each chronological year (M = 1.00). The other clocks are typically interpreted in reference to chronological age; the difference between one's epigenetic and chronological ages is considered an estimate of epigenetic age acceleration (EAA), a construct that is becoming widely studied in the context of physical health and aging.

EAA is predictor of many adverse physical health conditions outcomes, including all-cause mortality net of traditional risk factors (Chen et al., 2016). EAA is moderately heritable (e.g., the proportion of between-person variability in EAA attributable to genetic influences was estimated to be 41% by Levine et al., 2015), and several single nucleotide polymorphisms associated with EAA have been identified in genome-wide association studies, some of which are also involved in metabolic and immune pathways (Gibson et al., 2019). Despite EAA's moderate heritability and genetic overlap with physical health, emerging evidence suggests that some of its associations with adverse health conditions are environmentally mediated, that is, not strictly a result of genetic overlap. For instance, in a discordant twin design, EAA was linked to higher BMI net of additive genetic and common environmental confounding (Lundgren et al., 2022). In addition, EAA is less similar in older compared to young monozygotic twin pairs, suggesting environmental factors can exert a greater influence on DNA methylation over time (Talens et al., 2012). These results suggest that EAA is a robust biomarker of declining health that is not strictly a function of overlapping genetic forces. It is unclear if methylation causes aging processes

or is a biproduct, and longitudinal data and experimental animal studies will be crucial for understanding the direction of causality.

Consistent with the theory that epigenetic processes like methylation could be a mechanism by which environmental adversities become biologically embedded (Eachus & Cunliffe, 2018), Weaver et al. (2004) showed that rat mother nursing and grooming behavior impacts the DNA methylation of their offspring. Extending this finding to human psychosocial stress, Unternaehrer et al. (2012) demonstrated laboratory-induced psychosocial stress was associated with increased methylation levels of stress-related genes in circulating blood cells. Similarly, Duman and Canli (2015) demonstrated that, in addition to laboratory-based stress, early and recent self-reported stress relate to methylation levels. Social isolation in adult mice also leads to a wide range of epigenetic effects, including increased DNA methylation in the midbrain (Siuda et al., 2014).

Given that rat grooming behavior, various stressors in humans, and social isolation in mice all appear to have a direct influence on methylation, it is plausible that psychosocial adversities like loneliness would as well. However, in humans, loneliness has rarely been studied in relation to methylation or EAA. In a recent longitudinal study over two timepoints separated by 11 years, change in loneliness had a statistically significant, but modest association with change in the DunedinPACE measure of EAA, which was robust to demographics covariates, including SES, as well smoking and alcohol use (Beach et al., 2022). Similarly, Galkin et al. (2022) tested cross-sectional associations between various psychological factors with a novel biological aging variable “BloodAge”. The psychological factors (e.g., “rarely feels happy”, “restless sleep is rare”) collectively had a large effect, though the binary loneliness item did not have a significant effect net of the other factors. Phillips (2020) observed associations between loneliness and methylation at specific CpG sites located in genes associated with the CTRA, which, in a twin design were partially environmentally mediated. Though loneliness did not significantly relate to cognitive performance in the study, methylation at a specific site did mediate the non-significant association, suggesting that loneliness and cognitive health may be linked partially due to methylation pathways (Phillips, 2020). Similarly, Lynch and Beam (2022) presented preliminary evidence of a significant interaction between loneliness and EAA (PhenoAge) in predicting dementia risk. Overall, there has been little work exploring the association between loneliness and EAA, but the initial evidence suggests a modest link which may help explain the relationship between loneliness and cognitive decline.

EAA has been linked to related constructs, such as relationship attachment and social support. For instance, difficulty establishing close friendships characterized by mutual autonomy and relatedness from ages 13 to 18 predicted elevated EAA (GrimAge) at age 30, robust to demographics and cigarette smoking (Allen et al., 2022). Hillman et al. (2023) measured social support and social contact across four relationship types (spouse, children, friends, and family) and related these constructs to five different EAA measures. They found that friend support, family contact, friend contact, and child contact each significantly predicted two of the EAA measures, while family support predicted one, robust to covariation with demographics, smoking, and health comorbidities (Hillmann et al., 2023). In a sample of older adults from the Health and Retirement Study, there were

13 separate EAA measured computed. Volunteering status predicted decreased EAA in six of those measures; all six of the associations remained statistically significant and similar in magnitude after adjusting for demographic and health factors, while associations were somewhat attenuated when controlling for health behaviors (e.g., smoking), wherein four associations remained significant (Nakamura et al., 2023). Similar to loneliness, associations with relational variables appear modest, though consistent in terms of direction (i.e., more relational contact and greater support associates with decreased age acceleration).

