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Exploring links between pathogen avoidance motivation, COVID-19 case counts, and immune function

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Abstract

Objectives: The selection pressures exerted by pathogens have played important roles in shaping the biology and behavior of animals, including humans. Immune systems recognize and respond to cues of infection or damage by coordinating cellular, humoral, and metabolic shifts that promote recovery. Moreover, animals also possess a repertoire of behavioral tools to help combat the threat of pathogens, often referred to as the behavioral immune system. Recently, researchers have begun to examine how cognitive, affective, and behavioral disease avoidance mechanisms interact with the biological immune system.

Methods: The present study explored relationships among individual differences in behavioral immune system activity (e.g., pathogen disgust), shifts in SARS-CoV-2 infection risk (i.e., 7-day case averages), and immune function in a community cohort from McLennan County, Texas, USA ($n = 387$).

Results: Levels of disease concern were not consistently associated with immune markers. However, serum levels of IFN-γ, TNF-α, IL-2, and IL-8, as well as serum killing ability of *Escherichia coli*, each varied with case counts. Additional analyses found that case counts also predicted changes in stress physiology, but not subjective measures of distress. However, follow-up mediation models did not provide evidence that relationships between case counts and immunological outcomes were mediated through levels of stress.

Conclusions: The present project provides initial evidence that markers of immune function may be sensitive to changes in infection risk during the COVID-19 pandemic. This adds to the growing body of research finding relationships among behavioral and biological pathogen management mechanisms.

1 | INTRODUCTION

Pathogens have been a constant threat throughout the evolutionary history of eukaryotic organisms (Arkwright & David, 2005; Martin & Martin-Granel, 2006; Wolfe et al., 2007). Given the negative impact of infection on survival and reproduction, the potent selection pressures exerted by viruses, bacteria, fungi, and parasites have played important roles in shaping the biology and behavior of animals, including humans (Cagliani &

Sironi, 2013; Fumagalli et al., 2009; Shattuck & Muehlenbein, 2015). Organisms' immune systems have evolved to recognize and respond to cues of infection or bodily damage by coordinating cellular, humoral, and metabolic shifts that promote recovery (Schenten & Medzhitov, 2011; Sebina & Pepper, 2018; Wang et al., 2019). Moreover, animals also possess a repertoire of behavioral tools to help combat the threat of pathogens (Hart, 1988, 1990; Sarabian et al., 2018). These behaviors include grooming (Akinyi et al., 2013), foraging away from areas with high pathogen density (Weinstein et al., 2018), and avoiding sick conspecifics (Behringer et al., 2006), among many others. Such behavioral strategies for disease avoidance, and the cognitive and affective processes underlying them, are often referred to as the "behavioral immune system" (Schaller, 2011; Schaller & Park, 2011).

Research on the behavioral immune system finds that individuals are acutely attuned to, and motivated to avoid, cues of illness or infection in the environment. For example, stimuli associated with sickness or infection risk (e.g., vomit, contaminated food, disease vectors) often elicit the emotion of disgust (Curtis et al., 2004), which promotes avoidance of these items and the desire to engage in hygienic behaviors (Deacon & Olatunji, 2007; Olatunji et al., 2014; Porzig-Drummond et al., 2009). People are also capable of detecting sick conspecifics based on facial cues (Axelsson et al., 2017), scent (Olsson et al., 2014), and even gait (Sundelin et al., 2015). While cultural norms surrounding disease avoidance and management strategies differ around the world, the fundamental drive to detect and avoid sources of infection appears to be a near universal human phenomenon (Schaller & Murray, 2011).

More recently, researchers have begun to examine how cognitive, affective, and behavioral disease avoidance mechanisms interact with the biological immune system (Ackerman et al., 2018; Bradshaw & Gassen, 2021; Cepon-Robins et al., 2021; Gassen et al., 2018; Stevenson et al., 2012). While relationships between pathogen avoidance psychology and immune function may take various forms (Lopes, 2017), research to date suggests that levels of certain immune markers change in response to disease cues. For example, some studies have shown that just viewing images of disease cues is capable of eliciting an immune response. Stevenson and colleagues (Stevenson et al., 2012) found that showing participants images intended to evoke disgust resulted in elevated oral immune markers. Another study found that more IL-6 was produced by individuals' white blood cells in response to stimulation with lipopolysaccharide after exposure to pictures depicting people with symptoms of infectious disease (compared with pictures of firearms) (Schaller et al., 2010). Murine research has similarly demonstrated that exposure to just odors of sick (but not infectious) cage mates leads to increased production of illness-related volatile compounds in the urine of healthy mice (Gervasi et al., 2018). Taken together, these findings provide initial evidence that recognition of disease cues in the environment, even without an actual risk of infection, can be associated with immunological indicators. Although speculative, it is possible that preemptive immune activation prepares the body in anticipation of infection, or even itself plays a role in promoting disease avoidance behaviors (Gassen & Hill, 2019; Kelley et al., 2003; Muscatell & Inagaki, 2021).

Previous research has also linked variation in inflammatory activity to individual differences in pathogen avoidance motivation. Due to a combination of sociocultural, ecological, genetic, and developmental factors (Tybur et al., 2018), some people are especially attuned to disease cues from others and the environment. These individuals with high trait pathogen avoidance motivation are also more likely to engage in hygienic and disease prevention behaviors (Shook et al., 2020; Stangier et al., 2021) as well as exhibit heightened preferences for cues of health in others (Welling et al., 2007). In other words, people with high pathogen avoidance motivation are both especially sensitive to disease cues and more likely to take steps to mitigate infection risk. Recent research finds that perhaps by decreasing exposure to stimuli connoting infection risk or outright reducing infection frequency over time, high trait pathogen avoidance motivation may cooccur with downregulation of basal inflammatory activity. For example, one study found that college students with higher trait germ aversion, for whom disease concern is chronically elevated, tended to have lower baseline levels of inflammation than those less germ averse (Gassen et al., 2018). A more recent study of subsistence-based Ecuadorian Shuar communities similarly found that disgust sensitivity was negatively related to levels of inflammation, and to a lesser extent, macroparasite infection (Cepon-Robins et al., 2021).

