A prospective cohort study to determine prognostic factors associated with outcomes in primary care attenders with unexplained physical symptoms

Kethakie H Lamahewa

UCL

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I, Kethakie H Lamahewa, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

Background

Unexplained physical symptoms (UPS) that lack an organic explanation, even after appropriate investigation, are extremely common amongst UK primary care attenders but knowledge about their outcome is limited.

Aim

In a cohort of adult primary care attenders with UPS, this study aims to:
1) Investigate the outcome, in terms of the presence of UPS at six months follow-up and 2) Identify prognostic factors associated with somatic symptom severity, quality of life, anxiety, depression and health care use at six months follow-up.

Methods

Screening: Consecutive adults attending nine general practices completed a screening questionnaire to identify those with UPS.
Cohort study: Eligible participants completed the baseline questionnaire that enquired about somatic symptoms, quality of life, psychological well-being and past health and social history, and were followed-up after six months.

Results

Screening: Questionnaires were completed by 73% (2,826/3,896) of eligible attenders. Over two-thirds were female, median age was 42 years (IQR 30, 55) and median symptom severity score, based on the PHQ-15 was 7 (IQR 4, 11). Most (2,425/2,826 (86%)) had at least one UPS and around half (1,393/2,826 (49%)) had symptoms that were all unexplained (no explanation or diagnosis for any of their symptoms). Just under half (1,248/2,826, (44%)), had an explanation for their symptoms that included functional diagnoses (100/2,826 (4%)), psychological explanations (187/2,826 (7%)), or physical explanations or diagnoses (921/2,826 (33%)).

Cohort study: The cohort included 294 participants, were largely female (231/294 (79%)), with a median age of 44 years (IQR 32, 57)) and diverse ethnicity (43% white British). At baseline, the cohort had a high level of morbidity, with moderately severe somatic symptoms (11.5 SD 4.9). Most reported experiencing their symptoms for longer than a year. A third had clinically significant comorbid depression and anxiety.

Outcome: There was 245/294 (83%) followed-up at six months; mean PHQ-15 score was 10.5 (SD 5.3). Over a half reported unexplained symptoms (135/245 (55%)), just under half (103/245 (42%)) reported symptoms were still under investigation and only 26/245 (11%) reported that their symptoms had resolved. Options were not mutually exclusive and participants could choose more than one. The predictors of more severe somatic symptoms at follow-up were being female (B=1.31, 95% CI 0.12 to 2.50), higher somatic symptom severity (B=0.53, 95% CI 0.42 to 0.64), experience of childhood physical abuse (B=1.86 95% CI 0.27 to 3.45), perception of poor financial well-being (B=1.90, 95% CI 0.89 to 2.91) and lower physical functioning at baseline (B=-0.10, 95% CI -0.15 to -0.04).

Conclusion: Most people with UPS and high symptom severity are unlikely to improve over six months. Historical and current difficulties are associated with higher somatic symptom severity at follow-up. Future work should determine whether these findings are maintained over longer periods. The value of developing prognostic prediction models based on factors identified in this study should be explored.

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Abbreviations

CIDI	Composite International Diagnostic Interview
DSM	Diagnostic and Statistical Manual
GAD-7	Generalised Anxiety Disorder measure
GSE	Generalised Self-efficacy Scale
GP	General Practitioner
IMD	Index of Multiple Deprivation
LTE-Q	List of Threatening Experiences Questionnaire
MUS	Medically Unexplained Symptoms
NHS	National Health Service
PHQ-9	Patient Health Questionnaire Depression Measure
PHQ-15	Patient Health Questionnaire Somatic Symptom Measure
SF-12	Short Form-12 Quality of Life measure
SSD	Somatic Symptom Disorder
UK	United Kingdom
UPS	Unexplained Physical Symptoms
USA	United States of America
WSAS	Work and Social Functioning measure

Chapter 1 : **Introduction**

1.0 Chapter overview

In this chapter, I set the context for my thesis by highlighting the importance of the area of inquiry and the complexities surrounding research into the topic. First, I define unexplained physical symptoms and describe how terms, definitions and diagnostic classification have changed over time. Second, I outline the methods used to identify those with unexplained physical symptoms in research. Prevalence estimates of unexplained physical symptoms are then presented to highlight the extent of its burden globally and in the United Kingdom. This is followed by an overview of literature identifying factors associated with unexplained physical symptoms, in various settings. Finally, I discuss the burden of unexplained physical symptoms in terms of costs to health care, the difficulties in management and the impact on individuals.

1.1 Background

It is estimated that around 40% of primary care attenders experience symptoms such as headache, pain, dizziness, bloating and fatigue, which lack an obvious pathological explanation, even after appropriate investigation (Kroenke, 2003; Haller et al., 2015). These symptoms are often described as medically unexplained physical symptoms (Hennsingsen et al., 2011); although this term is considered to

be scientifically neutral by some, others suggest that it carries negative connotations for patients (Stone et al, 2002). Debate about the existing terminology and diagnostic classifications are on-going and are discussed in section 1.2 and 1.3. In this study, I use the broader term *'unexplained physical symptoms'* (UPS); the definition is discussed in section 1.2.

UPS can range from mild and transitory to chronic and debilitating (Brown., 2006; Rosendal et al., 2005), often resulting in functional impairment and distress (Zonneveld et al., 2013; Olde Hartman et al., 2009). About half of all suffers are thought to experience symptoms that persist for longer than one year (Brown, 2006; Rosendal et al., 2005; Olde Hartman et al., 2009; Steinbrecher and Hiller., 2011;). Costs incurred are high to both health care and the wider economy due to help seeking behaviours and loss of productivity (Bermingham et al., 2010).

Primary care is the first point of contact for most people and doctors report difficulties surrounding the appropriate management of patients (Stone, 2014). Many are referred to secondary care for specialist input (Olde Hartman et al., 2009); prevalence is reported to be as high as between 30 to 70 per cent (Stone et al., 2009; Nimnuan et al., 2001; Reid et al 2001). Better management at earlier stages in primary care may reduce the burden on patients and the numbers who go on to require long term care (RCGP, 2009). General Practitioners' decision making and care planning could be assisted by use of a prognostic tool to predict risk of poor outcomes like persistence of unexplained somatic symptoms or identify those who

will experience a more favourable outcome, such as the remission of symptoms. However, few prospective cohort studies have been conducted in primary care to explore outcome over time and to identify prognostic factors associated with outcome (Olde Hartman et al., 2009; Steinbrecher and Hiller., 2011; Creed et al., 2012).

My study will investigate the outcome of primary care attenders with UPS and identify prognostic factors associated with outcome in terms of somatic symptom severity, quality of life, depression, anxiety and health care use at six-month follow-up. The aims and objectives of the study are discussed in detail in Chapter 3.

1.2 Terminology

A variety of terms have been used to describe those with physical symptoms that lack an obvious explanation in terms of the disease process or structural pathology of organs or body systems, even after appropriate examination and investigation (Henningsen et al., 2011). These terms have changed with time, accompanied by conceptual changes in how disease and illness are defined and understood; they are often used interchangeably, widely contested and considered unsatisfactory due to the aetiological assumptions many of them convey (Sumathipala, 2005; Dimsdale et al.2013).

The terms ‘medically unexplained symptoms’ and ‘medically unexplained physical symptoms’ are used interchangeably in the literature and have been widely used in clinical and research settings, since the 1980’s (Creed et al., 2011). However, this term has been criticised over the years and considered to be unsatisfactory for a number of reasons. First, historically ‘medically unexplained symptoms’ were based on a biomedical model of illness (Henningsen et al., 2011; Dimsdale et al.,2013; Picariello et al., 2015); it was inherently dualistic, reinforcing the view that if disease was identified, symptoms were a ‘medical’ problem whilst symptoms that lacked an organic explanation were a ‘psychiatric’ problem (Sharpe et al., 2006). The term has also been criticised for describing symptoms by what they are not, rather than what they are and implying that ‘medicine’ has nothing to offer to those with these ‘unexplained’ symptoms (Henningsen et al., 2011, Picariello et al., 2015). Increasingly, it is used much more loosely to refer to physical symptoms of unknown cause, without implying an underlying psychological cause. However this term still carries some of the stigma of its historical association with mind body dualism (Sumathipala, 2005).

Another term that was widely used since the 1990’s was ‘somatisation’. It referred to ‘a tendency to experience and communicate somatic distress in response to psychosocial stress and to seek medical help for it’ (Lipowski, 1988). The term somatisation implied a psychological cause (Brown, 2006); it is criticised by those who were of the view that not all UPS reflect a psychological cause (Sharpe and Mayou, 2004). It is still used by some to refer to patients with multiple symptoms

without a diagnosis of an organic disease, who seek repeated medical care, synonymous with the broader definition of medically unexplained symptoms (van der Leeuw et al, 2015).

'Functional Somatic Symptoms' or 'Functional Somatic Syndromes' are also popular terms, historically originating from neurology (Picariello et al., 2015). Some use the term functional somatic symptoms to refer to medically unexplained symptoms as described earlier (Wessley et al., 1999), whilst others use the term functional somatic syndromes to refer to symptoms assumed to be a result of disturbances in functioning relating to specific organs and body systems (Picariello et al., 2015; Mayou and Farmer, 2002; Wessley., et al 1999). Certain functional syndromes are common to specific areas of medicine; for example, unexplained pain and joint stiffness, along with other symptoms such as fatigue are referred to as Fibromyalgia in Rheumatology (Mayou et al., 2005). Unexplained abdominal pain accompanied with bloating, constipation, diarrhoea and/or nausea is described as Irritable Bowel Syndrome in gastroenterology and unexplained chest pain referred to as non-cardiac chest pain in cardiology (Mayou et al., 2005). It has been suggested that these syndromes may not be distinct from one another as there is considerable overlap in the symptoms experienced (Wessely et al., 1999).

The term 'somatoform disorders' was first used when it was introduced as a diagnostic category in The Diagnostic and Statistical Manual for Mental Disorders classification, (3rd ed.; DSM-III; American Psychiatric Association [APA],1980)

(APA,2014). The main feature of somatoform disorders is the presence of UPS but not all those with UPS meet the criteria for somatoform disorder. Although it has undergone many changes over time, somatoform disorders have been considered to be on the severe end of the spectrum (Henningsen et al., 2011). This will be discussed further in the next section on diagnostic classifications (see section 1.3).

There has been a great amount of dissatisfaction amongst academics and patients regarding the terms used to describe patients with symptoms that lack an obvious pathological explanation (Creed et al.,2009; Creed et al., 2010). Over time various other abbreviations and suggestions have been made along with changes within international classifications. One that was and is still often used is abridged somatisation, which was originally derived as an abbreviated version of the DSM-III construct somatisation (Escobar et al., 1989; 1998a). It was developed to capture a wider population presenting with unexplained symptoms. To meet the criteria for abridged somatisation requires the presence of at least four symptoms based amongst men and six symptoms amongst females on the Somatic Symptom Index (Escobar et al 1989).

Other suggested terminology and criteria include 'Bodily Distress Syndrome' (Fink and Schroder, 2010), 'Multi-somatoform Disorder' (Kroenke et al., 2007) and Polysymptomatic Distress Disorder (Rief et al., 2011). A recent survey reported that amongst 844 lay participants, the most acceptable term was 'Persistent Physical Symptoms' which was preferred by 20% of respondents. This was closely followed

by: ‘Functional Symptoms’ (17%); ‘Medically Unexplained Symptoms’ (15%); and ‘Body Distress Disorder’ (13%). The least popular term was ‘Complex Physical Symptoms’ (5%) (Marks and Hunter, 2014). In 2013, The Diagnostic and Statistical Manual for Mental Disorders (5th ed.; DSM-5; American Psychiatric Association [APA],2013) introduced the new ‘Somatic Symptom Disorder’ category. This will be discussed in section 1.3.

As the above studies highlight, there appear to be no ideal term and the debate continues over which terminology should be used. I chose to use the term unexplained physical symptoms (UPS) at the inception of this study in 2012, as I considered it to be better suited for the study materials used in screening, recruitment and data collection, than any of the other terms discussed. In my opinion it does not carry the negative conations of other existing terms such as medically unexplained symptoms. I consider this term to be synonymous to medically unexplained symptoms, in its broader definition, referring to physical symptoms of unknown cause, but without implying an underlying psychological cause. In the next section I discuss the diagnostic classifications often used to identify and describe participants clinically and in research.

1.3 Diagnostic Classifications

A majority of studies of UPS use The American Psychiatric Association's Diagnostic and Statistical Manual for Mental Disorders (DSM) or the International Classification of Disease (ICD) nomenclature devices or coding systems to operationalise psychiatric diagnoses (refer Appendix 1.1). Many diagnostic interviews and questionnaires are aligned to these classifications and are described in section 1.4.1.

The DSM-III (APA,1980), introduced ‘somatoform disorders’ for the first time, as a diagnosis for syndromes unexplained by general medical conditions but not completely psychological, replacing the previous diagnostic category ‘neurosis’ (Hyler, 1984; Hiller and Rief, 2005).

Under the umbrella of somatoform disorders were four subcategories: somatisation disorder, conversion disorder (or hysterical neurosis, conversion type), psychogenic pain disorder and hypochondriasis. However, large numbers of people with unexplained symptoms did not meet the diagnostic criteria for any of these subcategories therefore they became considered as limited and restrictive (Kroenke et al 1997; Dimsdale et al.,2013).

Further revisions in the subsequent Diagnostic and Statistical Manual for Mental Disorders third and fourth revisions (3rd ed., rev.; DSM-III-R; American Psychiatric

Association [APA], 1987; 4th ed.; DSM-IV; American Psychiatric Association [APA] 1994) resulted in inclusion of new subcategories such as atypical somatoform disorder and undifferentiated somatoform disorders to make the diagnostic category more inclusive. This provided a way in which to capture and describe more of those in the general population or who were attending primary care with UPS. There was a concern that broadening the diagnostic criteria would lead to the over medicalisation of physical symptoms resulting in even transitional symptoms being labelled and treated in a clinical settings (Barsky and Borus, 1995). On the other hand, a more inclusive diagnostic classification would aid in health service development and planning by giving a better idea of the incidence (Barsky and Borus, 1995).

The DSM-IV (APA., 1994) also included the diagnoses: conversion disorder; pain disorder; hypochondriasis; body dysmorphic disorder (refer Appendix 1.1). Although these subcategories have features in common with somatisation disorder and undifferentiated somatoform disorder, such as the presence of unexplained symptoms, diagnoses of these required further specific criteria to be met. For example, the diagnoses of pain disorder required an associated psychological disorder; and hypochondriasis required the presence of preoccupation with fear, or the idea that one has a serious disease, based on misinterpretation of bodily symptoms which persists despite appropriate investigation and reassurance.

Despite the heterogeneity between the diagnostic categories, some studies rationalise that they are similar constructs and often group and study individuals meeting the diagnostic criteria for these together (Olde Hartman et al., 2009). For details on specific criteria that must be met for a diagnosis of somatisation disorder such as number and duration of symptoms, as well as listing the other categories included under somatoform disorders in DSM-IV see Appendix 1.1.

