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Associations of immunometabolic risk factors with symptoms of depression and anxiety: The role of cardiac vagal activity

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ABSTRACT

Objectives: This study examined 1) the cross-sectional relationships between symptoms of depression/anxiety and immunometabolic risk factors, and 2) whether these relationships might be explained in part by cardiac vagal activity.

Methods: Data were drawn from the Adult Health and Behavior registries ($n = 1785$), comprised of community dwelling adults (52.8% women, aged 30–54). Depressive symptoms were measured with the Center for Epidemiological Studies Depression Scale (CES-D) and the Beck Depression Inventory-II (BDI-II), and anxious symptoms with the Trait Anxiety scale of the State-Trait Anxiety Inventory (STAI-T). Immunometabolic risk factors included fasting levels of triglycerides, high-density lipoproteins, glucose, and insulin, as well as blood pressure, waist circumference, body mass index, C-reactive protein, and interleukin-6. Measures of cardiac autonomic activity were high- and low-frequency indicators of heart rate variability (HRV), standard deviation of normal-to-normal R-R intervals, and the mean of absolute and successive differences in R-R intervals.

Results: Higher BDI-II scores, in contrast to CES-D and STAI-T scores, were associated with increased immunometabolic risk and decreased HRV, especially HRV likely reflecting cardiac vagal activity. Decreased HRV was also associated with increased immunometabolic risk. Structural equation models indicated that BDI-II scores may relate to immunometabolic risk via cardiac vagal activity (indirect effect: $\beta = .012$, $p = .046$) or to vagal activity via immunometabolic risk (indirect effect: $\beta = -.015$, $p = .021$).

Conclusions: Depressive symptoms, as measured by the BDI-II, but not anxious symptoms, were related to elevated levels of immunometabolic risk factors and low cardiac vagal activity. The latter may exhibit bidirectional influences on one another in a meditational framework. Future longitudinal, intervention, and nonhuman animal work is needed to elucidate the precise and mechanistic pathways linking depressive symptoms to immune, metabolic, and autonomic parameters of physiology that predispose to cardiovascular disease risk.

1. Introduction

Mood disorders have long been suggested to confer risk for cardiovascular disease (CVD) (Regulies, 2002; Roest et al., 2010; Vogelzangs et al., 2010). Several physiological mechanisms are thought to

contribute to this risk, particularly those involving the autonomic nervous system and immunometabolic dysfunction (de Jonge et al., 2010; Penninx et al., 2013). Understanding the pathways that might link symptoms of depression and anxiety to CVD risk remains an important and open issue, as depression and anxiety disorders and CVD

Abbreviations: AHAB, Adult Health and Behavior; BDI-II, Beck Depression Inventory-II; BMI, body mass index; CES-D, Center for Epidemiological Studies; CFA, confirmatory factor analysis; CFI, comparative fit index; CI, confidence interval; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; ECG, electrocardiogram; HDL, high-density lipoprotein; HRV, heart rate variability; HF-HRV, high-frequency heart rate variability; IBI, inter-beat interval; IL, interleukin; IQR, interquartile range; LF-HRV, low-frequency heart rate variability; MetS, Metabolic Syndrome; MSD, the mean of absolute and successive differences in IBIs; RMSEA, root mean square error of approximation; SBP, systolic blood pressure; SEM, structural equation modeling; SDNN, standard deviation of normal to normal R-R intervals; SRMR, standardized root mean residual; STAI-T, Trait Anxiety scale of the State-Trait Anxiety Inventory

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are often highly comorbid and are among the leading causes of disability and disease burden worldwide (Baxter et al., 2017; Lépine and Briley, 2011; Lopez et al., 2006).

Work in clinical and community samples suggests that depressed mood may precede immunometabolic dysregulations. For example, major depressive disorder has been associated with risk for the metabolic syndrome (MetS), a cluster of CVD risk factors – insulin resistance, dyslipidemia, central adiposity, and elevated blood pressure – that increase risk for CVD events and mortality (Pan et al., 2012; Vaccarino et al., 2008). In community samples, depressive symptoms also predict risk for future MetS (Räikkönen et al., 2007). According to recent studies, markers of systemic inflammation, such as C-reactive protein (CRP) and interleukin (IL)-6, might be plausibly included as features of the MetS and may play a role in the pathogenic aggregation of its multiple components (Eckel et al., 2005; Marsland et al., 2010). Congruently, studies have related depression to increased levels of inflammatory markers (Davidson et al., 2009; Haapakoski et al., 2015; Messay et al., 2012; Raison et al., 2006). Regarding anxiety and immunometabolic dysregulation, existing evidence is inconclusive. Although anxious symptoms have been associated with the MetS (Carroll et al., 2009; Luppino et al., 2011; Roohafza et al., 2012) and systemic inflammation (Hoge et al., 2009; O'Donovan et al., 2010; Pitsavos et al., 2006), many studies show contrary results (Baune et al., 2012; Butnorienė et al., 2014; Dunbar et al., 2008; Skilton et al., 2007) for reasons that have yet to be clarified.

Depressive and anxiety disorders and related mood symptom profiles have also been linked to autonomic dysregulation, although the nature of this relationship remains debated. Among the most commonly investigated indices of autonomic activity are measures of heart rate variability (HRV), especially presumptive indicators of cardiac vagal activity, such as high-frequency HRV (HF-HRV) and respiratory sinus arrhythmia (RSA) (Task Force, 1996). Generally, negative mood states – such as depression and anxiety – are thought to decrease cardiac vagal activity (Bleil et al., 2008; Carney et al., 2005; Chalmers et al., 2014; Chang et al., 2013, 2012; Watkins et al., 1998). However, findings from several studies that distinguished medicated from un-medicated individuals observed that the relationship between depressed mood and suppressed cardiac vagal activity might be attributable to antidepressant use, as drug-naïve affected persons did not uniformly differ from healthy controls (Davidson et al., 2005; Hu et al., 2017; Licht et al., 2015, 2010a; Noordam et al., 2015; Udupa et al., 2011). The relationship of suppressed cardiac vagal activity to depression and anxiety is of interest because vagal dysregulation is often reported to accompany immunometabolic risk. For example, many studies have linked decreased HRV to increased levels of metabolic risk factors (Brunner et al., 2002; Kimura et al., 2006; Koskinen et al., 2009; Liao et al., 1998; Licht et al., 2010b; Min et al., 2008; Stein et al., 2007; Vrijkotte et al., 2015) and inflammatory markers (Araújo et al., 2006; Carney et al., 2007; Cooper et al., 2015; Haensel et al., 2008; Kon et al., 2006; Lampert et al., 2008; Sloan et al., 2007; Stein et al., 2008; Thayer, 2009). Evidence from longitudinal studies further suggests that autonomic or vagal dysfunction, as revealed by low HRV, may in fact precede metabolic abnormalities (Hu et al., 2016; Licht et al., 2013) and increased levels of systemic inflammation (Hu et al., 2018).

