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Bárbara Sofia Fernandes Esteves

# Relationship Between Adverse Childhood Experiences, Glycaemic control, and Metabolic profile in Type 2 Diabetes Mellitus: a study in the Portuguese Population

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**Trabalho efetuado sob a Orientação de:**

**Dra. Margarida Maria Carvalho de Figueiredo Ferreira Braga**

**E sob a Coorientação de:**

**Dr. João Sérgio de Lima Soares Neves**

**Dra. Raquel Ângela Silva Soares Lino**

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NOME

Bárbara Sofia Fernandes Esteves

| NÚMERO DE ESTUDANTE | E-MAIL |
|---|---|
| 201506467 | up201506467@edu.med.up.pt |

DESIGNAÇÃO DA ÁREA DO PROJECTO

Ciências Médicas e da Saúde; Medicina Clínica

TÍTULO DISSERTAÇÃO

Relationship Between Adverse Childhood Experiences, Glycaemic control, and Metabolic profile in Type 2 Diabetes Mellitus: a study in the Portuguese Population

ORIENTADOR

Margarida Maria Carvalho de Figueiredo Ferreira Braga

COORIENTADOR (se aplicável)

João Sérgio de Lima Soares Neves
Raquel Ângela Silva Soares Lino

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Faculdade de Medicina da Universidade do Porto, 09/04/2021

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Bárbara Sofia Fernandes Esteves

Dedico esta Dissertação de Mestrado,
realizado com muita dedicação, empenho e interesse,
aos meus pais, Maria da Glória Esteves e Fernando Esteves,
ao meu namorado, Eduardo Dixo,
e a todos os meus queridos amigos,
por todo o amor, apoio e compreensão.

A todos muito obrigado!

# Relationship Between Adverse Childhood Experiences, Glycaemic control, and Metabolic profile in Type 2 Diabetes Mellitus: a study in the Portuguese Population

*Authors*

Bárbara Esteves [a], João Sérgio Neves [bc], Raquel Soares[de] e Margarida Figueiredo-Braga[ae]

[a] Department of clinical neuroscience and mental health, Faculty of Medicine, University of Porto

[b] Department of surgery and physiology, Faculty of Medicine, University of Porto

[c] Service of endocrinology, diabetes, and metabolism, Centro Hospitalar Universitário São João

[d] Department of biomedicine, Faculty of Medicine, University of Porto

[e] i3S – Institute for Innovation and Research in Heath, Porto.

*Highlights*

- Adverse childhood experiences (ACE) are a form of early onset psychological trauma.
- ACE are associated with dysfunctional endocrine responses.
- ACE can increase the risk of metabolic disorders and psychiatric diseases.
- Patients with T2DM who reported ACE present poorer glycaemic control.
- Patients with T2DM and higher stress present poorer metabolic control.

*Abstract*

Background: Adverse childhood experiences (ACE) are highly prevalent in the general population. As a form of early psychological trauma, ACE alter metabolic, endocrine, and immunologic responses, and promote higher risk for several physical and psychiatric diseases in adulthood. A relationship has been reported between ACE and the diagnosis and control of type 2 Diabetes Mellitus (T2DM). This study goal was to evaluate the relationship between ACE, perceived stress, and clinical and laboratory profile in a group of T2DM patients.

Methods: Sixty-six adult patients with T2DM were submitted to a psychosocial evaluation, and clinical and laboratory data were retrieved from the clinical charts. The occurrence of ACE and stress levels were measured with the Adverse Childhood Experiences Questionnaire – Short Version (ACEQ) and the Perceived Stress Scale (PSS-10); metabolic (HbA1c, glycemia, BMI, lipid, and tensional profile), health behaviours, and T2DM clinical outcomes were examined.

Results: The mean age of the participants was 67.3 years (SD 10.5), the majority were males (65.2%), with a mean length of disease of 9.2 years. Forty-five reported at least one ACE. Participants presented a mean number of 2.4 (SD 2.57) ACE and a PSS-10 score of 15.1 (SD 7.38). From those presenting macro or microvascular lesions, 67.7% and 65.8%, respectively, reported ACE. A trend was found to higher HbA1c and glycaemia in patients with ACE; higher perceived stress was associated with poorer metabolic control.

Conclusions: More severe clinical and laboratory parameters of T2DM were detected in patients who reported adverse experiences during childhood. Specific metabolic profile and higher stress

levels found in this subgroup may indicate a dysfunctional endocrine response determined by early-life stressors.

*Abbreviations*

ACE, Adverse Childhood Experiences; T2DM, Type 2 Diabetes Mellitus; HPA, Hypothalamus-Pituitary-Adrenal; ACEQ, Adverse Childhood Experiences Questionnaire – Short Version; PSS-10, Perceived Stress Scale 10; HbA1c, glycated haemoglobin; BMI, Body Mass Index; HDL, High Density Lipoprotein; LDL, Low Density Lipoprotein; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure.

*Keywords*

Adverse Childhood Experiences; Perceived Stress; Metabolic Profile; Glycaemic Control; Type 2 Diabetes Mellitus

## 1. Introduction

Adversity has been described as the exposure to circumstances unfavourable to the normal human development. [1] During early years adverse circumstances are a form of psychological trauma, which are considered to impinge normal development, and to represent a supplementary risk to physical and psychological diseases. [2, 3] Adverse Childhood Experiences (ACE) are important stressors, which can result in physiological responses that can persist years after the threat is over. [4] Several events may be considered ACE - the direct exposure of a child to abuse, which can be physical, emotional or sexual, negligence, either physical or emotional, exposure to family disfunction, such as, domestic violence, parental separation and family members with alcohol or drug abuse, psychiatric disturbances or prison. [2, 5] In Europe, it is estimated that the prevalence for physical abuse is 22.9%, sexual abuse is 9.6% - being twice more common in females than males, emotional abuse reaches 29.1%, physical neglect 16.3%, and emotional neglect 18.4%. Being raised in dysfunctional families is also common. Consequently, the exposure to parental separation is 14.1% and to domestic violence is 14.6%. Having family members with alcohol and drugs dependency, corresponded to, respectively, 16.4 % and 2.6 %. In addition, 5.3% had a family member in prison and 10% had a family member with mental illness.[6] ACEs are strongly interconnected, the exposure to one ACE increases the likelihood of being exposed to several types of maltreatment [7] and enhance the risk of suffering severe, emotionally damaging, or chronic abuse. [2, 8] These types of experiences are associated to increased morbidity and mortality [1, 7, 9], namely obesity, endocrine, autoimmune, cardiovascular, pulmonary, and hepatic diseases, skeletal fractures, and cancer, in adulthood. [2, 3, 10-12]

Psychological trauma, like physical trauma, can trigger identical and standardized physiological stress response. [13, 14] The main controller of the stress reaction is the interaction between the hypothalamus and the autonomous nervous system (particularly the sympathetic nervous system (SNS)). Hypothalamus is responsible for the production of corticotrophin releasing hormone (CRH). [14, 15] The increase of CRH promotes the anterior pituitary gland to release adrenocorticotropic hormone (ACTH), which stimulates the adrenal glands to produce glucocorticoids. This constitutes the hypothalamus – pituitary – adrenal (HPA) axis. On a stressful situation, the HPA axis is activated, increasing the peripheral release of cortisol, decreasing the levels of growth hormone (GH), insulin growth factor 1 (IGF-1), luteinizing hormone (LH) and thyroid stimulation hormone (TSH). Stress can also activate the SNS and the adrenomedullary

systems, resulting in an increase in the noradrenalin, adrenalin, and interleukin 6 (IL-6). [14] High levels of catecholamines promotes a HPA axis response, and CRH stimulates the SNS.[15]

