



## Sleep quality and ACE polymorphism can influence the cardiac autonomic modulation of adolescents

Qualidade do sono e polimorfismo da ECA podem influenciar a modulação autonômica cardíaca em adolescentes

La calidad del sueño y el polimorfismo de la ECA pueden influir en la modulación autonómica cardíaca en adolescentes

Nivaldo de Jesus Silva Soares Junior<sup>1,2</sup>, Carlos Alberto Alves Dias-Filho<sup>1,3</sup>, Andressa Coelho Ferreira<sup>1</sup>, Flávio de Oliveira Pires<sup>1,2</sup>, Danielle da Silva Dias<sup>1,2</sup>, Rachel Melo Ribeiro<sup>1</sup>, Janaina de Oliveira Brito Monzani<sup>1,2</sup>, Vinícius Santos Mendes<sup>1</sup>, Carlos José Moraes Dias<sup>1,2</sup>, Cristiano Teixeira Mostarda<sup>1,2</sup>.

### ABSTRACT

**Objective:** Evaluate the association of the angiotensin-converting enzyme (ACE) I/D polymorphism and sleep quality influence the cardiac autonomic modulation of adolescents. **Methods:** 243 adolescents were divided into four groups: II+GSQ (II + Good Sleep Quality); II+PSQ (II + Poor Sleep Quality); ID/DD+GSQ (ID/DD + Good Sleep Quality); ID/DD+PSQ (ID/DD + Poor Sleep Quality). Blood pressure, body composition, physical activity level, sleep disorder, and sexual maturation were assessed to characterize the groups. Afterward, an electrocardiogram was performed to analyze heart rate variability, and oral mucosal cells was collected for genotypic research of angiotensin-converting enzyme. **Results:** The main finding of this study was a change in vagal action, systolic blood pressure (SBP), diastolic blood pressure (DBP), Heart rate (HR) and Pittsburgh Sleep Quality Index (PSQI) in the DD/DI+GSQ and DD/DI+PSQ groups in relation to the other groups. **Conclusion:** Adolescents with the D allele of ACE I/D polymorphism negatively influence Heart rate variability (HRV) regardless of sleep quality, and lousy sleep also negatively affects HRV. The two factors (D allele and PSQ) are even more harmful to the adolescent population, leading to various cardiovascular problems.

**Keywords:** Adolescent, Heart rate variability, ACE I/D polymorphism, Sleep quality.

### RESUMO

**Objetivo:** Avaliar a associação do polimorfismo da Enzima Conversora de Angiotensina (ECA) e a influência da qualidade do sono na modulação autonômica cardíaca de adolescentes. **Métodos:** 243 adolescentes foram divididos em quatro grupos: II+GSQ (II + Boa Qualidade do Sono); II+PSQ (II + má qualidade do sono); ID/DD+GSQ (ID/DD + Boa Qualidade do Sono); ID/DD+PSQ (ID/DD + má qualidade do sono). Pressão arterial, composição corporal, nível de atividade física, distúrbio do sono e maturação sexual foram avaliados para caracterizar os grupos. Em seguida, foi realizado eletrocardiograma para análise da variabilidade da frequência cardíaca e coletadas células da mucosa oral para pesquisa genotípica da enzima conversora de angiotensina. **Resultados:** O principal achado deste estudo foi alteração na ação vagal, Pressão arterial sistólica (PAS), Pressão arterial diastólica (PAD), Frequência cardíaca (FC) e Índice de qualidade do sono de Pittsburgh (PSQI) no grupo DD/DI+GSQ e DD/DI+PSQ em relação aos outros grupos. **Conclusão:**

<sup>1</sup> Laboratory of Cardiovascular Adaptation to Exercise (LACORE-UFMA), São Luís - MA.

<sup>2</sup> Postgraduate Program in Physical Education, Universidade Federal do Maranhão, São Luís - MA.

<sup>3</sup> Faculdade ITPAC Santa Inês - MA.

Adolescentes com o alelo D do polimorfismo da ECA influenciam negativamente a Variabilidade da Frequência Cardíaca (VFC), independentemente da qualidade do sono; e o sono ruim também afeta negativamente a VFC. Os dois fatores (alelo D e PSQ) são ainda mais prejudiciais à população adolescente, levando a diversos problemas cardiovasculares.

