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Social ties, health and wellbeing: A literature review and model

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Abstract

Humanity is facing an increasing burden of chronic disease and an aging population that will lead to more years lived with disability. Dealing with these issues is difficult, made more so by deteriorating social ties and decline in social connectedness, which may also impact on health and wellbeing. However, research on the association between social ties and health outcomes has been characterised by conceptual difficulties, controversy and simplistic models. Here we review the literature on the associations between social ties and health outcomes, identify various mechanisms through which these associations may arise, and propose a model on which future research activity could be based. We observe that social ties are an important contributor to health outcomes that may rival the effects of many traditional risk factors including smoking, alcohol consumption and physical activity. A complex network of behavioural, psychological and physiological mechanisms drives the health of individuals, and sociostructural factors will either facilitate or impede desired health outcomes within community ecosystems. The GENIAL [Genomics - Environment - vagus Nerve - social Interaction - Allostatic regulation – Longevity] model is proposed, and important mediators and moderators are characterised along a pathway to wellbeing and longevity. A major regulatory role is given to the vagus nerve – indexed by heart rate variability – as it is responsible for a host of psychological and physiological processes that will influence social ties, subsequent health and wellbeing. Future research needs to move beyond the disciplinary dilemma, initiate multi-disciplinary exchange, and facilitate new lines of interdisciplinary enquiry. We further argue that extending beyond the self by focusing on relationships with others and our connections to the environment will aid a much-needed transition to a more caring and understanding world.

Keywords

Social ties, social support, social integration, social cohesion, social connectedness, social isolation, loneliness, happiness, health and wellbeing, health outcomes, mechanisms, vagal function, allostasis heart rate variability, premature mortality, positive psychology, GENIAL model, pathways to health and wellbeing, statistical moderation and mediation

Abbreviations

BDNF: brain-derived neurotrophic factor

BMI: body mass index

CeA: central nucleus of the amygdala

CHD: coronary heart disease

CTRA: conserved transcriptional response to adversity

GENIAL model: Genomics - Environment - vagus Nerve - social Interaction - Allostatic regulation – Longevity

HR: hazard ratio

HRV: heart rate variability

LDL: Low-density lipoprotein

LG: licking and grooming

OR: odds ratio

OXTR: oxytocin receptor

VNS: vagal nerve stimulation

"Community, in a word, is the beating heart of life, and we neglect it at our peril."

Robin Dunbar (2010), How Many Friends Does One Need?**:** Dunbar's Number and Other Evolutionary Quirks

Social ties are linked to one's capacity to achieve and maintain health and wellbeing, driven by a fundamental human need to form social bonds, yet research on this topic has been contradictory, controversial and characterised by simplistic models. The construct of social ties is heterogeneous and multidimensional (1,2), comprising objective measures of network size and degree of participation in social activities (social support, social integration), as well as subjective measures such as the perception of social connectedness and loneliness. Similarly, the assessment of wellbeing has focused on at least three different aspects including life satisfaction, positive emotions and human flourishing (3-6). While it is not surprising that the literature is a minefield of contradictory findings and false leads, the scientific search for pathways to health and wellbeing is a noble endeavour and an important societal step forward. The goal for this book chapter is to consider the evidence for associations between social ties, health and wellbeing, examine what the mediating and moderating paths might be, and to propose a simplified, yet sophisticated working model on which future research activity could be based.

Varied definitions of wellbeing have led to some (initially) counter-intuitive findings. For instance, researchers have warned that overvaluing the need for happiness – paradoxically – leads to compromised wellbeing including increases in depressive symptoms and major depression (7). The reason for this is that people are often disappointed with their level of happiness, and may ultimately feel less happy (8). Furthermore, emphasising the importance of positive emotions over negative emotions is unproductive, as normal fluctuations in negative affect may have certain advantages including improved memory performance, reduction in judgmental errors, enhanced motivation and more effective interpersonal strategies (9,10). These findings highlight the 'upside of your downside' (10) and a need for emotional agility and psychological flexibility (11), rather than the importance of positive over negative emotions as has been argued (12,13) – and criticised (14,15) – previously. That said, the advantages of negative affect are likely specific to normal fluctuations in mood states, rather than more extreme forms of negative affect characteristic of the affective disorders, which are associated with impairments in attention and memory recall in particular (e.g. 16,17). While affective components of wellbeing will colour our psychological moments, 'eudaimonia' – a Greek word translated to human flourishing (18) – may have stronger associations with health and longevity (19,20) (see also: 21-23).

Much has been written about the potential effects of social ties on health outcomes, and intermediate variables along this pathway, yet conceptual difficulties (e.g. 24) and simplistic models (e.g. 25) have led to considerable controversy (e.g. 26) (see also 27). Two generic pathways through which health outcomes may arise are the effects of social ties regardless of the experience of stress and stress buffering (1). In this regard, social integration will promote positive psychological states leading

to health-promoting physiological responses, while social support will help to buffer the effects of stressful experiences by promoting less threatening interpretations of adverse events and effective coping strategies (1). Recent work in the field of positive psychology has focused on how social ties might impact on physical health. For instance, positive emotions have been associated with social connectedness and physical health (28,29) in a self-sustaining upward spiral dynamic (25,30). Positive psychological attributes – optimism and hedonic wellbeing in particular – have also been linked to increased engagement in positive health behaviours (e.g. healthy eating, physical activity) as well as improved cardiac health (28,29). While epidemiological findings from the UK Million Women Study observed no direct effects of happiness – in particular – on mortality over a 10-year period (20), analyses on the English Longitudinal Study of Ageing (31) came to different conclusions. This study however, focused on Eudaimonia, encompassing meaning, purpose and flourishing, and demonstrated that those in the highest quartile of wellbeing had a 58% reduced mortality risk, after adjustment for age and sex. After further adjustment for sociodemographic factors, this effect decreased to a still significant 30%. While it could be hypothesised that social personality traits such as sociability underpin these health outcomes, findings from the Terman Life-Cycle Study (32) suggest that this may not be the case. The Terman study (32) – conducted over more than 8 decades – shows that childhood sociability promotes social ties and flourishing in midlife, however, sociability was also associated with alcohol abuse. Therefore, sociability exerts differential influences on health. Other findings from the same study further indicate that cheerful children may grow up to be more careless about their health leading to an increased risk for premature mortality, which may include a substantial number of unverified suicides (33). These discrepancies and controversies in the field highlight a need for an up-to-date review of the literature and more sophisticated models of the associations between social ties, health and wellbeing, all goals of the present book chapter.

The aims of this chapter are threefold: (1) To examine the epidemiological evidence for a link between social ties, health and wellbeing. While this is a useful starting point to examine whether associations may exist, the epidemiological literature is less helpful in establishing causal mechanisms that may underpin such associations, leading us to the following aim: (2) To characterise potential mechanisms that might mediate or moderate associations between social ties, health and wellbeing, and explore how various mechanisms might overlap. (3) Based upon the reviewed evidence, we then sought to develop a model that might better explain the association between social ties and health outcomes; this was the third aim of our book chapter. A model is proposed and considerations for future research on this topic are discussed. Several points regarding our review should be noted: first, we discuss research published in a variety of distinct fields and disciplines, therefore, a comprehensive review of the literature is beyond the scope of our chapter. Instead, we draw upon relevant, published reviews, and highlight recent studies that build upon this work. Second, the World Health Organisation defines health as composed of physical, mental and social components. For the purpose of the current chapter,

we emphasise the importance of physical and mental components, allowing us to consider various mechanisms that might drive and support associations between social ties and health outcomes, the single best measure of which is longevity (6). Third, we have already noted that social ties are heterogeneous and multidimensional. Social ties may also be either positive or negative and the emotional tone of these relationships differentially impacts on health outcomes. Fourth, recent data suggest that social media use is associated with worse wellbeing (34-36). While one needs to be careful about generalising these findings to all online interactions (e.g. virtual support groups), real world interactions may be an especially important contributor to positive health outcomes. We now turn our attention to the epidemiological literature and the evidence supporting associations between social ties, health and wellbeing.

