# Preadolescents' Somatic and Cognitive-Affective Depressive Symptoms Are Differentially Related to Cardiac Autonomic Function and Cortisol: The TRAILS Study

Nienke M. Bosch, MSc, Harriëtte Riese, PhD, Andrea Dietrich, PhD, Johan Ormel, PhD, Frank C. Verhulst, MD, PhD, and Albertine J. Oldehinkel, PhD

**Objective:** To examine in a nonclinical sample of preadolescents the possibility that somatic and cognitive-affective depressive symptoms are differentially related with the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis. Depression is a well-known risk factor for cardiovascular disease and mortality. Dysregulation of the ANS and the HPA axis have been proposed as underlying mechanisms. Several studies suggest that only a subset of the depression symptoms account for associations with cardiovascular prognosis. **Methods:** Self-reported somatic and cognitive-affective depressive symptoms were examined in relationship to heart rate variability (HRV), spontaneous baroreflex sensitivity (BRS), and the cortisol awakening response (CAR) in 2049 preadolescents (mean age = 11.1 years; 50.7% = girls) from the Tracking Adolescents' Individual Lives Survey (TRAILS). **Results:** Physiological measurements were not associated with the overall measure of depressive symptoms. Somatic depressive symptoms were negatively related to HRV and BRS, and positively to the CAR; cognitive-affective depressive symptoms were positively related to HRV and BRS, and negatively to the CAR. Associations with the CAR pertained to boys only. **Conclusions:** Somatic and cognitive-affective depressive symptoms differ in their association with both cardiac autonomic and HPA axis function in preadolescents. Particularly, somatic depression symptoms may mark cardiac risk. **Key words:** depressive symptoms, autonomic function, heart rate, baroreflex, cortisol, children.

**ANS** = autonomic nervous system; **BP** = blood pressure; **BRS** = baroreflex sensitivity; **CAR** = cortisol awakening response; **CVD** = cardiovascular disease; **HPA** = hypothalamic-pituitary-adrenal; **HR** = heart rate; **HRV** = heart rate variability; **HRV-LF** = heart rate variability in the low-frequency band; **HRV-HF** = heart rate variability in the high-frequency band; **MI** = myocardial infarction; **SD** = standard deviation; **YSR** = Youth Self-Report.

## INTRODUCTION

Depression has been shown to be associated with worse prognosis and mortality in patients with various cardiovascular diseases (CVDs) (1–3). Also, without the presence or a prior history of heart disease, depressed individuals are at increased risk of CVD and cardiac death (4). Even subclinical levels of depressive symptoms have been found to be proportionally associated with cardiovascular mortality and morbidity in both patients with CVD and healthy individuals (4).

Alterations of the cardiac autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis have been proposed as possible physiological links between depression and cardiovascular prognosis (5,6). Low heart rate variability (HRV) and reduced baroreflex sensitivity (BRS) are not only well-established risk factors for cardiac mortality in patients with CVD (7), but have also been related to depression in individuals with (8,9) and without CVD (10,11). Likewise, elevated cortisol levels have been associated with CVD and increased mortality risk in patients with chronic heart failure (12,13) as well as with depression in individuals with (14) and without (15) CVD, although decreased levels of cortisol have also been reported (13,16).

Depression is a heterogeneous disorder, involving a range of cognitive, somatic, and affective symptoms. Several studies suggest that only a subset of the depression symptoms account for the associations with cardiovascular prognosis (17–19). De Jonge et al. (18) showed that, in patients with myocardial infarction (MI), somatic/affective depressive symptoms were associated with a poor cardiovascular prognosis 2.5 years later, whereas cognitive/affective depressive symptoms were not. These findings were recently replicated in a study by Linke et al. (19) in women with suspected myocardial ischemia. Furthermore, Watkins et al. (20) reported that somatic depressive symptoms in depressed patients with MI were more strongly related to medical comorbidity than nonsomatic (cognitive) depressive symptoms. Barefoot et al. (17), on the other hand, found that only affective and not somatic depressive symptoms predicted long-term mortality in a sample of patients hospitalized for coronary angiography. This seeming contradiction might partly be explained by different instruments used or item overlap. Barefoot's affective dimension overlapped considerably with De Jonge's somatic/affective dimension; that is, both contained sadness, crying, and irritability. In sum, despite differences in design, sample, and

From the Interdisciplinary Center for Psychiatric Epidemiology and Graduate Schools for Behavioral and Cognitive Neurosciences and for Health Research (N.M.B., H.R., J.O., A.J.O.), University Medical Center Groningen, University of Groningen, Groningen, Netherlands; Unit of Genetic Epidemiology and Bioinformatics (H.R.), Department of Epidemiology, University Medical Center Groningen, Groningen, Netherlands; Department of Child- and Adolescent Psychiatry (A.D.), University Medical Center Groningen, Groningen, Netherlands; and Department of Child and Adolescent Psychiatry (F.V., A.J.O.), Erasmus University Medical Center - Sophia Children's Hospital Rotterdam, Rotterdam, Netherlands.

Address correspondence and reprint requests to Albertine J. Oldehinkel, Interdisciplinary Center for Psychiatric Epidemiology, University Medical Center Groningen, CC72, P.O. Box 30001, 9700 RB Groningen, Netherlands. E-mail: a.j.oldehinkel@med.umcg.nl

Received for publication May 18, 2009; revision received July 21, 2009.

