

Evaluation of Cold Pressor Pain Response and Pain Catastrophization in a Healthy Nigerian Adult Population

Umar AH¹, Mohammed A¹, Ayo JO¹, Danjuma NM², Isa AS¹, Suleiman I¹,
Muhammad MS⁴, Muhammad UA¹, Muhammad A¹, Yusha'u Y¹, Ishaku AA⁵.

¹ Department of Human Physiology, Faculty of Basic Medical Sciences, Ahmadu Bello University, Zaria, Kaduna State. ² Department of Veterinary Physiology, Faculty of Veterinary Medicine, Ahmadu Bello University, Zaria, Kaduna State, ³ Department of Pharmacology and Therapeutics, Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria, Kaduna State. ⁴ Department of Human Physiology, Faculty of Basic Medical Sciences, Gombe State University, Gombe State. ⁵ Department of Human Physiology, Faculty of Basic Medical Sciences, University of Maiduguri, Borno State

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ABSTRACT

Background: Inter-individual variability in pain perception is an area of research interest to scientists due to its complexity and compounding nature. Dispositional characteristics have been known to influence pain response, a difference attributed to bio-psycho-social factors. In this study, differences in experimental cold pressor pain response and pain catastrophizing were evaluated among healthy adult population in Zaria, Nigeria. **Methodology:** A total of 161 apparently healthy subjects volunteered for the study. Cold pressor pain was induced by asking subjects to immerse their non-dominant hand in cold water at 2-4°C. Cut off time was 5 minutes. Pain catastrophizing was assessed using the visual analogue scale. **Result:** There was no significant effect of sex, age and ethnicity on cold pressor pain threshold and tolerance among the studied population, but females catastrophized more than males. **Conclusion:** Sex, age and ethnicity have no effects on cold pressor pain response among healthy adults in Zaria, Nigeria, but pain catastrophizing is higher in females than in males.

Keyword; Cold pressor pain; pain catastrophizing; Nigerian adults; sex

INTRODUCTION

The study of inter-individual variability, as an area of research interest, focuses on studying differences in bio-psychosocial outcomes between

subjects across diverse situations. Personality traits and cognitive abilities have specially received the most attention in this field.^[1] The perception of pain

*Correspondence: Umar AH. Department of Human Physiology, Faculty of Basic Medical Sciences, Ahmadu Bello University, Zaria, Kaduna State. Email: ahumar09@gmail.com

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depends on influences coming from sources such as the limbic system of the brain, down to ethno-cultural influences. It is believed that the expectation of the coping ability of individuals should determine the amount of pain that is actually perceived. Pain, a multi-dimensional sensory experience, is intrinsically unpleasant and associated with hurting and soreness. It varies in intensity (mild, moderate or severe), quality (sharp, burning or dull), duration (acute or chronic), referral (superficial or deep), and locality (localised or diffused). Pain can be adaptive and maladaptive. While adaptive pain contributes to survival by protecting the individual from injury or promoting healing when injury has occurred (symptomatic pain), maladaptive pain, on the other hand, is an expression of the pathologic operation of the nervous system (pathologic pain).^[2] There is a high degree of individual variability in pain, very likely due to complex environmental and multiple genetic factors. A number of genes play critical role in determining pain sensitivity, pain reporting and susceptibility to developing chronic pain. Advances in 'genome wide association studies' (GWAS), 'single nucleotide polymorphism' (SNPs) and role of epigenetics in modulation of pain has established the role of genetics in pain.^[3] Association and linkage human studies have identified a number of genes responsible for heritable conditions involving dramatic alterations in pain perception.^[4]

Sex differences in the perception of painful stimuli have been of interest to scientists for some time, and the consensus is that males show greater tolerance than females. Sex differences in experimental pain may depend on the stimuli used and the nature of the chosen end-point,^[5] and the magnitude of such differences may be affected by variations in the methodology used to induce the pain, such as the stimulus type, anatomic location, stimulus duration and characteristics, as well as stimulus application