Finally, there have been relatively inconsistent associations with psychopathology, with mixed evidence on the links between EAA and PTSD (Mehta et al., 2018; Verhoeven et al., 2018; Yang et al., 2020), schizophrenia (Higgins-Chen et al., 2020; Oblak et al., 2021), depression (Starnawaska et al., 2019; Oblak et al., 2021), and borderline personality disorder (Boström et al., 2023). For instance, the mean GrimAge value was considerably lower for a control group compared to a group with a diagnosis of borderline personality disorder, but significant differences were not observed across the other four measured EAA variables in a recent study by Boström et al. (2023). For PTSD, significant associations have been observed in both directions (Oblak et al., 2021). Overall, psychosocial stress tends to relate modestly with EAA, though evidence is limited and can be somewhat inconsistent across samples, perhaps reflecting methodological variability in, for instance, the specific clocks that are used and covariates that are modelled, while links with psychopathology are more tenuous.

While the choice of covariates when modelling the correlates of EAA can be inconsistent, most studies that relate EAA with psychosocial variables statistically control for factors that relate to demographics and health behaviors. Most epigenetic clocks will be regressed on chronological age before analyses so that the residuals are index of EAA. After that, demographic variables like sex, race, and socioeconomic status (SES) are often included as covariates to avoid artifactual confounding, given their consistent associations with EAA. For SES, it has been demonstrated that early life adversity, such as childhood poverty (McCrory et al., 2022) and family-level and neighborhood-level socioeconomic disadvantage (Raffington et al., 2021) both relate strongly to EAA. Similar to trends in life expectancy, women and Hispanic Americans have been shown to have lower EAA values on average than males and White Americans (Horvath et al., 2016), while African Americans have greater EAA (Tajuddin et al., 2019). For measures like DunedinPACE, which are not calculated in reference to chronological age, an additional control for chronological age is often used, as older individuals have been demonstrated to, on average, undergo faster EAA than younger individuals (Belsky et al., 2022). As for health behaviors, physical activity and especially smoking have strong associations with EAA (Oblak et al., 2021). The relationship with alcohol use appears to be nonlinear with greater age acceleration at high and low levels of intake (Beach et al., 2015). Health status and conditions (cardiovascular disease, cancer, diabetes, HIV infection, higher BMI), as expected, also have been shown to relate to elevated EAA (Oblak et al., 2021), though are less frequently controlled for, perhaps due to concern that partialing these components out of EAA would create difficulty in interpreting the construct (i.e., age acceleration net of health status).

Other methodological considerations include clock choice and the type of tissue sampled. Given an individual's methylation levels, various algorithms can be applied to estimate EAA using different linear combinations of the values across different CpG sites. First-generation clock algorithms derived from predicting a person's chronological age using their methylation levels, while second-generation clocks added clinical markers to the predictand side of the machine learning training model. As a result, the corresponding algorithms estimate a person's health using their methylation levels (noting that there is variability across clocks in the health markers used). Because, theoretically, an individual's overall health inclusive of their age overlaps with psychosocial and health variables more than just their age alone, second-generation clocks to be stronger predictors than the first-generation clocks (Oblak et al., 2021)[3]. DNA methylation profiling tends to be completed on participant blood samples, specifically peripheral blood mononuclear cells. It has been argued that these tissues are not the location in which the epigenetic impacts of exposures of interest (e.g., loneliness) theoretically would have the greatest biological consequences, rather brain cells would be more directly implicated (Eachus & Cunliffe, 2018). Initial evidence has validated that there is similarity in post-mortem brain and blood tissues in the gene expression profiles related to the CTRA (Canli et al., 2016, 2018), but further work of this kind and animal models will be crucial for determining the degree to the epigenetic effects of psychosocial stress vary across tissue types, given practical and ethical limitations on sampling other living human tissues. Finally, similar to the CTRA, though there are theoretical physiological pathways, considerable work is needed to test how the perception of psychosocial stress may lead to methylation differences.

c. Telomeres—At both ends of each human chromosome, there are repetitive DNA sequences called telomeres thought to protect the rest of the chromosome from becoming frayed or tangled, functioning like a cap. When cells divide, these caps become slightly shorter, and eventually, so short that the cell cannot divide and dies. As a result, telomeres become measurably shorter as humans age, and some theorize that this shortening may contribute to the biological processes underlying aging and some age-related diseases. It is unclear if telomere shortening and dysfunction initiates disease processes, though it likely plays a pathogenic role in disease, beyond merely being a correlate or marker (Chakravarti et al., 2021). Changes in telomeres are not epigenetic in nature, as they occur at the level of DNA sequence itself, but unlike most aspects of DNA sequence, telomeres are not mitotically stable and are not identical across cells (i.e., the number of repeats changes with cell division). Thus, it has been proposed that causing telomere shortening or dysfunction could be a potential mechanism by which psychological adversities like loneliness could become biologically embedded (Hawkley et al., 2005).