This work was supported, in part, by various grants from the Netherlands Organization for Scientific Research NWO (Medical Research Council Program Grant GB-MW 940-38-011; ZonMW Brainpower Grant 100-001-004; ZonMw Risk Behavior and Dependence Grants 60-60600-98-018 and 60-60600-97-118; ZonMw Culture and Health Grant 261-98-710; Social Sciences Council medium-sized investment Grants GB-MaGW 480-01-006 and GB-MaGW 480-07-001; Social Sciences Council Project Grants GB-MaGW 457-03-018, GB-MaGW 452-04-314, and GB-MaGW 452-06-004; NWO large-sized investment Grant 175.010.2003.005); the Sophia Foundation for Medical Research (Projects 301 and 393); the Dutch Ministry of Justice (WODC); the European Science Foundation (EuroSTRESS Project FP-006); and the participating universities.

DOI: 10.1097/PSY.0b013e3181bc756b



0033-3174/09/7109-0944

measures used, all studies concluded that cardiovascular prognosis and mortality could be predicted from some, but not all, symptoms of depression.

Although evidence has been accumulating that symptom dimensions of depression are differentially related to cardiovascular prognosis, associations with more general cardiac autonomic function largely remain to be determined. A study by De Jonge et al. (21) revealed that low HRV was related to somatic and not to cognitive depressive symptoms, which suggests the presence of such differential associations. However, this study was conducted in patients with MI, not in nondiseased individuals, which may have affected the results. At present, studies regarding young individuals without any CVD are lacking. Another issue that still needs clarification concerns the possibility that somatic and cognitive symptoms also have a differential relationship with HPA axis functioning, which could suggest a broader risk profile than just cardiovascular prognosis.

The purpose of this study was to investigate possible specific associations of somatic and cognitive-affective depressive symptoms with HRV, BRS, and the cortisol awakening response (CAR) in a large population cohort of preadolescents. The study sample was 10 years old to 12 years old, an age at which the large modifications in cardiac autonomic function observed in childhood tend to level off (22–24), and cortisol production rates resemble adult levels (25). Several studies (26–28), also within the present cohort (29,30), have examined and—sometimes—found associations of autonomic measures and cortisol with internalizing problems in children and adolescents, but none has explicitly focused on heterogeneity within the depressive spectrum so far.

## METHODS

### Subjects

This study is based on data from the Tracking Adolescents' Individual Lives Survey (TRAILS), a large cohort study of Dutch adolescents (31). The current paper concerns a cross-sectional analysis of data collected at baseline (March 2001 to July 2002), which involved 2230 children (response rate = 76.0%; mean age = 11.09 years; standard deviation [SD] = 0.56; 50.8% = girls). Detailed information about the sample selection and nonresponse has been given elsewhere (32). Parental written informed consent was obtained after complete description of the study, and all preadolescents participated in the measurements voluntarily. The study was approved by the Central Committee on Research Involving Human Subjects (CCMO).

Of the total sample of 2230 preadolescents, 2049 (91.9%) participated in the autonomic or HPA axis measurements (1868 in the autonomic measurements, 1768 in the HPA axis measurements). The participants did differ from the rest of the TRAILS sample regarding sex and depressive symptoms. Quality checks of the autonomic measurements, described by Dietrich et al. (33), resulted in 1781 reliable HRV and 1472 BRS measurements, with scores of self-reported depressive symptoms recorded for 1765 and 1462 subjects, respectively. Complete assayable morning cortisol samples were available for 1667 participants, of whom 1640 had valid self-reported depressive symptoms scores.

### Depressive Symptoms

Depressive symptoms were assessed by the Youth Self-Report (YSR), a self-reported evaluation of the child's emotional and behavioral problems in the past 6 months (34). Questionnaires were filled out at school in groups, under the supervision of one or more TRAILS assistants. The 13 items (covering depressed mood, anhedonia, loss of energy, feelings of worthlessness and guilt, suicidal ideation, sleep problems, and eating problems) of the YSR Affective Problems Scale (Cronbach's $\alpha = 0.77$) reflect symptoms of a Major Depressive Episode according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (35). Each item could be rated as 0 = not true; 1 = somewhat or sometimes true; or 2 = very true or often true. The scale score represents the mean item scores. The convergent validity of the Affective Problems scale with standardized clinical DSM-IV diagnoses of major depressive disorder and dysthymia has been found to be adequate (36).

Corrected-item-mean imputation (37) was employed to handle missing data if <30% of the items were unanswered. If more items were unanswered, the YSR scale was considered incomplete and the data were discarded in subsequent analyses ($n = 44$). Preliminary analysis showed that all item-total correlations were >0.35, except for the item "I sleep more than most kids" ($r = .24$), omission of which increased the internal consistency. The remaining 12 items were divided into a somatic subscale (five items, Cronbach's $\alpha = 0.58$) and a cognitive-affective subscale (seven items, Cronbach's $\alpha = 0.67$), based on item content. The items are listed in Table 1. Confirmative factor analysis using MPlus 3.11 software yielded empirical support for these two YSR subscales, with goodness-of-fit indices (Comparative Fit Index = 0.92; Tucker-Lewis Index = 0.94; root mean square error of approximation = 0.06; standardized root mean square residual = 0.06) that indicated an adequate fit to the sample data (38,39). The two depression dimensions were moderately correlated ($r = .46$).