As chronic stressors ACE can lead to an excessive and long activation of the stress response system [14] - chronically Cortisol and Catecholamines elevated levels, suppression of the growth axis (decrease in GH) and the reproductive axis (decrease in LH). [15, 16] Early hyper or hypo-activation of the stress systems can irreversibly affect cerebral, endocrine, metabolic, immunological and behaviour development. [14] Due to this chronic activation of the HPA axis, adults who have experienced ACE tend to have elevated basal cortisol levels.[7, 16] The chronic hypersecretion of stress peripheral mediators can result in insulin resistance, initial hyperglycaemia due to glucose synthesis and release by hepatocytes, accompanied by an increased level of insulin. Eventually, the capacity of pancreatic beta-cells to produce insulin starts to decrease and hyperglycaemia further increases.[14, 15] Cortisol can also interfere with insulin's action and inhibit its release by the pancreatic beta-cells. Glucocorticoids induce, progressively, insulin resistance, throughout regulation of multiple aspects in the glucose transportation system, regulated by insulin. They are also responsible for increasing glucose hepatic metabolism and decreasing glycogen production in skeletal muscle. Therefore, chronic hypersecretion of stress mediators originates a diabetogenic and pro-inflammatory environment,[15] leading to sarcopenia, osteoporosis, osteopenia, metabolic syndrome, hypercoagulation and depression. Metabolic syndrome is associated with insulin resistance (with or without the presence of T2DM), visceral obesity, dyslipidaemia (levels of triglycerides, total cholesterol or of LDL (low density lipoprotein) higher than the 90$^{th}$ percentile, or low levels of HDL (high density lipoprotein) lower than the 10$^{th}$ percentile for the general population) and arterial hypertension.[4, 14, 15] Elevated basal cortisol levels could also favour fat accumulation by inhibiting lipolysis. [17] Obesity is therefore an important risk factor for T2DM, cardiovascular and psychological abnormalities. Although ACE led to pro-obesity behaviours, the relationship between ACE and obesity persist even when confounding bias are excluded. [17-20] Adults that reported ACE present low sensitivity to inhibitory hormonal signals [9], resulting in a diminished capacity to glucocorticoids control HPA axis in response to psychosocial stress. [21] The exposure to ACE in the first decade of life, leads to clinically significant values of inflammatory biomarkers in adulthood [21] and metabolic abnormalities which can contribute to the progression of atherosclerosis, aiding the development of cardiovascular diseases. [4] In summary, psychological stress represents a potential risk factor for metabolic syndrome. [22-24]

As previously stated, chronic stress associated with ACE leads to behaviour modification, promoting risky behaviours, unhealthy lifestyles, low self-esteem, and conflict in interpersonal relationships. Victims of ACE can try to cope through avoidant, self-medicating (alcohol and tabaco abuse), compulsive (binge-eating) or self-harming behaviours. Early trauma is associated to food disorders, low physical activity, obesity and T2DM. Obesity is, by itself, one of the most relevant risk factors for T2DM. [7, 9, 10, 19, 25, 26]. In summary, the relationship between ACE and T2DM appear to depend on a dysfunctional health style with less physical activity and less quality food intake, and a diminished capacity to glucocorticoids control HPA axis in response to psychosocial stress. Bad glycaemic control increases the risk of micro and macrovascular repercussions, including cardiovascular disease (main cause of death), lower limb amputation, retinopathy, renal failure, and stroke. [27] As T2DM has become one of the most serious public health problems in multiple parts of the world in the last decades, [28] understanding the risk factors associated with T2DM development is of major importance. Adverse Childhood Experiences can be seen as a potentially modifiable risk factor for T2DM and obesity [10, 17]

Our aim is to evaluate the association between adverse childhood experiences (ACE) and higher levels of perceived stress and the development and control of type 2 Diabetes Mellitus (T2DM), and the metabolic profile. The overall prevalence of Diabetes Mellitus, in Portugal, in 2018, was 13.6%, reflecting a growth of 16.3% in the last 10 years, and T2DM is the most prevalent type. [27, 29] However, DM can be asymptomatic, so its prevalence may be underestimated. [30]

We characterized a population of T2DM patients and collected metabolic, sociodemographic, behavioural, clinical, and psychometric data. To the best of our knowledge, this is the first study addressing the occurrence of ACE and its impact in Portuguese patients with Type 2 diabetes.[8, 28, 31-37]

## 2. Methods

The study followed an observational cross-sectional design.

### *2.1. Population*

#### *2.1.1.Participant Selection*

Adult patients with T2DM, hospitalized in *Centro Hospitalar Universitário São João* (CHU São João) were invited to participate in the study. Those who voluntarily agreed to participate were screened for the presence of ACE and their levels of perceived stress was measured. All the patients were non-insulin dependent and free major neurologic pathologies. Those whose clinical data was not provided were excluded from the study.

#### *2.1.2.Psychosocial evaluation*

Participants who signed the informed consent form fulfilled two self-report psychological measures - the "Adverse Childhood Experiences Questionnaire – Short Version" , and the "Perceived Stress Scale".

The "Adverse Childhood Experiences Questionnaire – Short Version" is a self-report tool for adults, to determine whether they had experienced Adverse Childhood Experiences (ACE) or not.[38] The short version, validated in the Portuguese population, was used [1], being constituted by 17 dichotomous questions. The questionnaire reflects the subject's experiences until they pertain 16 years old age, and questions cover diverse types of ACE, emotional, physical, and sexual abuse, emotional, and physical negligence, parents' separation or divorce, exposure to domestic violence, substance abuse in the household, mental illness or suicide in the household and family member in prison. The total score of ACE is the sum of all positive answers. If a person answers affirmatively to one question, it is considered to have been exposed to ACE. [1, 38]

The "Perceived Stress Scale" (PSS) is a self-report instrument that aims to measure how the events are appraised as stressful, in consequence of their unpredictability, uncontrollability or their excess. [39] In this study, we used the Portuguese version of the PSS-10 [40, 41], which makes a good compromise in the number of items, making it easy to fill, and presenting acceptable psychometric properties. [40, 42] It is important to note that the PSS-10 reflects the perceived stress in the last month, not addressing isolated events. The PSS-10 uses a Likert scale with 5 points (0 never; 1 almost never; 2 sometimes; 3 often; 4 very often) and the results vary between 0 and 40. [40] The cut-off 18 [43] (which represents the $75^{th}$ quartile) was used to classify levels of perceived stress into low to moderate (PSS-10 $<18$) or high (PSS-10 $\geq 18$).

Sociodemographic variables and health behaviours were also collected and included in the analysis.

### *2.2. Clinical and metabolic evaluation*

#### *2.2.1.Clinical evaluation*

This evaluation considered the presence of T2DM complications, microvascular or macrovascular disease, the time since the diagnosis and the number of hospitalizations. It should be noted that the investigators only have the information of the hospitalizations that happened in public hospital, so these variables can be underestimated.