Given the above findings, it is plausible that symptoms of depression and anxiety might associate with cardiac vagal activity and immunometabolic risk factors. Moreover, existing evidence suggests that cardiac vagal dysregulation may partly account for the association between mood related symptoms and immunometabolic risk. The few studies that have formally tested the latter explanatory pathway have chiefly focused on cardiovascular mortality as a late-stage endpoint, and they have yielded contradictory conclusions. Carney and colleagues (Carney et al., 2005), for example, reported a partial mediation effect of low cardiac vagal activity on the relationship between depression and mortality, whereas Kamphuis and colleagues (Kamphuis et al., 2007) did not find such an effect. As far as we know, no study has tested

whether patterns of cardiac vagal activity reflected by metrics of HRV partly explain the relationship of depressive and anxious symptoms to immunometabolic risk factors in a preclinical context or non-clinical sample of adults. Moreover, we know of no studies that have tested alternative associational possibilities. For instance, immunometabolic risk may well account for the association of mood related symptoms with cardiac vagal activity, as cardiac autonomic activity may plausibly be disrupted by a greater risk burden that is consequent to depressive behaviors (e.g., from vascular, inflammatory, or metabolic sources).

Accordingly, the current study used a relatively large community sample of midlife people from the Adult Health and Behavior registries (AHAB-1 and AHAB-2) (Manuck et al., 2010; Wong et al., 2015) to test: 1) the relationships between symptoms of depression and anxiety and immunometabolic risk factors, and 2) whether observable relationships between depressive/anxious symptoms and immunometabolic risk might be partly explained (statistically mediated) by cardiac vagal activity using structural equation modeling (SEM). To permit more comprehensive testing, multiple indicators of HRV, including HF-HRV, low-frequency (LF)-HRV, standard deviation of normal-to-normal R-R intervals (SDNN), and the mean of absolute and successive differences in R-R intervals (MSD) were assessed in the present study. In this regard, LF-HRV and SDNN, although suggested to predominantly reflect cardiac vagal activity, are also influenced by sympathetic activity (Task Force, 1996; Reyes del Paso et al., 2013). Accordingly, such metrics might aid in more completely understanding the relationship between cardiac autonomic function with depressive and anxious symptoms and immunometabolic risk in a preclinical context. Finally, ancillary analyses were conducted to test for the moderating influence of sex, as well as alternative statistical mediation pathways.

2. Methods

2.1. Subjects

Data were derived from the University of Pittsburgh Adult Health and Behavior (AHAB) project phases 1 (AHAB-1) and 2 (AHAB-2), including behavioral and biological measurements of participants aged between 30 and 54 (Manuck et al., 2010; Wong et al., 2015).

AHAB-1 consisted of 1295 participants who were recruited in 2001–2005 via mass-mail solicitation from communities of Southwestern Pennsylvania in the United States (principally Allegheny County). Participants were excluded if they had a reported history of atherosclerotic CVD, chronic kidney or liver disease, past-year cancer treatment, major neurologic disorders, schizophrenia or other psychotic illness. Other exclusions included pregnancy and the use of insulin, glucocorticoid, antiarrhythmic, psychotropic, or prescription weight-loss medications.

AHAB-2 consisted of 490 participants who were recruited in 2008–2011, also via mass-mail solicitation and from the same geographic region. Exclusion criteria were the same as for AHAB-1, with the following additional exclusions: unemployment, occupational shift work, or working less than 25 h per week outside the home (this restriction was due to a sub-study focusing on occupational stress), stage 2 hypertension (systolic diastolic BP $\geq$ 160/100 mm Hg), high alcohol consumption ($\geq$ five portions at one occasion on three to four occasions per week), use of fish oil supplements (because of the requirements of another sub-study), and lipid-lowering or antihypertensive medications. Informed consent was obtained in accordance with approved guidelines of the University of Pittsburgh Institutional Review Board.

2.2. Depressive/anxious symptoms

Depressive symptoms were measured using the Center for Epidemiological Studies Depression Scale (CES-D) (Radloff, 1977) and the Beck Depression Inventory-II (BDI-II) (Beck et al., 1961). The CES-D is a 20-item self-report questionnaire to assess how frequently subjects

experienced symptoms of depression during the past week. The BDI-II is a 21-item measure of depression severity during the past week. Anxious symptoms were measured by the Trait Anxiety scale of the State-Trait Anxiety Inventory (STAI-T), a 20-item self-report scale to measure the general propensity to experience states of anxiety in response to perceived threats (Spielberger et al., 1970). In our sample, these questionnaires demonstrated high internal consistency (Cronbach's $\alpha = .90$, .85, and .92, for CES-D, BDI-II, and STAI-T, respectively). In addition, these questionnaires have shown adequate psychometric properties supporting their reliability and validity (Beck et al., 1988; Devins et al., 1988; Spielberger, 1983). The combined data of AHAB-1 and -2 yielded 1769 participants who completed the CES-D, 1775 participants who completed the BDI-II, and 1754 participants who completed the STAI-T.

Current diagnosis of a mood or anxiety disorder (including major depressive disorder, dysthymia, generalized anxiety disorder, panic disorder, simple phobia, social phobia, obsessive compulsive disorder, and post-traumatic stress disorder) was assessed with the Structured Clinical Interview for DSM-IV Axis I Disorder (SCID) (First et al., 1996) nonpatient edition (AHAB-1) and the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1997), Version 6.0 (AHAB-2).