**Palavras-chave:** Adolescente, Variabilidade da frequência cardíaca, Polimorfismo I/D da ECA, Qualidade de sono.

## RESUMEN

**Objetivo:** Evaluar la asociación entre el polimorfismo de la enzima convertidora de angiotensina (ECA) y la influencia de la calidad del sueño en la modulación autonómica cardíaca en adolescentes. **Métodos:** 243 adolescentes fueron divididos en cuatro grupos: II+GSQ (II+Buena Calidad del Sueño); II+PSQ (II+mala calidad del sueño); ID/DD+GSQ (ID/DD + buena calidad de sueño); ID/DD+PSQ (ID/DD + mala calidad del sueño). Para caracterizar los grupos se evaluó la presión arterial, la composición corporal, el nivel de actividad física, la alteración del sueño y la maduración sexual. Posteriormente, se realizó un electrocardiograma para analizar la variabilidad de la frecuencia cardíaca y se recolectaron células de la mucosa oral para la investigación genotípica de la enzima convertidora de angiotensina. **Resultados:** El principal hallazgo de este estudio fueron los cambios en la acción vagal, Presión arterial sistólica (SPA), presión arterial diastólica (DBP), Frecuencia cardíaca (FC) y Índice de calidad del sueño de Pittsburgh (PSQI) en los grupos DD/DI+GSQ y DD/DI+PSQ en relación con los demás grupos. **Conclusión:** Los adolescentes con el alelo D del polimorfismo ECA influyen negativamente en la Variabilidad de la frecuencia cardíaca (VFC), independientemente de la calidad del sueño; y la falta de sueño también afecta negativamente a la VFC. Los dos factores (alelo D y PSQ) son aún más perjudiciales para la población adolescente, dando lugar a varios problemas cardiovasculares.

**Palabras clave:** Adolescente, Variabilidad de la frecuencia cardíaca, Polimorfismo del gen ACE, Calidad del sueño.

## INTRODUCTION

Systemic arterial hypertension (SAH) is a worldwide public health problem, mainly because many people are affected by the disease, have many expenses in its treatment, and many deaths from SAH (KEARNEY, et al., 2005). The diagnosis of adolescent's with SAH is increasing, so this scientific interest in pathology in this population has been increasing since the publication in 2004 of the National High Blood Pressure Education Program Working Group, which brought an updated blood pressure classification in children and adolescents, to alert and justify for the population an increasingly early healthy lifestyle for adolescents (PROGRAM, 2005).

In this context, it is essential to identify any genetic and behavioral risk factors that influence the prevalence of this disease, such as sedentary lifestyle, dietary habits, stress, and sleep quality (GARG R, et al., 2013; PIETILÄ J, et al., 2015). Studies have shown that poor sleep quality represents a risk factor for the dysfunction of several physiological mechanisms leading to autonomic dysfunction and pathologies such as systemic arterial hypertension (SAH) in adults and adolescents (SOARES JUNIOR NJ, et al., 2023).

It is also believed that a family history of hypertensive parents increases the possibility of hypertension in adolescents, mainly when both parents manifest the disease (TOKER RT, et al., 2015). Besides these factors, genes can explain approximately 50% of the variation in blood pressure levels among individuals with a family history of hypertension (AMARA A, et al., 2018).

The regulatory components of SAH are present in the endocrine system in the form of the renin-angiotensin-aldosterone system (RAAS), which plays a fundamental role in the pathogenesis of SAH, increased production of RAAS products such as an angiotensin-converting enzyme (ACE), is associated with an increased risk of SAH, and it is essential to highlight that those genetic variants can alter the production of ACE (AMARA A, et al., 2018; GUNEY A, et al., 2013; SINGH M, et al., 2010). In addition to these genetic factors, an imbalance in the Autonomic Nervous System (ANS) is directly related to higher cardiovascular risk and SAH (THAYER

JF, et al., 2010; WULSIN LR, et al., 2015). This autonomic imbalance is related to a more significant activity of the Sympathetic Nervous System (SNS) being evaluated this autonomic function through a widely accepted and validated tool the heart rate variability (HRV) (Flynn JT, et al., 2017; Francica JV, et al., 2015) quantifying sympathetic cardiac and parasympathetic modulation.

