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Perceived social isolation, evolutionary fitness and health outcomes: a lifespan approach

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Sociality permeates each of the fundamental motives of human existence and plays a critical role in evolutionary fitness across the lifespan. Evidence for this thesis draws from research linking deficits in social relationship—as indexed by perceived social isolation (i.e. loneliness)—with adverse health and fitness consequences at each developmental stage of life. Outcomes include depression, poor sleep quality, impaired executive function, accelerated cognitive decline, unfavourable cardiovascular function, impaired immunity, altered hypothalamic pituitary–adrenocortical activity, a pro-inflammatory gene expression profile and earlier mortality. Gaps in this research are summarized with suggestions for future research. In addition, we argue that a better understanding of naturally occurring variation in loneliness, and its physiological and psychological underpinnings, in non-human species may be a valuable direction to better understand the persistence of a 'lonely' phenotype in social species, and its consequences for health and fitness.

1. Introduction

Social species possess a level of social organization that entails groups of adults living together relatively permanently and whose relationships with others endure from one time to the next. Sociality, often considered synonymous with group living ([1]; see also [2]), has, in the behavioural neurosciences, come to reflect a wide variety of affiliative behaviours that vary in type and complexity across social species [1–3]. Sociality hinges on behaviours that facilitate (or hamper) the formation and maintenance of social relationships with others. Deficits in social relationships provide a valuable perspective to gauge the importance of sociality to fitness and to human thriving. In infancy, the benefit of a relationship is clear. Without the parent's care and nurturing, the infant would almost certainly perish. But the critical role of social relationships does not end there. The parent–child bond is only the beginning of a life characterized by the formation and maintenance of relatively stable dyadic and group relationships that emerge at various developmental stages of life.

Perceived social isolation, colloquially known as loneliness, is a useful construct to examine the importance of social relationships for health and fitness [4]. People are with (or around) other people much of the time, with only few exceptions (e.g. inmates in solitary confinement; hermits who choose isolation). Group living—in families and larger communities and societies—virtually guarantees the availability of social others and thus minimizes the likelihood of becoming isolated. Group living does not guarantee, however, that each individual in the group will be able to satisfy his or her social needs. Perceived social isolation represents a mismatch between an individual's social needs and the provisions the social environment offers or is perceived to offer. The mismatch can be quantitative (i.e. too few relationships, potential or actual), but is usually more qualitative in nature [5]. That is, for some individuals and contexts, social relationships fail to engender the sense of connectedness and belonging that is critical for human thriving.

2. An evolutionary theory of loneliness

At each stage of human development, fitness—the ability to survive and reproduce—entails trade-offs between the costs and benefits associated with the expenditure of energy on motivations that ebb and wane in importance with development [6,7]. Fundamental motives—including those to satisfy physiological needs, ensure self-protection, affiliate with others, establish status, acquire and retain a mate, and become a parent—have been proposed to build on each other in a hierarchical fashion with development [7], and social motives permeate the entire hierarchy.

In the course of evolution, loneliness has been posited to serve adaptive ends by motivating connection and reconnection with others to ensure safety and survival. The danger of isolation and the need to protect oneself trigger implicit hypervigilance for social threat, together with greater anxiety and hostility, among other outcomes [8,9]. Potentially maladaptive social cognitions ensue, including attentional biases favouring negative social information, and self-fulfilling confirmation biases in which negative expectations and distrust adversely affect behaviour toward others (e.g. aggression). These behaviours tend to elicit fewer and qualitatively poorer interaction behaviours from others, thereby confirming the lonely person's negative expectations and reinforcing a sense of disconnection and loneliness. This 'regulatory loop' through which loneliness perpetuates itself contributes to lonely individuals' beliefs that they have little social value and little control over how they are received and accepted by others [10,11].

To the extent that loneliness functions adaptively and social connections are established or re-established, the perpetuation and consequences of loneliness are minimized. Transient feelings of loneliness (e.g. minutes, hours or occasional days) are experienced by most people and are often relatively mild. Nevertheless, transient feelings of loneliness can and do have aversive consequences, but these tend to be adaptive, affective states (e.g. sadness, anxiety) that motivate reconnection and are typically quick to dissipate upon reestablishment of a sense of connectedness. Transient loneliness may also have immediate and brief physiological effects (e.g. cortisol response to awakening), but most physiological systems accommodate transient perturbations without long-lasting consequences for health and functioning. Loneliness that arises from situational factors (e.g. geographical relocation, widowhood) may be longer-lasting and can elicit adverse behavioural and physiological consequences that, too, may resolve upon recovery from loneliness and reestablishment of satisfying social relationships. To the extent that individuals get 'stuck' in the regulatory loop and are unable to satisfy their social needs, however, chronic feelings of loneliness may ensue. More intense and enduring feelings of loneliness are believed to be the toxic players in persistent psychosocial problems and the slowly unfolding and unremitting physiological changes that can lead to clinical disease, disabilities and mortality.

