REVIEW ARTICLES



Chronic pain epidemiology and its clinical relevance

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Editor's key points

- Identifying risk factors allows development of healthcare strategies to reduce the burden of chronic pain.
- Around 20% of the population may be affected, with a huge impact on the wider society.
- Some risk factors cannot be changed (e.g. gender, age); others can be modified (e.g. pain severity, mood).
- Further epidemiological studies are an essential part of a chronic pain research strategy.

Summary. Chronic pain affects \sim 20% of the European population and is commoner in women, older people, and with relative deprivation. Its management in the community remains generally unsatisfactory, partly because of lack of evidence for effective interventions. Epidemiological study of chronic pain, through an understanding of its distribution and determinants. can inform the development, targeting, and evaluation of interventions in the general population. This paper reviews current knowledge of risk markers associated with chronic pain and considers how these might inform management and prevention. Risk factors include socio-demographic, clinical, psychological, and biological factors. These are relevant to our understanding of chronic pain mechanisms and the nature of, and responses to, current and future treatments.

Keywords: chronic pain; pain, psychological variables; risk; statistics, epidemiology

Epidemiology is the 'study of the distribution and determinants of health-related states or events in specified populations and the applications of this study to control health problems'. Good epidemiological research on chronic pain provides important information on prevalence and factors associated with its onset and persistence. Improving our understanding of associated factors will inform our clinical management, limiting severity, and minimizing disability.

There is a strong argument that the most recent estimations of global burden of disease have underestimated the contribution of chronic pain.² By 2030, the WHO predicts that the four leading contributors of global burden of disease will be unipolar depression, coronary heart disease, cerebrovascular disease, and road traffic accidents.3 Chronic pain is an important co-morbidity associated with all of these. But chronic pain is more than just a co-morbidity of other identifiable disease or injury. Chronic pain is now acknowledged as a condition in its own right, underpinned by an agreed set of definitions and taxonomy.^{4 5}

Approximately 20% of the adult European population have chronic pain⁶ and, in addition to the physical and emotional burden it brings, the financial cost to society is huge, currently estimated at more than €200 billion per annum in Europe and \$150 billion per annum in the USA.5 Fewer than 2% of sufferers ever attend a pain clinic⁶ with the remainder managed mainly in primary care, if anywhere.⁷

While important recent advances in understanding pain mechanisms bring the possibility of new treatments, management of chronic pain is nonetheless generally unsatisfactory; two-thirds of sufferers report dissatisfaction with current treatment and most chronic pain persists for many years.8 We need to understand the reasons for this, with a view to improving treatment.

In addition to research on the pathophysiology of pain mechanisms, it is important to understand the risk factors associated with the presence and development of chronic pain, as this will allow the design and targeting of preventive and management strategies. Risk factors include sociodemographic, clinical, psychological, and biological factors, and recent research has elucidated many of these, with potential clinical relevance. One important aspect is the translation of research on risk factors from animal or small human samples to the general population.⁹ This paper will review our current understanding of risk markers associated with chronic pain, considering how this might be applied to the prevention and management of chronic pain.

Socio-demographic factors associated with chronic pain

The socio-demographic factors associated with chronic pain are well described across different pain conditions¹⁰ (Box 1).



Box 1. Socio-demographic factors associated with chronic pain

- · Female gender
- Older age
- Lower socio-economic status
- Geographical and cultural background
- · Employment status and occupational factors
- · History of abuse or interpersonal violence

In addition to a female preponderance for chronic pain, women consistently report lower pain thresholds, lower pain tolerance, and greater unpleasantness (or intensity) with pain with different analgesic sensitivity. 11 There is some evidence for a biological basis for apparent sex differences in pain experiences involving oestrogens. 12 However, the greatest gender differences are seen in the prevalence of chronic pain syndromes.¹³ Recent evidence suggests that the occurrence of disabling chronic pain continues to rise with old age. Although the onset of pain per se does not have a clear relationship with age, 14 15 there is generally a higher prevalence of chronic pain in older age. 16 Given that the world's population aged >65 is likely to double in the next 40 years, treatment needs to take cognisance of painrelated co-morbidities and polypharmacy. Population-based studies of chronic pain have consistently shown that chronic pain occurrence is inversely related to socio-economic status¹⁷ 18 with evidence that people living in adverse socioeconomic circumstances experience more chronic pain and greater pain severity, 19 20 independent of other demographic, and clinical factors. There is also evidence of both geographical and cultural variation in occurrence of chronic pain.⁶

