Chronic pelvic pain in women of reproductive and post-reproductive age: a population-based study

Abimbola A Ayorinde[1]; Siladitya Bhattacharya[2]; Katie L Druce[1]; Gareth T Jones[1]; Gary J Macfarlane[1]

[1]Epidemiology Group, Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, Scotland, UK. [2]Institute of Applied Health Sciences, School of Medicine and Dentistry, University of Aberdeen, Aberdeen, Scotland, UK.

Corresponding author: Gary J Macfarlane, Epidemiology Group, Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, Scotland, UK.
Email:g.j.macfarlane@abdn.ac.uk; +441224 437143

Running title: A study of chronic pelvic pain in adult women

Category of manuscript: Original Article

Funding: Abimbola Ayorinde's PhD funded by the Medical Research Council. This study was funded by the British Pain Society (Mildred Clulow Award) and preparatory work by National Health Service Grampian.

Disclosure of conflict of Interests: Nothing to disclose

What is already known:

- There is a paucity of epidemiological data on chronic pelvic pain (CPP) in women particularly beyond the reproductive age.
- CPP, like other chronic pain conditions, may involve biological, psychological and social factors but attention to date has focussed on biological factors in disease aetiology.

What does this study add:

- -Heightened somatic awareness may be more strongly associated with CPP in women of post-reproductive years compared to women of reproductive years.

- Two subgroups of CPP cases can be differentiated by the absence/presence of psychosocial distress suggesting that stratified management approach may be more efficient.

Abstract

Background: Epidemiological studies on chronic pelvic pain (CPP) have focused on women of reproductive age. We aimed to determine the prevalence of chronic pelvic pain (CPP) in adult women and the differences in associated factors among women of reproductive age and older women. Also, to determine whether distinct sub-groups existed among CPP cases.

Methods: A cross-sectional postal survey was conducted amongst 5300 randomly selected women aged ≥25 years resident in the Grampian region, UK. Multivariable logistic regression was used to determine pregnancy-related and psychosocial factors associated with CPP. To identify sub-groups of CPP cases, we performed cluster analysis using variables of pain severity, psychosocial factors and pain coping strategies.

Results: Of 2088 participants, 309 (14.8%) reported CPP. CPP was significantly associated with being of reproductive age (Odds Ratios (OR) 2.43, 95% CI 1.69–3.48), multiple non-pain somatic symptoms (OR 3.58 95% CI 2.23–5.75), having fatigue (OR mild 1.74 95% CI 1.24–2.44, moderate/severe 1.82, 95% CI 1.25–2.63) and having depression (OR 1.61, 95% CI 1.09–2.38). CPP was less associated with multiple non-pain somatic symptoms in women of reproductive age compared to older women (interaction OR 0.51, 95% CI 0.28–0.92). We identified two clusters of CPP cases; those having little/no psychosocial distress and those having high psychosocial distress.

Conclusion: CPP is common in both age-groups, though women of reproductive age are more likely to report it. Heightened somatic awareness may be more strongly associated with CPP in older women. There are distinct groups of CPP cases characterised by the absence/presence of psychosocial distress.

Introduction

Chronic Pelvic Pain (CPP) in women refers to cyclical or non-cyclical pain in the lower abdomen lasting for at least six months, not due exclusively to menstrual periods, intercourse or pregnancy (Baranowski, A., 2012; Royal College of Obstetricians and Gynaecologists, 2012). CPP in women is an incapacitating condition which is associated with poor quality of life, decreased work efficiency as well as significant healthcare utilisation (Reiter, 1990; Mathias et al., 1996). CPP is often associated with disorders of various organ systems but some have proposed that it should be considered a syndrome in its own right in the absence of an obvious cause of pain (Daniels and Khan, 2010). Despite the significance of CPP, it has been virtually ignored in healthcare planning and resource allocation due to a lack of basic epidemiological data (Latthe et al., 2006).

Population-based studies on CPP have been mainly conducted in women of reproductive age since it is hypothesised that symptoms relate to pathology of reproductive organs (Mathias et al., 1996; Zondervan et al., 2001a; Grace and Zondervan, 2004; Pitts et al., 2008; Ayorinde et al., 2015). Studies which include older women would allow us to determine whether there are distinct features of pain reporting and associated factors amongst women of reproductive age. Epidemiological studies of other regional pains, such as back pain, have not generally identified age-related differences in their epidemiology (Docking et al., 2011).

Primary care practitioners are often not confident in managing CPP and affected women may not continue to seek medical advice because of disappointment with consultations (McGowan et al., 2007; McGowan et al., 2010). Guidelines recommend a multidisciplinary approach for management, especially when an obvious pathology cannot be identified (Royal College of Obstetricians and Gynaecologists, 2012; ACOG Committee on Practice, 2004; Engeler et al.,

2012). Many clinics are currently unable to provide such an approach and it may be that not all CPP patients require multidisciplinary treatment. Thus, it is important to identify whether there are specific sub-groups of women with CPP in terms of patterns of pain reporting and associated features which may inform management approaches.

We therefore undertook a population-based study to determine the prevalence of CPP in women across the entire adult age range. Pregnancy-related factors and psychosocial factors associated with CPP and the differences between women of reproductive age and older women were also determined. We also aimed to determine whether distinct sub-groups existed among cases based on the pattern of reporting pain, psychosocial features, and strategies they engage to deal with pain. These factors were selected because they may be aetiological factors in chronic pain or can influence management decisions.

Methods

A population-based cross-sectional survey, the Women's Health Study (WHEST), was conducted in 2013 in Grampian, north east Scotland. Grampian is an area of around 500,000 persons with equal proportion living in urban (Aberdeen city) and rural areas. Women who were at least 25 years old were randomly selected from the National Health Service Grampian Community Health Index, a list of all patients registered with general practices in Grampian. Over 95% of people in the UK are registered with at a general practice therefore it is a suitable population sampling frame (Health and Social Care Information Centre, 2012). The lower age limit of 25 was chosen since the contact records among people aged 18–24 years are often inaccurate because of mobility, but there was no upper age limit. Ethics approval was obtained

from National Health Service Research Ethics – North of Scotland (Reference number:12/NS/0100).

