Psychosocial vulnerability and early life adversity as risk factors for central sensitivity syndromes

Author Gareth T Jones PhD

Contact details

Epidemiology Group, Institute of Applied Health Sciences
School of Medicine and Dentistry, University of Aberdeen
Polwarth Building, Foresterhill, Aberdeen, AB25 2ZD, United Kingdom

Tel: +44 (0) 01224 437 143
E-mail: gareth.jones@abdn.ac.uk
Web: www.abdn.ac.uk/epidemiology
www.abdn.ac.uk/staffpages/gareth.jones

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ABSTRACT

The aim of this narrative review of the epidemiology of central sensitivity syndromes is to provide a summary of the role of early life adversity and psychosocial / psychological factors, in the epidemiology of six main syndromes: (i) fibromyalgia / chronic widespread pain; (ii) headache / migraine; (iii) irritable bowel syndrome; (iv) temporomandibular joint disorder; (v) interstitial cystitis; and (vi) endometriosis / vulvodynia / chronic pelvic pain.

The occurrence of each of the above syndromes vary between each other, and between studies. Prevalence ranges from interstitial cystitis, with a prevalence of approximately 14.5 per 100,000, to headache, with some estimates of lifetime prevalence to be around 66%.

Precise risk estimates vary between studies, conditions, and exposures, although there is consistent evidence to suggest an association between early life adversity and central sensitivity syndromes (based on the six syndromes under investigation). In further support of this, a number of studies have also demonstrated dose-risk associations. There is also considerable consistency in the literature to suggest a strong association between negative psychological and psychosocial factors, and the occurrence of central sensitivity syndromes and, again, there is some evidence of a dose-risk relationship.

The majority of studies in this field are cross-sectional or retrospective in design, and caution is advised when interpreting results. It is possible – indeed there is some evidence – that some findings may be subject to recall bias, and reverse causation is also a potential concern. However, there are also a number of prospective studies which provide more robust evidence.

INTRODUCTION

The term central sensitivity syndrome describes one, or more, of a number of overlapping conditions, that are characterised by hypersensitivity to various external (noxious and normally non-noxious) stimuli, and share the common mechanism of central sensitisation (1). Although they share some unifying features, the prevalence of these conditions varies considerably.

The aim of this review is not to provide a comprehensive systematic review of the epidemiology of all of the individuals conditions in this group. Rather, it is to provide a summary of the epidemiology of the major syndromes – namely (i) fibromyalgia / chronic widespread pain; (ii) headache / migraine; (iii) irritable bowel syndrome; (iv) temporomandibular joint disorder; (v) interstitial cystitis; and (vi) endometriosis / vulvodynia / chronic pelvic pain – and to focus, specifically on early life adversity and psychosocial vulnerability, in the widest sense, as risk factors for these conditions. Firstly, however, it is important, briefly, to consider the descriptive epidemiology of these conditions and syndromes under review.

DESCRIPTIVE EPIDEMIOLOGY

There are few good estimates of the prevalence of fibromyalgia in the general population. Using the American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia (2) several authors have demonstrated the prevalence to be 0.7 to 2.4% in Europe (3;4) and 2.0 to 3.3% in North America (5;6). Recently, new classification criteria have been proposed (7;8) although controversy currently exists surrounding their use, they are not formally adopted, and some have shown that prevalence varies from 1.7% to 5.4% depending on which criteria are used (9). Chronic widespread pain, often considered a proxy for fibromyalgia in research, has been studied more widely and prevalence estimates are consistent at around 10.5 to 13.5% (6;10-13).

In contrast, there is much variation in headache prevalence estimates between studies. However, comparing results between studies is not always simple, due to a methodological differences: some have reported that that differences in case definition explains much of the variance between studies (14), although the use of standardised diagnostic criteria reduces this variation. In a review of the worldwide literature, the lifetime prevalence of headache and migraine was reported to be 66% and 14%, respectively (15). Others have shown that the one-year prevalence of tension-type headache is 74% (16) although a more recent review reported the prevalence to be slightly lower, at 63% (17).

Like headache and migraine, prevalence estimates of irritable bowel syndrome can vary enormously. A recent review reported that prevalence estimates vary between 10% and 25% (18), although pooled data, across 80 separate study populations found a prevalence of 11.2% (19). As with headache, some of the variation may be explained by the use of different classification and diagnostic criteria, although other study differences may also explain some of the heterogeneity.

Temporomandibular joint disorder is one of the most common conditions leading to chronic facial pain. A number of recent studies have reported different prevalence estimates although, again, comparisons are difficult due to different case definition and methodological differences between studies. Some have shown the prevalence of jaw pain to be 30% (20), and two recent studies from the UK have shown a prevalence of orofacial pain to be between 23% and 26% (21;22).

Some estimates of the prevalence of interstitial cystitis came from a number of database studies. An initial study in Finland reported the prevalence to be 10.6 per 100,000 and 18.1 per 100,000 in men and women respectively (23). It has been noted that it is difficult to determine the extent to which different estimates represent true differences in prevalence, because of different study methods (24), and exemplifying this, a recent study in the USA demonstrated prevalence estimates ranging from 8 to 41 per 100,000 men and 45 to 197 per 100,000 women, depending on which of a number of different case definitions are employed (25).

Compared with many other pain syndromes, the study of the epidemiology of endometriosis, vulvodynia, and non-specific chronic pelvic pain is lagging behind the curve. In clinic populations, prevalence of endometriosis has been shown to vary between 4% and 50%, although data in the general population is more sparse (26). A large questionnaire-based survey in the USA found approximately 1 in 12 women reported symptoms consistent with vulvodynia (27). Others have demonstrated a similar prevalence in Europe, with a lifetime prevalence of 16% (28). And in a recent review of chronic pelvic pain, prevalence was shown to range between 5.7 and 27% (29). Among women with chronic pelvic pain, the prevalence of endometriosis was 70% (30). In this patient group, from the same studies, the prevalence of bladder pain syndrome was also high, at 61%.

THE ROLE OF EARLY LIFE FACTORS

Fibromyalgia / chronic widespread pain

A number of studies have demonstrated an association between chronic musculoskeletal pain in adulthood, and adverse childhood exposures. Using biographical interview techniques, Imbierowicz and Egle (2003) demonstrated that patients with fibromyalgia reported more childhood adversities than persons with medically explained chronic pain (31). They reported more sexual and physical maltreatment, poor inter-parent and parent-child relationships, and a number of other indicators of childhood adversity. Others have shown that women with fibromyalgia are more likely to report a history of childhood physical and sexual abuse (32), and others have shown an excess of prior hospitalisations and surgery (33) among individuals with chronic widespread pain. In this latter study, individuals with chronic widespread pain, identified by postal questionnaire, were five times more likely to self-report childhood hospitalisation (odds ratio (OR) = 5.1; 95% confidence interval: 2.0 to 13.0) and three times more likely to self-report childhood surgery (OR = 3.0; 1.2 to 7.2). However, when examining the relationship – among the same individuals – using primary care records, both effects were greatly attenuated and neither remained statistically significant (OR = 2.2; 0.9 to 5.5 and OR = 1.2; 0.5 to 3.4, respectively). Further examination of this revealed that individuals with

chronic widespread pain fairly accurately remembered this childhood exposures, whereas those without chronic widespread pain tended to under-report their exposure (33).

There are a number of limitations to previous work in this area. Chronic pain research, or at least the inferences from chronic pain research, suffers from the fact that chronic pain is insidious in onset (indeed, most accepted definitions of chronic pain require symptoms for at least three months before chronicity can be established) and it is difficult therefore to measure disease onset with any precision. There is also often an unknown latent period between exposure and outcome. But the biggest limitation when studying early life exposures, is that most evidence comes from case-control studies with retrospectively collected information on early life exposures, and seldom is there objective confirmation, or even third party verification, of these childhood exposures. McBeth et al., above, clearly demonstrated the potential for recall bias, and the exaggeration of effect that can occur. In order to examine the relationship adequately, it is important to measure childhood exposures in the absence of recall bias. Thus, prospective studies are required. These, by definition, take many years and accordingly are very – often prohibitively – expensive.

A number of papers have been published using data from the 1958 British Birth Cohort. This study, well documented elsewhere (34), comprised over 17,000 individuals all born in Great Britain in one week in March 1958. Although not initially planned as a longitudinal study, the cohort has been followed up on numerous occasions, most pertinently at ages 7yrs, 11yrs and 16yrs, at which point various early life exposures were recorded, and at 45yrs when information on chronic musculoskeletal pain was collected by self-completion questionnaire. Macfarlane et al (2009) demonstrated not only that the prevalence of chronic widespread pain was inversely proportional to socioeconomic status in adulthood, but that the same was also true for socioeconomic status at birth (35). Premature birth (<37 weeks) and very low birth weight (<1500g) were also associated with an increase in the risk of chronic widespread pain in adulthood, although these were not statistically significant (risk ratio (RR) = 1.3; 0.95 to 1.7, and RR = 1.5; 0.4 to 5.2) and, in the case of the former, completely explained by statistical adjustment for childhood behavioural problems and adult psychiatric disorder (36).

