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Chronic pain epidemiology – where do lifestyle factors fit in?

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Abstract
Chronic pain is common and complex and has a large impact on individuals and society. Good epidemiological pain data provide key information on the use of resources (both in general practice and in specialist clinics), insight into factors that lead to or favour chronicity and the design of interventions aimed at reducing or preventing the effects of chronic pain. This review aims to highlight the important factors associated with chronic pain, including those factors which are amenable to lifestyle intervention.

Keywords
Lifestyle, chronic pain, epidemiology

Introduction

It is estimated that approximately one in five of the adult population in Europe suffers chronic pain,[1] which is therefore more prevalent than asthma[2] or diabetes.[3] However, fewer than 2% of people with chronic pain ever attend a specialist pain clinic,[4] the remainder being managed mainly in primary care.[5] Studies consistently demonstrate that every measured dimension of health is worse when chronic pain is present than when it is not, and, in addition to this physical and emotional burden, the financial cost to society is huge (over €200 billion per annum in Europe, and $635 billion per annum in the USA in 2008).[6] Despite this, chronic pain remains under-recognised and unsatisfactorily treated, with pharmacological interventions dominating.

Chronic pain has long-term biological, psychological and social causes and consequences that are important in prevention and management. These include lifestyle factors (i.e. health-related behaviours or the potential results of these behaviours). The aim of this review is to examine factors associated with chronic pain – some potentially amenable to change or healthcare intervention – and their implications for reducing the burden of chronic pain in society.

Why is epidemiology of chronic pain important?

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'.[7]

Few diseases or conditions have a single causative factor or agent; most rely on multiple or combined circumstances for their development. Although chronic pain in an individual may have a single primary cause (e.g. injury or herpes zoster), there are other factors which influence the duration, intensity and spectrum (physical, psychological, social and emotional) of the effects of chronic pain, and the perception of these. However, it is the study of groups or communities with chronic pain, rather than individuals, that will give insight into its distribution and determinants; the

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Table 1. Factors associated with chronic pain.

Modifiable	Pain
	Mental health
	Other co-morbidities
	Smoking
	Alcohol
	Obesity
	Physical activity/exercise
	Sleep
	Nutrition
	Employment status and occupational factors
Non-modifiable	Age
	Sex
	Cultural background
	Socioeconomic background
	History of trauma/injury/ interpersonal violence
	Heritable factors (including genetic)

aetiology (factors which lead to or favour chronicity); prevention; prognosis; the impact on quality of life; evaluation of treatment strategies; and allocation of health service and educational resources.

Although research on the pathophysiology of pain mechanisms is important, an understanding of the risk factors associated with the presence and development of chronic pain remains key to informing clinical management, limiting pain severity and minimising disability.

What is known?

At a population level, factors known to be associated with chronic pain include physical, psychological and social variables;[8] a summary is laid out in Table 1. Some of the risk factors for the development and persistence of chronic pain that have been identified are not, or not directly, amenable to medical intervention (e.g. age, sex) but highlight the need for clinical awareness, suggest biological mechanisms, and provide opportunities for research. Others factors are certainly modifiable, particularly in a primary care environment and through self-management.

Modifiable factors associated with pain

Pain. Perhaps the most important clinical risk factor for chronic pain is pain itself – either acute pain or chronic pain at another site. The more severe the acute pain, and the greater the number of pain sites, the more likely it is that severe chronic pain will develop.[9,10] There is some evidence to suggest that brain changes associated with chronic pain may be reversible after effective treatment.[11,12] This highlights the importance of pain management, not just in the relief of suffering, but also as a preventative activity.

A recent neuroimaging study in healthy individuals found that brain 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 after the pain stimuli ceased.[13] That these anatomical changes within the brain occurred in the early stages of pain (before pain could be labelled as chronic) further suggests that early intervention will be important in preventing chronicity, though this remains to be tested clinically.

Mental health. Anxiety, depression and catastrophising beliefs about pain have been shown to be associated with the presence of chronic pain and with a poor prognosis in people with various pain conditions.[14–17] The temporal relationship between chronic pain and mental health remains unclear, and it is likely that there is a 'bi-directional aetiology'[18] – pain causing poor mental health and vice versa. In depressed patients, neuroimaging has provided evidence of disturbed prefrontal brain activity and a dysfunction of emotion regulation during experimental pain stimulation.[19] 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. Depression in chronic pain is probably less amenable to medical treatment in isolation, and outcomes are more favourable when depressive symptoms are addressed together with appropriate pain management.[20]

Contribution of 'multimorbidity' in chronic pain. The prevalence of chronic pain is higher in those with other chronic diseases than in those without.[21] For example, up to a third of people with coronary heart disease also have chronic pain, and a similar percentage of people with chronic obstructive pulmonary disease have chronic pain. As with others in the general population, the predominant mechanism of pain in people with major chronic diseases is musculoskeletal.[22] Not only does this add to the overall disease burden among these individuals, but the co-morbidity, co-prescribing and co-occurrence of disability all lead to greater challenges in managing each condition and reducing their impact. Those with severe chronic pain are up to three times more likely to die from ischaemic heart disease or respiratory disease than those with no chronic pain,[23] and this may be partly a result of reduced exercise capacity in those disabled by chronic pain.