Indeed, a vast literature on psychosocial correlates of telomere length has emerged, with (low) childhood SES, early life adversity, racial discrimination, marital status (not married/partnered), and (low) perceived social support emerging as the most consistent predictors of shorter telomere length (Rentscher et al., 2020). Perhaps surprisingly given the robust link with social support, associations with loneliness have been inconsistent across samples.

[3]As a result, second-generation clocks may be used in empirical research more commonly, but it could be argued that by not being trained on age alone, they index a more general biological health construct, rather than strictly age acceleration.

A modest but significant association between (shorter) telomere length (measured with quantitative polymerase chain reaction [qPCR]) and (greater) loneliness was observed in a community sample at midlife, moderated by heart rate variability (Wilson et al., 2019) and a moderate to large association was observed (measuring telomere length with the Southern blot, longitudinally 24 years after the loneliness measurement) in an older adult sample exposed to extreme stress (comprised of former prisoners of war; Stein et al., 2018). However, loneliness was not significantly associated with telomere length (measured with qPCR) in a different older adult community sample (Schaakxs et al., 2016). Similarly, several aspects of mental well-being, inclusive of lack of loneliness, each were not significantly associated with telomere length (measured with qPCR) in a separate, older adult community sample, both cross-sectionally and longitudinally (change in loneliness predicting change in telomere length six years later; Rius-Ottenheim et al., 2011). The results of these studies are summarized in Table 1, which suggests a preliminary modest link observed in small samples, but inconsistency across studies. While the vast majority of this work is cross-sectional, making inference about temporal sequencing in the link between psychosocial adversity and telomere length unwarranted, recent work has begun to explore interactions between loneliness, telomere length, and physical health (Wilson et al., 2019; Delgado-Losada et al., 2022).

Overall, the extent to which the experience of loneliness directly signals its host of biological correlates that make it reasonable to refer to as an “immunometabolic syndrome” remains largely unknown, as is the degree to which those theoretical physiological responses can become biologically embedded in the form of differential gene expression and telomere shortening. However, there is experimental evidence that lonelier individuals physiologically respond to acute stressors in atypical ways, that acute stress can lead methylation changes, that prolonged isolation has vast epigenetic effects in certain animals, and that similar epigenetic changes in humans are associated with a range of adverse health outcomes. Taken together, it is reasonable to hypothesize that prolonged feelings of loneliness have some direct effect on declining health mediated through its signaling of epigenetic changes. This may account for some of the association between loneliness and declining health, but considerable work is needed to elucidate the physiological pathways, while other plausible pathways exist as well.

3. Indirect Influence of Loneliness on Health Mediated through Health Limiting Behaviors

Different types of health-related behaviors are associated with loneliness to varying degrees. As an example, Lauder et al. (2006) showed that lonely individuals were more likely to be smokers and to be obese than non-lonely individuals, though were no more likely to have a sedentary lifestyle. In addition to smoking and physical activity, other health behaviors have been linked to loneliness including alcohol and other substance use, diet, sleep habits and quality, and medication adherence. We first review links between loneliness and each of these health-related behaviors before summarizing the small literature examining the extent to which they mediate the relationship between loneliness and health.

A. Substance Use

Because of its strong associations with DNA methylation, smoking is commonly a covariate in EAA studies. There is evidence that loneliness correlates with smoking as well, though the effect appears to be relatively modest (DeWall & Pond, 2011). In a systematic review, Dyal and Valente (2015) found that half of the published empirical studies meeting their inclusion criteria reported a significant, positive association between loneliness and smoking, with just one study reporting a negative association. Though they did not estimate an overall effect size, studies conducted with larger sample sizes were more likely to report significant findings, suggesting that some studies were underpowered to detect the modest link. More recent evidence suggests that the modest association generalizes to the Chinese young adult (Zhang et al., 2020) and both the English (Philip et al., 2022) and U.S. (Yang et al., 2022) older adult populations. Further, Wootton et al. (2021) presented Mendelian randomization evidence consistent with a bidirectional relationship between increased smoking (initiation, volume, and lower likelihood of quitting) and increased loneliness.

Loneliness has also been linked to alcohol use. Individuals with alcohol use problems report higher levels of loneliness and have poorer prognoses for recovery, on average (Akerlind & Hörnquist, 1992). Further, among those with alcohol use problems, loneliness is associated with greater consumption and riskier drinking behaviors (Akerlind & Hörnquist, 1987). In addition, loneliness relates to risk for unsupervised drinking in adolescent samples (Barbosa Filho et al., 2012; McKay et al., 2017), suggesting it may be an early risk factor for the development of use problems.

