Pain sensitivity and thermal detection thresholds in young adults born preterm with very low birth weight or small for gestational age at term compared to controls.

Running title: Pain sensitivity in low birth weight adults

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Abstract

The objective of this prospective long-term follow-up study was to investigate whether somatosensory function is altered among young adults born preterm with very low birth weight (VLBW; ≤1500 grams) or small for gestational age (SGA; <10th percentile) at term. In a blinded quantitative sensory testing protocol, we determined thermal detection, thermal pain and pressure pain thresholds and the response to prolonged supra-threshold heat among 51 VLBW, 66 term SGA and 86 term-born controls (birth weight ≥10th percentile) at 28 years. Self-reported chronic pain was also investigated. Except for increased sensitivity to cool in the term SGA group vs. controls, we found no significant group differences regarding thermal or pain thresholds. Overall, males had higher pain thresholds, and no significant interactions of group and sex were observed (p >0.14). Within the VLBW group, neonatal mechanical ventilation was associated with reduced sensitivity to cool, and length of mechanical ventilation correlated with lower pressure pain thresholds. The response to prolonged supra-threshold heat was similar between the groups, and the prevalence of self-reported chronic pain was not reliably different. In conclusion, low birth weight young adults were as sensitive to thermal and pain stimuli as term-born, normal birth weight controls, with the same sex differences.

Perspective

This is the first report on thermal and pain sensitivity among young adults born preterm with very low birth weight or small for gestational age at term. The negative results from a comprehensive quantitative sensory testing protocol oppose previous findings of altered sensory perception among children and adolescents born preterm.

Key words

Preterm birth
Small for gestational age
Quantitative sensory testing
Pain sensitivity
Chronic pain

Introduction

Preterm infants with very low birth weight (VLBW) spend their first weeks or months in the neonatal intensive care unit (NICU), and experience numerous painful procedures.[7,25] Concern has been expressed that preterm birth and exposure to pain in the neonatal period lead to lasting changes in the somatosensory system,[1] and long-term follow-up studies have indicated altered thermal and pain sensitivity among children and adolescents born preterm compared to term-born peers.[6,12,13,32,34] Findings from these studies include decreased sensitivity to non-painful thermal stimuli[34] and lower cold pain tolerance[32] among former extremely preterm-born children and adolescents (<26 weeks and <28 weeks/<1000 grams, respectively). Among VLBW (≤1500 grams)/very preterm (<32 weeks) individuals, lower pressure pain thresholds[6] and higher heat pain thresholds[12] have been shown compared to term-born peers. The latter study also found signs of increased sensitization and reduced habituation during tonic heat stimulation at pain threshold level.[12,13] It is not clear whether changes in thermal and pain sensitivity among preterm-born children and adolescents persist with advancing age, and studies on older NICU cohorts are requested.[33] At a previous follow-up, the VLBW group of this study had a higher prevalence of self-reported pain,[16] but to our knowledge, this is the first study to investigate thermal and pain sensitivity among adult VLBW individuals.

Although escaping the prolonged period of neonatal treatment, individuals born small for gestational age (SGA) at term may have been exposed to unfavorable prenatal conditions, with a possible vulnerability for diseases later in life. The association between low birth weight and susceptibility to cardiovascular disease in adulthood is well established.[3] Furthermore, our research group has shown that term SGA birth may be associated with many of the same adverse outcomes as those of preterm birth, including structural brain deviations,[37] decreased cognitive function,[20] mental health problems[17,22] and chronic pain.[16] However, we know little about the sensory function and pain sensitivity of term SGA individuals.

It can be hypothesized that an increased prevalence of self-reported pain among VLBW and SGA young adults is related to altered and increased sensitivity in pain-processing pathways within the nervous

system. The main aim of this study was accordingly to investigate whether sensory perception and pain sensitivity among VLBW and term SGA young adults differ from that of controls born at term with normal birth weight. Since the VLBW and term SGA groups reported more pain at a follow-up two years prior to the present study,[16] we also aimed to estimate the prevalence and two-year persistency of self-reported chronic non-specific pain among the study groups.

Methods

Study design

The study participants originate from a geographically based prospective long-term follow-up study of individuals either born preterm with VLBW (birth weight ≤1500 grams), SGA at term (birth weight <10th percentile adjusted for sex, gestational age and parity), or at term with normal birth weight (control group) during 1986-1988 in the region of Central Norway. All VLBW infants were admitted to the NICU at St. Olavs Hospital, Trondheim University Hospital, Norway. The term SGA and control groups were recruited randomly from para 1 and 2 pregnant women in the general population during the same time-period as part of a multicenter study investigating the risk factors for SGA birth.[2] The study groups have previously participated in several multidisciplinary follow-up studies,[8,15,17,22,26,27] including an assessment of self-reported pain at mean age 26 years.[16] The enrollment and exclusion of participants from baseline and up to 26 years have previously been described in detail.[16] Additional inclusion criteria for this sub-study was the ability to independently move from any movement aids to the examination table, and to sustain a supine position during the experimental procedure.

Participants

In the VLBW group, 83 were eligible for the present study, and 51 (61% of eligible) participated. Two of the participants were a twin pair. In the term SGA group, 101 were eligible, one could not be invited due to unknown address, and 66 (65% of eligible) participated. Among the 118 eligible in the control group, 86 (73% of eligible) participated. A flow diagram illustrating the number of participants from enrollment to participation is shown in Supplemental Figure 1.

Perinatal data

Birth weight and gestational age was available from the enrollment in the study for all participants. Information about the number of days on mechanical ventilation and number of days in the NICU or pediatric ward was retrieved from the medical charts of the VLBW participants after inclusion in the study. These variables were available in the study database.

Pre-test characteristics

Height and weight were measured using standardized equipment, and the body mass index was calculated by dividing body mass in kilograms by the square of the body height in meters. To monitor factors that could potentially affect the study results, a questionnaire was administered prior to the test procedure. This included questions on hormonal contraceptive use, last menstrual period, cigarette smoking, caffeine and alcohol consumption, medication use, total sleep time the night before the test and feeling of tiredness. The questionnaire also assessed presence of pain and headache prior to the test, and if present also the intensity of pain or headache (10 cm visual analogue scales). Furthermore, anxiety and depression were assessed with the Hospital Anxiety and Depression Scale (HADS).[36] This questionnaire comprises 7 items on anxiety and 7 items on depression symptoms, each with 4 response options scored from 0 to 3. We defined anxiety and depression by a cut-off of ≥8 on the respective HADS subscale based on previous literature indicating this as the optimal cut-off regarding sensitivity and specificity[5]. The HADS used with these cut-offs has been found to perform well as a brief assessment of anxiety and depression in the general population.[5] In the 22 first participants of the study, the HADS was not administered at the study visit, but was sent by mail

afterwards. Eighteen of these participants completed the HADS at home and returned it by mail (1 VLBW, 8 term SGA and 9 control participants), and 4 did not return the questionnaire (1 VLBW, 2 term SGA and 1 control participant). There were no substantial differences in the frequency of anxiety and depression among those completing the questionnaire at home and those completing it at the study visit. Excluding the participants who completed the questionnaire at home from the analyses did not affect the group-wise frequencies of anxiety or depression.

Experimental procedure

One experienced investigator performed all tests in a quiet room between 08:30 and 15:00, and the investigator was blinded to the birth weight group affiliation of the participants. None of the participants brought a companion to the procedure. The investigator read identical instructions from a manuscript prepared in advance to all participants. We collected data in 2015 and 2016. The overall sequence in the experimental session was thermal trial test, pressure algometry trial test, main test of thermal detection and pain thresholds, temperature calibration for the supra-threshold heat pain test, main test of pressure pain thresholds, and supra-threshold heat pain response test.

