HHS Public Access

Author manuscript

Psychosom Med. Author manuscript; available in PMC 2018 July 01.

Published in final edited form as:

Psychosom Med. 2017 ; 79(6): 614–621. doi:10.1097/PSY.0000000000000458.

Vagal Regulation of Cardiac Function in Early Childhood and Cardiovascular Risk in Adolescence

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Abstract

Objective—Poor behavioral self-regulation in the first two decades of life has been identified as an important precursor of disease risk in adulthood. However, physiological regulation has not been well-studied as a disease risk factor before adulthood. We tested whether physiological regulation at age two, in the form of vagal regulation of cardiac function (indexed by RSA change), would predict three indicators of cardiovascular risk at age 16 (diastolic and systolic blood pressure and body mass index).

Methods—Data came from 229 children who participated in a community-based longitudinal study. At age two, children were assessed for RSA baseline and RSA change [ln(ms)^2] in response to a series of challenge tasks. These same children were assessed again at age 16 for diastolic and systolic blood pressure (mmHg), height (m) and weight (kg).

Results—Regression analyses revealed that less RSA withdrawal at age two predicted higher diastolic blood pressure at age 16, adjusting for demographic characteristics (B = −3.07**, S.E. = 1.12, p = .006). Follow-up analyses demonstrated that these predictions extended to clinically significant levels of diastolic prehypertension (odds ratio = 0.43, 95% confidence interval, .22–.89). RSA withdrawal did not significantly predict adolescent body mass index or systolic blood pressure.

Conclusions—Vagal regulation of cardiac function in early childhood predicts select indicators of cardiovascular risk 14 years later. Early signs of attenuated vagal regulation could indicate an

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Conflict of Interest: The authors have no conflicts of interest to report.

increased risk for elevated blood pressure before adulthood. Future research should test biological, behavioral, and psychological mechanisms underlying these long-term predictions.

Keywords

Vagal Regulation; Cardiovascular Risk; Diastolic Blood Pressure; Childhood; Adolescence; Self-Regulation

INTRODUCTION

Obesity and hypertension are key risk factors for cardiovascular disease; these risk factors are increasingly common among young people in the United States (1–5). Such cardiovascular risk (CVR) in the early life course poses a public health burden: CVR initiates and contributes to morbidity and mortality from chronic diseases by young adulthood, with high costs for individuals, families, and society (6–11).

In recent years, deficits in childhood self-regulation have been identified as important predictors of later disease risk (12). Broadly speaking, self-regulation refers to a person's conscious or unconscious efforts to control his/her inner states or behaviors (13). It is a multi-dimensional construct that can be observed in physiological, cognitive, emotional, and behavioral domains. Tests of long-term predictions from early childhood self-regulation to cardiovascular disease risk before adulthood are currently rare. Indeed, the few extant studies were limited in focus to emotional and behavioral self-regulation (e.g., 14); and, while informative, these studies did not examine predictions from early childhood *physiological* regulation to adolescent hypertension and obesity. The current study addresses this gap by testing whether physiological regulation in early childhood—specifically vagal regulation of cardiac function, indexed by respiratory sinus arrhythmia in response to challenge—predicts diastolic and systolic blood pressure and body mass index (BMI) in adolescence.

Physiological regulation is one of the earliest-emerging dimensions of the multi-dimensional construct of self-regulation. Here we focus on vagal regulation of cardiac activity, which is observable beginning in infancy (15), and serves as one of the earliest foundations for other emerging dimensions of self-regulation, including cognitive, emotional, and behavioral regulation (16). The myelinated vagus nerve is part of the parasympathetic branch of the autonomic nervous system (ANS) that connects the brain with the heart (17, 18). It provides input into the sinoatrial node of the heart, which produces changes in cardiac activity and allows the organism to respond to stimulation and challenge (19). Vagal regulation of cardiac function can be measured non-invasively in early childhood using respiratory sinus arrhythmia (RSA, 19, 20, 21)—the naturally occurring beat-to-beat variability of the heart associated with inhalation and exhalation during spontaneous breathing (20). Here RSA measured at rest is termed "baseline RSA." A decrease in RSA from baseline to a challenging or arousing situation is referred to as high RSA withdrawal. Conversely, a lack of change or an increase in RSA from baseline to a challenging situation is referred to as low/no RSA withdrawal or RSA augmentation (15, 19, 22).

