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Pressure and cold pain threshold reference values in a large, young adult, pain-free population

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HIGHLIGHTS

- Provides reference pressure and cold pain threshold data for a 'healthy' young adult population.
- The data represent the most comprehensive and robust data available for young adults aged 21–24.
- Statistically significant, independent correlates of pain sensitivity measures are provided.
- The data enable more accurate interpretation of pain sensitivity in clinical pain disorders.
- Provides insight into the complex associations of pain sensitivity for use in future research.

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ABSTRACT

Background and aims: Currently there is a lack of large population studies that have investigated pain sensitivity distributions in healthy pain free people. The aims of this study were: (1) to provide sex-specific reference values of pressure and cold pain thresholds in young pain-free adults; (2) to examine the association of potential correlates of pain sensitivity with pain threshold values.
Methods: This study investigated sex specific pressure and cold pain threshold estimates for young pain free adults aged 21–24 years. A cross-sectional design was utilised using participants ($n = 617$) from the Western Australian Pregnancy Cohort (Raine) Study at the 22-year follow-up. The association of site, sex, height, weight, smoking, health related quality of life, psychological measures and activity with pain threshold values was examined. Pressure pain threshold (lumbar spine, tibialis anterior, neck and dorsal wrist) and cold pain threshold (dorsal wrist) were assessed using standardised quantitative sensory testing protocols.
Results: Reference values for pressure pain threshold (four body sites) stratified by sex and site, and cold pain threshold (dorsal wrist) stratified by sex are provided. Statistically significant, independent correlates of increased pressure pain sensitivity measures were site (neck, dorsal wrist), sex (female), higher waist-hip ratio and poorer mental health. Statistically significant, independent correlates of increased cold pain sensitivity measures were, sex (female), poorer mental health and smoking.
Conclusions: These data provide the most comprehensive and robust sex specific reference values for pressure pain threshold specific to four body sites and cold pain threshold at the dorsal wrist for young adults aged 21–24 years. Establishing normative values in this young age group is important given that the transition from adolescence to adulthood is a critical temporal period during which trajectories for persistent pain can be established.
Implications: These data will provide an important research resource to enable more accurate profiling and interpretation of pain sensitivity in clinical pain disorders in young adults. The robust and comprehensive data can assist interpretation of future clinical pain studies and provide further insight into the complex associations of pain sensitivity that can be used in future research.

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1. Introduction

Quantitative sensory testing (QST) as a measure of pain sensitivity, is being increasingly used to generate somatosensory profiles of patients in clinical pain studies [1,2] and to measure outcomes in randomised controlled trials [3,4]. However meaningful interpretation of data from these studies requires appropriate reference values for what is 'normal'. This ideally should be drawn from large population-based samples of 'healthy pain-free participants', adjusted for age, sex, and other potential confounders [5], thereby allowing for generalisability. Currently there is a lack of large population studies that have investigated pain sensitivity distributions in healthy people.

While there are some 'normative' datasets against which to reference clinical QST data [6–12], currently there is no comprehensive reference QST data specific to young adults. As the transition from adolescence to adulthood is a critical time during which trajectories for persistent pain can become established [13–16] there is value in establishing normative data for this young age group. Issues with the utility of current normative datasets for QST include a lack of adherence to recent calls for standardised definitions, and best practice recommendations to adjust for potential confounding variables such as age and sex [17]; datasets that include participants with pain [7,8]; having relatively small numbers in each age and sex range [9–11]; or wide ranging age groups [12]. There is thus a gap in knowledge of normal age-sex specific pain sensitivity distributions.

Further, without large cohort reference values to define 'normal' and an understanding of potential correlates, the interpretation of QST measures in pain studies is severely limited, as is their utility in management of people with pain [5,18]. Potential independent correlates associated with increased pain sensitivity to pressure and cold stimuli include younger age [6], female sex [19], increasing Body Mass Index [6,20], higher psychological symptoms of depression, anxiety, stress and catastrophizing, [2,6,21–23], decreased health related quality of life [6], lower physical activity and increased sedentary behaviour, [21,24,25], and smoking [8,26]. Only one normative study of pain sensitivity has investigated a broad range of potential correlates (demographic, psychological and health-related factors), but this study was limited by a relatively wide age range with small age-specific participant numbers [6].

Clinically, the assessment of an individual's pain sensitivity can inform treatment options [27]. In this context, exploring normative ranges for deep tissue pain sensitivity (pressure pain threshold: PPT) is particularly important given deep tissues are implicated in musculoskeletal conditions [28–32]. With the availability of affordable algometers, there is increasing use of PPT testing in clinical settings to assess and monitor tissue sensitivity levels Cold hypersensitivity (cold pain threshold: CPT) has also demonstrated clinical utility for predicting poor prognosis in whiplash associated disorders [33] and differentiating pain mechanisms in musculoskeletal pain conditions [18,23,34,35]. These two clinically relevant nociceptive stimuli can form part of a shorter QST protocol by limiting participant burden and improving time efficiency [36].