Another diagnostic categorisation system commonly used in the United Kingdom (UK) is the International Classification of Diseases (World Health Organisation [WHO], 1992). However, the majority of published research appears to refer to DSM classifications originating from the USA. Efforts were taken to align the International Classification of Diseases 10th revision (ICD-10) to the DSM-IV in terms of the diagnostic categories within the wider somatoform disorder category and to some extent these are similar (Frances, 2013). Being a general manual of illness, one of the main differences between the two diagnostic manuals is that the ICD-10 (WHO, 1992) emphasises a 'psychological' cause whilst the DSM-IV being exclusively a psychiatric diagnostic classification assumes a psychological cause and emphasises the presence of a significant impairment in day to day, work and social functioning as a result of the UPS. Details of ICD-10 (WHO, 1992) are provided in Appendix 1.1.

DSM-IV somatisation disorder was criticised by some, for being too restrictive and not capturing the true number of people burdened by UPS (Creed, 2006; Dimsdale et al., 2013). On the other hand, the newly included DSM-IV 'Undifferentiated

Somatoform Disorder' was considered to be too broad by others; capturing a large number of the general population (Dismsdale et al., 2013). An argument in favour of revisions was that many of the subcategories within somatoform disorders overlap and that there was a lack of clarity between boundaries (APA, 2013). It is suggested that the DSM-IV was difficult for non-psychiatrists to use and fundamentally that it was difficult to determine whether a symptom was medically unexplained (APA, 2013). Additionally, labelling individuals with essentially 'mental disorder' diagnoses through a process of exclusion was considered inappropriate, implying to patients that symptoms were not considered 'real' (APA, 2013). These arguments resulted in a major diagnostic change in The Diagnostic and Statistical Manual for Mental Disorders fifth revision DSM-5 (5th ed.; DSM-V; American Psychiatric Association [APA], 2013), which was published in 2013 after the inception of my study.

The Somatic Symptom Disorder (SSD) as defined in DSM-5 focuses on symptom behaviours and/or thoughts, which are disproportionate or excessive, but there are no requirements that the symptoms should be unexplained (APA, 2013). It is argued that the DSM-V criteria is too loose, as it requires only the presence of at least one bodily symptoms that has lasted for at least six months and is distressing or distributive to the individual (Dimsdale and Levenson, 2013). Critics argue that the new classification is over inclusive and will result in increasingly classifying symptoms as mental disorders (Frances, 2013).

The purpose of the new SSD classification is to identify those who experience burden from their physical symptoms, regardless of whether they are explained or not. However, early field work showed high false positive rates, picking up 7% of 'healthy' people in the general population as meeting the criteria for Somatic Symptom Disorder (Frances,2013).

Despite the concerns about how the SSD classification will work in practice and the over medicalisation of symptoms, it is important to remember that those who do meet the new criteria are likely to be individuals who seek help for their symptoms, whether a diagnostic label is attached to them or not. Therefore, such an inclusive classification will not only validate the distress and burden experienced by patients but also give a better idea of the extent of health care use amongst those undefined patients.

On the other hand, a new classification may not mean that attitudes towards those with unexplained symptoms will necessarily change overnight. Doctors may continue with their own pre-conceived biases and may not necessarily change how a patient is viewed or managed; how someone with a SSD and cancer is treated may still be very different to someone with SSD whose symptoms are considered unexplained. A new diagnostic criterion such as SSD may allow for a more inclusive level of identification, classification and estimation of the burden of such symptoms, paving the way for innovation in care and management for distressed patients. However, how the use of the DSM-5 SSD classification will work in practice

and if it will be used widely remains to be seen. In the next section, the identification of those with UPS is discussed.

1.4 Identification of UPS in research

Methods used in research to identify UPS have commonly included: structured diagnostic interviews administered by a clinician or suitably trained person; structured screening questionnaires either completed with an interviewer or self-reported; and clinical judgment following patient interview or review of medical records (Haller et al., 2015; Hilderink et al., 2013; Van Boven et al., 2011).

1.4.1 Structured Diagnostic Interviews

Some structured diagnostic interviews which have been commonly used in studies of UPS include: Diagnostic Interview Schedule (Robins, 1981); Composite International Diagnostic Interview (Robins et al., 1988, Robins, 1981); Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Wing, 1990, Fink et al., 1999, de Waal et al., 2004) and Structured Clinical Interview for DSM (SCID)(Spitzer, 1992). All were developed for the purpose of diagnosing psychiatric morbidity and were aligned to the either or both DSM and ICD manuals. Most were initially designed to be used by clinicians; some such as the CIDI and SCID were developed so that they could be administered by trained professionals in mental and psychiatric settings

(Brugha et al., 2001). They were later extended for use by trained lay interviewers (Brugha et al., 2001).

At the initial stages of my study, I considered using a diagnostic interview, specifically the Composite International Diagnostic Interview, third revision (CIDI 3.0, 2004), to identify a population comparable with those identified in previous studies but I decided against this for a number of reasons. First, I was interested in identifying a population with UPS who did not necessarily have an underlying psychological cause, and the interviews available were established for the purpose of identifying psychiatric morbidity. Secondly, a few people in primary care meet the diagnosis for somatoform disorders, but many more are likely to be burdened by UPS. Therefore, its use would likely result in identification of a population with limited relevance. Prevalence estimates according to different diagnostic criteria are discussed in section 1.5.

1.4.2 Structured screening questionnaires

Structured screening questionnaires have been used frequently for identification of somatic symptoms, explained or otherwise. Self-report questionnaires are valuable for gaining insight into patient perception of their symptoms (Paulhus and Vazire, 2007). Like interviews, they are subjective and can be affected by recall bias; however they are quicker to complete and less resource intensive than diagnostic interviews, which require trained interviewers and take longer to complete (Bucholz

et al., 1993). They are at times used to determine a sample suitable for further in-depth diagnostic interviewing (Bucholz et al., 1993).

A review of self-report symptom scales to assess somatic symptoms identified 40 questionnaires; the number of items in each ranged from five to 78, although close to half included 15 symptoms (Zijlema et al., 2013). Some of these questionnaires enquired about life time symptom experiences, most were based on the previous week or month. Questionnaires identified in the review included: Bradford Somatic Inventory (Mumford, 1989; Mumford et al.,1991); BSI-6: Brief Symptom Inventory (Derogatis and Melisaratos, 1983); PSC-17: Physical Symptom Checklist (Attanasio et al., 1984); Physical Symptom Checklist-51 (de Waal et al 2005); Patient Health Questionnaire (Spitzer et al 1999); PHQ-15: Patient Health Questionnaire, somatic symptom module (Kroenke et al., 2002); SCL-90: Symptom Checklist-90 Somatization (Derogatis and Unger, 2010), SSI- Somatic Symptoms Index (Escobar et al., 1989). Most items included in the questionnaires were found to be aligned to DSM and ICD diagnostic categories and many of the questionnaires overlap with each other. Most questionnaires provide a somatisation diagnosis or assessed the frequency (57%), severity (28%) or both frequency and severity (15%) of symptoms. Some of the questionnaires were adapted short forms of longer questionnaires; for example the Brief Symptom Inventory (BSI-6) was adapted from the SCL-90 SOM (Zijlema et al., 2013).

For my study, I chose the Patient Health Questionnaire somatic symptom module (PHQ-15) to determine somatic symptom severity (Kroenke et al., 2002). I provide a discussion based on the context under which my decision was made and discuss the properties of the PHQ-15 in section 4.9.1.

1.4.3 Clinician and researcher identification

In some studies, participants with UPS are identified based on general practitioners judgment of consultations or review of medical notes (De Gucht et al., 2004; Duddu et al., 2008; Morriss et al., 2012). General practitioner (GP) identification can lead to considerable variation in the populations identified due to variability in individual practitioner's judgement, especially if a study includes a number of sites and general practitioners. Some studies identify participants based on researcher's judgment (Speckens et al., 1996; Kooiman et al., 2004; van Dessel et al., 2014, Van der Weijden et al., 2003); similar issues of variability may occur and may be further exacerbated when electronic medical notes are reviewed, as these are already based on a doctor's judgement and subject to variation in case recording (Morriss et al 2012). Variations can be minimised by using strict inclusion and exclusion criteria but this method may be fairly resource intensive requiring the involvement and time of doctors and trained researchers. Use of medical records is discussed further in the next section (see 1.4.4).

1.4.4 Use of medical records

Some studies use electronic medical records and illness episode statistics for identification of those with UPS (van Boven et al., 2011; Morriss et al 2012; Dirkzwager and Verhaak, 2007). Electronic medical records have considerable value in providing access to large databases and large sample sizes (Khan et al., 2010). However, identifying patients with UPS from these are reported to be difficult (Den Boeft et al.,2014). Using electronic medical records, Den Boeft et al. (2014), found prevalence of patients with functional syndromes was much lower than would be expected. There may be variation in the main cause for the consultation entered by different clinicians or multiple Read codes[1] entered for the same problem (Morriss et al., 2012). Morriss et al., (2012) developed an algorithm to identify patients using electronic records, but found that the models were too sensitive for use in clinical screening. In section 1.5 I discuss the prevalence rates of UPS that have been reported.

1.5 Prevalence in primary care

Differences in how UPS are classified and identified can lead to variations in estimates of prevalence. It has been estimated that around 80% to 90% of people experience at least one or more symptom such as headache, pain, dizziness, bloating and fatigue over a period of two to four weeks (Kroenke, 2003; Olde

[1] Read codes are unique identifiers of clinical terms intended to provide a standard vocabulary for recording in primary and secondary care that have been used in the National Health Service (NHS) since the late 1980's (Benson, 2011).

Hartman et al.,2013). Although many of these symptoms may be self-limiting, a large proportion of people are likely to seek medical care (Kroenke, 2003). Therefore, it is important to have an idea of the prevalence, especially in primary care, as it is the first port of call for formal help-seeking for the majority of people.

Kroenke, (2003) in a review of five studies found that prevalence of UPS ranged from 20% to 74% in primary care, depending on how the symptoms were classified. Three of the studies in that review reported that around a third of somatic symptoms were unexplained. Kroenke, (2003) therefore suggested that whilst 20% is likely to be an underestimation and 74% an overestimation, a third was likely to be a reasonable estimate, as three studies involving different samples and methods reached similar conclusions.

Heterogeneous populations and methodological differences in existing studies limit direct comparisons, nevertheless they provide some insight into the distribution of symptom severity in the population based on the classifications they use. For example a recent systematic review of 32 studies originating from 24 countries with a total of 70,085 people explored the prevalence of somatoform disorders and medically unexplained symptoms in primary care (Haller et al., 2015). Studies included were based on subcategories of somatoform disorders in DSM-III-R, DSM-IV or ICD-10 (excluding hypochondriasis and body dysmorphic disorders) as well as subthreshold somatoform disorders and 'medically unexplained symptoms'. In the review, those with between six and 13 impairing UPS with a minimum duration of

two years were classified as having somatisation disorder, which is considered to be on the more severe end of the spectrum of somatoform disorders (Haller et al., 2015). Abridged somatisation disorder, which has been validated in primary care requires the presence of six impairing medically unexplained symptoms in women and four in men (Escobar, 1998). The least severe end of the spectrum of somatoform disorders, undifferentiated somatoform disorders (refer Appendix 1.1) is considered to be over exclusive by some (Kroenke et al., 1997) as it is based on the existence of just one unexplained symptom with a minimum duration of six months.

The review also includes those classified as having 'medically unexplained symptoms', which the authors define as those with at least one medically unexplained symptom that did not meet any of the diagnostic categories listed above (Haller et al., 2015). The studies included in the review reported that the point prevalence of somatisation disorder ranged from 0.8%, 95% CI 0.3% to 1.4% (using DSM-IV criteria and n= 28,727 participants) to 12.8%, 95% CI 10.2% to 15.3% (using questionnaires and n=20, 508 participants). Point prevalence of abridged somatisation disorder was 17.8%, 95% CI 14.6% to 21.3% (using clinical interviews and n=29,909 participants); undifferentiated somatoform disorder between 9.3%, 95% CI 6.6% to 12% (ICD-10, n= 2798 participants) and 38.1%, 95% CI 13.1% to 63.1%(DSM-III-R/DSM-IV, n=1356 participants); and medically unexplained symptoms 40.2%, 95% CI 0.9% to 79.4% and n=1237 participants (Haller, 2015). The review thus found, that the prevalence of less severe forms of UPS were greater

than the severe diagnostic classifications such as somatoform disorder (Haller et al., 2015).

Based on symptom scores, rather than diagnostic classifications as discussed above, Kroenke et al. (2002) explored symptom severity using data from 3000 primary care and 3000 obstetrics-gynaecology clinics attenders in USA, using the PHQ-15 questionnaire (described and discussed in section 4.9.1). The primary care sample was recruited from five general internal medicine clinics (n=1422) and three family practice clinics (n=1578). Prevalence of somatic symptoms for the primary care population by severity group showed that the largest numbers of participants scored minimal to low somatic symptom severity and distributions were as follows: PHQ-15 0-4 (minimal), 35% (n=1012); 5-9 (low), 35% (n=1012); (moderate) 10-14, 20% (n=594) and ≥15 (severe) 10% (n=291). Diagnostic interviews showed that the two samples in the study were fairly similar. Symptom severity distributions were also similar for the obstetrics-gynaecology sample, despite the sample consisting of only females (Spitzer et al., 2000).

Similar distributions have been identified amongst primary care attenders in general practices in other countries. For example, in a German primary care study, the distribution of symptom severity among 620 consecutive primary care attenders was reported to be as follows: PHQ-15: 0-4 (minimal) 24% (n=145); (low) 5-9 40% (n=249); 10-14 (moderate) 28% (n=169) and ≥15 (severe), 9% (n=57) (Steinbrecher and Hiller, 2011). This study is discussed in detail in Chapter 2 in the literature

review (section 2.8). Lowe et al. (2008) also found the prevalence of those who scored ≥15 (n=199/ 2091) across 15 primary care sites in the USA to be similar, at 9.5%. As described in section 4.9.1, this score is considered to be a likely cut-off for somatisation disorder; Haller et al (2015) reported a prevalence ranging from 0.8% (95% CI 0.3% to 1.4%) to 12.8% (95% CI 10.2% to 15.3%) in their review of studies in primary care. Creed et al. (2012), using the somatic symptom index amongst primary care attenders in the UK, found that 79% (n=588/741) experienced mildly bothersome symptoms (lower severity), regardless of the explained or unexplained nature of their symptoms, whilst 21% (153/741) scored more than 26 on the somatic symptom inventory which is considered the clinically significant cut-off point for moderate severity. The percentages that scored moderately severe symptoms were fairly similar to the percentages that met scores for moderate severity (scores of 10-14) in the studies described above which used the PHQ-15 (Creed et al., 2012).

Large variations in estimates of prevalence may lead to an over or underestimation of the size of problem, making it difficult to plan services for those with UPS. However, the prevalence of UPS may differ depending on how they are classified, these studies suggest that the distribution of symptom severity amongst those attending primary care are skewed with the majority likely to have mild to moderate symptom severity and fewer experiencing severe symptoms. This has been supported by the studies based on those at the more severe end of the

spectrum such as somatoform disorders, which were discussed earlier in this section.