There is evidence that several chronic physical conditions may increase the risk of chronic pain. This may occur directly, through increased nociception from the

periphery, resulting in central and peripheral pathophysiological changes associated with chronic pain,[24] or indirectly, by accumulated stress or load, with prolonged activation of the stress-regulation systems leading to breakdown of muscle, bone and neural tissue, resulting in more pain. This means that other co-morbid conditions (not associated with chronic pain) are likely to contribute to the reporting of chronic pain.

From a clinical point of view, this suggests that many of those presenting with chronic pain will have other conditions influencing their chronic pain and, more importantly, that an integrated approach to assessment and management of those with multiple conditions is needed. Chronic pain cannot be managed in isolation.

Smoking. Most studies show that the smoking rate in pain populations is higher than in the general population.[25,26] Heavy smokers tend to report more pain locations and also increased pain intensity compared with those who have never smoked.[27] However, the evidence for a direct causal relationship between smoking and pain is relatively weak. Although some have postulated that the aversive physiological effects of smoking cause or aggravate painful conditions, this has not been proven.[28] Others have suggested that concurrent depressive symptoms may mediate the effect of smoking on chronic pain outcomes,[29] supporting other evidence that, although smokers reported more pain, this association was weakened when controlling for depression.[30]

What remains unanswered is whether smoking cessation improves pain. This is compounded by relatively low rates of successful smoking cessation among patients attending pain clinics,[31] which is thought to be a result of patients using smoking as a way to manage pain-related emotional distress and as a distractor from pain. Nonetheless, smoking remains a major risk factor for cardiovascular disease, which has also been shown to be a major co-morbidity and cause of mortality among people with chronic pain.[23] The evidence to date suggests that the standard approach to smoking cessation may not be effective in this cohort and patients may require more intensive smoking interventions.

Alcohol. In ancient times, a cheap wine (Greek *oxos*; sharp wine or vinegar), sometimes called the soldiers' wine, was mixed with myrrh or gall and used as a pain reliever for those condemned to crucifixion or in extreme pain.[32] Today, we know that alcohol has only transient analgesic effects, but it is still used by the general public to self-medicate.[33] However, besides the inherent hazards of mixing alcohol and medications, the greatest pain-reducing effects occur when alcohol is consumed at doses exceeding guidelines for safe daily alcohol use. This ultimately has the net result of tolerance to alcohol's analgesic effects. Withdrawal from chronic alcohol use often increases pain sensitivity, which could motivate some people to continue drinking or even increase their drinking to reverse withdrawal-related pain.[34] Thankfully, results from a general population cohort in Denmark indicated that chronic pain patients are less likely to drink alcohol, even less than those on opioid medication.[35]

Obesity and chronic pain. The relationship between increased body mass index (BMI) and chronic pain in adults seems intuitive and may be related, in part, to increased weight-bearing on joints, reduced physical activity and deconditioning.[36] However, the relationship is more complex than simply one of mechanical overload, as demonstrated in community-based twin studies, where familial (genetic and environmental) factors were significant contributors to the association.[37] It is the impact of pain on functional status and health-related quality of life that is greater in obese individuals than in those with normal BMI.[38] While obese individuals are likely to have worse scores on pain subscales of health-related quality of life (HRQoL) instruments, the direct effect of weight on these measurements remains unclear.[39]

Likewise, in obese elderly individuals, there seems to be an increased prevalence of chronic pain among those with central obesity that is independent from other components of the metabolic syndrome, depression, anxiety and the presence of painful co-morbid conditions.[40] In these older adults a higher BMI was clearly associated with an increased incidence and prevalence of pain.[41,42]

Overall, the literature suggests an association between weight loss and improved pain outcomes, but the strength of the relationship varies by study and also aetiology/type of pain. The potential benefits of weight loss as a strategy for reducing or preventing chronic pain have yet to be demonstrated beyond that of osteoarthritis and other mechanical aetiology. There is some evidence to suggest that weight loss significantly predicts improvements in pain outcomes, even after controlling for depression, and this is probably attributed to improved self-esteem and pain perception.[43] Evidence from a small study using topiramate to induce weight loss in patients with chronic lower-back pain showed a reduction in pain symptoms as well as an improvement in HRQoL.[44] Nonetheless, and perhaps more importantly, we know that a greater body weight is one of the major risk factors for a higher blood pressure and that weight reduction lowers this blood pressure and associated cardiovascular risk.[45] This secondary prevention may be more important in

reducing overall impact than simply in reducing pain severity per se.

