

Low back pain

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Low back pain

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Abstract | Low back pain affects individuals of all ages and is a leading contributor to disease burden worldwide. Despite advancements in assessment and treatment methods, the management of low back pain remains a challenge for researchers and clinicians alike. One reason for the limited success in identifying effective treatments is the large variation in the manifestations, possible causes, precipitating and maintaining factors, course, prognosis and consequences in terms of activity interference and quality of life. However, despite these challenges, steady progress has been achieved in the understanding of back pain, and important steps in the understanding of the psychological and social risk factors, genetics and brain mechanisms of low back pain have been made. These new findings have given impetus to the development of new diagnostic procedures, evidence-based screening methods and more targeted interventions, which underscore the need for a multidisciplinary approach to the management of low back pain that integrates biological, psychological and social aspects.

Chronic pain is one of the most costly and prevalent sources of human suffering, especially in, but not limited to, modern industrialized societies. Low back pain is normally considered as pain, muscle tension or stiffness localized below the costal margin and above the inferior gluteal folds, with or without sciatica (pain travelling down the leg from the lower back). Almost everyone has a brief, acute episode of low back pain during their lifetime. Although many people with back pain recover within 1 year, some will develop a chronic condition with fluctuating or persisting pain of low or medium intensity, interrupted by periods of no pain or pain exacerbation¹. When back pain persists for >3 months, it is (by consensus) no longer considered as a symptom but as a disorder in itself that is maintained by factors that might be different from the initiating causes. Chronic back pain can be associated with functional disability and work incapacity, and can affect quality of life. Often, back pain does not occur in isolation, as many individuals with back pain also report pain in other regions of the body. A higher number of painful body regions is associated with higher functional disability, more work absences, more severe feelings of depression and anxiety and reduced quality of life^{2,3}. The large majority of patients with back pain have nonspecific pain, whereby an underlying pathology or a nociceptive contributor has not been identified⁴.

The societal and economic costs of back pain are high, and indirect costs are usually higher than direct medical costs. In Australia, the total cost for low back pain was estimated at AUD\$9 billion in 2001, but only

11% of this amount was accounted for by direct health-care costs^{5,6}. Similar proportions have been observed in the Netherlands and the United Kingdom⁷⁻⁹. Although the costs associated with back pain in the Netherlands have reduced from €4.3 billion in 2002 to €3.5 billion in 2007, the costs are still substantial and constituted 0.6% of the gross national product in 2007. In all these estimates, the majority of costs were attributed to productivity losses.

Traditionally, back pain was considered as a result of injury (the so-called injury model). This model is overly simplistic; the association is modest between physical loads with structural degenerative changes and pathology of the vertebral column or supporting structures, and pathological findings have been observed in asymptomatic individuals. A biopsychosocial model of back pain has been developed in which biological factors with modest effect sizes interacting with other risk factors are likely to contribute to the development of chronic back pain. The non-biological risk factors include negative beliefs and expectations about pain, emotional responses, pain behaviours, perceptions about the relationship between pain, health and work and societal obstacles.

In the International Classification of Diseases 10th revision (ICD-10), diagnostic codes for pain conditions, including low back pain, are included but do not account for the heterogeneity of chronic back pain in particular. Thus, a new classification of chronic pain has been developed for ICD-11 (REF.¹⁰), in which chronic back pain is classified under a new entity, 'chronic primary pain'.

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Chronic primary pain is defined as pain in at least one anatomical region that persists or recurs for >3 months and that is associated with substantial emotional distress or functional disability and that cannot be better explained by another chronic pain condition¹¹. In patients with chronic back pain as a symptom of another disease — such as endometriosis, pancreatitis, aortic aneurysm, renal colic, inflammatory bowel disease or rheumatoid arthritis — it is coded under the new classification ‘chronic secondary musculoskeletal pain’. The fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) included a pain-specific mental disorder, but this diagnosis was not retained in DSM-5 owing to the uncertain importance of medically unexplained pain and the lack of clarity about what psychological factors are of relevance in explaining the symptoms, among other reasons¹².

This Primer presents the current state of the art of the epidemiology, diagnostic triage, risk factors, prevention and management of low back pain. This Primer also reviews the current knowledge on the mechanisms of back pain, including genetic risk factors, neurobiology and cognitive, behavioural and emotional mechanisms.

Epidemiology

Low back pain is a substantial burden to patients and society (FIG. 1). Indeed, in the 2016 Global Burden of Disease Study, low back pain was the leading cause of years lived with disability (YLDs) and was in the top 10 causes of YLDs in all 188 assessed countries¹³. This high ranking is in large part due to the high prevalence of low back pain. In one systematic review of 165 studies from 54 countries, the mean point prevalence of low back pain in the general population was ~18% and 1-month prevalence was ~30%. Lifetime prevalence was ~40% and was particularly high in individuals 40–80 years of age and in

women, the latter of which have a 20% increased risk of low back pain compared with men¹⁴. Socio-economically disadvantaged groups are much more likely to report persistent pain and substantial interference with daily functioning than socio-economically advantaged counterparts^{15,16}. The risk of developing recurrent low back pain within a year after the resolution of an episode of acute low back pain is estimated to be ~25%¹⁷.

Most of the epidemiological data on low back pain concern western countries in Europe, the United States and Australia, although the prevalence in other regions has been assessed in some studies. The highest point prevalence of low back pain has been reported in high-income countries (32.9%), with lower rates in middle-income countries (25.4%) and low-income countries (16.7%) in some studies¹⁴. In one systematic review, the mean point prevalence of chronic low back pain in Latin America was estimated as 31.3%¹⁸. Another systematic review demonstrated a point prevalence of 32% in adults and 12% in adolescents in Africa; the mean lifetime prevalence, on the basis of six studies, was 62% in adults and 35% in adolescents¹⁹. The authors conclude that the prevalence of low back pain in Africa is comparable to the prevalence figures in western jurisdictions¹⁹. Studies evaluating the epidemiology of low back pain in Asia are scarce but have suggested that low back pain is a health problem among economically productive age groups and is associated with functional limitations in daily life activities^{20,21}. In general, studies used different definitions of back pain, differences in duration, its onset and whether or not people sought health care for their back problems, which may have influenced the reported prevalence rates.

Children, adolescents and elderly individuals

Low back pain has been suggested to start early in childhood, continue into adulthood and persist in elderly individuals, at least in a part of the general population²², although valid cohort data to confirm or refute this hypothesis are not yet available. Studying the prevalence of low back pain in children and adolescents might allow intervention at an earlier stage in the development of low back pain in the future. On the basis of 10 studies, a meta-analysis estimated the mean point prevalence of low back pain as 12% in children and adolescents <19 years of age, with a mean lifetime prevalence, based on 30 studies, of 39.9%²³. The prevalence of low back pain in children increases with increasing age; for example, a prevalence of 1% and 6% has been reported in children 7 years and 10 years of age, respectively, with a prevalence of 18% in adolescents 14 years and 16 years of age²⁴. On the basis of a review of 56 studies, lifetime prevalence reaches adult levels by 18 years of age²⁵.

Regarding the elderly, one review showed that the peak prevalence of low back pain occurred in individuals between 40 and 69 years of age, after which the prevalence declines¹⁴. Similar results were obtained in another study if all types of low back pain were considered; however, if only more severe forms are included, the prevalence steadily increased in individuals ≥65 years of age²⁶. Whether the proportion of individuals with nonspecific low back pain differs between young and elderly individuals is unclear. However, the proportion