*2.2.2.Evaluation of Metabolic Profile*

Glycated haemoglobin (HbA1c) and glycaemia were used to assess T2DM. HbA1c is the most reliable method of evaluation of control in T2DM since it constitutes the mean glycemia levels of the last three months, not showing as many biological variations, as glycemia. [44] To evaluate obesity, body mass index (BMI) was measured. In adults, male or female, obesity is present when BMI $\geq$ 30 kg/m$^2$ and excess weight is defined as BMI $\geq$ 25 kg/m$^2$. The lipid profile included total cholesterol, high density lipoprotein (HDL) fraction of cholesterol, low density lipoprotein (LDL) fraction of cholesterol and triglycerides. To evaluate the blood pressure profile one register of systolic blood pressure (SBP) and diastolic blood pressure (DBP) was measured. All the metabolic parameters were retrieved from the clinical charts.

2.3. *Procedures*

Patients hospitalized in CHU São João that obey the inclusion criteria and did not present any exclusion criteria, were invited to fulfil the two questionnaires. They received information about the study procedures and purpose, and the need to collect data from the clinical records. All the participants signed a consent form, approved by the Ethical Committee.

*2.4. Ethical considerations*

The study was submitted to the ethical committee of CHU São João. The project's number was 337/2020 and the submission was made 08 of September 2020. The committee approved the project in the 13 of October 2020.

*2.5. Statistical analysis*

The statistical analysis was performed using the IBM SPSS statistics 26. The two questionnaires applied allowed the division of the participants according to the presence of adverse childhood experiences and the presence of high levels of perceived stress. To study the relationship between these groups and the metabolic profile, the Kolmogorov-Smirnov and the Shapiro-Wilk tests were used to evaluate the distribution of the continuous variables. Those who presented a normal distribution were evaluated using the T-test for independent variables and the others were evaluated using the Mann-Whitney U test. The Pearson's Correlation test was used to evaluate associations between variables. Categorical variables were evaluated using the chi-square and the Fisher's exact tests.

## 3. Results

*3.1. Population Sociodemographic and Psychometric characterization according to the presence of ACE. Table 1*

The mean age of the participants is 67.27 years old (standard deviation (SD) of 10.57 years).

Forty-five participants presented at least one ACE. The mean number of ACE reported by the participants that presented at least one ACE was 3.51 (SD 2.39), the highest number of ACE reported was 11.

The two groups of patients divided according with ACE presence presented similar sociodemographic characteristics.

Perceived Stress in the last month was evaluated using the PSS-10, and the mean score in the total sample was 15.12 (SD 7.38). No statistically significant differences were found (p= 0.367) when comparing patients with or without ACE. (Table 1).

***Table 1:*** *Sociodemographic and Psychometric characterization of the studied population, showing the differences of the subgroups with or without the presence of at least one ACE.*

| | | Total n = 66 | Without ACE n = 21 | With ACE n = 45 | *P* |
|---|---|---|---|---|---|
| **Age** (years)[1] | | 67.27 (10.57) | 66.76 (12.93) | 67.51 (9.42) | 0.825[a] |
| **Gender**[2] | Male | 43 (65.2) | 14 (66.7) | 29 (64.4) | 0.860[b] |
| | Female | 23 (34.8) | 7 (33.3) | 16 (35.6) | |
| **School** (years)[1] | | 5.98 (2.88) | 5.83 (3.10) | 6.03 (2.84) | 0.892[a] |
| **Marital Status**[2] | Single | 5 (7.7) | 1 (5.0) | 4 (8.9) | 0.616[c] |
| | Married | 55 (84.6) | 19 (95.0) | 36 (80.0) | |
| | Widowed | 4 (6.2) | 0 | 4 (8.9) | |
| | Divorced | 1 (1.5) | 0 | 1 (2.2) | |
| **Total Ace Score**[1] | | 2.39 (2.57) | 0 | 3.511 (2.39) | |
| **Total PSS-10 Score**[1] | | 15.12 (7.38) | 13.76 (2.39) | 15.76 (6.99) | 0.233[a] |

[a] p value obtained using Mann-Whitney U Test. [b] p value obtained using the Chi-Square test. [c] p value obtained using the Fisher's exact test. [1] Mean (Standard Derivation). [2]n(%)

### *3.2. Characterization and prevalence of ACE. Table 2*

Of all the different ACE contemplated in the ACEQ, physical abuse was the most reported (n=22) followed by emotional abuse (n=21). Men presented higher prevalence in emotional abuse, physical abuse, sexual abuse, physical negligence and having a family member in prison. Women presented higher scores in emotional negligence, exposure to parental separation, and parental violence, exposure to alcohol or other drugs dependence and exposure to mental illness of a family member. Women have a superior prevalence of sexual abuse, however in our study the 2 cases of sexual abuse were reported by man.

We compared ACE report in our population with Europe's estimated ACE prevalence. Our patients presented higher scores of emotional and physical abuse, physical negligence, exposure to parental violence and exposure to mental illness in the family household than the European population, but lower sexual abuse, emotional negligence, parental separation and imprisonment of a family member. (Table 2).

***Table 2*** *- ACE distribution and comparison with the European Estimated Prevalence and by gender.*

| | ACEQ [1] | European Estimated Prevalence (2014)[2] | Gender Distribution[2] | |
|---|---|---|---|---|
| | | | Males | Females |
| **Emotional Abuse** | 21 (31.8) | 29.1 | 32.6 | 30.4 |
| **Physical Abuse** | 22 (33.3) | 22.9 | 39.5 | 21.7 |
| **Sexual Abuse** | 2 (3.0) | 9.6 | 3.0 | 0 |

| | | | | |
|---|---|---|---|---|
| **Emotional Negligence** | 12 (18.2) | 18.4 | 14.0 | 26.1 |
| **Physical Negligence** | 18 (27.3) | 16.3 | 30.2 | 21.7 |
| **Parental Separation** | 7 (10.6) | 14.1 | 7.0 | 17.4 |
| **Exposure to Parental Violence** | 18 (27.3) | 14.6 | 23.3 | 34.8 |
| **Exposure to Alcohol or Drug Dependence** | 13 (19.7) | 16.4[a]<br>2.6[b] | 14.0 | 30.4 |
| **Exposure to Mental Illness** | 8 (12.1) | 10.0 | 11.6 | 13.0 |
| **Prison of a Family Member** | 1 (1.5) | 5.3 | 1.5 | 0 |

[1] n(%). [2] %. [a] Alcohol dependence [b] Illegal drugs dependence

### *3.3. Population Sociodemographic and Psychometric characterization according to the levels of perceived stress. Table 3*

Patients were divided in two groups according to the PSS score: 43 patients classified as low to normal stress levels and 23 patients classified as high level.

Both groups presented similar age (p= 0.071), gender distribution (p= 0.593), education (p=0.928) and marital status (p= 0.190).

Patients with higher stress level (23.13; SD 4.65) showed a trend to higher total ACE score (mean of 3.09; SD 3.10), although the difference was not statistically significant (p= 0.196).