1.1 | Current research

While the body of research on relationships between pathogen avoidance psychology and the immune system expands, many questions remain unanswered. First, in addition to markers of inflammation, does perception of, or general sensitivity to, disease cues influence functional aspects of immunity? That is, changes to inflammation in response to acute exposure to disease cues or chronic pathogen concern (i.e., individual differences in pathogen avoidance motivation) could just reflect general arousal

or distress (Marsland et al., 2017). Findings that exposure to disease cues in the environment elicits functional changes in immunity, for instance, would lend additional support to the hypothesis that immune activation in this context serves to prepare the body for infection (i.e., rather than just arousal). Second, how is detection of disease cues transduced into shifts in immune function? One possibility, among many others, is that perception of disease cues elicits a stress response that, in turn, influences immune responses. Acute and chronic stress appear to have disparate effects on immune function, with the former often found to be selectively stimulatory and the latter largely inhibitory (Segerstrom & Miller, 2004). The extent to which stress influences immune function also depends on the intensity and type of stressor, and the type of immune response in question (Dhabhar, 2014). Mechanistically, both the activities of the autonomic nervous system and hypothalamic–pituitary–adrenal (HPA) axis regulate immune function, and in turn, cytokines and other immunological signaling proteins have been shown to modulate stress responses (Goshen & Yirmiya, 2009; Kenney & Ganta, 2014; Mueller et al., 2022). Accordingly, changes in immune markers might be preceded or accompanied by changes in activities of the autonomic nervous system and HPA axis. Third, are natural fluctuations in pathogen prevalence and infection risk sufficient to elicit an immune response? Previous studies have found that acute exposure to visual disease cues in the laboratory can influence immunity (Schaller et al., 2010; Stevenson et al., 2012), but it has yet to be tested whether immune responses map onto natural changes in actual infection risk, such as 7-day average case counts during the COVID-19 pandemic. Finally, do individual differences in pathogen avoidance motivation (e.g., germ aversion, disgust) interact with changes in infection risk to predict aspects of immune function?

In the current research, we explored relationships among individual differences in pathogen avoidance motivation, fluctuations in SARS-CoV-2 infection risk (indicated by changes in 7-day moving average COVID-19 case counts), stress physiology markers (i.e., resting blood pressure, heart rate, and serum cortisol level), mood and subjective distress, and serum levels of multiple cytokines: interleukin (IL)-2, IL-6, IL-8, IL-10, interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α). We also assayed the capacity of participants' serum to inhibit growth of *Escherichia coli* ex vivo—which is mediated via activities of the complement system, natural antibodies, antimicrobial peptides, and other humoral components—as a functional innate immune measure (French & Neuman-Lee, 2012; McQuillen et al., 1994; Prall et al., 2017). Using these data, we examined (a) whether relationships between 7-day COVID-19 case averages in the United States and immune makers emerged, (b) whether immune function was related to individual differences in pathogen avoidance motivation (i.e., disgust sensitivity, germ aversion, and perceived infectability), (c) whether interactions between case counts and individual differences in pathogen avoidance motivation predicted immune function, and (d) whether relationships between COVID-19 cases, individual differences in pathogen avoidance motivation, and immune function were accompanied by changes in stress physiology.

The current research was largely exploratory, aside from the general prediction that relationships between COVID-19 case counts, pathogen avoidance motivation variables, and immune function would emerge. However, based on the results of previous studies (Cepon-Robins et al., 2021; Gassen et al., 2018), we did predict that germ aversion and pathogen disgust would be negatively related to inflammatory markers (specifically, IL-6, IL-8, and TNF-α). Moreover, consistent with research finding that disease cues are capable of eliciting an immune response (Stevenson et al., 2012), we also predicted that COVID-19 case counts would be positively related to serum *E. coli* killing and cytokine levels.

2 | MATERIALS AND METHODS

2.1 | Procedure

Data used in the current research were collected as part of a longitudinal cohort study, the Waco COVID Survey. The Waco COVID Survey was a SARS-CoV-2 serology surveillance project of asymptomatic individuals living in McLennan County, Texas, USA, between July and November 2020. Detailed information about the project, demographic characteristics of the sample and county, and descriptive statistics for survey measures are published elsewhere (Gassen et al., 2021). The Waco COVID survey was approved by the Waco-McLennan County Public Health District as a public health surveillance activity, and as such, met the exclusion requirements for institutional review board approval at 45 CFR 46.102 (e) and (l) for Baylor University researchers, staff, and volunteers. The institutional review board of Ascension Providence Hospital and Medical Center of Waco, TX, approved participation of Waco Family Medicine researchers, staff, and volunteers. All participants provided informed consent prior to participation.

Data analyzed for the current study were included as part of the initial intake survey and first laboratory visit; 387 participants complete both arms of data collection

(243 female; M_{age} = 44.43, SD_{age} = 14.28). The intake survey was completed the week preceding the laboratory visit and included a number of demographic, personality, health, and risk perception questions. For the laboratory visit, participants arrived at the Madison Cooper Community Clinic of Waco Family Medicine where routine anthropometric and physiological measures were collected, followed by an intravenous blood draw and dried blood spot collection.

2.2 | Materials

2.2.1 | Pathogen disgust and perceived vulnerability to disease

To assess individual differences in participants' pathogen avoidance motivation, participants completed three measures adapted from previously validated scales. First, participants indicated how disgusting they found three scenarios from the Pathogen Disgust subscale of the Three Domains of Disgust Scale (Olatunji et al., 2012; Tybur et al., 2009) using a 7-point scale (1 = not at all disgusting, 7 = extremely disgusting): (a) "Sitting next to someone who has red sores on their arm"; (b) "Seeing some mold on old leftovers in your refrigerator"; and (c) "Seeing a cockroach run across the floor." Responses were combined into a mean composite score (Cronbach's α = .64).