Physical activity/exercise and chronic pain. Evidence for the benefits of exercise in patients with chronic pain is limited, in part because of the heterogeneity of studies, which are of varying quality and often specific to certain pain conditions, and a lack of clear definitions as to the exact format of exercise used. For example, supervised aerobic and strengthening exercise training has been found to have some benefits for patients with fibromyalgia symptoms.[46] However, this cannot be extrapolated to other chronic pain conditions. Walking (or treadmill walking) was not found to have a positive effect in the management of patients with lower-back pain.[47] Pooled data from fairly low-quality trials show that t'ai chi has a small positive effect for reducing pain and disability in people with chronic arthritis.[48] Studies of other forms, including Pilates, yoga or aquatic exercises, found very modest benefits for patients, but provided insufficient information as to the exact nature of the exercise component used.[49]

General advice, given along with specific advice about exercise and functional activities tailored to the individual, was found to be more effective for improving pain and work-related disability than non-specific advice alone.[50] As with weight-loss interventions, exercise is likely to be important in secondary and tertiary prevention and management of co-morbidities.

Sleep problems. A prospective survey from Norway, involving only women and over a 17-year period, found that disrupted sleep was a risk factor for the onset of chronic pain and predictive for pain persistence (but not worsening of pain).[51] Similarly, a recent prospective study from the UK suggests that addressing sleep problems in chronic pain patients may lessen their risk of developing depressive illness, which is associated with a poorer pain prognosis.[52]

Nutrition and pain. Adequate nutrition is a basic premise for good health and prevention of chronic disease. Nutritional strategies are not only potentially useful for improving pain management, but also important in reducing the known cardiovascular mortality associated with chronic pain. Unfortunately there is a dearth of robust evidence in human participants, with very few good-quality trials completed on diet supplementation to treat patients with chronic painful symptoms.[53,54]

Pre-clinical findings suggest that dietary omega-3/omega-6 ratio may have significance for inflammatory pain. Increasing omega-3 intake (found in fish) reduced patient-reported joint pain intensity, morning stiffness and the number of painful joints in patients with rheumatoid arthritis or joint pain secondary to inflammatory bowel disease.[55]

Pain itself is not just a reflection of noxious input but also an expression of plasticity in the brain. Knowing that the central nervous system has specific nutritional requirements, pre-clinical studies suggest that reducing polyamine-containing foodstuffs (e.g. bran, nuts, soybean) may reduce hyperalgesia[56] and has shown some early promise in cancer patients with metastatic disease.[57] Other dietary constituents that show early promise include some flavonoid compounds, alpha-lipoic acid (found in broccoli, spinach, yeast) and vitamin E for diabetic neuropathy.[58] On the other hand, there is some preliminary evidence to show that medically supervised modified fasting (300 kCal/day) for a defined and limited period (7–21 days) could be useful as an adjunctive therapeutic approach to enhance mood in chronic pain patients who are often affected by depression and anxiety.[59]

Of more clinical relevance is that food can interfere with drug absorption. Fruit juice (e.g. grapefruit juice) consumption in particular interferes with the metabolism or excretion of several drugs, increasing their bioavailability (and potentiating their side effects). Pre-clinical studies suggest that low-dose caffeine can interfere with the anti-nociception properties of certain antidepressants, for example amitriptyline[60], and that chronic caffeine consumption is related to withdrawal headache and sleep disturbance (see above).

Employment status and occupational factors. The occurrence of pain or the extent to which pain interferes with life may be influenced by partner or family responses to pain, demands and control at work, employer and co-worker reactions to pain, or even by broader issues such as the job market. Individuals who are not able to work because of illness or disability are also more likely to report chronic pain than those who are employed.[61] The influence of poor job control, expectations for return to work and fear of re-injury all contribute to occupational risk factors for the onset or persistence of pain.[62] This is an important area for further study as these factors are potentially modifiable.

Sunshine and vitamin D. There is some evidence to suggest a relationship between lack of sunshine, lower temperatures and pain reporting. However, pain was not deemed an inevitable consequence of such (colder) climatic conditions.[63] Instead the relationship may, at least in part, be mediated through lifestyle factors associated with cooler and duller days (less exercise, poorer sleep, higher reported boredom). Similarly, a seasonal effect could suggest a role for vitamin D, low levels of which in some (but not all) studies have been shown to be related to the report of pain.[64] However, a Cochrane

review of vitamin D supplementation for patients with chronic pain reported a benefit in reduction of analgesics used in only one of the four studies identified.[65]

Non-modifiable factors associated with pain

Although some risk factors are not directly amenable to intervention, they do highlight the need for clinical awareness and suggest underlying biological mechanisms.

Old age. The relationship between the onset of pain and old age is not straightforward.[66,67] There is generally a higher prevalence of chronic pain in old age,[61] and the occurrence of *more severe disabling* chronic pain increases with age.[68,69] Given that the world's population aged >65 is likely to double in the next 40 years,[70] the overall burden of chronic pain is also likely to rise exponentially. Treatment strategies will need to focus increasingly on pain-related co-morbidities and the risk of polypharmacy, both of which also rise with age.[21]

Female sex. Chronic pain syndromes generally have a higher prevalence in women.[71] There are several reviews that contrast the sex (biological) and gender (role) differences in pain experiences between males and females.[71–74] Consistent themes emerge: women are found to have lower pain thresholds and lower pain tolerance, experience greater unpleasantness (or intensity) with pain and have different analgesic sensitivity. Women are over-represented (or men under-represented) in the proportion of those seeking treatment for pain (even allowing for the greater prevalence of chronic pain in women in the community). There is some evidence to suggest that these gender-related differences are associated with age-related hormonal changes of puberty and menopause involving oestrogen,[75] but there is insufficient robust evidence to warrant sex-specific pain interventions.