However, in adult community samples, associations between alcohol and loneliness have been mixed. There is some evidence that between-individual differences in loneliness predict greater usage (Gutkind et al., 2022; Bragard et al., 2022; Shield et al., 2022). On the other hand, there is evidence that loneliness is not linked to greater drinking frequency (Rhew et al., 2021), greater at-risk or binge drinking, and slightly *lower* odds of drinking four to seven days per week (Canham et al., 2016), as well as within-individual increases in loneliness predicting *less* alcohol use (Bragard et al., 2022) and Mendelian randomization analyses being inconsistent with loneliness having a causal effect on drinking behaviors (Wootton et al., 2021). Others have suggested that the relationship between loneliness and greater alcohol use is mediated through factors like low self-esteem (Lau et al., 2023), perceived stress (Segrin et al., 2018), and food and alcohol disturbance (Herchenroeder et al., 2022). The complex pattern of results may suggest a non-linear relationship between loneliness and alcohol use in adult community populations. Indeed, diary evidence suggests that individuals may drink more on days where they feel either particularly high or low degrees of loneliness (Bragard et al., 2022b), in line with theories that alcohol can reduce feelings of isolation and cultivate an environment of “friendship and togetherness” (Segal, 1987, p. 303). It stands to reason that those feelings of isolation that are temporarily reduced may serve as a risk factor for the development of use problems and for worse outcomes among those with use problems.

Loneliness is consistently associated with increased use of other substances, such as cannabis and, though less frequently studied, opiates (Pedrero-Perez et al., 2021). For

instance, greater loneliness has been associated with greater cannabis usage in middle aged adult (Gutkind et al., 2022), young adult (Pandya, 2017; Rhew et al., 2021) and youth (Butler et al., 2023) samples. In addition, trajectories of increasing loneliness (Cadigan et al., 2023) and increased self-isolation (Bartel et al., 2020) through the COVID-19 pandemic have been linked to increased cannabis use. Across substances, Ingram et al. (2020) found that, based on a systematic narrative review, people with substance use problems report greater loneliness than the general population and that higher severity and duration of dependence is related to greater loneliness. Members of substance-dependent populations have been estimated to be five times more likely to identify loneliness as a serious concern compared to the general population (Ingram et al., 2018).

Overall, loneliness appears to be linked to substance use problems (though there is not enough data to differentiate by substance), as well as cigarette smoking and cannabis use in community samples (regardless of if a clinically significant use problem is present). The link with alcohol among people without use problems appears more tenuous and perhaps non-linear. Across each of these associations, the causal direction is unclear and plausible accounts for the association have been proposed in both directions. For instance, methamphetamine (Newton et al., 2009) and heroin (Itzick et al., 2019) users have reported that continued use was motivated by avoiding distressing feelings such as loneliness, and loneliness has been cited as a common trigger for relapse (Laudet et al., 2010; Levy, 2011). On the other hand, people with substance use problems have reported that family and friends often distance themselves because of their substance use (Ingram et al., 2020), together suggesting a bidirectional relationship.

B. Physical Activity, Diet, and Healthcare Adherence

Perlman and Peplau (1981) suggested that certain behaviors can both influence the experience of loneliness and be consequences of it. While there is limited evidence that this may be the case for some substance use, there is strong evidence that physical activity in older adulthood works in this manner. Pels and Kleinert (2016) conducted a systematic review and found that 12 of the 24 cross-sectional studies reported a direct negative relationship between loneliness and different aspects of physical activity, while an additional four reported indirect associations (e.g., moderation by gender, mediation by social support). Similar evidence has been found in clinical populations, with loneliness being cross-sectionally associated with lower physical activity in patients with schizophrenia (Vancampfort et al., 2011) and bipolar disorder (Vancampfort et al., 2013). In addition, each of the four longitudinal studies in the systematic review reported significant associations between loneliness and later declines in physical activity[4], while two of three relevant studies reported an effect (one direct, one indirectly moderated by gender) of physical activity on later loneliness. Further, interventions centered on physical activity have found favorable effects on loneliness (Hopman-Rock & Westhoff, 2002; Kahlbaugh et al., 2011; McAuley et al., 2000; Savikko et al., 2010; Tse et al., 2014), together suggesting a robust bidirectional association.

[4]Some recent work has been consistent in finding loneliness predicts decreased physical activity in the future (e.g., Yang et al., 2022) though null associations have been reported as well (Kobayashi & Steptoe, 2018; Schrempft et al., 2019).