It should be added that there is a heritable component to loneliness; roughly half of the variance in loneliness in the adult population has been attributed to additive genetic components [12], similar to heritability estimates of loneliness in children [13]. The heritable component has been posited to include variability in sensitivity to social isolation that might result in individuals feeling more or less lonely in similar circumstances [14], whereas the non-genetic component

includes, among other individual differences, variability in social cognitions that perpetuate loneliness.

3. Loneliness and its health effects across the lifespan

The study of the health effects of perceived social isolation may bring to mind a large literature on the health effects of social isolation in other social species. However, the definition of perceived social isolation (i.e. loneliness) as a subjective state stands in stark relief against the notion of social isolation as conceived in most animal research. Removing an animal from its social group and having it live alone, for instance, does not parallel the pain of perceived isolation in humans who have access to, if not relationships with, one or more social others. Nevertheless, social isolation in mammals has shown adverse consequences that foreshadow the dramatic effects of inadequate social relationship quantity or quality in humans. A sampling of recent studies (for a recent review see [15]) shows that socially isolated housing of various social animal species at various stages of life and for various durations results in altered behaviour (e.g. anxious, depression-like, aggressive, passive, cognition/memory), physiology (e.g. changes in basal or stress–reactive corticosterone, blood pressure, inflammation, immune responses, hippocampal function) and mortality (e.g. post-stroke outcomes) [16–24]. An animal model of naturally occurring loneliness would be of great value in furthering the understanding of the developmental contributors to loneliness in humans as well as mechanisms through which loneliness influences health and fitness [25], a topic to which we return later.

Table 1 summarizes the most recent research representative of studies that have examined health-relevant outcomes of loneliness. We focus on a select subset of outcomes that are relatively well studied; additional outcomes have been studied that are not included here (e.g. behavioural and psychiatric outcomes). The rows in this table depict the consistency with which loneliness-related health outcomes are studied across age groups. The columns depict outcomes studied within each age group and define the structure of the reviewed research in the subsequent sections. The loneliness measures used in these studies are typically multi-item validated scales. In childhood and adolescence, the multi-item Loneliness and Social Dissatisfaction Questionnaire [80] obtains graded responses on perceptions of loneliness in peer contexts (e.g. 'It's hard for me to make friends' and 'I feel alone'). In adults, loneliness is sometimes assessed with a single face-valid question that asks individuals to rate the degree or frequency of their feelings of loneliness, but the preferred measures are validated scales such as the De Jong-Gierveld Loneliness Scale [81] and the UCLA Loneliness Scale [82,83], both of which avoid the terms 'lonely' or 'loneliness' to reduce response bias. These multi-item scales obtain graded intensity (i.e. from not at all to very much) or frequency responses (i.e. from rarely or never to often or always) to evaluative statements about one's social context (e.g. 'I find my circle of friends and acquaintances too limited', 'I feel isolated from others' and reverse-scored items such as 'There are people I feel close to'). The result is a score that ranges from socially satisfied (i.e. non-lonely) to socially dissatisfied (i.e. very lonely), and that is positively skewed; most people report relatively low levels of loneliness.

Table 1. Health-relevant correlates and consequences of loneliness by age group.

outcome	later childhood and early adolescence (6 – 12 years)	adolescence (13 – 17 years)	early and mid-adulthood (18 – 49 years)	later adulthood (50+ years)
mental health	→ depressive symptoms [26 – 28]	→ depressive symptoms [29 – 32]	→ depressive symptoms [33 – 35]; depression, pain and fatigue [36]	→ depressive symptoms [37 – 39]; depression, pain and fatigue [36]
sleep	→ poor sleep quality [27]	→ poor sleep quality [40]; → shorter sleep duration [41]	poor sleep quality [40,42,43]	→ poor sleep quality [44,45]
executive control	impaired executive control [46]	→ impaired control over eating behaviour in overweight adolescents [47]	poorer attention regulation [48,49]; impaired control over eating behaviour [49]	impaired optimization of positive emotions [50]
self-reported health	→ poorer general health [27]; more somatic symptoms [28]	→ poorer general health [32,51]; see also [28,34]	→ poorer general health [33,34]	→ poorer general health [52,53]
healthcare utilization		→ increased frequency of doctor visits [32]	increased use of hospital emergency department [54]	increased likelihood of nursing home admission [55]
cognitive functioning				impaired cognitive abilities [56,57]; → cognitive decline and dementia [58 – 61]
immune functioning			impaired cellular immunity [62 – 65]; impaired humoral immunity [42]	
neuroendocrine functioning			→ increased cortisol response to awakening [42,66]	→ increased cortisol response to awakening [67,68]
inflammation			increased pro-inflammatory cytokine response to acute stress [69,70]	pro-inflammatory gene expression [71 – 73]
mortality				→ mortality [74 – 79]

→ refers to prospective effects of loneliness.