Some recent work undertaken in Germany found that gender differences go beyond pain prevalence and pain perception, and that women benefited more from a multimodal pain management programme than men.[76] Future studies are required that not only consider whether men and women respond differently to intervention type, but also compare effects for different pain conditions and treatment approaches.

Influence of ethnicity and cultural background. Pain is a complex personal experience influenced by multiple interactive biopsychosocial processes. However, there is similarity in the prevalence of chronic pain between developed (37%) and developing countries (41%) according to WHO World Mental Health Surveys.[77] There is some evidence that ethno-cultural differences in (experimental) pain perception correlate with clinical pain indices in a range of pain conditions, often with under-treatment in ethnic minority groups.[78–83] Interestingly, a greater pain sensitivity (pre-treatment) in certain ethnic groups has been shown to predict greater post-surgical pain[84,85] and with poorer outcomes from treatment for chronic pain.[86]

Socioeconomic background. Socioeconomic gradients in pain are a critical indicator that population-level factors are involved in the occurrence and consequences of chronic disease. Population-based studies of chronic pain have consistently shown that chronic pain prevalence is inversely related to socioeconomic status.[87,88] Furthermore, people living in adverse socioeconomic circumstances not only experience more pain; they also experience more *severe* pain.[89,90] There is some evidence to show that neighbourhood deprivation, low levels of education and (perceived) income inequalities are associated with the onset of pain interfering with daily activities.[91] In contrast, in the USA, higher neighbourhood socioeconomic status was associated with lower reporting of arthritic pain[92] and (in a separate study) better chronic pain outcomes at tertiary-level pain management.[93] Nonetheless, it is clear that political will and support are at least as important as clinical efforts in reducing chronic pain and its impact.

Trauma, injury and history of abuse or interpersonal violence. Beside the evidence for chronic post-surgical pain,[94,95] two large-scale national surveys found that pain is more common among people of any age who report a previous history of abuse or violence, in either a domestic or a public setting.[96,97] Chronic pain is therefore yet another serious adverse consequence of these events to which physicians should be alert.

The role of genetics in pain. Like other chronic conditions, pain has an important genetic contribution that is now being scrutinised. Hundreds of genes relevant to pain pathways have been demonstrated in animal studies,[98] and a smaller number have been demonstrated in humans.[99] Previous work has shown that sensitivity to painful stimuli and pain tolerability are, to a significant extent, determined by our genes.[100,101] It is clear that there is no unique 'pain' gene, but that a complex combination of genetic factors interacts with psychosocial and lifestyle factors to produce chronic pain.[102] Genes may act at a number of levels to influence the expression of chronic pain, including biological processes and behavioural and emotional responses. Identifying specific genes and their roles,

and distinguishing these from other sources of variation (gender, ethnicity, socio-cultural, psychological, etc.) is currently an important challenge.

There is some evidence that 'pain reporting' itself is a heritable phenotype, i.e. partly determined by genes, the shared milieu or environment, and their interaction.[103] There is also evidence from birth cohort studies that suggests that chronic pain conditions 'run in families', and that children of parents with chronic pain conditions are more likely to develop pain conditions themselves.[104–106] There are also certain clinical pain-related traits that are heritable, e.g. cold pressor pain, heat pain threshold and pinprick hyperalgesia[107,108] in response to painful experimental stimuli.[106] 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. The failure to address those non-genetic aspects (e.g. pain behaviour) as part of a pain management programme will prevent the effective treatment of pain symptoms.

A more immediate benefit of the new genetic insight into pain is more subtle. An appreciation of the fact that a substantial part of the variation in pain perception has a genetic basis has the potential to change attitudes of both patients and their carers towards the nature of the pain itself and the reasons underlying an individual's response to it. The knowledge that pain has a genetic basis (to some degree) may also allow a more precise understanding of the role of the environment in explaining the development of pain in genetically susceptible individuals.[109]

What does the future hold?

Chronic pain is now acknowledged as a condition in its own right, underpinned by an agreed set of definitions for most chronic pain conditions,[110] and there is a new sense of purpose shown by clinicians and governments, including in the UK.[111] The first hurdle is the better recognition of chronic pain. Dedicated coding within routinely collected data sources and disease registries is required to enable population and health system surveillance of chronic pain, large-scale studies of risks, treatments and outcomes, and crucially, visibility, linking chronic pain to existing (and better-funded) health priority areas such as cancer, injury, obesity and healthy ageing.[112]

Conclusion

The existence of both individual-level and population-level risk factors for the onset or persistence of pain suggests that opportunities for intervention exist at more than one level.[113] Research that ignores population-level factors and intervenes exclusively in high-risk individuals (e.g. specialist pain clinics) could limit options for reducing the overall community burden of chronic pain. Chronic pain management dominated by analgesic medication will fail to address adequately the role of activity, psychological factors and social factors in maintaining daily function. There are clear opportunities for all health professionals to facilitate changes in lifestyle that have the potential to improve morbidity and function in patients with chronic pain, simultaneously reducing the risks and impact of common co-morbidities. Further research is required to identify the most effective approaches, and this should be a priority for all health services.