The child development literature that examines vagal regulation has primarily focused on the effect of RSA withdrawal on emotional and behavioral outcomes (for a review of the literature, see 23). RSA withdrawal indexes how vagal input to the heart is reduced during times of challenge. Such withdrawal allows the organism to mobilize available physiological resources to respond to the challenge (15, 19, 24). Indeed, according to Porges' Polyvagal Theory (21), changes in RSA represent a highly evolved response to children's normative challenges—that is, challenges that children encounter in their everyday lives that do not immediately threaten their survival. Thus, RSA withdrawal may be a key factor in a complex interplay of hemodynamic responses and simultaneous activation of the sympathetic and parasympathetic nervous system that is directly involved in the development of CVR via physiological mechanisms (25–27).

Vagal regulation of cardiac function as indexed by RSA withdrawal may directly affect later CVR via its influence on the baroreflex arc (28), which is involved in maintaining homeostasis in blood pressure. RSA withdrawal also may indirectly influence later CVR by providing the organism with resources to engage in healthy behaviors. For example, children who have an increased capacity for vagal regulation of cardiac output may be more adept at engaging in healthy behaviors, such as strenuous exercise, which could contribute to superior plasticity in the vascular system by adolescence (29, 30). Taken together, low RSA withdrawal (which reflects a failure to increase heart rate in response to a challenge), in non-clinical healthy young populations may reflect a systematic alteration in the level of physiological regulation that is permissive for the development of CVR.

Although associations between low RSA withdrawal and obesity have been established *within* childhood (31), longer-term predictions from RSA withdrawal to later CVR—including to diastolic blood pressure (DBP) and systolic blood pressure (SBP)—are less well described. The adult literature suggests that RSA withdrawal-DBP associations could differ from RSA withdrawal-SBP associations (e.g., 28, 32). A developmental perspective also suggests that there could be developmental cascades of CVR, which would manifest themselves in differentiated associations between RSA withdrawal and different indices of CVR at a given point in time. For example, it is possible that DBP is an early risk marker of CVR that, in turn, predicts later increases in SBP (33). Indeed, diastolic hypertension is the predominant form of hypertension among young people (34); whereas, systolic hypertension becomes the predominant form of hypertension only later in life (33, 35). DBP is primarily driven by increased peripheral resistance caused by arterial vasoconstriction (33). It is thought to be an important correlate of cardiovascular health and critical indicator of hypertension independent of SBP. In turn, SBP is primarily driven by central aortic wall thickening and stiffening, which increases over time (36). Taken together, DBP, SBP, and BMI each deserve to be examined as separate markers of CVR.

Studies that have identified links between attenuated vagal regulation of cardiac output as indexed by low RSA withdrawal and poor cognitive, emotional, and behavioral outcomes in healthy community samples of children have primarily reported linear associations (for a review, see 23). Notably, a few studies have also suggested curvilinear associations, meaning that both too little RSA withdrawal (RSA augmentation) *and* too much RSA withdrawal in response to challenge predicted the poorest outcomes (37, 38). In addition, the adult

literature focused on cardiovascular health outcomes suggests that RSA augmentation may take a toll on the body over time (39) and increase risk for cardiovascular disease and mortality (40). Support for this line of thinking comes primarily from clinical adult populations (41). For example, participants with cardiomyopathy had significant reductions in the parasympathetically mediated high frequency area of the power density spectrum of heart rate variability, which illustrates augmentation of parasympathetic influences on the heart (42). It is unclear whether the same processes would apply to young, healthy children from the community.

The current study examined whether vagal regulation during early childhood predicted CVR (i.e., DBP, SBP, and BMI) approximately 14 years later, during late adolescence. Our primary index of vagal regulation was RSA withdrawal. Given the current state of the child development literature, our primary test was for linear associations. In follow-up analyses we also tested curvilinear effects to examine whether both high negative (RSA augmentation) *and* positive RSA withdrawal scores would predict adolescent CVR. Given that childhood RSA and adolescent CVR are both associated with childhood demographic risks and BMI (3, 31), we also tested whether these predictions held when demographic factors and childhood BMI were taken into account.

Methods

Participants

Participants included 229 children (136 females) from the longitudinal RIGHT Track Study. Four hundred and forty-seven participants were initially recruited at two years of age through childcare centers, the County Health Department, and the local Women, Infants, and Children program. Additional details about sample recruitment and the adolescent health assessments may be found elsewhere (43, 44). The recruitment sample was diverse; 62.9% of the children were European American, 32.4% African American, 3.3% biracial, and 1.4% of other race/ethnicity. Families were economically diverse; Hollingshead scores that take into account parental education, occupational prestige, employment, and marital status (45) ranged from 19 to 63 ($M = 42.44$). Hollingshead scores from 40 to 54 are typically representative of the middle class.