### Cardiac Autonomic Measures

Individual measurements of heart rate (HR) and blood pressure (BP) took place in a quiet room at school, generally in the morning (8:30 AM–12 PM) and occasionally in the early afternoon (1 PM–3 PM). Participants were informed about the procedure as they were in the supine position, and encouraged to relax and not to move or speak during the data acquisition. HR was measured by three precordial leads and continuous BP was measured by using a Portapres device (FMS Finapres Medical Symptoms, BV, Amsterdam, The Netherlands). Recordings did not start until signals had reached a stabilized steady state. Children were in the supine position for about 5 minutes before measurements were started. BP and HR signals were registered for 4 minutes as the patients were in the supine position during spontaneous breathing. Recordings were digitized, using a DAS-12 data acquisition card for notebooks (Keithley Instruments, Cleveland, Ohio), and stored on hard disk for offline analysis. The sample rate was 100 Hz. We used a special interpolation algorithm, which increased the time resolution for R-peak detection by a factor of 2.5. This resulted in interbeat intervals (IBIs) with

**TABLE 1. Items of the Somatic and Cognitive-Affective Depressive Symptom Scales**

| | Mean | SD | % Endorsing the Item[a] |
|---|---|---|---|
| Somatic symptoms | | | |
| Lack of appetite | 0.42 | 0.59 | 36.4% |
| Overtired | 0.23 | 0.46 | 21.2% |
| Reduced sleep | 0.48 | 0.67 | 38.5% |
| Trouble sleeping | 0.44 | 0.66 | 34.2% |
| Lack of energy | 0.35 | 0.57 | 30.4% |
| Cognitive-affective symptoms | | | |
| Loss of pleasure | 0.32 | 0.54 | 28.7% |
| Crying | 0.40 | 0.55 | 36.7% |
| Self-harm | 0.04 | 0.21 | 4.1% |
| Suicidal ideation | 0.09 | 0.33 | 8.3% |
| Feelings of worthlessness | 0.21 | 0.44 | 19.4% |
| Feeling of guilty | 0.31 | 0.53 | 27.7% |
| Sadness | 0.26 | 0.49 | 23.7% |

[a] Score 1 or 2.
SD = standard deviation.

sufficient resolution for HRV determination (40). Calculation of HRV and BRS was based on power spectral analysis, using the CARSPAN spectral analysis software program. CARSPAN allows for the Discrete Fourier Transformation of nonequidistant BP and IBI series. The analyzed time series were checked and corrected for artifacts, as described by Dietrich and colleagues (33). HRV was defined as the IBI power in the low-frequency (LF = 0.07–0.14 Hz) and high-frequency (HF = 0.15–0.40 Hz) band, respectively, and expressed in $ms^2$. Although sometimes debated (41), the HRV in the LF band (HRV-LF) is largely assumed to reflect both sympathetic and vagal modulation of cardiac control (42). HRV in the HF band (HRV-HF), which is associated with the respiratory cycle and often referred to as respiratory sinus arrhythmia, results from centrally mediated cardiac vagal activity. Hence, HRV-HF is considered as an index of vagal tone. BRS was defined as the mean modulus between systolic BP and IBI in the LF band and is expressed in ms/mm Hg (33,40,43).

We are aware of contrasting perspectives on the need to assess and control for respiration, as recommended by the Task Force of the European Society of Pacing and Electrophysiology in 1996 (44–47). However, research has shown that the amplitude of HRV is not affected by respiration frequency under baseline conditions (48). Another source of measurement variation is the use of spontaneous, instead of paced, breathing (49). When breathing spontaneously, children differ in their breathing patterns (50), but the method of spontaneous breathing provides sufficiently reliable HRV measurements, provided that the children breathe normally and avoid slow or irregular breathing (51).

### Cortisol

Participants received a verbal and written instruction to collect saliva at home immediately after waking up as they were still lying in bed (Cort1) and 30 minutes after awakening (Cort2), using the Sarstedt Salivette device (Nümbrecht, Germany). Participants were instructed not to collect saliva when feeling ill (e.g., having a cold, headache) or when menstruating, and if possible, to refrain from taking medication. Furthermore, both the sampling and the preceding day should be normal school days, without special events or stressful circumstances. Deviations from this protocol had to be recorded on an accompanying form. Concerning the sampling procedure, participants were instructed to rinse their mouth thoroughly with tap water and not to consume sour products or brush their teeth shortly before sampling saliva. Directly after sampling, saliva samples were stored by participants in their freezer and mailed as soon as possible to the institute. The mean self-reported sampling time of the morning samples was 7 AM for Cort1 and 7:30 AM for Cort2. Salivary cortisol was measured by a time-resolved immunoassay with fluorometric detection (DELFIA) with intra- and interassay coefficients of variation of 4.0% to 6.7% and 7.1% to 9.0%, respectively (52).

### Covariates

Sex, age, physical activity, physical health, and body mass index were included as covariates. Participants indicated their level of physical activity by reporting how often they performed sports, such as swimming, playing soccer, or horseback riding on a 5-point scale, ranging from 0 = (almost) never to 4 = six to seven times a week. Physical health was based on the number of parent-reported physical health problems of the preadolescent during the past year. Body mass index was calculated by dividing the weight (kg) by the square of the height ($m^2$). Information regarding oral contraceptives use and smoking was also available, but because none of the participants used oral contraceptives and only very few (<1%) were regular smokers, these variables were not included in this study.