On the association between social ties, health and wellbeing

Investigating the effects of loneliness and social isolation on coronary heart disease (CHD) and stroke across 16 longitudinal datasets (N=181,006), poor social ties were associated with a 29% increase in risk of incident CHD and a 32% increase risk in stroke (37) – two leading causes of morbidity globally – over 3-21 years. No differences were observed between the association of loneliness or social isolation with CHD, nor were there any differences between males and females. By contrast, outcomes from another meta-analysis (38) investigating the association between social ties and mortality risk – drawing conclusions from 148 studies comprising more than 300,000 participants – revealed a 50% increased likelihood of survival in those with stronger relationships over an average of 7.5 years follow-up. Importantly, this study excluded studies in which mortality was a result of suicide or injury and results were consistent across age, sex, initial health status, follow-up period and cause of death. This study also reported that the influence of social ties on reduced risk for mortality was comparable to other well-known factors including smoking cessation, abstaining from alcohol, engaging in physical activity, and having a lean body mass index (Fig 1).

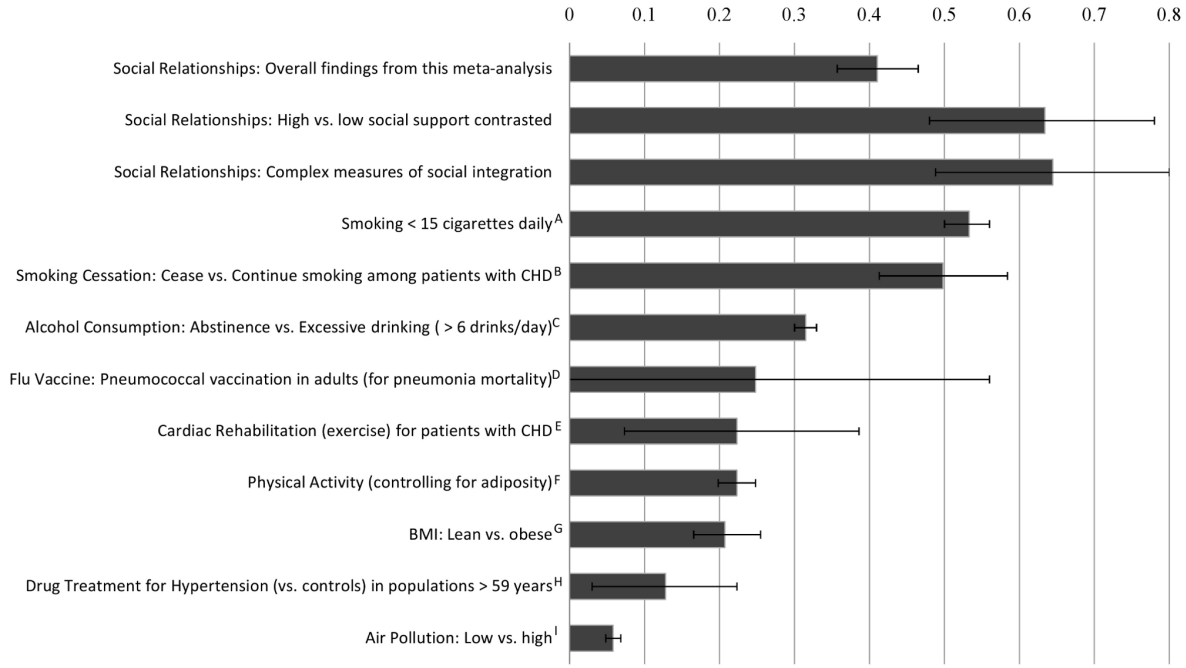

Fig 1: Comparison of odds (lnOR) of decreased mortality across several conditions associated with mortality. Effect size of zero indicates no effect. The effect sizes were estimated from meta-analyses. Figure from Holt-Lunstad et al., 2010 (38), reprinted with permission under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

This study (38) also reported that findings were strongest for complex measures of social integration comprising multiple components of social integration such as marital status, network size and participation (OR = 1.91; 95% CI 1.63 to 2.23) and lowest for binary indicators of residential status (living alone versus with others) (OR = 1.19; 95% CI 0.99 to 1.44). In a more recent study by these authors (39), social isolation, loneliness and living alone were examined as risk factors for mortality. A total of 70 studies with 48,673 participants were identified for inclusion in analysis. Findings revealed that social isolation, loneliness and living alone contributed to a 29%, 26% and 32% increased risk for mortality over a 7-year follow-up period, respectively. No differences were observed between objective (social contact and living alone) and subjective (feelings of loneliness) social isolation. It is also interesting to note that the authors observed that adults *less than* 65 years of age were at a greater risk of mortality when they lived alone or were lonely (OR = 1.57 for adjusted data), compared with older individuals under the same conditions (OR = 1.25 for those aged between 65 and 75, and OR = 1.14 for those aged older than 75). They (39) suggested that the widespread belief that health risks are greater in older adults may be inaccurate. The possibility that social isolation may have adverse effects in younger people is consistent with another study (40) that drew on data from four nationally

representative longitudinal studies spanning adolescence through to late adulthood. Social integration was associated with better physiological functioning in a dose-response fashion in both early and later life. This study (40) investigated structural and functional dimensions of social ties (social integration, social support, and social strain), examining their effects on objectively measured biomarkers of physical health (C-reactive protein, blood pressure, waist circumference, and body mass index). In adolescence, social integration was associated with a 40% lower odds of elevated inflammation, while social isolation (OR=1.27) raised the odds to a comparable degree with physical inactivity (OR=1.21). These physiological effects were partly explained by socioeconomic status, negative health behaviours (i.e. smoking, physical inactivity, obesity) and prior chronic disease. In older age, the effects of social isolation on hypertension risk (OR=2.42) even exceeded the effect of diabetes (OR=1.49). The important point from this study is that social integration and embeddedness in social networks during adolescence may impact on metabolic and cardiovascular functioning, and contribute to health risks even before symptoms of disease emerge.

Findings from another study (41) revealed that both social isolation and loneliness predict mortality over a 7-year follow-up period in 6,500 older people from the English Longitudinal Study of Ageing. Absolute proportions of deaths (n=918) were 21.9 vs. 12.3% for high and low/ average isolation groups, respectively, and 19.2 vs. 13.0% in the high and low/ average loneliness groups, respectively. However, the association with the emotional experience of loneliness was shown to be largely accounted for by baseline mental and physical health, and control for loneliness did not reduce the hazard ratio for social isolation, leaving the authors to conclude that loneliness may not be the primary mechanism through which social isolation transmits its effects. Similar non-significant findings had been reported in an earlier study when controlling for baseline health, functional limitations and depression (42). In the more recent study (41), the hazards ratio for mortality was 1.50 in the high social isolation group, and adjustment for demographic factors, baseline health status and depression was associated with a reduced, although still significant hazards ratio of 1.26. No sex differences were observed. The authors (41) discussion of their findings is illuminating, highlighting the important role of lifestyle factors and need for additional help to those who experience social isolation to engage in positive health behaviours to help reduce risk of mortality.

It is noted that conflicting findings for the effects of social ties have also been reported. For instance, outcomes from the Melbourne Collaborative Cohort Study (43) reported that objective assessment of social connectedness – defined using questions on marital status, the number of people in the household, number of relatives visiting each month, number of friends that could be visited without invitation and number of hours of social activity per week – was not associated with successful ageing 12 years later. The authors concluded that while social connectedness may be related to the perception of ageing well, it does not help avoid common conditions associated with ageing. Successful ageing was defined as age 70 years or over and absence of diabetes, heart attack, coronary artery bypass

graft surgery, angioplasty, stroke, cancer; impairment, perceived major difficulty with physical functioning; and low risk of psychological distress. These conflicting findings may reflect methodological differences associated with how social ties are defined and variable outcomes of interest for each study. In this case, the Melbourne Collaborative Cohort Study (43) explored quantitative aspects, rather than perceptions of social connectedness or the quality of the interactions. Other research has also demonstrated that social networks can have negative (44) as well as positive effects. This study investigated the spread of obesity through social ties over a 32-year period in 12,067 people recruited as part of the Framingham Heart Study. It was reported that the chance of someone becoming obese increased by 37-56% if he or she had had a spouse, sibling or friend who became obese, and these findings extended to three degrees of separation.