Of the original 447 participants, $n = 345$ had valid age two vagal data. Children without versus with RSA data did not differ at age two with respect to sex, $\chi 2$ (1, 447) = .519, $p = .471$, race, $\chi 2$ (1, 447) = .216, $p = .641$, SES, $\chi 2$ (256, 447) = 252.973, $p = .542$, and also with respect to childhood BMI, $\chi 2$ (386, 447) = .047, $p = .490$. These findings suggest that the children with RSA data did not differ in systematic ways from the original sample. Of the 345 children with RSA data at age two, 246 (71.3%) also had data on cardiovascular risk in adolescence, approximately 14 years later. Of this subsample, $n = 229$ had complete data on all covariates, including childhood socioeconomic status and childhood BMI. Compared to the original recruitment sample, the current sample did not differ with respect to race, $\chi 2$ (1, 447) = 1.307, $p = .253$, age two SES, $\chi 2$ (81, 447) = 69.585, $p = .813$, and childhood BMI, $\chi 2$ (180, 447) = 188.883, $p = .310$. The current sample did, however, include a higher proportion of females ($\chi^2(df = 1, 447) = 9.97$, $p = .002$), a finding that is not uncommon in

long-term longitudinal studies focused on health (46). Sex could be considered missing at random and ignorable provided that it is included in our statistical models (47).

Procedures

The study was approved by the Institutional Review Board of the University of North Carolina at Greensboro (#11-0360; PI Wideman and #09-0427; PI Calkins). Data collection occurred from August 1996 to July 2001 for age two assessments and from February 2010 to October 2015 for age 16 assessments. At each age, a primary caregiver (typically the mother) accompanied the child to the laboratory. Primary caregivers provided informed written consent for the child to participate before assessments began. At age 16, children also provided assent. Cardiac measures at age two were assessed in a laboratory playroom. Age two assessments started with a baseline/quiescent episode, during which children watched a five-minute video of a cartoon dog. Children were allowed to sit alone or in their mother's lap. This situation was selected as an age-appropriate baseline, because children watching cartoons typically engage in limited movement that could cause artifacts in cardiac data.

Following the baseline assessment, children participated in four regulatory challenge tasks in order to elicit physiological arousal and regulation/coping behaviors. The order of the tasks was the same for each child. The tasks were administered consecutively, with brief 2–3 minute breaks between tasks to allow children to play with their mother and to reduce fatigue and order effects. Challenge tasks included a fear task (2 minutes), in which the child was asked to play with a toy spider; a frustration task (2 minutes), in which the child was given a container with cookies that could not be opened; a teaching task (4 minutes), in which the mother was asked to help the child sort shapes; and a positive affect task, in which the child blew bubbles with the experimenter (2 minutes). The appendix provides detailed information about the scientific rationale and procedures for each task, and basic descriptive RSA withdrawal statistics for each task (Supplemental Digital Content 1).

The electrodes placed on the child's chest were connected to a preamplifier, the output of which was transmitted to a vagal tone monitor (VTM-I, Delta Biometrics, Bethesda, MD) for R-wave detection. Several children refused to wear the heart rate electrodes, others pulled on the heart rate leads, creating movement artifacts in greater than 5% of the data in the heart rate file; in addition, the data-collection equipment failed in some cases—resulting in the missing data described above. If the standard deviation across the epochs was greater than 1.00 for RSA—indicating a high degree of variability over the course of the episode and calling into question the validity of the mean RSA value—then that episode was excluded from subsequent analyses ($n = 5$).

At approximately 16 years of age, adolescents were invited for laboratory visits during which blood pressure and BMI were assessed. Primary caregivers provided informed written consent; adolescents provided informed written assent and were given $50 gift cards for their participation.