The large birth cohort investigated here provided an opportunity to capture more precise sex specific pressure and cold pain threshold estimates for young, pain-free adults. The aims of this study were: (1) to provide sex-specific reference values of pressure and cold pain thresholds in young pain-free adults; (2) to examine the association of site, sex, ethnicity, height, weight, smoking, health related quality of life, psychological factors and physical activity levels with pain threshold values.

2. Methods

2.1. Study Population

Cross-sectional data for this study was obtained from the Western Australian Pregnancy Cohort (Raine) Study (http://www.rainestudy.org.au). This is an ongoing birth cohort study that commenced with 2900 women who enrolled in the study before the 18th gestation week and 2868 children born, entered the initial birth cohort. Data has been collected at 1, 2, 3, 5, 8, 10, 14, 17, 20 and 22 years. The characteristics of the active participants were compared with census data collected in 2011 on all similarly aged young adults in Western Australia. The comparison showed that the sample remains widely representative for a range of variables including education level, employment status, income, marital status, number of offspring, hours worked and occupation. The 22 year follow-up data collection ran between March 2012 and July 2014. Further detail on full measures collected can be found at http://www.rainestudy.org.au/for-researchers/cohort-follow-ups/ [37].

2.2. Recruitment, sampling and data collection

All data used in this study were obtained at the 22 year follow-up. Data were collected as part of 4 h of testing followed by an overnight sleep study. For this follow up, 1065 individuals participated in pressure pain and cold pain threshold testing. Of the 970 participants who had pressure and cold pain threshold data, and completed questionnaire and physical assessment data on nominated correlates, 617 (280 female and 337 male) were classified as pain free and were included for analysis. Participants were considered pain free if they answered "no" to the question "do you have any current body pain?" from the Orebrö Musculoskeletal Pain Questionnaire (OMPQ).

Questionnaires were filled in before physical assessments and were checked for completion. Anthropometry measures and pressure and cold pain threshold testing were part of the physical assessment protocol conducted by twelve Raine research staff, all of who were thoroughly trained in the data collection procedures and used standardised protocols.

2.3. Quantitative sensory testing

Due to time constraints allowed for collecting data and to minimise the already significant participant burden, the sensitivity measures considered most clinical relevant were collected. A standardised protocol for QST consistent with current best practice recommendations [12,17], was used to measure PPT and CPT. All QST measurements were taken from the right side of the body, as side to side consistency in pain threshold measurements have been shown in people with [38] and without pain [12]. All testing was done in the early evening minimising the influence of circadian rhythms on pain sensitivity [39] and the order of testing was PPT, followed by CPT, as applying cold first has been found to increase the risk of mechanical hyperalgesia [40]. This testing sequence has been used previously [23]. Both PPT and CPT have demonstrated inter-examiner and intra-subject reliability with reasonable levels of standard error of measurement [41–43]. Excellent interrater and intrarater reliability for PPT testing by the Raine research staff has been demonstrated, with the caveat that an absence of any confounding of study estimates by rater should be checked due to a systematic rater bias identified [44].

2.4. Pressure pain thresholds

Pressure pain threshold (PPT) was established using a pressure algometer (Somedic AB, Sweden) with a contact area of 1 cm^2 applied perpendicularly to the skin with a ramp rate of 50 kPa/s. The ramp rate varies across studies and it is acknowledged slower ramp rates may be appropriate for the study of clinical pain populations [45]. PPT was defined as the moment the sensation of pressure became one of pressure and pain. Standardised instructions were read to participants: "The moment the pressure increases to a point where it first feels uncomfortable or painful, press and release the button. This means the very first onset of discomfort or pain and not the most pressure that you can bear". A cut-off pressure value of 1000 kPa was set for safety purposes [46]. Four trials were performed with a minimum 10 s rest between trials. The mean threshold was calculated for each site from the last three trials.

In order to capture widespread sensitivity data, four standardised sites were tested in the following sequence; the wrist, upper leg, upper trapezius and lumbar spine. These sites have been previously documented [2]. The wrist was tested at the middle of the dorsal aspect of the wrist joint line. The leg was tested at the muscle belly of tibialis anterior, approximately 2.5 cm lateral and 5 cm distal to the tibial tubercle. The upper trapezius was tested at the mid-point between the C7 spinous process and the lateral acromion. The lumbar spine was tested at the erector spinae, 2 cm lateral to the L4/L5 interspinous space.