(a) Infancy and early childhood (through about age 5)

In infancy, unmet physiological needs can only be met through the care of a social other—usually the parent. The metabolic costs incurred by the infant in alerting a parent of unmet physiological needs pale in comparison to the life-supporting benefits of having those needs met by a parent. Nutrition alone is insufficient to support health and fitness, however. This is evident from well-known research showing that infants fail to thrive when they lack social contact and comfort, even when nutrition is adequate [84–86]. Empirical evidence suggests that attachment security in mother–infant bonds builds on heritable differences in sensitivity to isolation [14]. One of the primary functions of social interactions in early life is to foster the learning of trust. Unresponsive and unpredictable parenting foster insecurity and distrust [87,88], qualities that can disrupt the foundation on which all subsequent relationships are built.

(b) Later childhood and early adolescence (6 – 12 years)

Humans' deeply social nature means that deficiencies in a sense of connectedness are—to put it colloquially—depressing. Although measurement of loneliness and depressive symptoms is often conflated (e.g. questions about loneliness are included in measures of depressive symptoms), the two constructs have been conceptually and statistically distinguished [8,83]. Their functional distinction is also evident. For instance, in a sample of 296 British children tested at 5, 9 and 13 years of age, persistent

loneliness in early childhood (i.e. at 5 and 9 years of age) predicted higher depressive symptoms at age 13 adjusting for depressive symptoms at age 9 [26]. Another study of 209 British pre-adolescents found that, relative to children who had maintained a low, stable level of loneliness between the ages of 8 and 11 years (52% of sample), those in the relatively high but declining level of loneliness group (48% of sample) reported more depressive symptoms at age 11 [27]. Do depressive symptoms matter for fitness? The inhibition of physical and mental activity that is present in clinical depression is believed to result in reduced reproductive fitness [89]. On the other hand, depressive symptoms have also been posited to enhance fitness to the extent that verbal and non-verbal expressions of sadness elicit the care and concern of others and, ultimately, re-inclusion in the social group [90–92].

Poor sleep is another consequence of perceived social isolation in this age group. How might this be relevant for evolutionary fitness? Sleep has throughout evolutionary history been a shared experience, in large part because co-sleeping provides a safe surround that promotes restful sleep [93]. Lonely children are implicitly hypervigilant specifically for social threat [94], signifying that they feel implicitly unsafe. A 3-year study that sampled children annually from 8 to 11 years of age found that, in comparison with the low, stable loneliness group, the high but declining loneliness group reported taking longer to get to sleep and more sleep disturbances than the former [27].

Given evidence that social cognitions go awry when people feel lonely [8], it is clear that learning to navigate the social world successfully is a cognitive challenge. Executive function, a cognitive capacity that includes the ability to exert self-control, is critical in this regard because it permits management of time and ideas for optimal social (and other) outcomes. In children of 4–12 years old, training to improve executive functioning was more effective when it was implemented together with training and opportunities for social development than when implemented alone [46]. The effectiveness of executive functioning training was also enhanced by training for emotional and physical development, but the social context is particularly important because executive function is highly relevant when managing interactions with potential competitors and threats. Indeed, executive function and social cognitive skills appear to improve hand-in-hand with brain development during adolescence [95]. This may help to explain the finding that feelings of loneliness, which are in part a reflection of inadequate or maladaptive social cognitive skills [96], are associated with impaired prefrontal cortical function, a region heavily implicated in executive control [10].

Although health is generally robust in late childhood and early adolescence, perceived health is nevertheless poorer in lonely than non-lonely children of this age. Harris *et al.* [27] found that the high but reducing loneliness group reported poorer general health at age 11 than the consistently low loneliness group. In a cross-sectional study of loneliness and victimization (e.g. bullying) in 419 Norwegian children in grades 1–10 (aged 7–16 years), more frequent loneliness was significantly associated with somatic symptoms (e.g. stomach ache, headache), sadness and anxiety [28], even after adjusting for victimization experiences. In fact, victimization was associated with symptoms only if accompanied by the experience of loneliness, suggesting that social cognitions, including a perceived threat of social isolation, are

mechanisms for the effect of socially isolating experiences on health symptoms.

(c) Adolescence (13–17 years)

Social acceptance by peers and the growing reciprocity of relationships in adolescence [97] pave the way for successful social encounters in later years, encounters that include potential mates and are thus directly relevant to reproductive fitness. Social acceptance also sets the stage for mental health, including a reduced likelihood of depression. A growing body of research shows that loneliness is a risk factor for depression in adolescence.[1] In a study that followed 585 children from Grade 1 to 10 (i.e. age 6–16 years), degree of loneliness at about age 12 predicted depressive and anxious symptomatology 1–3 years after adjusting for anxious/depressed symptoms at study onset [29]. A study of 478 youths followed annually between the ages of 12 and 18 years revealed that these adolescents followed five different loneliness trajectories. Those whose loneliness remained chronically high or whose loneliness was moderately high and declined slightly over this time interval had significantly higher levels of depressive symptomatology at age 18, and the largest increases in depressive symptoms since age 12, than those who were consistently non-lonely, whose loneliness was stable and low, or who exhibited a steep decline in loneliness during this time [30].