2.3. Immunometabolic risk

The components of immunometabolic risk were assessed in the morning after an overnight fast. At this visit, a medical history and medication use interview was administered, and measurement of body mass index (BMI; kg/m^2) and waist circumference was obtained. Systolic and diastolic blood pressure (SBP and DBP, respectively) were computed as the average of 2 readings measured by a sphygmomanometer after at least 5 min of rest in a seated position. Fasting serum triglycerides, HDL cholesterol and glucose were determined by the Heinz Nutrition Laboratory, University of Pittsburgh Graduate School of Public Health. Fasting serum insulin concentration was measured in duplicate with a radioimmunoassay (Code-a-count; Diagnostic Products, Inc, Los Angeles, CA). Of the total sample, 30 participants were excluded because of missing data on one or more metabolic components, rendering 1755 participants for analyses.

IL-6 was determined by a high-sensitivity quantitative sandwich enzyme immunoassay kit (R&D Systems, Minneapolis, MN). The assay standard range is from 0.156 to 10 pg/mL. IL-6 levels were extrapolated from a standard curve with linear regression from a log-linear curve. All samples were run in duplicate and the average coefficient of variation (CV) between samples was 5%. CRP was measured with the BNII nephelometer from Dade Behring (Newark, DE) using a particle-enhanced immunonephelometric assay. The assay range is 0.175–1100 mg/L. Intra-assay CVs ranged from 2.3 to 4.4% and inter-assay CVs ranged from 2.1 to 5.7%. Participants were excluded from analyses of inflammatory markers if they had chronic inflammatory disease or used medications known to impact immune function (cold medications, antihistamines, inhaled corticosteroids, immunosuppressants, or allergy shot in the previous 2 weeks). In addition, data on inflammatory markers were excluded when CRP concentrations were greater than 10 mg/L, due to the possibility of underlying inflammatory disease (Biasucci et al., 2004). In AHAB-2, the blood draw was rescheduled if participants reported symptoms of acute infection, receiving a vaccination, or use of antibiotics or antivirals in the previous 2 weeks. Possibly as a consequence, all levels of IL-6 fell below the maximum levels of detection of the assay (10 pg/mL). In contrast, common acute illnesses were not considered in the timing of the blood draw in AHAB-1. For this reason, we excluded individuals with levels of IL-6 > 10 pg/mL, but only when BMI was < 30 kg/m^2 , due to evidence that individuals with high levels of adiposity have elevated levels of IL-6 in the absence of acute illness. This resulted in 1546 participants with a valid measure for CRP and 1455 participants with a valid measure for IL-6.

2.4. Assessment of HRV and cardiac vagal activity

HRV measures were derived from a modified lead II electrocardiogram (ECG) recording protocol. Participants were seated in a temperature and sound-controlled chamber for a 10-min rest period, after which 5-min resting ECG recordings were obtained. Automated algorithms and visual inspection were used to correct artifacts in the ECG and the derived inter-beat interval (IBI) time series. Recording periods were divided into three 90-s epochs and were excluded based on percent artifact ($> 20\%$) and length ($> 10\%$ missing). By these criteria, there were missing HRV data for 61 participants. The following variables were averaged across retained epochs: high-frequency heart rate variability (HF-HRV), low-frequency heart rate variability (LF-HRV), the standard deviation of normal to normal R-R interval (SDNN), and the mean of successive and absolute differences in IBIs (MSD). The MSD is highly correlated to the more conventionally used RMSSD (Allen et al., 2007), which is also putative indicator of cardiac vagal activity (Berntson et al., 2005). SDNN, while often used as an index of total variability, covaries strongly with more specific measures of cardiac vagal control obtained during brief recording periods ($r = 0.8$ in this study) (Allen et al., 2007). To obtain HF-HRV and LF-HRV, the band-limited variance within the frequency range of 0.12–0.40 Hz and 0.04–0.12 Hz (Allen et al., 2007), respectively, was extracted using PhysioScripts (Christie and Gianaros, 2013). HRV variables were available for 1724 participants. Raw and de-identified data used to generate HRV metrics are available on request.

2.5. Covariates

Covariate adjustments were made for age, sex, years of education, race (non-Hispanic Caucasian or other), and study (AHAB-1 or AHAB-2). We also accounted for lifestyle factors: physical activity (estimated kilocalories expended per week by the Paffenbarger Physical Activity Questionnaire (Paffenbarger et al., 1993)), alcohol use (drinks/week), and smoking (cigarettes/day). From a medical history interview, we determined self-reported medical conditions and current medications, and included the following covariates: presence/absence of any non-excluded medical conditions and use of antihypertensive or lipid-lowering medications. Because it is linked to HRV metrics, respiration rate was included as a covariate (Allen et al., 2007; Berntson et al., 1997; Hirsch and Bishop, 1981). Respiration rate was computed from strain-gauge respiratory recordings obtained concurrently during EKG monitoring. The number of participants taking antidepressants was negligible ($n = 1$) and therefore antidepressant use was not included as a covariate.

2.6. Statistical analyses

Triglycerides, glucose, insulin, CRP, IL-6, HF-HRV, LF-HRV, SDNN and MSD exhibited skewed distributions and these variables were natural log transformed prior to analyses. Multiple linear regression analyses were first performed with IBM SPSS Statistics version 24 (IBM corp) to test the associations between depressive and anxious symptoms, HRV metrics, and immunometabolic risk factors. Covariates in the base models included age, sex, education, and study (and respiration rate when analyzing HRV). In subsequent models, additional covariate adjustments were made for physical activity, alcohol use, smoking, presence/absence of medical conditions, and use of antihypertensive or lipid-lowering medications. We added interaction terms to the models to test for study- and sex-dependent effects.

Following regression analysis, SEM was performed with Mplus (version 7) (Muthén and Muthén, 2004). Covariance matrices of models were analyzed using the maximum likelihood (ML) method. Confirmatory factor analyses (CFA) established cardiac vagal activity and immunometabolic risk latent variables. These latent variables were used to investigate possible mediating effects of cardiac vagal activity in

Table 1
Sample characteristics.