2.5. Cold pain threshold

To obtain the cold pain threshold, a thermal stimulator (Modular Sensory Analyzer (MSA), Somedic AB, Sweden) with a 12.5 cm^2 (25 mm × 50 mm) probe was used at one standardised body site. This site was the middle of the dorsal aspect of the wrist joint line, consistent with the test site for PPT. The baseline temperature was set as 32 °C with a cut off temperature of 5 °C. The temperature decreased at 1 °C/s until the participant first perceived pain and pressed the control switch to terminate the test. For CPT, the following instructions were given to participants "Allow the temperature to drop until the moment it reaches a point where it feels uncomfortably or painfully cold, and then press the button. This means the very first onset of discomfort or pain and not the most cold that you can bear". Four trials were performed with a 10 second rest period between trials. The mean threshold was calculated from the last three trials.

2.6. Other variables

In order to investigate for possible associations with QST measures, a number of other variables were collected.

2.7. Physical measures

With shoes removed, height (metres) was measured with a stadiometer and body mass (kilograms) was measured with digital scales [47]. BMI (kg/m^2) was calculated from these measures. BMI was further categorised into underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), over-weight (25.0–29.9 kg/m^2) or obese (≥30.0 kg/m^2). Waist and hip circumference were measured using a metric tape measure and a standardised protocol, to calculate the waist/hip ratio (WHR).

2.8. Smoking

Subjects were asked, 'Do you currently smoke cigarettes/cigars?' and were classified accordingly, as smokers or non-smokers.

2.9. Health-related quality of life

Health-related quality of life was measured using the Short Form-12, version 2 (SF-12) [48], a validated and reliable measure of health related quality of life. Twelve questions produce two summary measures: a Mental Component Summary (MCS); and Physical Component Summary (PCS) [49]. Each SF-12 scale is a norm-based score with a mean of 50 and standard deviation of 10, with higher scores indicating less disability [48]. The MCS and PCS of the SF12 were categorised into those with a score ≥50 and <50, to allow comparison with the study by Neziri et al. [6], in which SF36 scores were dichotomised.

2.10. Psychological Data

The Depression Anxiety Stress Scale 21 (DASS-21) was used to evaluate the severity of depression, anxiety and stress related symptoms. It is a valid and reliable questionnaire where a higher score indicates greater severity of symptoms [50], with established cut-off scores for mild, moderate, severe and extremely severe levels of each sub-scale [51].

2.11. Activity measures

Sedentary behaviour and physical activity were objectively measured over an eight day period using the Actigraph GT3X+ accelerometer (Actigraph, Pensacola, FL, USA) worn on the right hip continuously, except during bathing or aquatic activities. Data were recorded at 30 Hz and vertical axis movement counts 'per 60 second epoch' used in current analyses. Accelerometer data were downloaded and processed in SAS (version 9.3, SAS Institute, Cary, NC, USA) [52]. Common thresholds [53] were used to class each minute as sedentary (<100 counts per minute (cpm)), light intensity (100–1951 cpm), moderate intensity (1952–5724 cpm) or vigorous intensity (>5724 cpm). Minutes spent in moderate and vigorous physical activity (MVPA) per day; and sedentary time as percentage of non-MVPA time were calculated for each participant based on their valid days (≥10 h of waking wear time) [54].

2.12. Statistical analysis

To provide reference values for pain hypersensitivity, quantile regression analyses were conducted to determine the 5th, 10th and 25th for PPT [6], and 95th, 90th and 75th percentiles for CPT, estimated with bootstrapped standard errors (1000 replications). Reference values for pain hyposensitivity were determined using the 75th, 90th and 95th percentiles for PPT and 25th, 10th and 5th for CPT.

Multivariable independent correlates of PPT were determined with linear regression utilising generalised estimating equations, with an exchangeable correlation structure ($r = 0.76$) to account for the non-independence of the data due to repeated measures by site. Although the PPT was slightly right-skewed, logarithmic transformation did not significantly improve fit of the models and untransformed measures were used to facilitate clinical interpretation of regression coefficients. Multivariable independent correlates of CPT were determined using tobit regression, which was left-censored due to the lower limit of the testing equipment being 5 °C. For both PPT and CPT, a series of univariable analyses were initially performed for sex, site (PPT only), rater, ethnicity, height, weight, smoking, activity, quality of life and psychological measures. Sex interactions were tested for all correlates. Sex, and variables with sex-adjusted associations of $p < 0.15$, were entered into multivariable regression models, using a purposeful selection of covariates approach, to ensure no important confounding variables were omitted [55]. Covariates significant at $p < 0.05$ were

Table 1
Demographic, quality of life and psychological data summary statistics ($n = 617$).