Using a similar class-based approach to loneliness trajectories between age 7 and 15 in over 800 students, Schinka *et al.* [31] found that those with a stable low trajectory had significantly lower levels of depressive symptoms at age 15 than those with a chronic or a high increasing trajectory, who in turn had higher depressive symptoms than those with a moderate increasing or a decreasing trajectory. Suicidal ideation followed a similar pattern of effects such that those with a chronic or high increasing loneliness trajectory were, respectively, approximately 11% and 7% more likely to have reported suicidal ideation at age 15 than those in the stable low trajectory. Importantly, children who experienced high levels of loneliness in early childhood but whose loneliness decreased over time were 19 times less likely than the chronically lonely group, and 28 times less likely than the high increasing group, to have thought about suicide, and exhibited significantly lower levels of depressive symptoms at follow-up [31], suggesting that the effects of loneliness accrue over time and that remediation of loneliness may diminish adverse consequences for psychiatric outcomes such as suicidal ideation and depression. Other studies have shown that the effect of loneliness in middle childhood on suicidality in adolescence is explained, in part, by depression [99], once again suggesting that the effects of loneliness accrue and that indirect effects (e.g. through depression) represent mechanisms for the health and fitness impact of social inclusion and acceptance.

Evidence that executive functioning is affected by social factors in this age group is provided by a study of eating behaviour [47]. In a study of 59 adolescent males and females aged 12–14 years, an experimental manipulation (i.e. Cyberball) was used to simulate either social ostracism or inclusion, after which individuals completed a computer task that offered points exchangeable for (unhealthy) snack food or conversation/social time with a same-sex peer confederate. The number of times participants had to press the mouse to

earn points increased over the course of the task, and the numbers of presses were used to assess participants' motivation for eating or socializing. Participants were then given an opportunity to eat snack food. Overweight participants in the ostracism condition were more motivated to eat (more mouse button presses for food) and ate a greater quantity of food than overweight participants in the social inclusion condition. Normal weight participants did not show this effect [47]. Thus, the effect of social adversity—be that ostracism, rejection, isolation—seems to weaken the ability to self-regulate and may exacerbate the challenge of promoting beneficial changes in lonely overweight youths' eating behaviours.

The influence of loneliness on sleep observed in later childhood and early adolescence is also evident in adolescence. For instance, Mahon [40] found that loneliness was correlated with more frequent reported sleep disturbances, but not with reported sleep duration, in 11–17 year olds. In a recent study, 82 adolescents in transition between high school and college were outfitted with an 'Actiwatch' to quantify movement during the day and during sleep, enabling relatively objective assessments of sleep duration, latency and sleep efficiency. Data from four consecutive nights revealed that individual differences in loneliness moderated sleep duration and sleep latency after high stress days. At high relative to low levels of loneliness, sleep latency (i.e. time to fall asleep) and sleep duration were shorter after more stressful days [41]. Shorter sleep duration suggests that loneliness impairs the ability to recover from daily stress, and may leave lonely adolescents more vulnerable to stress-related mental, somatic and health complaints.

A sense of connectedness and belonging in childhood protects against later development of physical health problems. Qualter et al. [32] found that persistently high levels of loneliness as well as moderately increasing levels of loneliness between ages 5 and 17 were positively associated not only with depressive symptoms but also with frequency of doctor visits, and negatively associated with self-rated health at age 17. In a study of 11–15 year olds in nine European countries, affiliation deficits, as indicated by higher levels of loneliness, were associated with worse physical health and well-being; in addition, low well-being was associated with lower levels of social integration [51], suggesting a negative cycle of diminishing social connectedness and well-being. Together with data from late childhood and early adolescence, the foregoing research suggests that loneliness has health effects relatively early in life.

(d) Early and mid-adulthood (18–49 years)

In young adulthood, affiliative needs increasingly focus on identification of potential mates and formation of a permanent partnership, typically with someone of the opposite sex. Motives and societal expectations notwithstanding, some individuals fail to find a mate or choose to remain single. Single adults are unhappier than their marrying peers [100], even in Western cultures where expectations of marriage have loosened over time. Unmarried individuals also tend to be lonelier than married individuals [101,102]. Cohabitation does not offer the same protection against loneliness that marriage does [102], so companionship is insufficient to explain the benefits of marriage for a sense of connectedness. What does marriage offer that may protect against loneliness? A committed spousal relationship affords each partner the resources with which the other is endowed. These include material

resources, and also include shared social networks. In addition, a good quality spousal relationship lends each partner a sense of self-worth [103], an adult version of a secure attachment base [104] that facilitates greater engagement in the larger social world. A spousal relationship that protects against loneliness may be characterized by the partners' shared sense of 'we-ness' [105], and by each partner's experience of an 'expanded self' [106]. If a spousal relationship lacks trust and falls short in we-ness, the presumed benefits can no longer be unquestioningly assumed [105]. It is a task of young adults to find a mate who will buttress their individual level of confidence and self-worth and provide a foundation for the next stage in the life course—parenting.

