Chapter 2
Healthy Smoker: An Oxymoron? Maybe, But It Is More Complicated Than That

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2.1 Introduction

Today, diseases that contribute to morbidity and mortality have significantly changed from infectious agents as the main culprit to chronic conditions, in which pathogenesis occurs over years [1]. Using a biopsychosocial approach to disease, the level of one's psychological stress can exacerbate or slow the dysregulation of the body as it ages, either hastening or delaying the development of chronic conditions

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such as cardiovascular disease, obesity, type 2 diabetes, and major depression [2, 3]. This stress activates physiological systems evolved to support survival [4].

Stress is ubiquitous in life; however, rarely does an individual find themselves in a life-or-death situation, needing to survive. Yet, once stress is perceived, a cascade of biobehavioral adjustments occur which assist the individual's ability to engage with or retreat from the situation [5, 6]. Regardless of whether one engages or retreats, our bodily systems have the same response for managing the stressor: (1) activation of the sympathetic nervous system (SNS), (2) withdrawal of the parasympathetic nervous system (PNS), and (3) stimulation of the hypothalamic-pituitary-adrenal (HPA) axis [7, 8]. These neuroendocrine changes modulate a variety of hormone levels that affect the functionality of the entire body at inter- and intracellular levels.

Acute stress reactions are often advantageous as they assist the individual's ability to handle the situation successfully. Physiological systemic variability (e.g., cardiovascular and neuroendocrine reactivity) is necessary to navigate acute stressful experiences allowing individuals to identify, respond to, and recover from stress. However, chronic stimulation results in excessive demand on multiple bodily systems, leading to reduced variability in these physiological systems and, consequently, loss of adaptive function and more psychological stress [5, 9, 10], creating a vicious negative cycle that continually dysregulates the system as the "resting" state moves toward the activated state (see Fig. 2.1). *This physiological shift wreaks* havoc *on human health.*

The link between physiological dysregulation and stress has been observed in many populations, including individuals with major depression and anxiety disorders [11–14]. Even psychosocial factors such as loneliness and socioeconomic status are related to the negative physiological adaptations [15–17]. However, examining this stress evolution on physiological systems (Fig. 2.1; large red arrow) in humans can be difficult because life stressors are unpredictable, and psychological stress depends on the individual's perception. In addition, factors like depression, anxiety, loneliness, and chronic health conditions that are reliably associated with physiological dysregulation do not have precise start and end points for researchers to investigate changes linked to cyclic depressive episodes or disease flare-ups [11–14]. Thus, a human model of how acute stress transitions to chronic stress is critical to advance our fundamental understanding of how stress and psychosocial factors modulate physiological functioning (red arrow in Fig. 2.1).

Cigarette smoking has identifiable start and end dates; smokers can typically recall when they started and possibly stopped using cigarettes [18]. In addition, it is reliably linked to the "wear-and-tear" or dysregulation of multiple bodily systems (e.g., cardiovascular, immune, endocrine, etc.) [19] that mirrors the effects of stress on the body. Data from our lab suggest that before observable dysregulation (e.g., no current mental or physical health diagnosis or pharmacological treatment), *immune cells from smokers are less affected by stress hormones such as cortisol when compared to nonsmokers' immune cells* when controlling for known confounds like current depressive symptoms, childhood trauma, and recent stressful life events [20]. Immune cells resistant or insensitive to cortisol's effects also known as glucocorticoid resistance (GR) are a factor related to chronic disease [12]. GR