In summary, social ties appear to be an important contributor to health outcomes, that may rival many of the traditional risk factors including smoking, alcohol consumption and physical activity. While the epidemiological literature sheds light on the existence of associations, it is difficult to draw causal conclusions from this data. Therefore, the next important step is to understand how (i.e. mediation) and when (moderation) these associations might arise. In the next section, we shift our focus to potential mediators and moderators of the link between social ties and health, working towards a sophisticated model that might provide a foundation for future research activities.

Potential mechanisms

Social ties may impact on health outcomes through variety of tightly intertwined behavioural, psychological and physiological mechanisms (Fig 2).

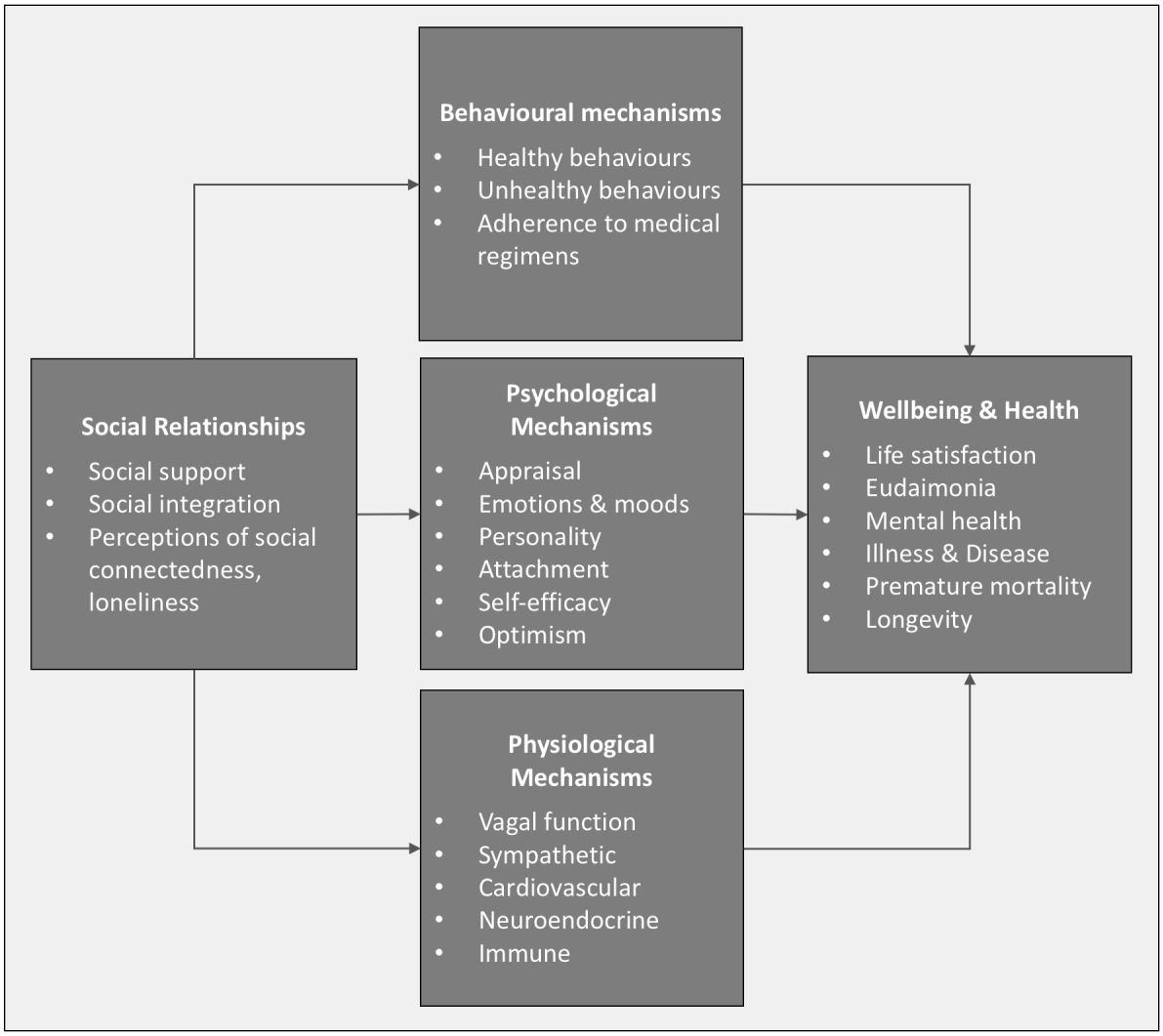

Fig 2: Summary of pathways that have been proposed to mediate or moderate the link between social ties, and health and wellbeing. The influence of sociostructural factors over these pathways is denoted by the grey box overlay, emphasising that the health of individuals is not achieved within a vacuum, but within community ecosystems. This figure summarises the mechanisms identified in previously published reviews on this topic (6,47-49,53,108,115,116,187,188). While the arrows are unidirectional, it is likely that pathways are bidirectional, reflecting the possibility that proposed mechanisms and some outcome measures of health and wellbeing will themselves impact on social ties (see Fig 4). Past research has been limited by simplistic models (e.g. positive social ties → health), highlighting a need for more sophisticated models (Fig 4) that consider the complexity of inter-relationships between various proposed mechanisms (Fig 2).

Social ties will influence whether individuals exercise, eat healthy food, smoke, consume alcohol, and use illicit drugs through social control and influence. In 1897, Emile Durkheim proposed that social integration and widely held norms function to regulate behaviour including the tendency for

suicide (45). More recent social capital (46) and social cognitive (47) theories provide further theoretical context for understanding how individuals, their relationships with others, and the communities in which they belong influence health behaviour. *Positive* social ties will promote healthy behaviours and reduce risky behaviours subsequently contributing to good health. In fact, it has been argued that if the benefits of positive health behaviours were able to be compressed into a single pill, this achievement would be declared a milestone in the field of medicine (47). However, *negative* social ties may lead to risky behaviours (e.g. smoking, alcohol abuse, drug use) with subsequent impacts on wellbeing. (See 48 for a review on the complex inter-relationships between social ties and health behaviours). These *negative* social ties have even been shown to extend to the spread of obesity (44) such that weight gain in one person is associated with weight gain in friends, siblings, spouse and neighbours. The authors point to the social nature of these associations, concluding that the perception of social norms regarding the acceptability of obesity may have contributed to the findings. Intriguingly, the authors further suggest that network phenomena might be exploited to spread positive health behaviours. While there has been significant debate over the extent to which individuals are able to achieve certain health outcomes, academics (46,47) emphasise the need for a combination of individualist and structuralist approaches to health promotion, involving a focus on individual self-efficacy in combination with sociostructural factors that impact on one's capacity to achieve health goals.

Psychological factors such as personality and attachment styles may mould the social environment, which may, over time, have effects on health outcomes. Findings from the Terman Life-Cycle Study (6,49) have pinpointed conscientiousness as the most important personality trait linked to longevity, and individuals with low conscientiousness as well as high neuroticism might be at especially high risk due to impulsivity, disorganisation, anxiety and high emotionality (6) (see also: 50). Personality factors have also been demonstrated to account for as much as 63% of the variance in subjective wellbeing (51). Other research (52) has demonstrated that only conscientiousness is related to mortality risk across 7 different cohorts including the British Household Panel Survey, 2006–2009; the German Socio-Economic Panel Study, 2005–2010; the Household, Income and Labour Dynamics in Australia Survey, 2006–2010; the US Health and Retirement Study, 2006–2010; the Midlife in the United States Study, 1995–2004; and the Wisconsin Longitudinal Study's graduate and sibling samples, 1993–2009. Individuals in the lowest tertile of conscientiousness were shown to have a 1.4 times higher risk of death compared to those in the top 2 tertiles, and this association was robust to adjustment for health behaviours, marital status and education.

Individual attachment styles – a dyadic characteristic – are also linked to health outcomes (53): secure attachment is associated with wellbeing and mental health (54), while insecure attachment predicts inflammatory illnesses 30 years later (55). Attachment theory (56-58) has made important contributions to understanding how early life experiences may shape the development of personality – an individual characteristic – and how adults perceive and react during various types of social

encounters. Attachment styles have been shown to influence close relationships as well as interactions with unknown people, perhaps underpinned by its effects on psychological moments (54,59). Attachment styles can be divided into two main categories: secure and insecure attachments. A secure attachment style develops when the primary care giver provides a secure base for the infant and responds consistently to restore emotional balance in times of distress. In contrast, an insecure attachment style will emerge if attachment figures are repeatedly experienced as unresponsive or inconsistent in their responses in times of need and stress. Further subdivisions of unsecure attachments include anxious and avoidant attachment styles. Avoidant attachment can be experienced when proximity seeking to the primary care giver is perceived as pointless or even dangerous because of the distress caused when proximity seeking fails. Anxious attachment styles occur when a perceived failure to handle threats independently encourages the infant to seek support despite the fact that attachment figures are experienced as inconsistent.