1.5.1 Prevalence in the UK

Few studies have explored the prevalence of UPS in primary care in the UK and estimates ranged from 10% to 35% (Mumford et al., 1991; Peveler et al., 1997; Duddu et al., 2008; Morriss et al., 2012). A frequently cited study of prevalence of UPS in primary care, in the UK, is a study by Peveler et al. (1997), based on consecutive attenders to 10 General Practices. These patients were assessed by two researchers, using the checklist of symptoms derived from the Diagnostic Interview Schedule; of the 175 patients assessed, 5% met the criteria for somatization disorder using the DSM-III-R criteria and 35% met the criteria for less severe, abridged somatisation (Peveler et al., 1997). Generalisation of these findings from almost twenty years ago to current estimates of prevalence in primary care may be difficult because of changes in population trends, as these have resulted in ageing populations and greater ethnic diversity.

However, more recently, Duddu et al. (2008) reported findings similar to Peveler's and colleague's findings; despite inclusion of a high South Asian population made up of 55% Pakistani participants prevalence of medically unexplained symptoms was 33% amongst 119 participants identified from a single general practice in Manchester (Duddu et al., 2008). Somatic symptoms were measured using the 13

item subscale of the symptom checklist (SCL-90R), which suggested that those with medically unexplained symptoms had a higher mean score than those with medically explained symptoms (6.9 SD 3.1 vs 4.3 SD 2.9). The presence of medically unexplained symptoms was then identified by a researcher with the use of general practice medical records, following the patients' consultation with the doctor.

A recent study used electronic medical records and general practitioner judgement to estimate prevalence of medically unexplained symptoms at 15% (127/828) and prevalence of severe medically unexplained symptoms at 8.8% (73/828) (Morriss et al., 2012). Medically unexplained symptoms were identified by GPs based on a scale that ranged from 'certain' to 'definitely not' and on a scale of severity that ranged from 'severe' to 'not relevant'. Severe symptoms were considered to be when the medically unexplained symptoms resulted in impaired functioning and distress (Morriss et al., 2012). Data from this study was used to develop 'The Nottingham Tool'; it is intended for use for commission purposes and provide an indication of numbers of people in a practice who are likely to have UPS (Moriss et al., 2012; Commissioning Support for London, 2011). Prevalence of severe medically unexplained symptoms was estimated at 0.84%; however due to the specific algorithm used, sensitivity was considered to be low. At this rate of prevalence, approximately 52,000 people would be expected to be identified with severe medically unexplained symptoms, based on Office for National Statistics data for 2009 (Commissioning Support for London, 2011). Although this translates to a

significant number when applied across the UK, rates of prevalence are likely to be much higher if a more sensitive algorithm was used.

As reported in international studies, estimates of prevalence also vary greatly in the UK. Those with severe UPS are likely to experience a greater burden and require more specialised care. The burden on patients and difficulties in management are discussed in sections 1.9 and 1.10; first I provide an overview of potential factors associated with UPS.

1.6 Potential factors to explore in a study of UPS

In the section, I discuss a broad range of factors that were explored to inform the development of this study; these include sociodemographic, physical, psychological, social and historical factors. I evaluated both cross-sectional and longitudinal studies of UPS, from various settings including primary and secondary care, to identify potential factors that may be associated with UPS. I retrieved studies of UPS defined in a variety of ways, such as somatoform disorders, abridged somatisation, and somatisation disorder. In order to limit the heterogeneity, I did not explore the literature based on functional syndromes (i.e. irritable bowel syndrome, chronic fatigue syndrome). I also made an effort to avoid studies based only on subcategories of somatoform disorders such as hypochondriasis or pain disorders; although some group these subcategories together (Olde Hartman et al., 2009). My

reason for exclusion was based on the fact that they potentially have different aetiology and illness course (Creed, 2009); this is discussed further in relation to the literature review (see section 2.3.1 and 2.3.2).

I also considered factors that have previously not been extensively explored in studies of UPS, based on theoretical decisions of potential association. In this situation I expanded my search to previously excluded populations to look at potential association of these factors with UPS.

1.6.1 Socio-demographic factors

Gender is considered to be an important factor associated with symptom reporting. Females report experiencing more somatic symptoms, more intensely and more frequently compared to males (Kroenke and Spitzer, 1998; Haug et al., 2004; Barsky and Borus, 2001). This variation is thought to be due to multiple reasons including biological differences in how pain is experienced, appraised, reported and social construction of gender, which is more accepting of female expressions of distress (Barsky and Borus, 2001). Studies in various settings report a higher prevalence of UPS in females, especially on the more severe end of the spectrum (Speckens et al., 1996; Kronke and Spitzer, 1998; Escobar et al., 1998; Verhaak et al., 2006). This association with gender is not so pronounced at the lower end of the severity spectrum, such as with abridged somatisation (Creed and Barsky et al, 2004; Escobar et al., 1998). Some studies report that the presentation and burden of UPS

are associated with a younger age in both primary and secondary care (Morriss et al., 2012; Nimnaun et al., 2001) whilst others find it to be the case among older populations attending both primary and secondary care (Escobar et al., 1998; Verhaak et al.,2006; Speckens et al., 1996; Gureje et al., 1997). Other factors identified as associated with a greater burden of unexplained symptoms include being unemployed (Fink et al., 1999; Verhaak et al., 2006), having a lower education level (Fink et al.,1999; Hotopf, 1999); being from a lower socioeconomic class (Fink et al., 1999; Nimnuan et al., 2001); and being widowed, divorced, or separated (Hotopf et al., 1999; Creed et al., 2012).

1.6.2 Number of symptoms, duration and severity

Having more symptoms, or a higher severity or longer duration of symptoms at presentation has been suggested to be associated with severity or persistence of UPS (Duddu et al., 2008; Jackson and Passamonti, 2005; Speckens et al., 1996; Kooiman et al., 2004).

A prospective study of 100 participants conducted in general medical out-patient clinics in the Netherlands, found that a greater number of UPS at baseline were associated with no improvement at 12 months follow- up (Speckens et al., 1996). However, this study included those with either somatisation disorder (thirteen symptoms prior to the age of 30 years) or hypochondriasis. A cross-sectional primary care study conducted in the UK reported that those with UPS (n=39) had a

greater number of symptoms compared to those with medically explained symptoms (n=73) (considered to be organic) (Duddu et al., 2008). This study was based on participants identified using three criteria, which included the absence of a diagnosis based on researcher judgement with the use of general practitioner notes, however the sample size of was fairly small. More recently, there is a growing body of literature which suggests that a greater number of symptoms, regardless of whether they are explained or unexplained, contribute to poor outcome (Creed et al.,2012; Jackson and Passamonti et al.,2005). This has been reported in a number of studies, including in UK primary care (Creed et al.,2012). Such findings of the burden associated with a greater number of symptoms regardless of the unexplained or explained nature have resulted in changes to DSM criteria and the introduction of the term somatic symptom disorder (see section 1.3). A recent review by Tomenson et al (2013) where secondary analysis was conducted on studies from four different sites, it was reported that total somatic symptom score was a better predictor of follow-up health status than UPS.

With regard to duration, shorter duration of symptoms at presentation is suggested to be associated with a better outcome. For example, in a study of consecutive primary care attenders in the USA (n=500), shorter duration of symptoms at presentation was associated with improved recovery at both three month and five year follow-up (Jackson and Passamonti, 2005).

Increasing the value of exploring somatic symptom scores and their association is being recognised. For example, in a review by Tomenson et al (2013) based on nine population-based studies (total population of 28,377), total somatic symptom scores was found to be associated with health status, after adjusting for depression, anxiety and general medical illness. In cross-sectional analyses based on five of the studies, total somatic score was correlated with past health care use after adjusting for confounders. In one prospective study baseline total somatic symptom score was correlated with retrospective but not prospective health case use.

This review included seven cross-sectional studies conducted in Germany, Norway and Sri Lanka and only two prospective studies conducted (one in Germany and one in the UK). The prospective study conducted in Germany was based on a cohort who were a part of the Prevention of Renal and Vascular End Stage Disease (PREVEND) study, which included an enhanced sample with elevated urinary albumin concentration; therefore it did not meet the criteria for my literature review but the UK based prospective study identified has been discussed in detail in Chapter 2.

Interestingly, in four sites where it was possible to explore the association of correlates with both the number of UPS and with total somatic symptom score, it was found that somatic symptom score had a greater association with health status than number of medically unexplained symptoms even after adjusting for

confounders. Hence, this review supports the use of total somatic symptom score as a better predictor of follow-up health status compared to UPS.

1.6.3 Comorbid anxiety and depression

Multiple somatic symptoms or UPS can occur with anxiety and depression (Kroenke, 2003; Smith et al., 2005; Van der Sluijs et al., 2015). Many primary care attenders with depression, present with somatic symptoms (Smith et al 2005; Tylee and Ghandi, 2005). Such presentation of somatic symptoms have been considered more common amongst certain cultures and groups where there is stigma attached to presenting with psychological distress (Bhugra and Mastrogianni., 2004), although there is a growing amount of literature that suggests that this is not necessarily always the case (Sidhaye et al 2013). Dowrick, (2004) suggests that some of the difficulties in distinguishing between UPS and different depressive disorders might be a result of the overlap and lack of distinction between symptom pattern, illness experiences and diagnostic categories.

Those with UPS are more likely to have higher rates of anxiety and depression compared to those with physical symptoms or UPS alongside physical symptoms (Van der Sluijs et al. 2015). It is estimated that around 50-75% of patients with UPS have a depressive disorder and approximately 40-50% have an anxiety disorder (Kroenke, 2003). The comorbidity between depression and/or anxiety and somatoform disorders range from 11% to 50% (De Waal et al., 2004, Lowe et al.,

2008; Mergl et al., 2007; Rosmalen et al.,2010; Steinbrecher et al., 2011; Van der Sluijs et al. 2015).

The relationship between UPS, and anxiety and depression is likely bidirectional and the temporal relationship remains unresolved (Lieb et al., 2007). Kroenke et al. (1994), found that the as the number of physical symptoms increased, the likelihood of both mood disorders and anxiety also increased for primary care patients (Kroenke et al., 1994). In this sample, the prevalence of anxiety disorder was 1%, 7%, 13%, 30%, and 48% for patients with 0-1, 2-3, 4-5, 6-8, 9+ symptoms; the prevalence of mood disorders was to 2%, 12%, 23%, 44% and 60%, respectively. Escobar et al. (2010) reported similar findings in a community based cross-sectional study in the USA of 4,864 individuals with both general physical symptoms and UPS. On the other hand, a large prospective study of mental illness in 15 primary care centres across 12 countries, found that baseline depression predicted the onset of abridged somatoform disorder (Gureje and Simon et al, 1999).

Therefore, some people may have somatic symptoms associated with depression or anxiety; some may experience depression and anxiety as a result of distress caused by their UPS; in others, symptoms may be considered physical or psychological expressions of common distress and treated as UPS with coexisting depression and anxiety (Henningsen et al., 2003). It is worth noting, however, that many people with UPS have no formal anxiety and depressive disorder or only have sub-threshold symptoms (Weselley et al, 1996; Jackson and Passamnoti, 2005).

1.6.4 Health related quality of life

Health related quality of life is an important and multi-dimensional concept that lacks a common definition (Tian-Hui et al., 2005). The WHO definition broadly includes social, physical and mental aspects (Guyatt et al., 1993). In the past, it was observed that despite improvements to medicine and technology resulting in changing patterns of morbidity, those with similar clinical characteristics and physiological measures did not always have the same outcomes (Guyatt et al., 1993). Therefore, self-reported measures of health related quality of life came to be regularly used to determine outcome amongst those with various diseases and long term conditions, including UPS.

The terms self-perceived health, self-reported health status, health related quality of life, quality of life, functioning and impairment are often used interchangeably but all essentially refer to the same concept. Studies of UPS frequently explored physical, mental or social functioning which are important components of quality of life (Koch et al., 2007; Koch et al., 2009; Löwe et al., 2008; Verhaak et al., 2006). In my study I use the term quality of life and refer to physical and mental health functioning.

Kroenke et al. (2002) observed that as bodily symptoms increased, painful and physical dimensions of health status all showed greater impairment; those who had the most severe symptom scores on the PHQ-15 had the greatest impairment in health status. Similar findings of, increasing symptom severity and association with

poor quality of life have been reported by others (Jackson and Passamonti, 2005). A population based cohort study that distinguished between unexplained and explained symptoms found a stronger association between medically unexplained symptoms and health related quality of life (HRQoL), compared with explained symptoms and HRQoL (Hinderlink et al., 2015). On the other hand, Gureje and Simon (1999) in their large prospective cohort based on 15 primary care centres in 12 countries found that that baseline perception of poor physical health was associated with the persistence of abridged somatisation at follow-up.

1.6.5 Childhood experiences

Childhood experiences such as exposure to illness in family members, poor childhood health, and traumatic experiences such as abuse and poor family dynamics are reported to be associated with UPS in adults. Stuart and Noyes (1999) suggest that childhood experiences may impact on stress responses and the development of personality, which in turn impact the experience and response to somatic symptoms as adults. In the following sections, I discuss a number of different types of childhood experience, which have been reported to be associated with UPS.

1.6.5.1 Experience of physical and mental health in family members

The experience of both physical and mental illness in parents during childhood and adolescence has been found to be significantly associated with multiple physical

symptoms and unexplained symptoms (Hotopf, 2002; Stuart and Noyes, 1999; Essau., 2007).

A nested case-control study carried out on a prospective birth cohort with over 3000 participants explored the association of childhood exposures at the age of 15 years with multiple physical symptoms in adults who were 36 years old (Hotopf, 2002). Poor health of parents but not the death of a parent was found to be associated with UPS, suggesting that experience of non-life threatening illness or medically unexplained symptoms in family members may impact illness behaviours such as increased symptom monitoring (Hotopf et al 2002).

In another study, Essau (2007) found that amongst adolescents (12 to 17 years) followed-up on average over 15 months; parental psychiatric disorders were associated with chronicity of somatoform disorders. Although this study was large (n=1,035), these findings are based on 64 individuals who met the criteria for DSM-IV somatoform disorder at baseline. At follow-up 23/ 64 still met the criteria for any somatoform disorder (including undifferentiated somatoform disorder, chronic pain disorder and conversion disorder) but it is not clear how many were lost to follow-up (Essau, 2007).

1.6.5.2 Experience of poor health during childhood

Craig et al. (1993) in the longitudinal South London Somatisation Study, found that among adult somatisers (n=44) identified in primary care, those with UPS had experienced a greater number of serious childhood illness compared with adults with physical, mixed or psychologising symptoms. In a later study which included women identified using general practice records and specialist units, Craig et al. (2002) found that the daughters of mothers considered to have suffered from somatisation were almost three times more likely to report that they had been exposed to illness in a parent. These same individuals were also more likely to report experience of neglect in childhood compared to other women who did not have somatising mothers (OR 2.9; 95% CI 1.4 to 6.1). Hotopf (2002) also explored the impact of childhood diseases on adult physical symptoms and found that only abdominal pain in childhood was associated with multiple physical symptoms in adults.