Conflict of interest

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References

1. Breivik H, Collett B, Ventafridda V, et al. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain* 2006; 10: 287–333.
2. To T, Stanojevic S, Moores G, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health* 2012; 12(204).
3. International Diabetes Federation. IDF Diabetes Atlas Update 2012, http://www.idf.org/sites/default/files/IDF_EUR_5E_Update_FactSheet1_0.pdf.
4. Breivik H, Collett B and Ventafridda V. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain* 2006; 10: 287–333.
5. Smith B and Torrance N. Management of chronic pain in primary care. *Curr Opin Support Palliat Care* 2011; 5(2): 137–142.
6. Institute of Medicine of the National Academies. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington, DC: National Academy Press, 2011.
7. Last R. *A Dictionary of Epidemiology*. 4th ed. Oxford: International Epidemiological Association, 2001.
8. Smith B, Macfarlane G and Torrance N. Epidemiology of chronic pain, from the laboratory to the bus stop: time to add understanding of biological mechanisms to the study of risk factors in population-based research. *Pain* 2007; 127: 5–10.
9. Bergman S, Herrstrom P, Jacobsson L, et al. Chronic widespread pain: a three year followup of pain distribution and risk factors. *J Rheumatol* 2002; 29: 818–825.
10. Elliott A, Smith B, Hannaford P, et al. The course of chronic pain in the community: results of a 4-year follow-up study. *Pain* 2002; 99: 299–307.

11. Rodriguez-Raecke R, Niemeier A and Ihle K. Brain gray matter decrease in chronic pain is the consequence and not the cause of pain. *J Neurosci* 2009; 29: 13746–13750.
12. Gwilym S, Fillipini N and Douaud G. Thalamic atrophy associated with painful osteoarthritis of the hip is reversible after arthroplasty; a longitudinal voxel-based-morphometric study. *Arthritis Rheum* 2010; 62: 2930–2940.
13. Teutsch S, Herken W and Bingel U. Changes in brain gray matter due to repetitive painful stimulation. *Neuroimage* 2008; 42: 845–849.
14. Boersma K and Linton S. Expectancy, fear and pain in the prediction of chronic pain and disability: a prospective analysis. *Eur J Pain* 2006; 10: 551–557.
15. van der Windt D, Croft P and Penninx B. Neck and upper limb pain: more pain is associated with psychological distress and consultation rate in primary care. *J Rheumatol* 2002; 29: 564–569.
16. van der Windt D, Kuijpers T, Jellema P, et al. Do psychological factors predict outcome in both low-back pain and shoulder pain? *Ann Rheum Dis* 2007; 66: 313–319.
17. Nijrolder I, van der Windt D and van der Horst H. Prediction of outcome in patients presenting with fatigue in primary care. *Br J Gen Pract* 2009; 59: e101–e109.
18. Von Korff M, Le Resche L and Dworkin SF. First onset of common pain symptoms: a prospective study of depression as a risk factor. *Pain* 1993; 55: 251–258.
19. Bar K, Wagner G, Koschke M, et al. Increased prefrontal activation during pain perception in major depression. *Biological Psychiatry* 2007; 62: 1281–1287.
20. Kroenke K, Bair M, Damush T, et al. Optimized antidepressant therapy and pain self-management in primary care patients with depression and musculoskeletal pain: a randomized controlled trial. *JAMA* 2009; 301: 2099–2110.
21. Barnett K, Mercer SW, Norbury M, et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* 2012; 380(9836): 37–43.