The final two constructs measured were germ aversion and perceived infectability, each assessed using three items taken from the Perceived Vulnerability to Disease scale (Duncan et al., 2009) responded to on a 7-point scales (1 = strongly disagree, 7 = strongly agree). Germ aversion was measured by responses to the statements: (a) "It does not make me anxious to be around sick people" (reverse-scored); (b) "I prefer to wash my hands pretty soon after shaking someone's hand"; and (c) "It really bothers me when people sneeze without covering their mouths." Perceived infectability was measured by responses to the statements: (a) "I am more likely than the people around me to catch an infectious disease"; (b) "In general, I am very susceptible to colds, flu, and other infectious diseases"; and (c) "I am unlikely to catch cold, flu, or other illnesses, even if it is going around" (reverse-scored). Responses were combined into mean composite scores (germ aversion: Cronbach's α = .41; perceived infectability: Cronbach's α = .73).

2.2.2 | Infection risk

To examine differences between rates of SARS-CoV-2 transmission in the United States at the time of individuals' study participation dates, data on 7-day moving average case counts were accessed from the Center for Disease Control and Prevention website (https://covid.cdc.gov/covid-data-tracker/#datatracker-home). We elected to use country-wide case counts in our analyses because they correlate strongly with Texas state case counts (r = 0.92 for rolling average during study period) and tend to dominate public attention (Anwar et al., 2020; Gozzi et al., 2020; Krawczyk et al., 2021).

2.2.3 | Blood pressure and heart rate

After resting in a sitting position for several minutes, participants' blood pressure and heart rate were measured three times using automatic upper arm blood pressure monitors (Omron HEM-907XL and BP785N). Averages of the triplicates for each systolic blood pressure, diastolic blood pressure, and heart rate were analyzed.

2.2.4 | Subjective mood and distress

To assess mood/affect, participants completed the Positive and Negative Affect Schedule (Watson et al., 1988), which reflected positive and negative affect in the week preceding participation (positive: α = .90, negative: α = .88). Participants also responded to two additional items using 7-point scales that measured helplessness ("COVID-19 makes me feel helpless.") and feelings of depression ("COVID-19 makes me depressed.") related to COVID-19.

2.2.5 | Cytokine assays

For serum isolation, whole blood was collected into 8 ml BD vacutainer tubes and left at room temperature for 30 min. Tubes were then centrifuged at 1000 *g* for 10 min. Sera were transferred into microcentrifuge tubes that were stored at −80°C until assayed for levels of interleukin IL-2, IL-6, IL-8, IL-10, IFN-γ, and TNF-α using an electrochemiluminescence multiplexing assay read on a MESO QuickPlex SQ 120 plate reader (Meso Scale Discovery, Rockville, MD). Intraassay coefficients of variation (CVs) were 2.98% (IFN-γ), 7.73% (IL-10), 5.79% (IL-6), 2.68% (IL-8), 4.18% (TNF-α), and 19.36% (IL-2).[1] Interassay CVs were 10.53% (IFN-γ), 8.69% (IL-10), 7.95% (IL-6), 8.36% (IL-8), 13.67% (TNF-α), and 8.22% (IL-2). In addition to levels of each cytokine, we also computed the ratio of IFN-γ to IL-10 to reflect T-helper cell 1 (Th1) and Th2 balance (Kidd, 2003), with higher values representing greater skew toward Th1 responses (i.e., cellular, inflammatory) over Th2 responses (i.e., humoral).

2.2.6 | Cortisol assays

Serum samples were assayed for levels of cortisol following manufacturer instructions (ALPCO, Salem, NH). Average intra-assay CV was 4.16%; the inter-assay CV was 6.56%.

2.2.7 | Serum bacterial killing assay

Bactericidal capacity of serum was assayed using *E. coli* ATCC #8739. Each lyophilized *E. coli* pellet containing approximately 10^7 colony-forming units per pellet was vortexed in 40 ml 10X sterile PBS (pH 7.4) that had been warmed for 30 min at 37°C and 95% humidity to produce a bacterial stock solution. 40 ml of CO_2 independent media was supplemented with 2.34 mg of L-glutamine. Participant samples were then diluted 1:25 with the media (200 µl total volume) and vortexed.

After 30 min of incubation, 1 ml of the bacterial stock solution was further diluted in 9 ml PBS and vortexed to produce a bacterial working solution; the working solution was kept cold on dry bath beads that were kept in a −20°C freezer prior to use. Next, 20 µl of the bacterial working solution was added to each participant sample (220 µl final volume) and vortexed. For the positive control, 20 µl of the working solution was added to 200 µl of CO_2 independent media. For the negative control, 20 µl PBS was added to 200 µl media.

All samples (including controls) were plated in triplicate onto trypticase soy agar plates. For each plate, 50 µl of bacteria mixed with sample or control was added and spread with a flame-sterilized bacteria spreader. Plates were then placed in an incubator at 37°C, 95% humidity, and atmospheric CO_2 levels for 16 h. Plates were then removed from the incubator and *E. coli* colonies were counted using a Protos 3 automated colony counter (Synbiosis, Cambridge, UK). Percent *E. coli* killing was calculated by dividing the average of the sample triplicates by the average of the positive control triplicates, subtracting this number from 1, and multiplying the difference by 100.

Average triplicate count CV was 15.21%. Note that this was calculated excluding samples for which two of the reads were 0 (indicating 100% *E. coli* killing). Aggregate CV values were also inflated by scale and the right-censored distribution of the data. For example, counts of 1, 0, and 2 for a given sample would yield a high CV at 81.65%, despite higher overall agreement on percent killing for each individual replicate (i.e., all >98% killing); a large portion of samples were at this high end of the range.

2.2.8 | Covariates

For all analyses, we controlled for a number of potential confounding variables, including age, sex, body mass index, time of sample collection, and whether or not the participant worked as a healthcare worker or first responder during the pandemic.