***Table 3:****Sociodemographic and Psychometric characterization of the studied population, showing the differences of the subgroups according to the levels of perceived stress.*

| | | Total<br>n = 66 | Low to Moderate Levels of Perceived Stress<br>n = 43 | High Levels of Perceived Stress<br>n = 23 | *p* |
|---|---|---|---|---|---|
| **Age[1]** (years) | | 67.27 (10.57) | 69.16 (10.45) | 63.74 (10.07) | 0.071[a] |
| **Gender[2]** | Male | 43 (65.2) | 29 (67.4) | 14 (60.9) | 0.593[b] |
| | Female | 23 (34.8) | 14 (32.6) | 9 (39.1) | |
| **School[1]** (years) | | 5.98 (2.88) | 6.07 (3.01) | 5.75 (2.63) | 0.928[a] |
| **Marital Status[2]** | Single | 5 (7.7) | 2 (4.8) | 3 (13.0) | 0.190[c] |
| | Married | 55 (84.6) | 38 (90.5) | 17 (19.5) | |
| | Widowed | 4 (6.2) | 2 (4.8) | 2 (8.7) | |
| | Divorced | 1 (1.5) | 0 | 1 (4.3) | |
| **Total Ace Score[1]** | | 2.39 (2.57) | 2.02 (2.18) | 3.09 (3.10) | 0.196[a] |
| **Total PSS-10 Score[1]** | | 15.12 (7.38) | 10.84 (4.37) | 23.13 (4.65) | |

[a] p value obtained using the Mann-Whitney U test. [b] p value obtained using the Chi-Square test. [c] p value obtained using the Fisher's exact test. [1] Mean (Standard Derivation). [2]n(%)

*3.4. Clinical and Laboratorial characterization. Table 4*

The mean time since diagnosis was 9.16 years (SD 5.14), being higher in the participants without ACE (10.15 years; SD 5.16), although this difference was not statistically significant (p=0.345). The time since diagnosis was higher in the participants with normal levels of stress (9.5 years; SD 5.45), although this difference was not significant (p=0.489).

On average, the participants had 5.83 (SD 6.86) hospitalizations, with higher number in participants without ACE (mean 6.90; SD 11.41). When comparing recent hospitalizations, higher number was found in participants with ACE (2.91; SD 2.17) in the last 5 years, and 1.87 (SD 1.08) in the last year.

In average, the number of hospitalizations was higher in participants with high levels of perceived stress (7.65; SD 10.58), in the last 5 years (3.39; SD 3.10) and last year (2.04; SD 1.19). These differences were not statistically significant.

The presence of T2DM complications was similar regarding the report of ACE (p= 0.627 for microvascular complications and p=0.942 for macrovascular complications). Identically T2DM complications were present in similar number according to the levels of perceived stress (p= 0.090 for microvascular complications and p=0.678 for macrovascular complications).

The variables used to evaluate the metabolic profile were HbA1c, glycemia, BMI, total cholesterol, HDL and LDL cholesterol, triglycerides, SBP and DBP. When comparing patients with and without ACE a trend was found to poorer glycaemic control, which is translated in higher HbA1c and glycaemia, in patients that presented at least one ACE. In this subgroup, the mean HbA1c was 7.41 (1.98) and glycaemia presented a mean of 189.53 (99.23). Forty-one participants presented high values of glycaemia (28 presented ACE). Both subgroups presented a mean HbA1c and a mean glycaemia higher than the target values (≤7% and ≤130mg/dL respectively).

The lipid profile included total cholesterol, HDL, LDL and triglycerides. Similar measures were detected in both subgroup with subtle differences – higher total cholesterol and triglycerides in the subgroup without ACE, and lower HDL, LDL in subgroup with ACE. The mean triglycerides value was 170.58 mg/dL (SD 94.43 mg/dL). Normal triglycerides are defined as levels <150mg/dL [47], all the subgroups presented means superior to normal.

Within the 66 participants, 30 presented low levels of HDL. The LDL target values depend on the cardiovascular risk. If the cardiovascular risk is very high, the target value of LDL is <55mg/dL, if the cardiovascular risk is high, the target value is <70mg/dL [45]. The average values of LDL, in both groups were superior to the target values defined, which indicates a poor control. Very high cardiovascular risk was present in 45 patients, 42 of which with elevated LDL, and high cardiovascular risk in 21, 14 of which presented hight levels of LDL.

The mean SBP was 134.23 mmHg (SD 21.16 mmHg) and the mean DBP was 72.95 mmHg (SD 11.69). The therapeutic target to T2DM is a SBP <140mmHg and a DBP <90mmHg[46], and all the average values are within the normal range.

A trend was found to higher levels of HbA1c, poorer lipid profile and higher levels of DBP in the patients that presented higher levels of perceived stress. All the variables of the lipid profile presented higher mean values in the participants with higher perceived stress levels, although not statistically different. The average values of LDL in the subgroup with normal stress levels (88.56 mg/dL; SD 41.06) and in the subgroup with high stress levels (93.22 mg/dL; SD 42.99), were superior to the target values defined. All the subgroups presented triglycerides level above the normal.

***Table 4:*** *Clinical and Laboratorial characterization of the studied population*

| | | Total n = 66 | Without ACE n = 21 | With ACE n = 45 | Low to Moderate Levels of Perceived Stress n = 43 | High Levels of Perceived Stress n = 23 | *p* |
|---|---|---|---|---|---|---|---|
| **Time since Diagnosis**[1] (years) | | 9.16 (5.14) | 10.15 (5.16) | 8.77 (5.13) | 9.5 (5.45) | 8.57 (4.57) | 0.345[a◊] 0.489[a▲] |
| **Total hospitalizations**[1] | | 5.83 (6.86) | 6.90 (11.41) | 5.33 (3.39) | 4.81 (3.24) | 7.65 (10.58) | 0.253[b◊] 0.508[b▲] |
| **Hospitalizations in the last 5 years**[1] | | 2.91 (2.46) | 2.90 (3.08) | 2.91 (2.17) | 2.64 (2.02) | 3.39 (3.10) | 0.473[b◊] 0.319[b▲] |
| **Hospitalizations in the last year**[1] | | 1.77 (1.01) | 1.55 (0.83) | 1.87 (1.08) | 1.62 (0.88) | 2.04 (1.19) | 0.313[b◊] 0.147[b▲] |
| **Microvascular complications**[2] | Not Present | 28 (42.4) | 8 (38.1) | 20 (44.4) | 15 (34.9) | 13 (56.5) | 0.627[c◊] 0.090[c▲] |
| | Present | 38 (57.6) | 13 (61.9) | 25 (55.6) | 28 (65.1) | 10 (43.5) | |
| **Macrovascular complications**[2] | Not Present | 35 (53.0) | 11 (52.4) | 24 (53.3) | 22 (51.2) | 13 (56.5) | 0.942[c◊] 0.678[c▲] |
| | Present | 31 (47.0) | 10 (47.6) | 21 (46.7) | 21 (48.8) | 10 (43.5) | |
| **Body Mass Index**[1] (kg/m$^2$) | | 28.54 (6.85) | 28.55 (7.11) | 28.54 (6.81) | 28.43 (5.99) | 28.75 (8.38) | 0.736[b◊] 0.662[b▲] |
| **HbA1c**[1] (%) | | 7.53 (1.75) | 7.07 (0.92) | 7.41 (1.98) | 7.37 (1.35) | 7.83 (2.31) | 0.293[b◊] 0.989[b▲] |
| **Glycaemia**[1] (mg/dL) | | 182.33 (89.35) | 166.90 (62.63) | 189.53 (99.23) | 186.33 (92.16) | 174.87 (85.34) | 0.645[b◊] 0.385[b▲] |
| **Total Cholesterol**[1] (mg/dL) | | 166.27 (45.11) | 174.81 (47.32) | 162.29 (44.01) | 162.70 (41.91) | 172.96 (50.86) | 0.277[b◊] 0.400[b▲] |
| **HDL Cholesterol**[1] (mg/dL) | | 43.00 (12.43) | 43.62 (12.00) | 42.71 (12.75) | 41.67 (10.61) | 45.48 (15.23) | 0.785[a◊] 0.239[a▲] |
| **LDL Cholesterol**[1] (mg/dL) | | 90.18 (41.47) | 91.45 (41.58) | 89.59 (41.88) | 88.56 (41.06) | 93.22 (42.99) | 0.545[b◊] 0.793[b▲] |
| **Triglycerides**[1] (mg/dL) | | 170.58 (94.43) | 183.90 (130.75) | 164.36 (72.64) | 169.30 (105.94) | 172.96 (70.06) | 0.918[b◊] 0.203[b▲] |
| **Systolic Blood Pressure**[1] (mmHg) | | 134.23 (21.16) | 134.86 (23.363) | 133.93 (20.32) | 135.60 (22.84) | 131.65 (17.77) | 0.870[a◊] 0.474[a▲] |
| **Diastolic Blood Pressure**[1] (mmHg) | | 72.95 (11.69) | 73.95 (11.56) | 72.49 (11.85) | 71.65 (10.93) | 75.39 (12.88) | 0.639[a◊] 0.218[a▲] |