Objective social isolation, especially in males, is recognized as a risk for malnutrition in elderly populations (Johansson et al., 2009; Vesnaver & Keller, 2011). Subjective feelings of loneliness are less frequently studied in that context, but preliminary results suggest a similar, but smaller association. In older adult samples, significant bivariate associations have been observed between loneliness and continuous measures of malnutrition risk (Schilp et al., 2011; Boulous et al., 2016; Eskelinen et al., 2016; Wei et al., 2023) and unintended weight loss (Sorbye et al., 2008). Generally, bivariate associations are modest (e.g., Odds Ratios 1.1-1.5), and, across two studies, were attenuated to be non-significant in models that account for other predictors (e.g., poor appetite, health issues, recent hospitalizations; Sorbye et al., 2008; Schilp et al., 2011), though, in one study, remained significantly associated after accounting for other lifestyle factors (Wei et al., 2023).

In other populations, loneliness has also been linked to eating behaviors. In a recent cross-sectional study of centenarians, loneliness was strongly associated with malnutrition risk (Jung et al., 2021), while being a modest predictor of unhealthy diets in college students (Jiang et al., 2022). Loneliness is also commonly observed in clinical eating disorders (e.g., anorexia nervosa, binge eating disorder) and is thought to contribute to symptoms (Levine, 2011). Statistically significant decreases in loneliness were observed in a sample of elderly adults who participated in a home-delivered meal program (Wright et al., 2015). Taken together, this evidence suggests that loneliness may be one of many factors that contribute to nutritional deficits in older adults, though the direction of causality is unresolved.

Similar to malnutrition, risk for medication nonadherence in the elderly is thought to be introduced by social isolation (DiMatteo, 2004). Though loneliness and social isolation are often “decoupled”, there is evidence that the experience of loneliness may also present risk. Loneliness has been cross-sectionally associated with poorer self-reported, general medical adherence in adult community sample (e.g., “seek health care when needed”; Segrin & Passalacqua, 2010), self-reported difficulty with medication adherence for patients with diabetes (Avci, 2018), as well as medication adherence for individuals with coronary heart disease (Fan et al., 2021), schizophrenia (Seki Öz et al., 2022), and hypertension (Hacihasanoglu Asilar et al., 2020).

Lu et al. (2020) presented a mediation model that attempted to represent the effects of loneliness and social isolation on medication adherence. Significant bivariate associations with poorer medication adherence were observed for both greater social isolation ($r = -0.16$) and greater loneliness ($r = -0.26$), loneliness and social isolation were positively correlated with each other ($r = 0.16$), and loneliness and low social support were modelled to mediate relationship between social isolation and poor adherence (Lu et al., 2020). Loneliness has also been studied in relation to health-promoting behaviors during the COVID-19 pandemic. Higher loneliness has been linked to less frequent handwashing across three studies, less intention to social distance across two of the three (Stickley et al., 2020; Kang et al., 2021; Dempster et al., 2022). Stickley et al. (2020) also measured mask wearing tendencies, which were similarly negatively predicted higher loneliness. Taken together, this evidence suggests loneliness confers risk for poorer healthcare across a number of conditions and novel situations.

C. Sleep Disturbances

The impact of loneliness on sleep has been widely studied. Holm et al. (2020) meta-analyzed of 84 articles across 110 samples, estimating moderate associations between loneliness and sleep problems cross-sectionally ($r = 0.34$) and longitudinally (rs = 0.25–0.30), suggesting a robust reciprocal relationship. Griffin et al. (2020) conducted a similar meta-analysis with more stringent inclusion criteria, identifying 27 relevant articles and calculating a comparable effect size for the cross-sectional association between loneliness and sleep disturbance ($r = 0.28$). However, they caution against conclusions about directionality given the limited longitudinal evidence. No association was found between sleep duration and loneliness. Across both meta-analyses, no significant moderators were identified, suggesting that the relationship is similar across age, race, and gender. Indeed, the authors of a recent systematic review of 11 articles concluded that there is a positive relationship between sleep disturbance and loneliness in older adult populations specifically (Azizi-Zeinalhajlou et al., 2022). Similar evidence exists for adolescents (Eccles et al., 2020) and young adults (Matthews et al., 2017). In the latter young adult twin study, a significant within-twin pair effect was observed, suggesting the association between loneliness and sleep disturbance is independent of genetic confounding (Matthews et al., 2017). While sleep quality variables are typically self-reported, associations extend to objective measures of sleep disturbance based on actigraphy data (Kurina et al., 2011; Benson et al., 2021), supporting the notion that there is a robust link between loneliness and sleep disturbance.