The impact of stress will be mediated by these psychological factors, consistent with the transactional model of stress and coping (60). While perceptions of risk may lead to the initiation of various coping mechanisms, it may also lead to psychological distress and adverse health outcomes (61). Research (62) demonstrates that attachment styles influence momentary affective states, cognitive appraisals and social functioning. Compared with securely attached individuals, individuals with anxious attachment reported higher negative affect, stress and perceived social rejection. Individuals with an avoidant attachment style reported decreased positive states and a decreased desire to be with others when alone. The appraisal of situations as stressful will have subsequent downstream effects that will then impact on health outcomes, increasing mortality risk two-to-three fold among middle-aged men and women aged 36-52 years (63). Similarly, other research (64) has shown that psychological distress increases risk for mortality from all causes, cardiovascular disease and external causes, even in those who do not come to the attention of mental health services. Furthermore, individuals who report a high degree of stress *and a belief that stress is harmful* have a 43% increased risk of premature death (61).

Physiological stress responses and the capacity to regulate these responses play a mediating role in pathways to health and wellbeing. Social isolation, low social support and *negative* social ties lead to chronic activation of immune, neuroendocrine and metabolic systems, increasing risk of cardiovascular disease (65,66). In rodents, social defeat – characterised by repeated physical attacks and declaration of subordination by the non-dominant animal – has considerable behavioural and physiological impacts. In the short term (minutes to hours) defeat produces vagal withdrawal, tachycardia, hypertension, elevated levels of glucocorticoids and catecholamines, and reduced concentrations of testosterone (67,68). Over the longer term (days and weeks), lasting changes in behaviour (anxiety), hypothalamic-pituitary-adrenocortical axis activity (increased), and neurotransmitter systems are observed (68). In fact, chronic psychosocial stress including threat of

physical attack and daily episodes of aggression by a dominant male over a period of 2-weeks led to structural damage at the level of the heart (fibrotic tissue accumulation) (69). While acute stress responses were observed to habituate over time, repeated episodes of social defeat led to a 6-fold larger amount of reparative tissue, increasing susceptibility to cardiac arrhythmias. These findings suggest that despite short-term adaptations to stress, chronic psychosocial stress will lead to multisystemic overstimulation (or 'allostatic load'), contributing to permanent pathological alterations (68,70). In humans, lasting social conflict increases the chance of getting a cold after exposure to a common cold virus (71) and risk of inflammation caused by social isolation is of similar magnitude to the risk associated with physical inactivity (40). By contrast, social connectedness and support are associated with positive affect, which might be associated with lower heart rate, higher rate variability, blood pressure and inflammatory markers, which benefit health (72). Social integration has also been found to decrease risk of physiological dysregulation in a dose-response manner (40). Research further now indicates that the vagus nerve – indexed by heart rate variability (or HRV) – may play a causal regulatory role over our psychological moments (Fig 3 and 4).

Two neurobiological models have been proposed that help to understand the link between psychological and physiological factors. These models include polyvagal theory (73-76) and the neurovisceral integration model (77-80), the major features of which are summarised in figure 3. Increased function within prefrontal-vagal pathways support prosocial behaviour and positive emotions, while decreased function facilitates response to environmental change, fight-flight-or-freeze responses and negative emotions. Increased function along prefrontal-vagal pathways is driven by cortical inhibition of the central nucleus of the amygdala (CeA), which then activates the vagus nerve within the nucleus ambiguus—increasing HRV— and facilitates socially engaging facial expressions and positive social interactions. The nucleus tractus solitarius within the medulla oblongata receives vagal afferent feedback from the viscera and internal milieu, and this information is then directed to cortical structures responsible for the top-down, flexible regulation of psychological moments (Fig 3, black arrows). By contrast, decreased function along prefrontal-vagal pathways is associated with responsiveness to environmental challenge (e.g. orienting) and withdrawal from the environment (e.g. fear, anxiety). Decreased function is driven by disinhibition of CeA (the major efferent source for modulation of cardiovascular, autonomic and endocrine responses) and vagal withdrawal, triggering fight-flight-or-freeze responses. Again, information relating to the status of the viscera and internal milieu are fed back to the nucleus of solitary tract and the cortex, allowing for subsequent regulation of psychological moments (Fig 3, grey arrows).

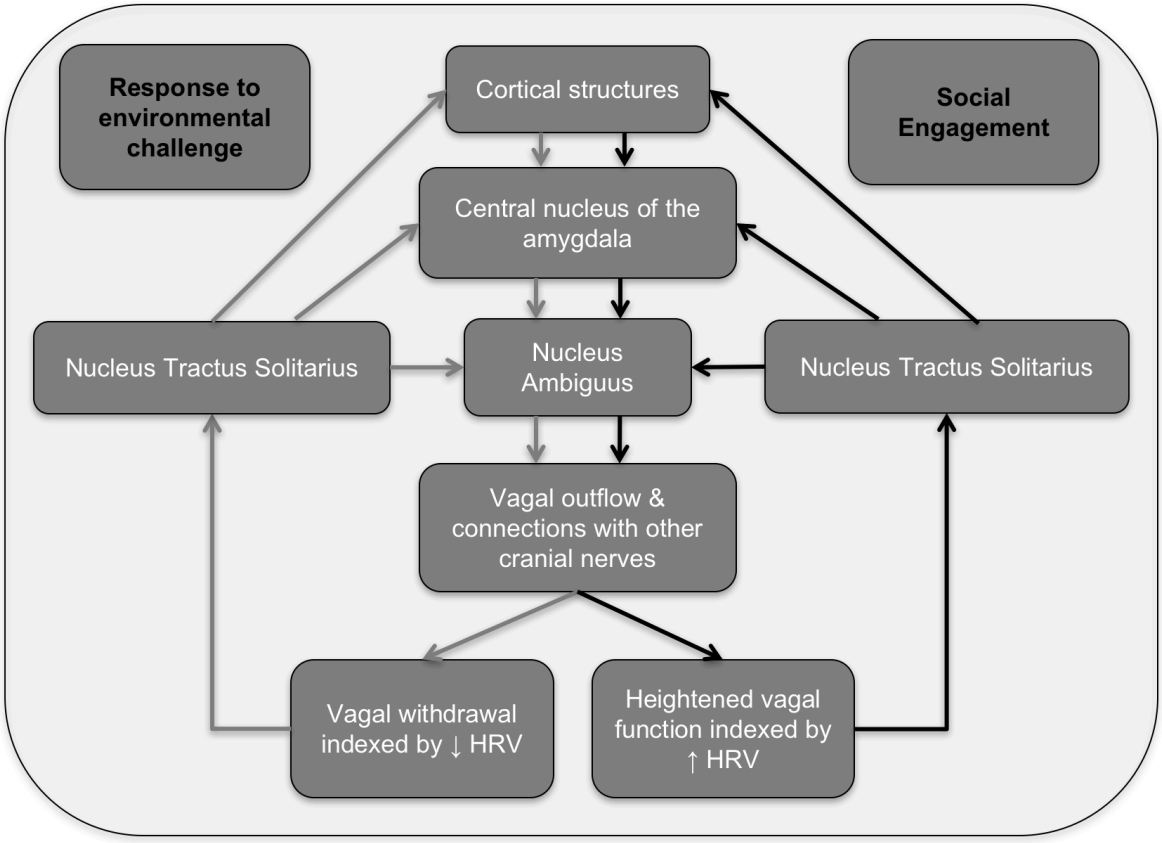

Fig 3: Neurobiological components and associated behaviours that contribute to a psychological moment. A prominent role is given to the vagus nerve within an integrated brain-body network that either facilitates engagement with others (black arrows) or supports rapid whole-body response to environmental challenge (grey arrows). The arrows represent both efferent projections from the brain, contributing to rapid alterations in vagal function and related behavioural responses, as well as afferent feedback from peripheral end organs allowing for effective regulation of ongoing processing. These bidirectional pathways from and to the brain provide a psychophysiological framework through which psychological moments reciprocally and prospectively contribute to alterations in vagal function (e.g. mutual causation between emotional experience and vagal function). Afferent projections also provide a theoretical basis through which many behavioural interventions such as massage, exercise, meditation, yoga and HRV biofeedback may be understood.

