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Cardiovascular risk factors in children and adolescents with anxiety disorders and their association with disease severity

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Abstract

Introduction: Studies suggest that anxiety is an independent predictor of adverse cardiovascular events. However, few studies have investigated the association between cardiovascular risk factors (RF) and severity of anxiety disorders (AD) in childhood and adolescents.

Objectives: To assess the prevalence of cardiovascular RF in children and adolescents with anxiety disorders and their association with disease severity.

Method: Cross-sectional study assessing nutritional and anthropometric RF, as well as % body fat (BF), blood pressure (BP), physical activity level, anxiety symptoms and severity of the anxiety disorder of children and adolescents.

Results: A total of 65 children and adolescents (8.6 ± 1.7 years) took part in the study. Excess saturated fatty acid intake (52.3%), high body mass index (50.8%), high BP (50.8%) and physical inactivity (50.0%) were the most prevalent cardiovascular RF. There was a significant association between the severity of the anxiety and the presence of 6 RF per patient (p=0.026), excess abdominal body fat as assessed by waist circumference (p=0.019) and concinity index (p=0.053), and excess % BF (p=0.035). Generalized anxiety disorder was significantly associated with high BP (p=0.044).

Conclusion: A high prevalence of cardiovascular RF was found in the present sample, and individuals with more severe anxiety had greater cardiovascular risk. The characterization of the cardiovascular risk in young populations, especially in individuals with AD who are therefore more susceptible to CVD, is crucial for the development of lifestyle interventions in these patients.

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Keywords: Adolescence. Anxiety. Children. Cardiovascular Disease. Risk Factors.

Resumen

Introducción: Evidencias sugieren que la ansiedad es una predicción independiente de los eventos cardiovasculares adversos. Entretanto, pocos estudios evaluaron la presencia de factores de riesgo (FR) para estas enfermedades en niños y adolescentes.

Objetivos: Identificar la prevalencia de FR cardiovasculares en niños y adolescentes diagnosticados con distúrbio de ansiedad y su asociación con la gravedad de la enfermedad.

Metodología: Estudio transversal que evaluó FR nutricional, antropométricos, % de gordura corporal (CG), presión arterial (PA), nivel de actividad física y escalas de síntomas y gravedad de la ansiedad.

Resultados: 65 niños y adolescentes (8.6 ± 1.7 años) fueron incluidos en el estudio. Cuento a los FR, el consumo excesivo de ácidos grasos saturados (52.3%), índice de masa corporal alto (50.8%), PA alterada (50.8%) y la falta de ejercicio físico (50.0%) fueron los más prevalentes. Hubo asociación significativa entre la mayor gravedad del disturbio y el acumulo de 6 FR (p=0.026), exceso de gordura abdominal medida por la circunferencia de cintura (p=0.019) y por el índice de concinidad (p=0.053) y exceso en el % GC (p=0.044).

Conclusion: Los resultados encontrados indican que hay una alta prevalencia de FR cardiovascular en la muestra estudiada y los pacientes más graves presentan mayor riesgo. La caracterización del perfil de riesgo en las poblaciones con predisposición a las enfermedades cardiovasculares es crucial para la elaboración de estrategias de intervención que oportunicen la reducción en la prevalencia de estas enfermedades.

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According to the World Health Organization (WHO), cardiovascular disease (CVD) is the most frequent cause of death in the world, accounting for 30% of worldwide deaths, of which 80% occur in medium- to low-income countries. Cardiovascular risk factors (RF), or aetiological variables which contribute to the development of CVD, are generally categorized as “non-modifiable,” as in the case of ethnicity, gender, age and genetic susceptibility, or “modifiable,” which include excess weight, abdominal fat, high blood pressure (BP), smoking, inadequate eating habits and infrequent physical activity.

In childhood, obesity has been shown to be predictive of higher mortality rates, especially due to its association with an increased risk of CVD.