Similarly, this autonomic dysfunction will also influence sleep quality, as it accompanies sleep deprivation and daytime sleepiness. Some studies point out poor sleep quality (PSQ) as a preponderant factor for cardiac autonomic dysfunction (MATTHEWS KA, et al., 2016). Therefore, due to few studies establishing this relationship between these risk factors, this article aimed to evaluate how much the association between I/D polymorphism and sleep quality can influence the cardiac autonomic modulation of adolescents.

## METHODS

### Sample collection

This analytical and cross-sectional study included adolescents of both sexes, aged between 11 and 18. The study had 243 adolescents (101 boys and 142 girls), who were initially divided into an Allele II group and another group of the ACE Polymorphism I/D was ID+DD Allele. Subsequently, the sleep quality was divided according to the allele of the ACE I/D polymorphism, defined in II+GSQ (Allele II + Good Sleep Quality), II+PSQ (Allele II + Low Sleep Quality), ID/DD+GSQ (Allele ID/DD + Good Sleep Quality), ID/DD+PSQ (Allele ID/DD + Low Sleep Quality).

The samples were classified into one of the two possible genotypes resulting from the ACE gene's polymorphism: one homozygous (II) genotype and two homozygous/heterozygous (ID or DD) genotypes. Students of the selected age group were invited to participate in the study upon furnishing the parents' informed consent form (ICF), which authorized their participation.

This study followed the recommendations of the Helsinki Declaration and Resolution No. 466/2012 of the National Health Council of the Brazilian Ministry of Health. It was approved by the Permanent Ethics Committee in Research Involving Human Beings of the Federal University of Maranhão (4.721.129) CAAE nº 46072721.7.0000.5087.

### Pittsburgh Sleep Quality Index

Sleep quality and occurrence of sleep disorders were evaluated using the Pittsburgh Sleep Quality Index (PSQI), as defined initially by Buysse (Bertolazi et al., 2011). The PSQI uses seven components: (a) subjective quality of sleep, (b) sleep latency, (c) duration of sleep, (d) habitual sleep efficiency, (e) sleep disorders, (f) use of medication to sleep, and (g) daytime sleepiness and disorders during the day.

The score for each component was determined separately, on a scale of 0 to 21 points, where the more excellent value of the score obtained, the worse the sleep quality. Score values between 0 and 4 represent good sleep quality, those between 5 and 10 represent poor sleep quality, and those greater than 11 indicate sleep disorders.

### Collection of oral mucosal cells

Exfoliated oral mucosal cells were obtained from the participants by gently brushing the buccal mucosa and buccal groove using a sterile swab. The collected cells were then stored at  $-20^{\circ}\text{C}$  until DNA isolation.

### Body composition analysis

An anthropometric evaluation was performed with the participant in the orthostatic position. The weight was measured using a Balmak digital scale (in kg), while the height was measured using a compact stadiometer, type EST 23 (in mm)., According to National Heart, Lung, and Blood Institute (NHBLI), all the measurements were performed by a trained professional (Gordon et al., 2013).

The bioelectrical impedance method (BIA) was carried out with the Maltron@ device, model BF906 (Maltron; Essex, UK), tetrapolar, 50 kHz. The procedure was performed in a supine position during the morning after fasting for 10-12 hours.

### **Evaluation of sexual maturation**

For the evaluation of sexual maturation, the criteria used by Tanner (Morris et al., 1980) were adopted. It is a self-evaluation method using images, considering the development of breasts in girls, penis in boys, and hair on genitals in both genders. Subsequently, the individuals were classified into one of the following five stages: 1st stage: Indicates that the individual is still in childhood (pre-pubertal); 2nd stage: Represents the beginning of the maturational period; 3rd and 4th stages: Shows the continuity of the maturation process; 5th stage: Indicates that the individual is a complete adult.

### **Measurement of blood pressure**

The protocol for blood pressure measurement (Omron® HEM-711 and Omron® 905) followed the norms of the VII Brazilian Hypertension Guideline (Barroso WKS, et al., 2021) and the IV Report on the Diagnosis, Evaluation, and Treatment of Hypertension in Children and Adolescents (FLYNN JT, et al., 2017). An optimal cuff size was used according to the arm size of the participants.

### **Assessment of the heart rate variability**

The HRV data were obtained in the supine position with spontaneous breathing. The time series of HR was acquired (Micromed Biotecnologia, WinCardio) by determining the RR interval with a 12-lead electrocardiogram, 1000 Hz sample rate, during 10 min and was analyzed in the time domain through the analysis of standard deviation of the range of regular beats (SDNN) and root-mean-square differences of successive R-R intervals (RMSSD). After visual inspection, the series of RR intervals was made by tuning the frequency cubic spline interpolation ( $f_i = 250$  Hz) and reducing the number of dots per decimation (18 times).