(that is whether the stimulus is self-applied).^[6] Sex and gender differences in pain sensitivity may be as a result of biological factors such as blood pressure, gonadal hormones and body size, and psychological factors such as fear of pain, catastrophizing, depression and anxiety.^[7] Males report lower pain intensity and unpleasantness, and greater pain tolerance than females.^[8] Problems associated with pain include decreased quality of life, negative mood and increased disability.^[9] Although physicians now have effective pain treatments at their disposal, pain remains one of the most poorly assessed and treated physical symptoms. Pain is a subjective human experience, with complex interactions between sensory and emotional components. Management of pain requires a multi-dimensional and interdisciplinary approach to assessment, and therapeutic strategies will require the use of both pharmacological and non-pharmacological interventions.^[10] In Nigeria, differences in pain perception among parturients have been shown to depend on factors such as culture, social status, prenatal education, counselling, support during labour and medical intervention.^[11] In many clinical conditions, biological markers of disease activity or tissue damage contribute only modestly to reported clinical pain, and it seems plausible that individual differences in nociception processing could influence clinical pain severity.^[12]

Advances in genotyping has revolutionised understanding of the influence of genetic predisposition and environmental variables, such as diet and general state of health, in individual's drug responses.^[4] Experience of pain is characterised by strong inter-individual variability, and is modified by interactions among numerous bio-psycho-social factors, including genetic influences. Disparities in pain assessment and treatment exist for all types of pain and across life span.^[13] Study among patients

with chronic pain has demonstrated an association between experimental pain responses and reported clinical pain, such that greater experimental pain sensitivity predicts higher levels of clinical pain.^[12] This study was designed to test the hypothesis that sex, age and ethnicity will affect experimental pain response in a healthy adult population in Zaria, Nigeria.

METHODOLOGY

This observational cross-sectional study was carried out in nine randomly selected secondary schools under the Zaria Zonal Education Authority. Observational cross-sectional study was used for this research. A total of 161 apparently healthy volunteers of ≥ 20 years were used for the study. The subjects included mostly secondary schools staff population around Zaria and environs in Kaduna State, Northern Nigeria. Sample recruitment was based on subjects' convenience, agreeing with the study protocol, qualified and willing to participate. Selected individuals were taught and given basic understanding about physiology of pain and were informed about the experimental procedures (verbally and in writing), as well as risks and contra-indications of all procedures. Informed consent was obtained from the subjects, as well as ethical approval from Health Research Ethics Committee of the Ahmadu Bello University Teaching Hospital, Zaria (ABUTH/HREC/N22/2015) prior to the study. Subjects were excluded if they reported significant psychiatric co-morbidity, prior or present alcohol abuse, use daily analgesics or have any neurological or inflammatory disease that could interfere with pain perception and pain report, such as diabetes, peripheral or central neuropathy, a chronic pain disorder, or current pain condition. Patients with a diagnosis of dementia were also excluded.

Cold pressor pain

Cold pressor pain was assessed using the method of Hines and Brown.^[14] Prior to the test, each participant was asked to put his or her hand in container filled with water at a temperature between 22-25°C, to enable every participant to start with the same baseline hand temperature. Subjects were asked to immerse their non-dominant hand (to about 5 cm above the wrist) in a container of cold water. The subjects were asked to keep their hand in the water for as long as possible, until the pain becomes intolerable, when they could remove their hand at any time.^[15] Water was maintained at 2 to 4 °C using ice. Pain threshold (time after which subject reported feeling pain) and tolerance (time for which the subject tolerated the pain) were measured in seconds using two separate stop watches.^[16] Cut-off time was set at 5 minutes.

Pain catastrophizing

Pain catastrophizing was assessed using the visual analogue scale, a 10cm line anchored by verbal descriptors (no pain to worst imaginable pain). The subjects were asked to indicate their pain intensity from 0 to 10.^[17]

Statistical Analyses

All analyses were carried out using SPSS version 23 software for windows (SPSS Inc, Chicago, IL, USA) and data obtained were presented as mean \pm SEM. Sex differences were analysed by Independent-Samples *t*-test. Age and ethnic differences were analysed by analysis of variance (ANOVA), followed by Tukey's *post-hoc* test to indicate significance (if any). Pain catastrophizing was analyzed by Mann-Whitney test (for sex differences) and Kruskal-Wallis test (for age and tribe). Values of $p < 0.05$ were considered significant.