### Data Cleaning

Participants with extreme (>3 SD from the mean) HRV ($n$ = 12) or BRS ($n$ = 12) values were excluded from ANS analyses, resulting in 1753 cases with valid HRV and 1450 cases with valid BRS data. There were fewer BRS than HRV data, because calculation of the BRS requires both valid HR and valid BP measurements, whereas calculation of the HRV is only based on HR data. Sixty participants were excluded from the cortisol analyses due to the use of corticosteroid-containing medication ($n$ = 22), extreme cortisol values (>3 SD from the mean, $n$ = 29), or lack of compliance with the protocol ($n$ = 9). Lack of compliance was defined as failing to take the first sample within 5 minutes of awakening or the second sample between 25 and 35 minutes after awakening. This resulted in 1580 participants for whom the CAR could be calculated. The CAR was measured by the trapezoid method, using the area under the curve with respect to the increase, as described by Pruessner et al. (53), which comes down to ((Cort2 − Cort1)/2) × 0.50. This measure emphasizes changes over time. For 459 (29%) of the 1580 participants, cortisol levels did not increase after awakening, but were lower than or equal to half an hour after awakening than immediately after waking up. This percentage of participants with a negative cortisol slope (CAR nonresponders) is comparable to percentages reported by others (54,55).

### Statistical Analysis

To approximate a normal distribution, all autonomic variables were transformed to their natural logarithm. In addition to the (transformed) levels of HRV-LF and HRV-HF, we also calculated normalized units, that is, the power in the LF and HF spectrum, respectively, divided by the total power minus the very LF component. Significance levels (two-tailed) were set at $p < .05$ for all analyses. All analyses were performed in SPSS (version 14, SPSS, Chicago, Illinois).

First, we examined associations of HRV, BRS, and CAR with overall depressive symptoms. Separate linear regression analyses were conducted with each physiological measure (HRV-LF, HRV-HF, BRS, and CAR) as the dependent variable and the overall depressive symptoms scale as the predictor. Subsequently, these analyses were repeated with the somatic and cognitive-affective depressive symptoms scales as predictors (in a single model, so adjusted for each other) to examine differences between the two subscales.

Gender, age, body mass index, physical activity, and physical health were considered possible confounders and therefore included as covariates in all analyses. Furthermore, for each of the depression variables entered in the regression models, we tested interactions with sex (coded as girls = 0; boys = 1) in a second step. In case of significant interaction effects, post hoc analyses in each of the subgroups were performed to explore the nature of the differences.

## RESULTS

### Descriptive Statistics

Items of the somatic and cognitive-affective depressive symptoms scale are listed in Table 1. Mean and SD values of all variables used in this study are shown in Table 2. As might be expected, the three autonomic measures were strongly correlated ($r_{HRVLF–HRVHF}$ = .81, $r_{HRVLF–BRS}$ = .69, $r_{HRVHF–BRS}$ = .64; all $p < .01$), whereas none of the autonomic measures was

**TABLE 2. Descriptive Statistics of the Variables Used in This Study**

| | Mean | SD | *n* |
|---|---|---|---|
| Overall depressive symptoms | 0.29 | 0.25 | 2049 |
| Somatic symptoms | 0.38 | 0.36 | 2049 |
| Cognitive-affective symptoms | 0.23 | 0.27 | 2049 |
| HRV-LF, ln($ms^2$) | 6.51 | 1.06 | 1753 |
| HRV-LF Nu | 0.47 | 0.03 | 1753 |
| HRV-HF, ln($ms^2$) | 7.44 | 1.33 | 1753 |
| HRV-HF Nu | 0.53 | 0.03 | 1753 |
| BRS, ln(ms/mm Hg) | 2.58 | 0.59 | 1450 |
| CAR, nmol/L | 0.96 | 1.75 | 1580 |
| Age | 11.07 | 0.54 | 2049 |
| Physical activity, range = 0–4 | 1.93 | 1.19 | 2038 |
| Physical health, range = 0–17 | 2.53 | 1.96 | 1796 |
| BMI | 18.01 | 3.03 | 2002 |

SD = standard deviation; HRV-LF = heart rate variability in the low-frequency band (0.07–0.14 Hz); HRV-HF = heart rate variability in the high-frequency band (0.15–0.40 Hz); Nu = normalized units; BRS = baroreflex sensitivity; CAR = cortisol awakening response; BMI = body mass index.

**TABLE 3. Physiological Variables Regressed on Overall, Somatic, and Cognitive-Affective Depressive Symptoms**

| | Dependent Variables | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | HRV-LF | | HRV-HF | | BRS | | CAR | |
| | $\beta$ | *p* | $\beta$ | *p* | $\beta$ | *p* | $\beta$ | *p* |
| Covariates | | | | | | | | |
| Gender | 0.08 | <.01 | 0.07 | <.01 | 0.12 | <.01 | −0.03 | .23 |
| Age | −0.03 | .31 | −0.06 | .01 | 0.00 | .98 | 0.01 | .76 |
| Physical activity | 0.04 | .03 | 0.04 | .14 | 0.02 | .46 | −0.03 | .26 |
| Physical health | −0.06 | .10 | −0.04 | .17 | −0.02 | .43 | 0.03 | .24 |
| BMI | −0.02 | .41 | −0.04 | .10 | −0.00 | .96 | 0.03 | .33 |
| $R^2$ | *1.6%* | | *1.7%* | | *1.6%* | | *0.1%* | |
| Overall depressive symptoms | 0.00 | .89 | 0.02 | .55 | 0.00 | .89 | −0.01 | .74 |
| $R^2$ *change* | *0.0%* | | *0.0%* | | *0.0%* | | *0.0%* | |
| Somatic symptoms | −0.07 | .02 | −0.04 | .14 | −0.07 | .02 | ♀: −0.03 | .43 |
| | | | | | | | ♂: 0.12 | <.01 |
| Cognitive-affective symptoms | 0.07 | .02 | 0.06 | .04 | 0.08 | <.01 | ♀: 0.00 | .94 |
| | | | | | | | ♂: −0.10 | .03 |
| $R^2$ *change* | *0.5%* | | *0.3%* | | *0.7%* | | ♀*: 0.1%* | |
| | | | | | | | ♂*: 1.4%* | |

HRV-LF = heart rate variability in the low-frequency band (0.07 to 0.14 Hz); HRV-HF = heart rate variability in the high-frequency band (0.15 to 0.40 Hz); BRS = baroreflex sensitivity; CAR = cortisol awakening response.

significantly correlated with the CAR ($r_{HRVLF–CAR} = .04$, $r_{HRVHF–CAR} = 0.05$, $r_{BRS–CAR} = .03$; all $p > .15$).