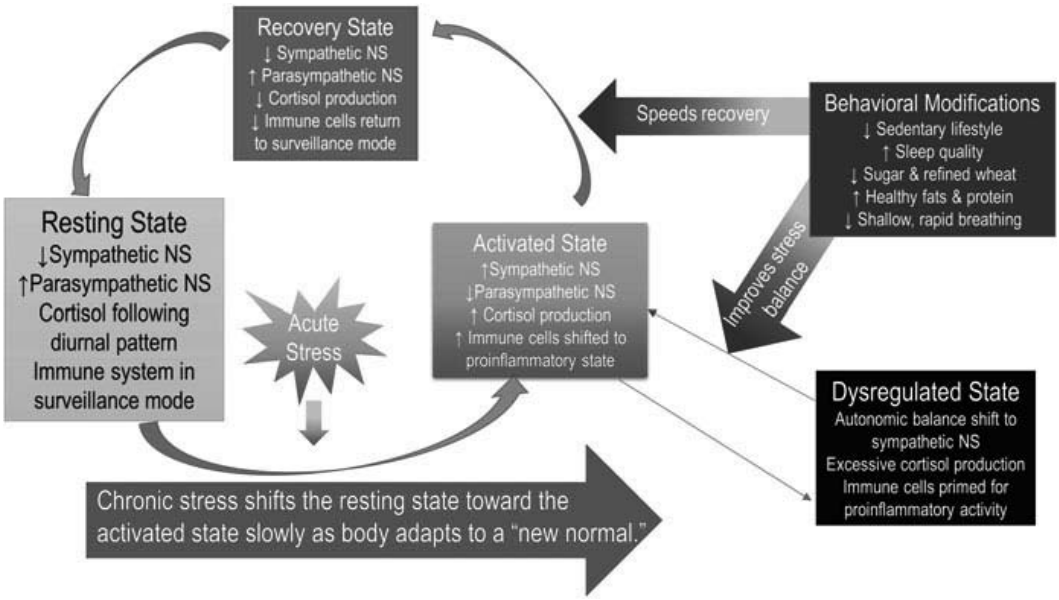

Fig. 2.1 Stress system activation and regulation. For non-stressed individuals, the body exists at rest for the majority of time. A stressful encounter drives the body into the activated state; the sympathetic nervous system and HPA axis activate to manage the stressor. The body moves into recovery and eventually returns to rest. This ability to move through activation and recovery fairly quickly demonstrates variability and less dysregulation (indicated by thicker blue arrows). However, in chronically stressed individual, their body spends less time at rest, slowly shifting their new baseline toward the activated state. If this process continues (along the red arrow), the individual's body adapts to a point where it becomes rigid and inflexible (indicated by the thin straight lines), maintaining a physiological state that is dysregulated until failure or disease development. However, via behavioral modification, an individual's system can reverse the dysregulation and approach the healthy, non-stressed stress system activation. Notably, the ability of an individual to make behavioral modifications is driven by the self, but the psychosocial environment (e.g., employment, leisure time) and sociocultural influences (e.g., public policy, government law) dramatically affect permanent lifestyle improvement. *NS* nervous system; *HPA* hypothalamic-pituitary-adrenal

reduces one of the body's most potent anti-inflammatory regulators, thereby driving physiological dysregulation.

Furthermore, we have explored the role psychosocial factors, such as loneliness, might play in this relationship. In our preliminary investigation [21], the interaction of *loneliness* and smoking status predicted changes in the immune cells' sensitivity to cortisol. Specifically, nonsmokers who reported greater loneliness had immune dysfunction mirroring that of smokers, suggesting that *loneliness in nonsmokers changed physiological functioning similarly to smoking cigarettes*. Since factors like smoking and loneliness have similar modulating effects on the immune system, we also investigated whether an individual's self-rated health might be a better predictor of immune dysregulation than simply smoking behavior.

Self-rated health (SRH) reliably predicts morbidity and mortality risk, especially among stress-related chronic conditions [22–24]. Outlined in a review, individuals who report higher SRH are more likely to participate in better health behaviors, report less psychological distress, and have greater socioeconomic status. Although these unique factors are associated with SRH, none of them explain all the variability observed within SRH [25]. Moreover, neither physician's rating of patient's disease nor clinical physical assessments reflect a patient's SRH or actual disease progression. This discrepancy highlights the disconnect between the current clinical practice and how the body is functioning. With this and the biopsychosocial lens in mind, we examined whether SRH was a better predictor of physiological functioning than a single health behavior: smoking. We also mirrored our smoking by loneliness interaction analysis by replacing smoking with SRH.

2.2 Methods

2.2.1 Participant Screening

We screened potential participants for medication use, current diagnosis or treatment for chronic diseases that influences neuroendocrine function or inflammatory outcomes, and lifetime tobacco smoking behavior. Twenty-four eligible smokers were brought into the lab immediately, while eligible never smokers were placed in a sample pool until they matched a smoker on sex, age, and body mass index (BMI). All sample characteristics are summarized in Table 2.1. Following a smoking participant session, we immediately contacted a matching never smoker to complete the lab session.

2.2.2 Laboratory Protocol

After a 12-h fast, participants arrived in the lab between 7 and 9 AM and provided their informed consent. Final eligibility requirements were reviewed with participants, including body temperature assessment, expired carbon monoxide levels to confirm smoking status (elevated in current smokers), and for females, screening for the presence of human chorionic gonadotropin (hCG) in their urine. Following eligibility confirmation, a blood sample was collected via venipuncture for immunoassay into lavender-topped blood collection tubes. Participants were provided with a variety of options for a pre-packaged breakfast and beverage. Sociodemographic and psychosocial questionnaires were completed after their meal and received compensation of $35 for their time.