RESULTS

Mean cold pressor pain threshold (in seconds) for male and female (23.67 ± 1.23 and 23.45 ± 1.37 respectively) was found to be statistically similar ($p = 0.931$; $T = 0.114$), though the males had slightly higher cold pressor pain threshold than the females. The male volunteers were found to have a relatively higher cold pressor pain tolerance (17.26 ± 1.58) than their female counterparts (17.05 ± 1.70), but the difference was also not significant ($p = 0.985$; $T = 0.087$) (Figure 1).

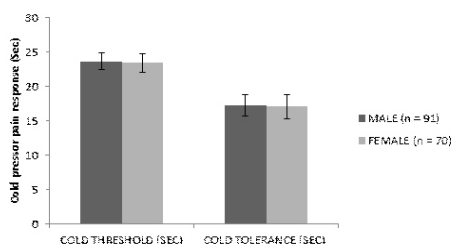


Figure 1: Sex differences in cold pressor pain threshold and tolerance among healthy Nigerian adult population of Zaria

Values do not differ significantly after subjecting the data to independent sample *t*-test ($p > 0.05$).

Age differences in perception of cold pressor pain showed no significant variation (ANOVA) among healthy adults in Zaria, Nigeria. Participants in the highest age group considered (above 50 years) had the least pain perception as indicated by their high threshold (28.42 ± 2.91), while those in the lowest age group (20–30 years) had the highest pain perception as shown by their low threshold (21.69 ± 1.18), though the differences did not statistically vary ($p = 0.127$; $F = 1.930$). Response to painful stimuli (tolerance) also showed no significant variation among the age groups ($p = 0.305$; $F = 1.218$) (Figure 2).

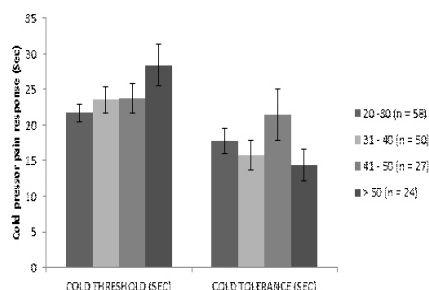


Figure 2: Age differences in cold pressor pain response among healthy Nigerian adults population of Zaria

Mean differences do not vary significantly across all age groups (ANOVA, $p > 0.05$)

Ethnic differences in pain threshold and tolerance using cold pressor pain test model showed no significant variation among healthy adult population of Zaria, Nigeria ($p = 0.343$ and $p = 0.408$, respectively). Participants belonging to the Fulani ethnic group had the highest pain threshold (28.45 ± 4.44) and the lowest pain tolerance (14.14 ± 2.76), while the Yorubas had the lowest pain threshold (22.38 ± 2.83). The highest pain tolerance was found among participants belonging to others ethnic group (21.90 ± 4.16) (Figure 3).

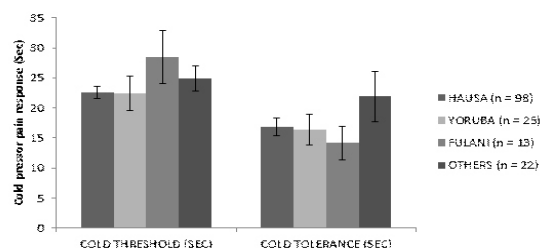


Figure 3: Ethnic differences in cold pressor pain threshold and tolerance among a healthy Nigerian adult population in Zaria

Mean difference showed no significant variation ($p > 0.05$) between all the ethnic groups (ANOVA)

Result of pain catastrophizing using the visual analogue scale showed that median difference in pain catastrophizing by sex was significant, with male participants having less pain catastrophizing score (4.68) than females (4.90) ($p=0.041$) (Figure 4).