2.2.9 | Data analysis plan

All analyses were conducted using R statistical software (R Core Team, 2019) and Mplus statistical software (Muthén & Muthén, 1998). Code for data analysis is included as a supplementary file (SF2). Extreme outliers >5 SD above sample mean were rare (0.3%–1.3% for a given variable), and these data were excluded from analyses. For each model, dependent immune, stress physiology, and subjective stress variables were regressed on germ aversion, perceived infectability, pathogen disgust, 7-day case averages, and the aforementioned covariates. Given that germ aversion, perceived infectability, and pathogen disgust are related constructs and likely to be correlated, we checked variance inflation factor (VIF) statistics for all models. Using the conventional cut-off of 5 (Vatcheva et al., 2016), we determined that all VIF statistics were below the threshold indicating multicollinearity (specifically, all values were below 1.2).

Several follow-up models were tested. The first set of follow-up models examined interactions between the pathogen avoidance motivation variables and case counts. The second set of follow-up models tested whether the pathogen avoidance motivation predictors and case counts indirectly predicted immune outcomes via levels of stress. These models examined if measures of stress physiology and subjective distress mediated relationships among pathogen avoidance motivation, infection risk, and immune function.

Given the large number of dependent tests conducted across models, a harmonic mean *p* value analysis was conducted to account for familywise error rate using the *harmonicmeanp* package (Wilson, 2019). The harmonic mean *p*-value (HMP) presents a method for controlling false positive rate in exploratory research with dependent *p*-values while overcoming the shortcomings of methods that operate poorly under test dependency and/or are excessively conservative (e.g., Bonferroni corrections) (Wilson, 2019). The HMP analysis provides an updated significance cut-off based on the number of total tests, as well as an aggregate *p*-value for a combined set of hypothesis tests. Nonsignificant HMP values suggest that all constituent tests are nonsignificant, while significant HMP values indicate that one or more of the tests are

statistically significant. Including main effects and interactions, 84 tests were conducted to examine the effects of pathogen avoidance motivation and 7-day case averages on the target outcomes (see SF2 for full list). Tests were assigned equal weights for the HMP analysis, per convention (Wilson, 2019).

Data for the bacterial killing assay were right-censored, with 14.5% of samples reaching 100% killing. Accordingly, data were analyzed using censored regression (tobit model) with the *VGAM* package in R (Yee, 2020). Given the low levels of IL-2 that occur in healthy serum, 35.66% of samples fell below the lower limit of detection. Because these values were known to fall below the standard curve, they were treated as left-censored and IL-2 data were also analyzed using censored regression. All other cytokine data, as well as cortisol data, were positively skewed and analyzed using generalized linear models with gamma distributions and a log link function (Goldsmith et al., 2020; Hernandez-Trejo et al., 2020; Mitchell et al., 2015). Data for blood pressure and heart rate were normally distributed and analyzed using linear regression.

3 | RESULTS

3.1 | Immune measures

3.1.1 | Germ aversion

Descriptive statistics for immune variables are presented in Table 1. Unstandardized regression coefficients and standard errors for all models are presented in Tables 2 and 3. Exact p values for each parameter are included in a supplementary file (SF3). The HMP analysis suggests that the effects of germ aversion, collectively, are no longer statistically significant when correcting for multiple tests (harmonic mean $p = .22$, cut-off: $p = .01$). Accordingly, the results below should be interpreted with caution.

Results reveal that higher levels of germ aversion are associated with diminished serum *E. coli* killing ($b = -5.48$, $p = .006$). That is, the serum of individuals who reported that they are more concerned about pathogen exposure inhibit the growth of *E. coli* less than those who are less concerned. While the main effects of germ aversion on cytokine levels do not reach statistical significance, there is a significant interaction between germ aversion and 7-day case averages predicting levels of IFN-γ ($b = 0.02$, $p = .02$) (Figure 1). Unpacking this interaction at high (one standard deviation above mean) and low (one standard deviation below mean) levels of germ aversion reveals that for individuals with high germ aversion, case numbers are not statistically significantly related to levels of IFN-γ ($b = 0.003$, $p = .77$). In general, people with high germ aversion have low levels of IFN-γ regardless of case counts. However, for individuals with low germ aversion, higher case numbers predict decreases in IFN-γ to levels approaching those of participants with higher germ aversion ($b = -0.03$, $p = .001$). In other words, highly germ averse participants have low serum levels of IFN-γ regardless of case counts. However, individuals who were less germ averse have high serum IFN-γ levels when cases were low, with decreasing levels as COVID-19 cases became more numerous.

3.1.2 | Perceived infectability

Results of the HMP analysis reveal that the effects of perceived infectability are no longer statistically significant

TABLE 1 Descriptive statistics

Variable	*n*	*M*	*SD*	Min	Max
Bacterial killing (%)	387	55.38	36.79	−39.00	100.00
IFN-γ (pg/ml)	387	7.76	11.38	0.78	107.63
IL-10 (pg/ml)	387	0.36	1.02	0.01	17.31
IL-2 (pg/ml)	249	1.49	20.12	0.01	317.72
IL-6 (pg/ml)	386	2.35	24.56	0.05	478.26
IL-8 (pg/ml)	387	13.06	17.12	3.38	285.96
TNF-α (pg/ml)	387	1.88	0.76	0.64	5.90
Systolic BP (mm Hg)	387	127.04	17.35	87.00	194.00
Diastolic BP (mm Hg)	387	83.91	11.76	51.00	132.00
Pulse (bpm)	387	76.92	13.17	44.00	127.00
Cortisol (μg/dl)	378	7.32	3.33	0.91	22.36

Abbreviations: BP, blood pressure; IFN-γ, interferon gamma; IL, interleukin; TNF-α, tumor necrosis factor-alpha.