Table 2.1 Average sample characteristics and change in inflammatory gene expression [mean ± SEM or number (%)] by smoking status and the overall sample

	Smokers ($n = 24$)	Never smokers ($n = 24$)	Overall ($n = 48$)
Age (years)	30.62 ± 1.64	30.50 ± 1.65	30.56 ± 1.15
BMI (kg/m^2)	26.41 ± 1.07	26.67 ± 1.05	26.54 ± 0.74
Sex (female)	10 (41.7%)	10 (41.7%)	20 (41.7%)
Race (white)	17 (70.8%)	13 (54.2%)	30 (62.5%)
Education complete			
Some college or less	9 (37.5%)	8 (33.3%)	17 (35.4%)
Bachelor's degree	13 (54.2%)	11 (45.8%)	24 (50.0%)
Graduate degree	2 (8.3%)	5 (20.8%)	7 (14.6%)
Pack-years	9.42 ± 1.88		
Nicotine addiction	3.34 ± 0.40		
Systolic BP (mmHg)	118.93 ± 1.84	116.22 ± 1.81	117.57 ± 1.29
Diastolic BP (mmHg)	71.46 ± 1.31	71.22 ± 1.91	71.34 ± 1.14
Heart rate (bpm)**	80.13 ± 1.73	71.29 ± 2.25	75.72 ± 1.55
Recent stressful life events*	2.79 ± 0.28	1.67 ± 0.33	2.23 ± 0.23
Childhood trauma*	44.25 ± 3.18	34.70 ± 1.79	39.57 ± 1.96
Depression**	12.79 ± 1.78	5.46 ± 0.81	9.13 ± 1.11
Perceived stress	20.00 ± 0.62	19.96 ± 0.36	19.98 ± 0.36
Anxiety**	30.21 ± 1.34	24.71 ± 0.72	27.46 ± 0.86
Sleep quality*	6.25 ± 0.60	4.37 ± 0.55	5.31 ± 0.43
Loneliness*	42.25 ± 2.38	35.33 ± 1.85	38.79 ± 1.57
Self-rated health*	58.33 ± 3.25	69.79 ± 3.98	64.06 ± 2.67
Cytokine mRNA expression			
ΔTNF-α*	8.09 ± 1.81	18.90 ± 4.07	13.50 ± 2.34
ΔIFN-γ*	3.31 ± 0.86	6.84 ± 1.42	5.04 ± 0.85
ΔIL-6	243.94 ± 157.49	273.14 ± 88.63	258.54 ± 89.42

Note. Group difference indicated: *$p < 0.05$; **$p < 0.01$
BMI body mass index; kg/m^2 kilograms per meter squared; *BP* blood pressure; *mmHg* millimeters of mercury; *bpm* beats per minute; Δ change from LPS gene expression to LPS+DEX gene expression; *TNF-*α tumor necrosis factor-alpha; *IFN-*γ interferon-gamma; *IL*-6 interleukin-6

2.2.3 Questionnaires

Participants self-reported their highest education level to estimate socioeconomic status, as education is considered less vulnerable to acute current economic conditions compared to income and job status [17]. In addition, they confirmed their sex and age as well as their smoking history for calculation of pack years as an estimate of lifetime tobacco exposure (i.e., number of packs smoked per day * number of years smoking). The Fagerström Test for Nicotine Dependence was used to assess smokers' dependence on nicotine [26]. Values were indicated as low (1–2), low to

moderate (3–4), moderate (5–7), and high (8+) levels of dependence; higher values indicate greater dependence.

Primary predictors were assessed via the following measurements. The UCLA Loneliness Scale was used to measure subjective feelings of loneliness and social isolation [27]. The scale is highly reliable and demonstrates good construct and convergent validity [27]. Higher scores indicate more subjective loneliness. Self-rated health was captured via a single item "In general, you would say your health is": with a 5-point Likert scale (poor, fair, good, very good, excellent) from the Medical Outcomes Study short-form 36 (SF-36) [28]. Higher values indicate better self-rated health.