Measures

Cardiovascular risk in adolescence—*Diastolic blood pressure (DBP*, in mmHg) and *systolic blood pressure (SBP*, in mmHg) were assessed by trained research technicians using either standard manual auscultation with a sphygmomanometer or an automatic cuff. However, in cases of electronic equipment failure, only manual assessments were made. In some cases, there were significant deviations in the manual and automated DBP and SBP results. When this occurred, subjects rested for an additional three to five minutes and additional manual DBP and SBP measures were taken to confirm results. Measurements were frequently checked by a supervisor and frequent refresher trainings were conducted with the team of research technicians. The mean of two readings was taken for DBP and SBP, respectively. Such averaging has been shown to have high validity (48). Dichotomous pre-/hypertension variables were computed using the age- and sex-adjusted height percentiles provided by the U.S. Department of Health & Human Services guidelines (49). According to these guidelines, values of DBP ≥ 80 mmHg or ≥ 90th percentile for age, sex, and height indicate diastolic prehypertension; values ≥ 95th percentile diastolic hypertension. Values of SBP ≥ 120 mmHg or ≥ 90th percentile for age, sex, and height indicate systolic prehypertension; values ≥ 95th percentile systolic hypertension.

Body mass index (BMI) was computed using the formula weight/(height^2). Height (m) and weight (kg) were measured by trained interviewers during participants' visits to the laboratory at ages four, five, seven, ten, and 16, and by participants' self-reports when a laboratory visit was not possible (at age 16). Age- and sex-adjusted BMI percentiles were assigned according to the Center for Disease Control (CDC) growth charts (50). CDC guidelines were also used for computing dichotomous overweight/obesity variables. Specifically, adolescents at BMI ≥ 85th percentile for their sex and age were coded as being overweight/obese (50). Among participants with both laboratory-measured and self-reported BMI, measurements were highly correlated (r = .97, p < .001).

Vagal regulation in early childhood—*Vagal regulation at age two* was assessed by baseline RSA and RSA change during challenge [in ln(ms)^2]; the appendix (Supplemental Digital Content 1) provides detailed information on the procedure for each task. The electrodes placed on the child's chest were connected to a preamplifier, the output of which was processed through a vagal tone monitor (VTM-I, Delta Biometrics, Inc., Bethesda, MD) for R-wave detection. A data file containing the interbeat intervals for the entire period of collection was transferred to a laptop computer for artifact editing. The resulting edited data were analyzed using the Porges (51) method of RSA calculation, which applies an algorithm to the sequential heart period data. The algorithm uses a moving 21-point polynomial to detrend periodicities in heart period that are slower than RSA. Next, a bandpass filter extracts variance in heart period within the frequency band of spontaneous respiration in young children, 0.24–1.04 Hz. The natural log of this variance was taken and reported in units of ln(ms)^2 in order to index RSA. These values were calculated for 30-second epochs within each episode and the resulting values were averaged across epochs within each episode. This method has been shown to be robust to changes in respiration rate (52). Therefore, respiration rate was not assessed separately, although this could be advisable for different methods of RSA assessment (53).

Baseline RSA was measured during a baseline/quiescent episode. RSA withdrawal was derived by subtracting the average RSA [in ln(ms)^2] during the respective challenge task from the average RSA [in ln(ms)^2] during the baseline episode. Negative difference scores represent an increase in RSA from baseline to task (i.e., RSA augmentation, or no RSA withdrawal in response to challenge); positive scores represent a decrease in RSA from baseline to task (i.e., high RSA withdrawal in response to challenge). The RSA change scores from the four challenge tasks had high reliability (α = .83); therefore, a mean RSA change score was created (similar to 37).

*Covariate*s included race, sex, childhood BMI, and childhood socioeconomic status. Hollingshead socioeconomic status scores (SES, 45) were computed using a weighted average of parental education, marital status, employment status, and occupational prestige assessed at ages four, five, seven, and ten. Childhood BMI was assessed by interviewers at age four, five, seven, and ten (height and weight were not measured at age two).

Analytic Strategy

The three continuous outcome variables (DPB, SBP, BMI) were predicted using separate hierarchical regression analyses in order to demonstrate the unique effects of RSA withdrawal on each of these indicators of CVR, adjusting for demographic characteristics and childhood BMI. In a first step, demographic covariates (sex, race, childhood SES) and childhood BMI were entered. In a second step, RSA withdrawal was entered to examine its unique contributions to the prediction of the respective outcomes.

In follow-up analyses, the squared term of RSA withdrawal was entered to examine whether both too little and too much RSA withdrawal predicted CVR. In additional follow-up analyses, clinically meaningful dichotomous CVR variables were predicted using logistic regression analyses.

