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The role of population-based cohorts in understanding the emergence and progression of musculoskeletal pain.

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The role of ~~observational~~ population-based cohorts in progressing the understanding of the emergence and progression of musculoskeletal pain

This article is a call to action for how ~~observational~~, prospective population-based cohorts (PCs) representative of the general population, and distinct from *clinical populations*, can help advance our understanding of the emergence and progression of musculoskeletal pain. The specific and novel focus of this article is on 'pain sensitivity in musculoskeletal conditions' [8] without a neuropathic component, as measured by quantitative sensory testing (QST), and currently the only feasible proxy for measuring pain sensitivity in large scale studies. We do not yet know in non-clinical populations when and how heightened pain sensitivity emerges in relation to musculoskeletal pain, or vice versa, and the implications for pain chronicity across the lifecourse. Identifying and characterising the emergence and association of pain sensitivity, amongst other biopsychosocial factors, with musculoskeletal pain in non-clinical populations is important for progressing an understanding of the role of this potential contributor to pain complexity.

1. Why this call to action and why now?

Compelling evidence from the last decade highlights the leading contribution of musculoskeletal pain to the Global Burden of Disease (GBD) [8] and critically, estimating the global burden of pain is now on the international research agenda [31]. Identifying risk factors for the emergence and progression of musculoskeletal pain, including heightened pain sensitivity, is critical especially given that current GBD estimates may underestimate the prevalence, mortality and morbidity of musculoskeletal pain [8]. In this context, the longitudinal and prospective design of PCs necessitates repeated measurements, thereby offering a temporal window to better characterize the relationship between pain sensitivity and trajectories into and out of musculoskeletal pain. Examples of PCs with data on both pain

sensitivity and musculoskeletal pain do exist (Table 1) as identified via searching Wiley, Medline and ScienceDirect databases (date of search, 08/04/2020) using search words "QST, pain sensitivity, musculoskeletal pain, cohort, population-based".

2. **Current insights on pain sensitivity and musculoskeletal pain conditions.**

One of the most significant knowledge advances in musculoskeletal pain in past decades relates to the role of the nociceptive system in the clinical pathophysiology of chronic pain [13,23,34,80]. Quantitative sensory testing refers to a set of psychophysical methods used to quantify somatosensory function, measuring responses to calibrated, graded, innocuous, or noxious stimuli (typically, electrical, mechanical or thermal) [17].

The use of QST to quantify pain sensitivity and nervous system function is cited from the late 1800's, with thermal methods to provoke noxious stimuli in humans recorded in 1884 [26]. The main application of standardised QST application has been in the field of neuropathic pain [37]. Since the 1990's, the use of QST to assess evoked responses to somatosensory testing in experimental animal, experimental human and patient models [5,15,19,40,41] of non-neuropathic musculoskeletal pain has accelerated. More advanced QST methodologies and novel QST equipment have been developed such as computer cuff for pressure pain sensitivity [3,24,52], better standardisation of testing protocols [60] and advances in the application of QST phenotyping for treatment response prediction [17]. Capture of dynamic QST measures such as conditioned pain modulation and temporal summation has been important as these 'relative' measures are less influenced by general baseline pain sensitivity.

Although equivocal, findings on pain sensitivity in musculoskeletal pain are well summarized across recent systematic reviews and meta-analyses of cross-sectional and prospective studies [19,30,38,40,68]. Emerging evidence from these and other studies suggest a correlation between heightened pain sensitivity (sensory 'gain') and persistence of musculoskeletal pain

[9,19,29,40,42,61], persistence of postoperative pain [43,53,54,79,81], severity of pain experience [68,69,78] and the development of musculoskeletal pain [25]. Sensitised central nociceptive pathways reflected in heightened pain sensitivity, also play an important role in persistent musculoskeletal pain [2] and potentially in the trajectory for future exacerbation of musculoskeletal pain [11].

While the understanding of the association between pain sensitivity in musculoskeletal pain is advancing, the role pain sensitivity (~~amongst~~along with other biopsychosocial factors [1,16,55]) and the influence of other biopsychosocial factors on pain sensitivity may have in the emergence of musculoskeletal pain and clinical trajectories [38], remains unclear. Interpreting QST data is challenging given these psychophysical measures are strongly regulated at multiple sites along nociceptive pathways and in the brain including influences on pain sensitivity from emotional and cognitive processes [56,66]. These same pathways may also be influenced by genetics, sex, environmental factors, medication, pain history and functioning of other biologic systems, including the endocrine and immune systems [16,20,21,39,45,46]. Yet comprehensive data on these factors and their temporal influence on pain sensitivity prior to and following the emergence of musculoskeletal pain are also lacking.