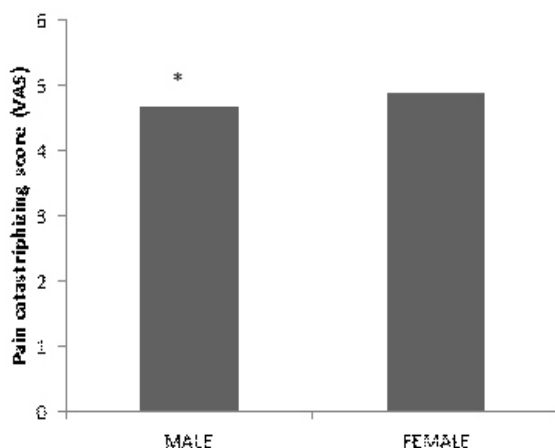


Figure 4: Median sex difference in pain catastrophizing among healthy Nigerian adult population in Zaria. *Difference is statistically significant ($p=0.041$) between males and females

Age differences on pain catastrophizing did not show statistically significant variation across the studied population groups. The highest catastrophizing score was found with participants in the 41–50 age group (5.5), while participants belonging to the 31–40 age group were found to catastrophize less than all the other age groups (4.54). The youngest age group of 20–30 had median visual analogue scale score of 4.66, while the oldest age group of 50 years and above had a score of 5.00 (Figure 5).

Ethnic differences on pain catastrophizing did not vary. Participants belonging to the Fulani ethnic group were found to have the highest VAS score of 5.14 (Highest pain catastrophizing), while those in

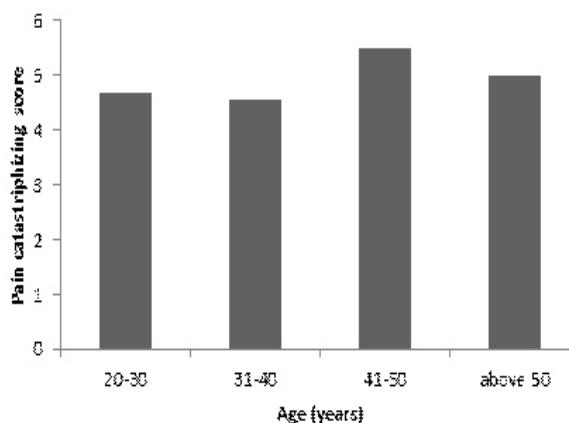


Figure 5: Effect of age (in years) on pain catastrophizing among healthy Nigerian adult population in Zaria

the others group had the least (4.33). The Hausas also had a higher VAS score than the Yorubas (4.95 and 4.50, respectively) (Figure 6).

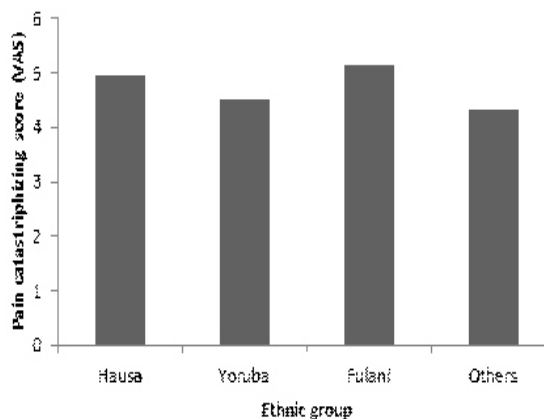


Figure 6: Ethnic difference in pain catastrophizing among a healthy Nigerian adult population in Zaria

DISCUSSION

Results of the present study showed that males had higher cold pressor pain threshold and tolerance than females, though the differences were not significant. This is in agreement with the finding of Mendpara *et al.*^[18] Ogedengbe *et al.*^[19] and Ahn *et al.*^[20] Nikolov *et al.*^[21] and Umar *et al.*^[22] reported higher cold pressor threshold in males, but no difference in cold pressor tolerance, while Edwards *et al.*^[23] and Silva *et al.*^[24] concluded that males have significantly higher cold pressor pain threshold and tolerance than females. Mitchell *et al.*^[25] reported that gender differences were found in the response to cold pressor pain, with men tolerating the stimulus for significantly longer period than women. Logan and Gedney,^[26] who assessed stability by using fore-head cold pressor applications, reported no differences in pain response between men and women. In another study of a Libyan population by Tashani *et al.*,^[27] cold pressor pain threshold was found to be significantly higher in men, but there were no significant differences between the sexes in pain tolerance, intensity, or unpleasantness. A study conducted by de Nazare *et al.*^[28] reported significantly lower cold pressor pain threshold in males than females. Men tend to respond to pain more slowly than women because of the traditional and social recognition that men must endure pain. Sex differences in responses to experimental pain have been investigated using a wide variety of stimulus modalities, including mechanical (blunt pressure and punctate mechanical stimuli), electrical, thermal (heat and cold), ischaemic, and chemical stimuli; for example, capsaicin and hypertonic saline. Pain responses have been assessed by a number of different outcome measures, including behavioural indices of threshold and tolerance, and self-report measures of pain intensity and unpleasantness.^[29] Cold stress, for example, stimulates free nerve