Secondary factors were measured via the following questionnaires. Depressive symptoms experienced within the past week were captured using the 20-item Center for Epidemiologic Studies Depression Scale (CES-D; [29]). It is a highly reliable and well-validated scale across many populations with a score of 16 established as a clinical cutoff indicating at risk for depression [30]. Values range from 0 to 60 with higher values indicating more depressive symptoms. Recent stressful life events encountered over the past 12 months were captured using a modified version of the Life Events Scale [31, 32]. Given the young adult to adult population, 14 life events focusing on interpersonal relationships and job-related issues were assessed. Participants had an option to provide up to three additional life events beyond the scope of events listed. Endorsed life events were summed, resulting in a range from 0 to 17. The Childhood Trauma Questionnaire (CTQ; [33]) was used to determine history and severity of five types of maltreatment during childhood: emotional abuse, physical abuse, sexual abuse, and emotional and physical neglect. It is a reliable scale with 4-month test–retest reliability and correlated well with structured interview-based rating of childhood abuse [33, 34]. The self-report measure uses a 5-point Likert scale with higher scores indicating greater exposure to childhood trauma. Sleep quality was assessed via the Pittsburgh Sleep Quality Index (PSQI), a well-validated and reliable measure of sleep with a cutoff suggesting clinical sleep disturbances [35]. Higher values indicate poorer quality sleep.

2.2.4 Glucocorticoid Receptor Sensitivity Assay

A modified version of the immunoassay previously reported to detect glucocorticoid receptor sensitivity was used [36]. Whole blood was diluted with phosphate-buffered saline (PBS) and exposed to one of the following treatments: no treatment (PBS), 100 nM dexamethasone (DEX), 1 ng/mL lipopolysaccharide (LPS), and DEX+LPS for 2 h at 37 °C with 5% CO_2. Following incubation, white blood cells were isolated, washed, and lysed to harvest cytokine mRNA via the PerfectPure RNA blood kit (5 PRIME, Gaithersburg, MD). Cytokine (IL-6, TNF-α, and IFN-γ) mRNA was quantified with real-time PCR, and each participant's data were normalized to their control treated value. For more specific details, please see our description in a previous publication [20].

2.2.5 Data Analysis

To examine glucocorticoid receptor sensitivity, we calculated the change in mRNA expression from LPS-treated immune cells to LPS+DEX-treated immune cells, resulting in positive change scores as all participants' immune cells were at least minimally sensitive to DEX. Separate hierarchical linear regressions were used to examine smoking status or self-rated health interactive effects with loneliness on the DEX suppression change score.

2.3 Results

Participants ($n = 48$) were 30.6 ± 1.2 years old, overweight (BMI $= 26.5 \pm 0.7\,\text{kg/m}^2$), and primarily identified as White (62.5%) and had completed a college degree (64.6%). In addition, 20 participants were female (41.7%). Smokers averaged 6.6 ± 1.4 years since starting smoking, and tobacco history ranged from 1–40 pack years with an average of 9.4 ± 1.9. Smokers were low to moderately dependent on nicotine (Fagerström score $= 3.3 \pm 0.4$). Compared to never smokers, smokers reported more depressive symptoms, higher number of childhood traumatic experiences and recent stressful life events, and poorer sleep and had an elevated heart rate ($t\ s(46) > -2.58, p\ s < 0.05$). In addition, all expected zero-order relationships among psychosocial variables existed (see Table 2.2). Critical to the primary predictors, better self-rated health was associated with never smoking ($r = -0.31, p < 0.05$).

Using hierarchical linear regression controlling for recent negative life events and childhood traumatic experiences, loneliness interacted with SRH to predict a significant change in TNF-α gene expression ($p = 0.002$), mirroring our previous finding with the interaction between loneliness and smoking [21]. Specifically, among those with higher SRH, as loneliness increased, the change in inflammatory gene expression in between LPS and DEX + LPS was smaller. However, there was no relationship between loneliness and immune function among those with poorer SRH (see Table 2.3 and Fig. 2.2). Importantly, the overall model including self-rated health explained more of the variance in the change in inflammatory gene expression in between LPS and DEX + LPS compared to smoking status, $R^2 = 0.26$ and $R^2 = 0.21$, respectively. For the change in IFN-γ and IL-6 gene expression, the patterns with smoking and SRH interacting with loneliness were similar but did not reach statistical significance.