Variables	n	AHAB 1	n	AHAB 2
Sociodemographics				
Age, years (mean $\pm$ SD)	1295	44.6 $\pm$ 6.7	490	42.8 $\pm$ 7.3
Female (%)	1295	52.7	490	52.9
Education, years (mean $\pm$ SD)	1295	15.7 $\pm$ 2.8	490	16.9 $\pm$ 2.9
Non-Hispanic Caucasian (%)	1295	83.5	490	81.8
Lifestyle & Health				
Physical activity, 1000 kcal/week (mean $\pm$ SD)	1295	2.4 $\pm$ 1.8	490	2.8 $\pm$ 2.1
Alcohol use, drinks/week (median (IQR))	1295	2.0 (1.0–4.0)	490	1.0 (0.0–4.0)
Smokers (%)	1295	14.5	490	12.4
Number of smoked cigarettes/day (median (IQR))	1295	13.0 (6.0–20.0)	490	6.4 (1.7–10.0)
Presence of medical conditions (%)	1295	40.3	490	30.4
Use of antihypertensive/lipid-lowering medication (%)	1295	9.8	490	0.4
Physiological measures				
Heart rate, beats/min (mean $\pm$ SD)	1246	65.0 $\pm$ 9.3	478	69.0 $\pm$ 10.9
HF-HRV (median (IQR))	1246	316.1 (149.8–619.9)	478	262.9 (108.7–615.9)
LF-HRV (median (IQR))	1246	228.8 (115.2–415.4)	478	183.0 (101.9–415.8)
SDNN (median (IQR))	1246	41.8 (31.5–54.3)	478	38.5 (28.3–53.3)
MSD (median (IQR))	1246	24.8 (16.9–35.0)	478	21.8 (12.9–34.1)
Respiration rate, breaths/min (mean $\pm$ SD)	1246	15.9 $\pm$ 2.2	478	16.0 $\pm$ 2.5
Mental health				
CES-D (median (IQR))	1285	6.0 (2.0–11.0)	484	6.0 (3.0–12.0)
BDI-II (median (IQR))	1285	3.0 (0.5–6.0)	490	3.0 (1.0–7.0)
STAI-T (median (IQR))	1270	30.0 (25.0–37.0)	484	31.0 (26.0–38.0)
Presence of current mood/anxiety disorder (%)	1295	13.1	490	2.0
Immunometabolic risk factors				
Triglycerides, mg/dl (median (IQR))	1270	98.0 (71.8–145.0)	485	91.0 (65.0–131.0)
HDL cholesterol, mg/dl (mean $\pm$ SD)	1270	53.5 $\pm$ 14.6	485	55.9 $\pm$ 15.0
SBP, mm Hg (mean $\pm$ SD)	1270	116.4 $\pm$ 13.5	485	115.1 $\pm$ 11.2
DBP, mm Hg (mean $\pm$ SD)	1270	78.3 $\pm$ 9.4	485	72.3 $\pm$ 8.2
Glucose, mg/dl (median(IQR))	1270	94.0 (88.0–101.0)	485	97.0 (91.0–104.0)
Insulin, μ U/ml (median (IQR))	1270	11.6 (8.6–15.8)	485	10.9 (9.0–13.7)
Waist circumference, cm (mean $\pm$ SD)	1270	91.9 $\pm$ 15.9	485	90.4 $\pm$ 14.1
BMI, kg/m ² (mean $\pm$ SD)	1270	27.4 $\pm$ 5.7	485	26.9 $\pm$ 5.2
CRP, ng/ml (median (IQR))	1110	0.9 (0.5–2.1)	436	0.8 (0.4–1.7)
IL-6, pg/ml (median (IQR))	1021	1.2 (0.8–2.0)	434	0.9 (0.6–1.3)

Note: IQR = interquartile range. Kcal = kilocalories. BMI = body mass index. HF-HRV = high-frequency heart rate variability. LF-HRV = low-frequency heart rate variability. SDNN = standard deviation of normal to normal R-R intervals. MSD = the mean of absolute and successive differences in inter-beat intervals. CES-D = Center for Epidemiologic Studies Depression Scale. BDI-II = Beck Depression Inventory-II. STAI-T = Trait Anxiety scale of the State-Trait Anxiety Inventory. HDL = high density lipoprotein. SBP = systolic blood pressure. DBP = diastolic blood pressure. BMI = body mass index. CRP = C-reactive protein. IL-6 = interleukin-6.

the relationship between depressive/anxious symptoms and immunometabolic risk, as well as alternative mediation pathways. Model fit indices were compared across alternative models. Because the χ^2 -test is sensitive to negligible sources of ill fit in large samples using real-world data, we also used multiple alternative fit indices to evaluate model fit. Adequate fit corresponds with the root mean square error of approximation (RMSEA) and its 90% confidence interval (CI) with values less than .05, the comparative fit index (CFI) close to .95 or greater, and the standardized root mean residual (SRMR) of less than .08 (Hooper et al., 2008). Analyses controlled for all a priori covariates (age, sex, education, study, physical activity, alcohol use, smoking, presence/absence of medical conditions, use of antihypertensive or lipid-lowering medications, and respiration rate).

3. Results

Table 1 shows that participants in AHAB-1 ($n = 1295$) had a mean age of 44.6 years (± 6.7 SD), and were 52.7% female and 83.5% non-Hispanic Caucasian. Participants in AHAB-2 ($n = 490$) had a mean age of 42.8 years (± 7.3 SD), with 52.9% females and 81.8% non-Hispanic Caucasians.

3.1. Regression analyses

Table 2 shows associations of depressive and anxious symptoms

with immunometabolic risk factors. In the first adjusted model, higher CES-D scores were associated with higher IL-6 ($\beta = .055$; $p = .029$), and higher STAI-T scores were associated with higher triglyceride levels ($\beta = .050$; $p = .030$). In addition, higher BDI-II scores were associated with higher triglycerides ($\beta = .064$; $p = .005$), glucose ($\beta = .064$; $p = .006$), waist circumference ($\beta = .058$; $p = .007$), BMI ($\beta = .056$; $p = .018$), CRP ($\beta = .063$; $p = .013$) and IL-6 ($\beta = .066$; $p = .008$) levels. After full covariate adjustments, the associations between BDI-II scores and triglyceride ($\beta = .055$; $p = .016$), glucose ($\beta = .051$; $p = .028$), waist circumference ($\beta = .059$; $p = .005$), BMI ($\beta = .064$; $p = .006$), and IL-6 levels ($\beta = .049$; $p = .049$) remained significant.

Table 3 shows that, of the depressive/anxious symptom scales, only a higher BDI-II score was statistically associated with a lower HF-HRV (model 1: $\beta = -.066$; $p = .003$, and model 2: $\beta = -.062$; $p = .006$), LF-HRV (model 1: $\beta = -.049$; $p = .031$, and model 2: $\beta = -.046$; $p = .046$), SDNN (model 1: $\beta = -.050$; $p = .031$, and model 2: $\beta = -.046$; $p = .049$), and MSD (model 1: $\beta = -.077$; $p = .001$, and model 2: $\beta = -.073$; $p = .002$).