In the same cohort, Jones et al (2007) produced an index of common childhood symptoms that had been recorded, at age 7yrs, by maternal report: vomiting or bilious attacks; abdominal pain; and headaches or migraine. They found that over one quarter of mothers reported that their child had one or more of these symptoms (20%, 7.1% and 1.5%, for one, two and three symptoms respectively.) The prevalence of chronic widespread pain among offspring, at 45yrs, was 11.8% but showed a marked increase among those who, at age 7yrs had had all three of these common symptoms (RR = 1.5; 1.03 to 2.3). This relationship was robust to adjustment for sex, childhood and adulthood socioeconomic status, and (adult) psychological distress (37) (see Table 1).

The same authors in 2009 examined the role of a number of early life adversities. They found a dose risk relationship to suggest the greater the extent of maternal separation in childhood, the greater the risk of chronic widespread pain in adulthood (38). Children who had experienced more than six months' maternal, prior to age 7yrs, were 40% more likely to report chronic widespread pain 38yrs later (RR = 1.4; 1.02 to 2.1). The association was even stronger among children exposed to period periods in local authority institutional care (RR = 1.9; 1.4 to 2.7). Various family adversities including parental relationship difficulties (RR = 1.4; 1.1 to 1.9), parental alcoholism (RR = 1.7; 0.99 to 3.0) and financial difficulties (RR = 1.8; 1.5 to 2.2) were also associated with an increase in the risk of chronic widespread pain in adulthood. And, while maternal death was associated in a doubling in the risk of adulthood chronic widespread pain (RR = 2.0; 1.08 to 3.9), no such association was observed with the death of the father (RR = 0.9; 0.5 to 1.7) (38).

Headache / migraine

A number of authors have studied the relationship between early life factors and headache. Anda et al (2010) studied a variety of adverse childhood experiences and the prevalence of headaches in adulthood – as self-reported by the question: are you troubled by frequent headaches? All adverse childhood experiences investigated were associated with an increase in the risk of headaches, ranging from parental separation

/divorce (RR = 1.1; 1.0 to 1.2), to physical and emotional abuse (1.4; 1.3 to 1.5, and 1.6; 1.4 to 1.7, respectively) (39). Using these variables, and the other adverse experiences under investigation (sexual abuse, witnessing domestic violence, and household member substance abuse, mental illness or imprisonment) the authors produced an 'Adverse Childhood Experiences (ACE) score', a count of the number of exposures experienced by each individual. They demonstrated a dose-risk relationship: compared to individuals with an ACE score of zero, those with 4 or ≥5 were twice as likely to report frequent headaches (OR = 2.0; 1.7 to 2.3, and OR = 2.1; 1.8 to 2.4, respectively) (39).

Tietjen et al (2012) demonstrated similar findings in women with migraine. One hundred women were recruited with migraine, with or without aura, plus 41 controls. Women with migraine were around 50% more likely to report adversity compared to controls (OR = 1.5; 1.1 to 2.2). Further, using the same methods as Anda et al., above, these authors computed an ACE score. They found that average ACE scores were higher in the migraine group (2.4 adverse childhood experiences), compared with controls (0.76 experiences) ($p<.001$), and also that adversity score was associated with headache frequency, and younger age of onset (40).

There is some evidence that the relationship between adverse experiences and headache starts in childhood. Waldie et al (2014) recruited 871 children at birth and followed them until age 11yrs when the prevalence of headache was determined (41). They found that children who reported recent bullying (defined as physical violence, verbal teasing, sexual harassment or racist comments more than five times during the previous six months) were significantly more likely to report tension-type headaches than other children (OR = 1.87; 1.20 to 2.92). The relationship with migraine was also positive, although of smaller magnitude and not statistically significant (OR = 1.30; 0.73 to 2.33).

However, the majority of studies in the field, including all the studies mentioned above, are retrospective in design. Childhood experiences were determined by questionnaire, after the onset of headaches, and it is not

possible to completely exclude the possibility of recall bias – i.e. that persons with and without headaches recall past exposures to a different extent, biasing the effect size of the observed relationship.

Collecting data prospectively, Aromaa et al (1998) recruited over 1000 families expecting their first child, and followed them from pregnancy for six years. They found that poor health, as assessed by maternal report, was associated with more than a doubling in the likelihood of headaches in the child (OR = 2.5; 1.1 to 5.8) (42). Headaches were also predicted by a number of other factors, both in infancy and childhood, including long-term disease at 5yrs (OR = 2.3; 1.3 to 4.1). However, various familial difficulties (parental divorce, one-parent family, several relocations and 'other parenthood variables') were not associated.

Using the 1958 British Birth Cohort, described above, Fearon and Hotopf found that recurrent childhood headaches not only predicted the occurrence of multiple physical symptoms in adulthood, and adult psychiatric morbidity, but also significantly predicted the occurrence of headaches at age 33yrs (OR = 2.2; 1.6 to 3.1), these results after adjusting for sex, socioeconomic status, a number of childhood variables, and psychiatric morbidity (43).

Irritable bowel syndrome

Investigating the association between early life experiences and irritable bowel syndrome. Drossman et al (1990) studied 206 women from a gastroenterology clinic. They found that those with functional gastrointestinal disorders were more likely than those with organic disease to report a history of sexual or physical abuse (OR = 2.1; 1.03 to 4.2, and OR = 11.4; 2.2 to 58.5, respectively) (44). Similarly, Walker et al (1993) compared 28 patients with irritable bowel syndrome and 19 with inflammatory bowel disease and found that those with irritable bowel syndrome reported a greater history of severe childhood sexual abuse (45). In constrast, Koloski et al (2005) identified 158 cases (persons with irritable bowel syndrome as per the Rome I criteria (46)) and 100 controls. These authors found no significant association between physical (OR = 0.62; 0.23 to 1.71), sexual (OR = 1.42; 0.75 to 2.66) or emotional abuse (OR = 1.12; 0.51 to 2.47) (47). And

Salmon et al (2003) examined 64 patients with irritable bowel syndrome and 61 with inflammatory bowel disease and found that those with functional disease were more likely to report childhood sexual (OR = 4.93; 1.33 to 18.27), physical (OR = 3.72; 1.51 to 9.16) and psychological (OR = 1.42; 0.68 to 2.97) abuse (48).

Moving away from the clinic, two studies by Talley et al studied the association in the general population. Firstly, among 919 residents of Olmsted County, Minnesota, irritable bowel syndrome was found to be significantly associated with sexual abuse, emotional or verbal abuse, and abuse in childhood and adulthood (49). Secondly, in a general population sample of 730 residents of Sydney, Australia, self-reported history of child abuse was associated with the occurrence of irritable bowel syndrome (OR = 2.02; 1.29 to 3.15). However, further analysis revealed that this relationship was confounded by age, gender, and psychological factors and, after adjusting for these factors the association was attenuated, and no longer statistically significant (OR = 1.34; 0.83 to 2.17) (50).

In addition to physical and sexual abuse, Bradford et al (2012) examined the potential role of other early life adverse experiences in the aetiology of irritable bowel syndrome. Compared to controls, patients with irritable bowel syndrome were more likely to report witnessing violence, being put down or ridiculed, familial mental or psychiatric illness, and being poorly treated or feeling ignored (OR ranging from 2.1 to 3.1).

As with headaches, the majority of studies have been case-control studies, where exposure data is collected retrospectively, and cannot be assumed to be completely free of recall bias. Using data from the 1958 British Birth Cohort, Goodwin et al (2013) failed to demonstrate an association between childhood adversity and the onset of irritable bowel syndrome in adulthood (51). Others, in contrast, have demonstrated such an association. Data is available from the Dutch Famine Birth Cohort, a study of over 2000 infants born in the Netherlands either late in World War II, or immediately post-war (52). Using this study, Klooker et al (2009) employed a retrospective cohort study, where individuals are selected based on their exposure, and outcomes (case irritable bowel syndrome) are assessed many years later. These authors demonstrated a significant trend such that the greater the exposure to severe wartime conditions in early life, the greater the

risk of irritable bowel syndrome, as determined at age 58yrs using the Rome II criteria. Compared to those conceived after the war, those exposed for 1yr and 1.5yrs were respectively 50% and 80% more likely to develop irritable bowel syndrome in adult life (RR = 1.5; 0.7 to 2.9, and RR = 1.8; 0.9 to 3.5) (53). However, the authors were unable to determine whether the increase in risk was associated with the stressful environment of war, severe under-nutrition, or the increased prevalence of infectious diseases.