The occurrence of pain, or the extent to which pain interferes with life, can be influenced by demands, expectations, control and fear of re-injury at work, specific occupational factors, employer and co-worker reactions to pain, or even by broader issues such as the job market.²¹ There is a growing body of literature from large-scale national surveys that pain is more common among people who report a history of abuse and violence at any age, in both domestic and public settings.²² ²³ This effect appears to be additional to the risk caused by physical injuries and pain, and highlights the need to elicit any history of domestic, sexual, or criminal violence in assessing the propensity to chronic pain and in managing its impact. A prospective populationbased study in the North of England (EpifunD study) concluded that there was a strong relationship between lack of sunshine, lower temperatures, and pain reporting, postulating climate as a possible risk factor.²⁴ However, this relationship may be, at least in part, mediated through lifestyle factors associated with cooler and duller days (less exercise, poorer sleep, and higher reported boredom). Similarly, a seasonal effect suggests the potential role of vitamin D, low levels of which in some (but not all) studies have been shown to be related to the report of pain.²⁵

Although many of these risk factors are un-modifiable or not amenable to medical intervention, it is important to recognize them, as they inform a targeted approach to chronic pain assessment and management. Dedicated coding and inclusion within routinely collected data sources and disease registries will enable routine population and health system surveillance of chronic pain. This will also aid visibility, linking chronic pain to existing (better-funded) health priority areas such as cancer, injury, obesity, and healthy ageing.²⁶ The existence of both individual-level risk factors and population-level risk factors for the onset or persistence of pain suggests that opportunities for intervention exist at more than one level.¹⁷ Ignoring population-level factors and intervening exclusively on high-risk individuals (such as in specialist pain clinics) could limit options for reducing the overall community burden of chronic pain.

Clinical and psychological factors associated with chronic pain

Chronic pain

Perhaps the most important clinical factor for chronic pain at a specific site is pain (acute pain, or chronic pain at a different site). The more severe the pain and the greater number of pain sites, the more likely severe chronic pain.⁸ ²⁷ ²⁸ This highlights the importance of pain management, not just in the relief of suffering, but also as a preventive activity. As Bingel and colleagues²⁹ highlighted, neuroimaging of pain has evolved from providing evidence that pain is processed in the brain at all to a sophisticated, mechanism-orientated research tool that can address a plethora of specific aspects related to the processing, perception, and modulation of pain. Functional brain imaging has provided objective proof of pain perception both in experimentally-induced and in disease-related pain.³⁰ From this, we now know that chronic pain patients display an altered brain activation in response to acute pain stimuli.³² There is also some evidence to suggest that brain changes associated with chronic pain may be reversible after effective treatment.^{33 34} In healthy individuals, neuroimaging studies have found that grey matter plasticity can be induced by repetitive experimental noxious stimuli as early as 8 days (after daily pain stimulus for 8 consecutive days), and that this receded between 22 days and 12 months later.³⁵ That these anatomical changes within the brain occur in the early stages of pain (before pain is labelled as chronic) further suggests that early intervention will be important in preventing chronicity, though this remains to be tested clinically.

It is uncertain whether there is pre-existing brain vulnerability to chronic pain, or whether these changes arise as a result of chronic pain. Even if brain responses are found to be tracking pain, these could conceivably represent co-located non-nociceptive functions. Mindful of these caveats, future neuroimaging has the potential to optimize treatment or even offer personalized therapy, improve pain diagnostics in those who cannot communicate this and indicate targets for drug development. The same straight is a same straight as a same straight in the same straight in

Mental health and multi-morbidity

Anxiety, depression, and catastrophizing beliefs about pain are associated with chronic pain and with a poor prognosis in people with various pain conditions.^{38–41} The temporal relationship between chronic pain and mental health remains unclear and is likely bi-directional. There is evidence that top-down (central and cognitive) influences on pain perception may be greater than peripheral input, as exemplified by the analgesic effect of placebo. 42 It is postulated that placebo analgesia can be potentiated by increasing endogenous opioid tone (e.g. after exercise) and, conversely, that anxiety reduces this endogenous effect. Functional imaging experiments suggest that reducing anticipatory anxiety can be potentially sustained for a period of up to 3 weeks, with a long-term cognitive shift in nociceptive processing.⁴² This suggests an important role for relatively straightforward psychologically-based interventions in primary care, aimed at creating and managing expectations, and harnessing the placebo effect. Further research on the nature and activation of the placebo effect is required to maximize this potential.