A pre-notification letter was sent to all selected participants informing them of the study followed by a survey pack (cover letter, an information sheet, the questionnaire and a pre-paid return envelope) a week later. Reminders were sent to non-responders two weeks after the initial questionnaire had been sent. Level of deprivation for participants was measured by the Scottish Index of Multiple Deprivation 2012 which uses income, employment, health, education, geographic access to services, crime and housing information to generate a single index for each area of small concentrations containing about 350 households (The Scottish Government, 2012). The deprivation score was categorised into quintiles with one being the most deprived and five the least deprived.

A questionnaire initially developed for a previous UK study on CPP was adapted and used in this study in relation to the items on CPP (Zondervan et al., 2001a). It asked for information on demographics, women's health, including pregnancy and childbirth. Pelvic pain was described as "any type of pain (cramping, shooting, stabbing, etc.) in the lower part of your belly (the area of your navel down) that you may have had in the last 12 months". Respondents recalled if, in the past 12 months, they had experienced: 'pelvic pain with periods, including irregular bleeding while on the pill or on hormone replacement therapy' (dysmenorrhoea); "pelvic pain during or in the 24 hours after sexual intercourse" (dyspareunia); "pelvic pain at times NOT with periods or sexual intercourse either on or off, or constantly" (pelvic pain). Pain present for at least six months was defined as chronic. Cases with CPP were defined as women who had not been pregnant and had, in the last three months, experienced persistent or

intermittent pain in the lower abdomen of at least six months duration that was not due exclusively to menstrual periods or intercourse. A 0-10 Numeric Rating Scale (NRS) was used to assess pain severity, where 0 is no pain and 10 is pain as bad as it could be.

Health state was assessed using the 10-item Patient Reported Outcomes Measurements Information System (PROMIS®) Global Health Scale version 1.1. This generates two item factors; global physical health component and global mental health component (Hays et al., 2009). The raw scores were converted to a T-Score using a T-score distribution provided by PROMIS®. These are standardised so that a score of 50 signifies the average for the United States general population (no data available for the UK) with a standard deviation of 10 points around the mean. Higher scores denote better health. The individual items of PROMIS® Global Health Scale can also be scored separately as single items. Hence, quality of life was measured by one of its items; "in general, would you say your quality of life is" with response option of "excellent", "very good", "good", "fair" or "poor".

The Patient Health Questionnaire-9 was used to assess depression (Kroenke et al., 2001). For major depression, a score of more than 10 has 88% sensitivity and 88% specificity. The 4-item Sleep Disturbance Scale assessed sleep problems in participants, with a score of >12 as an indication of sleep problems (Jenkins et al., 1988). It is widely used to assess sleep disturbance in research and has good internal consistency (Cronbach's alpha = 0.79). Fatigue was assessed using the 11-item Chalder Fatigue Scale which measures the intensity of physical and mental fatigue symptoms (Chalder et al., 1993). It has excellent internal consistency (Cronbach's alpha = 0.89). Fatigue was categorised into: absent (0); mild (1–3); and moderate/severe (4–11) based on previously published cut-offs (Halder et al., 2002). The seven-item Somatic Symptom Scale

was included to assess somatic symptoms (Othmer and DeSauza, 1985). All the symptoms included are listed in the American Psychiatric Association's criteria for somatisation disorder. Since the study assesses association with CPP, one item relating to sexual organs was substituted with "Have you ever lost your voice for more than 30 minutes" the construct validity of which has been demonstrated in a previous study (McBeth et al., 2001). For analysis, two items relating to pain ("have you ever had frequent trouble with menstrual cramps" and "did you have frequent pain in your fingers or toes") were removed because the study aimed to assess non-pain somatic symptoms. The cut off was adjusted to 2 out of 5 (compared to 3 out of 7 on the original scale).

Vanderbilt Pain Management Inventory was used to assess pain coping strategies in women with pain (Brown and Nicassio, 1987). It is an 18-item self-report instrument that evaluates how often patients with chronic pain use active or passive coping strategies when they experience moderate or greater pain intensity. Active coping involves direct effort from those with pain to keep functioning regardless of the pain or distract them from the pain, while passive coping involves transferring the responsibility to an outside source and allowing pain to adversely affect other areas of life. Participants were required to indicate the frequency at which they employ each of the 18 listed strategies (seven for active coping and 11 for passive coping) using a five point scale each scoring from 1 (never) to 5 (very frequently) and aggregated scores for each domain are obtained.

Based on findings from a previous UK study, a CPP prevalence of 20% was assumed. A sample size of 1850 was sufficient to give the study 90% power to identify a relationship, measured as an odd ratios (OR), with a magnitude of 1.5 OR (assuming 5% significance level) when

comparing the highest and the lowest quartiles of an exposure variable. This sample size is also adequate to estimate the prevalence of CPP with 95% confidence interval width ±2%. Assuming a participation rate of 35%, 5300 women were sampled.

Chi-squared tests were used to assess differences between proportions. Independent t-tests and Mann-Whitney tests were used to compare means and medians respectively. Logistic regression was used to determine the association between CPP and exploratory variables using complete-case analysis approach. The effects were described as odds ratio (OR) with 95% confidence intervals. All the variables assessed have shown associations with CPP or general pain in previous studies. In order to identify which of the variables are potential determinants of CPP based on the strength of the association, a non-automated backward elimination modelling approach was used. All variables which were associated with CPP at $p \leq 0.2$ in the univariable analysis were included in the initial multivariable model. Variables were retained if they contributed to the overall model fit at $p \leq 0.15$, as measured by a likelihood-ratio test. Variables that contribute least to the model were removed one at a time until the optimal model was achieved. In order to assess whether there were differences in factors associated with CPP in women of reproductive age (≤51 years) and those who were older, interaction terms were included. The interaction terms were included in the model one at a time and retained if they were statistically significant. Multivariable analysis was adjusted for demographic factors (education, marital status and level of deprivation). In order to determine if the multivariable model fits the data, Hosmer-Lemeshow test was computed.