22. Butchart A, Kerr E, Heisler M, et al. Experience and management of chronic pain among patients with other complex chronic conditions. *Clin J Pain* 2009; 25: 293–298.
23. Torrance N, Elliott A, Lee A, et al. Severe chronic pain is associated with increased 10 year mortality. A cohort record linkage study. *Eur J Pain* 2010; 14(4): 380–386.
24. Dominick C, Blyth F and Nicholas M. Unpacking the burden: Understanding the relationships between chronic pain and co-morbidity in the general population. *Pain* 2012; 153: 292–304.
25. Vogt MT, Hanscom B, Lauerman WC, et al. Influence of smoking on the health status of spinal patients: the National Spine Network database. *Spine (Phila Pa 1976)* 2002; 27: 313–319.
26. Weingarten TN, Moeschler SM, Ptaszynski AE, et al. An assessment of the association between smoking status, pain intensity, and functional interference in patients with chronic pain. *Pain Physician* 2008; 11: 643–653.
27. John U, Hanke M, Meyer C, et al. Tobacco smoking in relation to pain in a national general population survey. *Prev Med* 2006; 43: 477–481.
28. Shi Y, Weingarten TN, Mantilla CB, et al. Smoking and pain: pathophysiology and clinical implications. *Anesthesiology* 2010; 113: 977–992.
29. Goesling J, Brummett CM and Hasse AL. Cigarette smoking and pain: depressive symptoms mediate smoking-related pain symptoms. *Pain* 2012; 153: 1749–1754.
30. Hooten WM, Shi Y, Gazelka HM, et al. The effects of depression and smoking on pain severity and opioid use in patients with chronic pain. *Pain* 2011; 152: 223–229.
31. Hooten WM, Townsend CO, Bruce BK, et al. Effects of smoking status on immediate treatment outcomes of multidisciplinary pain rehabilitation. *Pain Med* 2009; 10(2): 347–355.
32. Proverbs 31:6.
33. Riley JL and King C. Self-report of alcohol use for pain in a multi-ethnic community sample. *J Pain* 2009; 10(9): 944–952.
34. Brennan P, Schutte K and Moos R. Pain and use of alcohol to manage pain: prevalence and 3-year outcomes among older problem and non-problem drinkers. *Addiction* 2005; 100: 777–786.
35. Ekholm O, Grønbaek M, Peuckmann V, et al. Alcohol and smoking behavior in chronic pain patients: the role of opioids. *Eur J Pain* 2009; 13(6): 606–612.
36. Hitt H, McMillen R, Thornton-Neaves T, et al. Comorbidity of obesity and pain in a general population: results from the southern pain prevalence study. *J Pain* 2007; 8: 430–436.
37. Wright LJ, Schur E, Noonan C, et al. Chronic pain, overweight, and obesity: findings from a community-based twin registry. *J Pain* 2010; 11: 628–635.
38. Marcus D. Obesity and the impact of chronic pain. *Clin J Pain* 2004; 20: 186–191.
39. Janke EA, Collins A and Kozak AT. Overview of the relationship between pain and obesity: What do we know? Where do we go next? *JRRD* 2002; 44(2): 245–262.
40. Ray L, Lipton R, Zimmerman M, et al. Mechanisms of association between obesity and chronic pain in the elderly. *Pain* 2011; 152: 53–59.
41. Heim N, Snijder M, Deeg D, et al. Obesity in older adults is associated with an increased prevalence and incidence of pain. *Obesity (Silver Spring)* 2008; 16: 2510–2517.
42. Shi Y, Hooten M, Roberts RO, et al. Modifiable risk factors for incidence of pain in older adults. *Pain* 2010; 151: 366–371.
43. Shapiro JR, Anderson DA and Danoff-Burg S. A pilot study of the effects of behavioral weight loss treatment on fibromyalgia symptoms. *J Psychosom Res* 2005; 59(5): 275–282.
44. Muehlbacher M, Nickel MK, Kettler C, et al. Topiramate in treatment of patients with chronic low back