1.6.5.3 Experience of trauma during childhood

Studies suggest that childhood abuse is associated with long-term health consequences such as greater number of physical symptoms, poor mental health, somatisation disorder and high health care utilisation in adults (Arnow, 2004; Kamiya et al; 2015; Norman et al 2012; Springer et al., 2007; Stone,2013; Spitzer et al., 2008;).

A cross-sectional study based on participants identified in a family practice clinic in the USA found that women with a history of child sexual abuse reported significantly higher somatisation scores based on the somatic symptom scale (SCL-90) compared to those who had not experienced abuse (Springs and Friedrich, 1992). McCauley et al. (1997) also found that on average women who had experienced abuse as children had more physical symptoms, somatisation, depression, anxiety and low self-esteem than those who had not. In a smaller study that included only 28 participants with DSM-IV somatisation disorder, Spitzer et al. (2008) identified sexual abuse as the only significant predictor of somatisation disorder. These findings must be interpreted with caution due to the small sample size. Whilst abuse may be on the extreme end of childhood trauma, other factors such as frequent arguments, conflict, emotional distance, poor support and low levels of cohesion within families are associated with UPS (Spitzer et al 2008; Brown et al 2005).

1.6.5.4 Stressful, negative or traumatic experiences

Several studies have found an increase in UPS following stressful or traumatic events such as psychosocial stress, conflict within families, experience of violence or abuse, accidents or large scale events such as natural disasters or war amongst adults (Cluaw et al 2003; Dorner et al., 2010; Wahlstrom et al 2013).

Dorner et al. (2010) explored factors associated with ten common physical symptoms, which included headache, pain, gastric complaints and insomnia in a cross-sectional study that used data from a survey of health-check-ups of 312 men and 374 women who attended clinics in Austria. They found that psychosocial stress was associated with greater numbers of physical symptoms. Discomfort in family/partnerships and pressure at work were associated with the number of symptoms experienced among males. Amongst females, discomfort in family/partnerships was strongly associated with physical symptoms, as well as several other factors: sexual dissatisfaction, pressure at work and social stress Dorner et al. (2010).

Many studies of abuse and violence focus on female experiences. In a cross-sectional study of 1931 women recruited from four sites that included community, primary care and internal medicine, McCauley et al. (1998) found that the number of physical symptoms increased, as severity of violence increased. Physical symptoms in the previous six months were measured using the Symptom Checklist 22 (SCL-22). They found that those who had experienced high levels of violence had higher SCL-22 scores than those who experienced low level of violence, who in turn had higher scores than those who had experienced no violence. Low-severity of violence was considered having been grabbed or being threatened with physical harm, whilst high severity violence referred to physical abuse (such as being hit or kicked) or being sexually abused (McCauley et al., 1998).

It has also been reported that UPS are common after disasters (Van der Berg et al., 2005). Several studies were conducted in the Netherlands after a large airplane crash in Amsterdam (Yzermans and Gersons, 2002) and an explosion at a firework factory, which impacted a whole town (Van Kamp et al., 2006). In a review of UPS after disasters, Van der Berg et al. (2005) identified factors such as female gender, physical damage (including themselves, loved ones or property) and post-traumatic stress symptoms were found to be significant predictors of UPS. However, due to the vast heterogeneity of the studies in terms of design, the authors found it was difficult to draw definite conclusions (Van den Berg et al., 2005).

Traumatic experiences such as war have been widely explored, mostly under the term 'Gulf-war syndrome' amongst veterans; high rates of distress and multiple UPS have been widely reported (Clawu et al., 2003; Iverson et al., 2007). However, as my study is a UK primary care population study, it is likely that the prevalence of those with such severe types of trauma and stress will be low.

1.6.6 Social support

A few studies have explored the role of practical or emotional support from family and friends in those with UPS. In a review of guidelines for doctors on managing UPS, Edwards et al. (2010) suggests that lack of social support is a predisposing and precipitating factor, initiating and maintaining UPS. Blankenstein, (2001) used data from two intervention studies in the Netherlands and identified social support as a

key factor associated with an increase in subjective health amongst participants identified with somatising patients. Some studies have reported on the role of current family relationships and unexplained symptoms qualitatively (see section 1.10).

I also identified some studies that explored the role of social support in unexplained symptoms but focused on functional syndromes specifically e.g. chronic fatigue syndrome (Prins et al., 2004; Brown et al., 2010). A Dutch primary care study used electronic medical records from 192 patients and found that those with persistent UPS reported more social isolation than those with a medical diagnosis or without persistent UPS (Dirkzwager and Verhaak, 2007).

1.6.7 Self-efficacy

A person's belief in their ability to exercise control over their lives and environment is an essential aspect of their ability to cope with difficult or unexpected situations (Falvo, 2013). Self-efficacy is regarded as an important factor influencing how people respond to trauma and stress as well as, increasingly, how individuals adapt to chronic illness (Scholz et al., 2002). Bandura described self-efficacy to be a fluid concept, regulated by external factors as well as personal factors regarding how people think (cognition), feel about themselves (affect), motivate themselves (motivation) and behave (decision-making) (Bandura, 1997).

Despite the potential role of self-efficacy in mediating how people perceive their symptoms and respond to them, few studies have explored its role amongst those with UPS. Existing studies have focused on samples that have experienced trauma (Murphy, 1998; Bödvarsdóttir and Elklit, 2004; Elikit and Christiansen, 2009). Murphy (1998) found that lower self-efficacy predicted somatisation amongst survivors after a volcanic eruption. Bödvarsdóttir and Elklit (2004) identified low self-worth, considered to be a proxy for self-efficacy, as associated with somatic symptoms, amongst those who had experienced the traumatic event of an earthquake but who had also developed post-traumatic stress disorder. In another study of 169 adults who had been affected by an explosion at a firework factory, Elikit and Christiansen (2009) found that feeling incompetent, was associated with somatization. Self-efficacy may therefore be a potentially valuable variable to explore in terms of outcome among primary care attenders with UPS.

1.7 Health service use

Patients with UPS make up a high proportion of primary care attenders and several studies have shown that UPS are associated with increased health care use as well as increased health care costs (Bermingham et al., 2010; de Waal et al., 2008; Veerhak et al., 2006; McDaid et al.,2011; Zonneveld et al., 2013). Studies consistently show that those with UPS have higher rates of GP contact, compared to those with diagnoses (de Waal et al., 2008). For example, in the USA, Barsky et al. (2005) found that somatising patients, when compared with non-somatising

patients had on average more primary care visits (five vs three) and more specialty visits (eight vs five). Similar rates of average attendance (five over a period of one year) were identified amongst patients identified with UPS by GPs, at ten practices in the UK (Taylor et al., 2012).

Much higher rates of an average of 20 contacts per year, per patient were found amongst 227 participants from three general practices in London (Commissioning Support for London, 2011). This rate was based on those with very severe somatic symptoms; approximately 1% of those registered in the practice. Patients were identified using specific criteria, which included frequent attendance, opiates use and high scores on the Nottingham Tool; this study was described in section 1.4.4 (Commissioning Support for London, 2011).

1.8 The cost of UPS

Patients with UPS consume healthcare disproportionately in all health care settings and incur high costs to health services and the wider economy (Bermingham et al., 2010). In the UK the ICD-10 category, which includes UPS is considered to be the fourth most expensive category in primary care and the most costly diagnostic category amongst outpatients (Creed et al., 2011). Estimates of costs may vary depending on how UPS are defined, the study populations included, the costs assigned to specific services, as well as the year and country in which the study was conducted.

Bermingham et al. (2010) estimated cost of UPS to the NHS, for those aged between 18 and 65 years, at £3 billion between the years 2008-2009; 10% of the annual healthcare budget that year. Costs based on GP consultations alone were estimated at £837 million. The annual cost to the wider economy as a result of output losses from sickness absence and reduced quality of life was estimated to be £14 billion. The Commissioning Support for London (2011) report estimated a cost of £307,000 to primary care for 227 patients with severe medically unexplained symptoms; this was a total cost of £2,200 per patient per year, including secondary health care costs (Commissioning Support for London, 2011).

Barsky et al. (2005) in a study conducted in the USA estimated that in 2002, at a national level, UPS accounted for 16.8% of the annual health care budget (almost 50 billion that year, in 2002 dollars). In a more recent study (Zonneveld et al., 2013), health care use of patients with UPS in the Netherlands was estimated at €3,123 (SD = €2,952), which increased to €6,815 per patient per year, when work related costs such as work absence and productivity were considered.

Referral rates to secondary care are high contributing to further costs incurred to primary care (Nimnuan et al.,2001; Stone et al., 2009; Burton et al.,2012). A case study of a patient with UPS and a diagnosis of somatisation disorder, spanning over 20 years estimated a cost of £209,391 (2003 cost), based on secondary care use

alone (i.e outpatient visits, inpatient stays, procedures and investigations) (Kinder et al 2004).

1.9 Difficulties for doctors in identifying and managing UPS

UPS are identified in clinical practice through a process that often involves the exclusion of serious physical diseases or potential psychiatric disorders (Rosendal et al., 2005). Although tests and investigations may be used to rule out any organic disease, a qualitative study with newly qualified doctors reported some ordering tests and investigations even when they were certain that no underlying organic cause would be found. Reasons for this included: to provide reassurance to the patient and for themselves; to avoid difficult consultations; and protect themselves against future litigation (Yon et al., 2015).

Some general practitioners have reported feeling pressured by patients to provide investigation and intervention (Wileman et al., 2002; Ring et al., 2004). However, unnecessary testing, inappropriate treatment or overtreatment may lead to iatrogenic consequences (Ring et al., 2004). These can result in a cycle of distress, anxiety and fear in patients, and encourage long term illness-behaviours such as repeated consulting (Hatcher and Arroll, 2008). Efforts to normalise symptoms, through for example use of negative investigations to reassure patients that likelihood of disease was unlikely, resulted in patients intensifying symptom

presentations, introducing new symptoms or providing evidence in support of their symptoms (Dowrick et al., 2004).

A large survey of 284 general practitioners in the UK found that the majority felt that UPS should be managed in primary care and saw their role as gatekeepers to prevent inappropriate investigations and provide reassurance to patients (Reid et al., 2001). However, half of the respondents felt that clearly effective management strategies were lacking. In another large study of 280 physicians in the USA, only 25% of physicians acknowledged their ability to help patients with UPS as very good or excellent; only 14% were very satisfied with their management of these patients and many doctors felt frustrated and unsatisfied with these consultations (Hartz et al., 2000). Others have also reported finding it difficult to engage in a helpful therapeutic relationship with such patients (Stone, 2013). A review of expert opinions in the management of UPS identified such as long-term and trusting relationships between the doctor and patient, good communication and reassurance as important in effective management of patients in the long term (Heijmans et al., 2010).

1.10 The impact of UPS on patients from a qualitative perspective

Qualitative studies are invaluable in providing in-depth insight into the lived experiences of those with UPS. These studies provide insight into patient experiences of accessing health care, their relationship with the doctors, the effort to make sense of their symptoms, the search for a diagnosis as well as the impact on their day to day lives and interpersonal relationships (Salmon et al., 2004; Ring et al., 2005; Nettleton, 2006; Sumathipala et al., 2008; Dwamena et al., 2009;).

The acute period following onset of UPS is reported as one of distress and uncertainty (Kornelsen et al., 2016; Nettleton et al., 2005) described by some patients as an 'emotional rollercoaster' (Kornelsen et al., 2016). Following early investigations and negative results, patients are in a state of conflict; in juxtaposition between the relief at lack of a serious illness and a continued sense of anxiety that no definitive cause has been found (Kornelsen et al., 2016; van Bokhoven et al., 2009). The search for a medical diagnosis is reported as an effort to find legitimacy for their symptoms (Charmaz, 1995; Nettleton et al.,2005). Patients report feeling that a lack of a diagnosis limits the treatment options available (Kornelsen et al., 2016) and the unpredictable illness course and trajectory makes it more difficult for them to come to terms with their symptoms (Stone, 2013).

Difficulties have been reported in terms of work and social life. The lack of a clear diagnosis and the uncertainty surrounding the trajectory of their symptoms creates pressure on work, finances and families (Korlsen et al., 2015; Nettleton et al., 2005). Strains on family relationships have been reported where patients who are more disabled by their symptoms feel entitled to be relieved from social obligations and receive greater support from their family (Dwamena et al., 2009). Such perceived unmet needs place a strain on relationships.

Patients feel further strain as they often feel misunderstood, disbelieved or rejected by doctors (Dirkzwager and Verhaak, 2007; Epstein et al., 2007). Repeated studies report that patients want to be taken seriously (van Bokhoven., 2009) and it is important that doctors believe their symptoms are genuine and that they are 'not made to feel like a drug seeker' (Kornelsen et al., 2016).

1.11 The clinical context of UPS

UPS are extremely common in primary care (see section 1.7) with considerable cost implication (see section 1.8) and management difficulties (see section 1.9). Unpublished research (Warner et al., 2013) revealed that many doctors learn to manage UPS through daily clinical experience with those consulting with the problem and/or by witnessing the clinical care delivered to these people by others, rather than through formal teaching or the use of guidance on management of people with UPS.

National Institute for Clinical Excellence (NICE) has not published any formal guidance on the management of UPS. There is, however, a document titled 'Guidance for health professionals on medically unexplained symptoms' developed by Chitnis and colleagues (2014) and endorsed by the Royal College of General Practitioners (RCGP), Psychiatrists (RC PSYCH), Royal College of Surgeons (RC Surgeons), UK Faculty of Public Health (FPH) and Rethink (mental illness charity). Developed by practitioners who have considerable expertise in the care of people with UPS, it outlines the cost and burden of UPS, potential risk factors, outcomes, potential interventions and it provides useful suggestions on consultation techniques in dealing with this problem in practice. Whilst some of the suggestions made in this document are likely to have arisen from the authors extensive clinical experience, a more careful assessment of the references used in this guideline, particularly those relating to the risk factors and outcomes highlights the scarcity of evidence on UPS in primary care, especially in the UK. Many of the studies mentioned in this document were conducted on those likely to differ from people attending primary care clinics who often present with multiple UPS. Rather, the studies included people with other psychiatric disorders, hypochondriasis, hysteria or somatoform disorder and most of the work was conducted on those seen in secondary care or living in the community rather than on people seen in primary care. These populations could have a very different course of illness, outcomes and risk factors.

1.12 Summary

This chapter has highlighted that UPS exist on a continuum, with a wide range of symptom severity in patients attending primary care (van Dessel et al., 2014). Terminology and diagnostic classification have changed over time, are considered to be unreliable by some and are still widely contested, making UPS difficult to identify, measure and manage. Methodological differences in studies have led to high heterogeneity making comparison difficult. Nevertheless, exploration of existing studies suggests that factors which may be associated with UPS over time can include: socio-demographic factors such as gender, age, level of education, financial well-being and employment status; the number, severity and length of symptoms; comorbid anxiety and depression; physical and mental health functioning; childhood experiences such as trauma and abuse; and current life experiences such as stress. Other aspects such as availability of social support, self-efficacy and health service use may also provide insights into the outcomes over time amongst those with UPS. In Chapter 2, I present my systematic review; which was carried out to identify studies that have explored outcome of those with UPS over time and identify prognostic factors associated with these outcome.