Variable	Mean (SD) or number (%)	Range
Age (years)	22.2 (0.6)	21.0–24.4
Sex (female)	280 (45.4%)	
Ethnicity (both parents Caucasian)	525 (85%)	
Height (cm)[a]	173 (9.6)	154 – 201
Weight (kg)[a]	75.9 (17.7)	42.4 –147.5
Hip/waist ratio[b]	0.83 (0.07)	0.65–1.08
BMI (kg/m^2)[a]	25.2 (5.4)	15.4 – 49.3
Underweight (<18.5)	13 (2.1%)	15.4–18.3
Normal (18.5–24.9)	374 (60.7%)	18.5–25.0
Overweight (25.0–29.9)	136 (22.1%)	25.1–30.0
Obese (<30.0)	93 (15.1%)	30.1–49.3
SF-12[f]		
PCS ≥50	471 (84.7)	24.6 – 67.3
MCS ≥50	280 (50.5)	11.7 – 68.5
Smoking[c] (yes)	90 (14.7%)	
DASS-21		
Depression[d]	5.9 (7.7)	0–40
Anxiety[e]	3.9 (5.0)	0–36
Stress[e]	7.9 (7.4)	0–42
Activity		
MVPA (minutes/day)[g]	37.5 (28.8)	0–243.2
Sedentary time (% of non-MVPA during wake time)[g]	63.7 (9.7)	28.6–87.4

[a] Missing data: [a] =1, [b] =2, [c] =3, [d] =49, [e] =51, [f] =62 , [g] =173, BMI: body mass index, DASS-21: depression anxiety stress scale 21, PCS: physical component summary, MCS: mental component summary MVPA: moderate-vigorous physical activity.

retained. Univariable associations were made using all cases available, candidate models were evaluated using cases with available data on all candidate variables, and final multivariable models were estimated using all cases with available data on variables included in final models. Each model was examined to ensure absence of influential observations and collinearity of variables, and linearity of associations and normality and homoscedasticity of residuals. Due to nonlinearity of association with PPT and CPT, BMI was parameterised as underweight, normal, overweight and obese in statistical models. Systematic differences between the 12 research personnel performing the tests in this study were checked. Although some testers' values were significantly different from others, inclusion of testers in our models confirmed a lack of confounding of the estimates of associations between PPT and covariates by differences between testers [55], and therefore testers were not adjusted for in final models. Stata/IC Version 13.1 for Windows (StataCorp LP, College Station, TX, USA) was used for all analyses.

2.13. Results

The demographic, quality of life, physical and psychological data of the 617 participants are summarised in Table 1. The mean (SD) age of participants was 22.2 (0.6) years with a range of 21.0–24.4, and 280 (45.4%) were female. The SF-12 PCS and MCS mean (SD) values were 55.2 (5.1) and 47.9 (9.6), respectively. Depression, anxiety and stress symptoms were reported as mild by 9.2%, 5.8% and 6.7% and moderate-severe by 14.3%, 12.7% and 8.5%, respectively. The high numbers of subjects with missing activity data ($n = 173$, 28.0%) represents poorer compliance with wearing the accelerometer. The participants' number of valid days wearing the accelerometer ranged from 1 to 15 with an average (SD) of 5.3 (2.4).

References values for PPT stratified by sex and site and CPT stratified by sex are shown in Table 2. For PPT and CPT, reference values for hypersensitivity are reported from the most sensitive to least sensitive, while reference values for hyposensitivity are reported from the least insensitive to most insensitive. For CPT, reference values for hyposensitivity are reported at the 5th, 10th and 25th percentile in females only. Values were unable to be estimated for males, as 38.8% of male participants reached the 5 °C minimum cut off.

Univariable and multivariable regression models for PPT are shown in Table 3. Variables with a p-value of <0.15 for univariable association with PPT were site, sex, BMI, WHR, SF12-MCS, smoking, DASS stress and sedentary time. In the multivariable model for PPT measures, site, sex, WHR and SF12-MCS were retained as statistically significant, independent correlates of PPT. The neck was the most sensitive PPT test site (i.e. lowest PPT), and both the neck and the wrist sites were significantly more sensitive than the back and leg PPT test site. The neck was significantly more sensitive than the wrist, and there was no significant difference between the back and leg sites. Males were significantly less sensitive (i.e. higher PPT) than females (mean difference = +141.6 kPa, 95% CI: 109.0, 174.3). WHR was associated with increasing pressure pain sensitivity (i.e. lower PPT) with PPT estimated to decrease by 28.2 kPa (95% CI: 5.6–50.8) with each 0.1 increase in WHR. Poorer mental health was associated with increased pressure pain sensitivity (i.e. lower PPT), those with MCS ≥50 were estimated to have 33.0 kPa (95% CI: 2.9–63.0) higher PPT values than those with MCS <50.