To identify whether distinct sub-groups existed among women with CPP, hierarchical cluster analysis with average linkage using squared Euclidean distances was performed. The dendrogram and Calinski and Harabasz pseudo-F index stopping rule were used to determine

the optimal number of clusters (Caliński and Harabasz, 1974). The hierarchical cluster analysis was performed in the group of women of reproductive age. In order to validate the clustering solutions, a K-means cluster analysis technique with Euclidean distances was performed in post-reproductive age women. The K-means clustering procedure divides the data in such a way that within-cluster variation is minimised while maximising the between-cluster variation. The following variables were included for cluster analysis; depression, multiple somatic symptoms, fatigue, sleep disturbance, quality of life, active coping, passive coping and pain severity. Since the variables were measured on different scales, they were standardised to have a mean of 0 and standard deviation of 1 to make them comparable. After clustering, discriminant function analysis was used to assess which of the variables contributes most to the differences between the clusters. All, data analyses were performed using STATA (StataCorp LP).

Results

A total of 5300 questionnaires were sent, 98 were returned undelivered and 2337 (44.9% of those delivered) were returned completed. Responders were more likely to be older (median age 53 vs 49 years) and live in a rural geographical location (response rate of 53.7% in remote rural areas vs 39.3% in large urban areas). A total of 249 women were excluded from the analysis; six failed to provide their date of birth, 91 had been pregnant in the last 12 months and 152 did not provide information on pelvic pain. This resulted in a total sample of 2088 women (median age 52 years, interquartile range (IQR): 42,63). Descriptive characteristics of the study population are shown in Table 1: 48% were in the reproductive age-group, 36.5% were educated to secondary school or below and 63.0% were married. Almost all (96.4%) responded that they were “white”, reflecting the ethnic composition of the Grampian area of Scotland (National Records For Scotland, 2014).

Three hundred and nine women reported CPP in the last three months, giving a three-month period prevalence of 14.8% (95%CI 13.3–16.3%). The median (IQR) NRS score for pain was 4 (3,6). Thirty-two women (10.4%) reported constant pain while 277 (89.6%) reported recurrent pain. Those who reported constant pain had higher NRS pain scores compared to those with recurrent pain [median (IQR) 7 (5,8) vs 5 (4,7) respectively; p=0.02]. Prevalence of CPP was significantly higher among women in their reproductive years, 20.5% (n=205/1001) compared to older women, 9.6% (n=104/1087); a difference of 10.9% (95% CI 7.9%–14.3%). Higher prevalence was observed among those with a university degree, vocational or professional qualifications and the lowest prevalence among those who had no educational qualifications (difference of 13.7%, 95% CI 6.4%–20.1%), but there was no significant association with marital status or level of deprivation (Table 1).

The mean (SD) global physical health and global mental health scores for the whole sample were 50.0 (8.7) and 49.9 (8.2) respectively. Compared to women without CPP, women with CPP scored significantly poorer in both physical health [mean (SD); 46.5 (8.5) versus 50.6 (8.4), difference of 4.1 95% CI 3.0–5.1] and mental health [mean (SD); 47.3 (8.2) versus 50.4 (8.1), difference of 3.1 95% CI 2.1–4.1]. Sleep problems were more common among women with CPP (29.2% versus 19.3%, difference of 9.9% 95% CI 4.7–15.6). Only 52.4% (n=162) of CPP cases reported being given a reason for their pelvic pain by a GP or hospital doctor. The most common reasons reported among those of reproductive age were irritable bowel disease (31.1%), endometriosis (20.4%) and ovarian cysts (20.4%) while for women of post-reproductive age the most common were irritable bowel disease (55.9%) and uterine/vaginal prolapse (16.9%).

As illustrated in Figure 1, of women in the sample who reported having had a period and being sexually active in the past 12 months, only 5.2% reported CPP alone. Many of them reported CPP with either dysmenorrhoea (13.7%) and/or dyspareunia (6.1%).

In univariable analysis, women of reproductive age were more likely to report CPP compared to older women (OR 2.43, 95%CI 1.89–3.14). More than 82% of all the participants had been pregnant at least once but history of pregnancy was not significantly associated with CPP (OR 0.85, 95% CI 0.62–1.15). CPP was associated with history of; infertility, ectopic pregnancy, miscarriage, termination of pregnancy, having at least one Caesarean section as well as nulliparity (OR ranging from 1.38 to 1.67). Stronger associations were observed between CPP and psychosocial factors compared to pregnancy-related factors. Those reporting CPP were about two to three times as likely to report multiple non-pain somatic symptoms, depression and fatigue (Table 2).

Eight factors were retained in the multivariable model including being of reproductive age (OR 2.43, 95% CI 1.69–3.48). Strong associations were also found with reporting multiple non-pain somatic symptoms (OR 3.58 95% CI 2.23–5.75), having fatigue (OR mild 1.74 95% CI 1.24–2.44, moderate/severe 1.82, 95% CI 1.25–2.63) and classified as having major depression (OR 1.61, 95% CI 1.09–2.38). Association between CPP and pregnancy-related factors were not so strong (OR ranging from 1.33 to 1.41) (Table 2). Reporting multiple non-pain somatic symptoms was less associated with CPP in women of reproductive age compared to older women (OR for interaction between reproductive age and multiple non-pain somatic symptoms

was 0.51, 95% CI 0.28–0.92). There was no statistically significant interaction between reproductive age and the remaining factors assessed (Table S1).

Of all women with CPP, 260 provided sufficient information for cluster analysis (180 women of reproductive age and 80 older women). Cumulative effect of missing data resulted in about 16% of the participants being excluded from cluster analysis but there were no important differences between those excluded and those with complete data. Among women of reproductive age, two clusters were identified (Figure S1, Table 3). Depression contributed most to the differences between clusters, followed by fatigue and multiple somatic symptoms. Active coping and pain severity had little discriminating ability for the two clusters. Cluster one (n=164, 91.1%) included women who had no depression, no fatigue, and minimal somatic symptoms. They also had no sleep disturbance, lower passive coping and better quality of life compared to those in cluster two. This can be labelled as those having little/no psychosocial distress. Cluster two (n=16, 8.9%) included women who had depression, moderate/severe fatigue, multiple somatic symptoms, sleep disturbance, high passive coping and their quality of life was not as good as those in cluster one. This cluster is described as those having high psychosocial distress.

The clustering solution was validated in the post-reproductive age: the characteristics of the clusters were similar to those of reproductive-age women (Table 3). That is, cluster one (n=43, 53.8%) had little/no psychosocial distress while those in cluster two (n=37, 46.3%) had high psychosocial distress. However, there are more women in the highly distressed cluster among post-reproductive age women. This may be partly due to differences in the clustering techniques used since K-means cluster analysis tends to produce clusters with similar sizes.