Results

Descriptive Statistics

Table 1 shows the means and standard deviations of all study variables. Consistent with recent work on nationally representative cohorts (e.g., 2, 54), our analytic sample showed some evidence of heightened cardiovascular risk. For example, the mean SBP of 115.78 mmHg was in the normal range, but near the prehypertension cut-off for individuals aged 16+ years old. In addition, the average adolescent BMI was 23.73, which was near the BMI = 25 cut-off used for defining overweight status among adolescents. Average RSA withdrawal was in the positive range [at .60 ln(ms)^2] indicating that, on average, vagal regulation occurred between baseline and challenge tasks at age two. Hence, similar to previously published data (55), the challenge tasks produced significant changes in children's RSA. Data for each individual challenge task are also summarized in Table S1 and Figure S1 (Supplemental Digital Content 1). One sex difference in CVR emerged (t = 4.14, p < .001): males had significantly higher SBP than females (M = 119.51 mmHg, SD = 13.37 and M = 113.31 mmHg, SD = 10.46, respectively).

Table 1 also shows correlations among all study variables. A significant negative association emerged between RSA withdrawal during childhood and DBP in adolescence: lower vagal regulation at age two was associated with higher DBP at age 16. Overall, correlations among the three CVR indicators in adolescence were significant, but only low to moderate in size (ranging from $r = .27$ to $r = .45$, $p < .001$).

Long-Term Predictions Towards Continuous CVR Outcomes

Table 2 shows the results of hierarchical regression models examining the role of age two RSA withdrawal in the prediction of age 16 DBP, SBP, and BMI, adjusting for demographics and childhood BMI. We discuss results for each outcome in turn.

Diastolic blood pressure—The covariates entered in Step 1 explained 8% of the variance in adolescent DBP. Sex, race, and childhood SES (entered in Step 1) did not predict age 16 DBP, but children with greater childhood BMI had higher DBP at age 16. Step 2 revealed that lower RSA withdrawal at age two (i.e., lower/attenuated vagal regulation) predicted higher levels of DBP at age 16 ($p = .006$). The addition of RSA withdrawal accounted for 4% of the variance in DBP.

Systolic blood pressure—The covariates entered in Step 1 explained 20% of the variance in adolescent SBP. Males had significantly greater SBP at age 16 compared to females. In addition, children with higher childhood BMI had significantly greater SBP at age 16. Step 2 showed that age two RSA withdrawal did not significantly predict age 16 SBP.

Body mass index—The covariates entered in Step 1 explained 60% of the variance in adolescent BMI. Children with minority race/ethnic status were more likely to have greater BMI at age 16, as were children from families with lower SES. In addition, childhood BMI was a strong predictor of adolescent BMI. Adjusting for these covariates, age two RSA withdrawal did not significantly predict age 16 BMI.

Taken together, children with low RSA withdrawal in response to challenge were at increased risk for greater DBP (but not SBP and BMI) at age 16.

Follow-up Analyses

In a first set of follow-up analyses, we used squared RSA withdrawal terms to test whether both too little and too much vagal regulation would predict adolescent CVR. None of the squared terms were significant, meaning that there is only a linear association between lower RSA withdrawal and greater DBP. In a second set of follow-up analyses, adolescent CVR outcomes were dichotomized using clinically meaningful criteria, and analyses were repeated using logistic regression models to predict pre-/hypertension and overweight/obesity status. These analyses replicated the significant association between age two RSA withdrawal and age 16 DBP. Specifically, lower RSA withdrawal predicted higher risk for meeting criteria for diastolic pre-/hypertensive status in adolescence (odds ratio = 0.43, 95% confidence interval, .22–.89, $p = .023$; see Figure 1) when adjusting for sex, race, childhood SES, and childhood BMI. In addition, lower RSA withdrawal predicted higher risk for

adolescent obesity status at the statistical trend level, adjusting for all covariates and childhood BMI (odds ratio = 0.59, 95% confidence interval, .31– 1.09, $p = .089$). Childhood RSA withdrawal did not significantly predict dichotomous systolic pre/hypertension in adolescence.

In a third set of follow-analyses, we used a proxy of sympathetic activity—changes in heart period between baseline and challenge, adjusting for RSA withdrawal—to predict CVR outcomes. No significant associations were found. In a fourth set of follow-up analyses, we dropped the positive affect ("blowing bubbles") task from the RSA withdrawal composite, which did not result in any notable changes in the findings. Finally, given a previous finding that RSA withdrawal interacted with race in the prediction of obesity (31), we tested whether such an interaction would be significant in the prediction of BMI/obesity in the current study, but this was not the case.