endings to regulate temperature by sending afferent signals to central nervous system. Activated receptors induce reflex vasoconstriction via stimulation of myelinated A δ fibres related to pain sensation, and non-myelinated C fibres that are responsible for perception of nociceptive stimuli.^[24] The lack of significant difference in cold pressor pain in the present result may be attributed to the fact that the subjects were properly oriented to control for psycho-social influences on their pain perception. The participants were oriented to report their actual and not psychological pain; thus, bringing the females' pain responses similar to those of the males.

Males are more motivated to suppress pain expressions due to socio-cultural and psychological influences of the male sexual role, while the female sexual role encourages pain expression and produces lower motivation to suppress pain. Sex of the experimenter may also be a factor in the outcome of the present study, as the entire experiment in all the subjects was carried out by the same male experimenter. Men and women have been reported to show lower pain sensitivity, when they were processed by biological male personnel than by biological female personnel for the cold pressor pain test. Meanwhile, women who interacted with a transgendered researcher reported higher pain sensitivity than women processed by biological male or female researchers.^[30] Experimenter appearance and possible personal biases, as well as biological, psychological, and social factors influence sex differences in pain response.^[31]

This study failed to assess the menstrual and pregnancy status of the female participants, as well as their blood sex hormonal level, which may modulate their pain response due to hormonal influence. Pain

sensation have been shown to increase during the luteal phase of menstrual cycle, and high serum progesterone and oestradiol concentrations correspond to lower values for pain intensity.^[24] Withdrawal latency was reported to be significantly reduced during the luteal phase, compared with the follicular phase. The follicular phase is characterised by high oestrogen levels and women were reported to be less sensitive to pain at a time when circulating oestrogen levels are high, as oestrogen has been shown to play a role in the regulation of opiate expression.^[21] Another compounding factor may be contraception practice of the female volunteers, which was also not evaluated in this study. In a study that evaluated sex differences in response to cold pressor pain in normally menstruating women, women maintained on oral contraceptives, and men, pain threshold was found to be higher in normally menstruating women compared with women maintained on oral contraceptives and men.^[32] The influence of sex hormones on pain-related variability in humans has been associated with the distribution of sex hormones and their receptors in areas of the peripheral and central nervous systems associated with nociceptive transmission. Chemical/hormonal contraceptives influence pain threshold and tolerance in females, as significantly lower ischaemic pain threshold has been linked to oral contraceptive use in healthy women.^[33]

Stening *et al.*^[34] reported that pain responses vary across the menstrual cycle, and that the differences are related to differences in hormone levels. Gonadal hormones have been suggested to play complex roles in pain sensation, which may be either pro-nociceptive or anti-nociceptive, depending on the hormone profile.^[21] Pain perception may be influenced not by absolute levels of sex hormones, but rather their dynamic changes, and it is possible that it is the reduced progesterone concentrations,

from a high level, rather than the progesterone concentration itself that triggers the increased pain sensations during late luteal phase.^[34] Sex steroid-dependent, gestation-associated anti-nociception has also been demonstrated in experimental animals, as well as pregnancy-induced analgesia in humans.^[34] It has been suggested that sex chromosomes and steroidal actions on development lead to differences in pain physiology between men and women. Animal and human studies also suggested that sex-specific hormones (for example oestrogen) influence sex-specific responses to pain. Further investigations have identified neurobiological differences between men and women in brain regions related to pain sensitivity, such as the periaqueductal gray and the strength of its connectivity with the amygdala, caudate and the putamen nuclei.^[35] Sex differences in the sensation of pain may vary significantly across studies because of the different methods used as well as the body area being stimulated. Other factors that can influence the results are the psychological characteristics of each participant, such as levels of anxiety, depression, or previous painful experiences of each subject.^[28]