Table 2.2 Summary of all zero-order correlations among study variables

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1. Age (years)	–	0.16	0.24	0.08	0.63**	0.26	−0.21	−0.06	−0.28	−0.15	−0.06	0.01	−0.15	0.03	0.09	−0.16	−0.02
2. BMI (kg/m^2)		–	−0.15	−0.06	0.20	0.00	0.01	0.19	−0.26	−0.21	−0.24	−0.03	−0.21	0.18	−0.01	−0.15	0.01
3. Gender (female)			–	0.04	0.07	−0.35	−0.25	−0.26	0.08	0.02	0.09	0.00	0.18	−0.04	0.06	0.08	0.07
4. Race (white)				–	−0.05	0.02	0.06	−0.16	−0.03	0.01	−0.02	0.17	−0.04	−0.05	0.17	0.16	0.19
5. Pack-years[a]					–	0.15	0.19	0.27	−0.21	0.07	0.28	N/A	−0.30	0.10	0.28	−0.16	−0.07
6. Nicotine addiction[a]						–	−0.10	0.01	−0.39	−0.30	−0.38	N/A	−0.35	0.19	0.09	−0.12	−0.20
7. Stressful life events							–	0.18	0.28	0.31*	0.14	0.36*	0.12	−0.11	−0.11	0.05	0.20
8. Childhood trauma								–	0.46**	0.40**	0.48**	0.36*	0.35	−0.37	−0.14	−0.15	−0.17
9. Depression									–	0.82**	0.65**	0.48**	0.75	−0.46	−0.12	−0.11	0.21
10. Anxiety										–	0.64**	0.47**	0.62**	−0.41**	0.03	0.01	0.20
11. Sleep quality											–	0.32**	0.42**	−0.41**	0.03	0.01	0.20
12. Smoker (yes)												–	0.32**	−0.31**	−0.34**	−0.31**	−0.02
13. Loneliness													–	0.50**	−0.22	−0.11	0.03
14. Self-rated health														–	0.14	0.04	−0.03
15. ΔTNF-α															–	0.67**	0.43**
16. ΔIFN-γ																–	0.37*
17. ΔIL-6																	–

Note. $N = 48$

BMI body mass index; kg/m^2 kilograms per meter squared; *mRNA* messenger ribonucleic acid; Δ change from LPS mRNA to LPS+DEX mRNA; *TNF*-α tumor necrosis factor-alpha; *IFN*-γ interferon-gamma; *IL*-6 interleukin-6

*$p < 0.05$; **$p < 0.01$

[a]Indicates correlations with only smokers $n = 24$

Table 2.3 Summary of hierarchical linear regressions examining the interaction between smoking status and loneliness (left) and self-rated health and loneliness (right) on the change in TNFα gene expression from LPS to LPS + DEX

Predictor	b	SE	R^2	ΔR^2	Predictor	b	SE	R^2	ΔR^2
Stage 1			0.03		Stage 1			0.03	
(Intercept)	21.017**	7.701			(Intercept)	21.017**	7.701		
SLEs	−0.860	1.496			SLEs	−0.860	1.496		
CT	−0.154	0.180			CT	−0.154	0.180		
Stage 2			0.12	0.09	Stage 2			0.08	0.05
(Intercept)	26.219*	9.916			(Intercept)	19.508	18.922		
SLEs	0.032	1.533			SLEs	−0.679	1.492		
CT	0.009	0.192			CT	−0.033	0.196		
Loneliness	−0.243	0.233			Loneliness	−0.266	0.253		
Smoking	−8.364	5.341			SRH	0.101	0.157		
Stage 3			0.21†	0.09*	Stage 3			0.26*	0.18**
(Intercept)	8.340	8.370			(Intercept)	11.337	7.715		
SLEs	0.337	1.481			SLEs	−0.619	1.352		
CT	0.053	0.1852			CT	−0.003	0.178		
Loneliness	−0.385	0.234			Loneliness	−0.453†	0.237		
Smoking	−7.920	5.138			SRH	0.119	0.143		
Loneliness X	0.967*	0.458			Loneliness X	−0.034**	0.011		
Smoking					SRH				

Note. $N = 48$. The model with SRH interacting with loneliness predicts ∼26% of the changes in TNF-α gene expression, while the model with smoking status interacting with loneliness predicts ∼21% of the changes in TNF-α gene expression

DEX dexamethasone; *SLEs* recent stressful life events; *CT* childhood trauma; *SRH* self-rated health; b unstandardized regression weight; ΔR^2 change in R^2 from prior stage