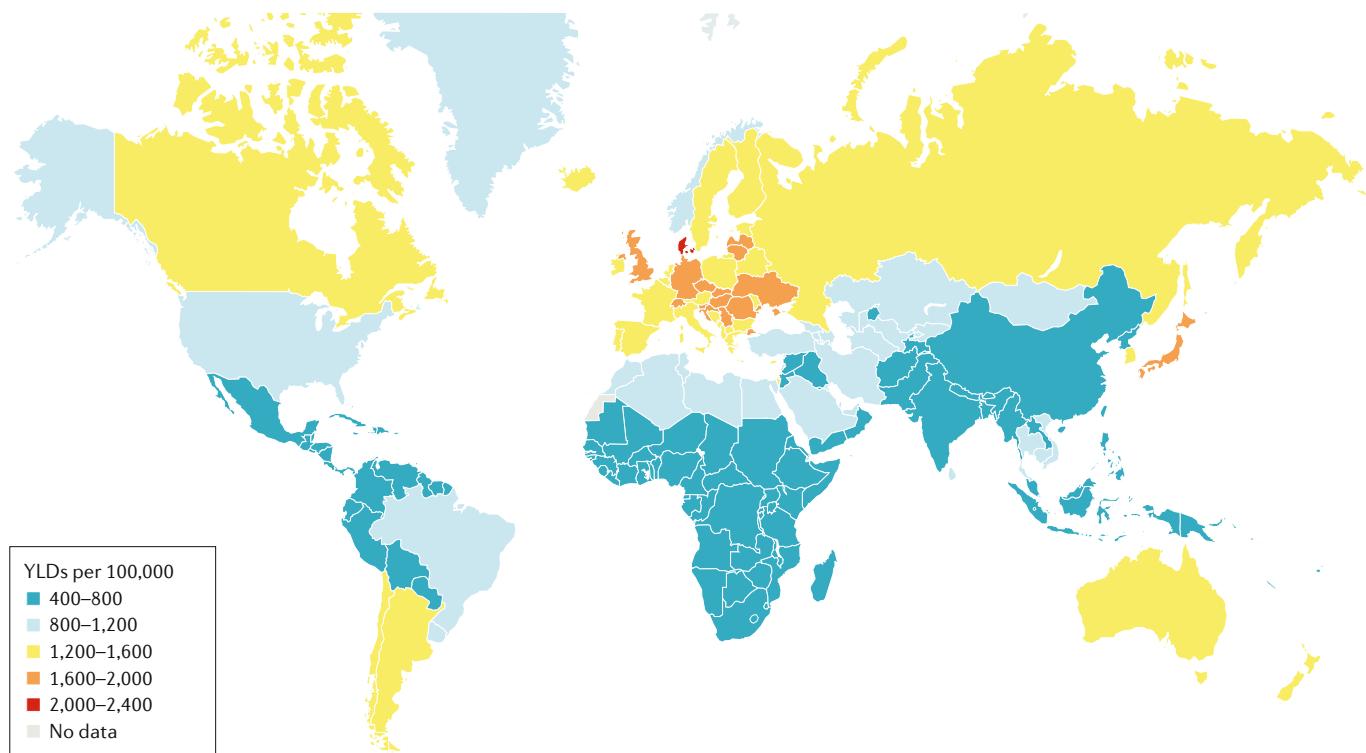


Fig. 1 | Years lived with disability for low back pain. Low back pain was one of the leading causes of years lived with disability (YLDs) in high-income, high-middle-income and middle-SDI (Socio-Demographic Index) quintile countries in 2016. Data from Global Burden of Disease Study, 2016 (REF.²⁴¹).

of individuals with comorbidities is most likely higher in elderly individuals.

Risk factors

Back pain is a complex and multifactorial condition that likely develops as result of the interaction between several risk factors²⁷. Given the high incidence of back pain, many individuals will experience an episode of acute low back pain at least once in their lifetime. However, some risk factors are associated with a higher occurrence of low back pain. Systematic reviews of risk factors for low back pain²⁸ and sciatica²⁹ have suggested that physical risk factors (such as prolonged standing and lifting heavy weights), an unhealthy lifestyle (such as smoking and obesity) and psychological factors (such as distress and the expectations that pain indicates bodily harm or injury) increase the risk of a back pain episode. In addition, manual tasks involving, for example, heavy loads, awkward postures and lifting objects not close to the body, as well as being distracted during an activity or task, were identified by patients as triggers of a new episode of sudden-onset acute low back pain³⁰.

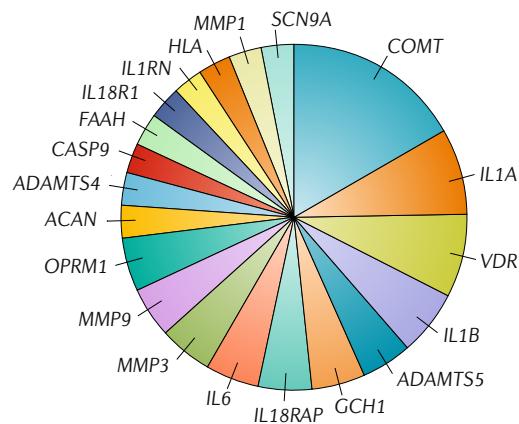
Genetic factors. The heritability of back pain has been estimated as 32–44% from twin studies^{31–33}. Familial genetic mutations with a high penetrance that have a Mendelian mode of inheritance and that co-segregate with Modic changes (pathological changes to the vertebral endplate, which can be observed using MRI) have been identified in two families with a history of sciatica³⁴. In addition, other mutations that contribute to diseases affecting the spine and cause back pain, such as

for spondylarthropathies, have been reported^{35,36}. Most data on the role of genetics in back pain have come from genetic association studies, which identified common polymorphisms with modest effect sizes; of these studies, genome-wide association studies (GWAS) are the gold standard and enable the estimation of the heritability of a trait that is attributable only to common genetic variants. On the basis of these studies, the heritability of back pain based on common genetic variants has been estimated as ~7%³⁷. However, only one back-pain-related GWAS meta-analysis on lumbar disc generation has been published to date, in which none of the cohorts had been studied in a previous meta-analysis^{38,39}. All other studies used a candidate gene approach in which pre-specified variants were studied on the basis of evidence-based assumptions of their involvement in the disease pathophysiology. Additional GWAS of back pain might provide new and reliable data on the genetic contribution to this condition, and current efforts are also currently underway to try to identify genetic variants associated with risk of acute episodes of back pain becoming chronic.

One review of genetic association studies on back pain revealed 47 studies that reported an association between 120 unique genetic variants (across 43 loci) and back-pain-related phenotypes (BOX 1). Of these genetic variants, 64 have been tested for association with various pain phenotypes (including low back pain) that were present for at least 3 months in a separate study, and 11 were replicated, reinforcing the role of some of these genes in the pathophysiology of chronic pain conditions, including back pain⁴⁰. Despite the identification of these risk variants, only the mechanisms underlying

Box 1 | Overview of genetics of low back pain

Several genes with at least two reported associations with back-pain-related phenotypes have been reported. Interestingly, the group of genes with replicated associations with the phenotype categories of pain intensity and lumbar disc degeneration do not overlap, indicating that distinct pathophysiological mechanisms are likely implicated in these conditions. Formal pathway analysis²⁴⁰ of all genes with reported associations with a back-pain-related phenotype revealed that the biological process extracellular matrix disassembly is statistically over-represented among them at a false discovery rate of 5%. Other relevant biological pathways significantly over-represented include inflammatory response and regulation of neurotransmitter levels. A summary of genetic associations with categories of back-pain-related phenotypes is presented in Supplementary Table 1.



the contribution of *GCH1* (REF.⁴¹) and *COMT*^{42,43} to several pain states, not exclusively back pain, have been investigated. *GCH1* encodes GTP cyclohydrolase 1 (GCH1), a rate-limiting enzyme for the synthesis of tetrahydrobiopterin (an essential cofactor for catecholamine, serotonin and nitric oxide production) that is increased in peripheral neuropathic and inflammatory pain states owing to enhanced GCH1 enzyme activity⁴¹. *COMT* encodes catecholamine-O-methyltransferase (COMT), which methylates and consequently deactivates catechol-containing substrates, such as adrenaline, noradrenaline and dopamine, and *COMT* variants that convey low enzyme activity contribute to increased pain via β_2 -adrenergic and β_3 -adrenergic receptors^{42–44}. Importantly, the majority of genetic associations with back pain have not been replicated, and the use of these variants to improve diagnosis and treatment of back pain remains to be ascertained and requires further study. In addition, as pain conditions share genetic pathways of vulnerability, variants that contribute to the diagnosis and treatment of back pain are most likely not specific and may, in fact, contribute to the diagnosis and treatment of other pain conditions⁴⁰.

Mechanisms/pathophysiology

The pathology underlying low back pain remains unknown in most cases, including individuals seeking medical care for acute or recurrent pain or chronic symptoms. Identifying the cause of back pain in these

individuals has been an elusive goal. As back pain is a symptom, the aetiology could be influenced by numerous factors, including local and systemic factors, such as structural failure of the musculoskeletal tissues; inflammatory and immunological responses; genetic predisposition; excessive static or dynamic loading; emotional state; behavioural and environmental factors; beliefs and expectations about what might happen with back pain in the future and whether it can be controlled; the social consequences following the expression of pain (increased empathy or rejection); and social systems^{45,46}. An individual's specific and variable response to a musculoskeletal insult might be a key determining factor for back pain.

The simplistic injury model of back pain

Despite the absence of a discernible illness or pathology in most individuals with low back pain, an injury model has long been used to explain this type of pain, particularly when pain occurs in the workplace. For many years, low back pain was considered a consequence of over-exertion or trauma from physically demanding activities, such as handling of heavy materials leading to damage or degeneration of the vertebrae, intervertebral discs or spinal muscles. However, this explanation is overly simplistic, particularly owing to the modest association of heavy physical demands with structural degenerative changes of these structures and pathophysiology⁴⁶. Several other lines of research have forced a re-evaluation of this 'injury' approach to low back pain. First, many episodes of acute low back pain do not fit within a physical injury model; in a study of 1,172 patients with acute low back pain, one-third could not recall a trigger for the episode³⁰. In addition, exposure to non-painful bodily triggers (such as being fatigued) or cognitive triggers (such as being distracted) was as hazardous as exposure to physical triggers (such as lifting weights), and exposure to both physical and non-physical triggers was associated with a higher risk of back pain than exposure to only one factor⁴⁷. Second, in cohort studies assessing the exposure to long-term suspected risk factors for back pain, job dissatisfaction and emotional distress were predictive of new back pain claims but not the physical aspects of work (such as spinal load) or the physical capacities of the worker (such as back muscle strength)⁴⁸. These data do not support a physical injury model of back pain.