Brain development is influenced by a child's early social environment. Limbic regions are in a critical period of growth in the first two years and these same neurobiological structures will mediate stress-coping capacities for the rest of the life span (81). Recent neuroimaging work has explored neuroanatomical differences underpinning different attachment styles in adulthood and how this may influence social and emotional processing (see 82 for review). Secure and insecure attachment styles may differentially recruit functional brain networks for interacting with others. According to a

functional neuroanatomical of adult attachment style on social processes (82), two neural compartments mediate automatic affective evaluations versus more controlled cognitive processes. These include systems for: 1) rapid, automatic affective appraisals (emotional mentalization), which is primarily involved in encoding basic dimensions of safety versus threat, or approach versus aversion tendencies in social contexts, and 2) controlled social processing and regulation (cognitive mentalization), operating in a more conscious, voluntary mode, which is involved in representing the mental states of others and regulating one's own behavior, thoughts, and emotions. These two functional components rely on distinct brain networks 1 (75,83,84), which involve limbic cortico-subcortical areas (e.g., amygdala, striatum, insula, cingulate, hippocampus) for affective evaluations, and fronto-temporal areas (e.g., medial prefrontal cortex, orbitofrontal cortex, superior temporal sulcus, temporo-parietal junction, etc.) for cognitive mentalization and regulation, respectively. Importantly, these components may entertain a reciprocal dynamic balance between each other. The model argues that specific attachment styles, emotions and behavioural responses are associated with the differential recruitment of these components.

Social engagement can only occur when the environment is perceived as safe and defensive circuits are inhibited. Therefore, an insecure attachment style – associated with impairments in vagal function (85) – will adversely impact the extent to which successful social engagement can occur. Vagal impairment will subsequently impact the degree to which downstream pathways are able to be regulated, having implications for health outcomes. There is increasing evidence for a regulatory role of the vagus nerve over downstream pathways (Fig 4). Recent studies (86,87) have demonstrated that chronically-administered vagal nerve stimulation (VNS) may trigger a host of benefical effects, and these effects were even observed in obese-insulin resistant rats fed a high-fat diet for 12 weeks. The authors reported that VNS decreased plasma insulin, insulin resistance, total cholesterol, triglyceride, LDL and visceral fat (87), relative to controls. VNS also decreased blood pressure, increased HRV and improved left-ventricular function (87). Finally, VNS exerted anti-oxidant, anti-apoptosis and anti-inflammation properties. In another study by these authors (86), VNS attenuated brain mitochondrial dysfunction, improved brain insulin sensitivity, decreased cell apoptosis and increased dendritic spine density, leading to improved cognitive function. These studies lend support to data from humans demonstrating that lower vagal function predicts elevated systemic inflammation – indexed by C-reactive protein – 4 years later (88). Other research has explored the pathways that might mediate the association between HRV and cognitive impairment (89), an important and relevant investigation considering that some researchers consider cognitive function to be an important component of wellbeing (6). While past studies had suggested that the vagus might regulate downstream pathways that could then impact on cognitive function, no prior study had investigated this possibility. Findings indicated that reduced vagal function was associated with increased insulin resistance – a feature of type II diabetes characterised by poor regulation of glucose in the body – leading to a thickening of the

carotid arteries (higher intima-media thickness), and cognitive dysfunction (89). These findings were further supported in 5 separate sensitivity and specificity analyses. It was concluded (89) that vagal function might provide a 'spark' that initiates a cascade of adverse downstream effects subsequently leading to cognitive impairment.

Common genetic variants have also been shown to impact on the social brain, which may have downstream effects on biological processes that contribute to disease and mortality. The gene coding for the oxytocin receptor (OXTR) has been shown to play an important role in contributing to individual differences in social behaviour and cognition (90,91). For example, the G allele of the single nucleotide polymorphism (*rs53576*) located in the OXTR has been shown to be associated with higher pro-sociality in nonverbal displays, as judged by outside observers' ratings of silent behaviour (92). By contrast, carriers of the OXTR rs53576 A allele have been shown to display lower levels of sensitive responsiveness to their toddlers (93), empathy (94) and positive affect (95). In fact, haploytpes constructed with three polymorphisms of the OXTR (rs53576, rs2254298 and rs2228485) are associated with positive affect, negative affect and loneliness (95). Others (96) have reported that the rs53576 polymorphism is essential for the stress buffering effects of social connectedness, such that those participants with at least one copy of the *rs53576* G allele display higher HRV when social support is provided during the Trier Social Stress Test, a standardised, laboratory-based assessment of psychological stress. Recent research (97) has further demonstrated that while variation in three neuropeptide receptor genes – oxytocin, β-endorphin, and dopamine – display important associations with sociality, endorphins and dopamine may have a much wider spectrum of effects than oxytocin. Furthermore, β-endorphin has been shown to operate effectively at dyadic and group levels (98-100) because its release can be triggered in others by touch, unlike oxytocin (97,100).

Research in the field of epigenetics has further demonstrated how life experiences can be written into DNA. For instance, some mother rats spend considerable time licking and grooming (LG) their pups while others do not. Offspring of mothers that show high levels of LG show differences in DNA methylation (one of several epigenetic mechanisms that cells use to control gene expression), as compared to offspring of low LG mothers (101). As adults, these rats displayed stress responses that were dependent on amount of LG. Specifically, rats that received the most LG had an optimal response to stress, while those that had received less LG displayed an exaggerated stress response. This work demonstrated that the epigenomic state of a gene can be established through behavioral programming. A decade of research now shows that LG is translated into biochemical signals that enter the DNA and program it differently, allowing the animal to equip itself for life and the environment. While caution is required over linking LG reactions in rats to high quality mother-infant interactions in humans, evidence in humans (102,103) supports the conclusion that maternal stress leads to lasting, broad, and functionally organized DNA methylation signatures in offspring, which may be linked to internalising and externalising disorders (104), lower cognitive and language abilities (105) and increased risk for

metabolic disease (106,107). These findings demonstrate the adverse effects that early life experience may have on health or disease.

In summary, a host of mechanisms have been proposed to influence the pathways to health outcomes, and community ecosystems may either facilitate or impede engagement in health behaviours. While a host of behavioural, psychological and physiological mechanisms have been proposed, research is typically characterised by a restricted focus on simple models involving single mediators or moderators in isolation. Recognising this issue, recent reviews (6,108) have highlighted a need for sophisticated models that take into account the complex pathways between social ties and health outcomes. This is our goal for the next section.

A model and foundation for future research activity

"To find a solution, we need a new way of understanding the problem."

Robert Maunder & Jonathan Hunter (2015), Love, Fear and Health

Heeding calls for more sophisticated models (6,108), this section of our book chapter makes an important contribution to the literature by bridging the gap from psychology through to epidemiology (109-111) and laying a foundation for future research activity. We propose the GENIAL model for pathways to wellbeing and longevity, a comprehensive model spanning Genomics and its interaction with the Environment through to health outcomes, highlighting a major regulatory role for the vagus Nerve over social Interaction and Allostatic regulation, subsequently leading to premature mortality or Longevity (Fig 4). Four key features of our model are worth emphasising. First, vagal function – indexed by HRV – plays a key regulatory role over pathways leading to either premature mortality or longevity (109). Second, vagal function will influence our psychological moments, cognitive functions, psychological flexibility to environmental change and capacity to engage with others (76,78,109,112), and plays a critical regulatory role over allostatic systems (70), providing a structural link between mental wellbeing and physical health. We further propose that individual differences in resting vagal function will influence capacity for regulating psychological and physiological mechanisms (discussed further below). Third, social ties are supported by and impact on vagal function, consistent with polyvagal theory (76) and the proposal that positive (negative) emotions and vagal function influence one another in an upward(downward)-spiral dynamic (25,113,114). Fourth, sociostructural factors within community ecosystems will either facilitate or impede health behaviour (47,115,116), subsequently impacting on vagal nerve function (25,76,113,114). Positive health behaviours as well as unhealthy behaviours will also be influenced by social ties directly (45-47).