TABLE 2 Regression coefficients and standard errors for immune models

Dependent variables								
Predictors	**Bacterial killing**	**IFN-γ**	**IL-10**	**IFN-γ/IL-10 ratio**	**IL-2**	**IL-6**	**IL-8**	**TNF-α**
Germ aversion	−5.48 (1.98)**	−0.03 (0.04)	0.01 (0.04)	−0.01 (0.04)	−0.03 (0.02)	0.03 (0.10)	−0.02 (0.03)	−0.02 (0.02)
Perceived infectability	2.24 (1.77)	−0.03 (0.03)	0.11 (0.03)***	−0.10 (0.03)**	−0.03 (0.02)	−0.15 (0.09)	0.05 (0.03)	0.02 (0.02)
Pathogen disgust	−0.98 (1.74)	−0.01 (0.03)	0.01 (0.03)	0.01 (0.03)	−0.04 (0.02)	0.02 (0.09)	0.01 (0.03)	−0.002 (0.02)
7-Day case average	0.79 (0.39)*	−0.02 (0.01)*	−0.002 (0.01)	−0.01 (0.01)	0.02 (0.004)***	0.01 (0.02)	−0.03 (0.01)***	−0.02 (0.003)***
Interactions								
Germ aversion*Cases	0.08 (0.37)	0.02 (0.01)*	0.01 (0.01)	0.01 (0.01)	0.001 (0.005)	−0.02 (0.02)	−0.004 (0.01)	0.002 (0.003)
Perceived infectability*Cases	−0.63 (0.32)†	0.003 (0.01)	−0.002 (0.01)	0.004 (0.01)	−0.004 (0.004)	−0.02 (0.01)	−0.01 (0.01)	−0.002 (0.003)
Pathogen disgust*Cases	−0.59 (0.30)*	−0.001 (0.01)	−0.002 (0.01)	0.01 (0.01)	−0.004 (0.004)	−0.002 (0.01)	−0.002 (0.01)	0.004 (0.003)

Note: Shown here are unstandardized regression coefficients and standard errors (parentheses).
Abbreviations: IFN-γ, interferon gamma; IL, interleukin; TNF-α, tumor necrosis factor-alpha.
*$p < .05$; **$p < .01$; ***$p < .001$; †$p < .06$.

after adjusting for multiple tests (harmonic mean $p = .02$, cut-off: $p = .01$). Thus, these results should be interpreted with caution.

Higher levels of perceived infectability predict higher levels of IL-10 ($b = 0.11$, $p = .0009$), as well as a lower IFN-γ/IL-10 ratio ($b = -0.10$, $p = .004$). This may reflect a Th2 skew among individuals high in perceived infectability (relative to those lower in this characteristic). While no other main effects of perceived infectability are statistically significant, an interaction between this variable and cases predicting *E. coli* killing is marginally statistically significant ($b = -0.59$, $p = .06$). This interaction was unpacked at high and low levels of perceived infectability (Figure S1). Results reveal no relationship between 7-day case averages and bacterial killing for individuals high in perceived infectability ($b = -0.03$, $p = .96$). On the other hand, increases in case numbers are related to increased serum *E. coli* killing for those low in perceived infectability ($b = 1.49$, $p = .005$). These results suggest that the serum of individuals who perceive themselves to be highly vulnerable to infection had moderate ability to inhibit *E. coli* growth. Furthermore, among those who perceive themselves to be less vulnerable, *E. coli* killing is low when COVID-19 cases were low, but high when cases increased.

3.1.3 | Pathogen disgust

No main effects of pathogen disgust reach statistical significance. However, there is a statistically significant interaction between disgust and cases predicting *E. coli* killing ($b = -0.59$, $p = .049$) (Figure 2). The pattern of this interaction resembles that of the interaction with perceived infectability in 7-day case averages. Specifically, for those high in pathogen disgust sensitivity, case numbers are not related to bacterial killing ($b = 0.03$, $p = .96$). However, greater case numbers are associated with higher bacterial killing for individuals low in disgust sensitivity ($b = 1.56$, $p = .005$). Similar to the interaction involving perceived infectability and case counts, these results may indicate that individuals lower in pathogen concern (here, disgust sensitivity, specifically) are more sensitive to environmental fluctuations in infection risk than those higher in concern. That is, for individuals low in disgust, serum *E. coli* killing increases alongside case counts, but this is not found for those high in disgust. As with the effects for germ aversion and perceived infectability, the pooled effects of pathogen disgust are not statistically significant when adjusting for multiple tests using the HMP analysis (harmonic mean $p = .29$, cut-off: $p = .01$).

TABLE 3 Regression coefficients and standard errors for measures of stress physiology

	Dependent variables			
Predictors	**Systolic BP**	**Diastolic BP**	**Pulse**	**Cortisol**
Germ aversion	−0.07 (0.74)	−0.45 (0.54)	−0.16 (0.61)	−0.003 (0.02)
Perceived infectability	0.19 (0.66)	0.38 (0.49)	0.12 (0.55)	−0.01 (0.02)
Pathogen disgust	−0.64 (0.65)	−0.53 (0.48)	0.25 (0.54)	0.02 (0.02)
7-Day case average	0.07 (0.15)	0.23 (0.11)*	0.27 (0.12)*	−0.01 (0.004)*
Interactions				
Germ aversion*Cases	0.02 (0.14)	0.09 (0.10)	0.12 (0.11)	0.004 (0.004)
Perceived infectability*Cases	0.08 (0.12)	0.10 (0.09)	−0.09 (0.10)	−0.002 (0.003)
Pathogen disgust*Cases	−0.13 (0.11)	−0.07 (0.08)	−0.08 (0.09)	−0.003 (0.003)

Note: Shown here are unstandardized regression coefficients and standard errors (parentheses).
Abbreviation: BP, blood pressure.
*$p < .05$.