pain: a randomized, double-blind, placebo-controlled study. *Clin J Pain* 2006; 22: 526–531.
45. Landsberg L, Aronne LJ, Beilin LJ, et al. Obesity-related hypertension: pathogenesis, cardiovascular risk, and treatment – a position paper of the Obesity Society and the American Society of Hypertension. *Obesity* 2013; 21: 8–24.
46. Busch AJ, Schachter CL, Overend TJ, et al. Exercise for fibromyalgia: a systematic review. *J Rheumatol* 2008; 35(6): 1130–1144.
47. Hendrick P, Te Wake AM, Tikkisetty AS, et al. The effectiveness of walking as an intervention for low back pain: a systematic review. *Eur Spine J* 2010; 19(10): 1613–1620.
48. Hall A, Maher C, Latimer J, et al. The effectiveness of Tai Chi for chronic musculoskeletal pain conditions: a systematic review and meta-analysis. *Arthritis Rheum* 2009; 61(6): 717–724.
49. Scottish Intercollegiate Guidelines Network. *SIGN guideline on chronic pain* (draft), 2012.
50. Liddle SD, Gracey JH and Baxter GD. Advice for the management of low back pain: a systematic review of randomised controlled trials. *Manual Therapy* 2007; 12(4): 310–327.
51. Nittera AK, Pripp AH and Forsetha KØ. Are sleep problems and non-specific health complaints risk factors for chronic pain? A prospective population-based study with 17 year follow-up. *Scand J Pain* 2012; 3: 210–217.
52. Campbell P, Tang N, McBeth J, et al. The role of sleep problems in the development of depression among those with chronic pain: a prospective cohort study. *Sleep* 2013; in press.
53. Sesti F, Capozzolo T, Pietropolli A, et al. Dietary therapy: a new strategy for management of chronic pelvic pain. *Nutr Res Rev* 2011; 24(1): 31–38.
54. Hagen KB, Byfuglien MG, Falzon L, et al. Dietary interventions for rheumatoid arthritis. *Cochrane Database Syst Rev* 2009; (1): CD006400.
55. Goldberg R and Katz J. A meta-analysis of the analgesic effects of omega-3 polyunsaturated fattyacid supplementation of inflammatory joint pain. *Pain* 2007; 152: 210–223.
56. Rivat C, Richebe P, Laboureyas E, et al. Polymamine deficient diet to reduce pain hypersensitivity. *Pain* 2008; 137: 125–137.
57. Cipolla B, Havouis R and Moulinoux J. Polyamine reduced diet (PRD) nutrition therapy in hormone refractory prostate cancer patients. *Biomed Pharmacother* 2010; 64: 363–368.
58. Mijnhout G, Kollen B, Alkhalaf A, et al. Alpha lipoic acid for symptomatic peripheral neuropathy in patients with diabetes: a meta-analysis of randomized controlled trials. *Int J Endocrinol* 2012: 456279.
59. Michalsen A, Kuhlmann M, Lüdtke R, et al. Prolonged fasting in patients with chronic pain syndromes leads to late mood-enhancement not related to weight loss and fasting-induced leptin depletion. *Nutr Neurosci* 2006; 9: 195–200.
60. Sawynok J. Caffeine and pain. *Pain* 2011; 152: 726–729.
61. Elliott A, Smith B, Penny K, et al. The epidemiology of chronic pain in the community. *Lancet* 1999; 354(9186): 1248–1252.
62. Shaw W, Linton S and Pransky G. Reducing sickness absence from work due to low back pain: how well do intervention strategies match modifiable risk factors? *J Occup Rehabil* 2006; 16: 591–605.
63. Macfarlane TV, Mcbeth J, Jones GT, et al. Whether the weather influences pain? Results from the EpiFunD study in North West England. *Rheumatology* 2010; 49(8): 1513–1520.
64. Straube S, Andrew Moore R, Derry S, et al. Vitamin D and chronic pain. *Pain* 2009; 141: 10–13.
65. Straube S, Derry S, Moore RA, et al. Vitamin D for the treatment of chronic painful conditions in adults. *Cochrane Database Syst Rev* 2010; (1): CD007771.
66. Dionne C, Dunn K and Croft P. Does back pain prevalence really decrease with increasing age? A systematic review. *Age Ageing* 2007; 35: 229–234.
67. Thomas E, Mottram S, Peat G, et al. The effect of age on the onset of pain interference in a general population of older adults: prospective findings from the North Staffordshire Osteoarthritis Project (NorStOP). *Pain* 2007; 129: 21–27.
68. Docking R, Fleming J, Brayne C, et al. Epidemiology of back pain in older adults: prevalence and risk factors for back pain onset. *Rheumatology* 2011; 50: 1645–1653.
69. Thomas E, Peat G, Harris L, et al. The prevalence of pain and pain interference in a general population of older adults: cross-sectional findings from the North Staffordshire Osteoarthritis Project (NorStOP). *Pain* 2004; 110: 361–368.
70. United Nations Population Division, Department of Economic and Social Affairs. *World Population Prospects: The 2010 Revision*. New York: United Nations Population Division, 2011.
71. Greenspan J, Craft R and LeResche L. Studying sex and gender differences in pain and analgesia: a consensus report. *Pain* 2007; 132: S26–S45.
72. Wiesenfeld-Hallin Z. Sex differences in pain perception. *Gend Med* 2005; 2: 137–145.
73. Unruh A. Gender variations in clinical pain experience. *Pain* 1996; 65: 123–167.
74. Craft RM, Mogil JS and Aloisi AM. Sex differences in pain and analgesia: the role of gonadal hormones. *Eur J Pain* 2004; 8: 397–411.
75. Craft R. Modulation of pain by estrogens. *Pain* 2007; 132: S3–S12.
76. Pieh C, Altmeppen J, Neumeier S, et al. Gender differences in outcomes of a multimodal pain management program. *Pain* 2012; 153: 197–202.
77. Tsang A, Von Korff M, Lee S, et al. Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. *J Pain* 2008; 9(10): 883–891.
78. Faucett J, Gordon N and Levine J. Differences in postoperative pain severity among four ethnic groups. *J Pain Symptom Manage* 1994; 9: 383–389.