Table 4 shows that all HRV variables were associated with almost all immunometabolic components in both the first and second adjusted models. After full adjustment, lower HF-HRV was associated with higher triglyceride ($\beta = -.060$; $p = .011$) and glucose ($\beta = -.055$; $p = .022$) levels. Lower LF-HRV was associated with higher triglycerides ($\beta = -.070$; $p = .002$), glucose ($\beta = -.063$; $p = .008$), waist circumference ($\beta = -.055$; $p = .011$), and BMI ($\beta = -.061$; $p = .010$).

Table 2

The relationship between depressive/anxious symptoms with immunometabolic risk factors.

Depression/anxiety scale	Immunometabolic risk factors																	
	Triglycerides		HDL cholesterol		SBP		Glucose		Insulin		Waist		BMI		CRP		IL-6	
	n	β	p	β	p	β	p	β	p	β	p	β	p	β	p	n	β	p
CES-D ^a	1739	.036	.12	-.008	.71	-.009	.71	.043	.064	.014	.55	.034	.11	.031	.19	1534	.044	.084
CES-D ^b		.026	.25	-.020	.34	-.015	.50	.025	.28	.020	.40	.030	.16	.032	.17		.027	.29
BDI-II ^a	1745	.064	.005	-.012	.57	-.005	.83	.064	.006	.023	.34	.058	.007	.056	.018	1539	.063	.013
BDI-II ^b		.055	.016	-.020	.35	-.008	.74	.051	.028	.032	.17	.059	.005	.064	.006		.049	.057
STAI-T ^a	1727	.050	.030	-.025	.24	-.028	.21	.025	.29	.008	.73	.015	.48	.008	.75	1522	.039	.13
STAI-T ^b		.032	.15	-.027	.20	-.037	.10	.005	.82	.009	.69	.004	.86	.002	.92		.024	.36

Note: HDL = high density lipoprotein. SBP = systolic blood pressure. BMI = body mass index. CRP = C-reactive protein. IL-6 = interleukin-6. CES-D = Center for Epidemiologic Studies Depression Scale. BDI-II = Beck Depression Inventory-II. STAI-T = Trait Anxiety scale of the State-Trait Anxiety Inventory.

Boldface indicates significance at $p < .05$.

^a Regression analyses were adjusted for age, sex, education, race and study.

^b Adjustment^a + additionally adjusted for smoking, alcohol use, physical activity, presence/absence of medical conditions, and use of antihypertensive or lipid-lowering medications.

Lower SDNN and lower MSD were associated with higher triglycerides (SDNN: $\beta = -.108$; $p < .001$, and MSD: $\beta = -.113$; $p < .001$), SBP (SDNN: $\beta = -.062$; $p = .009$, and MSD: $\beta = -.061$; $p = .011$), glucose (SDNN: $\beta = -.096$; $p < .001$, and MSD: $\beta = -.099$; $p < .001$), insulin (SDNN: $\beta = -.091$; $p < .001$, and MSD: $\beta = -.128$; $p < .001$), waist circumference (SDNN: $\beta = -.082$; $p < .001$, and MSD: $\beta = -.087$; $p < .001$), BMI (SDNN: $\beta = -.084$; $p = .001$, and MSD: $\beta = -.075$; $p = .002$), and CRP (SDNN: $\beta = -.066$; $p = .014$, and MSD: $\beta = -.089$; $p = .001$). Lower MSD was also associated with lower HDL cholesterol ($\beta = .059$; $p = .008$).

3.2. Structural equation modeling

BDI-II was the only scale associated with immunometabolic risk factors and HRV. Accordingly, mediation analysis by SEM was restricted to this scale. We established a latent variable putatively reflecting cardiac vagal activity including HF-HRV, LF-HRV, SDNN, and MSD. Within this model, we allowed LF-HRV and SDNN to covary in order to account for the putative and additional sympathetic nervous system contributions to these variables relative to the other variables of presumptive cardiac vagal control comprising the latent factor (Task Force, 1996; Reyes del Paso et al., 2013). By this latter approach, we thus interpret the remaining (residual) contributions of the indicators to the derived latent factor as predominantly vagal in origin hereafter. We also add here that additional SEMs were executed without LF-HRV as a

facet of the cardiac vagal latent variable. The results of the latter models were compatible with those presented here (results available on request). A latent factor for immunometabolic risk was established by a second-order factor model with five first-order factors having two indicators each: dyslipidemia (triglycerides and HDL), blood pressure (SBP and DBP), insulin resistance (glucose and insulin), adiposity (waist circumference and BMI), and inflammation (CRP and IL-6). After adjusting for all covariates, the model fit the data well ($\chi^2(82) = 251.83$, $p < .001$; RMSEA = .039, 90% CI [.033, .044]; CFI = .99; SRMR = .016). The mediation analysis showed a total ($\beta = .074$, $p = .018$, 95% CI [.012, .135]) and direct ($\beta = .062$, $p = .047$, 95% CI [.001, .123]) association between BDI-II and immunometabolic risk. In addition, a relationship was found between a higher BDI-II and lower cardiac vagal activity ($\beta = -.056$, $p = .036$), and between lower cardiac vagal activity and higher immunometabolic risk ($\beta = -.207$, $p < .001$). Congruently, there was an indirect effect of cardiac vagal activity on the association between BDI-II and immunometabolic risk ($\beta = .012$, $p = .046$, 95% CI [.000, .023]), providing cross-sectional evidence for statistical mediation. A graphical depiction of this model is shown in Fig. 1.

In alternative SEMs, we tested for several other indirect pathways. Model fit was comparatively poorer (for RMSEA, CFI, and SRMR) for pathways where BDI-II was treated as the mediator (vagal activity $\rightarrow$ BDI-II $\rightarrow$ immunometabolic risk: $\chi^2(126) = 1172.72$, $p < .001$; RMSEA = .077, 90% CI [.073, .081]; CFI = .93; SRMR = .050; immunometabolic risk $\rightarrow$ BDI-II

Table 3

The relationship between depressive/anxious symptoms and HRV.