In depressed patients, neuroimaging has provided evidence of disturbed prefrontal brain activity and a dysfunction of emotion regulation during experimental pain stimulation.43 44 This reinforces how factors, such as depression and anxiety associated with chronic pain, become part of the overall condition itself and augment the pain experience. A recent study from the UK in a chronic pain cohort found that sleep problems make depression worse in chronic pain, thus exacerbating a known risk factor. 45 Another prospective survey from Norway involving only women over a 17-yr period suggested that disrupted sleep and a higher number of non-specific health complaints were risk factors for chronic pain onset and persistence.⁴⁶ This ties in with work by Von Korff and colleagues⁴⁷ demonstrating that healthcare use in chronic pain patients over a 3-yr period was largely attributable to symptomatic and ill-defined conditions, lower priority chronic disease, acute disease, and mental healthcare and, more importantly, that lower healthcare use was associated with less severe pain and better psychosocial function regardless of cause. Addressing sleep problems in chronic pain patients may reduce chronic pain, lessen the risk of depressive illness development, and improve pain-related quality of life.

Chronic pain is more common among those with other chronic diseases than those without; this co-morbidity is associated with significantly poorer self-rated health, lower functional status, and lower ratings of overall quality of care. A recent study using a large New Zealand population cohort, found that the accumulation of stressful life events or physical and mental co-morbidity was independently associated with chronic pain. From an epidemiological point of view, this suggests that when investigating the contribution of co-morbidity (or adjusting for a confounding effect of co-morbidity), one may need to take into account the

presence of specific conditions and the accumulated load (count) of other co-morbidities. Clinically, the implication is that we need to address chronic pain as an important health component of multi-morbidity and chronic stress, and that doing so successfully might result in a corresponding improvement in overall health. Recent evidence has also shown that those with severe chronic pain have increased risk of all-cause mortality, independent of socio-demographic factors. In particular, those reporting severe chronic pain were more than twice as likely to have died 10 years later from ischaemic heart disease or respiratory disease than those reporting no or mild chronic pain. Therefore, chronic pain is a serious condition and risk marker requiring intensive management to minimize the detrimental impact on life and health.

Attitudes and beliefs about pain

In general, attitudes and beliefs about established pain are important predictors in identifying those who are likely to develop long-term and disabling pain.⁵⁴ ⁵⁵ A recent review concluded that women tend to cope better with pain when they use pain-attentional focus or re-interpreting pain sensation strategies, whereas distraction techniques may be more efficient among men.⁵⁶ Passive coping strategies (e.g. taking medication, resting, hot-cold packs) were associated with three times as many healthcare visits and doubling the level of pain-related disability.⁵⁷ compared with the use of active strategies (e.g. exercise). The development of effective self-management strategies, targeting relevant attitudes, is therefore an important step in reducing chronic pain and its impact. Based on epidemiological findings, there has been varied success with a public education campaign in changing public (and health practitioners') attitude towards back pain in Australia⁵⁸ with a reduced prevalence of reported back pain; however, in other areas, the effect was less apparent.⁵⁵ It remains unclear which communication strategies or media formats are most effective but more intensive, explicit and expensive media campaigns may be more effective than low-budget ones.