Univariable and multivariable regression models for CPT are shown in Table 4. Variables with a p-value of <0.15 for univariable association with CPT were sex, SF12-MCS, smoking, DASS stress, DASS depression and sedentary time. In the multivariable model for CPT measures, sex, SF12-MCS and smoking were retained as statistically significant, independent correlates of CPT. Males were significantly less sensitive to cold pain (i.e. CPT was elicited at a lower temperature) than females (difference = −3.5 °C, 95% CI: −5.4, −1.6). Better mental health (MCS ≥50) was associated with less sensitivity to cold pain (i.e. lower CPT temperature), those with MCS ≥50 were estimated to have −2.5 °C (95% CI: −4.4, −0.6) lower CPT values than those with MCS <50. Smoking was associated with less sensitivity to cold pain (i.e. lower CPT temperature) with CPT estimated to be 3.5 °C lower (95% CI: −6.5, −0.8) in smokers compared to non-smokers.

3. Discussion

The study has provided reference pressure and cold pain threshold data for a 'healthy' young adult population. The reference values reported here are currently the most comprehensive and robust data available for young adults aged 21–24. A major strength of this study is the consideration of the independent associations of a comprehensive number of potential known correlates of pressure and cold pain sensitivity, findings consistent with those previously reported in response to QST [56–58].

Comparing our data against current normative reference data highlights the most relevant comparison dataset as Neziri [6] who reported PPT data on 20–49 year olds for the same back and neck sites, using the same approach to data with percentiles for hypersensitivity and hyposensitivity (Table 5 shows a comparison with previously existing age, sex, site, and test specific reference data). In contrast, Magerl [9] using a moving average analysis, had an overall number of participants in each sex group of 90 resulting in small numbers in each of five decadal groups (age range 20–70), and did not report percentile values for hypersensitivity and hyposensitivity. Comparison with Neziri [6] shows our data consistently has a wider range of values and higher standard deviations. For example, the male PPT neck values ranged from 125 (P^5) to 793 (P^{95}, SD = 200) compared with Neziri [6] who reported values from 150 (P^5) to 451 (P^{95}, SD = 94). This discrepancy may reflect the larger numbers sampled for the current study, or differences in participants due to correlates known or unknown to be associated with pain sensitivity, including

Table 2
Reference values for pain threshold stratified by sex and site (N = 617).

Pain Threshold (PPT = kPa)	Females				Males			
	Number	Mean (SD)	Hypersensitivity (PPT: P^5, P^{10}, P^{25})	Hyposensitivity (PPT: P^{75}, P^{90}, P^{95})	Number	Mean (SD)	Hypersensitivity (PPT: P^5, P^{10}, P^{25})	Hyposensitivity (PPT: P^{75}, P^{90}, P^{95})
PPT back	275	382 (179)	135, 174, 250	475, 629, 726	334	541 (241)	194, 248, 346	717, 916, 999
PPT leg	277	394 (189)	156, 183, 246	506, 669, 779	334	520 (234)	218, 255, 344	665, 933, 998
PPT neck	277	245 (121)	92, 110, 155	319, 411, 488	334	353 (200)	125, 150, 214	434, 635, 793
PPT wrist	276	360 (144)	162, 194, 256	448, 568, 942	336	492 (217)	197, 244, 340	617, 825, 940
Pain threshold (CPT = °C)	Number	Mean (SD)	Hypersensitivity (CPT: P^{95}, P^{90}, P^{75})	Hyposensitivity (CPT: P^{25}, P^{10}, P^5)	Number	Mean (SD)	Hypersensitivity (CPT: P^{95}, P^{90}, P^{75})	Hyposensitivity (CPT: P^{25}, P^{10}, P^5)
CPT wrist	274	13.7 (8.3)	26.9, 25.6, 22.0	5.2, 5.0, 5.0	328	10.8 (7.3)	25.7, 23.6, 16.0	Not estimated[a]

[a] 38.8% of males reached the 5 °C cut off for CPT.
CPT = cold pain threshold; PPT = pressure pain threshold; P^5 = 5th percentile; P^{10} = 10th percentile; P^{25} = 25th percentile; P^{75} = 75th percentile; P^{90} = 90th percentile; P^{95} = 95th percentile.

geographic location and ethnicity [59]. This largely Caucasian cohort from a southern hemisphere, Mediterranean-style climate may differ in pain sensitivity from other cohorts due to ethnicity, lack of exposure to cold temperatures, sunlight exposure and inflammatory status [60]. Further comparison with other reference data testing similar sites is not appropriate, as these previous studies have included participants from the general population [8,61], without reporting pain status, thereby complicating interpretation. Including participants with musculoskeletal pain introduces variability into results and limits the post hoc use of data for reference purposes [5]. Screening for pain status here used the question "do you have any current body pain?" Therefore, we cannot exclude that some participants may have experienced pain at another time.