Potential local contributors to low back pain

Although most patients with back pain lack a clear, identifiable pathology responsible for their symptoms, a fairly small portion of patients (<5%) have traumatic or osteoporotic fractures that may contribute to back pain development or persistence. Although rare (~1% of cases), back pain can also result from conditions such as neoplasia, infection and inflammatory arthritis that directly affect the spinal structures. Pain also can be referred to the low back from many visceral conditions, including diseases of pelvic organs, such as prostatitis, endometriosis, renal disease (such as kidney stones), gastrointestinal disease and aortic aneurism, among other conditions, which have been estimated to account for ~2% of patients seeking primary care for low back pain.

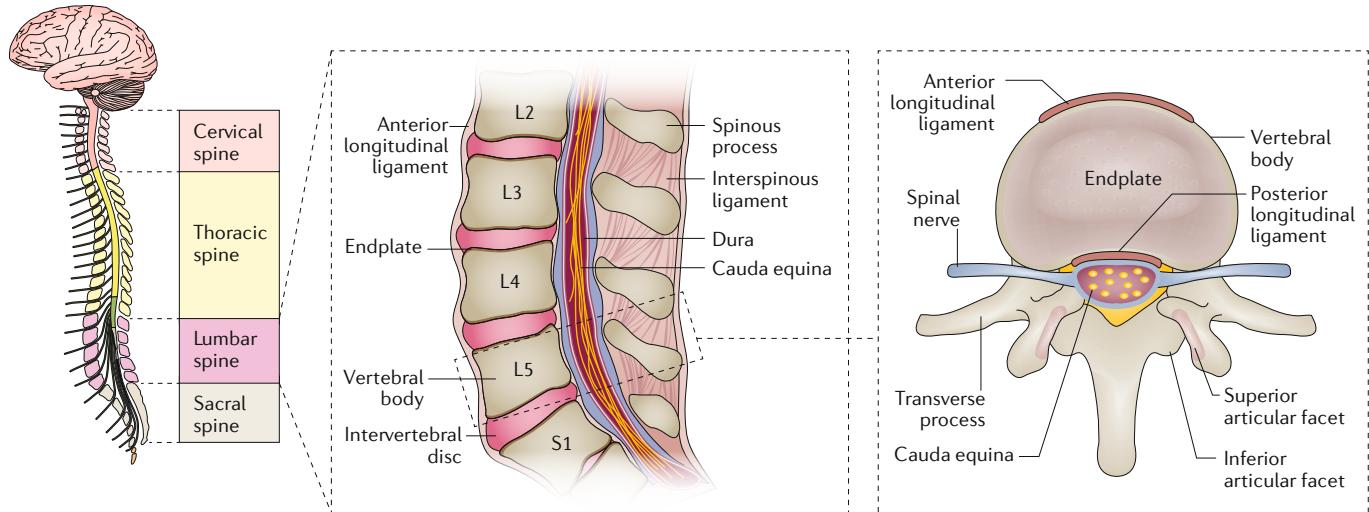


Fig. 2 | Vertebral anatomy. Although most patients with low back pain lack a discernible pathology that accounts for the pain, in extremely rare cases, damage to several structures within the vertebral column, including the facet joint, intervertebral disc, endplate or spinal nerves, can lead to back pain. Damage to these structures includes traumatic injury, inflammation or infection.

However, the main focus of this section is on lumbar spine contributors to low back pain.

Most structures of the lumbar region can contribute to low back pain if they are biochemically altered (for example, through inflammation) or damaged through degeneration or trauma (FIG. 2). Many spinal structures have sensory innervation, such as muscles, tendons, ligaments, fascia, facet joints, vertebrae, the outer annulus of the intervertebral disc, vascular tissue, the dura, nerve roots and dorsal root ganglia; however, the specific structures involved in common low back pain remain speculative.

Despite most of the intervertebral disc lacking sensory innervation, this structure has received the most attention as a nociceptive contributor of back pain, particularly with regards to disc degeneration. Indeed, the detection of disc degeneration by neuroimaging, often defined as a loss of signal intensity on T2-weighted MRI and disc narrowing, protrusion and extrusion, is modestly associated with back pain^{49,50}. Defects or lesions of the endplate beyond Schmorl's nodes (that is, protrusions of the nucleus pulposus of the intervertebral disc through the endplate into the vertebral body), such as erosion lesions, corner defects or calcification, have also received increasing attention. Although the aetiology of these endplate defects or lesions is poorly understood, variation in their character, distribution and prevalence suggests different aetiologies (for example, developmental, degenerative or traumatic) and that they represent different pathological processes⁵¹ with different implications for pain⁵².

In addition, Modic changes that affect the endplate, adjacent vertebral body and bone marrow have been evaluated as possible sources of back pain (FIG. 3). Three types of Modic changes can be detected via signal variations with different MRI sequences. Type 1 changes, which are associated with back pain⁴⁵, are speculated to represent bone oedema, inflammation and fibrovascular granulation tissue⁵³, whereas type 2 changes

represent fatty degeneration of the bone marrow and type 3 changes represent endplate sclerosis. Type 1 Modic changes have been attributed to physical trauma of the endplate, the localized action of inflammatory mediators, such as IL-1, and low-grade bacterial infection, with particular interest in *Cutibacterium acnes* (also known as *Propionibacterium acnes*) infection⁵⁴. Endplate disruption might be key for the development of Modic changes^{55,56}. Recently, the molecular and cellular features of bone marrow affected by Modic changes (type 1 and 2) and adjacent discs were compared with unaffected spinal levels in individuals undergoing multi-level spinal fusion for degenerative conditions. The results provided evidence of fibrogenic and pro-inflammatory crosstalk between bone marrow and adjacent discs at spinal levels affected by Modic changes, which may relate to pathogenesis and have implications for low back pain⁵⁷. In particular, large endplate lesions or defects and type 1 Modic changes have been found more frequently in individuals reporting back pain and seeking health care than Modic changes of any type (including type 2)^{49,52}. However, endplate defects and Modic changes are also present in individuals without back pain and, therefore, are of little use in differentiating those with or without back pain. Such findings by themselves might not be sufficient to cause back pain of such severity as to warrant reporting or seeking health care. Moreover, degenerative changes of spinal structures, including bone, endplates, discs, paraspinal muscle and vessels, develop together⁵⁸, making it challenging to identify specific findings or combinations of findings that might be more important contributors to back pain.

Other potential contributors to back pain are the facet joints, also called the zygapophyseal joints, spinal muscles and nerves. The facet joints are articulations of the posterior arch of the vertebrae and are innervated by the medial branches of the dorsal rami of the spinal nerve⁵⁹. In terms of spinal muscles, low back pain



Fig. 3 | Type 1 Modic changes. Type 1 Modic changes (arrows) correspond to bone oedema or inflammation and fibrovascular granulation tissue and can be observed in some patients with low back pain. However, these changes can be observed in asymptomatic individuals and, therefore, have been of little use to date in differentiating those with or without back pain. Adapted from REF.²⁴², CC-BY-4.0.

has been associated with smaller multifidus muscles, but the association with other paraspinal muscles is less clear, as is the association with muscle composition (for example, fatty infiltration). In an investigation specifically of dynamic trunk exercise to fatigue, there was no association found between resultant back pain intensity and spinal muscle damage, as indicated by increased intensity on T2-weighted MRI. Another study on exercise-induced pain suggested that initial reports of pain after intensive exercise were more strongly influenced by fear of pain, whereas the inflammatory process and pain sensitivity played a larger role for later pain intensity reports^{60,61}. In some individuals, pain typically radiates into the leg below the knee (such as in sciatica); in these individuals, the radiation pattern provides an indication of the involved segmental level. The pathophysiology of radicular pain is not fully understood but might be related to lesions that affect dorsal root ganglia or indirectly affect spinal nerves and nerve roots by ischaemia or inflammation of the axons within the nerve⁶². The spreading of the radicular afferent signal is a complex phenomenon, possibly with the involvement of the inflammatory cascade. Generally, most structures in the lumbar spine can be a potential source of pain, but reliable tests to identify the specific structure implicated for a given patient are lacking, as well as effective treatments specific for each structure.

MRI findings in asymptomatic individuals

The modest association of pain with the degree of musculoskeletal degenerative and pathological findings observed using imaging is not unique to back pain; the presence and degree of peripheral joint pain is also not

highly correlated with the extent of imaging findings of osteoarthritis. However, stronger associations have been observed in large, highly controlled studies of discordant knee pain and osteoarthritis within individuals, suggesting that substantial confounding and diluting of associations between relevant degenerative changes and pain reporting might be occurring. These findings challenge researchers to devise studies that more adequately adjust for confounding factors and to examine modifiers of the relationship between structural changes and other findings of interest and pain. Identifying anatomical and pathophysiological differences between individuals with and those without back pain who have similar extents of disc degeneration or other findings of interest on imaging might identify key factors of the pathology, modifiers and mechanisms of low back pain⁶³. In particular, inflammatory and immunological responses may be informative. It should also be kept in mind that disc, endplate, vertebral and other structural changes observed from imaging might contribute to low back pain, or alternatively might be markers of other conditions that lead to back pain.