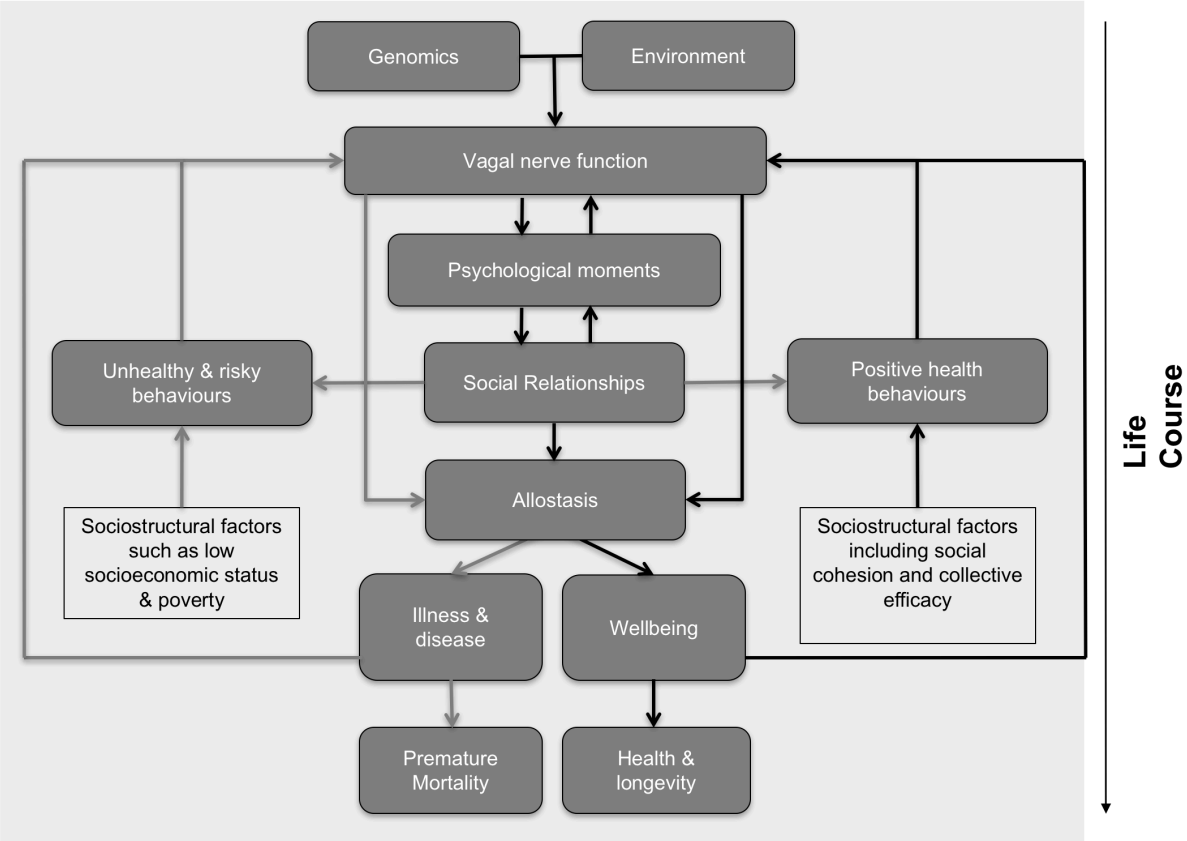

Fig 4: The G-E-N-I-A-L model: Genomics - Environment - vagus Nerve - social Interaction - Allostatic regulation – Longevity. The GENIAL model is a simplified, yet sophisticated model for better understanding pathways to premature mortality or longevity, drawing on evidence from multiple disciplines, highlighting important mediating roles for vagal nerve function and social ties. In this model, vagal nerve function impacts on and is influenced by social ties, and regulates a variety of allostatic mechanisms leading to either premature mortality or longevity. Vagal function provides a structural link between psychological moments and physiological processes. Illness and disease (and wellbeing) will further impact on vagal function in a downward (upward) self-sustaining spiral. Health behaviours and sociostructural factors represent important moderators of the pathways to health and wellbeing. Temperament (denoted by the light grey overlay) is a lens though which the world is viewed and foundation on which psychological moments arise.

At the top of the model (Fig 4), the role of genomics and interactions with the environment are proposed to play an important role in influencing individual variability in vagal function. Nurture and nature can no longer be regarded as discretely separate issues. Genetic susceptibilities are activated by environmental influences, a phenomenon labelled as the gene by environment interaction, and advances in epigenetics demonstrate how such interactions can shape health outcomes. Although research on the genomics of human wellbeing is in its infancy, there are several studies (22,23,117) that have laid a

foundation for future research in this area. Extended periods of stress and threat may increase expression of inflammatory genes, preparing the immunity system for a potential wound-related bacterial infection derived from social conflict. By contrast, positive socialization is hypothesised to increase transcriptional levels of antiviral-related genes, protecting the immune system against potential viral infections derived from increases in social interaction with other members of the species (118). While controversial (26,119,120) (but see: 121), this research lays a preliminary framework through which genomics will impact on downstream processes, including the vagus nerve (see Fig 4), which plays a key role in regulating the immune system (122-124), amongst others. A recent genome-wide association study on data from 59 cohorts (n=298,420) (117) identified 3 genetic loci that were associated with subjective wellbeing, defined by positive emotions and life satisfaction. Biological analyses revealed associations with anxiety disorders (ill-being), but only small genetic correlations with physical health phenotypes, including BMI, ever-smoker status, coronary artery disease, fasting glucose levels and triglyceride levels, further highlighting the need for more sophisticated models of pathways to health and wellbeing, as we present here. The construct of wellbeing in this study may have also contributed to the lack of associations with physical health.

Our model emphasises a critical role for the vagus nerve because it is responsible for the regulation of a host of psychological and physiological processes that impact on social ties, health and wellbeing, and vice versa. Several studies have demonstrated that nasal administration of oxytocin may augment vagal function (125,126), reflecting an enhanced capacity for social approach and engagement (127). These results together with genetic findings discussed above suggest that neuropeptides involved in social bonding – such as oxytocin, β-endorphin, and dopamine – may drive individual differences in vagal function, which then allow (or restrict) individuals from engaging in and maintaining social ties. These ideas are supported by other research (25,30,114) demonstrating that loving-kindness meditation leads to increased positive emotions, an effect moderated by baseline vagal activity. Results further indicated that increases in positive emotion led to further increases in vagal activity, a finding that was mediated by the perception of greater social connections. A simple model was proposed through which positive emotions might build physical health, an idea further developed here. The model put forward by these authors (25,30,114) suggests that associations between positive emotions and social ties might both drive and be supported by vagal function, representing a self-sustaining upward-spiral dynamic. We suggest that there may also be a bidirectional relationship between vagal tone and negative emotion, and this mutual causation may contribute to a self-sustaining, downward-spiral that leads to illness, disease and premature mortality. Reductions in vagal tone have been shown to precede affective disorder (128) and these reductions (129-132) are not ameliorated by antidepressant treatment (130,133) or even transcranial direct current stimulation (131), despite amelioration of symptoms.