D. Health Behaviors as a Mediator

Evidence has been inconsistent, to date, on whether health behaviors mediate the association between loneliness and declining health and mortality. Luo et al. (2012) demonstrated that physical exercise and smoking did not mediate the association between loneliness and mortality among participants from the Health and Retirement Study. On the other hand, Patterson and Veenstra (2010) showed that physical activity was a strong mediator of the association, while smoking status also had a modest, significant mediating effect. Luo and Waite (2014) present cross-lagged panel evidence from a Chinese sample consistent with physical activity but not smoking mediating the association. Segrin and Passalacqua (2010) present evidence that health behaviors (a latent variable indicated by substance abuse, medical adherence, sleep, exercise, and diet) mediated the association between loneliness and general health status. Of the health behaviors, loneliness was most strongly linked to poorer sleep and medical adherence. Similarly, Segrin and Domschke (2011) present evidence that “recuperative behaviors” (defined as sleep quality and participation in leisure activities) mediate the relationship between loneliness and general health. Christiansen et al. (2016) found that physical activity and poor sleep both had a large mediating effect on the relationship between loneliness and three health conditions (cardiovascular disease, diabetes, and migraine), neither daily smoking nor alcohol problems were impactful.

Luo et al. (2012) concluded that “the fact that loneliness continues to predict health outcomes when health behaviors are held constant suggests that loneliness alters physiology at a more fundamental level” (p. 912). With the exception of the Patterson and Veenstra (2010) study, the loneliness-mortality link remained statistically significant after accounting for health behaviors. This suggests health behaviors are mediators but not moderators of

the association, consistent with loneliness having an influence on health that cannot be explained by behavior alone. Based on the limited evidence to date, the most salient mediators appear to be physical activity and sleep quality, while more mixed or limited evidence exists for smoking and healthcare adherence, while little to no evidence has accumulated for diet or the use of other substances.

4. Confounders in the Relationship between Loneliness and Health

A. Genetic Overlap

A moderate to large portion of the variance in both loneliness and general health status is attributable to genetic differences between people. The heritability of loneliness is estimated to be around 30-55% with non-shared, rather than common, environmental factors accounting for the remaining variance (McGuire & Clifford, 2000; Distel et al., 2010; Schermer & Martin, 2019). Heritability estimates for self-rated health range from 30%-65% (Romeis et al., 2000; Silventoinen et al., 2006; Silventoinen et al., 2007). Similar estimates have been yielded for other general health phenotypes such as a wellness-based healthy physical aging index (53-57%; Reed & Dick, 2000), a disease-based healthy aging index (24%-39%; Sanders et al., 2013), and epigenetic age acceleration (41%; Levine et al., 2015). It is plausible that many pleiotropic genetic variants could be involved in the development of both of these phenotypes, that is, that some of the same genetic factors could influence both loneliness and physical health, explaining some of their covariance.

Indeed, genetic overlap between loneliness and various physical and behavioral traits has been estimated. Abdellaoui et al. (2019) conducted a genome-wide association study meta-analysis of loneliness (n = 511,280) and used linkage disequilibrium score regression to calculate genetic correlations with a wide range of traits. Moderate to strong genetic correlations were observed with various physical health markers, including self-rated health (r_g = −0.56), tiredness (r_g = 0.74), and father and mother's age at death (r_g = −0.37, −0.33). Small to moderate associations were observed with anthropomorphic traits (e.g., BMI, body fat, waist circumference; r_g = 0.18-0.25). Some cardiovascular disease phenotypes had null to modest genetic correlations with loneliness (e.g., type-2 diabetes and LDL, HDL, and total cholesterol; r_g = −0.10-0.04), while modest, but statistically significant genetic correlations were observed with coronary artery disease, myocardial infarction, and triglycerides (r_g = 0.14-0.19). Moderate to strong negative associations were observed for SES variables (e.g., educational attainment, income, (low) social deprivation; r_g = 0.27-0.51), while moderate negative associations were observed with some cognitive traits (IQ, Childhood IQ, verbal-numerical reasoning; r_g = −0.19 - −0.24), but not others (e.g., memory, reaction time r_g = −0.01, 0.00). Strong associations were observed for affective mental health variables (e.g., (low) subjective well-being, depressive symptoms, anxiety; r_g = 0.52-0.88), while moderate associations were observed for other aspects of mental health (e.g., schizophrenia, autism, Alzheimer's, ADHD, alcohol dependence, smoking initiation and cessation, cannabis use, eating disorders; r_g = 0.10-0.43).

Polygenic risk score analyses have supported the notion that there is a small to moderate genetic overlap between loneliness and coronary artery disease (Dennis et al., 2019), as well as larger overlap with self-rated health, tiredness, and affective mental health (Abdellaoui

et al., 2018). More recent molecular genetic work using bivariate causal mixture modelling has further supported the presence of genetic overlap with cardiovascular disease and mental health variables (Rødevand et al., 2021). In twin and family studies, moderate to strong genetic correlations between loneliness and personality traits, especially neuroticism and extraversion have been noted (Schermer & Martin, 2019; Freilich et al., 2022), as well as with symptoms of depression (Matthews et al., 2016) and borderline personality disorder (Schermer et al., 2020). Overall, this suggests that a small to moderate portion of the link between loneliness and health is due to overlapping genetic architectures. Most studies of loneliness and health do not benefit from genetically informed samples that can be used to model genetic and environmental sources of covariance, so this genetic confounding is contained within most observed phenotypic associations.