3. How might population-based cohorts help progress our understanding of pain sensitivity and musculoskeletal pain?

Progressing our understanding of pain sensitivity and the emergence and progression of musculoskeletal pain requires consideration of study design, methodologies and strategies to leverage current and future data. PCs vary in their nature and scope and can include i) birth cohorts, cohorts spanning a specific life phase or multiple life phases, ii) single generation or intergenerational investigation and designs, iii) a broad focus across health conditions

including musculoskeletal pain, or a specific focus on musculoskeletal pain [12,47,57,67] , iv) measures of physical, behavioural, self-report and biological data.

~~In progressing the understanding of the role of pain sensitivity in musculoskeletal pain, o~~One advantage of PCs is that they allow for repeated measures of pain sensitivity and concurrently identification of other important factors such as pain experience, physical activity, social context and psychological well-being. However, ~~to our knowledge~~ PCs have ~~previously~~ only captured pain sensitivity measures at only one time point, probably reflecting organisational and funding{Gilbert, 2021 #1709} challenges. ~~in individuals~~. QST collection at multiple time points requires numerous raters who are adequately trained and monitored for reliability of measurement. Understanding how pain sensitivity integrates temporally with multiple mediators and moderators can assist in identifying interdependency and trajectories into and out of pain, with the potential to identify critical treatment windows. Intergenerational PCs can assist the understanding of heritability of pain sensitivity and musculoskeletal pain by measuring environmental, genetic and behavioural factors [47,48,70,82]. PCs with a broad health focus may offer good protection against bias resulting from confounding due to the breadth of data covering potential and complex confounding factors of the association between pain sensitivity and pain experience [78].

Successful investigation of complex systems requires a complex systems approach study design to investigate interactions within the system [59]. Large datasets are required, increasing power and confidence in findings and allowing for contextualising of findings against geographic, cultural and ethnic influences. Such an approach requires harmonised and reliable data collection using best practice test protocols [4] with linkage of pain sensitivity and musculoskeletal pain data along other covariates such as mental health status, health care utilisation and costs [18]. Partnerships with other key international musculoskeletal

organisations including rheumatic health organisations are required to build capacity in systematically collecting, analysing and sharing high quality 'big data' [6,22,35] on pain sensitivity in musculoskeletal conditions. Organisations might include the European League Against Rheumatism, the International League Against Rheumatism, Osteoarthritis Research Society International, and the Global Alliance for Musculoskeletal Health and others, with the International Association for the Study of Pain taking a leadership role. There are opportunities to leverage and link data on pain sensitivity from longitudinal studies with use of the new ICD-11 coding for chronic musculoskeletal pain conditions [44,51,62,65,71,72].

The identification of a core minimum data set of QST measures that could feasibly be measured in PCs is required to minimise participant burden whilst developing a comprehensive, high quality data base. A minimum data set would include specific test stimuli (mechanical, thermal, electrical and chemical) and static and dynamic measures (conditioned pain modulation, temporal summation) of evoked pain in deep tissues and cutaneous tissues. Birth PCs in particular provide an opportunity to capture pain sensitivity measures before the emergence of musculoskeletal pain, allowing for investigation into how early life factors and critical developmental transition periods such as adolescence into adulthood may influence pain sensitivity and subsequent pain experience [10,77]. With QST feasible from at least 6 years of age [7], critical time points at which to collect pain sensitivity measures across this developmental period from young children to young adults requires identification.

However, PCs also have some design-specific limitations. Increasing attrition over time can result in a significant volume of missing data with the cohort becoming less representative of the general population. Financial costs and participant burden can compromise the breadth, detail and frequency of data collection, particularly in more broadly focused PCs. Mobile, bedside QST protocols can potentially assist by reducing attrition and participant burden,

particularly for those with chronic pain or multimorbidity. Finally, causality can never be definitively proven using PCs, as bias due to unmeasured confounding can never be ruled out [27,28], although modern methods of design and analysis are evolving to assist in minimising bias. Furthermore, the use of 'target trials' using data from PCs has been advocated in situations where RCTs are not feasible [28].

4. Conclusion

Despite substantial progress in elucidating nociceptive mechanisms in musculoskeletal pain and understanding pain sensitivity, the translation of evidence to: i. inform improved patient outcomes [13]; ii. guide global health policy initiatives [8] and; iii. identify phenotyping targets in clinical trials [14,17], remains challenging. Using PCs can address gaps in current knowledge by improving our understanding of pain sensitivity, and other factors, in relation to the emergence and progression of musculoskeletal pain. This call to action discusses considerations to inform a research agenda that can assist in addressing the global burden of musculoskeletal pain disorders.