Discussion

This study showed that, although women of reproductive age are more likely to report CPP, it is also common among older women. Further, heightened somatic awareness is more associated with CPP in older women compared to women of reproductive years. No other factor was differentially associated with CPP in the post-reproductive years. Two clusters exist among women with CPP; those having little/no psychosocial distress and those having high psychosocial distress regardless of age-group.

One of the strengths of this study is that it used the CPP case definition previously used in many other population-based studies from different countries (Zondervan et al., 2001a; Grace and Zondervan, 2004; Pitts et al., 2008; Garcia-Perez et al., 2010). This makes it easier to compare the results across studies. The WHEST questionnaire asked questions concerning women's general health, of which pelvic pain was one aspect so it was not obvious to participants that we were interested in pelvic pain. We believe this minimises selection bias which could occur if women with pelvic pain were more likely to participate in the survey. This conclusion is supported by the observation that those who responded after reminders were more likely to report CPP compared to those who responded before reminders (age adjusted OR: 1.23, 95% C1 0.96–1.59).

A potential limitation is the questionnaire response rate of 44.9%. However, this was higher than anticipated (35%) considering the current downward trends of response rates in epidemiological studies (Galea and Tracy, 2007). To assess the effect of non-response, analysis was repeated using weightings derived from the inverse of response rate for each of 10-year age-group/geographical location strata. The prevalence estimates derived in this way were

similar to those reported (weighted prevalence 15.0%, 95% CI 13.4–16.6 vs crude 14.8%, 95%CI 13.3–16.3%). Thus, there is no obvious reason to suggest that the results of the study have been affected by non-response. We believe the findings of this study are generalizable to other populations with similar socio-demographic characteristics. Prevalence of chronic pain is known to vary between countries which may reflect differences in culture and pain management conducts (Breivik et al., 2006). Therefore care must be taken when extrapolating the results to different populations for example low income countries. Another potential limitation is that sample size calculation was not based on cluster analysis but there are no specific rules regarding the number of cases needed to conduct cluster analysis. Some authors have suggested having at least ten cases for each variable (Cross, 2013). We used eight clustering variables in 180 cases to determine the clusters and the clustering solution was validated in 80 cases. It is generally better to have as many cases as possible and hence replication of the subgroups in larger samples will be useful.

Other postal surveys, using a similar case definition, found a prevalence of 21.5% in Australia, 24.0% in the UK and 25.4% in New Zealand (Zondervan et al., 2001a; Grace and Zondervan, 2004; Pitts et al., 2008). These higher prevalence estimates could be because these studies only sampled women of reproductive age. Prevalence of CPP among women of reproductive age in our sample was 20.5%. Recent population-based studies which included older women have reported comparable prevalence to the present study. One study, conducted in Brazil, reported CPP prevalence of 11.5% among 1278 women aged at least 14 years while the prevalence was 15.1% among women of reproductive age (Silva et al., 2011). Another study in Denmark reported a prevalence of 11.0% in a sample of 1179 women aged 18 years and above while prevalence of 13.6% was found among those aged 18–49 years (Loving et al., 2014). These

latter studies also showed the presence CPP across the age range but higher prevalence within the reproductive age.

It could be argued that the age difference in prevalence of CPP is due to age-related physiological changes within the reproductive system. Some chronic non-cancer pain conditions which are not related to the pelvis are also more common among women of reproductive age, for example fibromyalgia and temporomandibular disorder. Ovarian hormones are suggested to be involved in the modulation of many chronic non-cancer pain conditions, but the evidence is inconsistent except for endometriosis which is known to be highly dependent on oestrogen (Hassan et al., 2014). The mechanism, by which the ovarian hormones may be involved in many chronic non-cancer pain conditions, if at all, is still unclear.

Warren *et al*, hypothesised that CPP could be a functional somatic syndrome because it has many characteristics in common with, for example, irritable bowel syndrome and fibromyalgia (Warren et al., 2011). Such characteristics include pain, chronicity, being more common in women than in men, worsening by stress, correlation with depression, anxiety, physical and sexual abuse, absence of obvious pathology in many cases and comorbidity with other functional somatic syndromes. Studies have documented the co-existence of pelvic pain with fibromyalgia, IBS, chronic fatigue among other known functional somatic syndromes (Latthe et al., 2006; Aaron et al., 2001; Sinaii et al., 2002; Whitehead et al., 2007). Population based studies, including this study, show that the majority of the women who report CPP are likely to also report dysmenorrhoea and/or dyspareunia if they menstruate and are sexually active (Zondervan et al., 2001a; Grace and Zondervan, 2004; Pitts et al., 2008). Only about half of the women with CPP reported having a diagnosis for their pain, an observation which is similar

to those reported from previous studies in New Zealand, UK and USA (Mathias et al., 1996; Grace and Zondervan, 2004; Zondervan et al., 2001b).

Unlike pregnancy-related factors which showed only weak associations, all the psychosocial factors assessed were strongly associated with CPP in both age-groups. Further, having multiple non-pain somatic symptoms was more associated with CPP in older women. Psychosocial factors may be consequences of CPP; but studies have suggested that psychosocial factors may influence pain onset and persistence (Leino and Magni, 1993; Chung and Lin, 2013). Although cross-sectional studies cannot confirm causality, strong associations between such psychosocial factors and CPP have been consistently shown suggesting that they may indeed be causally related (Latthe et al., 2006). It has been shown for other regional pain syndromes that psychosocial factors do, in longitudinal studies, predict onset (Halder et al., 2002; McBeth et al., 2001; Gupta et al., 2007). Whether viewed as causes or consequences of CPP, the presence of psychosocial distress may make it difficult for affected women to engage fully with pain management intervention which could impede its effectiveness.