B. Other Confounders

Demographic and socioeconomic variables are other potential artifactual confounders which are often statistically controlled for when studying loneliness and health, though other unmeasured confounders can never be entirely ruled out. Affective personality traits (e.g., negative emotionality/neuroticism and low positive emotionality/extraversion) and depressive symptoms are complex to consider in the context of confounding because they are conceptually similar to and strongly associated with loneliness, with evidence of highly overlapping genetic influences (Schermer & Martin, 2019; Abdellaoui et al., 2019). Like personality traits, traditional loneliness scales are relatively “trait-like”, that is, have a high rank order stability (Mund, 2020). These scales arguably index the broad propensity to experience a high degree of negative and low degree of positive emotion in the context of interpersonal relationships as opposed to a transient emotional experience (Freilich et al., 2023). Negative emotionality more broadly, for instance, has also been linked to adverse health outcomes with similar mechanistic questions and theories (Lahey, 2009). It is likely that the processes linking both broad personality traits and loneliness, as traditionally measured, with health are similar, though more evidence is needed to conclude if there are notable differences.

C. Reverse Causation

There is limited work specifically examining the impact of physical health declines on loneliness. In their meta-analysis on the relationship between loneliness and mortality, Holt-Lunstead et al. (2015) ran “unadjusted”, “partially adjusted”, and “fully adjusted” models, corresponding to the inclusion of different covariates. The unadjusted models included no covariates, the partially adjusted models included just demographic covariates, and the fully adjusted analyses included multiple covariates, notably including concurrent health status, aimed at accounting for reverse causality (i.e., predicting mortality while controlling for the effect of concurrent impaired health on loneliness). In all three models, the weighted average effect sizes of loneliness on early mortality were statistically significant (weighted odds ratios of 1.49, 1.52, and 1.26 respectively), though significantly attenuated in the fully adjusted model, possibly suggesting an impact of reverse causation.

Previous reviews of mechanisms are centered on the impacts and consequences of loneliness on health and therefore feature only limited discussion of reverse causation (Hawkely &

Cacioppo, 2003; Hawkley & Cacioppo, 2010; Ong et al., 2016; Pourriyahi et al., 2021). However, some evidence of bidirectional relationships with health behaviors have been observed, such as substance use (Ingram et al., 2020; Wootton et al., 2021) and physical activity (Pels & Kleinert, 2016). In addition, reviews of the relationships between loneliness and both inflammation (Smith et al., 2020) and cardiovascular health (Hodgson et al., 2020) also consider bidirectional influences, citing, in the case of inflammation for example, the theoretical impacts of inflammatory cytokines on depressive symptoms, such as anhedonia, fatigue, and sleep difficulties (Felger & Lotrich, 2013), but do not include sufficient longitudinal data to estimate effects. Reverse causation appears to be plausible to varying degrees across different types of health problems, likely accounting for some portion of the cross-sectional associations with loneliness. However, robust longitudinal associations between loneliness and future cardiovascular (Valtorta et al., 2016), cognitive (Kuiper et al., 2015), and metabolic (Shiovitz-Ezra & Parag, 2019) health have been observed in meta-analyses, suggesting that accounting for reverse causation does not attenuate the links between loneliness and health entirely. Longitudinal evidence with inflammation is more limited (Smith et al., 2020).

5. Conclusion and Future Directions

Having robust associations with declining physical health, loneliness is a growing public health issue. Crucially, evidence is accumulating that there are effective interventions for reducing loneliness across the lifespan and across the individual, community, and societal levels (Bessaha et al., 2019; Eccles & Qualter, 2020; Hawkley, 2022). However, more work is needed to understand if, how, and when loneliness has a direct influence on health, and, subsequently, if reducing loneliness can be expected to have physical health impacts. Mechanistically, there are significant gaps in our knowledge of how psychosocial stress may lead to physiological changes. HPA axis disruptions that lead to changes in gene expression through methylation and the activity of transcription factor proteins are one promising area of research but are confounded by a number of unmeasured factors. As methylation profiles and epigenetic aging variables continue to become easier and less expensive to collect, researchers will be able to study them across a wider range of study designs and alongside a wider array of psychosocial variables.