Depression/anxiety scale	HRV								
	HF-HRV			LF-HRV		SDNN		MSD	
	n	β	p	β	p	β	p	β	p
CES-D ^a	1710	−.018	.42	−.005	.81	−.002	.93	−.030	.19
CES-D ^b		−.012	.58	−.002	.93	.003	.91	−.024	.30
BDI-II ^a	1716	−.066	.003	−.049	.031	−.050	.031	−.077	.001
BDI-II ^b		−.062	.006	−.046	.046	−.046	.049	−.073	.002
STAI-T ^a	1697	−.017	.43	−.003	.91	.006	.81	−.018	.44
STAI-T ^b		−.008	.71	.004	.85	.015	.52	−.006	.81

Note: HRV = heart rate variability. HF-HRV = high-frequency heart rate variability. LF-HRV = low-frequency heart rate variability. SDNN = standard deviation of normal to normal R-R intervals. MSD = mean of successive differences in inter-beat intervals. CES-D = Center for Epidemiologic Studies Depression Scale. BDI-II = Beck Depression Inventory-II. STAI-T = Trait Anxiety scale of the State-Trait Anxiety Inventory.

Boldface indicates significance at $p < .05$.

^a Regression analyses were adjusted for age, sex, education, race, study, and respiration rate.

^b Adjustment^a + additionally adjusted for smoking, alcohol use, physical activity, presence/absence of medical conditions, and use of antihypertensive or lipid-lowering medications.

Table 4
The relationship between HRV and immunometabolic risk factors.

HRV	Immunometabolic risk factors									
	Triglycerides		HDL cholesterol		SBP		Glucose		Insulin	
	n	β	n	β	n	β	n	β	n	β
HF-HRV ^a	1696	-.069	.005	.031	.17	-.027	.26	-.060	.015	-.052
HF-HRV ^b		-.060	.011	.024	.27	-.024	.31	-.055	.022	-.048
LF-HRV ^a	1696	-.079	.001	.021	.33	-.014	.55	-.064	.008	-.051
LF-HRV ^b		-.070	.002	.007	.73	-.014	.55	-.063	.008	-.045
SDNN ^a	1696	-.124	<.001	.047	.036	-.068	.004	-.104	<.001	-.102
SDNN ^b		-.108	<.001	.033	.14	-.062	.009	-.096	<.001	-.091
MSD ^a	1696	-.130	<.001	.071	.002	-.066	.006	-.107	<.001	-.138
MSD ^b		-.113	<.001	.059	.008	-.061	.011	-.099	<.001	-.128

Note: HDL = high density lipoprotein. SBP = systolic blood pressure. BMI = body mass index. CRP = C-reactive protein. IL-6 = interleukin-6. HRV = heart rate variability. HF-HRV = high-frequency heart rate variability. LF-HRV = low-frequency heart rate variability. SDNN = standard deviation of normal to normal R-R intervals. MSD = the mean of absolute and successive differences in inter-beat intervals. Boldface indicates significance at $p < .05$.

^a Regression analyses were adjusted for age, sex, education, race, study, and respiration rate.

^b Adjustment^a + additionally adjusted for smoking, alcohol use, physical activity, presence/absence of medical conditions, and use of antihypertensive or lipid-lowering medications.

II → vagal activity: $\chi^2(192) = 2390.51p < .001$; RMSEA = .091, 90% CI [.088, .094]; CFI = .86; SRMR = .073), as well as where BDI-II was treated as an outcome variable (vagal activity → immunometabolic risk → BDI-II: $\chi^2(126) = 1172.72$, $p < .001$; RMSEA = .077, 90% CI [.073, .081]; CFI = .93; SRMR = .050; immunometabolic risk → vagal activity → BDI-II: $\chi^2(192) = 2390.51p < .001$; RMSEA = .091, 90% CI [.088, .094]; CFI = .86; SRMR = .073).

Finally, there was equivocal evidence that immunometabolic risk vs. vagal activity were most appropriately modeled as outcome or mediator variables when BDI-II scores were modeled as the predictor. Hence, model fit indices were essentially equivalent between our hypothesized a priori model tested above (cardiac vagal activity as mediator) and an alternative model wherein immunometabolic risk was modeled as a statistical mediator of the association between BDI-II scores and cardiac vagal activity (indirect effect: $\beta = -.015$, $p = .021$, 95% CI [-.028, -.002]; model fit: $\chi^2(82) = 251.83$, $p < .001$; RMSEA = .039, 90% CI [.033, .044]; CFI = .99; SRMR = .016).

In aggregate, these findings indicate that depressive symptoms (BDI-II scores) may be better modeled as predictors and not as mediators or outcome variables in association with immunometabolic risk and cardiac vagal activity. In addition, immunometabolic risk and cardiac vagal activity appeared to be equivalently modeled as mediators and outcome variables (see Discussion).

3.3. Additional analyses

Secondary analyses tested whether the patterns of association differed between AHAB cohorts (1 and 2); however, interaction terms coding for cohort did not reach statistical significance.

We also tested for sex differences in the pattern of associations reported above. First, regression analyses with an interaction term for sex indicated that the relationships between some HRV metrics and immunometabolic components differed between men and women. Hence, stratified analyses (reported in [Supplementary Tables 1 and 2](#)) showed that the direction of the effects was similar for men and women, but some effect sizes were comparatively greater in men. We then used multi-group SEMs to examine whether our mediation models were significantly moderated by sex, but found no evidence that this was the case.

Because the ability of HRV metrics to index cardiac autonomic or vagal activity may be associated with the prevailing heart rate ([Gąsior et al., 2016](#)), we re-executed the SEMs with HRV variables corrected for the mean IBI (the reciprocal of heart rate) as described by Van Roon et al. ([van Roon et al., 2016](#)). The indirect effects in the models with cardiac vagal activity ($\beta = .009$, $p = .051$, 95% CI [.000, .017]) and immunometabolic risk ($\beta = -.011$, $p = .030$, 95% CI [-.021, -.001]) as mediators were not appreciably altered, suggesting that the present findings were not plausibly attributable to individual differences in basal heart rate (i.e., mean IBI).

In addition, further analyses tested the possible influence of current diagnoses of a mood or anxiety disorder. After statistically controlling for or excluding people with current mood or anxiety disorder diagnoses ($n = 137$), the total, direct, and indirect effects of the SEMs did not reach statistical significance.