Two distinct groups of women with CPP were identified. One of the clusters includes women who reported little/no psychosocial distress and had low passive coping scores whereas women in the other cluster had high psychosocial distress. Unsurprisingly those with high psychosocial distress had high passive coping scores which have been shown to be associated with poorer outcomes in chronic pain patients (Mercado et al., 2005). It is possible that the group of women with high psychosocial destress may benefit from intervention that goes beyond the standard medical intervention. This can be, for example, cognitive-behavioural therapy which is often used for other chronic pain conditions and has shown some benefits in improving coping,

reducing depressive mood and health seeking behaviour (Enright, 1997; McBeth et al., 2012). Although a higher proportion of older women were in the high psychosocial distress group compared to those who are younger, there were similar clusters in both age-groups. Other studies have also highlighted the need to identify patient groups for chronic pain in order to provide effective management strategies (Viniol et al., 2013; Shaw et al., 2007; Boersma and Linton, 2005). Even though the clustering variables and patient populations were different, all these studies also identified one sub-group which seems to have the most psychosocial distress which is similar to the findings of the current study. For example, one of the studies identified three sub-groups of patients with chronic low back pain based on variables of pain features, sociodemographic data, psychological characteristics and patient resources like coping strategies (Viniol et al., 2013). One particular subgroup which they described as "middle-aged patients with mental health distress and poor coping resources" appears to be the most distressed.

Care providers may be able to direct resource intensive management strategies more efficiently by identifying individuals who are more affected regardless of age-group. It is not practical to administer so many unidimensional measures to identify psychosocial distress and coping strategies in the clinic. There may be a need to develop screening tools, such as the 9-item Subgroups for Targeted Treatment (STarT) Back Screening Tool used for back pain, in order to help clinicians identify 'at-risk' groups (Hill et al., 2008). A randomised controlled trial has shown that stratified management approach in back pain using the STarT Back is effective in improving patient outcomes and also resulted in significant cost savings by directing more resource intensive interventions to those in the at-risk groups while giving minimal treatment to the low-risk group (Hill et al., 2011). Since the profiles of women with CPP is similar to those of other regional pain syndromes such as back pain, targeting appropriate care for persons

with more psychosocial distress at an early stage might also improve outcome in CPP management and lead to significant cost savings.

In conclusion, CPP is common in both women of reproductive and post-reproductive age. This study showed that psychosocial factors are strongly associated with CPP in both age-groups although heightened somatic awareness is more associated with CPP in women of post-reproductive years. Finally, grouping women with CPP based on their pattern of reporting associating psychosocial features, pain intensity and coping strategies identified sub-group of women who may require different management strategies. Stratified management approach may be necessary in order to ensure that affected women receive optimal care and healthcare resources are used efficiently. Studies are needed to assess the validity of classifying women based on identified psychological characteristics in predicting prognosis and to investigate whether the outcomes on the subgroups of women are indeed different.

Acknowledgments: We are also grateful to Professor Krina Zondervan for providing the survey questionnaire of which chronic pelvic pain items was used in this study. We appreciate the members of the Epidemiology Group at the University of Aberdeen who assisted greatly with the questionnaire mailings. We are also grateful to those who worked on data entry: Yetunde Adelusi, Stephen McCall and Matthew Macfarlane. We are thankful to the women who participated in the survey.

Contribution to Authorship: AAA contributed to the conception of the work, undertook the data collection and analysis, and drafted the manuscript. GJM, SB and GTJ contributed to the

conception of the study, gave assistance with data analysis and interpretation of results. KD contributed to data analysis and interpretation. All authors were involved in critically revising the document and approved the final version to be published.

References

Aaron, L. A., Herrell, R., Ashton, S., Belcourt, M., Schmaling, K., Goldberg, J. & Buchwald, D. (2001) Comorbid clinical conditions in chronic fatigue: A co-twin control study. J. Gen. Intern Med, **16**, 24-31.

ACOG Committee on Practice, B. (2004) ACOG practice bulletin no. 51. chronic pelvic pain. Obstet Gynecol, **103**, 589-605.

Ayorinde, A. A., Macfarlane, G.J., Saraswat, L. & Bhattacharya, S. (2015) Chronic pelvic pain in women: An epidemiological perspective. Womens Health. (Lond. Engl).

Baranowski, A., Abrams, P., Berger, R.E., Buffington, A., Collett, B., Emmanuel, A., Fall, M., Hanno, P., Howard, F. M., Hughes, J. & et al. (2012) Definition of chronic pelvic pain. In Anonymous *Classification of Chronic Pain.* The International Association for the Study of Pain.

Boersma, K. & Linton, S.J. (2005) Screening to identify patients at risk: Profiles of psychological risk factors for early intervention. Clin. J. Pain, **21**, 38-43; discussion 69-72.

Breivik, H., Collett, B., Ventafridda, V., Cohen, R. & Gallacher, D. (2006) Survey of chronic pain in europe: Prevalence, impact on daily life, and treatment. Eur J Pain, **10**, 287-333.

Brown, G. K. & Nicassio, P.M. (1987) Development of a questionnaire for the assessment of active and passive coping strategies in chronic pain patients. Pain, **31**, 53-64.

Caliński, T. & Harabasz, J. (1974) A dendrite method for cluster analysis. Communications in Statistics, **3**, 1-27.

Chalder, T., Berelowitz, G., Pawlikowska, T., Watts, L., Wessely, S., Wright, D. & Wallace, E.P. (1993) Development of a fatigue scale. J Psychosom Res, **37**, 147-153.

Chung, S. D. & Lin, H.C. (2013) Association between chronic prostatitis/chronic pelvic pain syndrome and anxiety disorder: A population-based study. PLoS One, **8**, e64630.

Cross C.L. (2013) Statistical and methodological considerations when using cluster analysis in neuropsychological research. In Cluster Analysis in Neuropsychological Research: Recent Applications, Allen DN and Goldstein G, eds. (New York: Springer) pp. 31.

Daniels, J. P. & Khan, K.S. (2010) Chronic pelvic pain in women. BMJ, **341**, 4834.

Docking, R. E., Fleming, J., Brayne, C., Zhao, J., Macfarlane, G.J., Jones, G.T. & Cambridge City over-75s Cohort Study collaboration (2011) Epidemiology of back pain in older adults: Prevalence and risk factors for back pain onset. Rheumatology (Oxford), **50**, 1645-1653.

Engeler, D., Baranowski, A.P., Elneil, S. & Hughes, J. (2012) EAU guidelines on chronic pelvic pain.

Enright, S. J. (1997) Cognitive behaviour therapy--clinical applications. BMJ, **314**, 1811-1816.