Becoming a parent might be expected to improve well-being to the extent that parenthood marks achievement of a socially expected and desired outcome. Consistent with this hypothesis, the degree of social integration in a nationally representative sample of 1933 childless adults was significantly higher in those who became parents over the next several years than those who remained childless [107]. However, other research has shown that parenthood tends not to protect against loneliness [102,108]. Similarly, in older age, parents and their childless peers do not differ in loneliness [109]. This may not be surprising given that the parent–child relationship is not a relationship of choice, nor is it a relationship of equals, and therefore would not be expected to generate a sense of connectedness and belonging in the parent. Instead, it may be that the birth of a child elicits a temporary strengthening of the parents' kin network that increases their feelings of inclusion and reduces loneliness.

Depressive symptoms in adulthood are a well-established outcome of loneliness. The most recent data supporting this link come from a nationally representative sample of adolescents (grades 7–12, aged 11–19 years) in the United States who were surveyed during the 1994–1995 school year (Wave 1), again 1 year later (Wave 2) and then at follow-up during 2000–2001 (Wave 3), when they were young adults (18–27 years old). Two groups of researchers used these data ($N \sim$ 10 000 with data at each wave) to examine the relationship of loneliness and other social adversities in adolescence with mental and physical health in young adulthood. Adam et al. [33] developed a 'cumulative relationship risk' measure and found that exposure to a greater number of risks (i.e. loneliness and low parental support in Waves 1 and 2, romantic relationship instability and intimate partner violence in Wave 3, loss/bereavement between Waves 1 and 3) elicited a dose response such that Wave 3 depressive symptoms increased by 0.07, 0.28, 0.42 and 0.44 s.d.s with one, two, three and four or more relationship risks, respectively, after controlling for baseline health, health behaviours and demographic variables. Goosby et al. [34] found that loneliness in Wave 1 increased the odds in Wave 3 of reporting enough depressive symptoms to warrant being classified as clinically depressed after controlling for demographic covariates and depressive symptoms in Wave 2. Vanhalst et al. [35] used a loneliness trajectory approach from age 15 to 20 years and found that depressive symptoms at age 20 were significantly higher in the chronically high loneliness group relative to the high and moderate decreasing, low increasing and stable low loneliness groups. The loneliness–depression link has also been documented in longitudinal studies of vulnerable populations (cancer survivors, spousal carer and their respective healthy, non-carer peers) in mid- to late-adulthood [36].

Loneliness has been linked with suicidal ideation and parasuicide in adulthood [110,111], where those with frequent feelings of loneliness had a greater likelihood of having had suicidal thoughts (21% versus 2.5% of those less frequently lonely), and a greater likelihood of having attempted suicide (8.4% versus 0.7% of those less frequently lonely) in a population-based sample of 19 724 individuals aged 15 years or more [111].

Sleep is poorer in lonelier adults, as has been shown in studies that rely on self-reported sleep duration, quality and efficiency [42] and studies that use an objective measure of various sleep parameters [43]. For instance, using a 'Nightcap' that recorded eyelid and muscle movement, Cacioppo *et al.* [43] found that lonely young adults exhibited more restless sleep as indicated by the amount of wake time during sleep, whether sleeping in the clinical research centre or during seven nights at home. Sleep duration did not differ as a function of loneliness. As was suggested above, heightened implicit vigilance for social threat may play a role in impaired sleep quality. In young adults, eye-tracking and fMRI methodologies have each provided evidence consistent with lonelier individuals being hypervigilant for social threat in particular [112,113], again raising the possibility that implicit processes may contribute to disruptions during the unconscious state of sleep.

Executive control is impaired in lonelier adults, as was shown in an experimental study that found poorer attentional focus in a dichotic listening task in lonely relative to non-lonely college students [48]. Attention regulation was also impaired in an experimental manipulation that threatened social exclusion [49]. This study also revealed that threatened social exclusion led to decrements in the ability to regulate eating behaviour [49], reminiscent of the effect of social exclusion on eating behaviour in obese adolescents [47].

Loneliness in young to mid-adulthood is embodied in early markers of physiological dysfunction. For instance, the cortisol response to awakening (the increase in circulating cortisol during the first 20–30 min post-awakening) is heightened following days with more intense feelings of loneliness ([66]; see also [42]). This effect has been ascribed to greater threat expectations of lonely individuals, and to the necessary but perhaps excessive release of cortisol that activates metabolic resources in anticipation of more stressful demands of the day [67]. Cortisol has immunosuppressive effects, and elevated cortisol levels in lonely individuals were associated with lower natural killer cell activity and poorer T-lymphocyte responses to mitogen stimulation [62,63]. Impaired cellular immunity is also evident in the greater rate of reactivation of latent herpesvirus [64] and Epstein–Barr virus [65] in lonelier individuals. Impaired humoral immunity has also been documented in young adults; loneliness was associated with poorer antibody response to a component of the flu vaccine [42].