Sensitivity Analyses

Adolescent blood pressure and BMI tend to be correlated, and research has shown that BMI can explain the association between DBP and SBP and vagal activity (32). Therefore, analyses using DBP and SBP as an outcome were repeated using adolescent BMI as an additional covariate. Results revealed no notable change in the predictions from childhood RSA withdrawal toward adolescent blood pressure with the inclusion of adolescent BMI.

Discussion

In recent decades, emotional and behavioral self-regulation have been identified as important precursors of adult health (e.g., 12). Physiological regulation during early childhood is thought to be one of the earliest foundations for other dimensions of self-regulation (15), but has rarely been tested as a predictor of later health outcomes. To our knowledge, this study is the first to show that regulation of the parasympathetic branch of the autonomic nervous system in toddlerhood, as indexed by reduced RSA withdrawal in response to a challenge, predicts select risk factors for cardiovascular disease in adolescence—especially DBP.

Cardiovascular risk consists of a heterogeneous set of indices (56). In our sample of adolescents, correlations among the different indices of CVR were low to moderate size. Predictions from childhood vagal regulation of cardiac function to later CVR indices were also differentiated. Early signs of attenuated vagal regulation of cardiac output as indexed by RSA withdrawal predicted later DBP and, marginally, clinical cut-offs for overweight/obesity status. However, it did not predict continuous or dichotomized later SBP. These findings are consistent with previous work that reported differentiated associations among RSA and indicators of CVR—including DBP and SBP—in adults (e.g., 28, 33, 57).

Vagal regulation of cardiac function during arousing situations is thought to reflect the organism's attention to and mobilization of resources for addressing challenge (15, 19, 24), which may have multiple links with later CVR. Children with better physiological regulation may cope with stressors more effectively, and may thus be shielded from the physiological effects of psychological stressors that are inevitably encountered by most children (e.g., 58). From a health behaviors perspective, children who have an increased capacity for vagal

regulation of cardiac output may also be more adept at engaging in healthy behaviors, such as strenuous exercise, which could contribute to superior plasticity in the vascular system by adolescence (29, 30). Indeed, vagal regulation of cardiac function is involved in the control of emotional, behavioral, and also social processes (15, 19, 24), contributing to cardiovascular health via multiple indirect pathways.

RSA withdrawal likely also has direct links with DBP. In healthy young adults, change in R-R interval fluctuations during RSA withdrawal directly mirrors change in DBP; thus RSA withdrawal could directly affect diastolic change (28). In contrast, the tolerable range of SBP is greater and therefore more susceptible to fluctuations, limiting its association with childhood vagal regulation (59). It is possible that DBP is a marker of early manifestations of CVR that signals risk for future elevations in other indicators of CVR. For example, age-related increases in DBP are typically observed before age-related increases in SBP (4). Consequently, vagal regulation of cardiac function in childhood could be an early indicator of a cascade from low vagal regulation to increased DBP, followed by increased SBP, and ultimately clinical cardiovascular disease endpoints. Future longitudinal research extending into adulthood should test this potential cascade more fully.

Predictions from attenuated vagal regulation of cardiac function toward BMI were marginally significant for the categorical overweight/obesity variable only. This was somewhat surprising given that predictions between vagal regulation and later BMI had been identified over a five-year period during childhood in a previous study using the same sample (31). However, the current study stretched over 14 years and across the developmental periods of childhood *and* adolescence, and took into account childhood BMI. Childhood BMI, sex, and race together accounted for 60% of the variance in adolescent BMI; it may have been difficult to identify predictors of changes from childhood to adolescent BMI over and above these variables. In addition, physiological, behavioral, and emotional processes of adolescence may introduce competing influences on BMI, decreasing the predictive power of early childhood vagal regulation of cardiac function on this outcome during the adolescent period. Moreover, the significant changes in body composition across adolescence likely introduce some fluctuations in BMI (e.g., 60). Taken together, associations between a measure of physiological regulation at age two and BMI at age 16 may be difficult to detect given the multiple competing influences on adolescent BMI and potential fluctuations of BMI within adolescence due to rapid changes in body composition.

Although some of the adult literature suggests that RSA augmentation is associated with later CVR (40), our follow-up analyses did not identify this linkage. Notably, our recruitment population consisted of young, healthy children in the community—for who cardiovascular risk processes may develop differently compared to adults, especially those adults who were already diagnosed with one or more cardiovascular problems.