### Depression Effects on Cardiac Autonomic Function

Overall depressive symptoms were not associated with any of the autonomic measures (Table 3). The somatic symptoms were significantly inversely associated with HRV-LF and BRS, but not with HRV-HF. The cognitive-affective symptoms were positively associated with all three ANS measures. None of the associations with the autonomic measures showed significant sex differences (all $p > .19$). Normalized HRV measures were not related to any of the depression (sub)scales (all $p > .17$).

As the standardized regression coefficients ($\beta$) indicated, the effect sizes were generally small. To illustrate the magnitude of the effects, we calculated the range of possible (i.e., based on depression scores between 0 and 2) HRV and BRS values, given the subscale models presented in Table 3 and assuming mean values on all covariates. Estimated HRV-LF scores ranged between 6.11 and 7.03, HRV-HF scores between 7.13 and 8.01, and BRS scores between 2.34 and 2.96. These maximum estimated differences were all <1 SD.

### Depression Effects on the CAR

Overall depressive symptoms were not associated with HPA axis function as measured with the CAR (Table 3). The effect of somatic symptoms on the CAR seemed significantly different for boys and girls ($\beta = 0.10$, $p = .02$), whereas a marginally significant interaction with sex was found for cognitive-affective symptoms ($\beta = −0.08$, $p = .07$). Post hoc analyses revealed that neither somatic nor cognitive-affective symptoms were associated with the CAR in girls, whereas in boys, somatic symptoms were positively related to the CAR and cognitive-affective symptoms were inversely related to the CAR (Table 3). Again, effect sizes were small. Possible estimated CAR values in boys ranged between 0.36 and 1.30.

## DISCUSSION

Overall self-reported depressive symptoms were not associated with HRV, BRS, and CAR in a large population cohort of preadolescents. After dividing the symptoms into somatic versus cognitive-affective symptoms, however, contrasting relationships with the physiological measures emerged. Somatic depressive symptoms were inversely associated with HRV and BRS, and positively with CAR, whereas cognitive-affective depressive symptoms were positively associated with HRV and BRS, and negatively with CAR. The associations with the CAR were only found in boys. The effect sizes were very small, but taking into account the nonclinical nature of the sample and the fact that both depressive symptoms and physiological measures are influenced by a multitude of factors, we feel that higher effect sizes could not be expected, and that the results should not be discarded as trivial.

Our findings are consonant with the growing evidence that depression is a heterogeneous disorder, which encompasses different underlying pathophysiological processes (56,57), and that only some depressive symptoms account for the relationship between depression and cardiovascular prognosis (17–20). De Jonge et al. (21) found that low HRV was associated with somatic symptoms of depression in patients with stable coronary heart disease. Our results confirm these findings in a population cohort of preadolescents without (overt) CVD and in whom depressive symptoms were generally mild at the most. We extended De Jonge's findings not

only to a nonclinical sample but also to other important indicators of physiological regulation, that is, BRS and CAR. Somatic depressive symptoms were more strongly associated with the LF band of HRV and BRS than with the HF band of HRV. It is tempting to speculate that the assumed dual innervation (sympathetic and vagal) reflected in the HRV-LF, as opposed to mainly vagal influences in the HRV-HF band, accounts for these differences. However, replication of this finding as well as prospective associations between LF power and pathology are needed before HRV-LF may be considered a prognostic tool similar to HRV-HF. The findings with regard to the normalized HRV measures suggest that the relative value of each power component was not related to any of the depression scales.

A recent meta-analysis by Chida and Steptoe (58), investigating the association between the CAR and psychosocial factors, concluded that there was a lack of overall associations in regard to depression, due to both increased and reduced CARs. The reverse effects found for somatic and cognitive-affective symptoms of depression might partially explain these inconsistent findings. Yet, our findings are counterintuitive. A high CAR, which has often been related to life stress (58), was associated with somatic depressive symptoms, whereas a blunted CAR, which has been related to fatigue (58), was associated with cognitive/affective symptoms. Furthermore, most effects found in prior studies (also) concerned females, whereas we only found associations in boys. So, although it is interesting that the differential effects for somatic and cognitive/affective symptoms did not only concern cardiac autonomic measures but the HPA axis as well, the nature of the cortisol effects is still puzzling.

The association of cognitive-affective depressive symptoms with high HRV was unforeseen, and contrary to results reported by De Jonge et al. (21), who did not find an association between HRV and the cognitive dimension of depression. However, their study concerned patients with stable coronary heart disease, whose age and lifestyle (e.g., smoking) differed markedly from our population. These factors may have accounted for the divergent findings in both studies. Our findings are in concordance with Rottenberg et al. (59,60), who reported a positive association between HRV-HF and cognitive-affective symptoms like sadness and crying in clinically depressed participants. Also, interesting in this respect are results reported by Koelsch et al. (61), who found that high HRV-HF was associated with high emotionality, and by Miller and Wood (62), whose study revealed that an increase in self-reported sadness was accompanied by an increase in HRV. Tentatively, the positive associations of cognitive-affective symptoms with cardiac autonomic measures might be explained by Porges' notion that high resting HRV(-HF) reflects perception of a safe environment, which allows social engagement and the expression of emotions (60,63). Whatever the reason, our findings as well as previous findings suggest that, in itself and when not associated with somatic symptoms, emotionality may not be associated with increased cardiac risk.