The amount and distribution of body fat are also known indicators of cardiovascular risk, with body fat distribution contributing more significantly than total body fat to the development of CVD. Also, Louise et al. (2012) when examining the association between depressive, anxiety symptoms and cardiovascular risk in children found that girls with higher scores of depression and anxiety had greater adiposity than male participants. These findings suggest the importance of gender-specific research in the area of CVD.

Hypertension (HTN), in turn, is a multifactorial condition characterized by sustained high BP and is frequently associated with functional and/or structural changes in the heart, brain, kidneys and blood vessels, as well as metabolic alterations, which lead to an increased risk of both fatal and nonfatal cardiovascular events.

Eating habits play an important role in the development of non-communicable chronic diseases (NCD) such as obesity and CVD. Dietary habits may therefore consist of risk markers for these diseases, especially since the combination of high cholesterol, lipid and saturated fatty acid intake with low fibre consumption contribute to the aetiology of dyslipidaemia, obesity, diabetes and HTN.

Furthermore, as sedentary lifestyles become more common, physical inactivity, which has been increasingly associated with poor health outcomes, appears to be a growing trend in both developed and developing countries. Observational and experimental data suggest that regular physical activity has beneficial effects on several cardiovascular RF, leading to decreases in body weight, BP, atherogenic dyslipidaemia, inflammation, fibrinolysis and endothelial dysfunction.

Evidence also suggests that anxiety may be an independent predictor of adverse cardiovascular events. Individuals with high levels of anxiety are at an increased risk of developing CVD such as congestive heart failure, myocardial infarctions and fatal ventricular arrhythmias. Recent studies have found that anxiety may have a similar impact to that of non-modifiable (age, gender and ethnicity) and modifiable vascular risk factors (smoking, alcohol intake, obesity, diabetes, dyslipidaemia and hypertension) on cardiovascular morbidity and mortality.

Although scientific evidence suggests that children and adolescents with ADs are at increased susceptibility to CVD, few studies have investigated the presence of cardiovascular RF in these populations. Therefore, the goal of the present study was to assess the prevalence of cardiovascular RF in children and

Abbreviations
AD: Anxiety disorders.
ADHD: Attention deficit/hyperactivity disorder.
BF: Body fat.
BMI: Body mass index.
BP: Blood pressure.
CI: Conicity index.
CVD: Cardiovascular disease.
DBP: Diastolic blood pressure.
DRI’s: Dietary Reference Intakes.
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders.
HTN: Hypertension.
KSADS-PL: Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version.
NCD: Non-communicable chronic diseases.
PAR: Physical activity recall.
PARS: Paediatric Anxiety Rating Scale.
PeNSE: National Student Health Survey.
RF: Risk Factors.
SBP: Systolic blood pressure.
SCARED-C: Screen for Children and Anxiety Related Emotional Disorders – Child version.
SFA: Saturated fatty acids.
TEI: Total energy intake.
TFA: Trans fatty acids.
UL: Upper tolerable intake level.
WC: Waist circumference.
WHO: World Health Organization.
WHHR: Waist-to-height ratio.
24HR: 24-hour dietary recall.

Introduction
Anxiety disorders (ADs) are characterized by feelings of fear and persistent and excessive worry which interfere with one’s ability to relax, and tend to occur in response to a specific object or situation in spite of the absence of any real threat. These symptoms most commonly present as generalized AD, post-traumatic stress disorder, panic disorder, and specific phobias. The prevalence of ADs in children and adolescents has been estimated to range from 15% to 20%. ADs occur at similar rates between boys and girls, but will gradually become more common in girls, with a ratio of 2:1 to 3:1 in adolescence.

ADs are often comorbid with one another, and are also related to the development of chronic conditions which may have an impact on quality of life and eventually lead to death. According to the World Health Organization (WHO), cardiovascular disease (CVD) is the most frequent cause of death in the world, accounting for 30% of worldwide deaths, of which 80% occur in medium- to low-income countries. Cardiovascular risk factors (RF), or aetiological variables which contribute to the development of CVD, are generally categorized as “non-modifiable,” as in the case of ethnicity, gender, age and genetic susceptibility, or “modifiable,” which include excess weight, abdominal fat, high blood pressure (BP), smoking, inadequate eating habits and infrequent physical activity.