Limitations and Future Directions

The current study had several limitations. First, although our predictions are long-term-longitudinal, they do not establish causality. It is possible that attenuated vagal regulation of cardiac function can be a consequence of underlying disease rather than a cause, and this has

been shown among clinical samples of adults (61, 62). However, our recruitment sample consisted of healthy two-year olds from the community; thus, this reverse direction of effect is unlikely in the current study. Second, blood pressure was not assessed during childhood. Thus, we were unable to test whether childhood vagal regulation of cardiac function predicted *increases* in DBP over time. Analyses did adjust for childhood BMI as a proxy of childhood cardiovascular risk. Third, other biomarkers of CVR (e.g., blood lipids) are currently not available for this sample. Future research should examine how ANS regulation relates to other components of CVR during the early life course (e.g., 57). Fourth, although the racial/ethnic composition of the sample corresponded to that of the counties from which it was drawn, the sample consisted mostly of white and African American participants. Our hypotheses should also be examined in other racial/ethnic groups, including Latino and Asian groups.

Fifth, we conceptualized a simplistic relation between vagal regulation of cardiac function and CVR; however, the physiological response of the body to challenge is much more complicated. We did not assess the role of the sympathetic nervous system and cardiac autonomic balance. A reciprocal pattern of parasympathetic withdrawal and sympathetic activation during stress affects heart rate (25, 26) and this balance of physiological processes might explain cardiovascular functioning. However, it is important to note that in childhood, parasympathetic nervous system activation is more dominant than sympathetic nervous system activation (63). Future research should assess the more complicated hemodynamic response of both sympathetic and parasympathetic activity as they jointly affect CVR. Follow-up analyses using an indirect proxy of sympathetic activity (i.e., changes in heart period between baseline and challenge, adjusting for RSA withdrawal) did not, however, result in significant findings. Finally, RSA withdrawal in childhood explained only a small amount of variance in adolescent DBP, and additional predictors, such as fitness and sedentary behaviors, should be explored. Research has indicated that physical exercise in overweight children can protect them from low vagal regulation of cardiac function (64); however, we did not adjust for physical activity.

Despite these weaknesses, it is notable that age two RSA withdrawal signaled risk for elevated DBP approximately 14 years later. RSA may be a relatively non-invasive early risk biomarker for later cardiovascular risk. If replicated in future research, our findings suggest several potential new avenues for prevention and intervention. From a psychological perspective, parental emotional support and sensitive caregiving can improve child physiological regulation, including vagal regulation of cardiac function (65, 66). Accordingly, preventions and interventions with caregivers that improve vagal regulation of cardiac function could potentially help reduce later CVR. From a physiological perspective, the body's own capacity for vagal regulation of cardiac function can be improved with pharmacological intervention (67). However, the utility of these medications in children has not been tested.

Conclusions

Early signs of attenuated vagal regulation of cardiac function may signal risk for later cardiovascular health problems. Most notably, this increased risk primarily centers around

DBP in the present sample. The identification of early vagal regulation as a risk marker for later cardiovascular disease has novel implications for detecting and preventing CVR. Prevention strategies such as sensitive caregiving and emotional support in early childhood may hold promise in interrupting this pathway to later CVR.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of Funding: Research reported in this publication was supported by the Eunice Kennedy Shriver National Institute of Child Health & Human Development of the National Institutes of Health under Award Number R01HD078346. Support also came from NIMH 55625, NIMH 55584 & NIMH 58144. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors thank the parents and children who have repeatedly given their time and effort to participate in this research and are grateful to the entire RIGHT Track staff for their help collecting, entering, and coding data.

Acronyms

ANS	autonomic nervous system
BMI	body mass index
CVR	cardiovascular risk
DBP	diastolic blood pressure
RSA	respiratory sinus arrhythmia
SBP	systolic blood pressure
SES	socioeconomic status