Then each beat was identified using the algorithm by Matlab™ program (Welch's method) that generates the result of spectral analysis with the respective bands of interest (HF, high-frequency: 0.4 to 0.15 Hz; LF, low-frequency: 0.15 to 0.04 Hz). Normalized LF and HF components of R-R variability were considered, respectively, as markers of cardiac sympathetic and parasympathetic modulation, and the ratio between them (LF/HF) was considered an index of the autonomic modulation of the heart (Kadish et al., 2001). The results were expressed in absolute values (HF ms<sup>2</sup> and LF ms<sup>2</sup>) and percentages (HF% and LF%).

### **Physical Activity Level Assessment**

The level of physical activity was analyzed using the International Physical Activity Questionnaire (IPAQ). The data were converted into METS (Metabolic Equivalent of Task) for better visualization. The IPAQ allows the evaluation of the physical activity carried out by the individual during the previous week, classifying it into high (greater than 1500 MET-min/week) vs. low levels of physical activity (less than 600 MET-min/week) (HAGSTRÖMER M, et al., 2008).

### **DNA Extraction and PCR**

The DNA extraction from the oral mucosa cells was carried out using the Axyprep™ Mailsorce Genomic DNA Miniprep Kit (Axygen Scientific - USA), following the manufacturer's instructions. The DNA was quantified, and subsequently, the DNA fragment containing the polymorphic site I/D of the ACE gene was sequenced using polymerase chain reaction (PCR).

The primers used in this PCR allowed the amplification of sequences with 190 base pairs (bp) for the DD genotype and 490 bp for the II genotype. Were used the sequences hECAf (5'-CTG GAG ACC ACT CCC ATC CTT TCT-3') and hECAr (5'-GAT GTG GCC ATC ACA TTC GTC AGA T -3'). The presence of both fragments served to identify the heterozygotes (ID). PCR was performed in a final reaction mixture of 12 µL volume, comprising 6 µL of GoTaq® (Promega, cat. No. M7122), 0.06 µL of primers (hECAr e hECAf), 1 µL of DNA, and 5 µL of ultrapure water. The reaction conditions in the thermocycler alternated between temperatures of 95.55 °C and 75 °C, following: 5 min at 95 °C, 40 cycles of 10 s at 95 °C, 10 s at 58 °C, 20 s at 72°C, and 5 min at 72 °C. The steps in this protocol promoted denaturation of the DNA, annealing the primers to sample DNA strands, and then an extension of the DNA strands, respectively. The PCR products were separated on 1% agarose gel, using 6 µL of the sample and 490 bp and 190 bp markers.

The samples were run for 1 h 40 min at 80V. Afterward, the samples were stained with ethidium bromide (40 min), and electrophoresis was performed at 100V. The fragments were subsequently observed under ultraviolet light. The samples were classified into one of the three possible genotypes resulting from the polymorphism of the ACE gene: two homozygous (DD and II) genotypes and one heterozygous (ID) genotype. To increase the specificity of the genotyping, the samples that presented the DD genotype were re-evaluated by a second PCR, using a specific primer for the incorporation were used the sequences: sense (5' TGG GAC CAC AGC GCC CGC CAC TAC-3'), hECAf, and anti-sense (5'-TCG CCA GCC CTA CCA TGC CCA TAA -3'), hECAr.

**Statistical analysis**

Data were subjected to the Kolmogorov-Smirnov normality test. To analyze the differences between the groups, t-test and two-way ANOVA with Bonferroni posthoc test were used. Hardy-Weinberg equilibrium was verified by comparing the observed and expected genotype frequency using the  $\chi^2$  test. The chi-squared test was performed to evaluate the association between qualitative variables. The level of significance was established at  $p < 0.05$ . Data are represented as mean  $\pm$  standard error of the mean. Statistica® 5.0 software was used for data analysis.

**RESULTS**

This study was conducted with 243 adolescents grouped according to the allele of ACE I/D Polymorphism and sleep quality of the adolescents.

**Table 1** - Presents sample characterization by dividing the groups based on alleles II and ID+DD together with sleep quality. Using gender data, physical activity level and sexual maturation parameters were within normal range by the Chi-square test, regardless of the group.