$^{\dagger}p < 0.10$; $^{*}p < 0.05$; $^{**}p < 0.01$

2.4 Discussion

Self-rated health (SRH) is a better predictor of psychological health and neuroendocrine to immune communication than smoking. Our data corroborate previously published data [24, 25, 37, 38] as SRH was more strongly related to depressive symptoms and loneliness compared with smoking status. SRH did interact with loneliness to predict the anti-inflammatory effect of glucocorticoids on immune cells, mirroring smoking status, and explained more of the variance between individuals' immune cell function. However, when examining the zero-order correlation, SRH did not predict physiological functioning, such as heart rate or immune function, like smoking status. This inconsistency appears to reinforce that SRH is a proxy for something greater than just individual health behaviors. Could SRH be estimating the "power" of thinking one is healthy or unhealthy?

Smoking tobacco cigarettes enables the absorption of nicotine, a potent physiological modulator. Nicotine is a sympathomimetic [39]; its effects on the body mimic that of the sympathetic nervous system. For example, smokers often have an

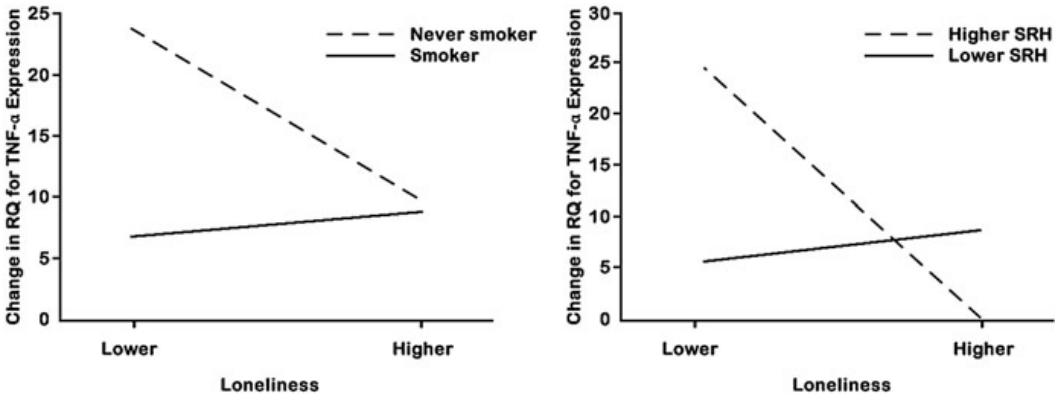

Fig. 2.2 The moderating effects of smoking (left) or self-rated health (SRH) (right) on the relationship between loneliness and change in TNF-α gene expression from LPS to LPS + DEX. On the left, the moderating effect of smoking on the relationship between loneliness and change in tumor necrosis factor-alpha (ΔTNF-α) gene expression. The line representing the never smoker group suggests that as loneliness increases, the change in TNF-α gene expression diminishes ($b = -0.878, t(41) = -2.34, p = 0.02$). On the right, the interactive effect of self-rated health (SRH) and loneliness on ΔTNF-α gene expression. The line representing higher SRH levels suggests that as loneliness increases, the change in TNF-α gene expression diminishes ($b = -1.06, t(47) = -2.89, p < 0.01$). Both analyses controlled for recent stressful life events and childhood trauma exposure. The solid lines representing smoking group (left) or lower SRH levels (right) do not significantly differ from zero, indicating there is no relationship between loneliness and the change in TNF-α gene expression. IFN-γ and IL-6 results followed the same pattern for both analyses; however, the interaction did not reach statistical significance

elevated resting heart rate [40, 41], suggesting that repetitive nicotine use shifts the autonomic nervous system into a state of imbalance like sympathetic dominance, creating dysregulation within the cardiovascular system. Cigarette smoking has also been linked to alterations in HPA activity compared to nonsmokers [42–46]. Finally, nicotine can directly communicate with immune cells via the alpha7 nicotinic acetylcholine receptor (α7 nAChR) [47, 48]. When stimulated by nicotine, these receptors diminish the inflammatory response [49]. Thus, a pharmacological factor like smoking tobacco can still be more related to health biomarkers than a global health measure, SRH. These results add to the difficulty of understanding the complex construct of health.

2.4.1 Why Loneliness?

Humans are social beings, and this desire for connection can be a motivator of behavior [50]. Throughout evolution, likelihood of survival increased when humans were part of a network that was invested in their welfare and cared about their well-being [51]. Over time, this ultimately led to a fundamental need to form close and caring bonds with other people [52]. Failure to fulfill this need may be detrimental to homeostasis and challenge our stress systems, resulting in chronic physiological activation.