There are several study design features that can enhance the inferences that can be made with epigenetic measures. For instance, to our knowledge, there have been no twin or family studies of loneliness and declining physical health or EAA. Given the moderate to strong genetic correlations between loneliness and physical health found with molecular genetic methods (Abdellaoui et al., 2018, 2019), it is unclear if associations are environmentally mediated or, rather, due primarily to overlapping genetic architectures. In addition, such a study would benefit from direct measurement of other potential confounders, such as health behaviors (most notably physical activity and sleep quality) and socioeconomic status, as well as of indicators of other potential mechanisms (e.g., RNA profiling for CTRA variables, telomere measurements) for comparison of effect sizes within the same sample. Studying these measures across multiple longitudinal waves would further enhance the ability to make causal inferences and test the possibility of reverse causation. Given that genetic variants associated with loneliness are beginning to be discovered, Mendelian randomization may

also be a fruitful approach for making causal inferences about the impact of loneliness on health and comparing mechanisms. Additional design features, such as the use of instrumental variables, that can further enhance causal inference are beginning to become more regularly used in psychological research and may have utility for understanding the impact of loneliness on health (Maydeu-Olivares et al., 2020).

Typically, other potential mechanisms or confounders will be included in a measurement model as a covariate to be "partialed out" of the relationship of interest. However, doing so may have undesirable consequences, especially when variables collinear, such as distorting the constructs of interest (Hoyle et al., 2023). At the very least, Holye et al. (2023) recommend that partialing should be based on a theoretical account of how the primary variable, covariates, and outcome variables are all interrelated, allowing the measurement model to support or falsify a hypothesis. Further, partialing issues are exasperated with greater measurement error, so the use of well-validated and reliable tools to measure well-defined constructs is beneficial. Moving forward, more attention should be paid to the stability of loneliness and its relationship with affective personality and psychopathology. Traditional loneliness scales tend to measure a construct that is more "trait-like" than "state-like", though conceptually loneliness is thought to vary regularly in changing environments (Mund, 2020). The measured construct is highly overlapping with broad negative emotionality (Abdellaoui et al., 2019b). The "state-like" qualities that may make loneliness distinct from affect may be more effectively measured in an intensively longitudinal study designs, captured in day-to-day within-person variability. Typically, duration of loneliness is not measured either; transient emotional experiences may relate differently to physiological and epigenetic variables than long-standing, chronic feelings, and intensively longitudinal designs may allow for inference on their bidirectional influences within individuals. Additional research of this sort will be crucial for understanding how loneliness becomes biologically embedded.

Acknowledgments

We have no known conflict of interest to disclose. CDF was supported by the National Institute on Drug Abuse (T32DA050560).

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Biodemography Soc Biol. Author manuscript; available in PMC 2024 November 27.

Table 1.

Summary of Studies on Loneliness and Telomere Length

Study	Sample	Loneliness Measurement	Telomere Measurement	Covariates	Effect
Wilson et al., 2019	n = 113 United States men and women at midlife (M_{age} = 51.0)	4-item New York University Loneliness Scale (Cronbach's alpha = 0.84; cross-sectional)	Quantitative polymerase chain reaction (cross-sectional)	Age, sex, race, education, BMI, social network size, resting heart rate, depression history	Loneliness x Heart rate variability b = 0.001, SE = 0.0004, p = 0.012
Stein et al., 2018	n = 83 Israeli ex-prisoners of war (M_{age} = 63.6 at follow-up when telomere length was measured)	20-item UCLA Loneliness Scale (Cronbach's alpha = 0.89; cross-sectional)	Southern Blot (24 years after loneliness measurement)	Age, BMI, depression, PTSD, dummy variables for smoking and substance use, perceived social support	Unadjusted r = −0.43, p < 0.001 Adjusted for covariates β = −0.38, p = 0.001
Schaakxs et al., 2016	n = 496 elderly Dutch men (M_{age} = 70.6)	11-item De Jong Gierveld Loneliness Scale (Cronbach's alpha not given; cross-sectional)	Quantitative polymerase chain reaction (cross-sectional)	Age, sex, education, cigarette years, alcohol use, physical activity, BMI, chronic diseases	Cross-sectional association: b = −2.38, SE = 4.47, p = 0.59
Rius-Ottenheim et al., 2011	n = 203 elderly Dutch men (M_{age} = 77.6) Follow-up on n = 144 (M_{age} = 84.1)	11-item De Jong Gierveld Loneliness Scale (Cronbach's alpha = 0.82; measured at two timepoints)	Quantitative polymerase chain reaction (measured at two timepoints)	Age, living arrangement, smoking status, alcohol consumption, physical activity, chronic diseases, and BMI	Cross-sectional association: β = 0.109, p = 0.16 Longitudinal association (Δ loneliness predicting Δ telomere length): β = 0.106, p = 0.43

Note. β = standardized multiple regression coefficient. b = unstandardized regression coefficient. *SE* = standard error. p = p-value for multiple regression coefficient. BMI = Body mass index.