4. Discussion

The current study builds on prior work by providing evidence for cross-sectional associations between depressive symptoms, as measured by the BDI-II, and greater immunometabolic dysregulation among otherwise healthy and largely un-medicated community dwelling adults. Additional novel findings suggest that lower cardiac vagal activity may partly explain the association between higher BDI-II scores and immunometabolic risk. However, alternate statistical mediation testing likewise suggested the possibility that higher BDI-II scores may relate to lower cardiac vagal activity via an immunometabolic pathway.

Fig. 1. Structural equation model for the association between BDI-II and immunometabolic risk mediated by cardiac vagal activity ($n = 1388$). Standardized path coefficients are reported. Model controls for age, sex, education, race, study, smoking, alcohol use, physical activity, presence/absence of medical conditions, use of antihypertensive or lipid-lowering medications, and respiration rate. Latent variables are represented by circles and observed variables as squares. $^{***}p < .001$. $^*p < .05$.

The finding of a relationship between depressive symptoms and reduced HRV in our predominantly antidepressant-naïve sample is notable, as previous studies have suggested that it is mainly antidepressant use that may drive this relationship (Davidson et al., 2005; Hu et al., 2017; Licht et al., 2015, 2010a; Noordam et al., 2015; Udupa et al., 2011). For instance, within the large cohort of the Netherlands Study of Depression and Anxiety, Licht and colleagues (Licht et al., 2008) found antidepressant use to strongly attenuate the relationship between major depressive disorder and HRV. However, a small significant association remained after adjusting for antidepressants. Our results add to evidence that, although antidepressants have been shown to play an important part, depressive symptoms might also be independently associated with autonomic dysregulation apart from pharmacological influences among otherwise healthy individuals (Kemp et al., 2012).

These results are partly in line with previous findings from AHAB-1 by Bleil et al. (2008), showing that trait negative affect was inversely associated with HF-HRV. In contrast to our results, the authors found significant associations of both depressive and anxious symptoms with suppressed HF-HRV. An important difference with the current study is that Bleil and colleagues used latent factors composed of several depressive (CES-D, BDI-II, and the Depression facet scale of the NEO Personality Inventory-Revised) and anxious symptom scales (the STAI-T, the anxiety facet scale of the NEO Personality Inventory-Revised, and the Harm Avoidance scale of the Temperament and Character Inventory), obscuring the effects of the separate scales as identified here. Although there was a high correlation (.75) between the depression scales in the current study, our results indicate that there is a considerable difference between these scales, as we found significant effects for the BDI-II, but not for the CES-D. A high correlation does not necessarily imply that scales measure the same construct, as high convergent validity can be achieved between scales that capture very different symptom profiles that are only minimally related (Fried, 2017). Indeed, it has been shown that the mean overlap among seven common depression scales is low, with the CES-D standing out in terms of idiosyncratic items (e.g. it captures items such as ‘people were unfriendly’ or ‘I felt that people disliked me’ that are not commonly

understood to belong to symptoms of depression and do not appear in other scales) and lesser overlap (.27 compared to a mean overlap of .36 among the other scales included in the study) (Fried, 2017). Similarly, the null-findings in the relationship between anxious symptoms with HRV, in contrast to results of Bleil and colleagues, might be due to differences in used anxiety questionnaires, as discrepancies in items may impact the measured construct (Bieling et al., 1998). Importantly, the Trait Anxiety scale of the STAI measures the general (dispositional) propensity to experience states of anxiety, as opposed to the BDI-II and the CES-D, which measure actual depressive symptoms experienced or reported over a recent period. The trait versus state issue might bear on explanations for why the STAI-T did not parallel the BDI-II findings. Finally, we examined a broader range of HRV metrics than Bleil and colleagues. These somewhat divergent results emphasize the need for careful attention to specific scale items and questionnaires and call attention to the need for a symptom-based approach to better understand which characteristics of depression and anxiety are truly associated with systemic physiology, particular autonomic metrics, and negative health outcomes.

Ample research has established the relationship between depression and immunometabolic risk factors (Davidson et al., 2009; Haapakoski et al., 2015; Messay et al., 2012; Pan et al., 2012; Räikkönen et al., 2007; Raison et al., 2006; Vaccarino et al., 2008), while evidence for anxiety is less reproducible (Baune et al., 2012; Butnorienė et al., 2014; Carroll et al., 2009; Dunbar et al., 2008; Hoge et al., 2009; Luppino et al., 2011; O'Donovan et al., 2010; Pitsavos et al., 2006; Roohafza et al., 2012; Skilton et al., 2007). We confirmed the association between higher BDI-II scores and metabolic factors and indicators of systemic inflammation. Again, we did not find significant associations between immunometabolic risk and the CES-D or the STAI-T, possibly due to the measured constructs in these questionnaires, as discussed above. Accordingly, discrepancies in anxiety scales might contribute to the general lack of convergent evidence for a possible relationship between anxious symptoms and immunometabolic dysregulation. It might also be that comorbid depressive symptoms partly account for some previously observed associations with indicators of anxiety.

In line with previous studies, HRV was associated with almost all

immunometabolic risk factors (Araújo et al., 2006; Brunner et al., 2002; Carney et al., 2007; Cooper et al., 2015; Haensel et al., 2008; Hu et al., 2016, 2018; Kimura et al., 2006; Kon et al., 2006; Koskinen et al., 2009; Lampert et al., 2008; Liao et al., 1998; Licht et al., 2013, 2010b; Min et al., 2008; Sloan et al., 2007; Stein et al., 2008, 2007; Thayer, 2009; Vrijkotte et al., 2015). Interestingly, HF-HRV – a presumptive indicator of cardiac vagal control – showed less consistent associations with immunometabolic components than the other measures. A possible explanation is that these measures, especially SDNN and LF-HRV, although likely reflecting vagal contributions in resting humans, have been shown to be influenced by the sympathetic nervous system as well (Task Force, 1996). Indeed, sympathetic activity has been suggested to track with immunometabolic components (Hu et al., 2016; Pongratz and Straub, 2014). However, we interpret the findings regarding LF-HRV with caution, as this measure is regarded as ambiguous with respect to precise influences from sympathetic, parasympathetic, and other complex neurophysiological determinants (Reyes del Paso et al., 2013). This caution is only warranted for the individual analyses with LF-HRV, because the latent variable derived from all HRV measures, as used in the SEM, would likely have extracted only their shared and presumptive cardiac vagal component. A future direction in this line of work would therefore be to test the relative specificity or consistency of different HRV metrics and non-HRV measures of autonomic function to associate with parameters of immune and metabolic physiology individually or in aggregate in longitudinal or related experimental designs.