Typically, research findings are interpreted from the vantage point of one's own discipline, a phenomenon known as the disciplinary dilemma. In the current book chapter, we have sought to build

on past work by bridging the gap between parallel lines of evidence from different fields of research. The vagus nerve is known to play an important role in maintaining homeostasis and achieving stability through change, a process known as 'allostasis'. The vagus plays an important role in regulating allostasis, yet past models tend to overlook this contribution. Multiple body systems are regulated by prefrontal-vagus pathways including the sympathetic nervous system and hypothalamic-pituitary-adrenal axis (76), inflammatory pathways (123,124), and metabolism including glucose regulation (134,135). The vagus nerve may also stimulate neurogenesis by regulating the expression of brain-derived neurotrophic factor (BDNF) (136,137), a key molecule involved in the regulation of metabolic efficiency, eating behavior, synaptic plasticity, and learning and memory (138). These alterations may contribute to improvements in cognitive function and mood observed with vagal nerve stimulation (139,140). It has even been suggested that the vagus might lead to sustainable epigenetic modifications (141). Diet and exercise have substantial anti-ageing effects, effects that may be mediated by afferent projections of the vagus (110,142,see 143), and research is beginning to demonstrate that these positive health behaviours can alter the epigenome that may then stabilise and become inherited (see 144 for review). Vagal function may therefore regulate (or fail to regulate) allostasis through various, complementary psychological and physiological mechanisms. The first of these is a generalised inhibitory function of prefrontal-vagal pathways that serve to 'sculpt' goal-directed behaviour (78), enabling the individual to better respond to environmental change, facilitating effective regulation of allostasis (145). Julian Thayer's neurovisceral integration model emphasises a tightly integrated brain-body network regulated by prefrontal-vagal pathways (77,78,80). The second potential mechanism is the role of vagus in stabilising physiological arousal leading to improved allostatic regulation. According to Stephen Porges' polyvagal theory (76), the myelinated vagus nerve in combination with other the cranial nerves support social engagement, providing a 'vagal brake' over the phylogenetically older sympathetic nervous system and unmyelinated vagus nerve. Further to this, Jos Brosschot's recently published psychological model of 'generalised unsafety' (111) argues that the stress response is a default physiological response – characterised by low HRV – that must be turned off, rather than a physiological response elicited by some trigger. Being part of a cohesive social network is proposed to be a critical safety signal that turns off this default, physiological stress response. The third mechanism through which vagal function regulates allostasis is the cholinergic anti-inflammatory reflex (123,124,135,146). According to Kevin Tracey's model, the vagal nerve controls immune function and proinflammatory responses such that the afferent vagus nerve is involved in the detection of cytokines and pathogen-derived products, while the efferent vagus is responsible for the regulation and control of cytokine release. In summary, impairment in vagal function will lead to chronic activation of the stress response and overstimulation of allostatic systems ('allostatic load' (70)). Dysregulation of allostatic systems will subsequently lead to ill-health from a host of conditions and diseases including disability, prolonged infection, delayed wound healing, obesity, diabetes, atherosclerosis, osteoporosis, arthritis, frailty, Alzheimer's disease, periodontal disease and cancer (109,110,147,148).

The model we propose here bridges a very large gap from psychology to epidemiology, illustrating an intimate link between psychological factors, health and wellbeing. Pathways to health and wellbeing are dependent on genetic and environmental factors that directly influence vagal function, supporting the capacity for social engagement and promoting effective regulation of allostatic systems, leading to resilience, psychological wellbeing and longevity or, if dysregulated, to psychiatric illness, physical disease and premature mortality. The model is obviously a simplification of reality, but provides a foundation on which future research on pathways to health and wellbeing could be developed. Bidirectional pathways that feedback on vagal function, psychological factors and social relationships are also recognized. In this regard, those with chronic conditions will have lower vagal function that will impact on capacity for social engagement, which will then limit one's capacity for social integration, leading to further social isolation. It is possible therefore, that those who would benefit the most from the effects of positive relationships will have fewer opportunities to experience them, leading to a downward spiral of negative emotions, social isolation, loneliness and ill-health. These considerations highlight opportunities for improving the lives of people living with chronic conditions.

In summary, the GENIAL model is novel for at least five reasons: First, vagal function is characterised as a major regulator and driver of health and wellbeing outcomes including longevity. By contrast, the field typically presents vagal function as one of many time-limited biomarkers that naturally fluctuate as the body maintains homeostasis (e.g. 6). Second, we build on prior research emphasising single mechanisms such as genomics (23,149), vagal tone (25,113,114) and personality (6) by accounting for the complexity and interactions between behaviour, psychological and physiological mechanisms as well as the influence of sociostructural factors. Third, by adding in vagal function as an upstream regulator of pathways to wellbeing and longevity, we build on earlier systemic models of health and disease such as the allostasis model (70), immune dysregulation theory (150), and the causal network model linking depression and coronary heart disease (151). Fourth, our model establishes a much-needed bridge between psychology and epidemiology, linking psychological factors to wellbeing (or illness and disease), contributing to longevity (or premature mortality). Fifth, our model combines individualist and structuralist approaches (47) to understanding health and wellbeing over the life course, thereby placing the health of individuals within the context of community ecosystems. While our model is obviously a simplification of reality, the statistician George Box explains: "Essentially, all models are wrong, but some are useful" (152).

Discussion and conclusions

Humanity is facing major challenges and uncertainty, highlighting an urgent need for social harmony, unity and understanding, yet, social relations are increasingly strained, fractious and

disconnected. Cultural shifts toward greater individualism and rapidly advancing technologies have led to an inflated sense of self and cultural narcissism (153). Society has become isolating, homeowners distrusting, and people are dying lonely deaths that remain undiscovered for long periods of time, a phenomenon the Japanese call 'kodokushi'. In the United Kingdom, more than a quarter of all households in 2016 include people living alone, increasing by 51% in those aged 45 to 64 years between 1996 and 2016 (154). Similar findings have been reported for the United States, according to the US Census Bureau (155). Strikingly, more than a third of homeowners think that their immediate neighbours cannot be trusted (156). Findings from the European Quality of Life Survey (2011/2012) indicated that around 1 in 10 people (11%) report feeling lonely all, most or more than half of the time and that just over a third of people surveyed wished they could spend more time with family and have more social contacts (156) (157). Astonishingly, other research indicates that around 3 in 5 teenagers (62%) report feeling lonely (158) increasing risk for mental ill health and other problems. Loneliness is associated with generalised distress, especially interpersonal sensitivity (low self-esteem) (159) and depression (160), and psychological distress has been shown to increase risk for all-cause mortality over an 8-year follow-up period (64). In fact loneliness may increase risk for mortality to such an extent that it is equivalent to smoking 15 cigarettes a day (38). Loneliness may lead to affective disorders – including major depression and anxiety disorders – which may reduce life expectancy by up to 18 years, an effect that is even greater than heavy smoking (161). It is not surprising therefore that mental health problems represent the largest single source of world economic burden attributable to non-communicable disease (162,163). The burden of mental health problems cost the UK economy an estimated £70 billion – or 4.5% of GDP – through direct costs associated with health and social services, and indirect costs associated with reductions in workforce productivity (164). A contributor to this problem is the substantial mental health treatment gap and lag. The mental health treatment gap refers to the numbers of people who need treatment that are not receiving it, reportedly exceeding 50% in all countries of the world and approaching 90% in those which are least resourced (165). The amount of time taken to receive care when it does exist – treatment lag – is estimated to be as long as 10 years (166). These astonishing figures present significant challenges to health care systems and one wonders whether policy-makers and health-care providers are sufficiently prepared to cope with the predicted rise in the prevalence of disability and chronic disease associated with ageing of populations globally. So how might scientific research impact on this current state of affairs?

In 2010, the World Psychiatric Association carried out a systematic survey of leaders of psychiatry in nearly 60 countries on the strategies needed to reduce the treatment gap and lag in relation to mental health, neurological conditions and substance abuse disorders (165). Three broad themes emerged: first, numbers of psychiatrists and other mental health professionals must increase; second, greater involvement by non-specialist providers is needed; and third, service users and their family members must be empowered to actively participate in service planning and delivery. The second and

third of these themes may be facilitated through a strategy known as task shifting, involving the delegation of health care – where appropriate – to less specialized health workers. By reorganizing the workforce in this way, task shifting can make more efficient use of the limited numbers of mental health professionals that are available. Task-shifting to non-specialist health workers has been shown to be a cost-effective way of improving outcomes for people with mental health disorders providing there is supervision and support from health care professionals (167). Social prescribing is another innovative and complementary approach to managing and addressing treatment gap and lag. Social prescribing aims to promote the use of the voluntary sector within health care settings by creating referral pathways that allow primary health care patients with non-clinical needs to be directed to local voluntary services and community groups in addition to having their medical needs met. The substantial gap and lag in treatment are societal problems and societal solutions including task shifting and social prescribing align well with mounting evidence –reviewed above – on the associations between social ties and health outcomes, and the way in which these associations are mediated. For example, task shifting looks to local communities and community initiatives to support people with chronic conditions, facilitating positive health outcomes. Social prescribing involves health care professionals prescribing community engagement in addition to lifestyle advice, psychological therapies and medication. However, for these solutions to be successful, better links need to be created between community organisations, the health care sector and academia, allowing for appropriate social environments to be constructed that will then facilitate evidence-based individual pathways to health and wellbeing. Such initiatives require vigorous empirical evaluation through strategic university partnerships.

