Title: The need for pediatric specifications for chronic pain diagnoses in ICD-11

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Chronic pain is a leading global health challenge [14], and estimated to impact at least 20% of the world's adult population [11]. This high prevalence is also starkly present in the pediatric population. Although the data are varied, up to 40% of youths experience weekly pain over a period of six months [10]. The burden of chronic pain may impair quality of life and negatively impact lifespan development [28]. As prevalence rates for chronic headaches, abdominal and musculoskeletal pain increased over the past decades [1,12,21], this "epidemic" poses an enormous challenge on our society and health care systems. The rate of pain persistence into adulthood is high, and young adults with a history of chronic pain are at higher risk for mental health problems conferring greater susceptibility for chronic disease [5]. Only timely identification, accurate diagnoses and early interventions during the onset of childhood pain can interrupt these unfavorable trajectories.

The inclusion of an independent category for chronic pain in the 11th version of the International Classification of Diseases (ICD-11) has been an important step towards the legitimization and standardization of chronic pain [31]. The drive was to highlight chronic pain as an independent condition, enhance visibility within the health care sector and facilitate diagnostic classification and implementation to align treatment pathways to chronic pain subtypes [27,31]. Valid and reliable chronic pain diagnoses are also important prerequisites to inform research agendas, health policies, and resource allocation [3]. However, the ICD-11 chronic pain definitions currently do not include pediatric-specific information and diagnostic criteria and scientific background about the respective entities have been derived from adult data. To date, field testing trials that have demonstrated diagnostic certainty, specificity, interrater reliability and utility have only been conducted in adult populations [3,18]. Because of differences in the neurodevelopmental biology and clinical phenotypes of chronic pain conditions between the adult and pediatric population, current ICD-11 definitions might not fully apply to younger individuals. For example, diagnosis of migraines using the International Classification of Headache Disorder-I (ICHD-I) diagnostic criteria in children resulted in high specificity, but low sensitivity [21]. Subsequent amendments proposed by the International Headache Society Committee in the second edition

(ICHD-II) to decrease in minimum duration of attacks to one hour was associated with an increase in the prevalence of migraine diagnoses from 11% to 28%, with an increase in diagnostic sensitivity (from 21% to 53%), while maintaining a specificity of 100%.

A key difference between children, adolescents and adults lies in their stages of neurodevelopment. Although there are similar neuroanatomical alterations such as lower grey matter density and functional hyperconnectivity in both adults and children with chronic pain compared to healthy controls [4], the nervous system undergoes substantial structural and functional maturational changes until young adulthood. Cortical gray matter density decreases, potentially as a consequence of synaptic pruning [29], and white matter fractional anisotropy, representing myelination and/or axonal packing, increases [20]. These neurodevelopmental changes occur at variable rates for different cortical networks up to the end of young adulthood. In contrast to adults, younger people's functional maps are more diffuse, less specialized, and comprise weaker long-range connections [15]. This indicates the remarkable transition from large undifferentiated local systems to specialized neural networks spanning distant regions [9], such as the pain connectome [19]. As chronic pain is related to changes in cortical networks which are still immature in the pediatric population [2], pain chronification may be underpinned by a different neurobiological substrate in children and adolescents compared to adults.

Accordingly, clinical characteristics of certain chronic pain conditions may differ between the adult and pediatric populations [16,24]. As introduced above, the manifestations of primary headache disorders are age dependent. Besides the shorter duration, migraines in children are primarily experienced as bilateral frontal headaches [25]. In contrast, adults commonly report unilateral prolonged headaches in the ocular or temporal regions [6]. These differences may reflect developmentally related phenotypic differences, and a disease progression that should be viewed as a continuum throughout the lifespan. Pediatric criteria in the ICDH were developed based on a systematic approach with collation of expert opinions, field testing of proposed criteria and inclusion of new scientific evidence [22,23]. Concurrently, since the 1980s, the Rome foundation has advanced

the development and classification of gastrointestinal disorders with a particular attention to age-based classifications (pediatric Rome criteria) [26]. This is evidenced in the evolution in the conceptualization of functional abdominal pain conditions [7]. For example, in the most recent update (Rome IV), subtypes of irritable bowel syndrome (IBS) in children were introduced to mirror the adult classification system. These steps were taken to refine pediatric research and enhance treatment opportunities for children and adolescents [8]. The importance of age-based diagnostic criteria is also evident in complex regional pain syndrome (CRPS) in which children manifest higher incidence of lower extremity involvement and colder skin temperature of the affected limb with less edema [30]. Along with the great strides that have been made to reclassify CRPS as a chronic primary pain syndrome in the ICD-11 [17], an important next step may be to include pediatric specifications within the CRPS criteria description.

The need for pediatric criteria is clear. However, demarking the transitions from childhood to adolescence into adulthood, and therefore defining criteria applicability is not trivial. The World Health Organization (WHO) definition of adolescence spans from 10 to 19 years [33]; hence, adulthood commencing at 20 years of age. However, the continuum of chronic pain over the lifespan is evident as 17% of adults with chronic pain report onset of pain in childhood [13], and over 60% of children with chronic pain experience its persistence as adults [32]. This highlights the need for diagnostic systems that account for the gradual physical, physiological and neurocognitive development across the lifespan. Including pediatric information within existing ICD-11 diagnostic codes could be a first step in this direction.

We strongly encourage discussions to (i) identify ICD-11 diagnostic codes that need additional pediatric information and (ii) examine whether there are chronic pain conditions unique to children currently not coded in the ICD-11. Pediatric specifications to the ICD-11 should then be proposed and tested for exhaustiveness and mutual exclusiveness, interrater reliability and practicability as well as their impact on treatment decisions and outcomes.

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Conflict of Interest. The authors declare that they have no conflict of interest.

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