Result of age differences on cold pressor pain responses did not show significant variation in the present study. The effect of age on pain sensation may be dependent on the type of pain induced. Study has shown that whereas pressure pain threshold decreases with age, heat pain threshold remain unchanged.^[36]

Umar *et al.*^[22] reported increase in cold pressor pain tolerance with advancing age among young adult population. In a meta-analysis of studies on pain threshold and tolerance by Lautenbacher *et al.*,^[37] pain threshold was reported to increase with age, especially using heat stimulus, while pain tolerance did not show substantial age-related changes. In a study by Wandner *et al.*^[38] that assessed a respondent's view of the typical young adult, middle-aged adult,

and older adult with respect to pain sensitivity and willingness to report pain using the age expectation of pain questionnaire, participants indicated that typical older adult is more sensitive to pain than typical younger adult. Frailty may be implicated in the influence of age on pain perception, as pain and frailty are both prevalent and have severe health impacts among older adults. Pain and depressive symptoms were reported to be positively associated with physical frailty, and depressive symptoms were associated with pain. The positive association of pain with frailty is persistent and partially mediated by depression, and co-morbid depression and pain have an additive interaction on physical frailty.^[39]

Animal studies examining the effects of age on pain sensitivity have resulted in conflicting observations that include increases, decreases or no change in cutaneous sensitivities with advancing age. Altered expression of neurotransmitters and receptors has been observed in the spinal cords of old animals. Immunohistochemical studies reveal decreased labelling of calcitonin gene-related peptide (CGRP), substance P, nitric oxide, and somatostatin in the dorsal horn of aged rats. Evidence of a progressive age-related loss of serotonergic and noradrenergic terminals in the dorsal horn also suggests the potential for changes in descending modulatory pathways. Decreased number of opiate receptors and the decreased efficacy of opiate-mediated antinociception may also contribute to age-related changes in the processing and perception of nociceptive information. Molecular alterations in gene expression for trophic factors, neuropeptides, cell adhesion molecules, ion channels or genes related to mitochondrial function and calcium handling are also additional contributing factors to age-related changes in pain perception.^[40] Evidence from both animal and human studies showed that the hypothalamic-pituitary-adrenal axis activity affect

glucocorticoid secretion and alter the synthesis of regulatory peptides, thus, influencing biological ageing and ultimately affecting the processing of pain.^[31] These age-related changes may be best conceptualised as a reduced capacity in the functional reserve of the pain system, at both ends of the intensity spectrum.^[41] Effect of ageing on pain depends on pathophysiologic, pharmacokinetic, and pharmacodynamic changes in the elderly as well as psychosocial factors,^[42] which were not assessed in this study.

Effect of ethnicity on cold pressor pain showed no significant variation in the present study, though participants belonging to the Fulani ethnic group were found to have relatively the highest pain threshold, and the lowest pain tolerance. Yorubas had the lowest pain threshold, while participants belonging to others ethnic group had the highest pain tolerance. Ethnic differences on experimental pain responses have been reported in the USA, with African-Americans reporting greater sensitivity (that is lower threshold) and reduced pain tolerance to a variety of pain tests when compared with non-Hispanic whites, including thermal pain, cold pressor pain, ischaemic pain and electrical stimulation.^[43] Ahn *et al.*^[44] also reported that Asian-Americans with knee osteoarthritis had significantly greater experimental pain sensitivity than non-Hispanic Whites. It has been reported that while African-Americans did not differ from whites on threshold measures of heat pain, ischaemic pain and cold pressor pain, they exhibited significantly lower tolerances for each of the stimulus modalities.^[45,46] Differences in a variety of socio-cultural factors, ranging from family traditions and religious beliefs influence disparities in pain. Ethnicity may have a major influence on the meaning of pain and how it is appraised and responded to emotionally and behaviourally.^[43] Racial/ethnic differences in