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Evidence also suggests that anxiety may be an independent predictor of adverse cardiovascular events. Individuals with high levels of anxiety are at an increased risk of developing CVD such as congestive heart failure, myocardial infarctions and fatal ventricular arrhythmias. Recent studies have found that anxiety may have a similar impact to that of non-modifiable (age, gender and ethnicity) and modifiable vascular risk factors (smoking, alcohol intake, obesity, diabetes, dyslipidaemia and hypertension) on cardiovascular morbidity and mortality.

Although scientific evidence suggests that children and adolescents with ADs are at increased susceptibility to CVD, few studies have investigated the presence of cardiovascular RF in these populations. Therefore, the goal of the present study was to assess the prevalence of cardiovascular RF in children and
adolescents with AD and their relationship with disease severity.

Method

This was a cross-sectional study from a larger randomized controlled trial entitled "The effect of Cognitive Behavioural Group Therapy versus Attention Bias Modification Using Threat Stimuli and their combination in children with ADs: a randomized clinical trial," which involved 6-to-12-year-old children and adolescents with symptoms of anxiety. Participants were screened by telephone and underwent a detailed careful diagnostic evaluation, supervised by a psychiatrist who specialized in childhood and adolescence. Patients diagnosed with Separation Anxiety Disorder, Social Anxiety Disorder and Generalized Anxiety Disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) were included in the study.

Children and their parents were invited to take part in the study and, if all inclusion criteria were met, were requested to sign informed consent forms and schedule an appointment for the assessment of disorder-related nutritional outcomes prior to the psychiatric intervention.

Sample size was calculated based on the study conducted by Hilmann et al., who investigated the association between symptoms of anxiety and depression and obesity in adolescent girls. With a 95% confidence interval and standard error margin of 0.1, assuming a prevalence of obesity of 19%, a sample of 60 children and adolescents with symptoms of anxiety. Participants were screened by telephone and underwent a detailed careful diagnostic evaluation, supervised by a psychiatrist who specialized in childhood and adolescence. Patients diagnosed with Separation Anxiety Disorder, Social Anxiety Disorder and Generalized Anxiety Disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) were included in the study.

Data was collected from October 2011 to December 2012 by a team of specially trained researchers. Socioeconomic data, pubertal stages, anthropometric measurements, bioelectric impedance, BP, physical activity habits and dietary intake values were investigated using a questionnaire designed specifically for this study.

Socioeconomic status was assessed using the Brazilian Economic Classification Criteria, which categorizes individuals into economic levels labelled A through E, where the former corresponds to the highest and the latter to the lowest possible socioeconomic status.

Stages of sexual maturation were assessed by patient self-reports based on Tanner stage drawings. These data were used to classify patients as prepubescent, pubescent and post-pubescent.

Anthropometric measurements, performed by nutritionist and trained students of nutrition, were taken according to WHO guidelines, and weight (Kg) (Marté scale) and height (m) (Altaexata® stadiometer) data were used to compute patient body mass index (BMI; kg/m²). Waist circumference (cm) was measured with an inelastic measuring tape (Secca®).

Patient nutritional status was classified according to BMI z-scores for age and gender, calculated using WHO reference standards with the AnthroPlus software, version 1.0.4. Patients were then grouped according to z scores into overweight (z + 1) and eutrophic or low BMI-for-age (z < +1).

Waist circumference (WC), waist-to-height ratio (WHtR) and concinity index (CI) values were used to estimate abdominal fat. These measures were classified using the 80th percentile for age, the 90th percentile (corresponding to 0.50) and 1.1 31, as cutpoints for WC, WHtR and CI, respectively.