Variables	II+GSQ (n= 35)	II+PSQ (n= 44)	ID/DD+GSQ (n= 78)	ID/DD+PSQ (n= 86)	$\chi^2$	
<b>Gender</b>						
Male	14	18	30	39	[0.859]	0.83
Female	21	26	48	47		
<b>Physical activity level</b>						
Active	28	34	53	55	[4.425]	0.21
Sedentary	7	10	25	31		
<b>Tanner's sexual maturation index</b>						
Stage 1	0 (0%)		1 (0.41%)		[2.409]	0.66
Stage 2	1 (0.41%)		2 (0.82%)			
Stage 3	15 (6.17%)		32 (13.16%)			
Stage 4	33 (13.58%)		81 (33.33%)			
Stage 5	30 (12.34%)		48 (19.75%)			

**Abbreviations:** GSQ: good sleep quality; PSQ: poor sleep quality. Statistical difference ( $P < .05$ ), based on Chi-squared test ( $\chi^2$ ). **Source:** Soares Junior NJ, et al., 2024.

**Table 2** Shows the D and I alleles' frequency and the distribution of genotypes (DD, DI, and II). Variables did not present statistically significant results. Table 3 observed the sample characteristics of other parameters and observed no statistically significant difference concerning age, waist circumference, and BMI.

**Table 2** - Frequency of the D and I alleles and the genotypes (DD, DI, and II).

Frequency of alleles (%)	GSQ (n= 113)	PSQ (n= 130)	$\chi^2$
	Allele total = 226	Allele total = 260	
Allele D	121 = (53.53 %)	123 = (47.30 %)	1.870.17
Allele I	105 = (46.46 %)	137 = (52.69 %)	
Frequency of genotypes (%)			
Genotype DD	43 = (38.05 %)	37 = (28.46%)	[2.63] 0.26
Genotype DI	35 = (30.97 %)	49 = (37.69 %)	
Genotype II	35 = (30.97 %)	44 = (33.84 %)	

**Note:** \*Statistical difference between the good sleep quality (GSQ) vs. poor sleep quality (PSQ) ( $P < 0.05$ ), based on Chi-squared test ( $\chi^2$ ). **Source:** Soares Junior NJ, et al., 2024.

**Table 3** - Characteristics of adolescents with II and DD/DI polymorphism and good or poor.

	II+GSQ	II+PSQ	DD/DI+GSQ	DD/DI+PSQ
Age (years)	15 ± 0.1	15 ± 0.1	16 ± 0.1	15 ± 0.3
SBP (mmHg)	112 ± 1.0	112 ± 1.2	116 ± 1.1	119 ± 2.0 <sup>#</sup>
DBP (mmHg)	65 ± 0.7	66 ± 0.8	69 ± 0.7 <sup>*</sup>	68 ± 1.4 <sup>*</sup>
HR (bpm)	78 ± 0.7	79 ± 1.3	79 ± 1.2	84 ± 2 <sup>*</sup>
Waist circumference (cm)	71.3 ± 0.6	70.0 ± 0.8	68.3 ± 0.7	70.2 ± 1.3
Body mass index (kg/m <sup>2</sup> )	20.8 ± 0.3	20.8 ± 0.3	20.7 ± 0.3	22.0 ± 0.5
PSQI	3 ± 2	8 ± 3 <sup>&amp;</sup>	3 ± 0.5	8 ± 0.7 <sup>&amp;</sup>

**Note:** SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; PSQI: Pittsburgh sleep quality index; Statistical differences (P < 0.05): \* vs II+GSQ; # vs II+PSQ; & vs DD/DI+GSQ.

**Source:** Soares Junior NJ, et al., 2024.

In addition to worsened sleep quality regardless of alleles, we see systolic blood pressure (SBP) and heart rate (HR) increased in the PSQ group, which has higher diastolic blood pressure (DBP) allele in the D allele group in both GSQ and the PSQ group. Data demonstrating the statistical difference. **Table 4** analyzed the relationship of these groups with the autonomic nervous system in the time and frequency domains. In this sense, there was a statistically significant difference in Mean RR, SD1, and SD2. Mean RR and SD1 showed reduced values in the DD/DI+PSQ group, and SD2 was lower in the DD/DI+GSQ group, as shown in the table.