Temporomandibular joint disorder

There are few studies of early life adversity and the relationship with temporomandibular joint disorder. Riley et al (1998) found that a high proportion of patients with temporomandibular disorders reported a history of physical and / or sexual abuse (54). The same authors subsequently demonstrated that, among 114 women with temporomandibular joint disorder, those with a history of physical abuse, as ascertained by structured clinical interview, reported significantly more pain than those who reported a history of sexual abuse, or no abuse (55). And Filingim et al (1997) compared the self-report of physical and sexual abuse among women with temporomandibular joint disorder and among age-matched controls. These latter authors demonstrated that cases were around one-third more likely to report a history of abuse, although this association was not statistically significant (56).

Interstitial cystitis

Several authors have examined the prevalence of physical and sexual abuse among people (most commonly women) with interstitial cystitis. Goldstein et al (2008) reported that, among 141 women attending a specialist clinic for pelvic floor disorders, the prevalence of physical, sexual and childhood sexual abuse (defined as abuse occurring before the age of 14yrs) was 31%, 36% and 21% respectively (57). Similarly, Carrico et al (2009) found that 28% of nearly 200 women with interstitial cystitis / painful bladder syndrome reported a history of abuse (58), and Seth et al (2008) reported that 25% of 119 consecutive, newly diagnosed women with the same condition had a history of sexual abuse (59). This latter study also showed that women

interstitial cystitis / painful bladder syndrome with a history of abuse exhibited a different clinical presentation compared to those without such a history.

Although these figures are alarming, they do not provide information on whether an abuse history is more common among persons with interstitial cystitis than one might expect. To ascertain whether there was an association between early life abuse and the occurrence of interstitial cystitis, Peters et al (2007) sent postal questionnaires to over 336 cases (215 with established disease, and 121 with a history suggestive of interstitial cystitis) and 464 age-matched controls. They found that cases were significantly more likely to report a history of abuse (OR[1] = 2.9; 2.1 to 4.0) (60), and the magnitude of effect was similar for sexual (OR = 3.3; 2.1 to 5.3), emotional (OR = 3.0; 2.1 to 4.3), or physical abuse (OR = 3.4; 2.1 to 5.5). Although information was collected on the age that the abuse happened, it is not clear whether this abuse was in childhood, adulthood, or both. However, the authors corroborated their findings with additional data from a clinic population. In this, from 37 women who reported some form of abuse, on 40% of occasions this occurred in childhood (<14yrs) or adolescence (14-19yrs).

Endometriosis / vulvodynia / chronic pelvic pain

Edwards et al (1997) looked specifically at childhood sexual or physical abuse, and recruited 89 women with vulvodynia, and 65 controls with specific, objective vulvar disease, and 166 controls from a dermatology clinic. They found no differences in the occurrence of early life abuse, physical or sexual, between vulvodynia cases and either control group (61). In a large systematic review of papers published to 2004, Latthe et al (2006) investigated a number of factors potentially associated with chronic pelvic pain in women (62). They found five studies that examined the association between non-cyclical pelvic pain and childhood physical abuse, and ten that examined childhood sexual abuse, comprising over 3000 study participants. These early

[1] Odds ratios were calculated from data presented in the paper based on data that 37.7% of cases reported abuse. However, elsewhere in the paper is states that this figure is 37.3%. If the latter is correct these calculations are slightly changed (OR = 2.8; 2.1 to 3.9), but the interpretation remains the same.

life exposures were associated with a significant increase in the risk of pain symptoms (pooled OR = 2.2; 1.6 to 3.1 and pooled OR = 1.5; 1.2 to 2.0, respectively).

Peters et al (2008) examined the association between physical, sexual and emotional abuse, and vulvodynia. They found that while there was an effect of sizeable magnitude (OR = 1.7; 0.4 to 6.7, OR =2.9; 0.7 to 11.4, and OR =2.1; 0.3 to 13.4, respectively) none were statistically significant (63). However, the study had only a small sample size (N = 70), which would have prejudiced against finding a significant association. Others have suggested no association between history of abuse and pelvic pain in women (64), although this study sample was highly self-selected, using an online questionnaire of women who frequented various vulvar pain discussion lists.

Others have shown strong significant associations to the contrary. Harlow and Stewart (2005) recruited 125 women with symptoms of vulvodynia, and 125 age-marched controls from Boston, MA, and asked them to complete a questionnaire survey including questions on physical, sexual and emotional victimisation, and the threat of the same (65). They demonstrated clear dose-risk associations between the level of abuse, and the likelihood of vulvodynia (see Table 2). The report of severe physical abuse was four times more common in cases than controls (OR = 4.1; 1.7 to 10.0), and the report of severe sexual abuse was over six times more common (OR = 6.5; 1.2 to 35.1). A perceived threat of danger at home, or at school, was also more commonly reported (OR = 2.1; 1.0 to 4.6, and OR = 5.0; 1.0 to 25.0, respectively). Interestingly, however, a perceived threat of danger in the neighbourhood was not associated (OR = 0.6; 0.2 to 1.7, respectively) (65).

And more recently, Khandker et al (2014) conducted a matched case-control study of women with vulvodynia (66). These authors found that cases were significantly more likely to report a history of severe physical (OR = 2.4; 1.3 to 4.4) and sexual abuse (OR = 9.7; 1.2 to 79.1), compared to controls. There was also evidence of dose-risk relationship, such that compared to those with no history of abuse, those with one perpetrator were twice as likely to have vulvodynia (OR = 2.0; 1.2 to 3.3), whereas those with multiple perpetrators were two and a half times as likely (OR = 2.4; 1.3 to 4.5).

Again, however, with retrospectively collected exposure data it is not possible to exclude the possibility of recall bias and longitudinal studies are needed. Wieser et al (2012), however, conducted a prospective cohort study to examine the association between childhood / adolescent physical and sexual abuse, and the risk of endometriosis (67). Although data on abuse was collected retrospectively, as part of a large ongoing cohort (the Nurses' Health Study, USA) this was in advance of any endometriosis diagnosis, and it is therefore unlikely that outcome status could have influenced the reporting of the exposure. In this high quality study over 60,000 women contributed over 0.75 million person-years of follow-up, and nearly 2000 incident premenopausal cases of laparoscopically-confirmed endometriosis were identified. Women who reported one episode of mild/moderate abuse, either emotional, physical, or sexual, experienced a significant increase in the risk of onset of endometriosis, compared to other women (hazard ratio (HR) = 1.1; 1.02-1.3). This increased with increasing 'dose' of exposure, such that those who reported chronic severe abuse of multiple types (emotional, physical, or sexual) were more than twice as likely to develop endometriosis than women without an abuse history (HR = 2.1; 1.6 to 2.7).

THE ROLE OF PSYCHOLOGICAL / PSYCHOSOCIAL FACTORS

Fibromyalgia / chronic widespread pain

There is a move, by some, for the classification of fibromyalgia to become more wholly psychosocial, and less reliant on physical examination. In 2010 the American College of Rheumatology published new diagnostic criteria for fibromyalgia[2] which dispensed with the tender-point examination and, in addition to widespread pain, comprised a physician estimate of the burden of somatic symptoms generally – focusing, in particular fatigue, on waking unrefreshed, and cognitive symptoms (7). However, there is little robust epidemiological evidence, from longitudinal studies, demonstrating an association between these symptoms and the onset

[2] At the time of writing, these criteria are still considered preliminary and should be used with caution.

of fibromyalgia (as defined by these, or the previous (establish) classification criteria (2)). Researchers, instead, have often used the proxy of chronic widespread pain.

The association between chronic widespread pain and psychological / psychosocial factors is well established (11;13;68;69). However, there are a number of high quality studies examining these putative risk factors, longitudinally, to determine the relationship with chronic widespread pain onset. In a large population-based study of working-age adults free of chronic widespread pain, various psychosocial factors predicted chronic widespread pain onset over the twelve month follow-up period including adverse illness behaviour (RR = 2.9; 1.6 to 5.3), and high health anxiety (RR = 1.5; 0.9 to 2.4) (70). Even after adjusting for a range of baseline mechanical factors, and baseline pain, illness behaviour was independently associated with chronic widespread pain onset (RR = 2.1; 1.2 to 3.9).

The same authors subsequently demonstrated that the two factors that best predicted the onset of chronic widespread pain were a high score on the Illness Behaviour Scale score (indicating a tendency towards hypochondriasis) and a high Somatic Symptom Score (three of more, of five common symptoms) (71). Compared to individuals with low scores on both of these scales, those meeting the above criteria experienced a fifteen-fold increase in the risk of chronic widespread pain onset over the twelve month follow-up period (RR = 15.3; 5.0 to 46.5). This was then replicated in a second study, although the risk estimates were greatly attenuated (although still considerable) (RR = 6.1; 3.7 to 10.3) (72). Further, these authors demonstrated that, even after adjusting for baseline (regional) pain these variables remained predictors of chronic widespread pain onset.