3.1. Pain sensitivity vs. site

The multivariable analysis for PPT measures showed the neck and wrist site to be significantly more sensitive than the back site. Pressure stimulates deep tissue nociceptors [62] and the variation

Table 3
Univariable and multivariable regression model for pressure pain thresholds (kPa).

Variable	Univariable		Multivariable	
	Coefficient (95% CI)	*p*-Value	Coefficient (95% CI)	*p*-Value
Site				
Back	Ref	<0.001[d]	Ref	
Leg	−4.7 (−15.5, 6.06)	0.390	−5.7 (−19.9, 5.5)	0.321
Neck	−164.8 (−175.6, −154.0)	<0.001	−165.2 (−176.4, −154.0)	<0.001
Wrist	−36.6 (−47.4, −25.8)	<0.001	−36.8 (−48.0, −25.6)	<0.001
Sex				
Females	Ref		Ref	
Males	131.6 (103.1, 160.2)	<0.001	141.6 (109.0, 174.3)	<0.001
Ethnicity				
Caucasian	Ref			
Non- Caucasian	4.5 (−37.8, 46.7)	0.837		
Waist/hip ratio[a]	12.7 (−8.5, 34.0)	0.240[e]	−28.2 (−50.8, −5.6)	0.014
BMI				
Under	−53.3 (−158.2, 51.5)	0.319		
Normal	Ref	0.050[f]		
Overweight	41.6 (4.2, 79.0)	0.029		
Obese	−17.6 (−60, −25.5)	0.424		
SF12				
PCS ≥50	−2.1 (−5.2, 1.1)	0.196		
MCS ≥50	2.2 (0.6, 3.9)	0.007	33.0 (2.9, 63.0)	0.032
Smoke				
No	Ref			
Yes	35.3 (−7.1, 77.7)	0.102		
DASS21				
Depression	−1.2 (−3.2, 0.9)	0.260		
Anxiety	−1.1 (−4.3, 2.0)	0.483		
Stress	−2.8 (−4.9, −0.7)	0.009		
Activity				
MVPA (mins/day)[b]	3.0 (−3.0, 9.0)	0.375		
Sedentary time[c]	−1.421 (−3.26, 0.417)	0.130		

[a] Coefficient represents the expected change in PPT for a 0.1 change in waist/hip ratio.
[b] Coefficient represents the expected change for a 10 minute change in MVPA.
[c] Coefficient represents the expected change for a 1% change in sedentary time.
[d] Omnibus *p*-value for group difference = 0.000, and after adjustment for sex *p* = 0.000.
[e] Waist/hip ratio coefficient (95% CI) and *p*-value after adjusting for sex = −25.0 (−46.5, −3.6), *p* = 0.022.
[f] Overall *p*-value for group difference = 0.050, and after adjustment for sex *p* = 0.577.
CI: confidence interval, BMI: body mass index, DASS-21: depression anxiety stress scale 21, PCS: physical component summary, MCS: mental component summary, MVPA: moderate-vigorous physical activity, sedentary time = percentage of non-MVPA during wake-time.

Table 4
Non-linear tobit regression table for cold pain threshold (°C).

Variable	Univarible		Multivariable	
	Coefficient (95% CI)	*p*-Value	Coefficient (95% CI)	*p*-Value
Sex				
Female	Ref			
Male	−4.2 (−5.9, −2.4)	<0.001	−3.5 (−5.4, −1.6)	<0.001
Ethnicity				
Caucasian	Ref			
Non-caucasian	0.5 (−2.1, 3.0)	0.722		
Waist/hip ratio[a]	−2.0 (−3.3, −0.7)	0.002		
BMI				
Under	1.4 (−4.7,7.6)	0.651		
Normal	Ref	0.241[d]		
Overweight	−2.3 (−4.5, 0.1)	0.054		
Obese	−0.9 (−3.5, 1.7)	0.502		
SF12				
PCS ≥50	0.2 (−0.4, 0.3)	0.120		
MCS ≥50	−0.1 (−0.2, 0.0)	0.013	−2.5 (−4.4, −0.6)	0.011
Smoke				
No	Ref			
Yes	−3.0 (−5.6, −0.4)	0.022	−3.6 (−6.5, −0.8)	0.013
DASS21				
Depression	0.1 (0.0, 0 2)	0.090		
Anxiety	0.0 (−0.2, 0.2)	0.949		
Stress	0.1 (0.0, 0.2)	0.060		
Activity				
MVPA (mins/day)[b]	0.1 (−0.2, 0.5)	0.462		
Sedentary time[c]	0.1 (0.0, 0.2)	0.050		