**Table 4** - Analysis of the heart rate variability of adolescents with DD/DI and II polymorphism in good and poor sleep quality conditions.

	II+GSQ	II+PSQ	DD/DI+GSQ	DD/DI+PSQ
<b>Time-domain</b>				
Mean RR (ms)	770 ± 10	772 ± 7	769 ± 8	714 ± 12 <sup>*</sup>
SDNN (ms)	53 ± 2	51 ± 3	49 ± 2	52 ± 3
RMSSD (ms)	52 ± 3	49 ± 3	54 ± 2	48 ± 5
pNN50 (%)	29 ± 3	32 ± 1.5	26 ± 3	25 ± 5
<b>Non-linear</b>				
SD1 (ms)	41 ± 1	37 ± 2	38 ± 2	34 ± 2 <sup>*</sup>
SD2 (ms)	68 ± 1	68 ± 2	61 ± 2 <sup>*</sup>	64 ± 2

**Note:** Mean RR, mean of RR intervals; SDNN, the standard deviation of RR intervals; RMSSD, square root of the square mean of the differences between adjacent normal R-R intervals, expressed in milliseconds; pNN50, percentage of adjacent intervals over 50 ms; SD1, the standard deviation of instantaneous beat-to-beat variability; SD2, the long-term standard deviation of continuous R-R intervals. Statistical differences (P < 0.05): \* vs II+GSQ; # vs II+PSQ; & vs DD/DI+GSQ. **Source:** Soares Junior NJ, et al., 2024.

## DISCUSSION

The objective of this study was to evaluate how much the association between ACE I/D polymorphism and sleep quality can influence the cardiac autonomic modulation of adolescents. The main findings show an autonomic dysfunction related to low sleep quality and possibly to the D allele of the ACE I/D polymorphism. Studies also show that high blood pressure may be influenced by autonomic modulation and sleep quality so an autonomic imbalance may represent early SAH development (MACÊDO SRD, et al., 2021).

Analyzing the research results obtained, they presented a homogeneous sample related to the adolescents participating in the study, also associated with age, BMI, and WC, which could influence other parameters such as HR, BP, and ANS. Magalhães 2020 reported the influence of BMI and WC on HRV in adolescents, high sympathetic activity, and reduced parasympathetic activity in individuals with high BMI and HRV values, representing higher cardiovascular risk (MAGALHÃES BC, et al., 2020). Therefore, the literature shows that higher BMI and WC are responsible for poor sleep quality and autonomic dysfunction. Our study showed no difference between the groups about BMI and WC, making the results more refined as to their objective which was to analyze the effect of ACE. The results also showed associations of poor sleep quality on SBP, DBP, and HR, indicating changes in hemodynamic parameters, which may lead to a pre-hypertension adolescent

population. And this is corroborated by several other studies that show the relationship between poor sleep quality and high hemodynamic values, with a higher chance of SAH development in adults or adolescents earlier an earlier (LO K, et al., 2018; LUO S, et al., 2021; YUAN Y, et al., 2021).

One of the essential findings of this study demonstrated a possible influence of the D allele in ACE gene polymorphism on these hemodynamic parameters. There was no statistically significant difference in hemodynamic parameters in the PSQ group that had the I allele but in the groups that presented the D allele. This difference was not influenced by sleep in DBP; that was elevated both in GSQ and PSQ groups, and the two had the D allele. Showed that there was no difference in DBP with the I allele but with the D allele groups regardless of sleep quality, justifying a possible influence of the allele in question.

The literature demonstrates the influence of the ACE D allele on SBP, DBP, and HR when showing that a single D allele of the ACE gene polymorphism is sufficient to increase serum ACE production in individuals who have it (KARAHAN Z, et al., 2016). As a result, individuals with the DD genotype showed approximately twice as much ACE activity as homozygotes II. Individuals with the ID genotype have an intermediate level of ACE activity between groups (RIGAT B, et al., 1990).

Thus, individuals with the DD genotype may be more exposed to higher levels of angiotensin II than those with genotype II. Thus, the increase in ACE synthesis potentiates the increase in sympathetic activity and the systemic vasoconstrictor responses due to greater angiotensin II production. In addition, other mechanisms such as a decrease in the endothelial signaling pathways triggered by bradykinin, which has a vasodilating action, consequently increasing blood pressure (AHN SY, et al., 2018).