Understanding the outcome of patients over time and the factors associated with improvement of symptoms, quality of life and other aspects of well-being can provide insights into potential ways in patients can be managed and the best course of action for individual patients.

Chapter 2 : **Systematic review of factors associated with unexplained physical symptoms in primary care**

2.0 Chapter overview

In this chapter, first I discuss the rationale, aims and objectives, and the methods used to identify the relevant literature for this systematic review. Second, the longitudinal studies that have been identified are described and synthesised with reference to the objectives of the review. Following a discussion of the identified studies and comparison to other existing literature, the strengths and limitations of the review are discussed. In the course of this chapter, when discussing individual studies I refer to the terminology originally provided in the studies. A discussion of wide range of terminology in this area was provided in section 1.2.

2.1 Introduction

A literature review was conducted to explore what is already known and to provide a rationale for my PhD study by systematically highlighting the knowledge gaps in the field and to inform the objectives of the study discussed in Chapter 3. Contextual information relevant to both the literature review and the study as a whole, with reference to terminology, diagnostic classifications and methods of identification were discussed in Chapter 1. Findings from this chapter along with

supplementary literature on factors associated with unexplained physical symptoms discussed in section 1.6 helped to inform the development of this study in terms of outcomes and prognostic variables explored.

2.2 Aim

The main aim of this literature review is to systematically identify and describe the outcomes over time in studies of participants with unexplained physical symptoms (UPS) in primary care and to determine which prognostic factors are associated with the identified outcomes.

2.2.1 Objectives

The specific objectives of this review are:

1) To conduct a systematic review of the literature on longitudinal studies of UPS, of adults (aged 18 years and above) who present to primary care, to determine outcomes in terms of somatic symptoms, quality of life (physical and mental health functioning), depression, anxiety and primary health care use.

2) To determine which risk factors are associated with poor outcome within these studies identified in objective 1.

2.3 Study Criteria

2.3.1 Terminology and diagnostic classifications

Conducting a literature review in the area of UPS was challenging due to the heterogeneity in terminology, diagnostic criteria and methods used for identification of study participants (refer sections 1.2 to 1.4).

I wanted to identify studies that included participants with physical symptoms lacking an organic explanation but not necessarily with underlying psychiatric morbidity. Many of the studies in the area of UPS have focused on those meeting psychiatric diagnostic classifications such as somatoform disorder (see section 1.3). But characteristics of those with more severe symptomology and are likely to differ and they make up a smaller proportion of those attending primary care (Haller et al.,2015).

Therefore, the usefulness of existing studies as applied to primary care populations may be limited. Hence, I chose to include studies based on UPS in the broad sense as discussed in section 1.2. Due to the wide heterogeneity and at times imprecise use of terms, regardless of the aetiology, I used a variety of terms related to UPS (Sumathipala,2005). Key words used are discussed in section 2.4 and shown in Appendix 2.0. I also included populations with somatic symptoms in keeping with the changing trends in terminology that were discussed in section 1.2.

Although I included somatoform disorders (DSM-IV and onwards), in order to reduce the variation in individual studies, I excluded papers published before 1994, which was the year in which DSM-IV (APA, 1994) was published (for details on diagnostic criteria see section 1.3). I also excluded studies based solely on diagnostic classifications conversion disorder, pain, hypochondriasis and body dysmorphic disorder, which are found under the umbrella of somatoform disorders. These disorders require further specific characteristics to be present in addition to UPS; inclusion would result in further heterogeneity of this already very heterogeneous body of literature. The key words used in the search are shown in Appendix 2.0.

2.3.2 Population

I chose to include studies based on adults aged 18 years and above, with UPS, identified in primary care. I decided to exclude studies which restricted participants to a single symptom localised to one specific area, such as studies based specifically on back pain. This is because the course is likely to be different when compared those UPS that are not localised to one specific area. I excluded studies based on frequent attenders with UPS.

Studies based exclusively on restricted populations such as those with psychiatric, psychological or emotional morbidity e.g. unexplained symptoms in people with depression only or which focused on severe personality dimensions such as alexithymia/neuroticism, were also excluded. Such studies would identify different

(potentially more adverse) outcomes compared to those with UPS, who were not specifically identified based on their level of psychological morbidity.

Finally, studies based solely on functional syndromes such as irritable bowel syndrome were excluded due to the possibility that they may have a different aetiology compared to those with multiple UPS across several domains and because of the presence of a medical 'label' such as irritable bowel syndrome or chronic fatigue syndrome may impact the course of the disorder and its symptoms.

2.3.3 Study design

I included only longitudinal cohort studies as my study focused on outcomes over a specified period of time; prospective studies were chosen in keeping with this design (Gordis, 2014). Cohort studies tend to be the most appropriate study design for exploring outcome over time. Other study designs such as case-control studies are retrospective, as the outcome has already been determined when identifying participants as cases and controls. Case-control studies are also likely to be prone to various sources of bias, including selection, recall and observational bias and may be impacted by reverse causality (Gordis, 2014; Sedgwick, 2014). The reasons for excluding intervention studies are discussed in the following section.

2.3.4 Intervention

I excluded studies based on interventions, as participants who agree to take part in a trial are likely to be different to those taking part in other types of studies (such as

observational) and therefore are not an externally valid and representative sample (Kennedy-Martin et al., 2015). Even if data from the control group or a waiting list sample were to be used, it is possible that those who entered/recruited into the trial as a control group (without an intervention) may subsequently show an improvement in outcomes due to potential placebo effect (Gupta and Verman,2013). Therefore, studies based on cohorts with UPS that were originally set up for other purposes, such as the delivery of an intervention were excluded.

2.3.5 Comparison group

In epidemiological studies, comparison groups may be: internal comparison groups, which are unexposed members of the same cohort; external comparison groups, which are unexposed cohorts with similar characteristics to the cohort of interest; or be drawn from the general population, a comparison that is used when only a small percentage of the cohort population are expected to be exposed (Gordis, 2014). As initial literature searches suggested that there were a limited number of studies in the area, I decided not to place any restrictions on comparison groups included.

2.3.6 Outcome

I decided not to restrict outcomes, as one of the objectives of the review was to identify all the outcomes that have been explored in prospective studies of UPS in primary care.

2.4 Search strategy

First, I conducted a quick exploration of the evidence base to identify potentially relevant studies in the area. I identified a systematic review by Olde Hartman and colleagues, conducted on the course and outcome of somatoform disorders, hypochondriasis and medically unexplained symptoms in primary, secondary and community settings (Olde Hartman et al., 2009). This helped inform the search strategy for my review but was further refined following discussion with my supervisors and with advice from a library specialist, on developing the keywords that would be utilised for the search strategy. Despite the decision not to exclude those identified based on the presence of psychological morbidity, as discussed in section 2.3, I decided to keep search criteria broad. Therefore keywords used included somatoform disorder, psychosomatic medicine, somatisation, non-organic, unexplained medical (symptoms, problems, conditions or complaints) (see Appendix 2.1).

Keywords for primary care identified using the database thesauri included primary care, general practice and family physician (see Appendix 2.2). Search terms were mapped onto MeSH subject headings where possible, combined using Boolean operators 'OR' and 'AND' and searched for within title and abstracts. Initial exploratory searches were carried out in order to refine the search strategy. Inclusion of keywords for prognostic and longitudinal studies such as prospective, prognostic, outcome, epidemiology, survival, risk, and follow-up were considered however these resulted in a considerable reduction in the number of papers (Altman, 2001; Wilczynski and Haynes, 2005). For example on MEDLINE this resulted in a reduction from 1783 to 380 papers. To minimise the risk of missing any potentially eligible studies, which may not have been captured using a more specific search strategy, I chose to include only keywords for UPS and primary care to increase the sensitivity of the search.

I conducted the final search in December 2012 using electronic databases MEDLINE (via Ovid 1946 to December to December 2012); Psychinfo (*via Ovid 1806* to December2012), EMBASE (via Ovid 1947 to December 2012) and CINAHL (via EBSCO, 1982 to December 2012). I limited the search to the English language and human studies only. The Cochrane library was searched for any relevant reviews and the British Library database was searched for any relevant dissertations or theses. In addition, reference lists of key papers and texts as well as included papers were screened for further relevant records.

2.5 Study Selection

Studies identified from the search were screened through a two-stage process, which are discussed below.

2.5.1 Titles, abstracts and full text screening

2.5.1.1 Stage 1:

First, I went through the database and removed papers judged to be definitely irrelevant; either not meeting the inclusion criteria for this review in terms of subject matter (for example studies that were based on functional syndromes) or study design (for example biomedical research) by referring to the title and when necessary, viewing the abstract to confirm irrelevance.

2.5.1.2 Stage 2:

At the second stage, I excluded studies that were not 1) longitudinal in design, 2) based in primary care or 3) on adult populations with UPS by once gain referring to the title and abstract and when necessary the full text. An independent assessor repeated this screening process. A cautious and inclusive approach was taken to resolve any discrepancy and where there was any disagreement, the paper was included in the next stage (see section 2.5), along with potentially eligible articles.

2.6 Data extraction and quality assessment

Data was extracted from papers considered to be potentially relevant to the review, using a data extraction sheet that was developed taking into account section A of the Critical Appraisal Skills Programme checklist for cohort studies (CASP,2013) and reference sources for the evaluation of quality of prognostic studies (Hayden and Bombardier, 2006). Type of data extracted included details on: the population of the study; outcomes measured; how the cohort was recruited; measurement of and controlling for confounding variables; and terminology and diagnostic criteria used. Irwin Nazareth (IN), the primary supervisor, and I went through the study summaries that I had prepared with consideration to the specific inclusion and exclusion criteria discussed in section 2.3. When necessary IN and I went back to the full text and consulted the rest of the study team (two supervisors with experience in general practice and epidemiology and one in statistics). The quality of eligible papers was critically appraised by adapting the STROBE statement for cohort studies (Von Elm et al., 2008). The full checklists with results are shown in Table 2.2 and included aspects of the research question, sample size and study design. To ensure a high-level of reliability, two independent reviewers carried out quality assessment. The authors of the included studies were contacted for further information to clarify on the methods and findings of the studies.

2.7 Data synthesis

Meta-analysis is considered to be the highest standard for combining data from a number of sufficiently similar studies (Gordis, 2014). However, when I first conducted a scoping search to familiarise myself with the published literature, it was evident that there were limited numbers of studies relating to the focus of my review and that amongst these, there was substantial heterogeneity particularly in terms of the how the populations had been identified. Therefore it was anticipated that the literature would be synthesised narratively. This decision was confirmed when only two studies were identified as meeting the eligibility criteria. The Centre for Review and Dissemination (CRD, 2009) suggest that when conducting narrative synthesis the descriptive process should be rigorous. In the following sections I describe the studies in detail with reference to the objectives of this review.

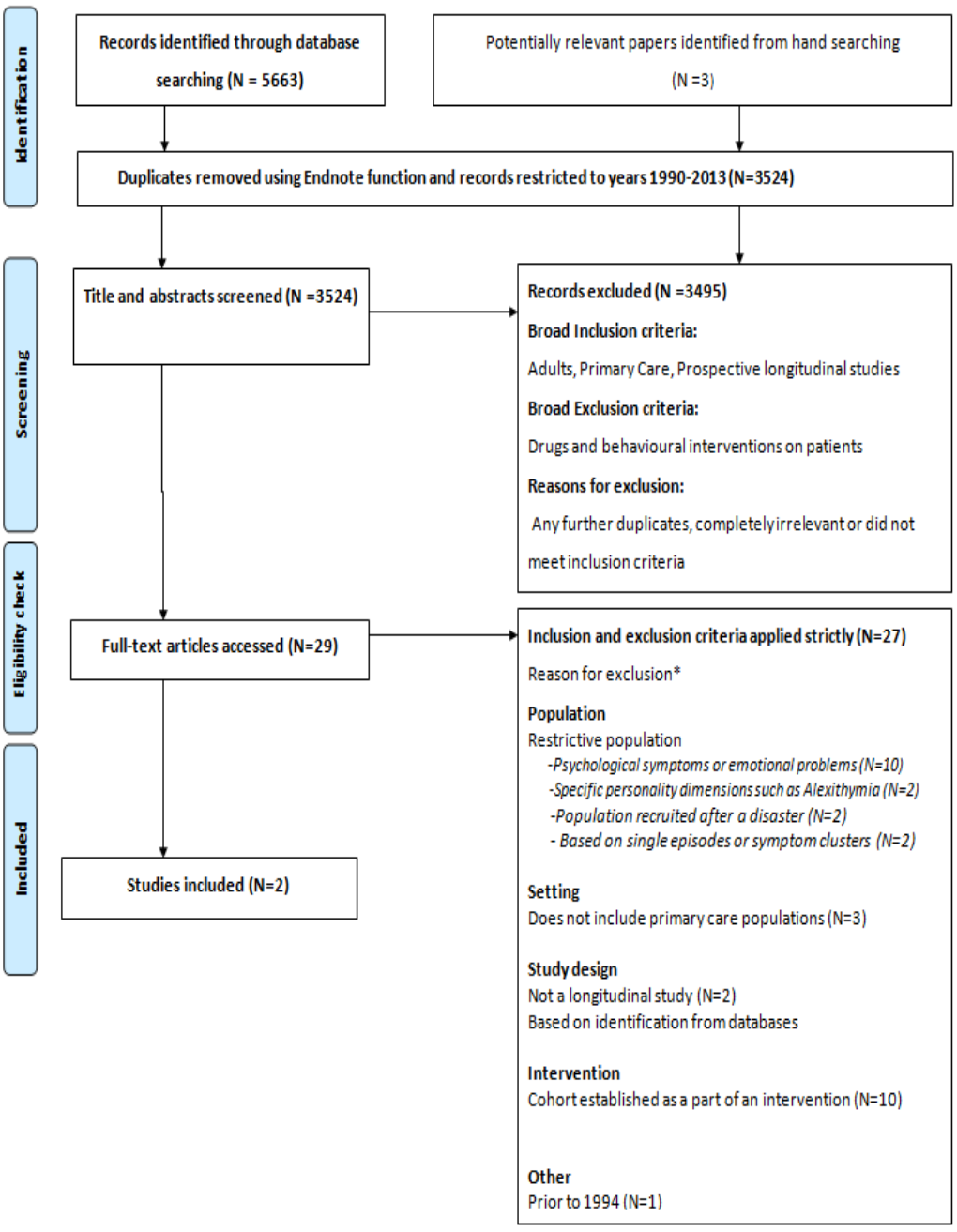
2.8 Results

2.8.1 Identification of studies

In total 5,663 papers were identified from the database searches that included: 1,783 papers identified using MEDLINE, 2,236 using EMBASE, 443 using CINAH and 1,201 using PsychInfo. After the first stage of screening, described in section 2.5.1.1, 3,524 papers remained. Following the second stage described in section 2.5.1.2, data was extracted from the full text of 29 potentially eligible studies, as described in section 2.6, and summarised. For some studies, there were multiple reasons for

exclusion (see figure 2.1 and Appendix 2.3). Finally, two studies were identified that met the inclusion criteria for the review. Most papers (n=27) were excluded because they were based on UPS amongst primary care attenders with psychological or emotional morbidity or included cohorts that had been established for the another purpose (i.e. testing an intervention) and were therefore based on a different populations to that which I was interested in for the purpose of this review. The PRISMA diagram in Figure 2.1 shows the study selection process and papers that were excluded and the reasons for their exclusion.