Thermal thresholds

Thermal thresholds were measured using Somedic MSA thermal stimulator (Somedic SenseLab AB, Norra Mellby, Sweden) with a 25 x 50 mm Peltier element thermode (baseline 32°C, slope 1°C/s, range 5-52°C). Quantitative sensory testing (QST) with the method of limits were used to determine cool and warmth detection thresholds and cold and heat pain thresholds (CDT, WDT, CPT and HPT, respectively). A trial test for all thermal modalities was conducted prior to the main test at the thenar site to ensure that the participants understood the instructions and were acquainted with the sensations. Testing of thermal thresholds were conducted in the fixed sequence CDT, WDT, CPT and HPT. Two sites, one at the upper and one at the lower limb, were stimulated consecutively; the left volar wrist, and the left leg medial to the anterior tibia, 16 cm distal to the inferior patellar margin. In one term SGA participant, thermal thresholds were assessed at the right leg. For thermal detection

thresholds, the participants were instructed to push the response button whenever they felt the first change in temperature, and a sequence of 5 successive stimuli were used. For pain thresholds, the participants were instructed to push the button whenever the feeling of heat or cold changed into the first sensation of pain, and a sequence of 4 successive stimuli were used. A random inter-stimuli interval of 4-6 seconds separated each stimulus within a sequence. If the participant acknowledged that they forgot to push the button, or pushed too early by mistake, a new sequence was started, and the results of the erroneous sequence were discarded.

Pressure pain thresholds

We measured pressure pain thresholds (PPT) with a hand-held digital pressure algometer (Algometer type II, Somedic SenseLab AB, Norra Mellby, Sweden). Pressure was applied manually with an even slope to two sites using a 1 cm^2 rubber tip; the medial phalanx of the 3rd finger on the left hand, and over the right anterior tibia, 16 centimeters distal to the inferior patellar margin. After a trial test, the algometer was applied three times in succession to each site, and the participant was asked to notify the investigator when the sensation of pressure changed to the first sensation of pain. We defined the PPT as the kilopascal (kPa) value at which the participant indicated pain.

Supra-threshold heat pain response

To investigate the response to supra-threshold heat, a 120 seconds continuous heat pain stimulation with constant temperature was applied to the left volar forearm. The MSA thermal stimulator was used, controlled by the Exposure30 software (Somedic SenseLab AB). The test procedure was similar to the protocol published by Uglem et al.,[29] originally based on Granot et al.,[10] but the stimulation period was prolonged to better explore temporal changes in central modulation of pain.[28,35]

A temperature that equaled 6 on a verbal numerical rating scale (NRS) ranging from 0 =no pain to 10 =unbearable pain was determined individually for each participant and used as stimulus temperature. Prior to the temperature calibration, a drawn illustration of a NRS ranging from 0 to 10 was shown to

the participants, with the meaning of the end points explained verbally. During the procedure, participants were exposed to a 7 second stimulus of heat exceeding the HPT (40°C - 48°C, based on previous pain thresholds observed with the method of limits and the judgement of the investigator). The participants were instructed to verbally report pain scores, and the highest reported NRS value determined if the temperature was increased or decreased for the next stimulus. A minimum of two consecutive stimuli were used to estimate a temperature that the participant rated as close as possible to NRS 6, and this temperature was recorded. A one-minute interval separated each stimulus during the temperature calibration.

During the subsequent main supra-threshold heat pain test, the temperature rose from 32°C to the previously determined NRS 6 temperature, and was kept constant for 120 seconds. The participants were notified when the temperature had reached the predefined level, and instructed to update their NRS values verbally whenever they felt the pain changing, while not being informed that the temperature was kept constant. The NRS value from the temperature calibration was stored as baseline NRS, and the last updated NRS value at each 10 seconds' interval from 10 to 120 seconds after reaching the target temperature were recorded for analysis resulting in 12 values available for the evaluation of temporal changes during the supra-threshold heat pain stimulation. The supra-threshold pain response was defined as the decrease or increase in NRS pain scores during the stimulus period. The participant could terminate the test at any time using the response button. If the test was terminated, a new test using a 1°C lower temperature was conducted, and the results of the first test were not considered for analysis. Two VLBW, two term SGA and three controls had one terminated attempt prior to the complete test, and one VLBW participant had two terminated attempts. In two VLBW, one term SGA and one control participant a complete test was not obtained, and these were excluded. Hence, 199 participants remained for the supra-threshold pain analysis.

Self-reported chronic pain

The participants completed a pain questionnaire identical to the one they answered at a previous follow-up two years earlier.[16] The questionnaire included pain duration ("Do you have bodily pain which has lasted for more than 6 months?") and severity ("How much bodily pain have you had during the past 4 weeks?", with the response options “none”, “very mild”, “mild”, “moderate”, “severe” or “very severe”). As in our previous study, chronic pain was defined as pain lasting >6 months and being moderate, severe or very severe during the past 4 weeks. This definition is identical to what was used in the large Norwegian population-based Nord-Trøndelag Health Study (HUNT)[19]. A sub-study of HUNT showed excellent agreement between reporting pain longitudinally during one year (pain reports at 3 or more occasions with three month intervals), and reporting pain lasting >6 months with moderate to very severe intensity during the past week at the end of the one-year study period.[18] In participants with available data on chronic pain from both time-points, we studied the longitudinal development in chronic pain prevalence, and investigated the two-year persistency of chronic pain.

Data analysis

We analyzed data using Stata 14 (StataCorp. 2013. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). All thermal thresholds were analyzed as the relative difference in degrees from 32°C, but absolute thresholds in °C are provided beside the relative differences from 32°C calculated from the raw data. To identify and remove obvious single erroneous measurements, we detected thermal threshold outliers by comparing each single measurement in each sequence of 4 or 5 measurements, to the calculated mean of the remaining 3 or 4 measurements. A single response was classified as an outlier if it was either three times higher, or less than one third of the mean of the remaining measurements in the sequence. Outliers were replaced with a missing value. In case of participants not reaching CPT within the hardware floor temperature of 5°C, the CPT was defined as 27°C (32°C - 5°C = Δ27°C), and as a censored response[21] since the participant’s true CPT may be at any level >27°C. This was the case for a substantial proportion of CPT measurements (126 (31%) of CPT

responses in the VLBW group, 203 (39%) in the term SGA group and 275 (40%) in the control group). For the PPT, thresholds were analyzed as kPa values.

Statistical methods

Group differences in pre-test characteristics were investigated with the Kruskal-Wallis test for continuous variables and the chi-square test for dichotomous variables. Mean thermal detection thresholds, thermal and pressure pain thresholds together with standard deviations (SD) were calculated for each site, and the distribution of thermal pain thresholds in each group were displayed graphically in dot plots. For the CPT, the censored responses were set to 27 when calculating the mean values and in the dot plots (Figure 1). Post-hoc unadjusted ("univariate") two-group differences in thresholds were explored with the Mann-Whitney U Test.