Headache / migraine

Several studies have examined the association between headache and psychological / psychosocial factors. In a large study of over 10,000 participants, a representative sample of the French adult general population, Radat et al (2008) identified a number of psychological factors independently associated with chronic daily

headache, and migraine, including higher levels of emotional distress, catastrophizing and avoidance coping strategies and an externalized locus of control (73). Zwart et al (2003) studied around 45,000 individuals as part of the Nord-Trøndelag Health (HUNT-2) Study, in Norway, and examined the relationship between psychological factors and headaches occurrence (74). The study demonstrated that both anxiety and depression were significantly associated with migraine (OR = 2.7; 2.3 to 3.2, and OR = 3.2; 2.8 to 3.6, respectively) and non-migrainous headache (OR = 2.2; 2.0 to 2.5, and OR = 2.7; 2.4 to 3.0, respectively). In both migraine and non-migraine, and in both depression and anxiety, a clear trend was observed between the relationship between headache frequency and psychological risk factor (see Table 3).

Others have shown, prospectively, that various work-related psychosocial factors predict headache severity longitudinally. In a large study of over 3500 employees from a wide range of occupational settings, Christensen and Knardahl found that the baseline report of high work demands and low levels of control was related to more severe headache at follow-up (75). Supporting the thesis that occupational factors may be important determinants of headache, Sjösten et al (2011) studied the effect of retirement on the occurrence of headache and showed a clear trend of decreasing prevalence associated with ceasing work – an effect that was greater among those with higher work stress (76).

The relationship between psychosocial factors and headache has also been examined in younger populations. Stensland et al (2013) examined 10,000 study participants aged 12-20yrs as part of the Young-HUNT-3 study. These authors found that those with recurrent headache (headaches at least once per month) were significantly more likely to report psychological distress than other individuals (OR = 2.1; 1.7 to 2.6 and OR = 1.9; 1.7 to 2.2, for males and females respectively) after adjustment for age, family structure, family economy, and the occurrence of potentially traumatic interpersonal events (77). Further, a dose-risk relationship was observed, such that the association got stronger with increasing headache frequency (see Table 3)

Others have demonstrated similar results. Data from the 1958 British Birth Cohort study showed that children who, at age 7yrs, were reported to have moderate or severe depression, were also more likely to suffer frequent headaches or migraine (43). Waldie et al (2014) found that children with migraine (OR = 4.4; 2.3 to 8.5) and tension-type headache (OR = 4.4; 1.1 to 8.5) were significantly more likely to report behaviour difficulties than other children (41). And in a case-control study of 42 children with chronic tension-type headache, and 124 controls, those with headache demonstrated significantly greater emotional and behavioural problems than their school peers (78).

Irritable bowel syndrome

Talley et al (1998) in a general population sample of 730 residents of Sydney, Australia, investigated the role of personality and psychological morbidity, in the epidemiology of irritable bowel syndrome (50). They found that those with irritable bowel syndrome, as ascertained by self-completion questionnaire using standardised questions (46), scored higher in terms of both neuroticism (Eysenck Personality Questionnaire (79) median = 5.0; inter-quartile range = 4.0 to 8.0, versus 3.0; 1.0 to 5.0) and general psychological morbidity (General Health Questionnaire (80) median = 2.0; 1.0 to 6.0, versus 0.0; 0.0 to 2.0), compared to other individuals. Indeed, the authors concluded that part of the association between early life abuse and irritable bowel syndrome – described previously – could be explained by neuroticism and psychological morbidity, as ascertained using these instruments.

Others have found similar associations. In a large population-based study in China, Xiong et al (2004) examined the relationship between irritable bowel syndrome, as assessed using the Rome II criteria (81), and a number of factors. Abdominal symptoms were recorded 'over the previous year' and, while it is not clear exactly the time period relating to exposures, it is assumed that it is the same. These authors found that negative life events (OR = 1.9; 1.1 to 3.2), psychological distress (OR = 2.2; 1.4 to 3.4) and negative coping style (OR = 1.2; 1.1 to 1.3) were all significantly associated with the occurrence of irritable bowel syndrome (82).

Rather than just relying on self-completion questionnaire responses, Ålander et al (2005) used a questionnaire to screen members of the general population in Sweden, and invited selected respondents into the clinic for more detailed assessment. From 911 questionnaire respondents, 141 individuals were identified with functional gastrointestinal disorders, plus 97 who were 'strictly free from of gastrointestinal symptoms (83). Focusing on a individuals with verified symptoms (or verified symptom-free) will inevitably exaggerate any association, and it is perhaps unsurprising that previously demonstrated associations were stronger in this study: the authors found that participants with functional gastrointestinal disorders experienced an more than an eight-fold increase in the likelihood of psychological illness, compared to those who were symptom free (OR = 8.4; 4.0 to 17.5).

Few studies have examined the relationship between psychosocial / psychological factors and abdominal pain / irritable bowel syndrome prospectively. Talley et al (2001), in a New Zealand birth cohort, identified individuals with irritable bowel syndrome according to both the Rome II criteria (81) and the (earlier) Manning criteria (84). They found no association between psychiatric history and irritable bowel syndrome with either criteria (85). In contrast, using data from the 1958 British Birth Cohort, Goodwin et al (2013) demonstrated that psychopathology at age 23 and 33yrs were both independently associated with the onset of irritable bowel syndrome (OR = 1.3; 1.01 to 1.5, and OR = 2.2; 1.7 to 2.8, respectively) (51). And Halder et al (2002) identified 1551 individuals, from a large population-based survey, who were free of abdominal pain. They found that, after adjusting for age and gender, those with high levels of anxiety (OR = 3.0; 1.8 to 5.0), depression (2.4; 1.4 to 3.9) adverse illness behaviour (OR = 7.4; 3.9 to 14.2), psychological distress (OR = 2.0; 1.3 to 3.3), and other somatic symptoms (OR = 2.6; 1.5 to 4.7) were significantly more likely to report new onset irritable bowel syndrome at fifteen month follow-up, than other individuals (86). Further, on multiple adjustment, adverse illness behaviour still significantly predicted the onset of irritable bowel symptoms (OR = 5.2; 2.5 to 11.0).

Temporomandibular joint disorder

Several good quality studies have examined, longitudinally, the association between psychological and psychosocial factors and orofacial pain / temporomandibular joint disorder. An early study, by Von Korff et al (1993), comprised more than 1000 enrollees of an Adult Health Maintenance Organization in the northwest United States examined the role of depression, as assessed using the Symptom Checklist 90-Revised (SCL-90-R) Depression scale, as a risk factor for a number of regional pain symptoms – back pain, headache, chest pain, abdominal pain and temporomandibular disorder pain (87). Over 800 of study participants were followed up three years after baseline. Compared to those with normal baseline depression scores, those with moderate (OR = 1.2) or severe (OR = 1.6) experienced an increase in the likelihood of temporomandibular disorder pain at follow-up, after adjusting for age, sex and educational attainment, although these findings were not statistically significant[3].

More recently, the same research group examined risk factors for temporomandibular disorder pain in adolescents. In a high quality prospective cohort study, LeResche et al (2007) recruited nearly 2000 children aged 11yrs from a large non-profit healthcare provider. Initial baseline screening was conducted by telephone, and included a comprehensive battery of putative risk factors, including general health status, indicators of school performance / school satisfaction, physical and sedentary activity levels, self-esteem, depression and somatisation (88). They were then followed up by questionnaire, three-monthly, for three years to determine the onset of pain symptoms. Participants were specifically instructed not to report trivial transient pains, and those who self-reported symptoms were invited for a clinical examination and interview with a dental hygienist. Factors associated with temporomandibular disorder pain included depression (OR = 1.9; 1.4 to 2.5), somatisation (OR = 2.2; 1.5 to 3.2), higher self-esteem (OR = 0.8; 0.7 to 0.9) and satisfaction with life in general: compared to those who reported that they were very satisfied, those who were satisfied (OR = 1.7; 0.9 to 2.9) or neutral / dissatisfied (OR = 4.2; 2.0 to 8.7) were more likely to develop symptoms over the follow-up period. Moreover, all of these variables, except depression, remained important independent predictors of temporomandibular disorder pain on multivariable analysis.

[3] Note: 95% confidence intervals are not presented in the paper, nor calculable from the data therein.

Finally, in another large, high quality study based in North Carolina (the Orofacial Pain Prospective Evaluation and Risk Assessment (OPPERA) study), Fillingim et al (2013) studied nearly 3000 individuals free of temporomandibular disorder, who were followed-up over five years to determine symptom onset. At baseline, extensive data was collected on a number of psychological variables including various aspects of psychological distress, personality type, anxiety, moods, psychosocial stress, catastrophizing and somatic symptoms. Many of the psychological variables that were assessed significantly predicted the incidence of temporomandibular disorder on univariate (demographically adjusted) analysis. A principal component analysis was conducted to distil down the number of potential risk factors in the model, and four distinct latent constructs were identified: (i) stress and negative affectivity; (ii) passive pain coping; (iii) active pain coping; and (iv) global psychological and somatic symptoms. After adjusting for these four variables, plus a number of demographic characteristics, only the latter remained a significant predictor of symptom onset (HR = 1.3; 1.2 to 1.5) (89).