The heterogeneous nature of depression is of interest in view of the different measurement instruments that are used to assess the syndrome. Somatic symptoms are omitted from some of these instruments, for instance, the Hospital Anxiety and Depression Scale (64). Other scales, such as the Hamilton Rating Scale for Depression (65), contain relatively many somatic items. These kinds of disbalances can mask differential relationships of cardiac autonomic and HPA axis function with subdimensions of depression, and may partly explain discrepant associations found between depressive symptoms and indices of the ANS and HPA axis. Our data provide a basis for more specific pathophysiological hypotheses on the relationship between depression and cardiovascular prognosis. Both the ANS and the HPA axis were associated with the depressive symptom dimensions, suggesting that depression as a— putative— cardiac risk factor may be mediated by multiple pathophysiological mechanisms.

This study had several limitations. First, the cross-sectional design does not allow inferences about causality. Whether depressive symptoms are the outcome or the cause of the physiological variables under study still needs to be determined. Second, the YSR Affective Problems scale was constructed on the basis of expert ratings of the original, empirically derived YSR items, and was not originally developed to assess depressive problems according to the DSM-IV criteria. Consequently, the items do not represent one-to-one counterparts with all DSM-IV criteria. Another limitation of the YSR Affective Problems scale is the use of a 6-month time window, which precludes a clear distinction between state and trait effects. As the severity of depressive problems may covary with physiological functioning (66), multiple assessments of physiological functioning and state depression are needed to distinguish between state and trait effects. Finally, the internal consistency of the two depression subscales was low, even when taking into account the small number of items. This probably influenced the estimated effects conservatively, and suggests that these scales are still heterogeneous. Heterogeneity within the cognitive-affective domain was also reported by Rottenberg (59), who found that sadness and crying were positively, and suicidal ideation negatively associated with HRV-HF (it should be noted, however, that this finding did not replicate in another study) (60). More fine-tuned patterns of association were beyond the scope of this article, but may be revealed in future studies.

In conclusion, the present study revealed that somatic and cognitive-affective depressive symptoms are differentially associated with the ANS and the HPA axis in preadolescents. Hence, alterations of the ANS that have been linked with cardiac risk are associated with somatic depressive symptoms as early as in preadolescence. Future research should take into account that associations between depression and HRV, BRS, and CAR variables are partly dependent on whether and how somatic and cognitive-affective symptoms are represented in the depression measures used.

*This research is part of the Tracking Adolescents' Individual Lives Survey (TRAILS). Participating centers of TRAILS include various*

*departments of the University Medical Centre and University of Groningen, the Erasmus University Medical Centre Rotterdam, the University of Utrecht, the Radboud Medical Centre Nijmegen, and the Parnassia Bavo group, all in the Netherlands. We are grateful to all adolescents, their parents, and teachers who participated in this research and to everyone who worked on this project and made it possible.*