In the main analyses of group differences in detection and pain thresholds, we used a multilevel mixed effects regression models for each response variable. Since likelihood-ratio tests showed that three-level models performed significantly better than two-level models for our data, single responses were nested within site (wrist or leg for the thermal thresholds and finger or leg for the PPT) and subject. The detection and pain thresholds were transformed to give an optimized distribution of the residuals ($CDT^{-0.5}$, $WDT^{-0.1}$, $CPT^{0.2}$, $HPT^{1.5}$ and $PPT^{0.5}$). Subsequently, after regression, the residuals and the estimates of random effects were plotted on quantile-quantile-plots and histograms to assess the distribution. As the distribution of residuals had some remaining skewness even after transformation, we fitted the regression models with a robust estimator of variance. Since the unequal distribution of censored CPT responses among the study group might lead to an underestimation of group differences, we used a statistical model accounting for censored data when analyzing the CPT.[21,29] The power to detect a moderate effect size =0.6×SD, comparing low birth weight and control groups in the present study based on two-tailed Student's t-test, was at least 88%. Sub-analyses excluding VLBW participants with cerebral palsy, those who had smoked cigarettes the last 3 hours prior to the test

and those who had taken analgesic or psychotropic drugs the last 12 hours prior to the test were performed.

Within the VLBW group, we explored the association between mechanical ventilation (yes/no) and QST thresholds with the Mann-Whitney U test. We calculated Spearman correlation coefficients between number of days on mechanical ventilation, length of NICU or pediatric ward stay and thermal detection and pain thresholds.

To analyze the group-wise response to prolonged supra-threshold heat pain and group differences in temporal change, we used a two-level mixed model where NRS ratings at each 10 seconds' interval were nested within subject. We used a two-tailed Student's t-test to analyze between-group differences in test temperatures.

We analyzed difference in self-reported chronic pain prevalence among the study groups with binary logistic regression. The development in chronic pain prevalence from age 26 to age 28 years was analyzed with McNemar's test for paired ordinal data.

Ethics

The study was approved by the Regional Committee for Health Research Ethics (#2015/581/REK midt), and the participants signed an informed consent form after receiving written and verbal information about the study.

Results

Characteristics of participants and non-participants

Birth weight and gestational age were comparable among participants and non-participants in the VLBW and term SGA groups, while control non-participants had a slightly lower birth weight than control participants (Supplemental Table 1). In the VLBW group, non-participants were more likely to be males.

Characteristics of the study groups

Characteristics of the study groups are shown in Table 1. As expected based on the study design, there were group differences in birth weight and gestational age. A minimal difference in age at participation was also observed. More VLBW participants had smoked cigarettes 0-3 hours before the test, and more VLBW and term SGA participants had taken medication the last 12 hours prior to the test. Otherwise, we did not observe significant differences between groups regarding background characteristics.

For the VLBW group, neonatal data was available for 50 of 51 participants. All VLBW participants were admitted to the NICU, and 30 (60%) received mechanical ventilation with a median number of days on ventilator of 4 days (range 1-63 days). The median number of days admitted to the NICU or pediatric ward after birth was 63 (range 23-386 days). Five VLBW participants had an intraventricular hemorrhage during the NICU stay, and 3 VLBW participants had cerebral palsy diagnosed in childhood.

Sensory and pain thresholds

Of 7304 single thermal responses in the study, we detected 29 (0.4%) outliers that were replaced with a missing value. Descriptive means of thermal detection thresholds and pain thresholds are shown in Table 2 and dot plots showing the group-wise distribution of thermal pain thresholds and their respective median in Figure 1. We found no differences in thermal detection thresholds between the VLBW and the control group. The VLBW group had a 1.1°C lower mean CPT at the upper limb and a

0.8°C lower mean CPT at the lower limb compared to controls (Table 2), but heat and pressure pain thresholds were not substantially different. Except for slightly lower CDTs, particularly at the lower limb, the threshold means and medians in the term SGA group were essentially similar to those of the control group (Figure 1, Table 2). Univariate statistical testing showed that, except for a statistically significant lower CDT at the lower limb for the term SGA group vs controls, all p values were ≥0.05.

Results from the multilevel regression models are shown in Table 3, with predicted margins displayed graphically in Figure 2. Three-way interactions between group, site and sex were not significant in any of the models, and we chose to simplify the models by only including the two-way interactions of most *a priori* interest. The final regression models included two-way interactions of group and site, and group and sex. Lower CPTs in the VLBW group vs the control group as indicated from the raw data (Table 2) were also seen in the predicted margins (Figure 2) and regression coefficients (Table 3), but the VLBW and control groups did not statistically significantly differ (p values >0.2). The term SGA group displayed significantly increased sensitivity to non-painful cold as indicated by lower CDTs compared to controls (Table 3). No other consistent differences were seen between the term SGA and the control group for thermal thresholds or the PPT. Hence, there were good agreement between the exploratory univariate statistical testing and the fitted multilevel regression models. In sub-analyses excluding VLBW participants with cerebral palsy (Supplemental Table 2), participants who had taken pain or psychotropic medication (Supplemental Table 3) or had smoked cigarettes prior to the test (data not shown), the results were essentially unchanged.

The lower limb was less sensitive to all thermal stimuli (all p values <0.001), but more sensitive to pressure pain (p <0.001). There were no significant interactions between group and stimulus site neither for temperature detection nor pain thresholds (all p values >0.17). Overall, males were less sensitive to cool and warm detection (predicted male-female differences were 0.2°C for the CDT (p =0.01) and 0.5°C for the WDT (p =0.001)). In the term SGA group, a significant group and sex interaction was observed, indicating that the male-female difference for the CDT was 0.4°C larger than

in the control group (p =0.007). Except for this significant interaction, we found no indication of sex differences in thermal detection thresholds among the study groups (p values >0.4). Males were less sensitive to thermal pain (predicted overall male-female differences were 6.4°C for CPT (p =0.009) and 2.0°C for HPT (p <0.001)) and pressure pain (predicted overall male-female difference 160 kPa (p <0.001)). We observed no robust evidence for interactions between sex and group for thermal pain thresholds (p-values >0.4) or for the PPT (p values >0.14), indicating that that males had equally higher pain thresholds, compared to females, in all study groups.

Association between perinatal variables and pain thresholds

Within the VLBW group, the number of days in the NICU or pediatric ward correlated weakly with the CDT and WDT (rho =0.33, p =0.02 for the CDT and rho =0.31, p =0.03 for the WDT), but not with the pain thresholds (p-values >0.16). VLBW participants who had received mechanical ventilation during the NICU stay had a higher CDT than did those not receiving mechanical ventilation (difference 0.4°C, p =0.04). Neonatal mechanical ventilation was not significantly associated with the WDT or pain thresholds (p-values >0.3). Among VLBW participants receiving mechanical ventilation (n =30), the number of days on mechanical ventilation did not correlate with thermal detection or pain thresholds (p values >0.3). The number of days on mechanical ventilation correlated significantly with a lower PPT (rho = -0.54, p =0.002).

Supra-threshold heat pain response

The individually determined test stimulus temperatures (°C) did not significantly differ between the VLBW (mean 46.4; SD 0.3) or the term SGA group (mean 46.7; SD 0.2) and the control group (mean 46.9; SD 0.2), p =0.2 and p =0.6, respectively. Results from the regression models with two-way interactions of time and sex with group showed no difference in initial mean NRS values between the groups (estimated margins for initial NRS was 5.7 for the VLBW group, 6.0 for the term SGA group and 5.8 for the control group, p values vs. the control group >0.1). The NRS pain scores during 120 seconds of continuous supra-threshold heat pain stimulation increased throughout the stimulation period in

the control group (p <0.001), and the changes in NRS scores over time were not different in the VLBW or term SGA group vs the control group (p >0.16, Figure 3). We found no significant interactions between group and sex (p values ≥0.06). When repeating analyses excluding VLBW participants with cerebral palsy, participants who had taken pain or psychotropic medication or had smoked cigarettes prior to the test, the results were not substantially changed (data not shown).