Galea, S. & Tracy, M. (2007) Participation rates in epidemiologic studies. Ann. Epidemiol, **17**, 643-653.

Garcia-Perez, H., Harlow, S.D., Erdmann, C.A. & Denman, C. (2010) Pelvic pain and associated characteristics among women in northern mexico. Int Perspect Sex Reprod Health, **36**, 90-98.

Grace, V. M. & Zondervan, K.R. (2004) Chronic pelvic pain in new zealand: Prevalence, pain severity, diagnoses and use of the health services. Aust Nz J Public Health, **28**, 369-375.

Gupta, A., Silman, A.J., Ray, D., Morriss, R., Dickens, C., MacFarlane, G.J., Chiu, Y.H., Nicholl, B. & McBeth, J. (2007) The role of psychosocial factors in predicting the onset of chronic widespread pain: Results from a prospective population-based study. Rheumatology (Oxford), **46**, 666-671.

Halder, S. L., McBeth, J., Silman, A.J., Thompson, D.G. & Macfarlane, G.J. (2002) Psychosocial risk factors for the onset of abdominal pain. Results from a large prospective population-based study. Int J Epidemiol, **31**, 1219-1225.

Hassan, S., Muere, A. & Einstein, G. (2014) Ovarian hormones and chronic pain: A comprehensive review. Pain, **155**, 2448-2460.

Hays, R. D., Bjorner, J.B., Revicki, D.A., Spritzer, K.L. & Cella, D. (2009) Development of physical and mental health summary scores from the patient-reported outcomes measurement information system (PROMIS) global items. Qual Life Res, **18**, 873-880.

Health and Social Care Information Centre (2012) Attribution data set GP-registered populations scaled to ONS population estimates - 2011.

Hill, J. C., Whitehurst, D.G., Lewis, M., Bryan, S., Dunn, K.M., Foster, N.E., Konstantinou, K., Main, C.J., Mason, E., Somerville, S., Sowden, G., Vohora, K. & Hay, E.M. (2011) Comparison of stratified primary care management for low back pain with current best practice (STarT back): A randomised controlled trial. Lancet, **378**, 1560-1571.

Hill, J. C., Dunn, K.M., Lewis, M., Mullis, R., Main, C.J., Foster, N.E. & Hay, E.M. (2008) A primary care back pain screening tool: Identifying patient subgroups for initial treatment. Arthritis Rheum, **59**, 632-641.

Jenkins, C. D., Stanton, B.A., Niemcryk, S.J. & Rose, R.M. (1988) A scale for the estimation of sleep problems in clinical research. J Clin Epidemiol, **41**, 313-321.

Kroenke, K., Spitzer, R.L. & Williams, J.B. (2001) The PHQ-9: Validity of a brief depression severity measure. J Gen Intern Med, **16**, 606-613.

Latthe, P., Latthe, M., Say, L., Gulmezoglu, M. & Khan, K.S. (2006) WHO systematic review of prevalence of chronic pelvic pain: A neglected reproductive health morbidity. BMC Public Health, **6**, 177.

Leino, P. & Magni, G. (1993) Depressive and distress symptoms as predictors of low back pain, neck-shoulder pain, and other musculoskeletal morbidity: A 10-year follow-up of metal industry employees. Pain, **53**, 89-94.

Loving, S., Thomsen, T., Jaszczak, P. & Nordling, J. (2014) Female chronic pelvic pain is highly prevalent in denmark. A cross-sectional population-based study with randomly selected participants. Scand J Pain, **5**, 93-101.

Mathias, S. D., Kuppermann, M., Liberman, R.F., Lipschutz, R.C. & Steege, J.F. (1996) Chronic pelvic pain: Prevalence, health-related quality of life, and economic correlates. Obstet Gynecol, **87**, 321-327.

McBeth J, Prescott G, Scotland G, Lovell K, Keeley P, Hannaford P, McNamee P, Symmons DP, Woby S, Gkazinou C, Beasley M, Macfarlane GJ. (2012). Cognitive behavior therapy, exercise, or both for treating chronic widespread pain. *Arch Intern Med,* **;172**,48-57.

McBeth, J., Macfarlane, G.J., Benjamin, S. & Silman, A.J. (2001) Features of somatization predict the onset of chronic widespread pain: Results of a large population-based study. Arthritis Rheum, **44**, 940-946.

McGowan, L., Escott, D., Luker, K., Creed, F. & Chew-Graham, C. (2010) Is chronic pelvic pain a comfortable diagnosis for primary care practitioners: A qualitative study. BMC Fam. Pract, **11**, 7-2296-11-7.

McGowan, L., Luker, K., Creed, F. & Chew-Graham, C.A. (2007) How do you explain a pain that can't be seen?: The narratives of women with chronic pelvic pain and their disengagement with the diagnostic cycle. Brit J Health Psych, **12**, 261-274.

Mercado, A. C., Carroll, L.J., Cassidy, J.D. & Cote, P. (2005) Passive coping is a risk factor for disabling neck or low back pain. Pain, **117**, 51-57.

National Records For Scotland (2014) Scotland's census 2011-national records for scotland table KS201SC- ethnic group-release 3A.

Othmer, E. & DeSauza, C. (1985) A screening test for somatization disorder. Am J Psychiatry, **142**, 1146-1149.

Pitts, M. K., Ferris, J.A., Smith, A.M., Shelley, J.M. & Richters, J. (2008) Prevalence and correlates of three types of pelvic pain in a nationally representative sample of australian women. Med J Aust, **189**, 138-143.

Reiter, R. C. (1990) A profile of women with chronic pelvic pain. Clin. Obstet. Gynecol., **33**, 130-136.

Royal College of Obstetricians and Gynaecologists (2012) Chronic pelvic pain, initial management (green-top 41). Royal College of Obstetricians and Gynaecologists.

Shaw, W. S., Pransky, G., Patterson, W., Linton, S.J. & Winters, T. (2007) Patient clusters in acute, work-related back pain based on patterns of disability risk factors. J Occup Environ Med., **49**, 185-193.

Silva, G., Nascimento, A., Michelazzo, D., Alves Junior, F., Rocha, M., Silva, J., Reis, F., Nogueira, A. & Poli-Neto, O. (2011) High prevalence of chronic pelvic pain in women in ribeirao preto, brazil and direct association with abdominal surgery. Clinics, **66**, 1307-1312.