[a] Coefficient represents the expected change for a 0.1 change in waist/hip ratio.
[b] Coefficient represents the expected change for a 10 minute change in MVPA.
[c] Coefficient represents the expected change for a 1% change in sedentary time.
[d] Overall *p*-value for group difference = 0.241, and after adjustment for sex *p* = 0.505.
CI: confidence interval, BMI: body mass index, DASS-21: depression anxiety stress scale 21, PCS: physical component summary, MCS: mental component summary, MVPA: moderate-vigorous physical activity, sedentary time = percentage of non-MVPA during wake-time.

Table 5
Reference value comparison.

Pain Threshold (PPT = kPa)	Females				Males			
	Number	Mean (SD)	Hypersensitivity (PPT: P^5)	Hyposensitivity (PPT: ^{P95})	Number	Mean (SD)	Hypersensitivity (PPT: P^5)	Hyposensitivity (PPT: ^{P95})
PPT back								
Waller[a]	275	382 (179)	135	726	334	541 (241)	194	999
Neziri[b]	75	260 (121)	119	528	75	398 (141)	200	653
PPT Neck								
Waller[a]	277	245 (121)	92	488	334	353 (200)	125	793
Neziri[b]	75	212 (74)	118	360	75	313 (94)	150	451
PPT wrist/hand								
Waller[a]	276	360 (144)	162	942	336	492 (217)	197	940
Magerl[c]	90[c]	255 (106)	Not reported	Not reported	90[c]	263 (175)	Not reported	Not reported
Pain threshold (CPT = °C)	Number	Mean (SD)	Hypersensitivity (CPT: P^{95})	Hyposensitivity (CPT: P^5)	Number	Mean (SD)	Hypersensitivity (CPT: P^{95})	Hyposensitivity (CPT: P^5)
CPT wrist								
Waller[a]	274	13.7 (8.3)	26.9	5.0	328	10.8 (7.3)	25.7	Not estimated[e]
Magerl[c]	90[d]	15.6 (7.2)	Not reported	Not reported	90[d]	11.2 (8.2)	Not reported	Not reported

[a] Age range 21.0–24.4.
[b] Age range 20–49.
[c] Age range 20–30.
[d] Number of all female or male subjects aged 15–75, decade 20–30 years: calculated from subjects between >15 and 35 years of age.
[e] 38.8% of males reached the 5 °C cut off for CPT.
PPT: pressure pain threshold; CPT: cold pain threshold.

seen in PPT between sites will reflect, at least in part, peripheral nervous system sensitivity that is also influenced by local anatomical variations in density of nociceptors and receptive fields [63]. Neziri [6] did not report testing for site differences for PPT, but comparing their back and neck site mean values suggests a smaller gap than our study, possibly reflecting the smaller sample size. The significant site variations support the need for site specific reference values from large cohorts.

3.2. Pain sensitivity vs. sex

The univariable and multivariable regression models for both PPT and CPT (Tables 3 and 4) show females being significantly more pain sensitive than males supporting the need for sex adjusted reference data. PPT and CPT regression models respectively shows PPT 141.6 kPa lower in females and CPT 3.5 °C higher in females. Higher pressure pain sensitivity in females is consistent with previous studies in pain free populations [6,9,64], mixed pain status populations [7,10,65], and pain populations [66,67]. Greater sensitivity to cold pain in females is consistent with previous studies in both pain free [6,9] and pain populations [66,68]. Systematic reviews have found females are consistently more pain sensitive to experimental pain than males across most pain modalities [19,69]. Studies investigating sex differences in pain sensitivity indicate reasonable evidence that psychological factors, social factors, coping strategies and differences in endogenous pain inhibition might partly explain these differences [70,71].

3.3. Pain sensitivity vs. BMI and WHR

In the univariable models unadjusted for sex, there was a non-linear association between BMI categories and PPT, however, this association attenuated when adjusting for sex (p = .577) and BMI categories were not considered for further multivariable modelling, consistent with previous findings from others regarding BMI and PPT [6]. In the current study, no association between CPT and BMI was identified, before or after adjustment for sex (p = 0.241 and 0.506 respectively), in contrast to a previous study [6] which demonstrated an association between less cold pain sensitivity and increasing BMI.