Self-reported chronic pain

A higher frequency of self-reported chronic pain was observed in the VLBW group compared to the control group (Table 1), but this difference did not reach statistical significance (odds ratio 1.9, 95% CI 0.8-4.5, p =0.14). The prevalence of chronic pain in the term SGA group was similar to that of the control group (Table 1, odds ratio 0.9, 95% CI 0.4-2.2). When studying the 175 participants with available data on chronic pain from a follow-up 2 years before, we observed that a higher percentage of VLBW participants reported chronic pain at 28 years as compared to at 26 years (Table 4), however, this change over time was not statistically significant. The VLBW group seemed to have a higher persistency of chronic pain compared to controls during this time-period (Table 4), but numbers were too small for statistical comparison. Overall, the prevalence of persistent chronic pain was low in all study groups (reported by 9% of VLBW, 11% of term SGA and 3% of control participants with data from both time-points).

Discussion

In this study, thermal detection thresholds, pain thresholds, sensitivity to prolonged supra-threshold heat and sex differences in thermal and pain sensitivity generally were similar in preterm VLBW, term SGA and term-born control young adults. Among VLBW participants, we found some associations linking increased severity of NICU variables with higher thermal detection thresholds and lower PPT.

The lack of substantial differences in thermal and pain sensitivity among VLBW participants across several sensory modalities observed in this study opposes most of the existing literature, reporting some group differences in somatosensory or pain sensitivity among preterm-born children and adolescents compared to term-born controls.[6,12-14,32,34] The participants of the present study are older than in previous studies,[6,12-14,32,34] and our negative results may suggest that alterations in sensory processing among individuals born preterm diminish between adolescence and young adulthood.

However, other differences in study design may also be discussed as potential reasons for the discrepant findings. Two of the previous studies included extremely preterm participants,[32,34] thus representing a more severe exposure than the VLBW participants in our study. Moreover, in the study of Walker et al., differences in thermal sensitivity were more pronounced in extremely preterm-born participants who required neonatal surgery.[34] Hence, a possible explanation for the discrepant results is differential exposure status. We did find an association of receiving mechanical ventilation with higher CDT, and a slight correlation of the length of NICU stay with higher thermal detection thresholds. This may support the findings of Walker et al.,[34] who reported higher thermal detection thresholds among extremely preterm-born schoolchildren. Although estimated with low precision, mean CPT was lower (i.e. higher sensitivity to cold pain) in the VLBW group, which is consistent with the study by Vederhus et al.,[32] reporting lower cold pain tolerance among extremely preterm-born adolescents.

Compared to previous studies reporting altered pain thresholds among very preterm/VLBW children and adolescents,[6,12,13] the design of the present study has advantages since it is prospective and was

conducted in a blinded manner. Thus, the negative findings regarding pain thresholds are important since, despite larger or comparable sample sizes, our study failed to demonstrate significant group differences in thermal and pressure pain thresholds. The findings of the present study do agree with a small study showing comparable heat pain thresholds among very preterm-born children (≤32 weeks) and term-born controls,[9] and a recent prospective study that reported no substantial differences in thermal detection and pain thresholds among children were born preterm (≤32 weeks) and received neonatal mechanical ventilation vs term-born controls.[30] Collectively, the findings of these studies suggest no substantial alterations in sensory or pain thresholds among very preterm-born VLBW young adults.

The lack of increased sensitivity to prolonged painful heat in the VLBW group compared to controls deserves particular attention, since this finding disagrees with previous findings of increased sensitization to a 30 second stimulus at HPT level among very preterm-born schoolchildren.[12] Comparison of pain responses to continuous stimulation at threshold and supra-threshold level may however be difficult, especially when pain threshold levels are different, as they were in the previous study.[12] A later, smaller, sub-study from the same research group did show a tendency towards increased sensitization also to a 30-second supra-threshold stimulus with an individually determined intensity.[14] However, another small study showed no group differences in the sensitivity to a 30-second stimulus at 46°C between very preterm-born children and term-born controls.[9] Our results add to the literature by showing no increased sensitivity to a 120-second supra-threshold heat pain stimulus among VLBW young adults, using an individually determined stimulus intensity that previously has been shown to reliably induce a response resembling temporal summation of pain.[10] Hence, the results of the present study do not suggest altered or abnormal temporal summation of pain in the central nervous system of young adults who were born preterm.

In the previous studies on extremely preterm-born children and adolescents,[32,34] no sex differences were found among preterm participants, while present among controls (term-born males had higher

cold pain tolerance[32] and were more sensitive to cold and heat[34] compared to term-born females). In our study, sex differences in sensory and pain thresholds (females more sensitive than males) were consistent across the VLBW and control groups. Although research on sex differences in pain sensitivity in the healthy population is not conclusive,[24] our findings agree with previous studies on thermal detection thresholds[4] and thermal and pressure pain[23] in healthy adults, as well as studies on pressure pain sensitivity[6] and cold pain sensitivity[31] among VLBW adolescents.

To our knowledge, this is the first study to assess sensory and pain processing among young adults born SGA at term. Our results indicated greater sensitivity to non-painful cold among term SGA females. The clinical importance of this is questionable, since the absolute difference from the control group was small, and the mean upper limb CDT for the term SGA group was within the adult thenar reference values (0.5-2.4°C) of our laboratory. We observed no differences among the other tested modalities, and the present study do not supply evidence for an association between term SGA birth and substantial alterations in thermal or pain sensitivity.

In a previous follow-up visit at 26 years, a higher proportion of VLBW and term SGA participants reported pain compared to controls.[16] In the present study, the prevalence of self-reported chronic pain was higher but not statistically significantly different in the VLBW vs. the control group, and term SGA young adults in the current study reported no more chronic pain than controls. Overall, the prevalence of persistent chronic pain was low, but the tendency towards a higher prevalence among VLBW young adults at both time-points may point towards a more persistent susceptibility to chronic pain among VLBW young adults. The lack of findings on increased pain sensitivity may indicate that other mechanisms than alterations in the somatosensory system may underlie an association of VLBW with chronic pain in adulthood.

Lack of information on neonatal painful procedures among VLBW participants is a limitation of this study. However, the number of days with mechanical ventilation has previously been shown to be closely related to the number of painful procedures during the NICU stay,[11,32] and we were able to use

this variable and the length of NICU stay as indicators of neonatal pain exposure. Although the attendance rate is remarkably high nearly 30 years after initial enrollment in the study, selective attrition may have induced bias, leading to an underestimation of the study findings. However, the perinatal characteristics of VLBW participants and non-participants were essentially similar, thus limiting this possibility. We interpret the negative CPT results with some caution because inter-individual variability was large, and a substantial number of measurements was censored, i.e. the participant's actual CPT was not reached. However, censored CPTs were common in all groups, and we applied a statistical method that accounted for censored responses. The prospective and population-based design of this study enhances the generalizability of our findings. However, differences in NICU care may influence the association of VLBW with alterations in pain sensitivity, and generalization to younger or older VLBW cohorts may not be appropriate.

In conclusion, the results of the present study provide the first report on thermal and pain sensitivity in preterm-born VLBW individuals that have reached adulthood, and the first report on sensory function among term SGA young adults. We found that young adults born preterm with VLBW or SGA at term did not display substantial differences in thermal detection thresholds, pain sensitivity or sensitivity to prolonged supra-threshold heat compared to term-born normal birth weight controls. Our results indicate that other mechanisms may explain increased pain reports in young adults with low birth weight.