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Table

Table 1: ~~Observational~~ Population-based cohorts representative of the general population investigating the association between quantitative sensory testing (QST) derived pain sensitivity data, musculoskeletal pain and other related measures[#]

Name (URL) and Geographic Location of Population Cohort Study	Initial recruitment year(s)	QST measures and body site	Average age or age range (years); sample size (N); sex (% female) for QST measures	Musculoskeletal pain measures	Key QST studies identified	Other key pain measures[¶]
The Raine Study (rainestudy.org.au) Western Australia, Australia	1989-1991 parents (Gen1) and their children born (Gen2)	PPT (wrist, neck, back, leg) CPT (wrist)	Gen2: 22 N=1067 50%	ÖMPSQ (22, 27-years), LBP measures (14, 17, 22, 27 years), neck posture and pain (17-years)	▪ Normative QST data at 22 years[75] ▪ Association between musculoskeletal pain and QST at 22 years[78] ▪ Association between early life stress and QST at 22 years[77] ▪ Association between menstrual pain severity and QST[64] ▪ Association between stress response and QST[50] ▪ Association between physical activity levels and QST[76]	Genetic, socioeconomic, lifestyle, sleep, physical activity, sedentary behaviour psychosocial, inter-generational data, work productivity, inflammation, stress response, lumbar spine MRI, gender health, HRQoL
			Gen1: 57 N=1092 58%	ÖMPSQ		
The Tromsø Study (en.uit.no)	Seven repeated surveys from		Tromsø 6: 30-87 N=10,486*	Presence of chronic pain, pain	▪ Association between persistent	Inflammation, stress response,

Tromsø, Norway	1974-2016 consisting of birth cohorts and random samples	Cold-pressor test tolerance (dominant hand) PPT (fingernail non-dominant ring finger) HPT (non-dominant forearm)	53%	distribution & characteristics (location, onset, intensity, impact on ADLs, distress levels)	▪ post-surgical pain and QST[33] ▪ Inflammatory mechanisms and QST[32]	physical activity, sedentary behaviour, sleep, persistent post-surgical pain, chronic disease (including cardiovascular, diabetes, osteoporosis), psychological, lifestyle, socioeconomic
			Tromsø 7: 40-99 N=21,083 53%	As for Tromsø 6		
Northern Finland Birth Cohort Study (oulu.fi/nfbc/) Oulu & Lapland, Finland	Children with expected date of birth in 1966 (NFBC 1966)	PPT (wrist, neck, back, leg) CPT (wrist)	46 (NFBC 1966) N=5,861 47%	ÖMPQ, STarT Back Tool,	▪ Association between endometriosis and QST at 46 years[74] ▪ Association between dental fear (anticipatory pre-visit and treatment) and QST at 46 years [36]	Genetic, lifestyle, socioeconomic, behavioural, inflammation, psychosocial dental, lumbar spine MRI, physical activity, gender health, dental health
The Danish study of Functional Disorders (DanFunD) (frederiksberghospital.dk) Denmark	2015	PPT (leg, neck) Cold pressor test (dominant hand) CPM	18-70 N=2,151 53%	Presence of pain from muscles or joints, Fibromyalgia Syndrome, Whiplash Associated Disorder	▪ CPM and pressure pain sensitivity in the adult Danish general population [63]	Irritable bowel syndrome, chronic fatigue syndrome, cardiovascular disease, diabetes, respiratory diseases, allergies, asthma

Adolescent Pain in Aalborg-2011 Denmark	2011	PPT (4 knee sites, tibialis anterior)	15-19 N=79 100%	Pain measures, Knee injury and Osteoarthritis Outcome Score	▪ Increased pressure pain sensitivity in female adolescents is associated with patellofemoral pain syndrome[58]	Demographic data, sports participation, HRQoL
Orofacial Pain: prospective evaluation and risk assessment (OPPERA) North Carolina, Maryland, New York & Florida, USA	2006-2008 (people free of TMD)	PPT (3 facial sites, neck, elbow) Heat pain sensitivity (forearm: threshold, tolerance, rating of suprathreshold stimuli, TS) Mechanical pain sensitivity (hand: threshold, tolerance, ratings of suprathreshold stimuli, TS)	18-44 N=2,737 N/A	Identify phenotypic and genetic predictors of first-onset TMD pain symptoms	▪ Pain sensitivity is associated with development of temporomandibular disorder[25] ▪ Demographic predictors of pain sensitivity[49]	Autonomic measures (cardiovascular), Short Form Health Survey, psychosocial
TwinsUK cohort (twinsuk.ac.uk) UK	1992	HPT (volar forearm)	N/A N=2,500 N/A	Fibromyalgia, low back pain, pelvic pain, knee osteoarthritis	▪ Association of inflammatory markers with heat pain sensitivity and osteoarthritis pain [73]	

[#] Population-based cohort studies investigating the association between QST-derived pain sensitivity data and musculoskeletal pain identified from a search of Wiley, Medline and ScienceDirect databases using search words “QST, pain sensitivity, musculoskeletal pain, cohort,

population-based"; ¶See study URL and publications for detail; PPT, Pressure pain threshold; CPT, Cold pain threshold; HPT, heat pain threshold; TS, temporal summation; CPT, Conditioned pain modulation; TMD, Chronic temporomandibular disorder; HRQoL, Health related quality of life; * cold-pressor tolerance; ÖMPSQ, Örebro Musculoskeletal Pain Screening Questionnaire; LBP, low back pain; N/A, not available; MRI, magnetic resonance imaging