Brain mechanisms

Brain imaging studies have begun to examine changes in brain structure and function that are related to back pain⁶⁴. Structural changes in grey matter have, for instance, been reported in the dorsolateral prefrontal cortex^{65–67}, thalamus, temporal lobes, insula and the primary somatosensory cortex in individuals with chronic back pain compared with healthy controls. Alterations in brain function have been investigated at rest and following peripheral stimulation. Changes in resting state activity and functional connectivity in patients with back pain compared with healthy controls have been observed in several brain regions, including the medial prefrontal cortex (mPFC), cingulate cortex, amygdala and insula^{68,69}. Following peripheral stimulation, patients with chronic back pain had increased activation of pain-related brain regions such as the primary and secondary somatosensory cortex and insula⁷⁰ and reduced activity⁷⁰ and functional connectivity⁷¹ of the periaqueductal grey, which is known to contribute to the top-down modulation of pain (FIG. 4).

The transition from an acute back pain state to chronic back pain might involve changes in the functional connectivity between the PFC and regions of the limbic system. Indeed, this was suggested in one longitudinal study that monitored individuals with subacute back pain for 1 year, after which back pain was persistent in some participants⁶⁸. In this study, participants with persistent pain showed an increased functional connectivity between the mPFC and the nucleus accumbens (NAc) at the initial assessment, compared with individuals who did not develop chronic pain⁶⁸, and structural and functional connectivity between the mPFC, amygdala and NAc was still different between groups after 3 years⁷². The consistent finding of smaller amygdala and hippocampus volumes over a period of several years in those who progressed to chronic pain suggests that these structural alterations might have existed before pain onset and, therefore, potentially predisposed

individuals to the development of chronic pain⁷². Other studies on back pain have demonstrated alterations in similar brain structures involved in cognitive-affective processing (such as the hippocampus and striatum)^{73–76}, and when compared with meta-analytic brain maps, the brain signature of chronic back pain more closely resembles that of emotion processing than that of acute pain⁷⁷. Additional functional changes in individuals with chronic back pain include reduced network efficiency⁷⁸ and whole-brain reorganization of functional connectivity^{79,80}, compared with healthy controls. Together, these findings advocate a perspective on chronic back pain that comprises structural and functional alterations in a dynamic network of interacting brain regions and that acknowledges the pivotal role of regions involved in pain-related processes beyond nociception in driving the development of chronic pain.

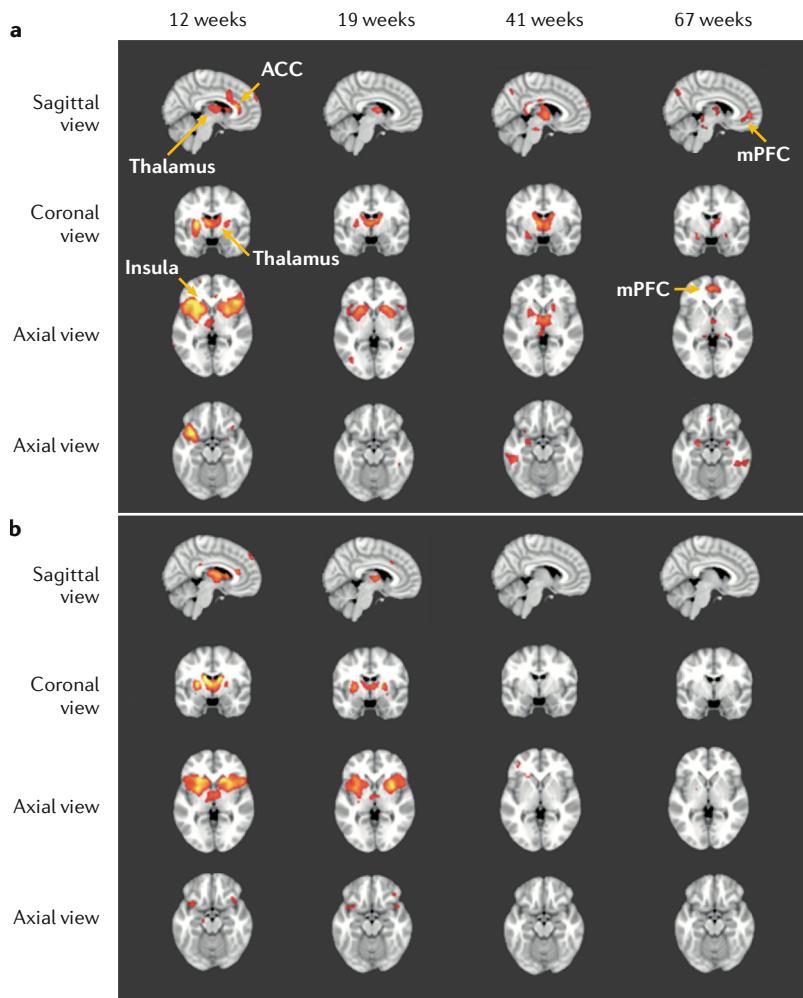


Fig. 4 | Changes in brain activity underlying the transition from acute to chronic back pain. Brain scans using functional MRI during early visits (12 weeks and 19 weeks) past pain onset show activation in brain regions commonly engaged during acute pain (such as the thalamus, anterior cingulate cortex (ACC) and insula). After ~1 year, significant activation differences among those who developed chronic pain (panel a) and those who did not (panel b) were found in the medial prefrontal cortex (mPFC) more closely linked to self-referential and emotional processing in the amygdala. Activation clusters are shown using a colour scale ranging from red (lower activation) to yellow (higher activation). The time points refer to the average duration past pain onset. Adapted with permission from REF.⁷⁷, Oxford University Press.

Cognition, emotion and behaviour

Pain is a motivational state that initiates early defensive and late recuperative behaviours, which primarily function to promote recovery from injury⁸¹. Predictions or expectations of the occurrence, magnitude and consequences of pain are generated on the basis of prior information about the state of the body (such as ‘this activity is likely to harm my back’). These predictions are influenced by a generative model of an individual’s own body (such as ‘my back is vulnerable’) and other metacognitions about health and illness (such as ‘there is nothing I can do to change my pain’ and ‘pain is always a sign of harm’). Predictions or expectations of pain can also be generated by an individual’s own experiences, in addition to verbal information and observations of what happens to other people in similar contexts⁸². From a Bayesian perspective, expectations of pain are compared with the actual sensation, which can confirm the prediction and the beliefs (a match) or, alternatively, lead to a prediction error that urges the individual to update these beliefs (a mismatch)^{83,84}. An individual’s homeostatic goal is to minimize prediction errors and to increase the accuracy of predictions (FIG. 5). Whether the prediction is corrected or not largely depends on the relative precision of the sensory input and the expectation of pain^{84–86}. If the sensory input is less precise, the perception will be more in line with the prior expectations and vice versa. Given the ambiguity and imprecise nature of low back pain, expectations can strongly influence the perception of pain, such that the expectation of back pain might be enough to increase its intensity or perceive innocuous sensations as painful^{87,88}.

In patients with back pain, misinterpretations of pain as a sign of physical harm⁸⁹ usually lead to pain-related fear and avoidance behaviours that further fuel the disability, depression and anxiety^{90–93}. Indeed, one meta-analysis demonstrated a moderate to large average sample size-weighted correlation coefficient of 0.42 (with a range of 0.33–0.45) for pain-related fear and disability in individuals with acute or chronic pain⁹⁴. Individuals reporting fear-avoidance beliefs had poorer work-related outcomes with subacute low back pain (that is, individuals with low back pain for between 4 weeks and 3 months), with odds ratios ranging from 1.05 to 4.64 in four cohort studies⁹⁵. By contrast, fearful beliefs in more-acute low back pain (with duration of <2 weeks) and chronic low back pain (duration of >3 months) did not predict return to work⁹⁵. These results suggest that modifying negative expectations regarding return to work might avoid delayed recovery and the development of chronic pain in individuals with low back pain during the subacute phase. In addition, one systematic review and meta-analysis demonstrated self-efficacy, psychological distress and pain-related fear as significant mediators of the effect of pain on disability⁹⁶.

The prediction of pain can be influenced by classical (Pavlovian) conditioning, which is the association of pain with neutral cues that precede the occurrence of pain. These cues can be non-painful tactile, visceral or proprioceptive sensations that activate the pain memory. As a result, these conditioned stimuli elicit defensive avoidance behaviour, which is adaptive in the

acute phase⁹⁷. However, excessive reliance on defensive behaviours can paradoxically maintain or increase pain-related fear⁹⁸ and, therefore, compromise daily activities, interfere with work and social participation and lead to negative affect⁹⁹. For example, avoidance behaviour precludes the possibility to test whether the triggers are still predicting pain or harm, thereby maintaining fear^{100–102}. In addition, generalization can occur, during which perceptual or conceptual variations of the original stimulus also elicit avoidance behaviour. One study demonstrated that patients with chronic musculoskeletal pain more strongly generalize their pain expectancies from a painful movement to movements that were never associated with pain than healthy controls¹⁰³. That is, patients may insufficiently discriminate between stimuli or situations that are safe from those that are painful. In addition, preliminary evidence suggests that hyperalgesia (the same stimulus eliciting a higher pain response than usual) and allodynia (a non-nociceptive stimulus eliciting a pain response) can be considered learned (conditioned) responses^{88,104}, explaining why the cortical representation of non-nociceptive stimuli is disrupted in people with chronic pain. For example, people with chronic back pain may have lower proprioceptive acuity, with disruptions in the perceived size and alignment of body parts¹⁰⁵.