[a] *p* value obtained using the independent-samples T test. [b] *p* value obtained using the Mann-Whitney U test. [c] *p* value obtained using the Chi-Square test. [◊]*p* value for the ACE distribution. [▲]*p* value for the Levels of Perceived Stress distribution. [1] Mean (Standard Derivation). [2]n(%)

*3.5. Unhealthy behaviours. Table 5*

Unhealthy behaviour, specifically alcohol consumption and smoking, were evaluated in the studied population. When considering these consumptions and the presence of ACE, no statistically significant difference was found (p= 0.412 for tobacco and p=0.394 for alcohol). However, ACE total number is higher in the group with unhealthy behaviours. Groups divided according to PSS scores did not show statistically significant differences (p=0.066 for tobacco and p=0.569 for alcohol). Higher levels of perceived stress were shown in patients with unhealthy behaviours. Males consume more alcohol and tobacco than females (p<0.001 and <0.001 respectively). Age is lower in smokers (p=0.022) and blood pression is higher in patients with unhealthy lifestyle. The overall metabolic profile is worst in the patients without unhealthy behaviours. The HDL is the exception, being statistically significantly lower in smoker patients (p=0.034).

***Table 5**: Possible Confounders. Unhealthy Behaviours.*

| | | Tobacco | | Alcohol | | |
|---|---|---|---|---|---|---|
| | | No Smoker n = 36 | Smoker n = 30 | No Consumer n = 41 | Consumer n = 23 | *p* |
| **ACE** | **Without ACE**[1] n = 21 | 13 (61.9) | 8 (38.1) | 15 (71.4) | 6 (28.6) | 0.412[a◊] |
| | **With ACE**[1] n = 45 | 23 (51.1) | 22 (48.9) | 26 (60.5) | 17 (39.5) | 0.394[a▲] |
| | **Total ACE**[2] | 1.94 (2.04) | 3.10 (3.00) | 2.30 (2.67) | 2.43 (2.25) | 0.161[b◊] 0.470[b▲] |
| **Levels of Perceived Stress** | **Low to Moderate**[1] n = 43 | 27 (62.8) | 16 (37.2) | 28 (66.7) | 14 (33.3) | 0.066[a◊] |
| | **High**[1] n = 23 | 9 (39.1) | 14 (60.9) | 13 (59.1) | 9 (40.9) | 0.549[a▲] |
| | **Total PSS-10**[2] | 13.94 (7.30) | 16.59 (7.60) | 14.70 (7.00) | 15.43 (8.19) | 0.116[b◊] 0.877[b▲] |
| **Gender** | **Males**[1] n = 43 | 16 (37.2) | 27 (62.8) | 20 (47.6) | 22 (52.4) | <0.001[a◊] |
| | **Females**[1] n = 23 | 20 (87.0) | 3 (13.0) | 21 (95.5) | 1 (4.5) | <0.001[a▲] |
| | **Age**[2] | 69.14 (10.99) | 64.97 (8.61) | 67.65 (11.18) | 68.39 (8.91) | 0.022[b◊] 0.721[b▲] |
| | **BMI**[2] | 29.67 (7.51) | 27.06 (6.02) | 28.69 (7.22) | 28.50 (6.69) | 0.067[b◊] 0.872[b▲] |
| | **HbA1c**[2] | 7.56 (1.67) | 7.50 (1.90) | 7.51 (1.49) | 7.27 (1.56) | 0.874[b◊] 0.563[b▲] |
| | **Glycaemia**[2] | 177.14 (77.38) | 189.21 (105.47) | 190.63 (86.24) | 168.65 (98.73) | 0.944[b◊] 0.112[b▲] |
| | **Total Cholesterol**[2] | 168.91 (43.1) | 162.97 (49.47) | 172.35 (42.26) | 150.78 (28.47) | 0.417[b◊] 0.051[b▲] |

| | | | | | |
|---|---|---|---|---|---|
| **HDL**[2] | 46.03 (13.24) | 39.66 (10.96) | 44.60 (12.58) | 40.35 (12.01) | 0.034[c◊] 0.219[c▲] |
| **LDL**[2] | 93.37 (40.1) | 85.9 (44.72) | 92.21 (39.58) | 83.19 (33.94) | 0.491[b◊] 0.327[b▲] |
| **Triglycerides**[2] | 157.40 (69) | 183.93 (118.16) | 169.23 (95.36) | 165.61 (97.26) | 0.331[b◊] 0.421[b▲] |
| **SBP**[2] | 134.23 (22.53) | 135.38 (18.64) | 131.30 (21.89) | 137.26 (20.01) | 0.610[c◊] 0.311[c▲] |
| **DBP**[2] | 72.89 (11.1) | 73.0 (12.17) | 72.20 (11.51) | 73.35 (12.40) | 0.701[c◊] 0.819[c▲] |
| **Total**[1] | 36 (54.5) | 30 (45.5) | 41 (64.1) | 23 (35.9) | |

[a] *p* value obtained using the Chi-Square test. [b] *p* value obtained using the Mann-Whitney U test. [c] *p* value obtained using the independent-samples T test. [◊] *p* value for tobacco variable. [▲] *p* value for alcohol variable. [1] n(%). [2] Mean (Standard Derivation).

### *3.6. Microvascular and Macrovascular complications. Table 6*

T2DM may present microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (myocardial infarction, stroke, and peripheral arterial disease) complications, associated with the length of disease and usually representing a poor glycaemic control. The mean time since the diagnoses in the participants without microvascular complications was 7.02 years (SD 3.64) and when microvascular complications were present it was 10.73 years (SD 5.54), (p=0.004). In terms of macrovascular complications, the mean length of disease was 7.40 years (SD 3.63) for those participants without these complications in comparison with participants showing macrovascular complications (11.17 years; SD 5.88; p=0.003). Microvascular complications where present in higher number when hospitalizations were more frequent - total hospitalizations (p=0.006), in the last 5 years (p=0.023) and in the last year (0.017). Macrovascular complications showed statistically significantly higher number according number of total hospitalizations (p=0.002), and in the last 5 years (p=0.003).