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Table 1. Characteristics of the study groups*.

	VLBW N = 51 (26 females)			Term SGA N = 66 (32 females)			Control N = 86 (48 females)		
	n			n			n		
Birth weight (grams), mean (SD)	51	1198	(231)	66	2936	(211)	86	3761	(472)
Gestational age (weeks), mean (SD)	51	28.8	(2.6)	66	39.7	(1.2)	86	39.8	(1.2)
Cerebral palsy	51	3	(6)	66	0	(0)	86	0	(0)
Age at participation, mean years (range)	51	28.3	(27.3-29.9)	66	28.6	(27.4-29.8)	86	28.5	(27.6-29.7)
Body mass index (kg/m^2), mean (SD)	50	26.3	(5.6)	66	25.3	(5.2)	86	25.3	(4.6)
Women: Hormonal contraceptives	25	13	(52)	32	21	(66)	48	19	(40)
Women: Days since LMP, median (25pc, 75pc)	19	23	(15, 95)	25	16	(10, 24)	39	22	(11, 59)
Caffeine intake the last 3 hours	51	25	(49)	66	30	(45)	85	35	(41)
Medication intake last 12 hours†	51	13	(25)	66	13	(20)	85	7	(8)
Pain or psychotropic medication last 12 hours	51	5	(10)	66	4	(6)	85	3	(4)
Alcohol consumption‡ the last 3-12 hours	51	0	(0)	66	1	(2)	85	3	(4)
Cigarette smoking last 3 hours	51	9	(18)	66	3	(5)	85	6	(7)
Sleep hours prior night, mean (SD)	51	6.5	(1.4)	66	6.6	(1.4)	84	6.8	(1.1)
Not tired before the test	51	22	(43)	66	25	(38)	85	30	(35)
Very tired before the test	51	0	(0)	66	4	(6)	85	1	(1)
HADS Anxiety sub-scale ≥8	49	12	(24)	63	14	(22)	85	17	(20)
HADS Depression sub-scale ≥8	49	5	(10)	63	5	(8)	85	5	(6)
Headache present before the test	51	5	(10)	66	4	(6)	85	9	(11)
If yes, VAS headache intensity (cm), mean (range)	5	2.3	(0.2-4.5)	4	2.0	(1.0-3.3)	9	3.0	(1.0-5.0)
Pain present before the test	50	12	(24)	66	13	(20)	85	18	(21)
If yes, VAS pain intensity (cm), mean (range)	12	2.8	(0.8-6.2)	13	2.8	(0.2-5.0)	18	2.2	(0.5-5.7)
Self-reported chronic pain$	51	13	(25)	66	9	(14)	86	13	(15)

Numbers indicate n (%) unless otherwise is stated.
VLBW: Very low birth weight (≤1500 grams). SGA: Small for gestational age (birth weight <10th percentile). Control: Normal birth weight at term. SD: Standard deviation. LMP: Last menstrual period. pc: Percentile. HADS: Hospital Anxiety and Depression Scale. VAS: Visual analogue scale (10 cm).
*Except for obvious group differences in gestational age and birth weight ($p < 0.0001$), a slight difference in age at participation ($p = 0.03$) and differences in the rates of cigarette smoking the last 3 hours ($p = 0.04$) and medication intake the last 12 hours ($p = 0.02$), there were no significant group differences in background characteristics (Kruskal-Wallis and chi-square tests).
†Participants that reported taking any medication except hormonal contraception.
‡Participants reporting consuming any alcohol amount. No participants reported consuming alcohol the last 3 hours prior to the test.
$Pain lasting >6 months and being moderate, severe or very severe during the past 4 weeks.

Table 2. Observed thermal detection thresholds[*], thermal pain thresholds[*] and pressure pain thresholds by birth weight group and stimulation site.

	Cool detection threshold		Warmth detection threshold		Cold pain threshold[†]		Heat pain threshold		Pressure pain threshold	
	Decrease below 32°C		Increase above 32°C		Decrease below 32°C / °C		Increase above 32°C / °C		kPa	
	Upper limb	Lower limb	Upper limb	Lower limb	Upper limb	Lower limb	Upper limb	Lower limb	Upper limb	Lower limb
VLBW	1.3 / 30.7 (0.5)	2.6 / 29.4 (1.5)	2.5 / 34.5 (1.0)	5.5 / 37.5 (3.1)	17.0 / 15.0 (8.1)	19.4 / 12.6 (7.6)	12.8 / 44.8 (3.7)	14.1 / 46.1 (3.2)	949 (231)[‡]	719 (229)
Term SGA	1.2 / 30.8 (0.4)	2.2 / 29.8 (1.3)[**]	2.4 / 34.4 (0.9)	5.2 / 37.2 (2.5)	18.2 / 13.8 (7.5)	21.0 / 11.0 (7.9)	13.5 / 45.5 (3.4)	14.0 / 46.0 (2.5)[$]	946 (205)	736 (185)
Control	1.4 / 30.6 (0.7)	2.5 / 29.5 (1.0)	2.3 / 34.3 (0.8)	5.1 / 37.1 (2.6)	18.1 / 13.9 (7.9)	20.2 / 11.8 (7.8)	13.4 / 45.4 (3.5)	14.1 / 46.1 (2.7)	985 (215)	751 (203)

kPa: Kilopascal. VLBW: Very low birth weight (≤1500 grams). SGA: Small for gestational age (birth weight <10th percentile). Control: Normal birth weight at term.

[*]Thermal thresholds are reported as the positive differences from start temperature (32°C) before the slash and absolute values in °C after the slash with standard deviation in parenthesis.

[**]P value vs controls 0.02. Otherwise, all p values indicating differences in thresholds in the VLBW and term SGA group vs. the control group were ≥0.05 (Mann-Whitney U test).

[†]A substantial number of CPT measurements were censored, i.e. the participants did not reach their CPT above the hardware-set 5°C floor temperature (126 (31%) in the VLBW group, 203 (39%) in the term SGA group, and 275 (40%) in the control group). For this reason, CPT means are underestimated compared to the predicted CPT margins in Figure 2 because the censored responses were set to 27°C (32°C - 5°C).

[‡]Upper limb PPT is missing for 1 VLBW participant.

[$]Lower limb HPT is missing for 1 term SGA participant.

Table 3. Multilevel regression coefficients with 95% confidence intervals (CI) for thermal detection, thermal pain and pressure pain thresholds.

	Upper limb			Lower limb		
	Beta*	95% CI*	p	Beta*	95% CI*	p
Cool detection threshold						
VLBW vs. control group	0.01	-0.1, 0.1	0.84	-0.06	-0.4, 0.3	0.71
Term SGA vs. control group	-0.1	-0.2, 0.008	0.047	-0.3	-0.5, -0.004	0.03
Warmth detection threshold						
VLBW vs. control group	0.1	-0.2, 0.4	0.39	0.2	-0.6, 0.9	0.65
Term SGA vs. control group	0.1	-0.1, 0.3	0.38	0.04	-0.6, 0.6	0.92
Cold pain threshold†						
VLBW vs. control group	-2.3	-8, 3.3	0.38	-4.1	-12, 3.4	0.26
Term SGA vs. control group	-0.6	-6.1, 4.9	0.82	-0.2	-8.0, 7.6	0.96
Heat pain threshold						
VLBW vs. control group	-0.7	-1.8, 0.5	0.28	-0.03	-0.9, 0.9	0.99
Term SGA vs. control group	-0.03	-1.0, 1.0	0.92	-0.2	-0.9, 0.6	0.67
Pressure pain threshold						
VLBW vs. control group	-37	-108, 33	0.29	-41	-107, 25	0.22
Term SGA vs. control group	-49	-114, 16	0.14	-23	-81, 34	0.42

VLBW: Very low birth weight (≤1500 grams). SGA: Small for gestational age (birth weight <10th percentile). Control: Normal birth weight at term.