## REFERENCES

1. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. Psychosom Med 2004;66:802–13.
2. Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146,538 participants in 54 observational studies. Eur Heart J 2006;27:2763–74.
3. Van Melle JP, De Jonge P, Spijkerman TA, Tijssen JG, Ormel J, Van Veldhuisen DJ, Van den Brink RH, Van den Berg MP. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. Psychosom Med 2004;66: 814–22.
4. Van der Kooy K, Van Hout H, Van Marwijk H, Marten H, Stehouwer C, Beekman A. Depression and the risk for cardiovascular diseases: systematic review and meta analysis. Int J Geriatr Psychiatry 2007;22:613–26.
5. Grippo AJ, Johnson AK. Biological mechanisms in the relationship between depression and heart disease. Neurosci Biobehav Rev 2002;26: 941–62.
6. Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. Arch Gen Psychiatry 1998;55:580–92.
7. La Rovere MT, Pinna GD, Hohnloser SH, Marcus FI, Mortara A, Nohara R, Bigger JT, Camm AJ, Schwartz PJ. Baroreflex sensitivity and heart rate variability in the identification of patients at risk for life-threatening arrhythmias: implications for clinical trials. Circulation 2001;103: 2072–7.
8. Watkins LL, Grossman P. Anxiety reduces baroreflex cardiac control in older adults with major depression. Psychosom Med 1999;61:334–40.
9. Stein PK, Carney RM, Freedland KE, Skala JA, Jaffe AS, Kleiger RE, Rottman JN. Severe depression is associated with markedly reduced heart rate variability in patients with stable coronary heart disease. J Psychosom Res 2000;48:493–500.
10. Broadley AJ, Frenneaux MP, Moskvina V, Jones CJ, Korszun A. Baroreflex sensitivity is reduced in depression. Psychosom Med 2005;67: 648–51.
11. Vaccarino V, Lampert R, Bremner JD, Lee F, Su S, Maisano C, Murrah NV, Jones L, Jawed F, Afzal N, Ashraf A, Goldberg J. Depressive symptoms and heart rate variability: evidence for a shared genetic substrate in a study of twins. Psychosom Med 2008;70:628–36.
12. Güder G, Bauersachs J, Frantz S, Weismann D, Allolio B, Ertl G, Angermann CE, Stork S. Complementary and incremental mortality risk prediction by cortisol and aldosterone in chronic heart failure. Circulation 2007;115:1754–61.
13. Bhattacharyya MR, Molloy GJ, Steptoe A. Depression is associated with flatter cortisol rhythms in patients with coronary artery disease. J Psychosom Res 2008;65:107–13.
14. Otte C, Marmar CR, Pipkin SS, Moos R, Browner WS, Whooley MA. Depression and 24-hour urinary cortisol in medical outpatients with coronary heart disease: the Heart and Soul Study. Biol Psychiatry 2004; 56:241–7.
15. Pruessner M, Hellhammer DH, Pruessner JC, Lupien SJ. Self-reported depressive symptoms and stress levels in healthy young men: associations with the cortisol response to awakening. Psychosom Med 2003;65:92–9.
16. Ahrens T, Deuschle M, Krumm B, Van der Pompe G, Den Boer JA, Lederbogen F. Pituitary-adrenal and sympathetic nervous system responses to stress in women remitted from recurrent major depression. Psychosom Med 2008;70:461–7.
17. Barefoot JC, Brummett BH, Helms MJ, Mark DB, Siegler IC, Williams RB. Depressive symptoms and survival of patients with coronary artery disease. Psychosom Med 2000;62:790–5.
18. De Jonge P, Ormel J, Van den Brink RH, Van Melle JP, Spijkerman TA, Kuijper A, Van Veldhuisen DJ, Van den Berg MP, Honig A, Crijns HJGM, Schene A. Symptom dimensions of depression following myocardial infarction and their relationship with somatic health status and cardiovascular prognosis. Am J Psychiatry 2006;163:138–44.
19. Linke SE, Rutledge T, Johnson D, Vaccarino V, Bittner V, Cornell CE, Eteiba W, Sheps DS, Krantz DS, Parashar S, Bairey Merz CN. Depressive symptoms dimensions and cardiovascular prognosis among women with suspected myocardial ischemia. A report from the National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation. Arch Gen Psychiatry 2009;66:499–507.
20. Watkins LL, Schneiderman N, Blumenthal JA, Sheps DS, Catellier D, Taylor CB, Freedland KE. Cognitive and somatic symptoms of depression are associated with medical comorbidity in patients after acute myocardial infarction. Am Heart J 2003;146:48–54.
21. De Jonge P, Mangano D, Whooley MA. Differential association of cognitive and somatic depressive symptoms with heart rate variability in patients with stable coronary heart disease: findings from the Heart and Soul Study. Psychosom Med 2007;69:735–9.
22. Goto M, Nagashima M, Baba R, Nagano Y, Yokota M, Nishibata K, Tsuji A. Analysis of heart rate variability demonstrates effects of development on vagal modulation of heart rate on healthy children. J Pediatr 1997;130:725–9.
23. Massin M, Von Bermuth G. Normal ranges of heart rate variability during infancy and childhood. Pedriatr Cardiol 1997;18:297–302.
24. Silvetti MS, Drago F, Ragonese P. Heart rate variability in healthy children and adolescents is partially related to age and gender. Int J Cardiol 2001;81:169–74.
25. Kenny FM, Preeyasombat C, Migeon CJ. Cortisol production rate. II. Normal infants, children, and adults. Pediatrics 1966;37:34–42.
26. Goodyer IM, Bacon A, Ban M, Croudace J, Herbert J. Serotonin transporter gene, morning cortisol and subsequent depression in adolescents. Br J Psychiatry 2009;195:39–45.
27. Kagan J, Reznick JS, Snidman N. The physiology and psychology of behavioral inhibition in children. Child Dev 1987;58:1459–73.
28. Monk C, Kovelenko P, Ellman LM, Sloan RP, Bagiella E, Gorman JM, Pine DS. Enhanced stress reactivity in pediatric anxiety disorders: implications for future cardiovascular health. Int J Neuropsychopharmacol 2001;4:199–206.
29. Bosch NM, Riese H, Omel J, Verhulst F, Oldehinkel AJ. Stressful life events and depressive symptoms in young adolescents: modulation by respiratory sinus arrhythmia? The TRAILS study. Biol Psychol 2009;81: 40–47.
30. Greaves-Lord K, Ferdinand RF, Oldehinkel AJ, Sondeijker FEPL, Ormel J, Verhulst FC. Higher cortisol awakening response in young adolescents with persistent anxiety problems. Acta Psychiatr Scand 2007;116: 137–44.
31. Huisman M, Oldehinkel AJ, de Winter A, Minderaa RB, de Bildt A, Huizink AC, Verhulst FC, Ormel J. Cohort profile: the Dutch 'TRacking Adolescents' Individual Lives' Survey'; TRAILS. Int J Epidemiol 2008; 37:1227–35.
32. De Winter AF, Oldehinkel AJ, Veenstra R, Brunnekreef JA, Verhulst FC, Ormel J. Evaluation of non-response bias in mental health determinants and outcomes in a large sample of pre-adolescents. Eur J Epidemiol 2005;20:173–81.
33. Dietrich A, Riese H, van Roon AM, van Engelen K, Ormel J, Neeleman J, Rosmalen JGM. Spontaneous baroreflex sensitivity in (pre)adolescents. J Hypertens 2006;24:345–52.
34. Achenbach TM, Rescorla LA. Manual for ASEBA School-Age Forms and Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth, and Families; 2001.
35. Achenbach TM, Dumenci L, Rescorla LA. DSM-oriented and empirically based approaches to constructing scales from the same item pools. J Clin Child Adolesc Psychol 2003;32:328–40.
36. Ferdinand RF. Validity of the CBCL/YSR DSM-IV scales Anxiety Problems and Affective Problems. J Anxiety Disord 2008;22:126–34.
37. Huisman M. Imputation of missing item responses: some simple techniques. Qual Quant 2000;34:331–51.
38. Hu L, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: conventional criteria versus new alternatives. Structural Equation Modeling: A Multidisciplinary Journal 1999;6:1–55.
39. Marsh HW, Hau KT, Wen Z. In search of golden rules: comment on hypothesis-testing approaches to setting cutoff values for fit indexes and dangers in overgeneralizing Hu and Bentler's (1999) findings. Structural Equation Modeling: A Multidisciplinary Journal 2004;11:320–41.
40. Greaves-Lord K, Tulen J, Dietrich A, Sondeijker FE, Van Roon AM, Oldehinkel AJ, Ormel J, Verhulst FC, Huizink A. Reduced autonomic