Pain and avoidance behaviour can also be maintained by operant conditioning (law of effect), in which the valence of behavioural outcomes influences the likelihood that this behaviour will be maintained^{106,107}. For example, when individuals do something to avoid or reduce their pain, which has a beneficial effect on pain, they keep repeating it. Psychological treatments, and cognitive-behavioural therapy in particular, aim to challenge patients' beliefs and pain-outcome expectancies and encourage them to sample their interoceptive environment differently (see Management)¹⁰⁸.

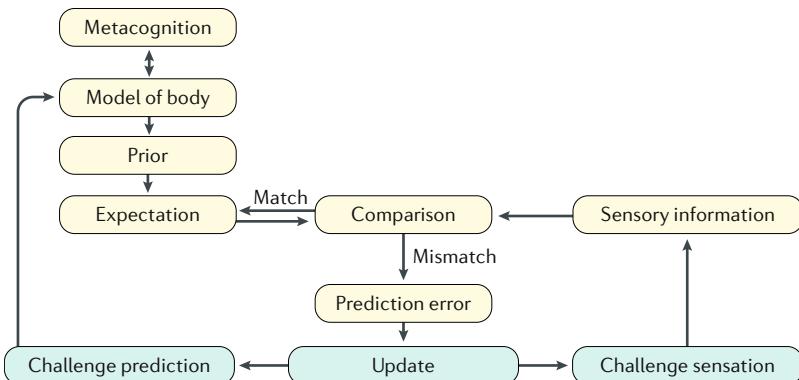


Fig. 5 | How expectations shape back pain. Expectations (such as ‘this event will cause pain’) are derived from an idiosyncratic and generative model of the body in pain with hierarchically structured beliefs. Metacognitions are high-level beliefs that include the possibility of control (such as ‘there is nothing I can do to relieve pain’), whereas a prior is a lower-level belief about a state of the body (such as ‘lifting objects increases the pain’). Expectations about upcoming sensations are compared with incoming sensory information (not restricted to nociception), and the difference between the expectation and the sensory input is called the prediction error. The individual’s homeostatic goal is to minimize prediction errors through at least two updating possibilities: confirming the expectation (the person feels what she/he expects; ‘match’) or learning (‘mismatch’). In the latter, updating the prediction is challenged and replaced by an adapted one (the person learns that it is different than expected). Learning may create more accurate predictions and a more valid generative model of the body.

Diagnosis, screening and prevention

Classification of low back pain

Clinical practice guidelines recommend a diagnostic triage approach in which patients with low back pain are classified into one of four broad categories: those with a visceral disorder (for example, patients with kidney stones), a specific spinal disease (such as axial spondyloarthritis), radicular syndromes or nonspecific low back pain¹⁰⁹. In primary care, the majority of patients have nonspecific low back pain (typically 90% of patients)^{110,111} and, when pain persists for >3 months, many of these patients will fit the ICD-11 criteria for chronic primary pain¹¹. Typically, <1% of back pain presentations to primary care are caused by visceral or spinal diseases^{112,113}. Identifying these disorders is important as they are managed differently from nonspecific low back pain or radicular syndromes.

Diagnostic work-up

A clinical assessment is used to identify patients with suspected specific spinal disease or visceral disorders who require further diagnostic work-up. Both non-specific low back pain and radicular syndromes do not require further initial diagnostic work-up, as their initial management is the same as for both disorders. However, if a patient does not respond to a therapy trial and is a candidate for surgery, imaging (for example, using MRI) is indicated to identify an abnormality that could be addressed by surgery.

Diagnostic work-up during the initial clinical assessment is warranted only in individuals with suspected spinal pathology or visceral disease. Red flags, such as unexplained weight loss, have traditionally been used to identify patients with a higher probability of these conditions (TABLE 1); however, few red flags have high diagnostic accuracy¹¹⁰. For example, some guidelines for the management of back pain endorse the use of the ‘thoracic pain’ red flag to screen for cancer, but the presence of thoracic pain has both a positive and a negative likelihood ratio of 1.0, which is not informative (the sign is equally common in those with and those without cancer)¹¹⁴. The most common problem with red flags is false positives; 80% of patients presenting to primary care have at least one red flag, although <1% of patients have a specific spinal pathology¹¹¹. Given this discrepancy, a more useful approach when deciding which patients require further diagnostic work-up is to rely upon the smaller subset of red flags with promising diagnostic accuracy and consider a combination of red flags in the context of a full clinical assessment¹¹⁵. In addition to the red flags, other flags have been assigned to different kinds of prognostic factors, including orange (psychiatric symptoms), yellow (cognitive, emotional and behavioural), blue (work-related) and black (system-related) flags¹¹⁶ (TABLE 1).

To identify patients who require further diagnostic work-up, some guidelines take into account the consequences of a missed diagnosis and the certainty of the diagnosis; for example, the imaging guidelines for the American College of Physicians recommend deferring diagnostic work-up pending a trial of therapy in patients with a low suspicion of cancer but suggest immediate

Table 1 | ‘Flag’ model of low back pain

Flag	Nature	Examples
Red	Alerting features that when present raise suspicion of serious pathology	<ul style="list-style-type: none"> • New bladder or bowel dysfunction (possible cauda equina syndrome) • Intravenous drug use, fever or recent infection (possible spinal infection) • Previous history of cancer (possible vertebral metastases)
Orange	Psychiatric symptoms	<ul style="list-style-type: none"> • Clinical depression • Personality disorder
Yellow	Beliefs, appraisals and judgements	<ul style="list-style-type: none"> • Unhelpful beliefs about pain: indication of injury as uncontrollable or likely to worsen • Expectations of poor treatment outcome • Delayed return to work
	Emotional responses	<ul style="list-style-type: none"> • Distress not meeting criteria for diagnosis of mental disorder • Worry • Fears • Anxiety
	Pain behaviour (including pain coping strategies)	<ul style="list-style-type: none"> • Avoidance of activities due to expectations of pain and possible re-injury • Over-reliance on passive treatments, such as hot packs, cold packs and analgesics
Blue	Perceptions about the relationship between work and health	<ul style="list-style-type: none"> • Belief that work is too onerous and likely to cause further injury • Belief that workplace supervisor and workmates are unsupportive
Black	System or contextual obstacles	<ul style="list-style-type: none"> • Legislation restricting options for return to work • Conflict with insurance staff over injury claim • Overly solicitous family and health-care providers • Heavy work, with little opportunity to modify duties

Flags refer to potential risk factors for the development of persistent pain and associated disability: these are suspicion of serious biological pathology (red flags); psychiatric symptoms that probably require specialist mental health referral (orange flags); psychological risk factors, such as fears and unhelpful beliefs (yellow flags); workers' perceptions that their workplace is stressful, unsupportive and excessively demanding (blue flags); and observable characteristics of the workplace and nature of the work as well the insurance and compensation system under which workplace injuries are managed (black flags). Adapted with permission from REF¹¹⁶, Oxford University Press.

further diagnostic work-up of individuals with suspected cauda equina syndrome (whereby compression of the nerve roots of the cauda equina causes loss of motor and sensory function) and infection (such as epidural abscess) owing to the adverse consequences of delayed diagnosis¹¹⁷. The precise diagnostic work-up depends on the suspected underlying disorder. Patients with suspected vertebral compression fracture require imaging of the vertebral column to confirm or exclude the diagnosis. Referral to a rheumatologist is indicated in those with a strong suspicion of axial spondyloarthritis, whereas referral can be delayed in those with lower suspicion until more scientific evidence becomes available.

Screening for risk of chronic pain

Although many patients who seek care for an episode of acute low back pain improve, ~10–15% of patients develop chronic pain and disability^{115,118,119}. Owing to the considerable suffering and cost associated with chronic pain, preventing its development is essential^{120–122}. However, identifying these patients at early stages is challenging.

Screening tools have been developed to help clinicians assess the risk of a patient seeking care for acute pain developing chronic pain and its related disability, such as the Örebro Musculoskeletal Pain Screening Questionnaire (ÖMPSQ)¹²³ and the STarTBack tool¹²⁴. These tools assess psychological and social factors and include questions about duration of pain, emotional distress, fear-avoidance beliefs, self-perceived functioning and expected return to work, which are associated with the development of chronic-pain-associated

disability^{121,125}. Both tools have been validated in the clinic, and the ÖMPSQ can predict the risk of future work absenteeism due to pain¹²⁶ but can less accurately predict pain outcomes, whereas STarTBack predicts future function but is less accurate in predicting work disability and pain outcomes. The short version of these screening tools requires little time to undertake and can reliably stratify individuals into low, medium and high risk of pain-related disability¹²⁶. Although these screening tools are not perfect, and research is focusing on improving them, they are nevertheless adequate for classifying patients in clinical settings¹²⁷. Preferably, the patient completes the screening tool during their first clinical visit to estimate their risk. In addition, these screening tools might also be useful in isolating the most potent risk factors for chronic-pain-associated disability. Indeed, the ÖMPSQ has been successfully used to identify high-risk cases and then to provide an intervention aimed at the elevated risk factors for these workers^{127,128}. Patients with a higher risk of chronic-pain-associated disability will likely need a more-thorough assessment before starting treatment to ensure that the proper targets have been identified.