Figure 2.1 PRISMA diagram showing study identification and selection process



* For some papers, there were multiple reasons for exclusion

2.8.2 Characteristics of the included studies

Two studies were identified for inclusion in the final review. One study was conducted in the UK, by Creed and colleagues (Creed et al., 2012) and the other conducted in Germany by Steinbrecher and Hiller, (2011). The two studies were very different in terms of the way in which participants were defined, method of recruitment and how the analyses were conducted.

The study by Creed et al. (2012) was based on participants identified from general practice lists and based on somatic symptom count, including those with explained and unexplained symptoms. The study by Steinbrecher and Hiller, (2011) was based on primary care attenders who met DSM-IV diagnostic criteria for somatoform disorders as well as a group with medically unexplained symptoms. It is not very clear who is included in the latter group. Efforts to contact the authors were unanswered. But by referring to another paper based on the same study (Steinbrecher et al., 2011), it appeared that this group included those with $\geq$1 medically unexplained symptom who did not meet the criteria for somatoform disorder at follow-up, although this is not explicitly stated in the paper (Steinbrecher et al., 2011). Both studies included one year follow-up and details of the studies are provided in Tables 2.1; the variables collected and questionnaires used in the study are detailed in Table 2.6.

2.8.2.1 Creed et al. (2012)

Creed et al. (2012) identified the study cohort from a sample of 2,985 general practice patients, aged between 25-65 years. The authors reported that they were unable to contact some people who were identified at the start of the study, due to incorrect addresses or death (n=495). Of the 1,999 who returned questionnaires, they excluded close to a quarter of returned questionnaires due to missing information (n=553). Baseline data were therefore only available for 1,443/2,490 (58%); non-responders were reported to be more likely to be male and younger in age.

Postal questionnaires included the Somatic Symptom Inventory (SSI), a similar measure to the PHQ-15 (see section 4.9.1 for details on PHQ-15), to determine symptom severity at baseline and follow-up. The SSI is based on 13 somatic symptoms: muscle soreness, fatigue and weariness, pain in the lower back, fullness in head, hot or cold spells, pain in the abdomen, muscles twitching, trouble with vision, ringing or buzzing in ears, faintness or dizziness, constipation, breathing difficulty, nausea or vomiting. Unlike the PHQ-15, it excludes gender exclusive symptoms such menstrual problems. Symptoms are rated on a scale ranging from 1 (not at all) to 5 (a great deal) over the previous six months and scores can range from 13-65. At one year follow-up the authors reported that questionnaires were returned by 741 out of the 1443 (51%) people who responded at baseline. Responders and non-responders were described as similar in terms of their baseline somatic symptom severity (Creed et al., 2012). Further details of the study are

provided in Table 2.1. The findings of this study in relation to the objectives of this review are discussed in section 2.9.

2.8.2.2 Steinbrecher and Hiller (2011)

Steinbrecher and Hiller (2011) used the Patient Health Questionnaire, somatic symptom module (PHQ-15) (see 4.9.1 for details on PHQ-15) to screen consecutive general practice attenders for somatic symptom severity. Those with more than two questions missing, under the age of 18 years, with language problems (non-German speakers or other difficulties) or psychotic disorders were excluded. Although a stated aim of the study was to identify a high risk group, the paper reported that 312/620 (50%) of those who were screened at the first stage were consecutively selected and invited for the next stage of the study. I contacted the authors to clarify how this high-risk group was identified using a consecutive sampling method but I received no response.

I was able to obtain some clarity on the sampling method by referring to another paper based on the same study, in which Steinbrecher and Hiller (2011) highlighted that the authors had aimed to recruit at least 80% of the 'high scorers'. Therefore, it appeared that patients within each of the severity groups (i.e. PHQ-15 0-4; 5-9; 10-14; 15≥) were consecutively selected and those within the high severity group were oversampled, rather than a consecutive selection process amongst all those who were screened (n=620). The sample included 79% of those who scored PHQ-15 ≥15

and 27% of those who scored PHQ-15 0-4; this would explain to some extent the larger proportions of high scorers were recruited using the quoted consecutive recruitment method. This is however an assumption and no details of a stratified sampling method are given in the paper (Steinbrecher and Hiller, 2011).

Of those who were screened, 308/312 (99%) completed a baseline diagnostic interview; it included questions based on the modified version of the somatoform disorder module from the Composite International Diagnostic Interview. In addition, symptoms that were identified during the interview were assessed by the GP as medically unexplained, mixed or explained. The authors reported there were no significant differences between those who were recruited for diagnostic interviews and those who were not; in terms of age, education and household composition, although a greater number of females took part and the sample included greater numbers with higher PHQ-15 scorers. I discuss the findings of this study in further detail, with reference to the objectives of this review in section 2.9.

Table 2.1 Study characteristics of the papers included in the review

First author, year, country	Creed et al., 2012	Steinbrecher and Hiller, 2011
Type of study	Prospective population-based cohort study of primary care patients	Prospective cohort study
Country	England	Germany
Aims	• To determine the risk factors for high total somatic symptoms • To determine whether high baseline total somatic symptom count predicts poor health status one year	• To compare different courses of SFD (remission, persistence, incidence) to each other in reference to psychosocial impairment, cognitive illness representation and attribution style. • To identify significant predictors for the course of somatoform disorder and medically unexplained symptoms
Terminology used	Somatic symptoms	Somatoform disorders, Medically Unexplained Symptoms
Method of identification	Somatic symptom inventory	• PHQ-15 • Diagnostic interview • GP confirmation of explained or unexplained nature of symptoms
Sampling	Simple random sampling	Consecutive attending patients
Setting	Two general practices in North West England (one rural and one inner-city area)	Two primary care practices in Muniz Germany
Initial sample/screened	• 2985 questionnaires posted • 495/2985 wrong address or dead • 1999/2985 returned questionnaires • 553/1999 returned questionnaire were not useable • 1443/1999 returned questionnaires were included at baseline	• Consecutive sampling identified n=648 • 4.3% excluded or dropped out • 312/620 invited for interview

Baseline sample characteristics	• Sample size: 1443 • Mean age of responders (N=1443): 47 years *Other data provided only for those who completed both baseline and follow-up N=741* • Female: 432/741 (58%) • Mean age: 49 years • < 12 years education: 207/741 (28%) • Two or more current illnesses: 59/741 (8%)	• Sample size n=308 • Females: 220/308 (71%) • Mean age: 46 years (SD 16) • <12 years education: • 125/308 (49%) • Mean PHQ-15 score 9.8 (SD 5.1) • Mean number of MUS: Females=3.8 (SD 4.1)/ Males=2.8 (SD 4.4) • Mean number of MES: Females 1.6 (1.7) /Males 1.8 (2.1) • Mean number of mixed symptoms: Females 4.2 (3.6)/ Males 2.3 (3)
Follow-up sample characteristics	Sample size N=741	Sample size N=277 Mean age: 47.7 years (SD 16.4)
Response rate	• 1443/2490 (58%) returned usable baseline questionnaires • 741/1443 (51%) returned follow-up questionnaires	• 648 patients screened consecutively (does not report total sample approached) • 308/312 (99%) completed diagnostic interview and a set of questionnaires • 277/308 (90%) had follow-up data
Length of follow-up	One year	One year

2.8.3 Quality of the studies

Both studies were judged to be of moderate or poor quality. The study by Creed et al. (2012) met acceptable standards of reporting in 17/21 areas considered in the quality assessment tool and was judged as moderate in quality. The second study, by Steinbrecher and Hiller (2011), met acceptable levels of reporting on only 14/21 of the areas in the quality assessment tool and was judged to be of poor quality.

There were issues on key aspects such as a lack of a sample size calculation, a small sample size and too many variables included in the prognostic models. Details of the assessment of the studies are shown in table 2.2. However, due to the limited numbers of relevant studies, neither was excluded from the review based on the quality.

Table 2.2 Quality checklist of the studies included in the review, developed using the CASP tool (CASP, 2013) and references sources for evaluation of prognostic studies (Hayden et al., 2006).

	Creed et al., 2012	**Steinbrecher and Hiller, 2011**
1. Research question defined?	Yes	Yes
2. a) Sample size calculated? **b) Sample size adequate?**	Yes Yes	Not calculated No
3. Study design adequate?	Yes	Yes
4. Source population clearly described	Yes	Yes
5. Symptom duration at inception taken to account?	No	No (reported but unclear if used in modelling)
6. Is the study population representative? (Did a reasonable number from those eligible take part in the study or were those who took part in the study similar in characteristics to those who did not take part in the study?)	No: Those sent questionnaires were assumed to be representative of GP list populations. Baseline: non-responder were more likely to be young and male. Follow-up: responders, older and more likely to be married.	No: More educated than the general population and more females. Oversampled for those with higher symptom severity on PHQ-15
7. Completeness of follow-up described (Are those lost follow-up significantly different from those who took part in the	Yes (as above)	No

whole study?)		
8. Completeness of follow-up adequate-Response rates is >70%?	No	Yes
9. Prognostic factors/ risk factors well defined?	Yes	Yes
10. Prognostic factors measured appropriately	Yes	Yes
11. a) Outcome defined **b) Is the outcome appropriateness**	Yes Yes	Yes Yes
12. Confounders defined and measured	Yes	Yes
13. Confounding accounted for by appropriate methods?	Yes	Yes
14. Analysis described	Yes	Yes
15. Analysis appropriate	Yes	No (too many variables included in the models)
16. Analysis provides sufficient presentation of data	Partly	Yes
17. External validation of results -are the study findings generalisable?	No	No
18. a) Follow-up length described? **b) Is the follow-up length appropriate?**	Yes Yes	Yes Yes
21. General internal validity- Is there risk of bias within the study?	Unsure	Unsure
22. Evidence supporting conclusions	Yes	No
Number of areas meeting acceptable standards and overall quality	17/21- Moderate	14/ 21-Poor

2.8.4 Outcomes of UPS

2.8.4.1 Symptom related outcomes

As described in section 2.2, the aim of this study was firstly, to describe the outcomes identified in eligible studies. Both studies identified primarily explored outcomes relating to symptoms, although these were defined and measured in different ways. Creed et al (2012) referred to somatic symptoms, using the Somatic Symptom Inventory (SSI) which was described in section 2.8.2.1. The SSI scores were divided into categories: ≤25, 26-30 and ≥31. High scorers were considered to be those who scored ≥26. The percentages of participants who scored ≤25 and ≥26 on the SSI were similar at baseline and one year follow-up and are shown in Table 2.3. Data related to change in somatic symptom severity over time, from baseline to follow-up were not provided in the paper, although 104/741 (14%) were reported to have high scores >26 at both baseline and follow-up. The authors were contacted and provided mean SSI scores for baseline and follow-up. These showed only minor changes in the overall mean SSI scores over time (21.35, SD 6.56 and 20.99, SD 6.56 respectively). I was unable to obtain data on the change in symptom severity score of participants from baseline to follow-up; for example, number of participants who scored ≥26 at baseline and experienced a reduction in symptoms from baseline to follow-up. Creed et al. (2012) also did not report on the percentage of those with unexplained or mixed symptoms, which may have been useful for cross comparison with existing studies on UPS. Further details on outcome are reported in Table 2.3.

Table 2.3 Creed et al. (2012): proportion of participants with severity scores <26 vs. ≥ 26 (using the SSI scores), at baseline and at follow-up

Severity scores (somatic symptom Inventory)	Baseline N= 1443 n/ N (%)	Follow-up N=741 n/N (%)
≤25 (low severity)	1139/1443 (79%)	588/741 (79%)
≥26 (high severity)	304/1443 (21%)	153/741 (20%)

Steinbrecher and Hiller (2011) focused on changes in somatoform disorder in terms of persistence (no change in symptoms), new (increase in number of symptoms), and remission (reduction of symptoms) at follow-up. The Diagnostic Interview (a modified version of the Composite International Diagnostic Interview), International Diagnostic Checklist (to enquire about current and previous psychological disorders and to evaluate and operationalise the DSM-IV individual mental disorders) and GP diagnoses were used to determine whether symptoms were medically unexplained, explained or mixed and to obtain somatoform disorder diagnoses.

Steinbrecher and Hiller (2011) reported findings only for those who took part in both the baseline and follow-up (n=277). At baseline, 84/277 (30%) screened met the criteria for DSM-IV somatoform disorder. This included 39 with undifferentiated somatoform disorder (any one or more symptoms that result in very strong impairment) and 43 who met the criteria for somatoform pain disorder (≥1 impact of the symptom pain, is greater than that of any other symptoms, present for twelve months or more). At follow-up, 43/84 (51%) who met the criteria for somatoform disorder at baseline were identified with persistent somatoform

disorder, 41/84 (49%) had remitted somatoform disorder. In addition, 13/277 (5%) met the criteria for a new somatoform disorder (see Table 2.4)

Table 2.4 Symptom related outcomes explored in the included studies

	Creed et al., 2012	**Steinbrecher and Hiller, 2011**
Outcomes	High somatic symptoms • 153/741 (21%)scored ≥26 on SSI at follow-up • Persistent high symptoms- 104/741 (14%) scored ≥26 at baseline and follow-up	Course of somatoform disorder (SFD) • Persistent - 43/84 (51%) • Remission – 41/84 (49%) • New somatoform disorder at follow-up (n=13)
Recovery rate	Recovery rate was not reported clearly; in discussion section it suggests that two-thirds of those with high scores had 'numerous' symptoms 1 year later	Remitted in n=41/84 (49%) with somatoform disorders

2.8.4.2 Quality of life/ self-reported health status

As discussed in section 1.6.4, a number of different terms are used to refer to quality of life. Most studies use variations of the Medical Outcome Survey Short Form Questionnaire (Ware and Sherbourne, 1992). Creed et al., (2012) explored quality of life as a secondary outcome, referred to in the paper as impaired health status, using the 12- item Medical Outcome Survey Short Form Questionnaire (SF-12) (Ware et al 1996). The SF-12 has 8 health domains which include: physical functioning, bodily pain, general health, vitality, social functioning and emotional and mental health. The scoring algorithm generates aggregated physical and mental health component summary scores, weighted against general population norms;

scores range from 0 (the lowest level of health) to 100 (the highest level of health). In addition, Creed et al. (2012) used the EuroQol thermometer (Williams, 1990) to determine self-reported health on the day, and includes questions on mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EuroQol generates an overall score ranging from 0 (worst imaginable) to 100 (best imaginable).

Findings of SF-12 and EuroQol thermometer scores at baseline and follow-up are shown in Table 2.5. Creed et al., (2012) found that mean physical functioning scores decreased amongst all severity groups; the greatest decrease at one year follow-up amongst those who had the highest baseline SSI scores ($\geq$31) (mean at baseline = 40.0, SD 12 vs. mean at follow-up = 38.7, SD 12.8) . Mean mental health functioning scores decreased slightly from baseline to follow-up, amongst those who scored 26-30 (mean at baseline= 45.5, SD 10.6 vs mean at follow-up= 44.5, SD 10.8) and $\geq$31 (mean at baseline=36.3, SD 11.8 vs mean at follow-up= 35.4, SD 12.1). Those who scored $\leq$25 at baseline showed a slight increase in mental health functioning at follow-up (mean at baseline= 49.9, SD 9.4 vs mean at follow-up= 50.9 SD 9.2). This suggests that the most severely affected had worse mental health at follow-up, whereas those less severely affected tended show some small improvement. The EuroQol thermometer also showed a decrease in functioning amongst the two high severity groups; this was largest amongst those who had scores $\geq$31 (mean baseline score 60.2, SD 21.9 vs mean follow-up score 55.7, SD 22.4).