Physiological regulation of blood pressure, accomplished through changes in cardiac output (the volume of blood ejected by the heart) and vascular resistance (peripheral arterial dilation/constriction that affects blood flow), differs between lonely and non-lonely young adults. Although blood pressure itself does not differ as a function of loneliness in this age group, lonely young adults achieve comparable blood pressure levels with higher levels of vascular resistance than their non-lonely peers [114,115]. This has significance for long-term health outcomes because heightened vascular resistance contributes to shear stress on the lining of vessels, a precursor to structural vascular changes that play a role in hypertension and atherosclerosis.

Young adulthood is a time of relatively robust physiological resilience. Loneliness-related physiological dysregulation has long-term consequences for health, however, that appear to accumulate over time [116]. Loneliness combined additively with other adverse relationship experiences between adolescence and young adulthood to increase the odds of reporting poor physical health in young adulthood [33]. Examined individually, loneliness in adolescence was sufficient to significantly increase risk for fair or poor self-rated health in young adults [34]. Loneliness has also been associated with increased use of a hospital emergency department, even though baseline chronic illness and illness severity did not differ as a function of loneliness [54]. Caspi *et al.* [117] found a dose–response effect of loneliness on cardiovascular health; the greater the number of occasions individuals felt lonely across early childhood, adolescence and young adulthood, the greater their number of cardiovascular risk factors at age 26 (i.e. BMI, systolic blood pressure, cholesterol levels, glycated haemoglobin concentration, maximum oxygen consumption). Similarly, Goosby *et al.* [34] found that loneliness in adolescence predicted a greater risk for high cholesterol, high blood pressure and overweight/obesity in young adulthood. The effect of loneliness on these metabolic risk factors was shown to be explained in part by depression and low parental support in adolescence.

In sum, findings across a wide variety of physiological indicators suggest that loneliness has the potential to increase risk of morbidity. The most likely source of risk appears to have an inflammatory component as indexed by physiological indicators observed to differ as a function of loneliness, including high blood pressure, obesity, high cholesterol, increased cortisol and impaired immunity. In addition, loneliness has been associated with increased levels of inflammatory cytokines in lonelier healthy young adults during acute stress [69], with similar effects observed in adult middle-aged women [70].

(e) Later adulthood (50+ years)

The motivation to enhance one's status and esteem through work and contributions to the larger group is a social drive that retains importance in later adulthood as parenting responsibilities subside. Self-esteem is facilitated by a sense of belonging and self-worth that are, in turn, the result of group acceptance and valuation of the individual. The sense of identity and personal value associated with a purposeful job may explain why, in a nationally representative sample of adults 57–85 years old in the National Social Life, Health and Aging Project, those who continued to work had lower levels of loneliness at baseline and smaller increases in loneliness at a 5-year follow-up than those who were or became retired and stopped working, even after adjusting for age and health status (LC Hawkley 2014, unpublished data).

In essence, loneliness signifies a breakdown in self-worth, connectedness and belonging [118], and thereby jeopardizes fitness. In older adults, the breakdown in the social self takes a toll on mental and physical health and well-being, Not surprisingly, loneliness continues to exhibit a robust and prospective association with depressive symptoms in older age [37–39]. In addition, sleep quality continues to be jeopardized by feelings of loneliness in this age group. Sleep duration tends not to differ between lonely and non-lonely

older adults, but the same amount of sleep is less restful and results in greater daytime fatigue and dysfunction [44]. In a diary study, heightened daily feelings of loneliness preceded poorer nightly sleep quality [45], and poor sleep exerted a small but significant effect on next-day feelings of loneliness. This recursive loop operates outside of consciousness, signifying that some effects of loneliness are not easily controlled.

Executive control is also impaired in older adults as it was in younger age groups. For instance, engaging in healthful lifestyle behaviours such as regular exercise requires self-discipline; lonelier older adults are less successful in doing so and are more likely to disengage from exercise over time [50]. In addition, self-reports indicated that lonelier individuals exert less effort in optimizing their positive emotions, a maladaptive emotion regulation habit that impairs the ability to regulate other self-control behaviours [119], and that explained a lower likelihood of engaging in physical activity [50].

Loneliness has been shown to contribute to cognitive decline and dementia [10,56–61], effects that have a profound impact on quality of life and further distance the sufferer from his or her social network. Gow et al. [56] examined cognitive functioning in a cohort of 70 year olds and found a significant inverse association between loneliness intensity and general cognitive ability, processing speed and memory. In another study of older adults (mean age = 75 years), loneliness was associated with global impairments in cognition independent of depression and social network integration [57]. In a study of 75–85 year olds, loneliness was not associated with cognitive functioning at baseline, but predicted a greater decline at a 10-year follow-up [58], suggesting that loneliness accelerates ageing effects. Similarly, Wilson et al. [59] found that loneliness predicted a more rapid decline in cognitive performance at a 4-year follow-up and greater risk of Alzheimer's disease [60]. Cognitive function was inversely associated with loneliness at baseline (mean age = 65.6 years) and at 4-year follow-up in a sample of over 6000 adults in the English Longitudinal Study of Aging [61]. Cognitive status may contribute to poorer social interactions and an increased sense of social isolation, however, thus instantiating a recursive loop that reprises the tight link between cognitive development and social functioning in childhood and adolescence.