Body composition was estimated by bioelectrical impedance analysis using a Biodinamics® 450 analyser (Biodinamics®, Seattle, WA, EUA). The % body fat (BF) and % lean mass were then calculated using age and gender norms provided by the manufacturer. Excess BF was defined as > 25% in men and > 30% in women.

In addition to anthropometric and body composition measurements, BP, physical inactivity and dietary sodium, trans fats, saturated fatty acids and cholesterol intake were also considered cardiovascular RF.

BP was measured in duplicate with an interval of 15 minutes using an oscillometric method with an automatic sphygmomanometer (OMRON HEM 705-CP). The mean of the two measurements was used for data analysis. BP was classified according to the normative values obtained from the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents, which considers blood pressure to be normal when systolic (SBP) and diastolic blood pressure (DBP) < 90th percentile, defines prehypertension as SBP and/or DBP 90th percentile but < 95 percentile, and diagnoses HTN when SBP and/or DBP 95th percentile for gender, age and height. In the present study, individuals with SBP and DBP < 90th percentile were considered to have normal BP; while patients with values > 90th percentile were categorized as having high BP.

Participants' physical activity levels were assessed through a 24-hour physical activity recall (PAR) of the day preceding the interview. Participants were classified as suggested by Cale (1994) as: a) active 40 kcal/kg/day; b) moderately active: 37 to 39.9 kcal/kg/
day; c) inactive: 33 to 36.9 kcal/kg/day; and d) very inactive: < 32.9 kcal/kg/day. Active and moderately active individuals were categorized into the same group for data analysis, as were inactive and very inactive participants.

Energy and nutrient intakes (cholesterol, trans fats, saturated fatty acids and sodium) were assessed through a 24-hour dietary recall with the help of a photo album. Food intake was quantitatively assessed using the Nutribase® software (Version NB7 Network; Phoenix, AZ, USD) and nutrient adequacy was assessed using Dietary Reference Intakes (DRI’s). Sodium intake was considered inadequate when its intake was above its tolerable upper intake level (UL). UL were considered due to the high sodium intake reported in Brazil25. Cholesterol, saturated fatty acids (SFA), trans fatty acids (TFA) intakes were considered adequate when cholesterol intake was below 300mg/day, SFA 10% of total energy intake (TEI) and TFA 1% of TEI.

The presence of the following RF was considered when calculating the number of RF per patient: high BMI, WC, WHR, CI, % BF (bioimpedance), BP, physical activity, and TFA, SFA, cholesterol and sodium intakes.

Categorical variables were expressed as frequencies and percentages, and continuous, normally distributed variables as means and standard deviations. Variables with skewed distributions were expressed as medians and interquartile ranges. Pearson’s chi-squared tests and Fisher’s exact tests were used to analyse associations between categorical variables, and Student’s T-tests and Mann-Whitney U-tests were used to compare means and medians, respectively. Data were analysed using the Statistical Package for Social Sciences software, version 18.0, and results were considered significant at p < 0.05.

The present study followed all ethical standards provided by the Brazilian Guidelines and Regulations for Human Research Protection (Resolution 196/96), and was approved by the Research Ethics Committee of the Clinical Hospital of Porto Alegre.

Results

The sample comprised 65 children and adolescents with a mean age of 8.6 ± 1.76 years, most of whom were female (53.8%). General characteristics of the sample are shown in Table I. According to self-assessments of sexual maturity, 43 (66.2%) of participants were classified as prepubescent. Most participants were classified as socioeconomic status B (n=31; 50%), which corresponds to a mean family income of R$1,669.00 to 2,804.00. The most prevalent AD in the sample was separation anxiety (82.8%), followed by generalized anxiety disorder (79.3%), social anxiety (29.3%) and agoraphobia (25.9%). The most common comorbid conditions with AD were attention deficit/hyperactivity (ADHD) disorder, with a prevalence of 24.1%, and depression, reported by 17.2% of participants.
Table II presents the prevalence of cardiovascular RF in the total sample. The most prevalent RF were excess SFA intake (52.3%), elevated BMI (overweight or obesity) (50.8%), high BP (50.8%) and physical inactivity (50.0%). Bioelectrical impedance analysis showed that 40.3% of participants had excess total BF, although the prevalence of excess abdominal fat as indicated by WC, WHtR and CI were 36.9%, 29.2% and 24.6%, respectively.