Table 2.5 Change in mean physical and mental health functioning scores and EuroQol from baseline to 12 month follow-up.

Instrument used	Baseline Mean (SD)			Follow-up Mean (SD)		
	SSI ≤25	SSI 26-30	SSI ≥31	SSI ≤25	SSI 26-30	SSI ≥31
Physical health functioning (SF-12)	52.1(7.8)	44.6 (9.7)	40 (12)	51. 9 (7.5)	44.1 (10.8)	38.7 (12.8)
Mental health functioning (SF-12)	49.9 (9.4)	45.5 (10.6)	36.3 (11.8)	50.9 (9.2)	44.5 (10.8)	35.4 (12.1)
EuroQol thermometer	82.9 (13.1)	73.7 (16.1)	60.2 (21.9)	83.2 (13.4)	71.1 (17.2)	55.7 (22.4)

2.8.5 Prognostic factors associated with outcomes identified from the included studies

2.8.5.1 High somatic symptoms scores, medically unexplained symptoms and somatoform disorders diagnostic

Overall, both studies collected data on similar baseline variables and explored their associations with the outcomes including: sociodemographic factors; symptoms at baseline; psychological factors (such as depression and anxiety); quality of life/ health functioning; personality dimensions; and current experiences (see Table 2.6 for questionnaires that were used). However, they also explored a number of variables which were unique to their own study including social support and health

service contact (Creed et al.,2012) and childhood experiences (Steinbrecher and Hiller,2011).

Table 2.6 Baseline variables collected and standardised measures used in the two included studies

Baseline variables collected and standardised measures used		
	Creed et al., (2012)	**Steinbrecher and Hiller, 2011**
Socio-demographic characteristics	• Age, gender, marital status, years of education, employment	• Age, gender, marital status, education (<12 or ≥12 years)
Somatic symptoms	• Somatic symptom count- *Somatic symptom inventory*	• Number of chronic diseases/somatic symptoms- - *Composite International Diagnostic Interview* • No of MUS -*GP assessment* • Somatization -*Brief Symptom Inventory*
Psychological functioning	• Anxiety and depression – *Hospital anxiety and depression score*	• Depression, Anxiety, Hostility, Phobic anxiety, Paranoid ideation, Psychoticism, Global severity, Obsessive-compulsive, Interpersonal sensitivity - *Brief Symptom Inventory*
Functioning	• Physical and mental health functioning -*SF-12 and EuroQoL*	• Functional disability due to health condition - *WHO-Disability-Assessment-Schedule II*
Social support	Presence of a close confidant	X
Personality	• Personality traits of neuroticism and other correlates -*The Revised NEO Personality Inventory*	• Cognitive and emotional representations of illness and illness comprehension-*The Brief Illness Perception Questionnaire- (Causal attributional styles: vulnerability, psychological factors, somatic disease, distress)* • Dysfunctional cognitive characteristics associated with somatisation and hypochondriasis –*Cognitive Characteristics Associated*

		Cognitions About Body in Health Questionnaire: Catastrophizing cognitions; Autonomic sensations; Bodily weakness; Intolerance of bodily complaints; Health habits • Hypochondriasis -Whitley Index
Childhood experiences	• Physical or sexual abuse <16 years age -*The Child Physical and Sexual Abuse questionnaire* • Perceived maternal care and support-*The Parental Bonding Instrument*	X
Current experiences	• Stressful/Negative experiences *List of Threatening Life Experiences*	• Stressful/Negative experiences *List of Threatening Life Experiences*
Health service contacts	x	• Number of GP consultations in previous twelve months • No of psychotherapeutic sessions

Creed et al. (2012) conducted multiple regression analyses to explore the association between baseline variables and somatic symptom score (high somatic symptoms ≥26 vs ≤25). Due to the small sample size in the higher SSI groups, those scoring SSI ≥26-30 and ≥31 were grouped together into a single category (n=104). All models were adjusted for gender, anxiety, depression and recent injury or illness and each additional variable from those listed in Table 2.6 was, in turn, added to the model one at a time. Baseline factors which were significantly associated with high SSI scores (≥26) included being separated, widowed or divorced (OR= 2.84, 95% CI 1.37 to 5.88), having less than 12 years of education (OR= 3.34, 95% CI 1.82 to 6.12), no close confidante (OR= 2.56, 95% CI 1.11 to 5.94), being off work due to illness or injury (OR=4.43 95% CI 2.20 to 8.89) and recent serious illness or injury (OR= 2.40,

95% CI 1.04 to 5.56) adjusted for gender, anxiety and depression, and recent serious illness.

High SSI scores were also significantly associated with: older age (mean 49.8, SD 11.1); neuroticism (mean 26.9. SD 8.4); anxiety (mean 9.9, SD 3.9); depression (mean 7.6, SD 4.4); and impaired health status on the SF-12 physical component score (mean 40.0, SD 12.0) and the EuroQol (mean 60.2, SD 21.9). Odds ratios for these associations were not provided by the authors (Creed et al., 2012).

Steinbrecher and Hiller (2011) used ANCOVA to compare baseline psychological characteristics between the different somatoform disorders groups (persistent n=43, new n=13, remitted=41) at follow-up and two additional groups 'other mental disorder at baseline' (n=27) and 'no mental disorder at baseline' (n=153) and conducted post-hoc pairwise comparisons across group to identify where the significant effects occurred. This process alongside theoretical considerations informed the variables included in the multiple regression analysis to identify predictors of somatoform disorders and medically unexplained symptoms at follow-up. However, due to the multiple pairwise comparisons, it is likely that some significant findings were due to chance. Furthermore, the sample size is too small to robustly test so many variables in the models; hence the findings of this study need to be interpreted with caution. The more variables one wants to include in the model, the larger the sample size is required. Additionally, although it is described as a prognostic model, they did not check the fit of the model or check for validity.

Steinbrecher and Hiller, (2011) conducted prediction model for two groups; those identified as having medically unexplained symptoms (n=220) and those who are reported as those with somatoform disorders (n=65). It is not clear why there is a reduction in numbers included in the prognostic models from the total of 277 in the study.

They included 25 independent variables, which included all the variables shown in Table 2.6 and individual components of some of the questionnaires used. These were: gender, education, age, number of chronic somatic diseases, number of mental disorders, number of routine psychotherapeutic sessions, current depression disorder, current anxiety disorder, negative life events, total number of symptoms, number of medically unexplained symptoms, illness perception, causal attribution: vulnerability, causal attribution: psychological factors, causal attribution: somatic disease, causal attribution: distress, catastrophising cognitions, autonomic sensation, bodily weakness, intolerance of bodily complaints, health habits, illness anxiety, functional disability, psychosocial impairment and number of GP consultations.

Baseline depression was significantly associated with a decrease in the likelihood of persistence of medically unexplained symptoms at follow-up (OR=0.12, 95% CI 0.01 to 0.85). Other factors associated with a reduced likelihood of medically unexplained symptoms at follow-up included number of medically unexplained

symptoms at baseline (OR=0.77, 95% CI 0.70 to 0.80), illness perceptions (OR= 0.97, 95% CI 0.94 to 0.99), casual attribution style: distress (OR=0.90, 95% CI 0.82 to 0.98) and catastrophising cognitions (OR=0.91, 95% CI 0.84 to 0.99). Negative life events (OR=1.30, 95% CI 1.00 to 1.60), causal attribution style: vulnerability (OR=1.10, 95% CI 1.0 to 1.20) and somatic disease (OR= 1.10, 95% CI 1.00 to 1.20) were predictive of persistence of medically unexplained symptoms at follow-up, although for many of the variables significance was borderline, as indicated by the confidence intervals.

With regard to the prediction of somatoform disorder at follow-up, again all 25 variables that were included in the medically unexplained symptom model were included. Current depressive disorder (OR=0.001, 95% CI 0.00 to 0.72), causal attribution style: vulnerability (OR=0.64, 95% CI 0.42 to 0.97) and functional disability (OR=0.72, 95% CI 0.54 to 0.97) all appeared to be significantly protective, reducing the likelihood of somatoform disorder persistence. On the other hand, odds of persistence of somatoform disorder increased by three times for each negative life event (OR=3.20, 95% CI 1.10 to 9.60) experienced at baseline. The model for MUS was reported to correctly predict 75% of cases for medically unexplained symptoms and that for somatoform disorder 81% of cases.

2.8.5.2 Quality of life/ self-reported health status

Creed et al. (2012) also explored the association between baseline high somatic scores and health status at the end of the 12 month follow-up using ANOVA with SF-12 and EQ-5D as dependent variables. The authors described that the baseline high somatic symptoms score was highly significantly associated with a worse physical health functioning but not with mental health functioning (based on the SF-12) and worse overall health (based on the EQ-5D). However, no effect sizes were provided in the paper.

2.9 Discussion

This systematic review highlights the paucity of prospective cohort studies exploring course and outcome of UPS in primary care. Only two papers that met the inclusion criteria were identified. Following quality assessment by two independent reviewers, it was determined that that the study by Creed et al. (2012) was of moderate quality and that by Steinbrecher and Hiller (2011) was of poor quality. This was largely due to flaws in the study design and analyses. The substantial heterogeneity of the two studies meant they were difficult to compare as it would not be appropriate to combine their findings.

In the following section, I discuss the two studies included with respect to objectives of my systematic review. I compare the findings with some studies that did not meet the specific inclusion and exclusion criteria for my review (see section

2.3); reasons for exclusion are also highlighted in Figure 2.1 and summarised in Appendix 2.3. These included, the cohort being recruited as a part of an intervention, inclusion of those who specifically have psychological or emotional distress (for example somatised mental disorders), participants not identified from primary care or other reasons such as inclusion of a very specific study cohort. These studies provide some insight into rates of symptom remission and persistence amongst those identified with UPS in primary care, as well as potential prognostic factors that may be significantly associated, despite the differences study designs and specific populations that are included.

2.9.1 Outcomes of UPS in the included studies and comparison to studies excluded from the review

In the study by Creed et al. (2012) there is limited information on the outcome of participants over time. The percentages that met the criteria for low and high severity were similar, at both baseline and follow-up however, information on change in severity from baseline to follow-up was limited. For instance, they reported that 14% had high severity (SSI $\geq$26) at both baseline and follow-up. It may be possible that some with high scores at baseline moved to the lower score group (i.e. an improvement). Equally it is not possible to determine the percentage of low scores at baseline went on to experience an increase in symptoms at follow-up. Only slight changes in physical and mental health functioning, as well as on overall

quality of life based was observed; those with higher scores on the SSI showed a decrease in functioning at follow-up. Steinbrecher and Hiller, (2011) provide more information in terms of symptom related outcome. At follow-up 51% met the criteria for persistent somatoform disorder and 49% had remitted somatoform disorder.

Rates identified by Steinbrecher and Hiller (2011) are similar to two studies of medically unexplained symptoms in primary care, identified by Olde Hartman et al. (2009) in a review of the course and prognosis of somatoform disorders, hypochondriasis and unexplained symptoms. These two studies did not meet the inclusion criteria for my review as they included different populations to that of interest to my study (De Gutch et al., 2004; Gureje and Simon, 1999). De Gutch et al. (2004) reported that 169/318 (53%) experienced a decrease in their number of symptoms, whilst 107/318 (34%) had an increase and 31/318 (10%) remained the same at six month follow-up (De Gutch et al., 2004).[2] Gureje and Simon, (1999) found 522/1071 of study completers continued to meet the criteria for current abridged somatistion at one year; a weighted estimate of 45.9%.[3] Another study primary care study that did not meet the inclusion criteria (but was also not included in the review by Olde Hartman et al.,2009), found lower rates of resolution

[2] This study of primary care attenders in Netherlands identified those with medically unexplained symptoms and personality dimensions such as neuroticism and alexithymia using a self-reported questionnaire with DSM-IIIR/DSM-IV somatisation headings, physical examination by their physician, patient's medical record and/or the results of additional diagnostic testing.

[3] This study used data from 15 sites in 14 countries; only 20% of those included in the study met the criteria for abridged somatisation disorders at baseline but the sample also included those with depression and anxiety disorders. At the screening stage this study oversampled for those with higher psychological distress using the General Health Questionnaire.

of symptoms.[4] At three month follow-up 37% of the cohort reported complete symptom resolution; 43% felt better, 12% were unchanged, and 8% were worse. When this cohort was studied using the criterion of multi-somatoform disorder, that is three unexplained symptoms which had been present for a period of two years, 56% (23/41) reported symptom improvement at three month follow-up (Jackson and Kroenke, 2008).

2.9.2 Prognostic factors associated with outcomes identified from the included studies and compared to studies excluded from the review

With regard to the second objective of this review, Creed et al. (2012) identified factors such as marital status, absence of a close confidant, being off work due to an illness or injury, recent serious illness or injury, older age, lower physical health functioning, lower self-perceived quality of life, anxiety, depression and childhood psychological abuse were associated with higher somatic symptoms at one year follow-up. These factors are consistent with what has been reported in other studies of UPS (see section 1.6) and that were excluded from my review for reasons highlighted in Figure 2.1. These studies also identified many of the similar factors as associated with poor outcomes relating to symptoms (see Appendix 2.4. for

[4] This study was carried out based on a cohort initially set up several years before for an educational trial of doctors; all consecutive attenders were eligible for participation. Symptom severity was measured using the PHQ-15 (Jackson & Passamonti, 2005).

individual prognostic factors and effect sizes). These symptoms related outcomes included: persistence of symptoms, increase in their severity, persistence of diagnostic status (i.e. somatisation or abridged somatisation) and emergence of a new syndrome (Craig et al., 1993; De Gutch et al., 2004; Gureje and Simon, 1999; Hilbert et al., 2010 and Koch et al., 2009; Jackson and Passamonti, 2005).

Creed et al. (2012) also explored a secondary outcome quality of life and found that high somatic symptoms at baseline were significantly associated with poor physical functioning and quality of life at follow-up. Similar findings have been reported by others (Hansen et al., 2011; Kroenke et al.,2002). Hansen et al., (2011)[5] found that higher symptoms, specifically more than four symptoms at baseline were associated with poor quality of life, based on the physical and mental functioning domains, at one year follow-up. A fairly recent review by Tomenson et al (2013) warrants mention. Based on nine population-based studies (total population of 28,377) they found that total somatic symptom score was associated with poor health status, after having making adjustments for depression, anxiety and general medical illness. However, this review included seven cross-sectional studies and two prospective studies. The prospective study conducted in Germany was based on a cohort who were a part of the Prevention of Renal and Vascular End Stage Disease (PREVEND) study (Rosmalen et al 2011), which included an enhanced sample with elevated urinary albumin concentration hence, not meeting the criteria for inclusion in my literature review. But the other UK based prospective study by Creed and

[5] This study also did not meet the inclusion for the review as it had been originally set up for intervention to improve recognition and treatment of functional disorders by GPs.

colleagues that has already been discussed in this chapter was included (Creed et al 2012). Interestingly, in the same review by Tomenson and colleagues (2013), data was used from four sites to explore the association of correlates with both the number of UPS and with total somatic symptom score. Somatic symptom scores had a greater association with health status than the number of medically unexplained symptoms even after adjusting for confounders.