In older age, lonelier adults report poorer health [52,53] and a greater likelihood of being admitted to a nursing home [55]. In addition, lonelier older adults are at greater risk for morbidity and mortality [74–77,120,121], although one study found that the effect of loneliness was not independent of the also significant mortality risk associated with objective social isolation (i.e. infrequent social contact and civic participation) [77]. The severity of the effects is often linked to the frequency or duration of exposure to feelings of loneliness. In the Health and Retirement Study, loneliness predicted all-cause mortality over a 4-year follow-up, an effect that was greater in chronically than situationally lonely adults [78]. Another study found that cardiovascular mortality rates were higher at 14-year follow-up in individuals who reported being lonely frequently in comparison to those who reported never being lonely [79]. Chronic loneliness was prospectively associated with incidents of coronary heart disease during a 19-year follow-up of women in the National Health and Nutrition Survey [122]. Research among middle-age and older age adults showed not only that blood pressure was higher in lonelier adults [123], but that a persistent trait-like aspect of loneliness predicted larger increases in blood pressure over a 4-year follow-up period [124].

In a reprisal of neuroendocrine effects seen in young adulthood, chronically high levels of loneliness predicted a larger cortisol response to awakening in middle-aged adults [68], an effect that was also observed among 50–67 year olds in the Chicago Health, Aging, and Social Relations Study [67]. Cortisol is regulated by the hypothalamic–pituitary–adrenocortical (HPA) axis, and a dysregulated HPA axis also contributes to inflammatory processes that play a role in hypertension, atherosclerosis and many other chronic diseases of ageing. Regulatory control of gene expression contributes to HPA functioning, and gene expression profiles differ as a function of loneliness [71–73]. Genome-wide microarray analyses of leucocytes from middle- and older age adults, followed by bioinformatics analyses, revealed upregulation of pro-inflammatory markers, including the highly potent pro-inflammatory transcription factor nuclear factor-kappa B (NF-κB), and downregulation of anti-inflammatory markers, including transcriptional activity of the glucocorticoid receptor, in lonely compared with non-lonely middle- and older age adults [71,72]. Conversely, a successful intervention to reduce loneliness [73] downregulated the NF-κB-related pro-inflammatory gene expression profile and tended also to reduce C-reactive protein, a serological marker of inflammation.

Subsequent research has shown that the cellular origins of differentially expressed transcripts have the marks of an evolutionarily preserved sensitivity to the social environment. A friendly social environment that fosters close social contact poses greater risk for viral infection, which would favour upregulation of antiviral and T-helper 1 immune responses over antibacterial responses. A socially hostile environment that increases risk for injury poses a threat of bacterial infection, which would favour upregulation of innate antibacterial and T-helper 2 adaptive immune responses, and this is what was seen [71]. The evolutionarily ancient plasmacytoid dendritic cells and monocytes, both antigen-presenting cells, were the leucocytes of origin that were sensitive to loneliness and contributed disproportionately to the loneliness difference in transcriptional expression [72]. The fact that an age-old sensitivity has persisted to the present day speaks to the ongoing importance of the social environment and perceptions of inclusion or isolation for evolutionary fitness.

4. Implications for future research

In this review, we have focused on a considerable literature documenting physiological and health consequences of loneliness in humans and have argued that these consequences can impact an individual's fitness across the lifespan. One of the most salient observations of this review, starkly evident in table 1, is that research on the health consequences of loneliness is most prevalent in older age groups, which is perfectly understandable given that this is the age at which clinical disease and disability set in. However, many chronic diseases of ageing have their origin in physiological disturbances earlier in life that only gradually become manifest in disease. It is noteworthy, therefore, that research on the health-relevant consequences of loneliness in earlier adulthood is clustered in young adulthood, leaving large gaps in our knowledge of how physiology is affected by loneliness in middle adulthood (30–50 years). Even less is known about how loneliness affects physiological changes that

begin as early as childhood, if not earlier. Does loneliness in childhood influence concurrent or prospective immune or neuroendocrine functioning, for example? Vaccinations and immunizations are administered during childhood and early adolescence; do lonely children exhibit a less robust vaccine response? If so, what are the implications for health concurrently or in later life? Children who experience bullying and other forms of social adversity are highly susceptible to feelings of loneliness, even years later [125]; does the stress of these experiences influence the functioning of the HPA axis? If so, is it a programmatic influence that alters HPA functioning in later years? This may have implications for inflammatory processes that contribute to chronic diseases across the lifespan (e.g. diabetes, obesity).