Interstitial cystitis

Although more commonly thought to be of organic aetiology, a number of studies have investigated the role of psychological factors in the epidemiology of interstitial cystitis. Firstly, in a case-control study of 47 patients and 31 age-matched controls, Fan et al (2008) investigated the relationship between interstitial cystitis and psychological profile. After adjusting for age, those with interstitial cystitis were found to have significantly higher scores in terms of both depression and anxiety ($p<.001$). Further, among cases, the severity of bladder pain was also significantly correlated with both depression and anxiety ($r = 0.30$; $p=.042$, and $r = 0.41$, $p=.004$, respectively) (90).

Secondly, Wright et al (2010), assessed depression, anxiety and stress in a large female twin study from the northwest United States. Interstitial cystitis / painful bladder syndrome was defined as self-reported pain, pressure, or discomfort in the pelvis, groin, or upper thigh that worsens when [your] bladder fills, plus either

(i) frequent urination, or (ii) relief with urination (91). Nearly 8% of the 1165 female twins met the definition for interstitial cystitis / painful bladder syndrome. After adjusting for within-pair familial contributions, compared to twins without urological symptoms, those symptomatic women were found to be significantly more likely to report stress (OR = 2.2; 1.2 to 3.8) and post-traumatic stress disorder symptoms (OR = 2.2; 1.3 to 3.5). Similar associations were observed with anxiety (OR = 1.8; 1.0 to 3.3) and depression (OR = 1.6; 0.8 to 3.0), albethey of borderline significance.

And thirdly, Nickel et al (2010) administered a comprehensive series of psychological questionnaires to 207 female patients with interstitial cystitis / painful bladder syndrome and 117 controls matched for age, partner-status and education (92). Cases were less likely to be in employment (OR = 3.9; 2.2 to 6.7). They also scored worse on all somatic symptom and psychological-based parameters that were evaluated, including pain, sleep, depression, catastrophizing, anxiety, and stress, and reported poorer quality of life and more sexual / social function problems (p-values ranging from <.001 to .016).

However, although a number of studies have demonstrated a clear and consistent association between psychological and psychosocial factors and interstitial cystitis / painful bladder syndrome, there are no large, high quality prospective studies. In the absence of longitudinal evidence one should always be cautious in interpretation, as it is not possible to rule out reverse causation. This is particularly pertinent in conditions such as interstitial cystitis / painful bladder syndrome, when the physical symptoms may so obviously lead to stress, anxiety and depression (for example).

Endometriosis / vulvodynia / chronic pelvic pain

Latthe et al (2006) conducted a large systematic review of factors associated with chronic pelvic pain in women. The review focused on dysmenorrhoea, dyspareunia, and non-cyclical chronic pelvic pain, although studies that included women with vulvydynia alone were excluded. In total, 111 papers were included, published up to 2004, comprising nearly 100,000 women (62). Across a number of studies, adverse

psychological factors were found to be consistently associated with an increase in the occurrence of all three chronic pelvic pain syndromes under investigation (see Table 4). Most putative risk factors were only examined in a couple of studies, although anxiety, depression and somatisation were found to have received more attention. Anxiety was shown to be associated with between a two-fold and three-fold increase in the likelihood of symptoms (OR = 2.8; 0.7 to 11.5, OR = 3.2; 1.8 to 5.9, and pooled OR = 2.3; 1.4 to 3.7 for dysmenorrhoea (one study), dyspareunia (one study) and non-cyclical chronic pelvic pain (five studies) respectively). For somatisation / psychosomatic symptoms, a similar relationship was found with dysmenorrhoea (pooled OR = 3.0; 1.4 to 6.5 (three studies)) and non-cyclical chronic pelvic pain (pooled OR = 8.0; 5.2 to 12.4 (eight studies). While, for depression, although the same was seen for dysmenorrhoea (pooled OR = 2.6; 0.98 to 6.8 (two studies) and non-cyclical chronic pelvic pain (pooled OR = 2.7; 1.9 to 3.9 (eight studies)), the one study that examined dyspareunia reported a much larger effect (OR = 7.8; 2.6 to 23.6). While one should, ordinarily, be cautious about drawing conclusions from only one study, it is compelling that these latter findings are consistent with the associations observed with other outcomes.

Wang et al (2004) was able to examine the relationship between stress and dysmenorrhoea longitudinally, in a cohort study from China. Stress was recorded, prospectively, in a daily diary, by 388 healthy nulliparous women for an average of around three menstrual cycles, and dysmenorrhoea was defined as two or more days of menstrual pain within a single menstrual cycle. After controlling for multiple menstrual cycles per participant, and statistically adjusting for age, body mass index, education, various occupational characteristics and passive smoking, these authors found that, compared to those with low stress, those with high stress were more than twice as likely to report dysmenorrhoea (OR = 2.4; 1.4 to 4.4) (93). Further, the authors subsequently demonstrated that the effect was strongest among women with a history of dysmenorrhoea (OR = 4.6; 2.6 to 8.3, and OR = 10.4; 4.9 to 22.3, for medium and high stress respectively, compared to low stress) although was still present, albeit of borderline significance, among those with no prior history of symptoms at baseline (OR = 1.3; 0.7 to 2.2, and 2.1; 0.9 to 5.2, for medium and high stress respectively).

DISCUSSION

There is remarkable consistency in the risk relationships between early life adversity, and psychological / psychosocial factors, central sensitivity syndrome, at least as exemplified by the conditions discussed above. Other conditions exist within the central sensitivity syndrome spectrum and have been described variably, including myofascial pain syndrome, periodic limb movements in sleep and multiple chemical sensitivity. The fact that only six main syndromes have been discussed (notwithstanding the fact that several comprise a few different disorders) is not deliberate cherry-picking of literature to support an *a priori* argument but, instead, because this is where the bulk of the relevant literature lies.

The fact that early life adversity has similar risk associations across a number of conditions, is consistent with the thesis that the aetiology of these conditions is similar – or at least may share common elements. What is less clear, however, is the mechanism(s) by which these early life factors may influence adult health. Some have postulated a cumulative effect of multiple risk factors acting together – that early life adversity somehow 'primes' the individual to be more susceptible or vulnerable to exposures later in life. Others have suggested that early life adversity sets an individual off on an adverse life 'trajectory' on which they will accumulate other exposures. And others have proposed a biological programming effect, where early life adversity 'resets' various biological axes, leading the individual to be less well able to deal with later life stressors.

Some have presented data to support neurobiological changes among individuals exposed to early life adversity. McCrory et al (2011) summarise the results of several studies that report atypical hypothalamic-pituitary-adrenal (HPA) function – something shown to predict the onset of chronic widespread pain in adulthood (94) – among children who have experienced abuse or maltreatment (95). This is also supported in rodent studies where mother-pup separation has been shown to lead to altered HPA activity, and an altered stress response (96). Teicher et al (2003) in a review of the neurobiological consequences of early stress and childhood maltreatment presented evidence of neuro-developmental changes associated with

early life stress, including diminished corpus callosum and hippocampal volume, although evidence is not consistent (97). More recently, Gupta et al (2014) has demonstrated a number of differences in resting state neural networks associated with adverse early life events (98). And finally, there is considerable evidence of the plasticity of the developing nervous system, in animal models, and the hyper- and hypo-sensitivity that can arise given sufficient (painful) insult (99).

Although more work is required to elucidate the precise mechanism by which early life adversity may impact detrimentally of future health, and it is probably a combination of the above three pathways – the cumulative effect, the trajectory effect, and the biological effect. What is convincing, however, is that one should at least view later life exposures in the context of early life experiences.

The majority of epidemiological studies in this area are limited. Over and above the usual concerns (small sample size; lack of standardisation of case definition; etc.) investigating the role of early life factors is particularly difficult. Studies need to be retrospective – and are demonstrably susceptible to recall bias (33), or prospective – and incredibly time-consuming. The investment required for a high quality cohort study, examining the role of early life factors on any number of outcomes, is immense. These studies tend to be funded by Government, with multiple interested parties, any data on many exposures and many outcomes. While they provide a fantastic research resource, doing many things for many people, they often lack the breadth of data to allow the researcher to investigate any one question in detail. In the 1958 British Birth Cohort, for example, many early life adversities were recorded dichotomously – present, or absent – by the parent (most commonly the mother) when the cohort participant was 7yrs of age. And in terms of outcome data, in the case of chronic widespread pain this was recorded at a single point in time, by self-completion questionnaire, at 45yrs (38). While the method of outcome measurement was acceptable, and common to many large-scale epidemiological studies, there is no information on the timing of onset of pain, or on pain severity, or disability, and it remains, therefore, a rather crude estimate of symptom status.