***Table 6****: Microvascular and Macrovascular Complications*

| | Microvascular Complications | | Macrovascular Complications | | |
|---|---|---|---|---|---|
| | Not present n = 27 | Present n = 37 | Not present n = 34 | Present n = 30 | *p* |
| **Time Since Diagnosis**[1] (years) | 7.02 (3.64) | 10.73 (5.54) | 7.40 (3.63) | 11.17 (5.88) | 0.004[a◊] 0.003[a▲] |
| **Total hospitalizations**[1] | 3.85 (3.17) | 7.21 (8.34) | 4.09 (3.43) | 7.83 (9.08) | 0.006[b◊] 0.002[b▲] |
| **Hospitalizations in the last 5 years**[1] | 2.22 (1.93) | 3.39 (2.70) | 2.23 (1.91) | 3.70 (2.81) | 0.023[b◊] 0.003[b▲] |
| **Hospitalizations in the last year**[1] | 1.41 (0.69) | 2.03 (1.13) | 1.66 (1.06) | 1.90 (0.96) | 0.017[b◊] 0.162[b▲] |
| **HbA1c**[1] (%) | 7.59 (1.98) | 7.49 (1.59) | 7.56 (2.07) | 7.50 (1.32) | 0.920[b◊] 0.314[b▲] |
| **Glycaemia**[1] (mg/dL) | 169.78 (71.60) | 190.79 (101.12) | 173.34 (75.41) | 192.23 (104.96) | 0.736[b◊] 0.714[b▲] |

[a] *p* value obtained using the independent-samples T test. [b] *p* value obtained using the Mann-Whitney U test. [◊]*p* value for the Microvascular Complications distribution. [▲]*p* value for the Macrovascular Complications distribution. [1] Mean (Standard Derivation).

### *3.7. Correlations between psychometric variables and clinical and laboratory parameters in T2DM*

A positive correlation was found between the PSS-10 total score and the DBP value (p=0.047; r=0.246). The ACE total score did not presented correlations with the clinical and laboratory parameters studied variables. Age presented a negative correlation with school years attendance (p=0.010; p=-0.396).

As expected HbA1c presented a positive correlation and with the total cholesterol (p= 0.036; r=0.260). Age, conversely, showed a negative correlation with HbA1c (p=0.002; r=-0.374). The number of hospitalizations in the last 5 years also presented a correlation with HbA1c (p=0.045; r=0.250), but no correlation was found for the total number of hospitalization (p = 0.841) or the ones that occurred in the last year (p= 0.716).

HDL presents a negative correlation with the number of hospitalizations in the last 5 years (p=0.028; p= -0.272), so the patients with higher number of hospitalizations in the last 5 years presented lower levels of HDL.

Blood pressure parameters are also positively correlated with each other (p<0.001; r=0.505) Moreover DBP presented a positive correlation with BMI (p=0.033; r=0.262) and a negative correlation with age (0.009; r= -0.321).

## 4. Discussion

This study goal was to evaluate the relationship between the occurrence of adverse experiences during childhood experiences, the level of perceived stress and the metabolic and clinical profile in a group of T2DM patients.

ACE were present in about two-thirds of the studied population and the most reported was physical abuse, which is compatible with the findings of previous studies. [6, 28, 47] Adverse experiences have different distributions within gender and women tend to report higher levels of ACE. [5, 28, 48]

In our study the mean values of HbA1c and glycaemia were higher in participants with ACE, however the difference was not statistically significant. The patients with ACE showed a tendency for poorer glycaemic control. As an early form of psychological trauma, which can cause chronic stress, ACE may generate a hyperglycaemic status, which increases the risk for T2DM. In patients with T2DM, these types of traumatic events can lead to a worst glycaemic control. [25, 49, 50]

Of the patients with T2DM complications, which can be microvascular (diabetic retinopathy, diabetic nephropathy, and diabetic neuropathy) or macrovascular (myocardial infarction, stroke, or peripheral arterial disease), two thirds of them had at least one ACE. These experiences cause a hyper-reactivity to stress, increased inflammatory levels and metabolic abnormalities, contributing to a pro-atherosclerotic environment. [4] Atherosclerosis is an important factor for the development of complications, particularly at macrovascular level. The patients with complicated disease presented more hospitalizations, in a statistically significant form, although it was not possible to discriminate the reason for the hospitalization. Participants with complications seem to present also more comorbidities, resulting in more hospitalizations. As indicated in the result section, the mean levels of HbA1c were higher in the participants

without complications. However, in the literature the lesions are described as more common in participants with poorer glycaemic control [27], as shown by higher glycaemia levels in participants with complications. These types of lesions appear more frequently when the time since diagnosis is longer, as our results showed. The participants without ACE presented a longer length of disease but fewer complications. This could indicate that although with shorter evolution, the occurrence of previous traumatic events is associated with more frequent microvascular and macrovascular lesions, a more severe evolution of T2DM. The hyperglycaemic environment, resulting of the dysfunction of the HPA axis and the pro-inflammatory effect, observed in patients with ACE contributed to the vascular lesions. The clinical presentation of the participants also include the number of hospitalizations, particularly in the most recent ones, and the presence of vascular complications. Overall, the clinical parameters tend to be worst in the participants with ACE.

Adverse Childhood Experiences lead to the development of unhealthy lifestyles that can increase the risk of metabolic disease. The unhealthy choices evaluated - tobacco use and alcohol consumption were more common in patients with ACE, even though in this subgroup, the majority did not present these type of behaviours. [12, 26, 28] The participants with these consumptions presented higher levels of reported ACE. One interesting finding in the data is that the patients with alcohol and tobacco use presented better glycaemic control, which is not corroborate by the literature. Our participants with higher levels of perceived stress in the last month presented more unhealthy behaviours in particular tobacco consume in accordance with previous reports. [40, 51] Conversely, higher levels of stress were associated with tobacco and alcohol consumption.

Patients with ACE presented higher mean levels of daily stress and find difficult to deal with unpredictable and uncontrollable hassles, measured by the PSS-10. Traumatic experiences contribute to the development of psychiatric problems like anxiety. [7, 9] When psychiatric disorders are present, the stress levels tend to be higher. It has been postulated that the occurrence of early stressful events may impinge stress reactivity in adulthood [16]. Patients with higher levels of stress in the last month presented poorer metabolic profile. As said above, psychological stress triggers the same response as physical stress, increasing the levels of cortisol and sympathetic nervous system. These could be the reason of the poorer metabolic control in the patients with higher stress level. The lipid profile seemed to be more affected by the acute stress than the chronic stress, in line with previous studies which showed a relationship between acute perceived stress and worst lipid control, especially triglycerides. [22, 52, 53] The perceived stress also has an effect in the tensional profile, particularly in the diastolic blood pressure. The correlation between the level of stress and the diastolic blood pressure, found in this study, agrees with the findings in others. [22] On the other hand, in our sample older people tend to express lower levels of perceived stress, possibly demonstrating the development of coping behaviours [40, 51]. As frequently reported, women tend to register higher levels of stress. [40, 51, 54, 55]. Gender differences in stress response have been indicated as potential risk factor for health problems.