flexibility as a predictor for future anxiety in girls from the general population: the TRAILS study. Psychiatry Res, In Press.
41. Eckberg DL. Sympathovagal balance: a critical appraisal. Circulation 1997;96:3224–32.
42. Parati G, Mancia G, Di Rienzo M, Castiglioni P, Taylor JA, Studinger P. Point: counterpoint: cardiovascular variability is/is not an index of autonomic control of circulation. J Appl Physiol 2006;101:676–82.
43. Van Roon AM, Mulder LJ, Althaus M, Mulder G. Introducing a baroreflex model for studying cardiovascular effects of mental workload. Psychophysiol 2004;41:961–81.
44. Robbe HW, Mulder LJM, Rüddel H, Langewitz WA, Veldman JBP, Mulder G. Assessment of baroreflex sensitivity by means of spectral analysis. Hypertens 1987;10:538–43.
45. Berntson GG, Bigger JT Jr, Eckberg DL, Grossman P, Kaufmann PG, Malik M, Nagaraja HN, Porges SW, Saul JP, Stone PH, van der Molen MW. Heart rate variability: origins, methods, and interpretive caveats. Psychophysiology 1997;34:623–48.
46. Grossman P, Van Beek J, Wientjes C. A comparison of three quantification methods for estimation of respiratory sinus arrhythmia. Psychophysiology 1990;27:702–14.
47. Ritz T, Dahme B. Implementation and interpretation of respiratory sinus arrhythmia measures in psychosomatic medicine: practice against better evidence? Psychosom Med 2006;68:617–27.
48. Denver JW, Reed SF, Porges SW. Methodological issues in the quantification of respiratory sinus arrhythmia. Biol Psychol 2007;74:286–94.
49. Pitzalis MV, Mastropasqua F, Massari F, Passantino A, Colombo R, Mannarini A, Forleo C, Rizoon P. Effect of respiratory rate on the relationships between RR interval and systolic blood pressure fluctuations: a frequency-dependent phenomenon. Cardiovasc Res 1998; 38:332–9.
50. Saul JP, Berger RD, Albrecht P, Stein SP, Chen MH, Cohen RJ. Transfer function analysis of the circulation: unique insights into cardiovascular regulation. Am J Physiol 1991;261:H1231–45.
51. Pinna GD, Maestri R, La Rovere MT, Gobbi E, Fanfulla F. Effect of paced breathing on ventilatory and cardiovascular variability parameters during short-term investigations of autonomic function. Am J Physiol Heart Circ Physiol 2006;290:424–33.
52. Rosmalen JG, Oldehinkel AJ, Ormel J, de Winter AF, Buitelaar JK, Verhulst FC. Determinants of salivary cortisol levels in 10–12 year old children; a population-based study of individual differences. Psychoneuroendocrinology 2005;30:483–95.
53. Pruessner JC, Kirschbaum C, Meinlschmid G, Hellhammer DH. Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. Psychoneuroendocrinology 2003;28:916–31.
54. Kudielka BM, Kirschbaum C. Awakening cortisol responses are influenced by health status and awakening time but not by menstrual cycle phase. Psychoneuroendocrinology 2003;28:35–47.
55. Broderick JE, Arnold D, Kudielka BM, Kirschbaum C. Salivary cortisol sampling compliance: comparison of patients and healthy volunteers. Psychoneuroendocrinology 2004;29:636–50.
56. Gold PW, Chrousos GP. Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states. Mol Psychiatry 2002;7:254–75.
57. Antonijevic IA. Depressive disorders—is it time to endorse different pathophysiologies? Psychoneuroendocrinology 2006;31:1–15.
58. Chida, Y, Steptoe, A. Cortisol awakening response and psychosocial factors: A systematic review and meta-analysis. Biol Psychol 2009;80: 265–78.
59. Rottenberg J. Respiratory sinus arrhythmia as a predictor of outcome in major depressive disorder. J Affect Disord 2002;71:265–72.
60. Rottenberg J, Chambers AS, Allen JJ, Manber R. Cardiac vagal control in the severity and course of depression: the importance of symptomatic heterogeneity. J Affect Disord 2007;103:173–9.
61. Koelsch S, Remppis A, Sammler D, Jentschke S, Mietchen D, Fritz T, Bonnemeier H, Siebel WA. A cardiac signature of emotionality. Eur J Neurosci 2007;26:3328–38.
62. Miller BD, Wood BL. Influence of specific emotional states on autonomic reactivity and pulmonary function in asthmatic children. J Am Acad Child Adolesc Psychiatry 1997;36:669–77.
63. Porges SW. The polyvagal perspective. Biol Psychol 2007;74:116–43.
64. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–70.
65. Hamilton MA. Rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62.
66. Chambers AS, Allen JJ. Vagal tone as an indicator of treatment response in major depression. Psychophysiology 2002;39:861–4.