Caution is also advised regarding the importance of many of the exposures discussed above at the population level. Many of the early life adversities discussed are rare (although by the same token a number seem alarmingly common!). While these exposures may confer an excess risk, from a population perspective, they account for only a minor proportion of the overall disease burden. If the aim is to reduce chronic widespread pain, headache, temporomandibular joint disorder, etc., it is arguably more important, from a public health perspective, to reduce the depression, anxiety and psychological stress, than to remove the early life adversity. Although this sounds, initially, rather perverse, at the population level the number of cases that could be prevented is a function not only of the risk associated with any one exposure, but also the prevalence of that exposure.

Conclusion

In summary, this narrative review has examined the evidence for the role of early life adversity and psychological factors in the epidemiology of six major symptoms, part of the spectrum of central sensitivity syndrome: (i) fibromyalgia / chronic widespread pain; (ii) headache / migraine; (iii) irritable bowel syndrome; (iv) temporomandibular joint disorder; (v) interstitial cystitis; and (vi) endometriosis / vulvodynia / chronic pelvic pain. There is clear consistency, across a large number of studies, that both early life adversity, and a number of aspects of psychological vulnerability, are significantly associated with each of these conditions. The majority of evidence comes from retrospective studies, and recall bias is a concern. However, there are a several high quality prospective cohort studies that provide robust data in support of the risk-relationships observed. Future work should try to elicit the possible mechanism(s) of action of these aetiological associations, and should consider possible therapeutic strategies that might alleviate the effect of these exposures.

REFERENCES

1. Yunus MB. Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes. Semin Arthritis Rheum 2007 Jun;36(6):339-56.
2. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 1990 Feb;33(2):160-72.
3. Prescott E, Kjoller M, Jacobsen S, et al. Fibromyalgia in the adult Danish population: I. A prevalence study. Scand J Rheumatol 1993;22(5):233-7.
4. Carmona L, Ballina J, Gabriel R, et al. The burden of musculoskeletal diseases in the general population of Spain: results from a national survey. Ann Rheum Dis 2001 Nov;60(11):1040-5.
5. White KP, Speechley M, Harth M, et al. The London Fibromyalgia Epidemiology Study: the prevalence of fibromyalgia syndrome in London, Ontario. J Rheumatol 1999 Jul;26(7):1570-6.
6. Wolfe F, Ross K, Anderson J, et al. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 1995 Jan;38(1):19-28.
7. Wolfe F, Clauw DJ, Fitzcharles MA, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res (Hoboken) 2010 May;62(5):600-10.
8. Wolfe F, Clauw DJ, Fitzcharles MA, et al. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. J Rheumatol 2011 Jun;38(6):1113-22.
9. Jones GT, Atzeni F, Beasley M, et al. The prevalence of fibromyalgia in the general population: a comparison of the american college of rheumatology 1990, 2010, and modified 2010 classification criteria. Arthritis Rheumatol 2015 Feb;67(2):568-75.
10. Schochat T, Raspe H. Elements of fibromyalgia in an open population. Rheumatology (Oxford) 2003 Jul;42(7):829-35.
11. Hunt IM, Silman AJ, Benjamin S, et al. The prevalence and associated features of chronic widespread pain in the community using the 'Manchester' definition of chronic widespread pain. Rheumatology (Oxford) 1999 Mar;38(3):275-9.
12. Bergman S, Herrstrom P, Hogstrom K, et al. Chronic musculoskeletal pain, prevalence rates, and sociodemographic associations in a Swedish population study. J Rheumatol 2001 Jun;28(6):1369-77.
13. Croft P, Rigby AS, Boswell R, et al. The prevalence of chronic widespread pain in the general population. J Rheumatol 1993 Apr;20(4):710-3.
14. Scher A, Stewart WF, Lipton RB. Migraine and headache: a meta-analytic approach. In: Crombie IK, Croft PR, Linton SJ, LeResche, L., Von Korff M, editors. Epidemiology of pain—a report of the Task Force on Epidemiology of the International Association for the Study of Pain.Seattle: IASP Press; 1999. p. 159-70.
15. Stovner LJ, Hagen K, Jensen R, et al. The global burden of headache: a documentation of headache prevalence and disability worldwide. Cephalalgia 2007 Mar;27(3):193-210.
16. Rasmussen BK, Jensen R, Schroll M, et al. Epidemiology of headache in a general population--a prevalence study. J Clin Epidemiol 1991;44(11):1147-57.
17. Stovner LJ, Andree C. Prevalence of headache in Europe: a review for the Eurolight project. J Headache Pain 2010 Aug;11(4):289-99.
18. Canavan C, West J, Card T. The epidemiology of irritable bowel syndrome. Clin Epidemiol 2014;6:71-80.

19. Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. Clin Gastroenterol Hepatol 2012 Jul;10(7):712-21.

20. Goulet JP, Lavigne GJ, Lund JP. Jaw pain prevalence among French-speaking Canadians in Quebec and related symptoms of temporomandibular disorders. J Dent Res 1995 Nov;74(11):1738-44.

21. Macfarlane TV, Kenealy P, Kingdon HA, et al. Orofacial pain in young adults and associated childhood and adulthood factors: results of the population study, Wales, United Kingdom. Community Dent Oral Epidemiol 2009 Oct;37(5):438-50.

22. Macfarlane TV, Blinkhorn AS, Davies RM, et al. Oro-facial pain in the community: prevalence and associated impact. Community Dent Oral Epidemiol 2002 Feb;30(1):52-60.

23. Oravisto KJ. Epidemiology of interstitial cystitis. Ann Chir Gynaecol Fenn 1975;64(2):75-7.

24. Jones CA, Nyberg L. Epidemiology of interstitial cystitis. Urology 1997 May;49(5A Suppl):2-9.

25. Clemens JQ, Meenan RT, Rosetti MC, et al. Prevalence and incidence of interstitial cystitis in a managed care population. J Urol 2005 Jan;173(1):98-102.

26. Cramer DW, Missmer SA. The epidemiology of endometriosis. Ann N Y Acad Sci 2002 Mar;955:11-22.

27. Harlow BL, Kunitz CG, Nguyen RH, et al. Prevalence of symptoms consistent with a diagnosis of vulvodynia: population-based estimates from 2 geographic regions. Am J Obstet Gynecol 2014 Jan;210(1):40-8.

28. Vieira-Baptista P, Lima-Silva J, Cavaco-Gomes J, et al. Prevalence of vulvodynia and risk factors for the condition in Portugal. Int J Gynaecol Obstet 2014 Dec;127(3):283-7.

29. Ahangari A. Prevalence of chronic pelvic pain among women: an updated review. Pain Physician 2014 Mar;17(2):E141-E147.

30. Tirlapur SA, Kuhrt K, Chaliha C, et al. The 'evil twin syndrome' in chronic pelvic pain: a systematic review of prevalence studies of bladder pain syndrome and endometriosis. Int J Surg 2013;11(3):233-7.

31. Imbierowicz K, Egle UT. Childhood adversities in patients with fibromyalgia and somatoform pain disorder. Eur J Pain 2003;7(2):113-9.

32. Boisset-Pioro MH, Esdaile JM, Fitzcharles MA. Sexual and physical abuse in women with fibromyalgia syndrome. Arthritis Rheum 1995 Feb;38(2):235-41.

33. McBeth J, Morris S, Benjamin S, et al. Associations between adverse events in childhood and chronic widespread pain in adulthood: are they explained by differential recall? J Rheumatol 2001 Oct;28(10):2305-9.

34. Power C, Elliott J. Cohort profile: 1958 British birth cohort (National Child Development Study). Int J Epidemiol 2006 Feb;35(1):34-41.

35. Macfarlane GJ, Norrie G, Atherton K, et al. The influence of socioeconomic status on the reporting of regional and widespread musculoskeletal pain: results from the 1958 British Birth Cohort Study. Ann Rheum Dis 2009 Oct;68(10):1591-5.

36. Littlejohn C, Pang D, Power C, et al. Is there an association between preterm birth or low birthweight and chronic widespread pain? Results from the 1958 Birth Cohort Study. Eur J Pain 2012 Jan;16(1):134-9.

37. Jones GT, Silman AJ, Power C, et al. Are common symptoms in childhood associated with chronic widespread body pain in adulthood? Results from the 1958 British Birth Cohort Study. Arthritis Rheum 2007 May;56(5):1669-75.

38. Jones GT, Power C, Macfarlane GJ. Adverse events in childhood and chronic widespread pain in adult life: Results from the 1958 British Birth Cohort Study. Pain 2009 May;143(1-2):92-6.