Health and wellbeing do not automatically emerge once "the swamps of suffering are drained" (168). Therefore, the domain of positive psychology has much to offer those wondering how the treatment gap and lag might be managed. Positive psychology refers to the scientific study of human flourishing and an applied approach to enabling individuals, communities and organisations to thrive (169,170). We now know that the influence of life circumstances is far less than what might be expected, highlighting opportunities for targeted intervention. Wellbeing is determined by 3 factors (171): a genetically determined set-point, intentional activity and circumstantial factors according to a 50-40-10 formula. While genetics accounts for approximately 50% of the population variation in happiness, life circumstances only make a small contribution, around 10%. The important point here is that intentional activities contribute remaining variance – in the order of 40% – providing considerable opportunities for increasing wellbeing through structured activities such as engagement in positive interventions (172). Social ties clearly make an important contribution to wellbeing, through social support, social integration as well as perceptions of social connectedness and loneliness. In the current chapter, we have emphasised how social ties and engagement with others might contribute to increased wellbeing, through a host of closely intertwined mechanisms within community ecosystems (see Fig 4).

The focus of positive psychology on what makes life worth living is beginning to impact on community initiatives to improve the quality of life in neighbourhoods and cities. Here are some examples, that emphasise a key role for social ties and positive relationships with others for transitioning to a better world. The first example – the Transition Network (http://transitionnetwork.org/) – is a community-led movement that seeks to address some of the world's biggest challenges – economic decline, social inequality and climate change – by connecting with ourselves, others and the natural world, while developing and promoting positive possibilities such as urban food markets, community energy projects, and local currencies such as the Brixton Pound. Another example is the 'Happy City Initiative' (http://www.happycity.org.uk/), which aims to enhance community wellbeing through cultural and cooperative activities that extend beyond economic progress. Central to this initiative is the quality of relationships with others, in addition to supportive and active communities, and the availability of opportunities for meaningful engagement with others. Yet another example is the 'Down to Earth Project" (http://www.downtoearthproject.org.uk/), which aims to improve people's lives through outdoor communitarian activities and wellbeing programs. Anecdotally, we have seen the lives of those with acquired brain injury transformed by engaging in outdoor activities such as the "Building Community" project, which involves building sustainable facilities for future community activities. Further examples include the Action for Happiness initiative, which involves delivering training packages based on positive psychology and disseminating skills to communities (http://www.actionforhappiness.org/), and social prescription of nature-based interventions (173,174). While it remains to be seen whether these community-based initiatives will succeed over the long term and the extent to which health and wellbeing is improved in the process, programmes like these have great potential for transformative change.

The epidemiological transition to non-communicable disease including mental ill-health, diabetes, obesity and cardiovascular disease is now the dominant source of disease burden. Chronic disease has replaced acute (and communicable) disease as leading burdens of morbidity, mortality, and health care expenditures (167,175-181). However, our models of health care have not adapted to reflect these changes. The traditional approach to health care is the 'acute medical model', which involves the passive receipt of care. The assumptions underpinning this model is that illness is likely to be short-lived, and thus the aim of care is 'cure' and 'return to a pre-illness state of health' (182). Although the acute care model is extremely important and is responsible for the saving of many lives, it does not provide an effective model for chronic care. Chronic disease is different (167) to acute disease as cure is usually not possible. Treatment outcomes for people with chronic conditions are contingent on an effective collaboration between clinician and patient. For example, encouraging patient adherence to treatment regimens, and adoption of recommended lifestyle changes etc. Thus, patients are no longer passive recipients of care, but need to be active and equal partners in the management of their chronic

disease. The acute medical model is further limited by a narrow definition of 'health' that is focused on illness or impairment, rather than flourishing.

Researchers (116) have argued that a complete understanding of social ties and their associated health outcomes will only be achieved through a more holistic approach to community health by defining communities as "human ecological systems". (Readers may be interested in looking at the work of Nicholas A. Christakis in particular, who focuses on how social networks impact on health and wellbeing). The structure and organization of communities have important implications for community health, especially sociostructural factors (Fig 4). An increasing body of work has examined the health of individuals and populations within the context of community ecosystems. For instance, a recent study (183) reporting on associations between psychological language that is used on the Twitter platform and county-level heart disease mortality, argued that tweets of younger adults may disclose characteristics of their community, reflecting the physical and social environments that influence the health behaviours and stress experiences of their residents. This study (183) examined associations between 148 million county-mapped tweets across 1,347 counties, and county-level, age-adjusted mortality rates for atherosclerotic heart disease obtained from the Centers of Disease Control and Prevention. Patterns reflecting negative social ties, disengagement and negative emotions emerged as risk factors, while positive emotions and psychological engagement emerged as protective factors. Intriguingly, the authors reported that their model based only on Twitter language predicted mortality better than a model combining 10 common demographic, socioeconomic, and health risk factors, including smoking, diabetes, hypertension, and obesity. This focus on systems is also consistent with recent calls (184) for researchers to approach psychopathology as a system, drawing on developments in dynamical systems theory, network theory, chaos theory, and other branches of the complexity sciences. Together with new insights offered by the GENIAL model, these methodological developments may help to transform our understanding of pathways to health and wellbeing within the context of the health of individuals and their community ecosystems.

In summary, we have reviewed the literature on associations between social ties and health outcomes, identified various mechanisms that might underpin the association, and proposed the GENIAL model [Genomics - Environment - vagus Nerve - social Interaction - Allostatic regulation – Longevity] for pathways to wellbeing and longevity, emphasising social ties as an important mediator along this pathway. We suggest that past research on the link between social ties and health outcomes has been held back for at least four reasons. First, the field has been characterised by multiple competing simplistic models leading to calls for more sophisticated models (6,108) that take into account the complex pathways between social ties and health outcomes, as well as more robust statistical methods that could then be applied, drawing on for example, developments in complex systems theory and dynamics (184). Second, the field typically considers the vagal nerve as an epiphenomenon of the stress response, rather than a regulator of multisystemic, downstream pathways that can lead to either

premature mortality or longevity. This is despite available theory (76-78,122) and data (88,89,185) that provide a framework through which to understand how the vagus might regulate downstream systems. Third, research on vagal tone is typically conducted with a restricted focus on the individual, rather than their connections with others, social integration and community ecosystems, further highlighting a need for drawing on modern analytical methods. Fourth, research findings are typically interpreted from the vantage point of one's own discipline, a phenomenon known as the 'disciplinary dilemma'. While this is understandable, it is also unfortunate. It could be argued that the greatest insights in science arise through multi-disciplinary exchange, allowing for new lines of interdisciplinary and even transdisciplinary enquiry to arise.

Future research will benefit from investigating more sophisticated models of pathways to health and wellbeing, and drawing on recent developments in statistical methods (e.g. 186) to large datasets. Multidisciplinary collaboration and interdisciplinary science is essential for a more complete understanding of the mechanisms underpinning the associations between social ties, health and wellbeing. Our working hypothesis underpinning the GENIAL model proposed here, is that vagal function plays an important regulatory role over pathways to health and wellbeing, which include psychological factors, social ties and allostatic processes. Understanding that the health of individuals is not achieved within a vacuum, we recognise that physical and social environments will either impede or facilitate individual pathways to health and wellbeing. Within this framework, gene-environment interactions will contribute to individual differences in vagal function that will both influence and be influenced by psychological moments and social ties. Individual differences in vagal function will lead to variation in regulation of allostasis, and if regulation is optimal, one will be set along pathway to wellbeing, health and longevity; however, if dysregulated, the course will be set for illness, disease and premature mortality. The GENIAL model has important implications for a) teaching service users about the importance of emotional flexibility and relationships with health outcomes and b) creating social contexts that facilitate positive experiences and social ties especially for those with chronic conditions, who experience fewer opportunities for social integration and relationships with others. It is our hope that future research will proceed by combining individualist and structuralist approaches to health and converge into a transdisciplinary science that draws on developments in complex systems theory and dynamics, leading to a better understanding of how social ties influence human health, and ultimately, better care for managing patients with chronic mental disorders and physical disease.

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