*Regression coefficients and confidence intervals are re-transformed to represent difference in °C from baseline (32°C) for thermal thresholds and kilopascal values for the pressure pain threshold.

†A number of CPT measurements were censored because the participants did not reach their pain threshold above the hardware-set 5°C floor temperature. The regression coefficients that indicates between-group differences in CPT are therefore larger than the difference in mean CPT between the VLBW and control groups calculated from the raw data in Table 2.

Table 4. Prevalence n (%) of self-reported chronic pain* for VLBW, term SGA and control young adults attending both study visits at 26 and 28 years of age.

	n	26 years	28 years	p†	Persistency‡
VLBW	47	7 (15)	13 (28)	0.15	4 (57)
Term SGA	56	12 (21)	7 (13)	0.13	6 (50)
Control	72	6 (8)	9 (13)	0.55	2 (33)

VLBW: Very low birth weight (≤1500 grams), SGA: Small for gestational age (birth weight <10th percentile), Control: Normal birth weight at term.
*Pain lasting >6 months and being moderate, severe or very severe during the past 4 weeks.
†p indicates change in chronic pain prevalence from 26 to 28 years.
‡Chronic pain reported at 28 years among those reporting chronic pain at 26 years.

Supplemental Table 1. Characteristics of participants and non-participants.

	VLBW		Term SGA		Control	
	Participants n = 51	Non-participants n = 32	Participants n = 66	Non-participants n = 35	Participants n = 86	Non-participants n = 32
Males/females, n/n (% males)	25/26 (49)	22/10 (69)	34/32 (52)	20/15 (57)	38/48 (44)	13/19 (41)
Birth weight (g), mean (SD)	1198 (231)	1132 (257)	2936 (211)	2891 (263)	3761 (472)	3543 (329)
Gestational age (weeks), mean (SD)	28.8 (2.6)	28.8 (2.6)	39.7 (1.2)	39.5 (1.3)	39.8 (1.2)	39.4 (1.3)

VLBW: Very low birth weight (birth weight ≤1500 grams). SGA: Small for gestational age (birth weight <10th percentile). Control: Normal birth weight at term. SD: Standard deviation.

Supplemental Table 2. Multilevel regression coefficients with 95% confidence intervals (CI) for thermal detection, thermal pain and pressure pain thresholds, excluding VLBW participants with CP (n =3).

	Upper limb			Lower limb		
	Beta*	95% CI*	p	Beta*	95% CI*	p
Cool detection threshold VLBW vs. control group	0.01	-0.1, 0.1	0.85	-0.06	-0.4, 0.3	0.72
Warmth detection threshold VLBW vs. control group	0.1	-0.1, 0.4	0.34	0.2	-0.6, 1.0	0.62
Cold pain threshold† VLBW vs. control group	-2.2	-7.8, 3.5	0.43	-4.5	-12, 2.8	0.21
Heat pain threshold VLBW vs. control group	-0.6	-1.7, 0.5	0.31	-0.1	-1.0. 0.9	0.89
Pressure pain threshold VLBW vs. control group	-38	-108, 32	0.29	-24	-90, 42	0.48

VLBW: Very low birth weight (≤1500 grams). Control: Normal birth weight at term.
*Regression coefficients and confidence intervals are re-transformed to represent difference in °C from baseline (32°C) for thermal thresholds and kPa values for the pressure pain threshold.
†A number of CPT measurements were censored because the participants did not reach their pain threshold above the hardware-set 5°C floor temperature. The regression coefficients that indicates between-group differences in CPT are therefore larger than the difference in mean CPT between the VLBW and control groups calculated from the raw data in Table 3.

Supplemental Table 3. Multilevel regression coefficients with 95% confidence intervals (CI) for thermal detection, thermal pain and pressure pain thresholds, excluding participants who had consumed pain or psychotropic medication the last 12 hours prior to the test (5 in the VLBW group, 4 in the term SGA group and 3 in the control group).

	Upper limb			Lower limb		
	Beta*	95% CI*	p	Beta*	95% CI*	p
Cool detection threshold						
VLBW vs. control group	-0.02	-0.1, 0.1	0.82	-0.1	-0.4, 0.2	0.50
Term SGA vs. control group	-0.1	-0.2, -0.003	0.03	-0.3	-0.6, -0.1	0.01
Warmth detection threshold						
VLBW vs. control group	0.1	-0.2, 0.4	0.42	0.3	-0.5, 1.1	0.46
Term SGA vs. control group	0.1	-0.2, 0.3	0.61	0.02	-0.6, 0.6	0.95
Cold pain threshold†						
VLBW vs. control group	-2.3	-7.8, 3.1	0.38	-3.2	-11, 4.3	0.39
Term SGA vs. control group	0.01	-5.7, 5.7	1.0	0.4	-7.6, 8.5	0.93
Heat pain threshold						
VLBW vs. control group	-0.7	-1.9, 0.5	0.28	0.1	-0.8, 1.1	0.70
Term SGA vs. control group	0.1	-1.0, 1.1	0.89	-0.1	-0.9, 0.7	0.76
Pressure pain threshold						
VLBW vs. control group	-39	-112, 33	0.29	-54	-121, 12	0.11
Term SGA vs. control group	-24	-88, 40	0.44	-15	-74, 44	0.60

VLBW: Very low birth weight (≤1500 grams). SGA: Small for gestational age (birth weight <10th percentile). Control: Normal birth weight at term.

*Regression coefficients and confidence intervals are re-transformed to represent difference in °C from baseline (32°C) for thermal thresholds and kPa values for the pressure pain threshold.

†A number of CPT measurements were censored because the participants did not reach their pain threshold above the hardware-set 5°C floor temperature. The regression coefficients that indicates between-group differences in CPT are therefore larger than the difference in mean CPT between the VLBW and control groups calculated from the raw data in Table 3.