Genetic risk factors and heritability

Evidence from birth-cohort studies suggests that chronic pain conditions 'run in families', so that children of parents with chronic pain conditions are more likely to develop pain conditions themselves. ⁵⁹ ⁶⁰ Previous work has shown that sensitivity to painful stimuli and pain tolerability are, to a significant extent, determined by our genes. ⁶¹ ⁶² More recently, it has been shown that genetic effects in chronic pain are important alongside measured environmental factors in the development and severity of chronic pain. ⁶³

It is unlikely that there is a unique pain gene, rather that multiple genes are associated with the development, processing and perception of chronic pain.⁶⁴ The most studied gene in relation to pain is catechol-O-methyltransferase



(COMT), an enzyme that degrades neurotransmitters including dopamine. Although the list of proposed genes associated with chronic pain is constantly expanding, 64 no consistent results have been observed in genetic association studies. 65 This partly reflects the fact that candidate genes have generally been studied in animal samples or small human samples. Those that have been conducted in human population-based studies⁶⁶ 67 have found associations between β-2-adrenergic receptor (a target of epinephrine in the neuroendocrine signalling pathway) and a single nucleotide polymorphism on chromosome 5 with chronic widespread pain, but not the COMT gene and pain.⁶⁷ Genes may conceivably act on a number of levels to influence its expression, driving behavioural, and emotional responses. Distinguishing the influence of genes from other environmental sources of variation (maternal, socio-cultural, clinical, and psychological effects) represents a major challenge that requires large, well-phenotyped general population familybased samples, such as Generation Scotland (www. generationscotland.co.uk).⁶⁸

There is some evidence that pain reporting itself is a heritable phenotype based on evidence from radiographic degree of joint damage in twins.⁶⁹ There are also certain clinical pain-related traits that are particularly heritable (e.g. cold pressor pain, heat pain threshold, and pinprick hyperalgesia)⁶² in response to painful experimental stimuli. However, heritability is just a relative measure of genetic variation. The potential for genetic studies to underestimate the contribution of the shared environment is of particular significance for pain. An indication of the subtlety of gene action is evidenced in recent animal studies that have shown neural plasticity to be determined by epigenetic (DNA-modifying) interaction with environmental stimuli.⁷⁰ Recent findings indicate that older adults reporting chronic pain and high stress had significantly shorter chromosome telomere length than individuals reporting no chronic pain and low stress.⁷¹ Further research into the association of telomere length with chronic pain onset and the consequences of pain persistence is required.

Improved genetic knowledge will herald the discovery of novel biological pathways and molecular targets for analgesic action and drug development.⁷² Genetics also brings with it the promise of screening to help target individuals who might be susceptible to pain with a view to prevention and help identify those that might benefit from specific therapies, though it may be difficult to apply this to the individual in the clinic.⁷³ Gene-transfer techniques are under development as an approach to treating neuropathic pain, 74 though application in the clinic is some way off. A more immediate benefit of the new genetic insight into pain is more subtle.⁷⁵ The knowledge that a substantial part of the variation in pain perception has a genetic basis has the potential to inform clinical discussions with (genetically susceptible) patients about pain, its causes, responses and management in the same way as a family history of other chronic diseases (e.g. asthma and diabetes).

Translating epidemiology into the clinical setting

Recent work from the UK has shown promise of a novel approach to chronic pain consultations and assessment, based on elegant longitudinal epidemiological studies of risks and outcomes. Using identified risk factors, a stratified care approach to back pain was tested by predicting poor prognosis (StarT Back) in clinical and economic benefits compared with current best practice in primary care. 76 Although the effect size was relatively small, there was significant improvement in the primary outcome measure (disability) at both 4- and 12-month follow-ups and also in secondary outcome measures, including physical and emotional functioning, pain intensity, quality of life, days off work, global improvement ratings, and treatment satisfaction. This pragmatic study also moved beyond highly selected. specific study populations to a real-world primary care population, including multi-factorial effects of co-morbidities. This is an example of direct application of epidemiology research applied in the clinical setting. Others have shown that a collaborative approach in primary care may be more effective than one simple approach in those with chronic pain and concurrent depression,⁷⁷ ⁷⁸ again highlighting co-morbidity associated with chronic pain and the need for a multidisciplinary approach to treatment.

Conclusion

We need to recognize that multiple dimensions of chronic pain cannot be addressed by understanding nociception only. It is clear that socio-demographic, clinical, and genetic factors associated with chronic pain are important in identifying, designing, and targeting relevant interventions in chronic pain and that current research needs to integrate this epidemiological research towards the prevention and management of chronic pain.

Declaration of interest

None declared.

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