79. Stewart WF, Lipton RB and Liberman J. Variation in migraine prevalence by race. *Neurology* 1996; 47: 52–59.
80. Meshack AF, Goff DC, Chan W, et al. Comparison of reported symptoms of acute myocardial infarction in Mexican Americans versus non-Hispanic whites (the Corpus Christi Heart Project) *Am J Cardiol* 1998; 82: 1329–1331.
81. Edwards CL, Fillingim RB and Keefe FJ. Race, ethnicity and pain: a review. *Pain* 2001; 94: 133–137.
82. Green CR, Anderson KO, Baker TA, et al. The unequal burden of pain: confronting racial and ethnic disparities in pain. *Pain Med* 2003; 4(3): 277–294.
83. Fillingim RB. Social and environmental influences on pain: implications for pain genetics. In: Mogil JS (ed) *The Genetics of Pain*. Seattle: IASP Press; 2004, p. 283–303.
84. Bisgaard T, Klarskov B, Rosenberg J, et al. Characteristics and prediction of early pain after laparoscopic cholecystectomy. *Pain* 2001; 90: 261–269.
85. Granot M. Can we predict persistent postoperative pain by testing preoperative experimental pain? *Curr Opin Anaesthesiol* 2009; 22(3): 425–430.
86. Edwards RR, Doleys DM, Lowery D, et al. Pain tolerance as a predictor of outcome following multidisciplinary treatment for chronic pain: differential effects as a function of sex. *Pain* 2003; 106: 419–426.
87. Blyth F. Chronic pain – is it a public health problem? *Pain* 2008; 137: 465–466.
88. Poleshuck E and Green C. Socioeconomic disadvantage and pain. *Pain* 2008; 136: 235–238.
89. Brekke M, Hjortdahl P and Kvien T. Severity of musculoskeletal pain: relationship to socioeconomic inequality. *Soc Sci Med* 2002; 54: 221–228.
90. Eachus J, Chan P, Pearson N, et al. An additional dimension to health inequality: disease severity and socioeconomic position. *J Epidemiol Community Health* 1999; 53: 603–611.
91. Jordan K, Thomas E, Peat G, et al. Social risks for disabling pain in older people: a prospective study of individual and area characteristics. *Pain* 2008; 137: 652–666.
92. Canizares M, Power J, Perruccio A, et al. Association of regional racial/cultural context and socioeconomic status with arthritis in the population: a multi-level analysis. *Arth Rheum* 2008; 59: 399–407.
93. Fuentes M, Hart-Johnson T and Green C. The association among neighborhood socioeconomic status, race and chronic pain in Black and White older adults. *J Nat Med Assoc* 2007; 99: 1160–1169.
94. Kehlet H, Jensen TS and Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet* 2006; 367: 1618–1625.
95. Macrae WA. Chronic post-surgical pain: 10 years on. *Br J Anaesth* 2008; 101: 77–86.
96. Ellsberg M, Jansen H, Heise L, et al. Intimate partner violence and women's physical and mental health in the WHO multi-country study on women's health and domestic violence: an observational study. *Lancet* 2008; 371: 1165–1172.
97. Sachs-Ericsson N, Kendall-Tackett K and Hernandez A. Childhood abuse, chronic pain, and depression in the National Comorbidity Survey. *Child Abuse Negl* 2007; 31: 531–547.
98. LaCroix-Fralish ML, Ledoux JB and Mogil JS. The Pain Genes Database: an interactive web browser of pain-related transgenic knockout studies. *Pain* 2007; 131(3): e1–e3.
99. Diatchenko L, Nackley A, Tchivileva I, et al. Genetic architecture of human pain perception. *Trends Genet* 2007; 23(12): 605–613.
100. Norbury T, MacGregor A, Urwin J, et al. Heritability of responses to painful stimuli in women: a classical twin study. *Brain* 2007; 130: 3041–3049.
101. Nielsen C, Stubhaug A, Price D, et al. Individual differences in pain sensitivity: genetic and environmental contributions. *Pain* 2008; 136: 21–29.
102. Mogil J. Pain genetics: past, present and future. *Trends Genet* 2012; 28(6): 258–266.
103. MacGregor A, Li Q, Spector T, et al. The genetic influence on radiographic osteoarthritis is site specific at the hand, hip and knee. *Rheumatology* 2009; 48: 277–280.
104. Grøholt K, Stigum H, Nordhagen R, et al. Recurrent pain in children, socio-economic factors and accumulation in families. *Eur J Epidemiol* 2003; 18: 965–975.
105. Jones G, Silman A, Power C, et al. Do common symptoms in childhood increase the risk of chronic widespread pain in adults? Data from the 1958 British Birth Cohort Study. *Am J Epidemiol* 2006; 163: S14.
106. Hocking L, Generation Scotland Morris A, et al. Heritability of chronic pain in 2195 extended families. *Eur J Pain* 2012; 16: 1053–1063.
107. Nielsen C, Stubhaug A, Price D, et al. Individual differences in pain sensitivity: genetic and environmental contributions. *Pain* 2008; 136: 21–29.
108. Norbury T, MacGregor A, Urwin J, et al. Heritability of responses to painful stimuli in women: a classical twin study. *Brain* 2007; 130: 3041–3049.
109. Macgregor A. The genetic epidemiology of pain. In: Croft P, Blyth FM and Van der Windt D (eds) *Chronic Pain Epidemiology: From Aetiology to Public Health*. New York: Oxford University Press, 2010, pp. 83–99
110. IASP. *Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms*. Available at: (1986, accessed 13 June 2013).
111. Johnson M. *It's only pain…?* London: RCGP, 2012.
112. Blyth F, van der Windt D and Croft P. Introduction to chronic pain as a public health problem. In: Croft P, Blyth FM and van der Windt D (eds) *Chronic Pain Epidemiology: From Aetiology to Public Health*. New York: Oxford University Press, 2010. p. 279–287.
113. Blyth FM. Chronic pain – is it a public health problem? *Pain* 2008; 137: 465–466.