Primary prevention

Many popular prevention interventions for low back pain are still based on the view that low back pain is a physical injury¹²⁹. Accordingly, ergonomic approaches are used to control excessive strain, protect the spine and prevent injury, including safe lifting guidelines, workplace redesign and ergonomic furniture. However, despite the popularity of these approaches, and although

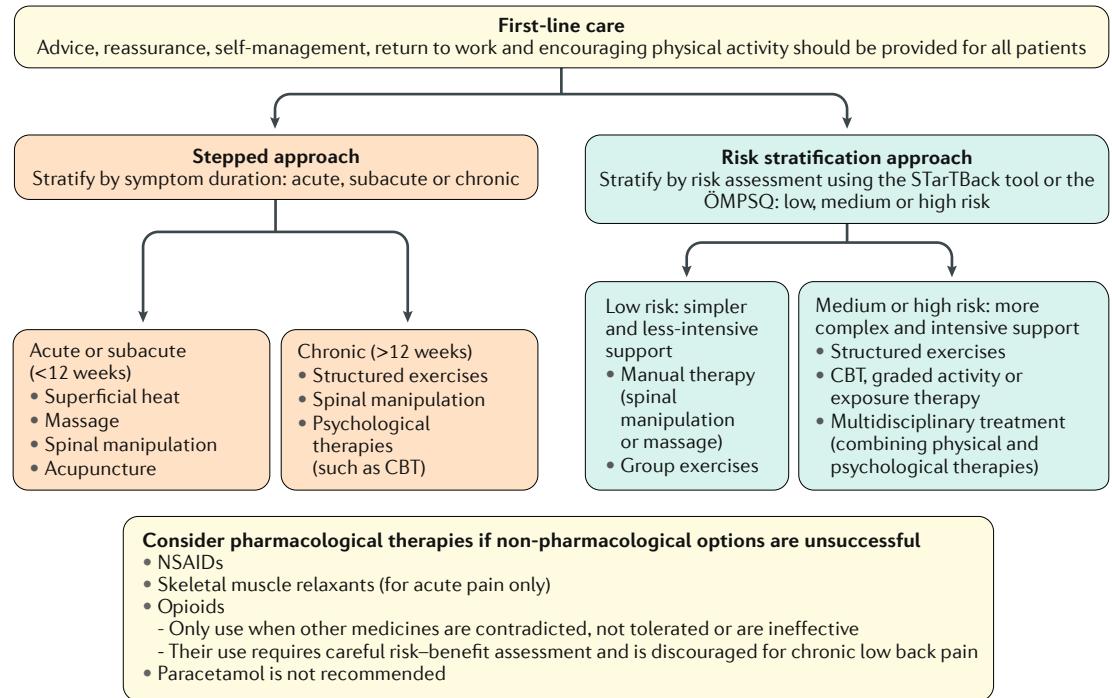


Fig. 6 | Management of low back pain. The management of low back pain can include two common approaches. The traditional stepped-care approach entails stratifying patients according to the duration of symptoms, followed by initially simple care with progression to more complex care if initial treatments are ineffective. A more recent approach is to use validated risk stratification tools, such as the STarTBack Screening Tool or the Örebro Musculoskeletal Pain Screening Questionnaire (ÖMPSQ), to stratify patients on the basis of their risk of chronic-pain-related disability into different care pathways. Following stratification, treatment is then matched to the patient's risk level. Pharmacological therapies are considered only if non-pharmacological options are unsuccessful. CBT, cognitive-behavioural therapy. Reproduced with permission from Almeida M, Saragiotto B, Richards B & Maher CG. Primary care management of non-specific low back pain: key messages from recent clinical guidelines. *Med. J. Aust.* 2018; **208** (6): 272–275. © Copyright 2018 The Medical Journal of Australia.

some are mandatory workplace regulations, few trials have investigated the efficacy of these strategies. One of the most well-known is a randomized controlled trial (RCT) involving 2,534 US postal workers that demonstrated no reduction in the incidence of work-related low back pain with education in safe work practices and ergonomic redesign of the workplace¹³⁰. Although this result was surprising at the time of publication of this study, the current understanding of the diverse risk factors for low back pain suggest that the one-dimensional prevention approach used in this trial could be insufficient¹³⁰.

A systematic review of prevention interventions composed of 21 RCTs and 30,850 individuals demonstrated that common strategies such as back supports, shoe insoles and education for avoiding back injuries lacked evidence that they do prevent low back pain¹³¹. The only effective intervention in this study was exercise, or exercise in combination with education, the latter of which reduced the risk of an episode of low back pain by 45%. These exercises were not confined to the spine but aimed to improve aerobic fitness, strength, flexibility and skill or coordination. Although physical exercise can have a large preventive effect on low back pain, it requires considerable commitment from participants^{131,132}. Indeed, one trial that demonstrated a 50% reduction in work absenteeism due to back pain required participants to attend 20 exercise sessions over 3 months (which

is consistent with recognized guidelines for exercise prescription)¹³³. Whether the effects of exercise on back pain prevention are a result of the improved physical capacity to tolerate stress on the spine or the improved relationships with co-workers and employer and job satisfaction is unknown.

Management

Clinical practice guidelines encourage clinicians to adopt a biopsychosocial perspective for the management of low back pain¹⁰⁹. Patients are taught to self-manage their condition, and clinicians are encouraged to adopt a stepped approach to care to avoid unnecessary or overcomplicated treatment (FIG. 6). To this end, back pain management should be started in a primary care setting rather than in a specialist setting. Nonspecific low back pain is not a medical emergency; thus, it should not be managed in the hospital emergency department¹³⁴. A treatment option for individuals with low back pain is a risk stratification approach, which aims to limit progression to chronic back pain. This approach involves a risk-targeted treatment strategy, whereby individuals of high risk receive targeted treatments to prevent the development of chronic pain and individuals at low risk receive less-intensive therapies. In individuals with chronic back pain and interference with daily life (>3 months), management preferably takes place in a multidisciplinary setting.

Risk stratification approach

Secondary prevention aims to prevent the development of chronic-pain-associated disability in individuals at high risk. As previously mentioned, patients seeking care for an acute episode of back pain can be stratified according to their level of risk of chronic-pain-associated disability (see Screening for risk of chronic pain, above), and subsequent interventions are guided by the risk assessment. Consequently, individuals with a low risk are treated with simple, conservative methods such as education, the advice to resume daily activities and re-activation (that is, a programme to regain physical function), which promote healing. Individuals at higher risk receive more complex interventions to address risk factors and prevent further development of the pain and its associated disability problem^{121,135–138}.

Historical approaches. Understanding the current treatment recommendations for low back pain is enhanced by examining historical approaches. Until the 1990s, treatment for acute episodes of low back pain often included medical procedures, such as epidural steroid injections, opioid administration, surgery or bed rest; however, these interventions were not more effective than natural recovery, were expensive and were associated with adverse effects^{139–142}. Because of increasing injury claims, another previous treatment approach was to provide all individuals seeking care for back pain with an early intervention often consisting of education, physical therapy and exercise, but this did not prevent the development of chronic pain^{143,144}. In addition, as psychological factors are prominent risk factors for back pain, several studies have provided psychological counselling to all patients seeking care, although this treatment did not improve outcomes compared with usual care¹⁴⁵. Analyses of these difficulties suggested two ways forward: targeting interventions on the basis of risk factors to identify individuals with a high risk of developing further pain-associated disability and providing adequate interventions that specifically address the relevant issues, including psychological and social risk factors that have been identified^{116,146,147}.

Risk-guided treatment. Targeting treatments for low back pain to the risk profile of a patient is speculated to lead to better outcomes, although the research on individualized treatments is complicated and robust studies are rare. In one trial, targeting therapeutic interventions on the basis of patients' risk was superior to treatment as usual in primary care with regard to function and costs, although the effect size at 1 year was small (0.19)¹⁴⁸. The selection of a preventive intervention has varied, but the need to address psychological and social factors is evident^{125,149,150}.

In individuals with low risk who have no specific spinal pathology, clinical guidelines for the management of nonspecific low back pain in primary care recommend advising the patient to return to normal activities as soon as possible, in addition to self-managed methods of pain relief and education about the causes and possible self-management of the pain^{109,151}. Individuals at medium risk should be monitored to enable rapid response to recurrences or lack of improvement.

Individuals at high risk require special attention. Although these patients might initially have sought medical attention for an acute pain episode, the episode might reflect an exacerbation of a recurrent, well-established condition; whether this is the case can usually be ascertained in a clinical interview. Individuals at high risk should not delay intervention in the hope of full recovery as it greatly increases the risk of chronic-pain-associated disability; if targets for intervention are not clear in these patients, further psychosocial assessment is warranted before proceeding. In addition, offering high-risk patients a psychologically informed treatment appears important for successful resolution of the pain problem¹⁵². Although the treatment of patients at high risk can be challenging, results are quite encouraging when the intervention is targeted towards the specific psychological and social risk factors, although this is under-researched^{116,136,148,152–154}.