Sinaii, N., Cleary, S.D., Ballweg, M.L., Nieman, L.K. & Stratton, P. (2002) High rates of autoimmune and endocrine disorders, fibromyalgia, chronic fatigue syndrome and atopic diseases among women with endometriosis: A survey analysis. Hum Reprod, **17**, 2715-2724.

The Scottish Government (2012) Scottish Index of Multiple Deprivation 2012: A National Statistics Publication for Scotland. Edinburgh.

Viniol, A., Jegan, N., Hirsch, O., Leonhardt, C., Brugger, M., Strauch, K., Barth, J., Baum, E. & Becker, A. (2013) Chronic low back pain patient groups in primary care--a cross sectional cluster analysis. BMC Musculoskelet Disord, **14**, 294-2474-14-294.

Warren, J. W., Morozov, V. & Howard, F.M. (2011) Could chronic pelvic pain be a functional somatic syndrome? Obstet Gynecol, **205**, 199.e1-199.e5.

Whitehead, W. E., Palsson, O.S., Levy, R.R., Feld, A.D., Turner, M. & Von Korff, M. (2007) Comorbidity in irritable bowel syndrome. Am J Gastroenterol, **102**, 2767-2776.

Zondervan, K. T., Yudkin, P.L., Vessey, M.P., Jenkinson, C.P., Dawes, M.G., Barlow, D.H. & Kennedy, S.H. (2001a) The community prevalence of chronic pelvic pain in women and

associated illness behaviour. Brit J Gen Pract, **51**, 541-547.

Zondervan, K. T., Yudkin, P.L., Vessey, M.P., Jenkinson, C.P., Dawes, M.G., Barlow, D.H. & Kennedy, S.H. (2001b) Chronic pelvic pain in the community--symptoms, investigations and diagnoses. Am J Obstet Gynecol, **184**, 1149-1155.

Figure Legends

Figure 1: Venn diagram showing the prevalence % (n) and overlap of CPP, dysmenorrhoea and dyspareunia in the past three months among 729 women who had periods and were sexually active in the past 12 months.

Figure S1: Dendrogram for cluster analysis of reproductive-age women with CPP based on the patterns of reporting depression, multiple somatic symptoms, fatigue, sleep disturbance, quality of life, active coping, passive coping and pain severity.

Footnote: The dashed line shows the partition point at which the clustering solution was optimal in consultation with Calinski and Harabasz pseudo-F index stopping rule. The shaded areas show the participants grouped before the partition point.

Tables

Table 1: Demographic characteristics of study participants (n=2088)

Characteristic	Total in group n (%)	With CPP n (%)	Prevalence of CPP (95% CI)
Age range, years			
25–34	255 (12.2)	54 (21.2)	21.2 (16.1–26.2)
35–44	392 (18.8)	86 (21.9)	21.9 (17.8–26.0)
45–54	491 (23.5)	78 (15.9)	15.9 (12.6–19.1)
55–64	506 (24.2)	61 (12.1)	12.1 (9.2–14.9)
65–74	312 (14.9)	23 (7.4)	7.4 (4.5–10.3)
75–84	104 (5.0)	7 (6.7)	6.7 (1.9–11.6)
85–94	28 (1.3)	0 (0)	0 (0–12.3)
Educational qualification			
No educational qualifications	137 (6.6)	10 (7.3)	7.3 (2.9–11.7)
Secondary school	624 (29.9)	81 (13.0)	13.0 (10.3–15.6)
Vocational qualifications	379 (18.2)	61 (16.1)	16.1 (12.4–19.8)
Professional qualifications	386 (18.5)	57 (14.8)	14.8 (11.2–18.3)
Undergraduate degree	248 (11.9)	52 (21.0)	21.0 (18.9–26.0)
Postgraduate degree	211 (10.1)	33 (15.6)	15.6 (10.7–20.6)
Other	79 (3.8)	13 (16.5)	16.5 (8.2–24.7)
Unspecified	24 (1.2)	2 (8.3)	–
Present marital status			
Married	1,316 (63.0)	201 (15.3)	15.3 (13.3–17.2)
Single (cohabiting)	188 (9.0)	33 (17.6)	17.6 (12.1–23.0)
Single (not cohabiting)	182 (8.7)	35 (19.2)	19.2 (13.5–25.0)
Divorced/separated	226 (10.8)	29 (12.8)	12.8 (8.5–17.2)
Widowed	154 (7.4)	11 (7.1)	7.1 (3.1–11.2)
Unspecified	22 (1.1)	0 (0)	–
Level of Deprivation			
1	93 (4.5)	17 (18.3)	18.3 (10.4–26.2)
2	196 (9.4)	29 (14.8)	14.8 (9.8–19.8)
3	411 (19.7)	82 (20.0)	20.0 (16.1–23.8)
4	626 (30.0)	76 (12.1)	12.1 (9.6–14.7)
5	750 (35.9)	104 (13.9)	13.9 (11.4–16.3)
Missing	12 (0.6)	1 (8.3)	–