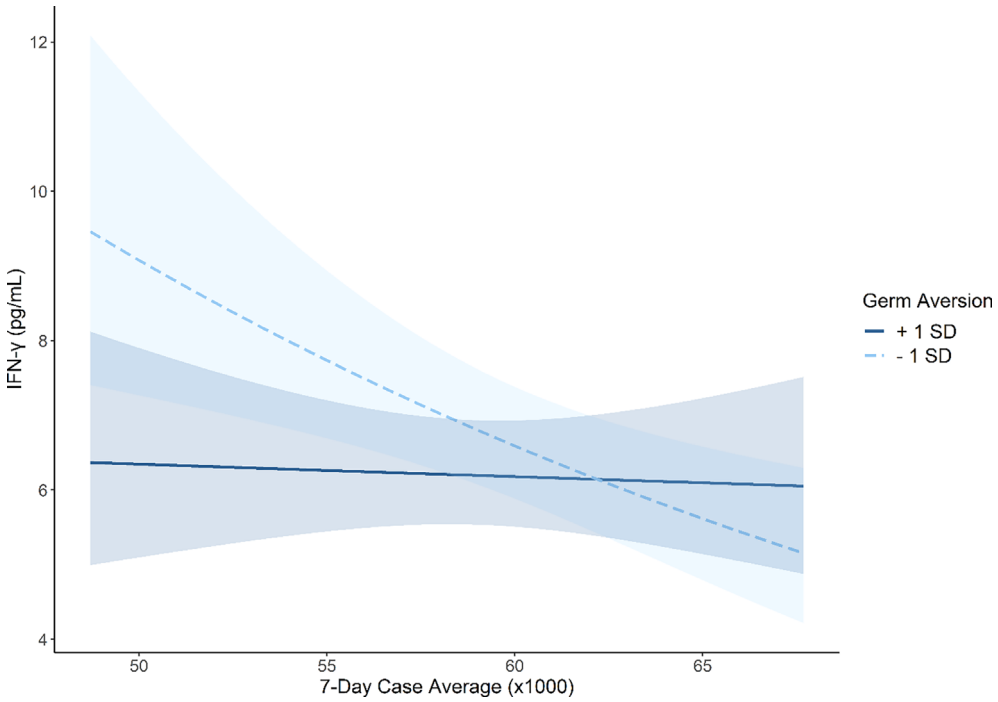

FIGURE 1 Interaction between germ aversion and case counts predicting levels of interferon-gamma (IFN-γ).

3.1.4 | Infection risk

Statistically significant main effects of 7-day case averages are found for a number of immunological endpoints. First, higher case averages at the time of participation are associated with greater serum *E. coli* killing ($b = 0.79$, $p = .04$). Higher cases also predict higher levels of IL-2 ($b = 0.02$, $p = .0001$). On the other hand, higher case numbers are negatively related to levels of each IFN-γ ($b = -0.02$, $p = .03$), IL-8 ($b = -0.03$, $p = .00002$), and TNF-α ($b = -0.02$, $p = .000000003$). Importantly, the aggregate effects of 7-day case averages remain statistically significant after correcting for multiple tests (harmonic mean $p = .0000001$, cut-off: $p = .03$).

3.1.5 | Covariates

Relationships between covariates and each immunological outcome are presented in Table S2. One notable set of findings involves employment as a first responder or healthcare worker during the pandemic. Specifically, individuals who work in these sectors have higher levels of both IL-10 ($b = 0.22$, $p = .009$) and TNF-α ($b = 0.37$,

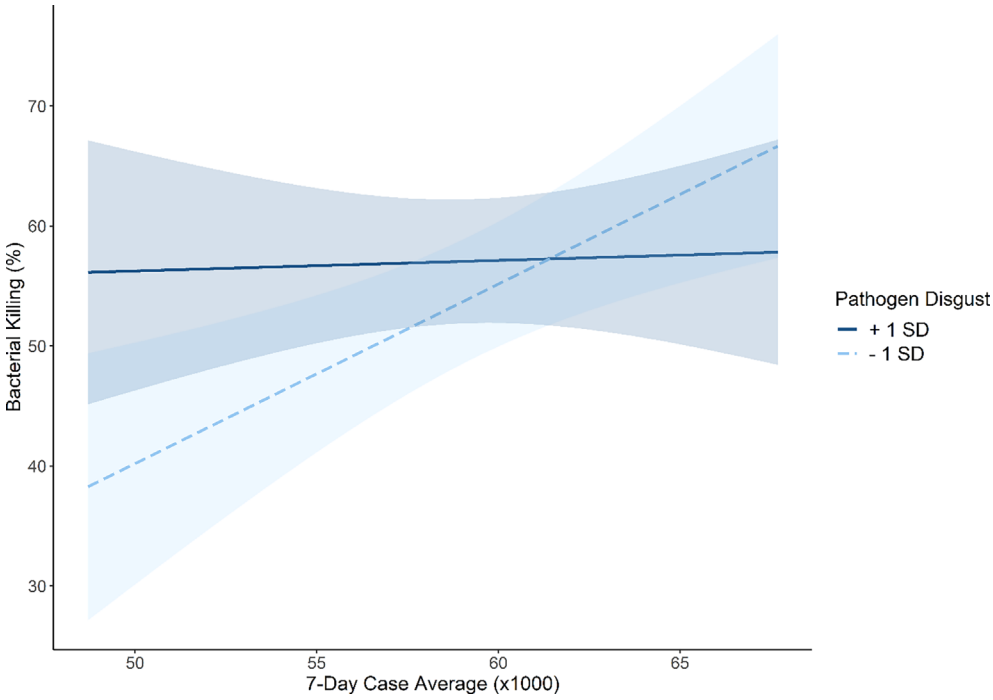

FIGURE 2 Interaction between pathogen disgust and case counts predicting levels of serum killing of *E. coli*.

$p = .000002$) compared with those who are not first responders or healthcare workers.

3.2 | Stress physiology measures

Individual differences in germ aversion, perceived infectability, and pathogen disgust are not significantly related to blood pressure, heart rate, or cortisol levels (see Table 3 for statistics). Although 7-day case averages do not statistically significantly predict systolic blood pressure, greater numbers of cases are related to both higher diastolic blood pressure ($b = 0.23$, $p = .03$) and higher heart rate ($b = 0.27$, $p = .01$), but lower levels of cortisol ($b = -0.01$, $p = .02$). No interactions reach statistical significance.