As part of the management of high-risk patients, one approach has been to offer a psychologically informed prevention programme as an adjunct to medical care that includes reassurance that the condition is not harmful and education about the importance of being active¹⁵⁵. At high risk, patients are offered a cognitive-behavioural therapy prevention programme that aims to eliminate barriers to activity and work. This programme typically includes techniques to empower the patient, through, for example, re-activation (that is, regaining physical function), learning how to reduce the bothersomeness of pain and stress through self-management and solving problems as they arise (for example, applying these techniques to new situations and dealing with flare-ups)^{116,121,156}. A series of studies have demonstrated a reduction in work disability and health-care utilization for between 1 and 5 years in high-risk patients stratified using the ÖMPSQ and then treated with a standardized cognitive-behavioural therapy programme^{156–160}. Other psychologically informed treatments based on cognitive-behavioural therapy principles¹⁶¹ in primary care have also shown encouraging, albeit smaller, effects^{116,162}. To increase the accessibility of psychologically informed interventions, these programmes have been delivered by other trained health-care professionals, such as physical therapists^{135,163}. Administering this treatment only to patients at higher risk of chronic pain is more efficient as trials that delivered psychologically informed treatment to patients at any risk yielded disappointing results compared with usual treatment^{116,163–165}.

In terms of preventing pain-related work disability, providing work accommodations (such as modified return to work) and communication with the workplace has been found to be effective^{166–170}. For example, in one study, workers at high risk were randomized to usual care or a programme providing both the worker and her/his supervisor skills training in communication and problem-solving¹²⁸; the programme reduced work absences and health-care utilization whereas improving overall health compared with usual care. Similarly, a programme to enhance communication between patients and their work supervisors was evaluated among high-risk patients seeking primary care and significantly increased work ability¹⁷¹.

Stepped-care approach

Non-pharmacological treatments. Compared with previous guidelines for the management of patients with nonspecific back pain, more recent guidelines from the United Kingdom¹⁷², United States¹⁷³, Belgium¹⁷⁴ and Denmark¹⁷⁵ recommend self-management, exercise and physical therapies, before pharmacological treatment, for the treatment of back pain. These changes are driven partly by new data on treatment effectiveness but also by concern about the potential for harm with some pain medicines, such as opioids¹⁷⁶ and NSAIDs¹⁷⁷. Supervised exercise programmes are effective for the prevention of low back pain¹³¹ and for managing chronic, but not acute, low back pain¹⁷⁸. The form of exercise programme does not seem to be particularly important, as many forms of exercise are beneficial, including yoga, tai chi, motor control exercise, graded activity and pilates, although for both prevention and management the exercise programmes were usually not confined to local spine exercises but focused on the whole body and included strengthening, stretching, cardiovascular and coordination exercises. Exercise is normally contraindicated only in patients with low back pain that arises from a serious pathology, such as a fracture or infection; however, caution or adaptation of the exercise programme might be necessary if patients have a comorbidity, such as respiratory or cardiovascular disease¹⁷⁸.

Across these guidelines, the recommendations for non-pharmacological care of chronic low back pain are fairly consistent. For all patients with pain, initial care should comprise education about the causes and self-management of pain, reassurance, encouragement to remain active and advice on self-care options (such as relaxation or yoga). Patients who fail to respond to this approach or patients who require more complex or intensive care (based on risk assessment) can receive additional treatments such as structured exercises, spinal manipulation or cognitive-behavioural treatment. The types of effective treatments for acute low back pain are different from those for chronic low back pain. Electrotherapy, manual traction and belts, corsets or foot orthotics are not recommended for either acute or chronic pain.

Pharmacological treatments. Acute (<3 months duration) and chronic (>3 months duration) nonspecific low back pain and radicular syndromes have different pharmacological treatment approaches, although a stepped approach is recommended for both. Although traditionally failure to respond to initial, simple approaches was the indication to try a more complex treatment (an approach analogous to the WHO analgesic ladder), more recent research has challenged this approach, as some medicines are ineffective for low back pain (such as paracetamol)¹⁷⁹ and other therapies have unknown efficacy (such as opioids for acute low back pain)¹⁸⁰. A small range of pain medications are recommended for nonspecific low back pain in guidelines from the United States¹⁷³. NSAIDs or muscle relaxants can be considered in individuals with acute low back pain who did not respond to non-pharmacological treatments, with

an NSAID at the lowest possible dose for the shortest duration possible as the first option.

In chronic low back pain, head-to-head trials of NSAIDs have not shown a difference in pain relief; there are no data on cyclooxygenase-2 (COX2)-selective NSAIDs. NSAID use should be accompanied by monitoring of the patient's risk factors for gastrointestinal disorders, and gastrointestinal protective treatments should be commenced if warranted. Tramadol or duloxetine are second-line pharmacological options for chronic pain, although opioids are recommended only if the potential benefits outweigh the risks for individual patients and after a discussion of known risks and realistic benefits with patients. Strong opioids are associated with a small short-term improvement, although there is no difference in pain reduction when long-acting or short-acting opioids are used. Weak opioids, such as tramadol, used in combination with paracetamol (acetaminophen) can be used for acute back pain and when NSAIDs are contraindicated, not tolerated or have no effect. By contrast, the UK guidelines do not recommend the use of paracetamol as monotherapy, opioids, tricyclic antidepressants or serotonin and noradrenaline reuptake inhibitors for acute and chronic low back pain¹⁷². Selective serotonin reuptake inhibitors and muscle relaxants are contraindicated for acute and chronic back pain. Anticonvulsants are not recommended for low back pain¹⁸¹.

Management of specific pain causes

Radiofrequency facet denervation. For low back pain originating from the lumbar facet joints, the target for interventional treatment is the medial branch of the dorsal ramus, which innervates the facet joints. A facet joint nerve block using a local anaesthetic is performed to determine whether pain is partly caused by facet joint involvement^{59,182}; if confirmed, patients can be offered a radiofrequency denervation of the medial branch of the dorsal ramus to try and achieve long-term pain relief. National Institute for Health and Care Excellence (NICE) guidelines from the United Kingdom¹⁸³ recommend considering radiofrequency denervation only when the main source of pain originates from the facet joints, when pain is moderate to severe, and only when evidence-based multidisciplinary treatment has failed. However, one study that included three RCTs failed to demonstrate any superiority with adding radiofrequency denervation to a standardized exercise programme for the treatment of low back pain originating from the facet joints¹⁸⁴. The latter study elicited a scientific debate regarding the methods and interpretation used^{185–187}. At present, this uncertainty is not resolved.

Managing radicular syndromes. Whether common oral pain medications should be used for radicular syndromes is uncertain¹⁸⁸. The use of gabapentinoids for this indication has increased, although one trial demonstrated no benefit of pregabalin over placebo¹⁸⁹. For acute or subacute radicular pain lasting for >2–3 weeks, epidural corticosteroid combined with local anaesthetic administration can be considered⁶². Therapies can be delivered to the epidural space in two routes — interlaminar or transforaminal — of which the latter was associated

with more effective drug delivery to the nerve root¹⁹⁰. Epidural injection of local anaesthetic and corticosteroids can reduce radicular pain and might also reduce the number of surgical candidates¹⁹¹. Considering the high risk of intravascular injection when attempting to reach the epidural space, the use of imaging guidance is obligatory during this procedure. In addition, this treatment is an off-label use of corticosteroids; thus, written informed consent from the patient is mandatory.

Surgery. No guidelines recommend surgery for the treatment of nonspecific low back pain as in the absence of a clear anatomical basis of low back pain, there is no surgical target. UK guidelines¹⁷² recommend spinal decompression for patients with radicular low back pain that is potentially caused by degenerative disc disease when non-surgical treatment has not improved pain or function. UK guidelines specifically advise against disc replacement surgery for patients with disc degeneration and advocate that spinal fusion for disc degeneration and/or facet joint-related pain should be used only in RCTs.

Multidisciplinary interventions for chronic pain

A multidisciplinary approach is recommended for individuals with chronic low back pain. These programmes usually adopt a biopsychosocial approach; involve a combination of educational, physical, cognitive, behavioural, social and/or work-related components; and are often delivered by a team of health-care providers with expertise in different fields. Most programmes include a graded activity approach¹⁹², whereby patients are encouraged to gradually increase their activity levels towards individualized life goals and to reduce the amounts of rest and drug intake. Such multidisciplinary interventions were more effective than usual care and physical treatments at decreasing pain and disability in one Cochrane systematic review and meta-analysis and were more effective in terms of work outcomes than physical treatment¹⁹³. Given the multi-component nature of these interventions, there is a need for identifying the precise mechanisms of action. Knowledge about the specific components that are required for treatment efficacy and the corresponding dose will inform the development of treatments with improved cost-effectiveness^{194,195}.

One novel and more specific multidisciplinary treatment for non-specific low back pain is aimed at directly challenging the catastrophic misinterpretations of pain and various expectations about the relationship between physical activities and pain and/or back injury. The treatment is designed to create harm expectation violations (or prediction errors) by exposing patients to movements or activities that they consider harmful or that they predicted to increase pain¹⁹⁶. During treatment, these individuals' predictions are challenged and brought in line with the incoming sensory and safety information, which provides an opportunity for learning new and more accurate predictions. Such treatments can considerably reduce levels of pain-related fear¹⁹⁷ and the perceived harmfulness of physical activities¹⁹⁸ and are cost-effective¹⁹⁹. However, the effects of these treatments on disability levels were no different than a graded activity

approach¹⁹⁷, except when the intervention was studied in replicated single-case experiments^{200–202}. A possible reason for this difference is that the latter included personalized measures of disability and goals whereas the RCTs used standard or global outcome measures¹⁰⁸.