Table 2: Factors associated with CPP

Factors	With CPP n (%)	Without CPP n (%)	Univariable analysis OR (95% CI)	[a]P-value	[b]Multivariable Model OR (95%CI)
Infertility					
No	258 (83.5)	1567 (88.1)	1		
Yes	51 (16.5)	212 (11.9)	1.46 (1.04–2.03)	0.03	
Ever being pregnant					
No	60 (19.4)	301 (16.9)	1		
Yes	249 (80.6)	1478 (83.1)	0.85(0.62– 1.15)	0.28	
Ectopic Pregnancy					
No	298 (96.4)	1746 (98.2)	1		
Yes	11 (3.6)	33 (1.9)	1.95 (0.98–3.91)	0.06	
Miscarriage					
No	236 (73.4)	1460 (82.1)	1		1
Yes	73 (23.6)	319 (17.9)	1.42 (1.06–1.89)	0.02	1.33 (0.96–1.85)
Termination of pregnancy					
No	247 (79.9)	1547 (87.0)	1		1
Yes	62 (20.1)	232 (13.4)	1.67 (1.23–2.28)	0.001	1.40 (0.99–1.99)
Nulliparity					
No	224 (72.5)	1408 (79.2)	1		1
Yes	85 (27.5)	371 (20.9)	1.44 (1.09–1.90)	0.01	1.41 (0.997–1.99)
Caesarean delivery					
No	257 (83.2)	1552 (87.2)	1		
Yes	52 (16.8)	227 (12.8)	1.38 (1.00–1.92)	0.05	-
Multiple somatic symptoms (SSS[c])					
No (0-1)	185 (61.7)	1459 (83.6)	1		1
Yes (2-5)	115 (38.3)	286 (16.4)	3.17 (2.43– 4.13)	<0.0001	3.58 (2.23–5.75)
Missing	12 (3.9)	56 (3.2)			
Fatigue (CFS[d])					
None (0)	131 (43.4)	1088 (64.3)	1		1
Mild (1-3)	73 (24.2)	313 (18.5)	1.94 (1.42– 2.65)	<0.0001	1.74 (1.24–2.44)
Moderate/severe (4-11)	98 (32.5)	290 (17.2)	2.81 (2.10– 3.46)	<0.0001	1.82 (1.25–2.63)
Missing	7 (2.3)	88 (5.0)			
Depression (PHQ-9[e])					
No (0-10)	228 (76.5)	1530 (89.0)	1		1
Yes (10-27)	70 (23.5)	189 (11.0)	2.49 (1.83– 3.38)	<0.0001	1.61 (1.09–2.38)
Missing	11 (3.6)	60 (3.4)			
Age-group					
>51 years	104 (33.7)	983 (55.3)	1		1
≤51 years	205 (66.3)	796 (44.7)	2.43 (1.89–3.14)	<0.0001	2.43 (1.69–3.48)
[f]Reproductive age X multiple non-pain somatic symptoms					0.51 (0.28 –0.92)

[a]P-value for univariable analysis

[b]Multivariable model adjusted for demographic factors (education, marital status, level of deprivation)

[c]Somatic Symptoms Scale

[d]Chalder Fatigue Scale

[e] Patient Health Questionnaire-9

[f]Interaction term

Hosmer-Lemeshow test-statistics indicated that the model was of good fit (HL $\chi 2=3.87$, df=8, p=0.87)

Table 3: Characteristics of clusters of women with chronic pelvic pain in the reproductive and post-reproductive age-groups.

	Reproductive age[b]		Post-reproductive age[c]	
Factor (Measure)[a]	Cluster 1 (n=164)	Cluster 2 (n=16)	Cluster 1 (n=43)	Cluster 2 (n=37)
Depression (Patient Health Questionnaire-9)	4 (2,7)	18 (15,20)	2 (2,4)	10 (7,12)
Fatigue (Chalder Fatigue Scale)	1(0,5)	7 (1,10)	0 (0,1)	5(3,7)
Somatic symptoms (Somatic Symptom Scale)	2 (1,3)	4 (3,5)	2 (1,3)	3 (2,4)
Quality of life (PROMIS®)	4 (3,4)	3 (2,3)	4 (4,5)	3 (2,3)
Passive coping (VPMI[d])	22 (17,28)	36 (29,41)	19 (15,24)	28 (25,30)
Sleep disturbance (Sleep Disturbance Scale)	7 (3,10)	19 (15,20)	4 (3,10)	14(9,17)
Pain intensity (NRS)	5 (3,7)	6 (4,7)	3 (3,4)	6 (4,7)
Active coping (VPMI[d])	20 (16,24)	22 (16,24)	22 (19,26)	20 (17,22)
[e]Age (years)	41 (34,46)	43 (36,50)	60 (57,65)	61 (57,65)

[a] Median (IQR) score for each measure

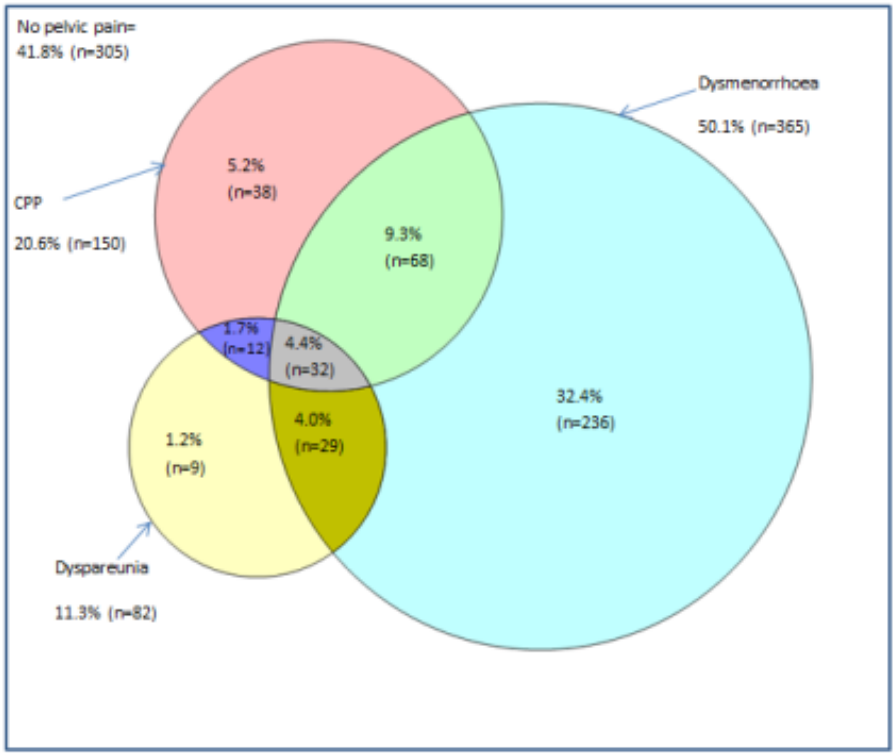
[b]Clusters generated by Hierarchical clustering

[c]Clusters generated by K-means clustering

[d]Vanderbilt Pain Management Inventory

[e]Age was not included as a clustering variable.

Figures


No pelvic pain=
41.8% (n=305)
Dysmenorrhoea
50.1% (n=365)
CPP
20.6% (n=150)
5.2%
(n=38)
9.3%
(n=68)
1.7%
(n=12)
4.4%
(n=32)
32.4%
(n=236)
4.0%
(n=29)
1.2%
(n=9)
Dyspareunia
11.3% (n=82)