39. Anda R, Tietjen G, Schulman E, et al. Adverse childhood experiences and frequent headaches in adults. Headache 2010 Oct;50(9):1473-81.

40. Tietjen GE, Khubchandani J, Herial NA, et al. Adverse childhood experiences are associated with migraine and vascular biomarkers. Headache 2012 Jun;52(6):920-9.

41. Waldie KE, Thompson JM, Mia Y, et al. Risk factors for migraine and tension-type headache in 11 year old children. J Headache Pain 2014;15:60.

42. Aromaa M, Rautava P, Helenius H, et al. Factors of early life as predictors of headache in children at school entry. Headache 1998 Jan;38(1):23-30.

43. Fearon P, Hotopf M. Relation between headache in childhood and physical and psychiatric symptoms in adulthood: national birth cohort study. BMJ 2001 May 12;322(7295):1145.

44. Drossman DA, Leserman J, Nachman G, et al. Sexual and physical abuse in women with functional or organic gastrointestinal disorders. Ann Intern Med 1990 Dec 1;113(11):828-33.

45. Walker EA, Katon WJ, Roy-Byrne PP, et al. Histories of sexual victimization in patients with irritable bowel syndrome or inflammatory bowel disease. Am J Psychiatry 1993 Oct;150(10):1502-6.

46. Drossman DA, Richter JE, Talley NJ, et al. The Functional Gastrointestinal Disorders: Diagnosis, pathophysiology, and treatment — a multinational consensus. Boston: Little Brown; 1994.

47. Koloski NA, Talley NJ, Boyce PM. A history of abuse in community subjects with irritable bowel syndrome and functional dyspepsia: the role of other psychosocial variables. Digestion 2005;72(2-3):86-96.

48. Salmon P, Skaife K, Rhodes J. Abuse, dissociation, and somatization in irritable bowel syndrome: towards an explanatory model. J Behav Med 2003 Feb;26(1):1-18.

49. Talley NJ, Fett SL, Zinsmeister AR, et al. Gastrointestinal tract symptoms and self-reported abuse: a population-based study. Gastroenterology 1994 Oct;107(4):1040-9.

50. Talley NJ, Boyce PM, Jones M. Is the association between irritable bowel syndrome and abuse explained by neuroticism? A population based study. Gut 1998 Jan;42(1):47-53.

51. Goodwin L, White PD, Hotopf M, et al. Life course study of the etiology of self-reported irritable bowel syndrome in the 1958 British birth cohort. Psychosom Med 2013 Feb;75(2):202-10.

52. Roseboom T, de RS, Painter R. The Dutch famine and its long-term consequences for adult health. Early Hum Dev 2006 Aug;82(8):485-91.

53. Klooker TK, Braak B, Painter RC, et al. Exposure to severe wartime conditions in early life is associated with an increased risk of irritable bowel syndrome: a population-based cohort study. Am J Gastroenterol 2009 Sep;104(9):2250-6.

54. Riley JL, III, Robinson ME, Kvaal SA, et al. Effects of physical and sexual abuse in facial pain: direct or mediated? Cranio 1998 Oct;16(4):259-66.

55. Campbell LC, Riley JL, III, Kashikar-Zuck S, et al. Somatic, affective, and pain characteristics of chronic TMD patients with sexual versus physical abuse histories. J Orofac Pain 2000;14(2):112-9.

56. Fillingim RB, Maixner W, Sigurdsson A, et al. Sexual and physical abuse history in subjects with temporomandibular disorders: relationship to clinical variables, pain sensitivity, and psychologic factors. J Orofac Pain 1997;11(1):48-57.

57. Goldstein HB, Safaeian P, Garrod K, et al. Depression, abuse and its relationship to interstitial cystitis. Int Urogynecol J Pelvic Floor Dysfunct 2008 Dec;19(12):1683-6.

58. Carrico DJ, Sherer KL, Peters KM. The relationship of interstitial cystitis/painful bladder syndrome to vulvodynia. Urol Nurs 2009 Jul;29(4):233-8.

59. Seth A, Teichman JM. Differences in the clinical presentation of interstitial cystitis/painful bladder syndrome in patients with or without sexual abuse history. J Urol 2008 Nov;180(5):2029-33.

60. Peters KM, Kalinowski SE, Carrico DJ, et al. Fact or fiction--is abuse prevalent in patients with interstitial cystitis? Results from a community survey and clinic population. J Urol 2007 Sep;178(3 Pt 1):891-5.

61. Edwards L, Mason M, Phillips M, et al. Childhood sexual and physical abuse. Incidence in patients with vulvodynia. J Reprod Med 1997 Mar;42(3):135-9.

62. Latthe P, Mignini L, Gray R, et al. Factors predisposing women to chronic pelvic pain: systematic review. BMJ 2006 Apr 1;332(7544):749-55.

63. Peters K, Girdler B, Carrico D, et al. Painful bladder syndrome/interstitial cystitis and vulvodynia: a clinical correlation. Int Urogynecol J Pelvic Floor Dysfunct 2008 May;19(5):665-9.

64. Gordon AS, Panahian-Jand M, Mccomb F, et al. Characteristics of women with vulvar pain disorders: responses to a Web-based survey. J Sex Marital Ther 2003;29 Suppl 1:45-58.

65. Harlow BL, Stewart EG. Adult-onset vulvodynia in relation to childhood violence victimization. Am J Epidemiol 2005 May 1;161(9):871-80.

66. Khandker M, Brady SS, Stewart EG, et al. Is chronic stress during childhood associated with adult-onset vulvodynia? J Womens Health (Larchmt) 2014 Aug;23(8):649-56.

67. Wieser F, Vitonis A, Rich-Edwards J, et al. Abuse in childhood and risk of endometriosis. Fertility and Sterility 98[3], S218. 2012.

68. Macfarlane GJ, Croft PR, Schollum J, et al. Widespread pain: is an improved classification possible? J Rheumatol 1996 Sep;23(9):1628-32.

69. Benjamin S, Morris S, McBeth J, et al. The association between chronic widespread pain and mental disorder: a population-based study. Arthritis Rheum 2000 Mar;43(3):561-7.

70. McBeth J, Harkness EF, Silman AJ, et al. The role of workplace low-level mechanical trauma, posture and environment in the onset of chronic widespread pain. Rheumatology (Oxford) 2003 Dec;42(12):1486-94.

71. McBeth J, Macfarlane GJ, Benjamin S, et al. Features of somatization predict the onset of chronic widespread pain: results of a large population-based study. Arthritis Rheum 2001 Apr;44(4):940-6.

72. Gupta A, Silman AJ, Ray D, et al. The role of psychosocial factors in predicting the onset of chronic widespread pain: results from a prospective population-based study. Rheumatology (Oxford) 2007 Apr;46(4):666-71.

73. Radat F, Lanteri-Minet M, Nachit-Ouinekh F, et al. The GRIM2005 study of migraine consultation in France. III: Psychological features of subjects with migraine. Cephalalgia 2009 Mar;29(3):338-50.

74. Zwart JA, Dyb G, Hagen K, et al. Depression and anxiety disorders associated with headache frequency. The Nord-Trondelag Health Study. Eur J Neurol 2003 Mar;10(2):147-52.

75. Christensen JO, Knardahl S. Work and headache: a prospective study of psychological, social, and mechanical predictors of headache severity. Pain 2012 Oct;153(10):2119-32.

76. Sjosten N, Nabi H, Westerlund H, et al. Influence of retirement and work stress on headache prevalence: a longitudinal modelling study from the GAZEL Cohort Study. Cephalalgia 2011 Apr;31(6):696-705.

77. Stensland SO, Dyb G, Thoresen S, et al. Potentially traumatic interpersonal events, psychological distress and recurrent headache in a population-based cohort of adolescents: the HUNT study. BMJ Open 2013;3(7).

78. Battistutta S, Aliverti R, Montico M, et al. Chronic tension-type headache in adolescents. Clinical and psychological characteristics analyzed through self- and parent-report questionnaires. J Pediatr Psychol 2009 Aug;34(7):697-706.

79. Grayson DA. Latent trait analysis of the Eysenck Personality Questionnaire. J Psychiatr Res 1986;20(3):217-35.

80. Goldberg DP. The detection of psychiatric illness by questionnaire: a technique for the identification and assessment of non-psychotic psychiatric illness. Oxford: Oxford University Press; 1972.

81. Thompson WG, Longstreth GF, Drossman DA, et al. Functional bowel disorders and functional abdominal pain. Gut 1999 Sep;45 Suppl 2:II43-II47.

82. Xiong LS, Chen MH, Chen HX, et al. A population-based epidemiologic study of irritable bowel syndrome in South China: stratified randomized study by cluster sampling. Aliment Pharmacol Ther 2004 Jun 1;19(11):1217-24.