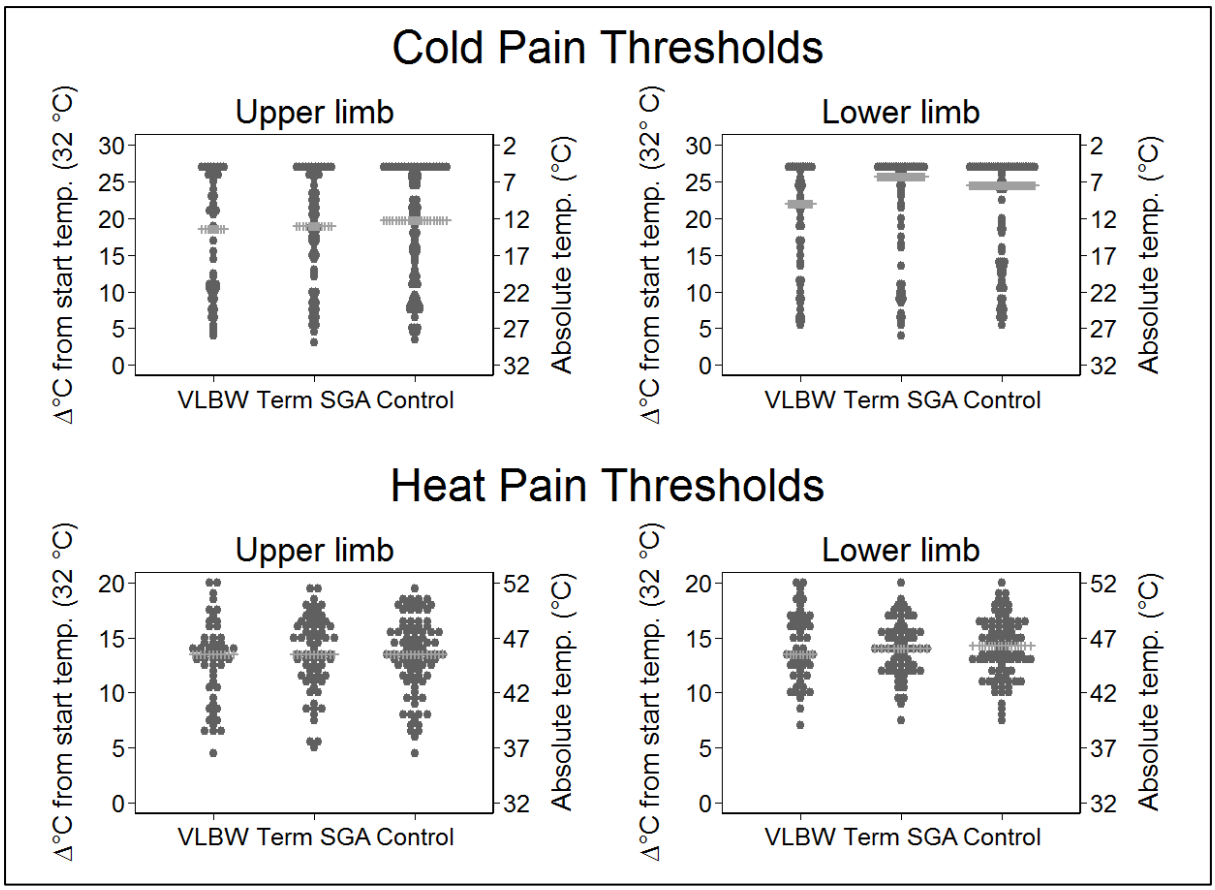


Figure 1. Cold and heat pain thresholds at the two stimulated sites (upper and lower limb) by birth weight group (VLBW group (very low birth weight; birth weight ≤1500 grams), term SGA group (small for gestational age, birth weight <10th percentile at term) and control group (born at term with birth weight ≥10th percentile). Dot plot illustrating the distribution of thermal pain thresholds within each group, with a horizontal spiked line indicating the group median.

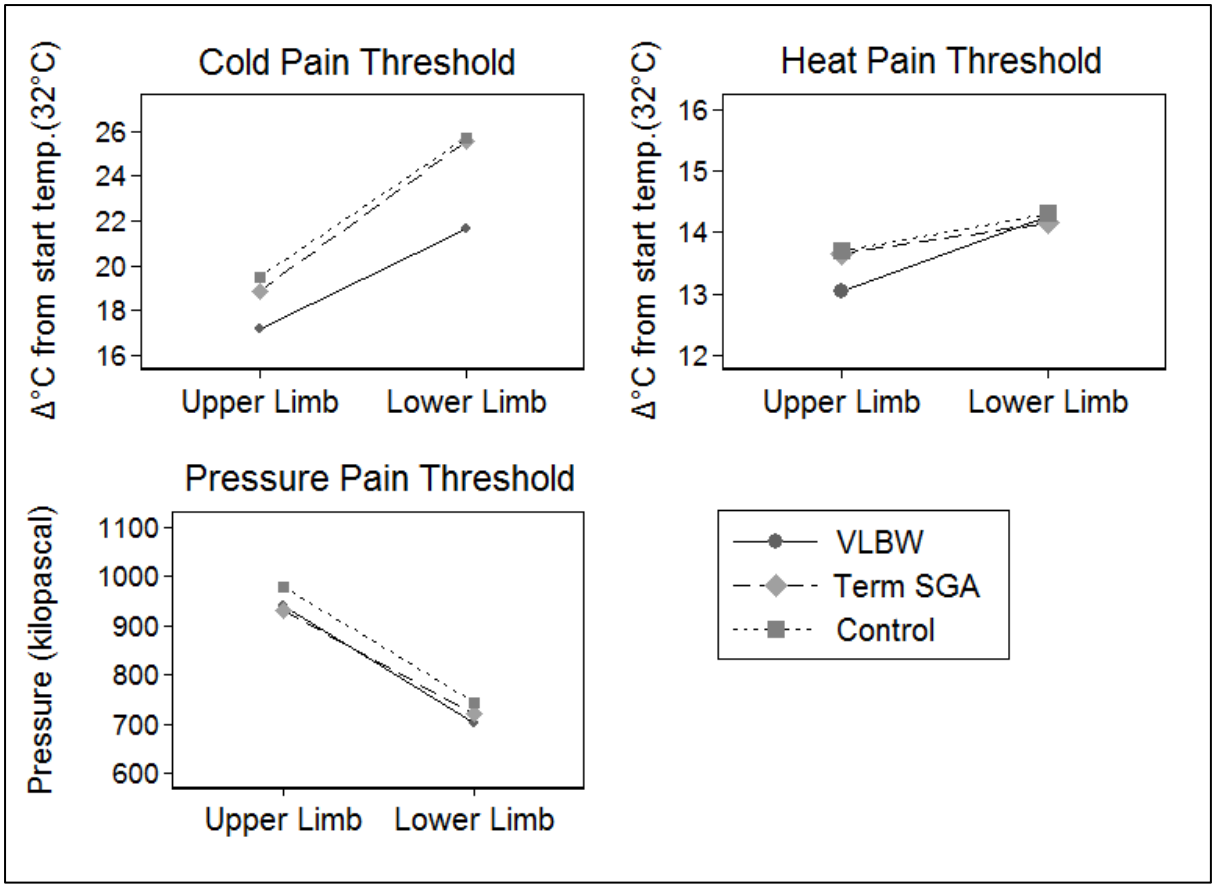


Figure 2. Cold and heat pain thresholds in young adults born preterm with very low birth weight (VLBW; ≤1500 grams), small for gestational age (SGA; birth weight <10th percentile) at term, or at term with normal birth weight (controls). Graphic illustration of estimated margins from the multilevel models with adjustments for sex at the two stimulation sites (upper and lower limb). The Y-axis represents the relative temperature difference from the start temperature of 32°C. The margins for the cold pain thresholds is estimated accounting for censored responses, and are thus not directly comparable to the calculated means in Table 3. There were no statistically significant differences between the VLBW or term SGA group and the control group.