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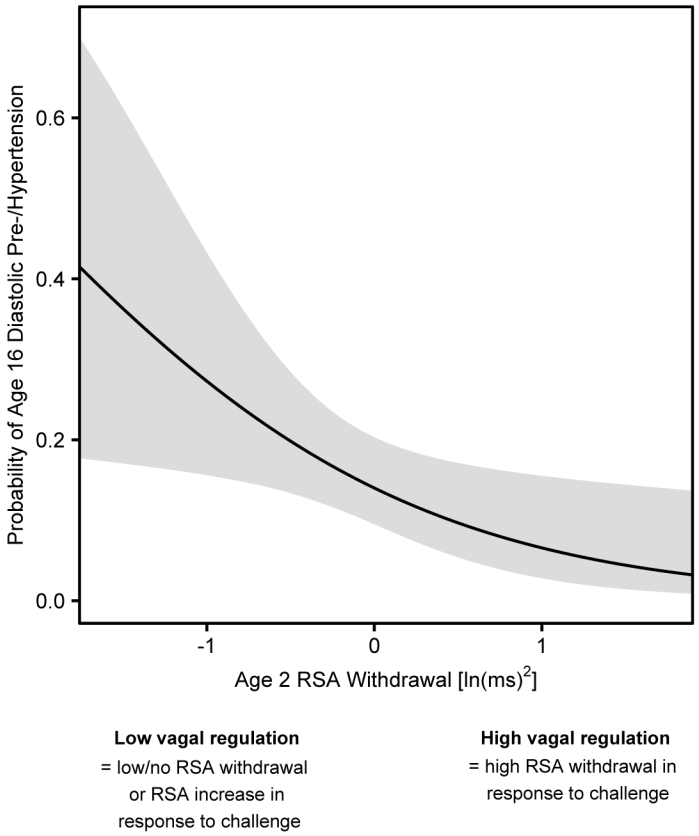

Figure 1.

Results from logistic regression model predicting the probability of meeting clinically significant criteria for diastolic prehypertension or hypertension as a function of RSA withdrawal at age 2. (Gray shading indicates 95% confidence interval).

Table 1

Means, standard deviations, and correlations for participants' cardiovascular risk, vagal regulation, and study covariates.

Variable	M	SD	1	2	3	4	5	6	7	8	9
1. Ado DBP	69.12	9.37	--	.28***	.27***	0.27***	−.13†	−.17**	.00	−.01	−.04
2. Ado SBP	115.78	12.31		--	.45***	.33***	.09	−.01	−.22**	.18*	−.16*
3. Ado BMI	23.73	5.51			--	.76***	.07	−.02	.06	−.16*	−.16*
4. Child BMI	17.53	2.76				--	.09	.05	.06	.16*	−.16*
5. Child baseline RSA	5.41	1.23					--	.50**	−.11	.18*	.01
6. Child RSA Withdrawal	0.60	0.60						--	−.10	−.03	.16*
7. Sex[a]									--	−.03	−.16*
8. Race[b]										--	−.34***
9. Child SES	42.63	9.42									--

† p < .10,

* p < .05,

** p < .01,

*** p < .001

Note. Total N = 229

[a] Sex is dichotomized 0 = Males (n = 93, 41%) 1 = Females (n = 135, 59%)

[b] Race is dichotomized 0 = White (n = 147) 1 = Race/Ethnic minority status (n = 81)

Ado = Adolescent; BMI = body mass index (in kg/m^2); DBP = diastolic blood pressure (in mmHg); RSA = respiratory sinus arrhythmia [in ln(ms)^2]; SBP = systolic blood pressure (in mmHg); SES = socioeconomic status

Table 2

Regression coefficients, standard errors, and variance explained by hierarchical regression models of age 2 RSA withdrawal predicting age 16 cardiovascular risk factors, adjusting for covariates.

	Diastolic Blood Pressure				Systolic Blood Pressure				Body Mass Index			
Predictor variables	**R^2**	**ΔR^2**	**B**	**SE**	**R^2**	**ΔR^2**	**B**	**SE**	**R^2**	**ΔR^2**	**B**	**SE**
Step 1	.08	.08 **			.20	.20 ***			.60	.60 ***		
Sex[a]			−0.34	1.35			−6.61 ***	1.65			−0.43 ***	0.48
Race[b]			−1.09	1.40			2.30	1.74			1.51 **	0.52
Child SES			−0.02	0.08			−0.15	0.09			−0.05 **	0.03
Child BMI			0.92 ***	0.24			1.38 ***	0.29			1.43 ***	0.09
Step 2	.11	.04 **			.20	.00			.60	.00		
RSA withdrawal			−3.07 **	1.12			−0.63	1.39			−0.26	0.40

† p < .10,

* p < .05,

** p < .01,

*** p < .001

Note. Total N = 229 (93 males, 136 females). Unstandardized regression coefficients are presented

[a] Sex is dichotomized 0 = Males (n = 93, 41%) 1 = Females (n = 135, 59%)

[b] Race is dichotomized 0 = White (n = 147) 1 = Race/Ethnic minority status (n = 81)

BMI = body mass index (in kg/m^2); RSA = respiratory sinus arrhythmia [in $ln(ms)^2$]; SES = Socioeconomic status