Nutrient intake analyses revealed a high prevalence of excess dietary SFA intake. Even when UL values were used as a basis of comparison for sodium intake, 21.5% of the sample was found to consume high levels of this micronutrient. Furthermore, the median energy intake in the sample was 1793.45 kcal (1551.47-2137.92 kcal) (Table II).

The assessment of the relationship between symptom scales and the severity of anxiety (scores displayed in

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Table I, which revealed that individuals with more than six RF had higher PARS scores (20.46 ± 5.22 vs. 22.37 ± 1.54; p=0.039) if compared with individuals with six or less risk factors. No differences were detected when considering SCARED scores (33.84 ± 13.04 vs. 35.00 ± 14.84; p=0.781). A median-split of PARS scores was then used to divide the sample into those with less (21 points) or more severe anxiety (22 points).

Table II displays also the association between RF and the severity of anxiety (PARS). PARS scores 22 (indicative of more severe anxiety) were associated with the presence of over six RF (p=0.026), excess abdominal fat according to WC (p=0.019) and CI (p=0.053), and excess %BF (p=0.035).

The median number of RF was 3 (0-10) and the distribution of RF in the full sample and in each anxiety severity group is shown in Figure 1. The figure highlights the presence of an especially high number of RF in patients with severe anxiety.

When the association between RF and the most prevalent ADs was assessed (separation anxiety and generalized anxiety disorder), only the latter was significantly associated with high BP (p=0.044) (data not shown).

### Table III

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Reliability</th>
<th>Validity</th>
<th>Cutoff</th>
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<td>SCARED</td>
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<td>*IC: 0.90</td>
<td>DISCR: anxiety disorders vs. other psychiatric disorders *DX: 23</td>
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<td></td>
<td>TR: 0.86</td>
<td>DISCR: anxiety disorders vs. other psychiatric disorders (81.8% Sens;</td>
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<tr>
<td></td>
<td>*TR: 0.81</td>
<td>*DISCR: anxiety disorders vs. control (52% Spec)</td>
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</tr>
<tr>
<td>K-SADS-PL</td>
<td>TR: 0.8 (current); 0.6 (lifetime)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>IR: 93%-100% (current); 100% (lifetime); *κ = 0.9 (anxiety)</td>
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<tr>
<td>PARS</td>
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<td>CONV: 0.61 (CGI-S)</td>
<td>TREAT: 8-10</td>
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<td>DIVG: 0.18-0.33 (CDRS)</td>
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<tr>
<td>K-SADS-PL</td>
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</table>

Discussion

The goal of this study was to assess the prevalence of cardiovascular RF in children and adolescents with AD and their relationship with disease severity. The most prevalent RF in the sample were high BMI (overweight or obesity), high BP and sedentarism, as well as excessive SFA and sodium intake. Patients with more severe anxiety were more likely to display altered WC, CI and %BF values, as well as a higher number of RF. Of the most prevalent AD in the sample, generalized anxiety disorder was the only one found to be significantly associated with high BP.

The most prevalent ADs in the sample were separation anxiety, generalized anxiety disorder and social anxiety. These findings are in agreement with those of Pine et al. (2001)\textsuperscript{26}. As for the instruments used to diagnose and establish the severity of anxiety, mean SCARED and PARS scores were found to be higher than those reported by Kendall et al. (2010)\textsuperscript{27} who found mean scores of 23.40 ± 15.10 and 19.16 ± 4.19 on these scales, respectively, in a sample of young patients seeking treatment for moderate to severe anxiety symptoms.