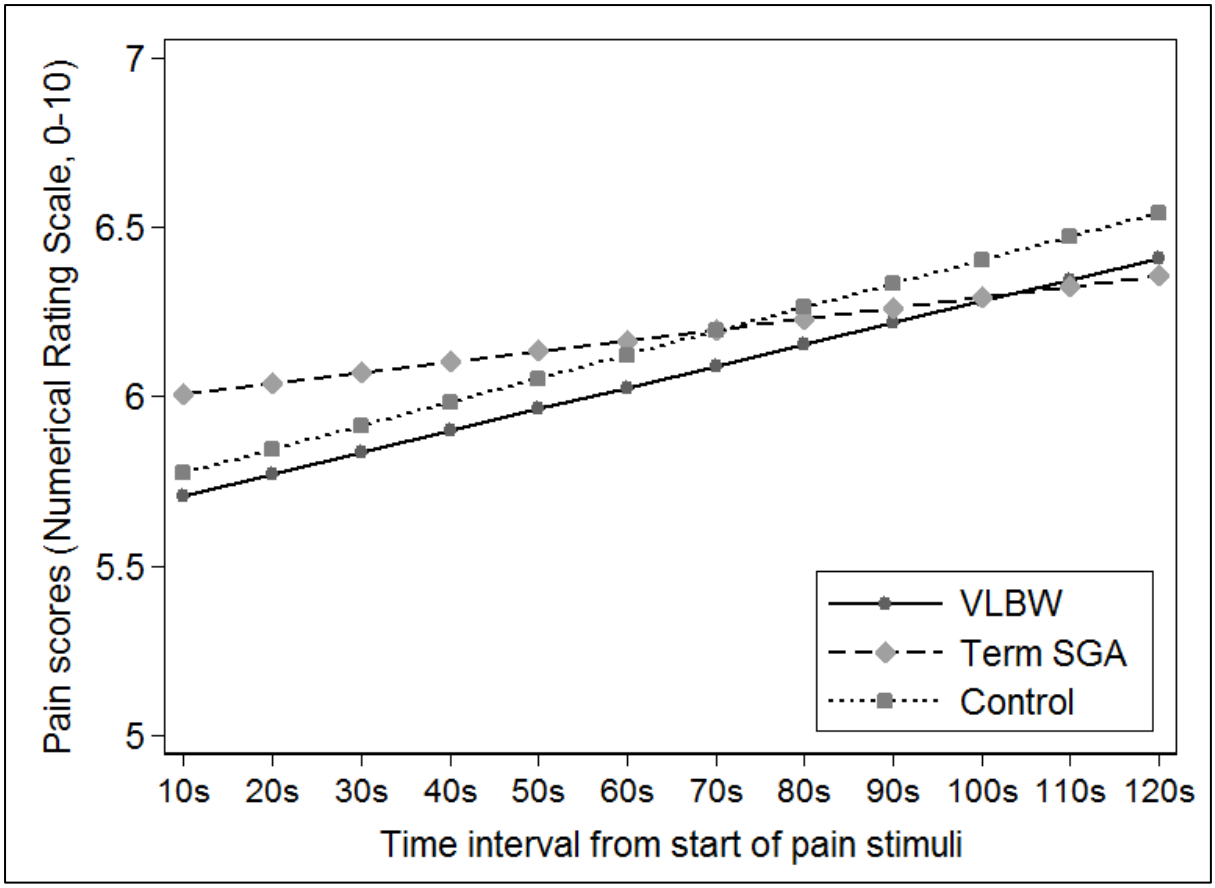
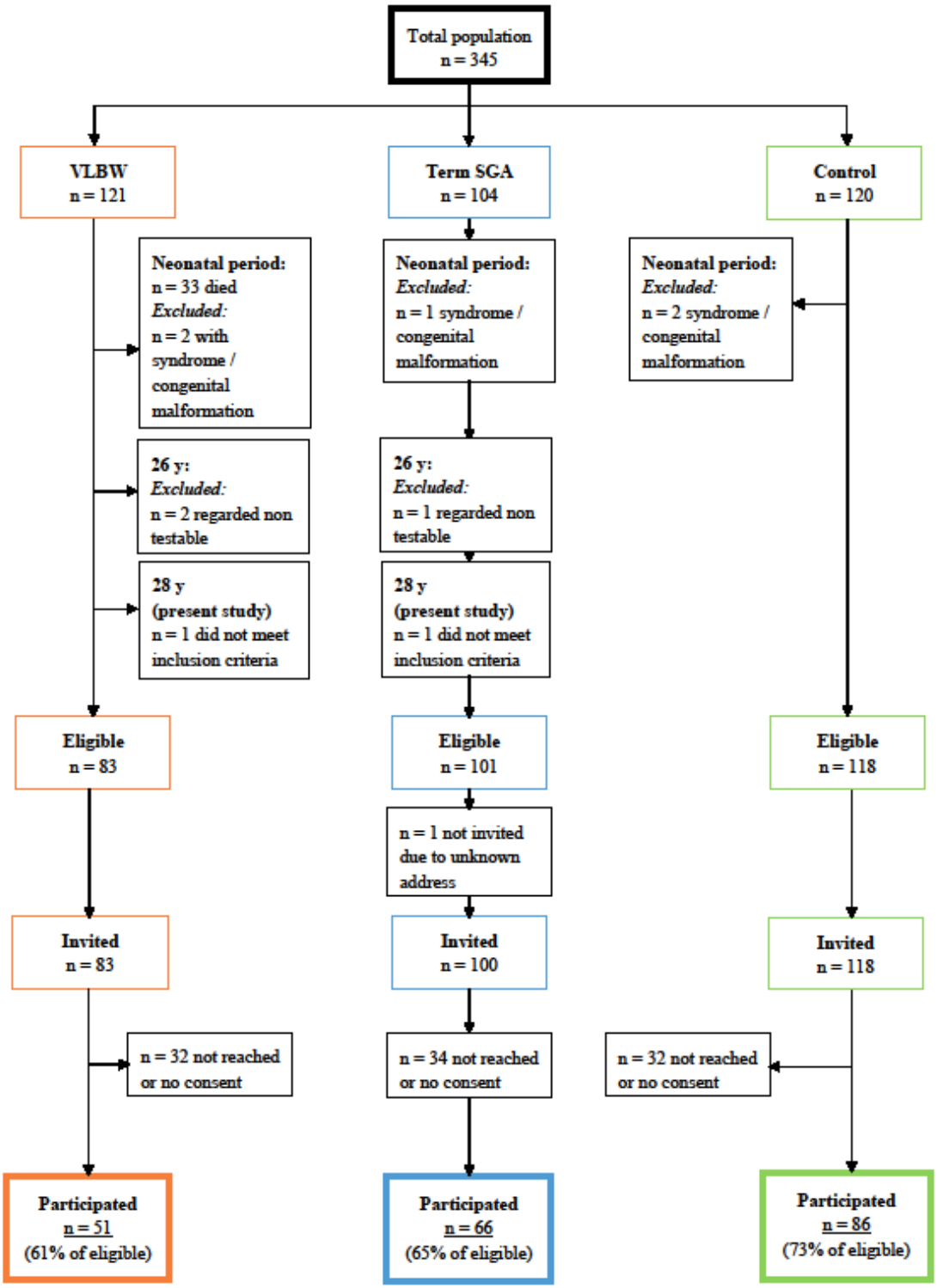


Figure 3. Numerical rating scale (NRS) pain scores during 120 seconds of continuous heat pain stimulation in young adults born either preterm with very low birth weight (VLBW, ≤1500 grams), small for gestational age (SGA, birth weight <10th percentile) at term, or at term with normal birth weight (controls). Graphic illustration of estimated margins from the multilevel model with adjustments for sex. The X-axis represents the 12 time points where NRS values were recorded. The Y-axis represents NRS pain scores (range 0-10, where 0 =no pain and 10 =unbearable pain). Neither the difference in initial NRS nor the difference in temporal change between the VLBW or the term SGA groups and the control group were statistically significant.



Supplemental Figure 1 Flow chart of the study population.