The BMI levels were similar between the participants independently of the ACE presence or the levels of perceived stress, contrary to what is described in the literature. The presence of ACE favours the appearance of pro-obesity lifestyles, such as binge-eating and sedentarism. However, it appears to exist a relationship between ACE and obesity, even when the confounding agents are excluded. [17-20, 28] Higher levels of perceived stress also appear to be associated with obesity. [22, 56-58]

More severe clinical and laboratory parameters of T2DM was detected in patients who reported adverse experiences during childhood or higher levels of perceived stress, which show the possible association between phycological stress, either in its acute form (measured by the perceived stress in the last month) or in chronic form (measure by the presence of ACE), and the metabolic profile in T2DM patients. The results suggest the possibility of a dysfunctional

endocrine response, provoking a hyperglycaemic and pro-inflammatory environment, caused by the traumatic psychological experiences in early age.

This study focused on a small population of T2DM, with only 66 participants, which proved to be insufficient for more statistically significant results. In part, the small population is due to the SARS-Cov2 pandemic, which limited the free access of the investigators to the hospital, reducing the number of possible participants. It is recommended in future studies to use a larger population.

Other limitation was the access to the number of hospitalizations, because the authors only had information concerning public hospitals. If the patients were hospitalized in private hospitals, that information was not available. Therefore total number of hospitalizations and the most recent, can be underestimated.

The participants were hospitalized in the "*Centro Hospitalar e Universitário de São João"* for different reasons, and different comorbidities could be present. This could be a limitation and a potential source of bias. In terms of the laboratory parameters, the most recent measurement was collected. Longitudinal laboratory assessment could have contributed to uncover causality relationship between psychosocial variables and laboratory profile.

An important lifestyle parameter would have been the physical activity. People that present ACE, tend to present a more sedentary lifestyle. This variable was not available in patients' clinical records. Future studies should evaluate the role of physical activity in T2DM control in the presence of ACE.

In summary, the results of the present study suggest a trend of poorer glycaemic control in patients with ACE and T2DM, and a trend of poorer metabolic control in patients with higher levels of stress.

Type 2 Diabetes Mellitus is a very common disease and when aggravated with a poor glycaemic and metabolic control can be associated to high levels of morbidity and mortality. Adverse childhood experiences and the higher levels of stress contribute to a more severe presentation of T2DM, a major public health concern, and its detection could be an opportunity for better vigilance and higher quality of clinical care.

## Authors Contribution

Conceptualization, BE and MFB; methodology, BE, JSN and MFB; formal analysis and investigation, BE; writing original draft preparation, BE, MFB and RS; writing review and editing, BE, MFB, RS and JSN; funding acquisition, N/A; resources, N/A; supervision, MFB, JSN and RS.

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## Conflicts of Interest

The authors declare no conflicts of interest.

## Informed Consent Statement

All participants filled an informed consent.

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies.***

| | Item No | Recommendation | Page No |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | NA |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 6 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 8 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 8; 9 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 9 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 9 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants | 9 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 9: 10 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 9; 10 |
| Bias | 9 | Describe any efforts to address potential sources of bias | NA |
| Study size | 10 | Explain how the study size was arrived at | 10 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 10 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 10 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 10 |
| | | (*c*) Explain how missing data were addressed | NA |
| | | (*d*) If applicable, describe analytical methods taking account of sampling strategy | NA |
| | | (*e*) Describe any sensitivity analyses | NA |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 10; 12 |
| | | (b) Give reasons for non-participation at each stage | NA |
| | | (c) Consider use of a flow diagram | NA |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 10; 12; 13; 15: 16 |
| | | (b) Indicate number of participants with missing data for each variable of interest | NA |
| Outcome data | 15* | Report numbers of outcome events or summary measures | 13; 14; 15; 16; 17 |

| | | | |
|---|---|---|---|
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | NA |
| | | (*b*) Report category boundaries when continuous variables were categorized | 9 |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | NA |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 17 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 19 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 18; 19 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 17; 18 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 18 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 19 |

*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

1) Title and abstract
   a) The study's design was not provided in the title or abstract. The study's design was not provided in the title or abstract. The authors indicate the study's design in the methods section, in page 9 "The study followed an observational cross-sectional design."
   b) "Sixty-six adult patients with T2DM were submitted to a psychosocial evaluation, and clinical and laboratory data were retrieved from the clinical charts."; "More severe clinical and laboratory parameters of T2DM were detected in patients who reported adverse experiences during childhood. Specific metabolic profile and higher stress".
2) Introduction:
   2) "In summary, the relationship between ACE and T2DM appear to depend on a dysfunctional health style with less physical activity and less quality food intake, and a diminished capacity to glucocorticoids control HPA axis in response to psychosocial stress."; "As T2DM has become one of the most serious public health problems in multiple parts of the world in the last decades, understanding the risk factors associated with T2DM development is of major importance. Adverse Childhood Experiences can be seen as a potentially modifiable risk factor for T2DM and obesity."
   3) "Our aim is to evaluate the association between adverse childhood experiences (ACE) and higher levels of perceived stress and the development and control of type 2 Diabetes Mellitus (T2DM), and the metabolic profile."; "We characterized a population of T2DM patients and collected metabolic, sociodemographic, behavioural, clinical, and psychometric data."
3) Methods:
   4) "The study followed an observational cross-sectional design."
   5) "Adult patients with T2DM, hospitalized in Centro Hospitalar Universitário São João (CHU São João) were invited to participate in the study". The periods of recruitment, exposure, follow-up, and data collection are not included in the Methods section.
   6) "Adult patients with T2DM, hospitalized in Centro Hospitalar Universitário São João (CHU São João) were invited to participate in the study. Those who voluntarily agreed to participate were screened for the presence of ACE and their levels of perceived stress was measured. All the patients were non-insulin dependent and free major neurologic pathologies. Those whose clinical data was not provided were excluded from the study."
   7) "The total score of ACE is the sum of all positive answers. If a person answers affirmatively to one question, it is considered to have been exposed to ACE"; "The cut-off 18 (which represents the 75th quartile) was used to classify levels of perceived stress into low to moderate (PSS-10 <18) or high (PSS-10 ≥18)."; "the presence of T2DM complications, microvascular or macrovascular disease, the time since the diagnosis and the number of hospitalizations."; "Glycated haemoglobin (HbA1c) and glycaemia were used to assess T2DM"; "evaluate obesity, body mass index (BMI)"; "included total cholesterol, high density lipoprotein (HDL) fraction of cholesterol, low density lipoprotein (LDL) fraction of cholesterol and triglycerides. To evaluate the blood pressure profile one register of systolic blood pressure (SBP) and diastolic blood pressure (DBP)".
   8) "Participants who signed the informed consent form fulfilled two self-report psychological measures - the "Adverse Childhood Experiences Questionnaire – Short Version", and the "Perceived Stress Scale"." "All the metabolic parameters were retrieved from the clinical charts."; "(…) were invited to fulfil the two questionnaires. They received information about the study procedures and purpose, and the need to collect data from the clinical records."
   9) No efforts to address bias were specified in the text.
   10) "Patients hospitalized in CHU São João that obey the inclusion criteria and did not present any exclusion criteria, were invited to fulfil the two questionnaires."
   11) "The two questionnaires applied allowed the division of the participants according to the presence of adverse childhood experiences and the presence of high levels of perceived stress."; "the Kolmogorov-Smirnov and the Shapiro-Wilk tests were used to evaluate the distribution of the continuous variables"
   12)

a) “To study the relationship between these groups and the metabolic profile, the Kolmogorov-Smirnov and the Shapiro-Wilk tests were used to evaluate the distribution of the continuous variables. Those who presented a normal distribution were evaluated using the T-test for independent variables and the others were evaluated using the Mann-Whitney U test. The Pearson’s Correlation test was used to evaluate associations between variables. Categorical variables were evaluated using the chi-square and the Fisher’s exact tests.”

b) “T-test for independent variables and the others were evaluated using the Mann-Whitney U test.”; “evaluated using the chi-square and the Fisher’s exact tests.”

c) Missing data were not addressed in the statistical analysis.

d) No analytical methods of sampling strategy were applied.

e) No sensitivity analyses was applied.