Loneliness has a substantial link to stress and physiological dysregulation on par with the adverse effects of obesity and inactivity [53]. Moreover, loneliness has been associated with premature death especially when comorbid with depression [54], mirroring accelerated death observed in tobacco smokers [55]. However, little research investigates the mechanism of physiological dysregulation prior to confounding factors like aging or major stressful life events (e.g., natural disaster or chronic disease diagnosis) [15, 56–60]. Thus, our data showing that, similar to smoking, having lower SRH and elevated loneliness alters the communication between the neuroendocrine and immune systems and should give pause to clinicians and the general population. Moreover, future health studies should continue this line of research and collect data on psychosocial factors as well as the traditional health behaviors and SRH question.

2.4.2 Importance of an Acute to Chronic Stress Model in Humans

Chronic stress and physiological dysregulation are linked to disease pathogenesis and mortality [1]. Evidence points to faulty neuroendocrine regulation of the immune system [12, 61]. Yet our understanding about how or when acute stress activation transitions to chronic stress dysregulation is poor. Psychological stress is difficult to investigate because perception, including coping skills and life experiences, plays such a dominant role in the physiological response. Our previous reports [20, 21] combined with this data suggests that tobacco smoking may provide an avenue to observe early dysregulation as it develops. Further, glucocorticoid sensitivity appears to be similarly affected by pharmacological and psychosocial stressors. Overall, these findings may support the theory that stress activation, regardless of source, ultimately ends up challenging our physiology via the same pathways.

If we discover how physiological systems begin to lose variability or become dysregulated, then we can focus on ways to halt or slow this change. A system's ability to vary in its functionality is related to its ability to adapt and successfully manage the situation. This general rule applies to most living organisms as well as physical systems in nature [9]. Hence, discovering a human model to investigate the loss of physiological variability could yield novel ways to inhibit, slow, or repair the physiological dysregulation.

The current literature examining stress and physiological dysfunction lacks a good human model. Chronic stress is pervasive and unpredictable, making it difficult to methodically examine the development of physiological dysregulation. Animal models can provide great insight into human physiology, but they have limitations including direct application of face valid acute or chronic stressors. Specifically, psychological and psychosocial stress is difficult to create when working with rodents, and efforts to do so often incorporate some form of a physical stressor.