A second observation is that little is known about the consequences of diverse loneliness trajectories across the lifespan. An exception is research conducted in children and adolescents that reveals considerable consequential variability at these developmental stages. What happens to these loneliness trajectories as children enter later adolescence and early adulthood? Can lonely children become socially contented adults (or vice versa), and if so, what are the implications for health and fitness? Do the consequences differ from those who have always felt socially satisfied and not lonely? Harris *et al.* [27] found that high loneliness in middle childhood had long-lasting effects, even when reduced to normal levels by pre-adolescence. Caspi *et al.* [117] showed that childhood isolation/loneliness had an independent adverse effect on cardiovascular risk even after accounting for cumulative exposure to loneliness across childhood, adolescence and young adulthood. Findings such as these argue for the fundamental importance of early experiences of perceived social connectedness and belonging for health and fitness. Additional research is needed to trace loneliness trajectories with greater temporal resolution across the entire lifespan to better understand when and how loneliness matters for diverse health-related outcomes.

5. Loneliness research in non-human species

As described above, loneliness at its core reflects a mismatch between social needs and social attainment; as such, there is no reason to presume that loneliness is restricted to the human species. The physiological processes that are activated by loneliness—involving sleep, HPA activity, and cardiovascular and immune function—and that contribute to a decrement in health, and presumably fitness, are phylogenetically quite old (e.g. [18]). Does loneliness exist in other species, and if so, are the same physiological processes involved? Being able to study this phenomenon in other species is likely to be very informative [15], enabling lines of study that cannot be done with humans, and, owing to shorter generation times, providing more direct answers to the question of whether, when and how loneliness might impact fitness.

First steps in this direction have documented the development of a naturally occurring rhesus macaque model of loneliness that focuses on animals with low social attainment and distinguishes between adult male monkeys with little social motivation ('truly low social') versus those with an apparent desire for more social connections ('manifestly low social') [25]. A human classification scheme employed to develop the animal model of loneliness used the size of the network with whom people reported having frequent interactions as a preliminary index of social interest, but then subdivided those with large or small networks into those who felt they had a choice over the amount of time they spent socializing on a daily basis. Choice helped to distinguish between introversion (i.e. high choice representing a preference for a small network and/or infrequent interactions) and loneliness (i.e. low choice representing a preference for a larger network and/or more frequent interactions). Accordingly, those with a small network and a low perceived degree of choice were the loneliest group, significantly lonelier than those with a small network and a high degree of choice, and those with a large network regardless of degree of choice [25]. The manifestly low social rhesus monkeys thus best paralleled the loneliest human group. These were animals that had high frequencies of 'tentative' social behaviours, such as approaching or walking by another animal, but low frequencies of 'complex' social behaviours like maintaining proximity and contact, or engaging in social grooming. In fact, these 'lonely' rhesus monkeys had frequencies of 'tentative' behaviours that were as high as those seen among high-sociable animals, but their levels of 'complex' behaviour were as low as those seen in the 'truly low sociable' animals. In short, the manifestly low-sociable (putatively lonely) animals had a mismatch between their presumed social interest (as manifested in their high levels of behaviours that would initiate social interaction) and their social attainment (as indicated by lower levels of proximity, contact and grooming). In comparison to the truly low-sociable (putatively introverted) monkeys, the behaviour of these 'lonely' animals, in more formalized behavioural tests, confirmed their greater social interest.

Next steps in this line of research will include an examination of variation in physiological outcomes as a function of group differences in the animal typology. For example, as described above, loneliness in older adult humans is associated with a gene transcriptional profile that facilitates inflammation, and a dysregulated HPA axis. Preliminary results from our monkey studies show similar results. We believe that our demonstration of naturally occurring 'loneliness' in rhesus monkeys not only identifies a heretofore unstudied aspect of social functioning in non-human primate groups, but will also permit studies designed to examine early experience risk factors that put particular individuals onto a 'loneliness' developmental trajectory. Moreover, such a model will enable us to explore possible treatment options (e.g. placement of lonely adults with animals that will not activate the hypervigilance that is often seen when lonely humans attempt interaction with same-aged peers) that might mitigate the health-related (cardiovascular, neuroendocrine and inflammatory) consequences of loneliness. Achieving a better understanding of naturally occurring variation in social connectedness, and its physiological and psychological underpinnings, in non-human species may be a valuable direction to better understand the (likely) persistence of a 'lonely' phenotype in any social species, and its consequences for health and fitness.

6. Conclusion

Up to 80% of those under 18 years of age and 40% of those over 65 years of age report being lonely at least sometimes, and 15–30% of the general population suffer from chronic

loneliness [120]. These are sobering prevalences, but they also indicate that most people, most of the time, do not feel lonely. Understanding the factors that protect against loneliness may suggest intervention targets that harness the power of social connectedness to reduce the health and fitness consequences of loneliness.

Endnote

[1]But see Lasgard *et al.* [98], who failed to find a prospective relationship between loneliness and depressive symptoms over a shorter follow-up period of 1 year in a sample of 500 17-year-old high school students.

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