Relationships among covariates, blood pressure, and heart rate are shown in Table S3. Interestingly, first responders and healthcare workers have lower blood pressure (systolic: $b = -3.58$, $p = .04$; diastolic: $b = -3.37$, $p = .005$) than those not working in these fields. Heart rate is also lower in first responders and healthcare workers ($b = -3.52$, $p = .01$).

3.3 | Subjective distress measures

3.3.1 | Germ aversion

Germ aversion does not predict self-reported positive affect (See Table S1 for results), but higher germ aversion is related to higher negative affect ($b = 0.08$, $p = .004$), feelings of helplessness ($b = 0.41$, $p = .000004$), and feelings of depression ($b = 0.22$, $p = .03$); no interactions with case counts reach statistical significance.

3.3.2 | Perceived infectability

Results reveal that higher perceived infectability predict lower positive affect ($b = -0.11$, $p = .0001$), as well as higher negative affect ($b = 0.07$, $p = .01$), feelings of helplessness ($b = 0.44$, $p = .0000006$), and feelings of depression ($b = 0.43$, $p = .000005$).

3.3.3 | Pathogen disgust

Pathogen disgust is not significantly related to positive affect, negative affect, or feelings of helplessness (see Table S1). However, higher levels of pathogen disgust predict greater feelings of depression due to COVID-19 ($b = 0.25$, $p = .005$).

3.3.4 | Covariates

See Table S4 for relationships between covariates and subjective distress measures. Notably, older participants tend to report greater positive affect ($b = 0.01$, $p = .000005$), as well as lower negative affect ($b = -0.01$, $p = .000000007$), helplessness ($b = -0.03$, $p = .00004$),

and feelings of depression ($b = -0.02$, $p = .003$). Healthcare workers and first responders also report less negative affect ($b = -0.13$, $p = .000004$) and helplessness ($b = -0.49$, $p = .05$) than those not working in these fields.

3.4 | Follow-up mediation models

Multivariate mediation models are tested to examine indirect effects between the predictors (i.e., pathogen avoidance motivation variables, infection risk) and immunological outcomes via objective and subjective stress measures (see Figure 3 for conceptual diagram). Specifically, objective and subjective stress markers are entered as mediators and regressed on the predictors of germ aversion, perceived infectability, pathogen disgust, and COVID-19 case counts (*a* path), and immunological outcomes are regressed on both the mediators (*b* path) and predictors (*c* path). Because *a* paths are already reported (Tables 2, 3, and S1), we additionally report only *b* paths (Table S5) and *c* paths (Table S6). Per convention, we report the direct effect of X on Y (i.e., controlling for mediators), the indirect effects of X on Y through mediators (product of *a* and *b* paths), and the total effects of X on Y (sum of direct and indirect effects), per convention (Baron & Kenny, 1986). Significant specific indirect effects (indirect effect through individual mediators) are reported in-text; all other specific indirect effects are not statistically significant ($ps > 0.05$).

Results of the follow-up mediation models provide additional support for the primary analyses (Table S6). Specifically, the direct effects of COVID-19 case counts on serum *E. coli* killing, as well as levels of IFN-γ, IL-2, IL-8, and TNF-α are statistically significant, suggesting that controlling for potential stress-related mediators does not change the pattern or significance of the results reported above. There was little evidence that subjective distress or stress physiology markers statistically mediate relationships between COVID-19 case counts (or the other predictors) and the target immune outcomes. That is, no total indirect effects are significant, and only two specific indirect effects reach statistical significance: (a) the relationship between perceived infectability on levels of IL-10 through negative affect ($b = -0.01$, $p = .04$) and (b) the relationship between COVID-19 cases on levels of IL-10 through cortisol levels ($b = -0.03$, $p = .02$). Overall, these results do not seem to indicate that fluctuations in COVID-19 case counts influence the measured immunological outcomes through changes in subjective or objective stress markers.

4 | DISCUSSION

The current research explores relationships among individual differences in pathogen avoidance motivation, COVID-19 case counts, and multiple measures of immune function and stress physiology. COVID-19 case counts are consistently related to immunological outcomes, but the direction of the relationships differs across immune measures. That is, higher numbers of cases at the time of participation (during the early pandemic phase when death rates were among the highest, vaccines and therapeutics were unavailable, and standards of care were still being developed) are related to greater serum *E. coli* killing and higher levels of IL-2, but lower levels of IFN-γ, IL-8, and TNF-α. While it is not possible to determine the casual mechanisms that mediate this pattern of results, we hypothesize that concern over increases in case counts (and associated infection risk) may play a role. Consistent with this hypothesis, higher case counts are also related to elevations in resting diastolic blood

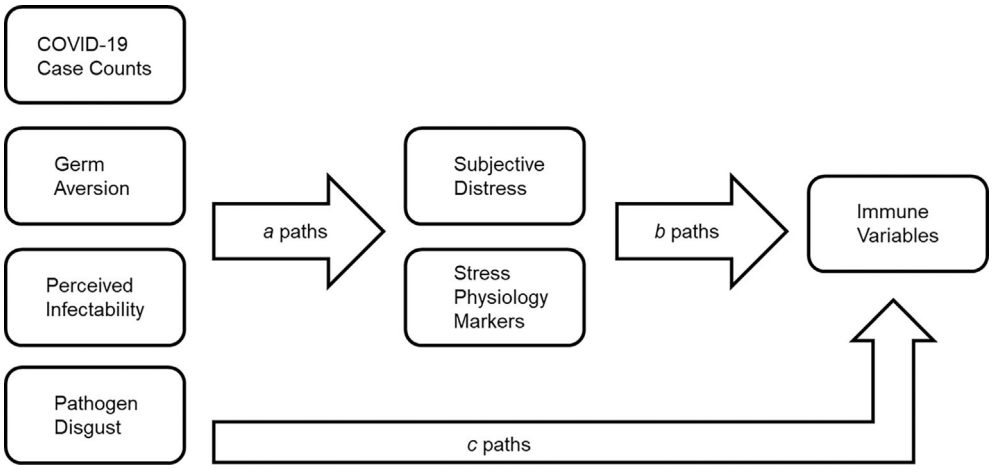

FIGURE 3 Conceptual representation of exploratory mediation models.

pressure (and to a lesser extent systolic) and heart rate, perhaps indicative of heightened sympathetic nervous system activity. On the other hand, higher case numbers are negatively related to levels of cortisol, perhaps reflecting a blunted cortisol response similar to what has been found to occur after protracted exposure to stressors (Lam et al., 2019; Stetler & Miller, 2005).