Although there was no univariable significant association between PPT and WHR, when adjusted for sex, higher WHR was significantly associated with increasing pressure pain sensitivity (p = 0.022) and the association remained significant in the multivariable model (Table 3). Conversely, increasing WHR was significantly associated with less cold pain sensitivity in the univariable model, but there was no significant association in the multivariable model. The association between PPT and WHR in this study controls for site differences, sex and psychological status and suggests increasing pain sensitivity as WHR increases. The significant association of WHR but not BMI with sensitivity to pressure maybe due to WHR being a better measure of central adiposity, whereas BMI does not take into account the distribution of body fat [72]. There is a strong association between WHR and metabolic risk, independent of BMI, which reflects central obesity [73,74]. Current evidence also demonstrates central obesity increases levels of circulating pro-inflammatory cells, and this finding suggests shared underlying mechanisms that could modulate both pain sensitivity and metabolic health [75,76].

3.4. Pain sensitivity vs. smoking

In our study, smoking was associated with less cold, but not pressure, pain sensitivity. In the multivariable model accounting for sex and mental well-being (SF12 MCS), the CPT of smokers was an estimated 3.6 °C lower (i.e.; less sensitive) than non-smokers. Findings from human studies investigating the association of smoking and pain sensitivity have been mixed, probably reflecting small sample sizes, different ages and health status of participants, and mixed methods [8,77,78]. Anti-nociceptive properties of nicotine on the central nervous system have been demonstrated [79] and combined with the human studies demonstrate that nicotine can have a significant but variable association with pain sensitivity. This highlights the need to include smoking as a confounder when investigating associations with pain sensitivity.

3.5. Pain sensitivity vs. psychological health

Regarding DASS-21 scores, the only significant univariable association identified was for the stress sub-scale with both PPT and CPT, however neither association was significant after adjustment for sex, in the multivariable model. In multivariable models, better mental wellbeing as measured by the SF12 MCS was associated with less pressure and cold pain sensitivity. Neziri [6] also reported a better SF-36 score was associated with less pain sensitivity. However, a systematic review found the association of depression and anxiety symptoms with pain sensitivity to be ambiguous, consistent with the current findings of different associations with different measures of psychological health [70]. The severity of symptoms may be important, with depressive disorder having an association with increased cold pain sensitivity [22]. Catastrophizing has also been shown to be associated with greater thermal pain sensitivity [68,80]. While there is some evidence of an association with psychological health and pain sensitivity, it may depend on the measure used, construct considered and level of symptoms.

3.6. Pain sensitivity vs. activity

There was no significant association of MVPA and sedentary time with pain sensitivity. Physical activity has been proposed to elicit exercise induced hypoalgesia via recruitment of endogenous pain modulatory systems [81]. The association of activity measured via accelerometry and pain sensitivity has only been investigated in one other small (n = 21) study. Here, evidence was demonstrated in female participants of an association between meeting activity recommendations and lower pain sensitivity, whereas sedentary time had no association [82]. Other studies [83,84] have used subjective self-report activity questionnaires, with lower pain sensitivity found in participants doing more vigorous activity. Investigations using specific laboratory based exercise interventions have found an immediate association between high level activity and reduced pain sensitivity in healthy participants [24,85,86]. Despite a large sample and valid activity measurement, our study did not find significant associations between activity and pain sensitivity. The variables MVPA and sedentary time used here might not be optimal to capture how physical activity is associated with pain sensitivity.

In conclusion, this study currently provides the most comprehensive sex specific reference value data for young adults aged 21–24 years of pressure pain threshold at four body sites and cold pain threshold at the dorsal wrist. This large cohort provides more robust values than existing, smaller studies and further, the population-based, non-clinical cohort provides generalisability and limits participant selection bias. These data will provide an important research resource to enable more accurate profiling and interpretation of pain sensitivity in clinical pain disorders in young adults. The robust and comprehensive data can assist interpretation of future clinical pain studies and provide further insight into the complex associations of pain sensitivity that can be used in future research.

Ethical issues

Ethics approval for the Raine Study Cohort 22 year follow up was obtained from the University of Western Australia (UWA) (RA/4/1/5202).

Author contributions

Significant contributions to this work were made by all authors listed: conception and design (RW, AS, POS, MS, LS), literature review (RW, AS, POS, HS, JMcV, LS), data collection (RW, AS, LS), statistical analysis (RW, AS, HS, LS), writing design (RW, AS, POS, HS, JMcV, LS).

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Conflict of interest

All authors declare no conflicts of interest (RW, AS, POS, HS, MS, JM, LS).

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