The mediation analysis implemented by SEM suggested that the association between depressive symptoms and immunometabolic risk may be partly explained by suppressed cardiac vagal activity. A potential mechanism of action for such a putative pathway is that psychological distress accompanying depressive mood states leads to neuroendocrine or central autonomic outflow alterations, affecting autonomic outflow in the periphery (Musselman et al., 1998). In turn, such autonomic dysregulations across multiple organ and physiological systems could plausibly modulate glucose and fat metabolism (Kyrrou and Tsigos, 2009; Romijn and Fliers, 2005), liver metabolism (Yi et al., 2010), and virtually all other components of daily energy expenditure (Hjemdahl, 2002). In addition, previous studies on the autonomic nervous system and inflammation suggest that higher vagal activity may exert an anti-inflammatory effect by inhibiting the production of pro-inflammatory cytokines, the so-called cholinergic anti-inflammatory pathway (Tracey, 2002). When vagal activity is low, the lack of cholinergic inhibition may lead to increased systemic inflammation, which appears consistent with prior work indicating an inverse association between several metrics of HRV and inflammatory markers (Cooper et al., 2015; Marsland et al., 2007). Although autonomic pathways are plausible biologically, there may be other mechanisms that explain the link between depression and immunometabolic dysregulations or a bidirectional association between autonomic activity and immune or metabolic physiology (Pan et al., 2012). Indeed, the existence of other underlying mechanisms is supported by a significant direct pathway between depressive symptoms and immunometabolic risk in our study.

In extension, when testing other candidate pathways, all but one mediation model had comparatively poorer fit than our *a priori* model where cardiac vagal activity was treated as a statistical mediator. This exception was a model where immunometabolic risk was treated as a mediator between depressive symptoms and vagal control, which had an essentially identical model fit. The plausibility of such a pathway is supported by research indicating that metabolic, preclinical vascular disease, and immune factors may influence autonomic function (e.g., Tentolouris et al., 2008). In addition, it is possible that metrics of HRV and components of immunometabolic risk may be best conceptualized or considered as indicators of a broader, aggregate, and correlated (non-independent) clustering of systemic risk factors that mutually influence one another through bidirectional or feedback pathways.

Moreover, depressive symptomatology might exhibit parallel effects on autonomic and immunometabolic dysregulations that unfold simultaneously. The present cross-sectional findings provide an empirical basis for future longitudinal, mechanistic, or interventional work designed to adjudicate between the above possibilities.

Additional findings merit consideration and inform the interpretation of the possible pathways linking depressive symptoms to suppressed cardiac vagal activity and immunometabolic risk. First, as the ability of HRV to index autonomic or vagal activity may be influenced by the prevailing heart rate (Gašior et al., 2016), we performed additional analyses with HRV measures corrected for the reciprocal of heart rate (the mean of the inter-beat interval; IBI). These analyses suggested that the observed mediation pathways were not solely dependent on individual differences in mean heart rate (or IBI). This is the first such observation to our knowledge, and thus adds support for the use of HRV metrics in this area of research. Second, we examined possible interactive effects with sex using multi-group SEM models. We found no statistical evidence for moderation by sex. Third, the observed indirect effect (mediation pathway) for both models did not reach statistical significance after controlling for/excluding individuals with current mood or anxiety disorder diagnoses. Indeed, BDI-II scores were higher among individuals with a current mood or anxiety disorder diagnosis (mean = 8.1, SE = 7.4; $n = 137$) compared to those without evident psychopathology (mean = 3.7, SE = 4.1; $N = 1251$). The latter pattern of results may suggest the influence of a restricted range of variance or clinical threshold effects.

Findings from the present study should be interpreted within the context of its strengths and limitations. Strengths include our relatively large sample of otherwise healthy community dwelling adults without confounding pathologies and the measurement of many relevant confounding biological, behavioral, and demographic factors. In addition, this is one of few studies to perform mediation analyses in this field. Notwithstanding, this is a cross-sectional study, and therefore we cannot draw causal inferences. As noted above, alternative mediation pathways are possible and longitudinal and interventional studies are needed to shed more light on questions of causality. In addition, although we adjusted for many potential confounders, we cannot rule out residual confounding by variables that have not been measured. Finally, participants comprising the AHAB registries may not reflect a generalizable sample. In aggregate, these participants exhibited comparatively less demographic, racial, and ethnic variability than other epidemiological, clinical, and community samples in this literature. Moreover, exclusionary criteria (e.g., use of psychotropic medications, unemployment, etc.) may have restricted variability in mood-related symptoms. As a result, observed effect sizes may under- or mis-estimate the magnitude of associations at the population level or may vary depending on sample characteristics in future research.

Overall, our study found a relationship between depressive symptoms as measured by the BDI-II and immunometabolic risk. Our results suggest that reduced cardiac vagal activity may be in the pathway between symptoms of depression and immunometabolic dysregulation. However, alternate statistical mediation testing also suggested that depressive symptoms may relate to low cardiac vagal activity via an immunometabolic pathway, as well as the possibility that cardiac autonomic or vagal activity and immunometabolic factors are not necessarily dissociable as clustered or inter-related risk factors. Research investigating pre-clinical pathways between mental health and cardiovascular outcomes are important for the development of intervention and prevention strategies. Future (longitudinal), interventional, and nonhuman mechanistic animal studies are warranted to confirm our findings and adjudicate between different possible models, to further explore the effects of different depressive and anxious symptom dimensions, and to determine temporal ordering of the observed associations in association with cardiovascular disease risk.

Declaration of interest

Conflict of interest: none declared.

Author contribution statement

M.X. Hu formulated the research question, performed statistical analyses, wrote the manuscript, and incorporated feedback from all co-authors. F. Lamers, A.L. Marsland, and M.F. Muldoon provided feedback in all drafts of the manuscript and critically interpreted the results. D.C.-H. Kuan and A.G.C. Wright helped with statistical analyses. B.W.J.H. Penninx, E.J.C. de Geus, S.B. Manuck, and P.J. Gianaros reviewed and provided feedback for the research question, provided feedback in all drafts of the manuscript, and critically interpreted the results.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.bbi.2018.06.013>.

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