Societal interventions

Treating individual patients with low back pain might not be sufficient to address the most disabling health condition globally^{203,204}. As previously mentioned, low back pain is highly prevalent and is strongly influenced by patient beliefs and expectations, in addition to societal contingencies such as compensation and disability policies. Back pain is also commonly mismanaged²⁰⁵. Societal-level interventions to improve back pain health outcomes include mass media campaigns to improve the understanding of low back pain in the general public^{206,207}, addressing the fears and expectations of health-care providers^{208,209}, removing compensation and disability policies that encourage disability and implementation studies that attempt to address important evidence-practice gaps²¹⁰.

Quality of life

Back pain has considerable negative effects on the quality of life of affected individuals. Individuals with new-onset back pain have an increased risk of lower quality of life scores²¹¹, and the negative effect on quality of life increases with persistent pain²¹¹. Patients with chronic back pain report a quality of life that is lower than individuals without pain and that is comparable to those of individuals with life-threatening diagnoses^{212,213}. In addition, back pain is associated with worry and fears, particularly about the (sense of) self and social relationships and especially when pain persists longer than expected^{214,215}. In one study, back pain was summarized as the psychological effect of the unpredictable omnipresent nature of pain, which is unpredictable for the self, wellness and the future²¹⁶. Population and patient cohort studies have demonstrated associations between back pain and other problems, such as functional disability, anxiety, depression, fearful beliefs about the meaning of pain, (work-related) avoidance behaviour, stress, increased health-care utilization, insomnia, reporting of more somatic comorbidity and unemployment^{211,217}.

Given the effect of back pain on quality of life, the multidimensional assessment of health-related quality of life is increasingly acknowledged as indispensable for the study of back pain^{212,218}. The generic 36-item Short Form Health Survey²¹⁹, which includes 8 dimensions of health summarized in a mental and physical component score, is recommended to assess the self-reported health state of patients with back pain. The generic and cross-cultural nature of this survey allows comparisons between various studies.

Owing to previous data, and the acceptance of the biopsychosocial approach to back pain, persistent back pain is considered a health condition that is affected by a combination of physical, psychological, environmental, cultural and social factors²¹⁸. In fact, these factors might affect the perceived quality of life more than the pain itself²¹⁷. In addition, negative beliefs such as catastrophic

misinterpretations of pain and expectancies about the inability to predict and to control pain are strong correlates of quality of life in individuals with back pain^{99,212,217}. Leaving these factors unchallenged can result in a risk of a higher disease burden²²⁰.

Outlook

Despite an exponential increase in research on the epidemiology, mechanisms and treatment of low back pain, and increased consensus among international guidelines, serious challenges remain. The large variability in clinical presentation, a wide range of course and prognosis, insufficient understanding of the underlying mechanisms and limited success in identifying effective treatments make low back pain a challenge for clinicians and researchers. However, increasing efforts are focusing on promising research avenues.

Risk factors

Although the research into the risk factors for low back pain has shifted from a pathophysiological towards a biopsychosocial perspective, improvements are still needed. For example, the current data might be misleading as most epidemiological studies have included a selected group of individuals in which those from low-income and middle-income countries, young individuals and elderly individuals are under-represented²²¹. Also, the focus of studies has mainly been on the level of the individual beliefs, emotions and behaviour of the person with back pain, and extending these towards both extremes of the biopsychosocial realm might increase their effectiveness — modifiable biological risk factors (for example, epigenetic mechanisms in the acute-to-chronic pain transitioning) and societal risk factors (for example, workplace and family responses, and health-care providers' beliefs and attitudes). Experience-dependent regulation of gene expression might mediate responses to acute physical or mental stressors and could help in the development of tools for the early identification of risk and severity assessment in complex cases²²². On the other end of the spectrum, understanding the role of the negative expectations and social context factors that surround the individual with low back pain may be as important understanding those of the patient. Health-care providers' recommendations for activity and return to work vary widely and reflect their personal expectancies towards back pain and not necessarily the patients' clinical and work conditions^{223,224}. Accordingly, future research should test whether these potentially iatrogenic expectancies, which could perhaps be introduced as novel 'white' flags, directly or indirectly influence patients' outcomes.

Positive resilience factors that might protect against the development of chronic low back pain and disability have been identified and are under study. To this end, resilience is not merely characterized by the absence of risk factors or pathology but is considered a dynamic process that enables the individual to flexibly adapt to severe adversity over the life course²²⁵. Studying how resilience buffers against the influence of risk factors might increase the precision of our prediction models in low back pain.

Neurobiology

Several aspects of the role of the brain in back pain require further investigation. For example, the specificity of previous findings must be established to differentiate changes specific to back pain from those reflecting chronic pain more generally or from processes associated with (chronic) back pain. Direct comparisons between chronic pain conditions within the same study should identify syndrome-specific alterations, but results from these studies should be interpreted with caution as causality is extremely difficult to establish²²⁶. In addition, further longitudinal studies are needed to identify which alterations in brain structure and function underlie the transition to chronic back pain and which are the result or a correlate of an already established chronification. Moreover, most studies have focused on pain intensity ratings as the most relevant behavioural parameter in back pain; however, this disorder is also characterized by profound alterations in behaviour (such as avoidance of painful movement), which might be induced and maintained by independent brain networks; these factors also require further study. Finally, psychological processes underlying alterations in corticolimbic structures need to be differentiated and characterized in more detail to enable stratification in the prevention and treatment of chronic back pain.

Management

Although several management options are available for low back pain, current systematic reviews and meta-analyses reveal small effect sizes (often not exceeding 0.50)²²⁷. At least three ways of improving the care of individuals with back pain have been proposed. One is personalizing treatments by testing in whom what treatment works and how the treatment works^{228–230}; the treatment can then be offered to the patient who is expected to benefit from that particular treatment. This process might improve efficacy by more systematically identifying the mechanisms underlying the treatment outcomes. Second, stratified models of care exist and have some evidence they are superior to non-stratified primary care²³¹. Stratification can be based on symptom duration (stepped approach) or on the result of a risk assessment (risk stratification approach) (FIG. 6). Third, the replicated Single-Case Experimental Design (SCED) is another underutilized methodology and might improve the care of patients with back pain^{232,233}. An SCED is an interrupted time series design in which one patient is observed repeatedly during a certain time frame under different levels (for example, baseline versus treatment) of at least one outcome. SCEDs are flexible, are fairly easy to implement in the practice of health care, elegantly bridge the gap between research and practice, and have available methodological quality standards^{234,235}.

In addition to these novel approaches, there is also a need for cost-effective technologies that can improve the global reach of evidence-based interventions for low back pain. Among such interventions are low-tech booklets or more advanced eHealth and mHealth approaches implemented via the Internet and using virtual reality technologies or gaming platforms that

- can be used via mobile and wireless applications^{236,237}. Using similar methodology, evidence-based messages supporting self-management could be disseminated using social media and smartphone technology²³⁸. This technology is still largely uncharted territory but is likely to be promising. Finally, novel back pain management approaches are needed that also reach socio-economically vulnerable groups, such as ethnic minorities and individuals with low literacy, low educational attainment and low income²³⁹.
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Author contributions

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Competing interests

J.W.S.V. is chief investigator or associate investigator on multiple previous and current research grants from Belgium, including the Flemish Government, Research Foundation Flanders (FWO Vlaanderen) and the National Institute for Health and Disability Insurance (NIHDI). He has received travel expenses for speaking at conferences from the professional associations hosting the conferences and has received honoraria for reviewing grants from government grant agencies and honoraria for marking theses from universities. C.G.M. is chief investigator or associate investigator on multiple previous and current research grants from government research agencies from Australia (for example, the National Health and Medical Research Council (NHMRC) of Australia), Brazil (for example, São Paulo Research Foundation (FAPESP)) and the Netherlands (for example, the Netherlands Organisation for Health Research and Development (ZonMW)). For the past 12 years, his salary has been covered by research fellowships from Australia's NHMRC or the Australian Research Council. His research has also received funding from philanthropic (for example, Arthritis Australia) and government agencies (for example, NSW WorkCover). He has received travel expenses for speaking at conferences from the professional associations hosting the conferences and has received honoraria for talks from professional associations and the industry hosting the talks, honoraria for reviewing grants from government grant agencies and honoraria for marking theses from the relevant university. C.G.M. received supplementary industry funding for two investigator-initiated NHMRC-funded trials. The first trial (PACE) had co-funding from GlaxoSmithKline. Pfizer provided the study medicine for the second trial, PRECISE, at no cost, but provided no other funding. J.V.Z. is a member of the Executive Board of the World Institute of Pain (WIP). M.G. declares that she is bound by confidentiality agreements that prevent her from disclosing her competing interests in this work. S.J.L. is chief investigator or associate investigator on multiple previous and current research grants from Sweden, including Vetenskapsrådet, FORTE, Riksbankens Jubileumsfond, REHSAM and Örebro University. He has received travel expenses for speaking at conferences from the professional associations hosting the conferences and has received honoraria for reviewing grants and giving educational lectures. All other authors declare no competing interests.

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Supplementary information

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Örebro Musculoskeletal Pain Screening Questionnaire (ÖMPSQ): <https://www.oru.se/english/research/research-environments/hs/champ/questionnaires/>
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