As for the association between generalized anxiety disorder and elevated BP, Rogeness et al. (1990)\textsuperscript{28} also found higher BP in psychiatric inpatients with AD as opposed to those with conduct disorders or major depression. However, the AD found to be associated with elevated BP in that specific study was separation anxiety.

Our results also revealed that approximately half the children and adolescents assessed had three or four cardiovascular RF (44.7%). This is in accordance with findings reported by Molina et al. (2010)\textsuperscript{29}, who found that over 50% of a sample of children without psychiatric disorders presented with two or three RF. However, the study in question assessed fewer RF than the present study (excess weight, high BP, sedentary leisure activities four hours a day and inadequate nutrition).

The prevalence of high BP and overweight in the present sample (both 50.8%) was significantly higher than that identified in another Brazilian study on children and adolescents without ADs, in which the prevalence rates of high BP and overweight were 11% and 22.1%, respectively\textsuperscript{30}. However, our results regarding excess weight corroborate the findings of the Brazilian Family Budget Survey, which found a significant increase in the prevalence of overweight (34.8% in boys and 32.0% in girls) and obesity (16.6% in boys and 11.8% in girls) in children aged between five and nine years. These values were significantly higher than those found in teenagers aged between 10 and 19 years. The prevalence of excess body weight and obesity in boys and girls in this age range was of 27.3% and 23.4%, respectively\textsuperscript{31}.

Sedentarism in childhood and adolescence is a known RF for CVD. The lower frequency of walking/riding bicycles and the increased use of cars for individual transportation are some contributors to the decrease in children’s physical activity levels. Children have also been engaging in less active play and sports during their free time, tending to spend significant amounts of time engaging in sedentary activities such as watching television, playing videogames and using the computer\textsuperscript{32}. In the present study, 50% of the sample was classified active or very active, which differs from the findings obtained by Mazaro et al. (2011)\textsuperscript{33}, who reported that only 27.1% of the children in their sample regularly engaged in physical activity, and from the results of the National Student Health Survey (PeNSE) conducted in 2012 in year nine students in Southern Brazil, which found that 36.3% of respondents had a physically active lifestyle\textsuperscript{34}. However, it is important to note that the method used by these studies to measure physical activity levels was distinct from that employed in the present study.

The association between CVD and eating habits developed in childhood is also a noteworthy point. Although the relationship between eating habits and chronic disease is well established\textsuperscript{35}, the relationship between dietary habits and the increased prevalence of RF may not be as evident in children. We therefore underscore the importance of investigations into the contribution of different RF to the increased prevalence of CVD, such as those which helped to establish the association between the intake of certain nutrients and elevated BP\textsuperscript{36}.

Our findings regarding nutrient intake may also be compared to others in the literature. A study by Joyce et al. (2009)\textsuperscript{37}, for instance, found that children and adolescents had a mean SFA intake of 27.3 and 32 grams, respectively, which is higher than the corresponding values obtained in the present study. Additionally, the previously cited study found that only 6% of participants aged between five and 12 years, and only 11% of those aged between 13 and 17 years, consumed adequate amounts of SFA (10%). Although the intake values found in the present study were lower than those reported in other studies in the literature, the number of individuals found to consume more SFA than recommended is still alarming, as this feature has been found to be associated with an increased risk of CVD.

We also concluded that a significant number of patients in the sample consumed more sodium than recommended. Veiga et al. (2013)\textsuperscript{38} also assessed nutrient intake in Brazilian adolescents aged 10 to 18 years, and found that individuals of both genders, but especially males, tended to consume over 3.000mg of sodium daily, which is far from the reference value of 2.300mg\textsuperscript{39}. The high-sodium diets reported by both samples may be associated with the high prevalence of processed foods in the Brazilian diet\textsuperscript{40}.

In the present study, excess body fat was found to be more common among females. A similar finding was reported by Louise et al. (2012)\textsuperscript{41} who assessed the as-
Acknowledgements

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References

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