Another highlight of the study is the altered autonomic variables Mean RR, SD1, and SD2. In the DD/DI+PSQ group, we observed a reduction in Mean RR and SD1, which are variables that represent the Parasympathetic Nervous System demonstrating the negative influence of poor sleep quality and the D allele on the autonomic nervous system. As in hemodynamic parameters, the variable SD2 of the autonomic nervous system showed a statistically significant difference represented by a reduction in the DD/DI+GSQ group. This result also confirms the influence that the D allele of the ACE gene polymorphism has on the ANS. Thus, this reduction even in the GSQ group demonstrates reduced parasympathetic activity in the GSQ group determining the relationship of the ACE gene polymorphism in autonomic parameters.

The literature also corroborates these findings as in the Marzbanrad F 2012 study whose objective was to investigate autonomic dysfunction parameters that may be under the influence of ACE I/D genotypes and potentially demonstrate an association between parameters of autonomic dysfunction with ACE genotypes (MARZBANRAD F et al., 2014; NG E, et al., 2012).

Other findings place a possible negative influence of the D allele on HRV, however in conjunction with other genetic factors such as AGT M235T polymorphism but highlighting the small sample (149 individuals) of the study and only Japanese males (NISHIKINO M, et al., 2006).

The literature shows that ACE Genotype I/D differs among races (Wang et al., 2000). Therefore, other population samples should investigate the putative associations between ACE polymorphisms and ANS function. Thus, with a more representative sample than the previous ones, this study demonstrated a possible relationship between the ACE I/D polymorphism and the sleep quality in HRV of individuals and adolescents.

## CONCLUSION

This article worked with a very specific population that has been increasingly studied around the world with the aim of making life in adulthood healthier. We can conclude an important association that adolescents with the I/D polymorphism of the ACE D allele negatively influence HRV, regardless of sleep quality. Poor sleep also negatively affects HRV, and the two factors (D allele and PSQ) are even more harmful to the adolescent population, leading to various cardiovascular problems. Thus, the importance of sleep quality was observed to be even greater in the presence of the ACE genetic polymorphism. Thus, we highlight the importance of good sleep quality in influencing several parameters for adolescent health and quality of life.

## ACKNOWLEDGMENTS

Foundation for Research and Scientific and Technological Development of Maranhão - FAPEMA (Universal - 01293/16), INFRA – 02226/21 Edict 10/2021 and BEPP 07/2021 FAPEMA; - Coordination for the Improvement of Higher Education Personnel (CAPES-BRAZIL) - Finance Code 001. Foundation for Research and Scientific and Technological Development of Maranhão - Coordination for the Improvement of Higher Education Personnel (CAPES-BRAZIL) - Finance Code 001. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