However, results of follow-up mediation models raise doubts about a mediating role of stress in relationships between COVID-19 case counts and the measured immunological outcomes found here. Although the direct effects of case counts on the immune dependent measures remain significant while controlling for subjective and objective stress mediators, indirect effects through those mediating variables are not consistently significant. Furthermore, subjective stress measures are not generally related to 7-day average COVID-19 case counts. Contrary to predictions, these results do not lend evidence that COVID-19 related distress provides a link between fluctuations in case counts and immune function.

Nonetheless, it is possible that COVID-19 related distress impacts immune function through psychological and physiological processes not measured in the current research, or on a time scale not captured by our single session assessments. Future research would benefit from a repeated sampling approach to compare fluctuations in infection risk, stress markers, and immune function within-subjects over time. Additional work may also explore other potential mediating mechanisms, such as changes in diet, exercise, or social behaviors that could confound relationships between COVID-19 case counts and immunity during the pandemic.

The effects of individual differences in pathogen avoidance motivation on immune markers are inconsistent, and these effects do not remain statistically significant after correcting for familywise error rate. However, patterns of results found in the current research do resemble those from previous studies. In particular, higher germ aversion is associated with diminished serum *E. coli* killing and generally lower levels of IFN-γ (see interaction with case counts). Previous research has linked higher levels of germ aversion with lower baseline levels of inflammation (Gassen et al., 2018), with similar results found for high disgust sensitivity in a separate study (Cepon-Robins et al., 2021). Such results are often interpreted as higher pathogen avoidance motivation leading to reduced pathogen exposure, and as a result lower inflammation. However, the current research was cross-sectional, and thus, the results may operate in the opposite direction. For example, it is possible that individuals with reduced immune performance exhibit greater desire to avoid pathogens behaviorally to compensate. This explanation is consistent with the idea of compensatory prophylaxis (Fleischman & Fessler, 2011), although support for that hypothesis has been mixed (Jones et al., 2018).

Higher perceived infectability is also related to higher levels of IL-10 and lower IFN-γ/IL-10 ratio, but not any other outcomes. No main effects of pathogen disgust reach statistical significance. One interesting set of results emerged that involved working in healthcare or as a first responder during the COVID-19 pandemic. Healthcare workers/first responders have higher levels of IL-10 and TNF-α, with lower resting blood pressure and heart rate. Higher levels of cytokines in these individuals may reflect greater exposure to disease cues than the general population. While it is unexpected that those in healthcare would have lower stress physiology markers given the hazards inherent in these occupations, it may also be true that healthcare workers and first responders engage in more physical activity than the general public. Moreover, these results could reflect habituation to the risk of infection that likely occurs in healthcare settings (Kasperson et al., 1988).

The present research has limitations that must be considered. First, the current study was cross-sectional. Accordingly, causal relationships between case counts and immune markers cannot be inferred from these data. Future research would benefit from tracking stress hormones and immune markers longitudinally to examine the extent to which an individual's biology is calibrated to fluctuations in infection risk over time. It is also worth keeping in mind that the current data were collected during the first year of the COVID-19 pandemic. As the pandemic continues, people's attitudes and risk perception are expected to change (e.g., pandemic fatigue) (MacIntyre et al., 2021). Accordingly, the nature of the relationship between pathogen avoidance psychology and immune function may, too, change. This is important to consider when comparing and contrasting the results of the current research with those of studies conducted prior to, and after, the pandemic. Next, the measures of individual differences in pathogen avoidance motivation used in the present study were truncated and had poor internal consistency. More reliable and comprehensive measures of this construct may yield more consistent, robust relationships with immunity. Furthermore, although all scales used in the current research were previously validated to capture "trait" pathogen avoidance motivation, research suggests that levels of these variables have changed since the onset of the pandemic (Hromatko et al., 2021). Another fruitful area for future research might involve examining whether measures of immune function in a population have also changed compared with before the pandemic; this might be

tested using public releases of data collected in one of the many ongoing longitudinal studies of aging.

5 | CONCLUSION

In summary, the results of the current research provide initial evidence that markers of immune function may be sensitive to changes to infection risk during the COVID-19 pandemic. These results may lay the groundwork for future research to unpack the psychological and biological mechanisms through which information about infection risk translates into shifts in health and immune function. Additional studies may lend insights into whether such immunological shifts have implications for disease vulnerability amidst a global pandemic.

AUTHOR CONTRIBUTIONS

Michael P. Muehlenbein and Erich J. Baker conceived the Waco COVID Survey and implemented it with Sally P. Weaver. Michael P. Muehlenbein wrote the survey, designed the study, and obtained the funding. Erich J. Baker designed and managed the websites. Tomasz J. Nowak, Jeffrey Gassen, and Michael P. Muehlenbein managed the enrollment. Jeffrey Gassen and Tomasz J. Nowak lead the data collection. Michael P. Muehlenbein and Jeffrey Gassen conceived the paper. Tomasz J. Nowak and Jeffrey Gassen conducted the statistical analyses. Alexandria D. Henderson and Edward Thum contributed to data collection and manuscript preparation. Jeffrey Gassen and Michael P. Muehlenbein wrote the manuscript. All authors contributed to manuscript revision.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to report.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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ENDNOTE

[1] The intraassay CV for IL-2 was inflated because most values were at the bottom of, and many below, the standard curve. See data analysis plan for additional details.

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