83. Ålander T, Svärdsudd.K., Johansson S-E, et al. Psychological illness is commonly associated with functional gastrointestinal disorders and is important to consider during patient consultation: a population-based study. BMC Med 2005;3:8.

84. Manning AP, Thompson WG, Heaton KW, et al. Towards positive diagnosis of the irritable bowel. Br Med J 1978 Sep 2;2(6138):653-4.

85. Talley NJ, Howell S, Poulton R. The irritable bowel syndrome and psychiatric disorders in the community: is there a link? Am J Gastroenterol 2001 Apr;96(4):1072-9.

86. Halder SL, McBeth J, Silman AJ, et al. Psychosocial risk factors for the onset of abdominal pain. Results from a large prospective population-based study. Int J Epidemiol 2002 Dec;31(6):1219-25.

87. Von Korff M, LeResche L, Dworkin SF. First onset of common pain symptoms: a prospective study of depression as a risk factor. Pain 1993 Nov;55(2):251-8.

88. LeResche L, Mancl LA, Drangsholt MT, et al. Predictors of onset of facial pain and temporomandibular disorders in early adolescence. Pain 2007 Jun;129(3):269-78.

89. Fillingim RB, Ohrbach R, Greenspan JD, et al. Psychological factors associated with development of TMD: the OPPERA prospective cohort study. J Pain 2013 Dec;14(12 Suppl):T75-T90.

90. Fan YH, Lin AT, Wu HM, et al. Psychological profile of Taiwanese interstitial cystitis patients. Int J Urol 2008 May;15(5):416-8.

91. Wright LJ, Noonan C, Ahumada S, et al. Psychological distress in twins with urological symptoms. Gen Hosp Psychiatry 2010 May;32(3):262-7.

92. Nickel JC, Tripp DA, Pontari M, et al. Psychosocial phenotyping in women with interstitial cystitis/painful bladder syndrome: a case control study. J Urol 2010 Jan;183(1):167-72.

93. Wang L, Wang X, Wang W, et al. Stress and dysmenorrhoea: a population based prospective study. Occup Environ Med 2004 Dec;61(12):1021-6.

94. McBeth J, Silman AJ, Gupta A, et al. Moderation of psychosocial risk factors through dysfunction of the hypothalamic-pituitary-adrenal stress axis in the onset of chronic widespread musculoskeletal pain: findings of a population-based prospective cohort study. Arthritis Rheum 2007 Jan;56(1):360-71.

95. McCrory E, De Brito SA, Viding E. The impact of childhood maltreatment: a review of neurobiological and genetic factors. Front Psychiatry 2011;2:48.

96. McCrory E, De Brito SA, Viding E. Research review: the neurobiology and genetics of maltreatment and adversity. J Child Psychol Psychiatry 2010 Oct;51(10):1079-95.

97. Teicher MH, Andersen SL, Polcari A, et al. The neurobiological consequences of early stress and childhood maltreatment. Neurosci Biobehav Rev 2003 Jan;27(1-2):33-44.

98. Gupta A, Kilpatrick L, Labus J, et al. Early adverse life events and resting state neural networks in patients with chronic abdominal pain: evidence for sex differences. Psychosom Med 2014 Jul;76(6):404-12.

99. Schwaller F, Fitzgerald M. The consequences of pain in early life: injury-induced plasticity in developing pain pathways. Eur J Neurosci 2014 Feb;39(3):344-52.

TABLES

Table 1 ***Association between early life factors, and chronic widespread pain in adulthood – data from 1958 British Birth Cohort Study (37;38)***

		Risk ratio (95% CI)*
*Common childhood symptoms – before 7yrs***		
Number of symptoms	0	1.0
	1	1.1 (0.9-1.2)
	2	1.0 (0.8-1.3)
	3	1.4 (0.96-2.2)
Early life adversity – before 7yrs		
Maternal separation	None	1.0
	<1wk	1.0 (0.9 to 1.2)
	1wk to 1 month	1.1 (0.96 to 1.3)
	1-6 months	1.2 (0.9 to 1.5)
	>6 months	1.4 (0.9 to 1.9)
Ever in institutional care	No	1.0
	Yes	1.7 (1.2 to 2.3)
Death of father	No	1.0
	Yes	0.9 (0.5 to 1.6)
Death of mother	No	1.0
	Yes	2.0 (1.1 to 3.7)
Parental separation	No	1.0
	Yes	1.3 (0.99 to 1.7)
Parental alcoholism	No	1.0
	Yes	1.3 (0.8 to 2.4)
Parental financial difficulties	No	1.0
	Yes	1.6 (1.3 to 1.9)

* Adjusted for sex, childhood and adulthood socioeconomic status, and (adult) psychological distress.

** Maternal report, at 7yrs, of vomiting/bilious attacks, abdominal pain, and headaches/migraine.

Table 2 Association between childhood physical / sexual / emotional adversity, and vulvodynia – data taken from Harlow and Stewart (2005) (65)

		Odds ratio (95% CI)
Physical abuse		
Never physically or sexually harmed		1.0
Physically harmed as a child	Moderately abused	1.3 (0.7 to 2.5)
	Severely abused	4.1 (1.7 to 10.0)
Source of physical harm	Non to family member	1.1 (0.6 to 2.2)
	Family member	3.6 (1.6 to 8.0)
Sexual abuse		
Never physically or sexually harmed		1.0
Sexually harmed as a child	Moderately abused	1.5 (0.6 to 4.1)
	Severely abused	6.5 (1.2 to 35.1)
Source of sexual harm	Non to family member	1.8 (0.7 to 4.9)
	Family member	4.4 (0.9 to 22.9)
Emotional adversity		
Frequency of family support	Often / very often	1.0
	Sometimes	1.4 (0.7 to 3.0)
	Never / rarely	2.6 (1.3 to 5.1)
Felt danger at home	Never	1.0
	A few times, or more	2.1 (1.0 to 4.6)
Felt danger in neighbourhood	Never	1.0
	A few times, or more	0.6 (0.2 to 1.7)
Felt danger at school	Never	1.0
	A few times, or more	5.0 (1.0 to 25.0)

Table 3 ***Association between depression / anxiety, and migrainous / non-migrainous headache – data from the (Nord-Trøndelag Health) HUNT-2 and Young HUNT-3 Studies (74;77)***

	Odds ratio (95% CI)		
	Depression	**Anxiety**	**Psychological distress**
*Non-migrainous headache (adults)**			
No headache	1.0	1.0	
<7 days per month	1.7 (1.5 to 2.0)	2.0 (1.8 to 2.3)	
7-14 days per month	3.4 (2.7 to 4.2)	4.9 (4.1 to 5.8)	
>14 days per month	4.9 (3.8 to 6.3)	6.3 (5.0 to 7.7)	
*Migrainous headache (adults) **			
No headache	1.0	1.0	
<7 days per month	2.0 (1.6 to 2.5)	2.3 (2.0 to 2.7)	
7-14 days per month	4.2 (3.2 to 5.6)	5.6 (4.6 to 6.8)	
>14 days per month	6.4 (4.4 to 9.3)	6.9 (5.1 to 9.4)	
*Recurrent headache (adolescents)***			
Monthly			1.7 (1.5 to 2.0)
Weekly			2.2 (1.9 to 2.6)
Daily			2.8 (2.0 to 3.8)

* Odds ratios adjusted for sex, age and education

** Odds ratios adjusted for sex, age, family structure, family economy and potentially traumatic interpersonal events

Table 4 Association between psychological factors, and chronic pelvic pain – data from Latthe et al (2006) (62)

	Odds ratio (95% CI)		
	Dysmenorrhoea	**Dyspareunia**	**CNCPP***
Emotional difficulties	2.2 (1.5 to 3.3)		
Psychological symptoms	3.7 (2.1 to 6.6)		
Anxiety	2.8 (0.7 to 11.5)	3.2 (1.8 to 5.9)	2.3 (1.4 to 3.7)
Depression	2.6 (0.98 to 6.8)	7.8 (2.6 to 23.6)	2.7 (1.9 to 3.9)
Suicidal tendency	2.5 (1.5 to 4.0)		
Somatisation / psychosomatic symptoms	3.0 (1.4 to 6.5)		8.0 (5.2 to 12.4)
Psychological abuse			2.5 (0.5 to 11.2)
Disturbed puberty/painful early memories			3.8 (1.7 to 8.2)
Unsatisfactory relation with mother/spouse			4.0 (1.6 to 10.1)
Extroversion			0.8 (0.1 to 4.4)
Hysteria			4.8 (2.5 to 9.3)
Neuroticism			4.0 (0.7 to 23.0)
Paranoia			13.9 (4.0 to 48.0)
Borderline syndrome			3.0 (0.8 to 11.1)
Current phobias			3.9 (0.7 to 21.7)
Post-traumatic stress disorder			5.5 (0.5 to 58.8)

* Chronic non-cyclical pelvic pain