experimental pain sensitivity were reported to be more pronounced with supra threshold than with threshold stimuli.^[47] Statistically significant ethnic difference in post-operative pain score and morphine usage has been reported, which persisted after controlling for age, body mass index and duration of operation.^[46] In addition to socio-cultural factors, ethnic disparities in pain are also associated with biological and psychological influences. Ethnic group differences in allele frequencies for polymorphisms of pain-related genes; for example, the Catechol-O-methyltransferase (COMT) and mu opioid receptor (OPRM1) genes may contribute to ethnic differences in pain responses. This is because the COMT and OPRM1 genes have been associated with pain-induced mu-opioid receptor binding, experimental pain sensitivity, and risk for developing chronic pain.^[44] The lack of significant ethnic differences in the present study may be attributed to acculturation among the different ethnic groups studied, as acculturation to American culture was reported to be associated with lower experimental pain sensitivity among ethnic minorities in the USA.^[20]

Result of pain catastrophizing in the present study showed that median difference in pain catastrophizing by sex was significant, with male participants having less pain catastrophizing score than females; that is, females catastrophize more than males. Age and ethnicity, on the other hand, did not significantly influence pain catastrophizing outcomes. Pain catastrophizing, in this study, was determined using the VAS, which is a widely used evaluation tool in the scientific and clinical universe.^[24] The findings of the present study are in agreement with those of Edwards *et al.*,^[23] Mendpara *et al.*^[18] and Umar *et al.*^[22] that also reported higher pain catastrophizing score in females than in males. Study indicated that sex differences in complaints of

painful day-to-day symptoms are accounted for by the significant differences between men and women in reports of catastrophizing.^[23] It has been suggested that thought intrusion may be interpreted as signals of coping failure, thereby increasing the threat value of pain stimulus, nevertheless, catastrophizers may expect that their pain experience will be high regardless of variations in thought intrusions.^[49] The present study found that pain catastrophizing was significantly associated with cold pressor pain threshold outcomes, which agreed with the report of Trost *et al.*^[50] that showed that high levels of catastrophizing are associated with heightened pain intensity, psychological distress and disability. Thorn *et al.*^[51] suggested that sex difference in pain catastrophizing is partially accounted for by the dispositional tendency to describe oneself as emotionally vulnerable. Women were reported to catastrophize more than men in response to osteoarthritis pain,^[52] and it has been suggested that female may possess a lower diffuse noxious inhibitory control neural circuitry, which predisposes them to pain catastrophizing.^[53]

In this study, the result showed no significant effect of age on pain catastrophizing, which is in agreement with the finding of Lynch *et al.*^[54] that showed no sex or age differences in pain catastrophizing, but disagree with the result of a study by Ruscheweyh *et al.*,^[55] which showed pain catastrophizing changes during life-span, with a higher engagement of emotional versus sensory pain processing in younger compared with older adults. Absence of significant ethnic differences in pain catastrophizing in the present study may be due to close genetic association of the studied population, as pain catastrophizing has been associated with specific genotypes. Ethnic differences in pain catastrophizing has been demonstrated in a study by Hsieh *et al.*,^[56] where Chinese subjects reported greater catastrophizing

than European Canadian. COMT diplotype (high versus low activity) has been shown to modulate pain ratings and pain catastrophizing in shoulder pain, where low COMT activity is associated with higher pain ratings and higher tendency for pain catastrophizing.^[51] Another compounding factor for lack of significant effect of ethnicity on pain catastrophizing in the present study may be poor assessment measure, resulting from being asked to characterize pain using an unfamiliar descriptive context. People from different cultures conceptualize and describe pain using different cognitive frameworks. For example, when asked to rate their pain on a linear numeric scale, some Native American patients tended to choose a “favorite or sacred” number instead of the number that correctly indicated their level of pain.^[57]

CONCLUSION

Threshold and tolerance for experimental cold pressor pain were not affected by sex, age and ethnicity among an adult population of Zaria, Nigeria, but females were found to catastrophize more than males. Further study should be carried out using different experimental pain models.

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