4) Results

13) Participants

a) “Forty-five participants presented at least one ACE.”; “divided in two groups according to the PSS score: 43 patients classified as low to normal stress levels and 23 patients classified as high level.”

b) Of all the participants that agreed in participating in the study, they filled both questionnaires, so no reason of non-participation was pointed out.

c) The use of a flow diagram was not considered in this study.

14) Descriptive data

a) “The mean age of the participants is 67.27 years old (standard deviation (SD) of 10.57 years). Forty-five participants presented at least one ACE. The mean number of ACE reported by the participants that presented at least one ACE was 3.51 (SD 2.39), the highest number of ACE reported was 11.”; “(…)43 patients classified as low to normal stress levels and 23 patients classified as high level. Both groups presented similar age (p= 0.071), gender distribution (p= 0.593), education (p=0.928) and marital status (p=0.190). Patients with higher stress level (23.13; SD 4.65) showed a trend to higher total ACE score”; “The mean time since diagnosis was 9.16 years (SD 5.14), being higher in the participants without ACE (…) was lower in the participants with normal levels of stress (9.5 years; SD 5.45)”; “On average, the participants had 5.83 (SD 6.86) hospitalizations, (…) , in the last 5 years (3.39; SD 3.10) and last year (2.04; SD 1.19).”; “ The presence of T2DM complications was similar regarding the report of ACE”; “Higher levels of perceived stress were shown in patients with unhealthy behaviours. Males consume more alcohol and tobacco than females”; “The mean time since the diagnoses in the participants without microvascular complications was 7.02 years (SD 3.64) and when microvascular complications were present it was 10.73 years (SD 5.54), (…), and in the last 5 years (p=0.003)”; “ACE total number is higher in the group with unhealthy behaviours.”; “Microvascular complications where present in higher number when hospitalizations were more frequent – total hospitalizations (p=0.006), in the last 5 years (p=0.023) and in the last year (0.017). Macrovascular complications showed statistically significantly higher number according number of total hospitalizations (p=0.002), and in the last 5 years (p=0.003)”

b) Not applied since no missing data was found in the variables of interest.

15) “When comparing patients with and without ACE a trend was found to poorer glycaemic control, which (…) In this subgroup, the mean HbA1c was 7.41 (1.98) and glycaemia presented a mean of 189.53 (99.23). (..)A trend was found to higher levels of HbA1c, poorer lipid profile and higher levels of DBP in the patients that presented higher levels of perceived stress. All the variables of the lipid profile presented higher mean values in the participants with higher perceived stress levels, although not statistically different. and in the subgroup with high stress levels (93.22 mg/dL; SD 42.99)”; Table 4; “Age (p=0.022) and blood pression is higher in patients with unhealthy lifestyle, and the overall metabolic profile is worst in the patients without unhealthy behaviours. The HDL is the exception, being statistically significantly lower in smoker patients (p=0.034)”; Table 5; “A positive correlation was found between the PSS-10 total score and the DBP value (p=0.047; r=0.246).”

16)

a) No confounder-adjusted estimates were analysed.

b) Explicit in the methods section "The total score of ACE is the sum of all positive answers. If a person answers affirmatively to one question, it is considered to have been exposed to ACE"; "The cut-off 18 (which represents the 75th quartile) was used to classify levels of perceived stress into low to moderate (PSS-10 <18) or high (PSS-10 ≥18)."

c) Not relevant for the present study.

17) "Age presented a negative correlation with school years attendance (p=0.010; p=-0.396)."; "HbA1c presented a positive correlation and with the total cholesterol (p= 0.036; r=0.260). Age, conversely, showed a negative correlation with HbA1c (p=0.002; r=-0.374). The number of hospitalizations in the last 5 years also presented a correlation with HbA1c (p=0.045; r=0.250), but no correlation was found for the total number of hospitalization (p = 0.841) or the ones that occurred in the last year (p= 0.716)."; "HDL presents a negative correlation with the number of hospitalizations in the last 5 years (p=0.028; p= -0.272), so the patients with higher number of hospitalizations in the last 5 years presented lower levels of HDL."; "Blood pressure parameters are also positively correlated with each other (p<0.001; r=0.505) Moreover DBP presented a positive correlation with BMI (p=0.033; r=0.262) and a negative correlation with age (0.009; r= -0.321)."

5) Discussion

18) "In summary, the results of the present study suggest a trend of poorer glycaemic control in patients with ACE and T2DM, and a trend of poorer metabolic control in patients with higher levels of stress."

19) "This study focused on a small population of T2DM,"; "Other limitation was the access to the number of hospitalizations, because the authors only had information concerning public hospitals. If the patients were hospitalized in private hospitals, that information was not available. Therefore total number of hospitalizations and the most recent, can be underestimated."; "The participants were hospitalized in the "Centro Hospitalar e Universitário de São João" for different reasons, and different comorbidities could be present. This could be a limitation and a potential source of bias."; "Longitudinal laboratory assessment could have contributed to uncover causality relationship between psychosocial variables and laboratory profile."; "An important lifestyle parameter would have been the physical activity. ... This variable was not available in patients' clinical records."

20) "In our study the mean values of HbA1c and glycaemia were higher in participants with ACE, however the difference was not statistically significant. The patients with ACE showed a tendency for poorer glycaemic control. (…) In patients with T2DM, these types of traumatic events can lead to a worst glycaemic control."; "(…) the mean levels of HbA1c were higher in the participants without complications. However, in the literature the lesions are described as more common in participants with poorer glycaemic control, as shown by higher glycaemia levels in participants with complications."; "Overall, the clinical parameters tend to be worst in the participants with ACE."; "One interesting finding in the data is that the patients with alcohol and tobacco use presented better glycaemic control, which is not corroborate by the literature. Our participants with higher levels of perceived stress in the last month presented more unhealthy behaviours in particular tobacco consume in accordance with previous reports."; "Patients with higher levels of stress in the last month presented poorer metabolic profile (…) The lipid profile seemed to be more affected by the acute stress than the chronic stress, in line with previous studies which showed a relationship between acute perceived stress and worst lipid control, especially triglycerides."; "The correlation between the level of stress and the diastolic blood pressure, found in this study, agrees with the findings in others."; "The BMI levels were similar between the participants independently of the ACE presence or the levels of perceived stress, contrary to what is described in the literature."; "More severe clinical and laboratory parameters of T2DM was detected in patients who reported adverse experiences during childhood or higher levels of perceived stress, which show the possible association between phycological stress, either in its acute form (measured by the perceived stress in the last month) or in chronic form (measure by the presence of ACE), and the metabolic profile in T2DM patients."

21) "a small population of T2DM, with only 66 participants, which proved to be insufficient for more statistically significant results. In part, the small population is due to the SARS-Cov2 pandemic, which limited the free access of the investigators to the hospital, reducing the number of possible participants. It is recommended in future studies to use a larger population."

6) Other information

22) “This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors."

# METABOLISM

Clinical and Experimental

**AUTHOR INFORMATION PACK**

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