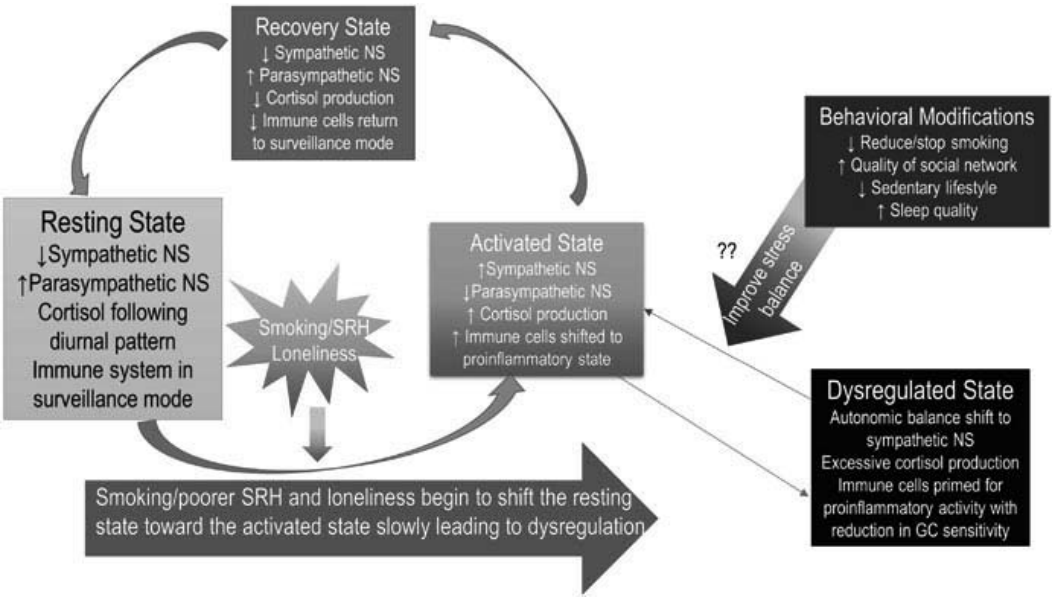

Fig. 2.3 Current study data and stress system activation and regulation. Displaying our findings in the context of the model described in Fig. 2.1, chronic stress as indexed by tobacco smoking, self-rated health (SRH), or loneliness begins to shift the individual's physiology toward the dysregulated state, which was measured by immune cells' sensitivity to lipopolysaccharide (LPS) and change in tumor necrosis factor-alpha (TNF-α gene expression from LPS to LPS+DEX exposure. It is hypothesized (indicated by ??) that reduction in smoking or a successful quit attempt would reverse the observed immune dysregulation. In addition, lowering loneliness via enhancing social connectedness and increasing SRH would also result in reversal of the insensitive immune cells. *NS* nervous system; *DEX* dexamethasone

Cigarette smoking behavior represents a naturally occurring phenomenon to examine initial physiological changes. Physiological dysfunction observed in smokers does not start on day one of smoking initiation; reduction in system flexibility, or dysregulation, occurs over years of smoking behavior, allowing the observation of the transition from acute stress to chronic stress. This slow progression makes smokers an ideal group with which to investigate how these changes occur and what factors outside of smoking might hasten or delay dysregulation. In addition, physiological recovery from chronic stress might be exhibited following smoking cessation in former smokers, as highlighted in Fig. 2.3.

2.5 Conclusions

Health is "complicated." As clinicians and researchers, we must focus on the physical and mental health with a complexity lens that appreciates all aspects of each individual [62]. Based on our data, "healthy smoker" is an oxymoron since compared to never smokers, smokers had reduced glucocorticoid sensitivity prior to clinical disease diagnosis. When does the dysregulation start? It is uncertain

as the variability among our smokers' tobacco history was limited and we could not examine relationships between the immune outcomes and tobacco exposure characteristics; thus, more research is necessary. However, healthiness is not as simple as one behavior or one label, like "smoker." Our data also supports the potent role of perceived factors like SRH and loneliness, a psychosocial stressor, among never smokers on the balance between neuroendocrine and immune communication. Taken together, stress influences neuroendocrine system's anti-inflammatory effect on the immune system, which may be the beginning of chronic disease development.

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The Journey

Dr. Bennett's Journey: "Complexity from Theory to Practice"

I was "systems" focused long before I could fathom what that meant. Being raised in a traditional patriarchal household and one of five kids with only one brother, I started to see systems—biases, symbiosis, imbalances, etc.—at a young age. I rarely took my parents' responses at face value and pushed to understand more. During my undergraduate training, I decided that a single major wasn't going to prepare me to address current health problems. So, I added psychology to my premedical biology training—I began to learn about young new fields, like health psychology and psychoneuroimmunology, that examine the complex interactions of multiple systems involving inter- and intra-level phenomena, also labeled as "cell to society" or "neuron to neighborhood." After a series of complex psychosocial events in my life (i.e., getting married and the birth of my son), I attended graduate school at Penn State and earned my PhD in Biobehavioral Health. There, my training included the reading of Don Ford's *Humans as Self-constructing Living Systems* [63], giving words and conceptualization of how the human and its behavior are the product of multiple physiological systems interacting with the environment, which has multiple levels and systems that influence the human's behavioral choices—a never ending cycle.

Narrowing my focus, I developed a greater appreciation for connections between the neuroendocrine and immune systems as well as how psychological and social factors lead to changes in the stress response. Stress allows the outside world into our body whether it is psychological, social, physical, or pharmacological, leading to an evolutionarily engrained and relatively predictable response that supports survival. Today, the stress systems are activated too often and for too long, resulting in negative adaptations that are linked and may drive development of chronic illness—physical and mental illnesses. Here I am now trying to develop a way

to compare psychological or subjective stress to an objective stress like nicotine exposure via tobacco use—thinking it will give us a glimpse into how acute stress transitions into chronic stress. If I'm on to something, the complexity surrounding stress and health will unfold as my career continues.

Take-Home Message

- Stress drives development and progression of today's most prevalent diseases.
- Little is known about the transition from the healthy acute stress response to the dysregulated chronic stress response.
- Loneliness, a psychosocial stressor, appears to be just as detrimental on immune function as tobacco smoking, a pharmacological stressor.
- Self-rated health, a sum greater than its parts, is a better predictor than smoking status, a single negative health behavior.
- Health must be viewed as the culmination of the body interacting with its environment—external (e.g., social relationships, socioeconomic status, etc.) and internal (e.g., communication between the nervous and immune systems) factors.

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