## REFERENCES

1. AHN S-Y e GUPTA CJFIP. Genetic programming of hypertension, 2018; 5: 285.
2. AMARA A, et al. Thrombosis/Hemostasis, A. The effect of ACE I/D polymorphisms alone and with concomitant risk factors on coronary artery disease, *Clinical and Applied Thrombosis/Hemostasis*, 2018; 24: 157-163.
3. BARROSO WKS, et al. Brazilian guidelines of hypertension, 2020; 116: 516-658.
4. BERTOLAZI AN, et al. Validation of the Brazilian Portuguese version of the Pittsburgh sleep quality index. *Sleep medicine*, 2011; 12: 70-75.
5. FLYNN JT, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics*, 2017.
6. FRANCICA JV, et al. Cardiac autonomic dysfunction in chronic stroke women is attenuated after submaximal exercise test, as evaluated by linear and nonlinear analysis. *BMC cardiovascular disorders*, 2015; 15: 1-8.
7. GARG R, et al. The isometric handgrip exercise as a test for unmasking hypertension in the offsprings of hypertensive parents, *Journal of clinical and diagnostic research: JCDR*, 2013; 7: 996.
8. GORDON D, et al. Publication of trials funded by the National Heart, Lung, and Blood Institute, New England. *Journal of Medicine*, 2013; 369: 1926-1934.
9. GUNEY A, et al. Effects of ACE polymorphisms and other risk factors on the severity of coronary artery disease. *Genet Mol Res*, 2013; 12: 6895-6906.
10. HAGSTRÖMER M, et al. Concurrent validity of a modified version of the International Physical Activity Questionnaire (IPAQ-A) in European adolescents: The HELENA Study, *International journal of obesity*, 2008; 32: S42-S48.
11. KADISH AH, et al. ACC/AHA clinical competence statement on electrocardiography and ambulatory electrocardiography: A report of the ACC/AHA/ACP–ASIM Task Force on Clinical Competence (ACC/AHA Committee to Develop a Clinical Competence Statement on Electrocardiography and Ambulatory Electrocardiography) Endorsed by the International Society for Holter and Noninvasive Electrocardiology. *Circulation*, 2001; 38: 2091-2100.
12. KARAHAN Z, et al. Association between ACE Gene Polymorphism and QT Dispersion in Patients with Acute Myocardial Infarction. *The open cardiovascular medicine journal*, 2016; 10: 117.
13. KEARNEY PM, et al. Global burden of hypertension: analysis of worldwide data. *The Lancet*, 2005; 365: 217-223.
14. LO K, et al. Subjective sleep quality, blood pressure, and hypertension: a meta-analysis, *The Journal of Clinical Hypertension*. *The Journal of Clinical Hypertension*, 2018; 20: 592-605.
15. LUO S, et al. Relationship of quality and duration of sleep with hypertension among adults in Guangzhou. *Zhonghua yu Fang yi xue za zhi [Chinese Journal of Preventive Medicine]*, 2021; 55, 853-859.
16. MACÊDO SRD, et al. Cardiac Autonomic Modulation is a Key Factor for High Blood Pressure in Adolescents. *Arquivos Brasileiros de Cardiologia*, 2021; 117: 648-654.
17. MAGALHÃES BC, et al. Effect of obesity on sleep quality, anthropometric and autonomic parameters in adolescent. *Sleep Science*, 2020. 13: 298.
18. MARZBANRAD F, et al. Relationship between Heart Rate Variability and angiotensinogen gene polymorphism in diabetic and control individuals. 36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE, 2014. pp. 6683-6686.



19. MATTHEWS KA., PANTESCO EJSM. Sleep characteristics and cardiovascular risk in children and adolescents: an enumerative review. *Sleep medicine*, 2016; 18: 36-49.
20. MORRIS NM e UDRY JRJJOY. Validation of a self-administered instrument to assess stage of adolescent development. *Journal of youth and adolescence*, 1980; 9: 271-280.
21. NG E, et al. WEKA machine learning classification in identifying autonomic dysfunction parameters associated with ACE insertion/deletion genotypes, *Proceedings of the IASTED International Conference Biomedical Engineering, BioMed*, 2012; pp. 161-166.
22. NISHIKINO M, et al. Genetic variation in the renin-angiotensin system and autonomic nervous system function in young healthy Japanese subjects. *The Journal of Clinical Endocrinology & Metabolism*, 2006; 91, 4676-4681.
23. PIETILÄ J, et al. Exploratory analysis of associations between individual lifestyles and heart rate variability-based recovery during sleep. *37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). IEEE*, 2015; pp. 2339-2342.
24. PROGRAM NHBPE. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents US Department of Health and Human Services, National Institutes of Health. *Pediatrics*, 2004.
25. RIGAT B, et al. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. *The Journal of clinical investigation*, 1990; 86: 1343-1346.
26. SINGH M, et al. Pathogenesis and clinical physiology of hypertension. *Cardiology clinic*, 2010; 28: 545-559.
27. SOARES JUNIOR NJ, et al. Sleep quality and regular physical activity in reducing cardiac risk. *Breathing*, 2023; 27: 953-960.
28. THAYER JF, et al. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. *Encyclopedia of Behavioral Medicine*, 2010; 141: 122-131.
29. TOKER RT, et al. Circadian blood pressure rhythm in normotensive offspring of hypertensive parents. *Cardiology journal*, 2015; 22: 172-178.
30. WANG J-G e STAESSEN JAJE. Genetic polymorphisms in the renin-angiotensin system: relevance for susceptibility to cardiovascular disease, *European journal of pharmacology*, 2000; 410: 289-302.
31. WULSIN LR, et al. Autonomic imbalance as a predictor of metabolic risks, cardiovascular disease, diabetes, and mortality. *The Journal of Clinical Endocrinology & Metabolism*, 2015; 100: 2443-2448.
32. YUAN Y, et al. Poor sleep quality is associated with new-onset hypertension in a diverse young and middle-aged population. *Sleep medicine*, 2021; 88: 189-196.