Steinbrecher and Hiller, (2011) observed that negative life events, autonomic cognitions and chronic physical illness at baseline were significant predictors of poor outcome at follow-up, in terms of persistence of medically unexplained symptoms and somatoform disorder. On the other hand, a greater number of medically unexplained symptoms at baseline, illness perceptions, distress cognitions, catastrophising cognitions and functional disability were significantly associated with better outcome (reduced likelihood of the persistence of medically unexplained symptoms and somatoform disorders). Incidentally, they identified the causal attribution style, vulnerability as associated with persistence of medically unexplained symptoms but with lower likelihood somatoform disorder persistence. This difference in findings, may be due to chance; limitations relating to study methodology are discussed in section 2.10

Some of these findings identified by Steinbrecher and Hiller (2011) are counter intuitive to what may be expected and contradict previous findings. They found higher levels of symptoms at baseline were associated with recovery over time but

others have reported that higher baseline symptoms are associated with a poor outcome (Jackson and Passamonti, 2005; Speckens et al., 1996; Kooiman et al., 2004). However, Jackson and Passamonti (2005) did not distinguish between those with explained and unexplained symptoms in their study. Speckens et al (1996) and Kooiman et al., (2004) also found similar findings to Jackson and Passamonti (2005) but were carried out with outpatient setting.

Steinbrecher and Hiller, (2011) identified depression as a protective factor against persistence of medically unexplained symptoms and somatoform disorders, whilst Gureje and Simon (1999) for example found depression and anxiety to be associated with a worse outcome. Steinbrecher and Hiller (2011) suggest that comorbid depression may lead to earlier help-seeking and professional treatment and that remission of these disorders may result in remission of the somatic symptoms. Whilst this may be a possibility, it is more likely that other unexpected findings identified by Steinbrecher and Hiller (2011) are a result of the study design and methods used in the analysis. Most notable error is that the sample size of the somatoform disorder group was small (n=63) and too many variables were included in the multivariable analyses. Most confidence intervals for factors identified as significant are wide and large confidence intervals place greater uncertainty on the findings. These issues are discussed in detail in the section 2.10.

2.10 Strengths and limitations of the studies included in the systematic review

Both studies move away from the traditional view of UPS as expressions of psychological distress by using symptom counts such as the SSI and the PHQ-15. Although, Steinbrecher and Hiller (2011) still uses the DSM-IV somatoform disorders to identify groups within the study.

The two included studies had several methodological weaknesses, which call for caution in interpreting their results. Internal and external validity are important aspects of epidemiological studies. Internal validity refers to the strength of the study based on the way in which it has been carried out. It takes into consideration any bias that may have occurred as a result of how participants were selected, drop outs and the methods of analysis. External validity refers to how generalisable findings from the study sample are, to the populations from which they were drawn, as well as to other (Gordis,2014). Boffetta, (2011) argue that the focus on external validity of studies is often misguided as populations are continuously changing and representativeness even within the source population will not be maintained. They therefore suggest that greater emphasis should be placed on the internal validity of a study (Boffetta, 2011). Nevertheless both external and internal validity are important concepts in epidemiology and in the following section I will discuss both but focus more on the latter.

2.10.1 External validity

Both studies included patients from two GP practices. Creed et al. (2012) included two general practices from two areas with different socioeconomic features; one rural and the other non-rural. However they report that baseline non-responders were likely to be young and male whilst the follow-up responders were older and more likely to be female. Steinbrecher and Hiller, (2011) on the other hand did not provide much information on the characteristics of the population from which their sample were drawn. They do however report that the study sample was more educated and more likely to be females which can limit the external validity and the generalisability of these findings.

2.10.2 Internal validity

In the following section I discuss important aspects of internal validity: selection bias, response rates and statistical power, in relation to the papers included in my systematic review.

2.10.2.1 Selection bias

As mentioned in the previous section, Creed et al. (2012) report differences in those who took part in the study compared to those who did not respond. This is often the case with primary care studies, and may reflect the characteristics of general practice attenders (Patel et al., 2003). Steinbrecher and Hiller (2011) oversampled for high scorers; this does not appear to be accounted for in the analysis, leading to

concerns about the internal validity of the study. Limited information is provided on the source population. Over half of the baseline respondents were reported to be twice as educated as the general German population; those with higher education may have been more inclined to participate. Furthermore, Steinbrecher and Hiller (2011) do not provide information on the size of the source population other than to say that 620 consecutive primary care attenders completed the questionnaires during the screening stage and therefore it is unclear how many were actually approached.

2.10.2.2 Drop out / response rate

Creed et al. (2012) initially report a response rate of 75% in their paper, based on those who agreed to be contacted for follow-up when returning baseline questionnaires (741/988) rather than calculating this based on all those who returned baseline questionnaires (n=1,443). Therefore, their actual response rate is much lower than they initially report and closer to 50% (741/1,443). Lower response rates are likely to lead to potential bias, especially if those who response differ in a meaningful way, to those who do not. The authors do note this as a limitation and point out that the sample was older and included more females than the sample from which it was drawn. However SSI scores amongst those who responded at follow-up and those who didn't are noted to be similar and the authors mention adjusting for non-response in their analyses.

In the study by Steinbrecher and Hiller, (2011), response rate at follow-up was 90% which is highly satisfactory, considering the well-known difficulties in achieving high response rates in primary care studies (Patel et al., 2003).

2.10.2.3 Statistical power

Creed et al. (2012) were unable to reach the sample size which they had initially calculated, and provided a post-hoc power calculation. This suggests that the study has 80% power to include up to 26 covariates and provides some confidence in the results. Post-hoc sample size calculations are considered to be unacceptable under conventional methods of sample size calculation (Hoening and Heisey et al 2001). However, it does suggest that the findings of the regression analyses can be interpreted with some confidence, especially as only few variables are included in each of the models.

Steinbrecher and Hiller, (2011) did not report a sample size calculation for their study. The sample size of the somatoform group was very small (n=63) and 25 covariates were included in the prognostic model. A rule of thumb is often used to determine sample size for regressions and prognostic models which use continuous outcome (Harrell et al., 1996; Mallet et al., 2010). It suggests that for each independent variable included in the model at least ten participants should be included and for categorical variables, this is based on ten events per independent variable in the smaller group (Harrell et al., 1996; Mallet et al., 2010). This would

suggest that the sample size calculation for this study was inadequate for the number of variables included in the predictive models. For the medically unexplained symptom model, although the sample size is much larger (n=220), it is likely that the number of covariates included is still too high. Therefore, the findings must be interpreted with caution; regardless of the reporting of significant findings, the large confidence intervals place uncertainty on these findings. In the next section, I discuss the strengths and limitations of my systematic review.

2.11 Strengths and limitations of my systematic review

One of the main strengths of this review is that the protocol and design of this review was conducted with discussion and feedback from clinicians practising in general practice with expertise in UPS. I tried to ensure that all relevant papers were identified by careful development of a comprehensive search strategy and the use of four key e-databases for identification of the literature (see section 2.4). The British Library database was searched for any relevant PhD theses and reference lists of selected key papers were hand searched. Two reviewers were involved in deciding which papers met the inclusion criteria and in judging the quality of the included papers. Due to the time and resource intensive process of translating studies, I decided to limit the review to papers to those which were in English only. However, it is possible that limiting the language to English may have resulted in missing some relevant studies. It is also possible that some relevant papers within the grey literature may have been missed.

It can be argued that the strict inclusion and exclusion criteria may have resulted in exclusion of relevant literature from the systematic review. However, I believe that this has resulted in identification of two studies which are relevant to the primary care attenders and changing concepts of UPS.

Studies that were excluded from the review warrant mention as they highlighted the extent of the heterogeneity amongst studies that are widely acknowledged in the UPS literature. These studies highlighted the variability in terminology, definitions, diagnostic criteria and study designs. In addition to the outcomes already discussed relating to symptoms and quality of life in relation to the studies included in the this systematic review (see section 2.9), a number of studies have also explored predictors of high health care use or high levels of health care visits in primary care (Blankenstein, 2001, De Waal et al., 2008, Hilbert et al., 2010, Hansen et al., 2011, Kisely and Simon 2006). These studies identified factors such as being female, higher health care use at baseline, presence of medically unexplained symptoms (as opposed to explained symptoms), and less availability of social support as being significantly associated with higher health care use at follow-up. Some of the excluded studies also report that UPS at baseline were associated with depression and anxiety at follow-up (Cape et al., 2001; Downes-Grainer et al., 1998; Kisely and Simon, 2006).

2.12 Conclusion

Despite UPS being reported to be extremely common in primary care, this systematic review highlights the limited number of good quality studies that explore UPS amongst primary care populations. It has shown that around half of people identified with somatoform disorder continue to meet the criteria a year later. Some limited information based on somatic symptom scores suggested that around 14% of those with high scores at baseline continue to have high scores at follow-up.

The two studies included in my review have identified prognostic factors that may be important to explore when examining the longer-term outcome for people with UPS. These include: sociodemographic characteristics (being female, marital status, years of education, age), past experiences (negative life events) and current physical health (being off work due to illness or injury, recent serious illness or injury, chronic physical illness, physical health functioning), social factors (no close confidante) and psychological factors (anxiety, depression, mental health functioning) factors. Prognostic factors relating to high somatic symptom scores were similar to those identified in studies of UPS based in other settings and on populations identified using different diagnostic criteria.

However, there is a need for consistency and agreement on how populations with UPS in primary care are defined. Studies should move beyond the narrow diagnostic criterions such as somatoform disorders used in the past, to those which have

broader inclusion criteria resembling patients encountered in primary care (Scot and Sensky,2003).

This systematic review therefore supports the development of studies which recruitment participants with varying degrees of UPS as a symptom based approach may be more appropriate for primary care.

Chapter 3 : **Rationale, aims and objectives**

3.0 Chapter overview

In the introductory and systematic review chapters, I discussed the challenges of conducting research into unexplained physical symptoms, due to different and changing terminology, diagnostic classifications and methods of identification used in studies over time. In this chapter, I will discuss the rationale for my study as well as the aims and objectives.

3.1 Study rationale

Very few studies have explored the course of unexplained physical symptoms in primary care populations or the prognosis of patients with unexplained physical symptoms (Olde Hartman et al, 2009; Steinbrecher and Hiller 2011; Creed et al 2012). The use of a prognostic tool can inform general practitioners' decision making and care planning for individuals with unexplained physical symptoms. It could also predict the risk of poor outcomes like persistence of unexplained somatic symptoms and/or could identify those who will experience a more favourable outcome, such as the remission of symptoms.

Hemingway and colleagues, (2013) describe prognostic research under the four components outlined below. They suggest that such research should inform clinical decision-making, management approaches and health policy.

i) Overall prognostic research, which describes future outcomes in people with a specific disease or health condition, in relation to diagnostic and treatment practices.

ii) Prognostic factor research, which aims to identify specific factors, associated with outcomes of interest.

iii) Prognostic model research where multiple prognostic factors are combined to predict the risk of a future clinical outcome amongst individual patients. This includes model development, external validation and evaluation of impact.

iv) Finally, use of prognostic information to effectively manage and treat based on individual characteristics.

My study focuses on identifying prognostic factors associated with a number of outcomes, a key component in the development of prognostic models and clinical prognostic tools. The aims and objectives of my study are described in detail in section 3.2 and 3.3.

For the purposes of this thesis, I use the term *unexplained physical symptoms (UPS),* to describe those who report somatic symptoms on the patient health questionnaire somatic symptoms module (PHQ-15) as *bothersome,* but for which no

known explanations or diagnosis is reported. Those that met the study inclusion criteria had a minimum of three UPS and a score of five on the PHQ-15. These eligibility criteria are discussed further in section 4.3. Within this context, the next section will describe in detail the study aims and objectives.

UPS includes symptoms of various forms. I have already highlighted the heterogeneity in the definition of UPS in other studies (see chapter 1.2, 1.4, 2.8 and appendix 2.3). Many studies have included people with single symptoms, functional syndromes or those meeting specific diagnostic criteria. In my study, I have chosen to focus on those with multiple UPS. The rationale for this is that those with multiple UPS have a different underlying aetiology to those with single symptoms; they also have a greater illness burden and present more complex management dilemmas to doctors than those with single UPS. As discussed in chapter 2.3.2 those with functional syndromes such as irritable bowel syndrome are likely to have a different aetiology compared to those with multiple UPS across several domains. The presence of a medical 'label' such as irritable bowel syndrome or chronic fatigue syndrome may impact on the course of the disorder and its symptoms. Those meeting the diagnostic criteria for somatoform disorders are likely to be burdened by higher levels of psychiatric morbidity and be on the more severe end of the spectrum, compared to those attending primary care. Likewise, I have not focused on frequent attenders alone. Although, this group presents its challenges with respect to their management in primary care and even though some of them may include people with UPS, many will have existing chronic physical conditions,

severe mental disorders and other types of psychological distress and thus constitute too heterogeneous a study group. This would make the epidemiological investigation of such people less meaningful. With these considerations in mind, the next section will describe in detail the study aims and objectives

3.2 Study aims

In a cohort of adult primary care attenders with UPS, this study aims to:

i) Investigate the outcome in terms of the presence of UPS at six months follow-up.

ii) Identify prognostic factors associated with somatic symptom severity, quality of life, anxiety, depression and health care use at six months follow-up.

3.3 Objectives

The objectives of each stage of the study are as follows:

Stage 1: Screening

To describe the characteristics of primary care attenders in terms of current somatic symptoms, self-reported explanation or previous diagnosis for the symptoms, whether they were consulting about the symptoms on that day, gender and age for the complete cohort and stratified by symptom severity.

Stage 2: Longitudinal study

i) To describe the characteristics of the cohort with UPS, stratified by gender.

ii) To describe the outcome of primary care attenders with UPS in terms of proportion of participants whose symptoms are resolved, received an explanation for symptoms, still under investigation or were unexplained at six months.

iii) To investigate prognostic factors associated with persistence of somatic symptoms at six month follow-up.

iv) To investigate prognostic factors associated with secondary outcomes namely, reduction in quality of life or increase in depression, anxiety and primary health service use at six month follow-up.

In the next chapter I will discuss the methods of the study in detail.

Chapter 4 : **Methods**

4.0 Chapter overview

In this chapter I present details on the design of my study, including study setting, study population, ethical considerations and recruitment. Second, I discuss the development of questionnaires for data collection (including the selection of the tools and scales used). Finally, I discuss the methods used in the analysis of data collected.

4.1 Study design

The study consisted of two main components:

i) Identification eligible participants in general practice waiting rooms using a screening questionnaire.

ii) A prospective cohort study with six month follow-up.

Each component of the study is discussed in turn.

4.2 Study setting

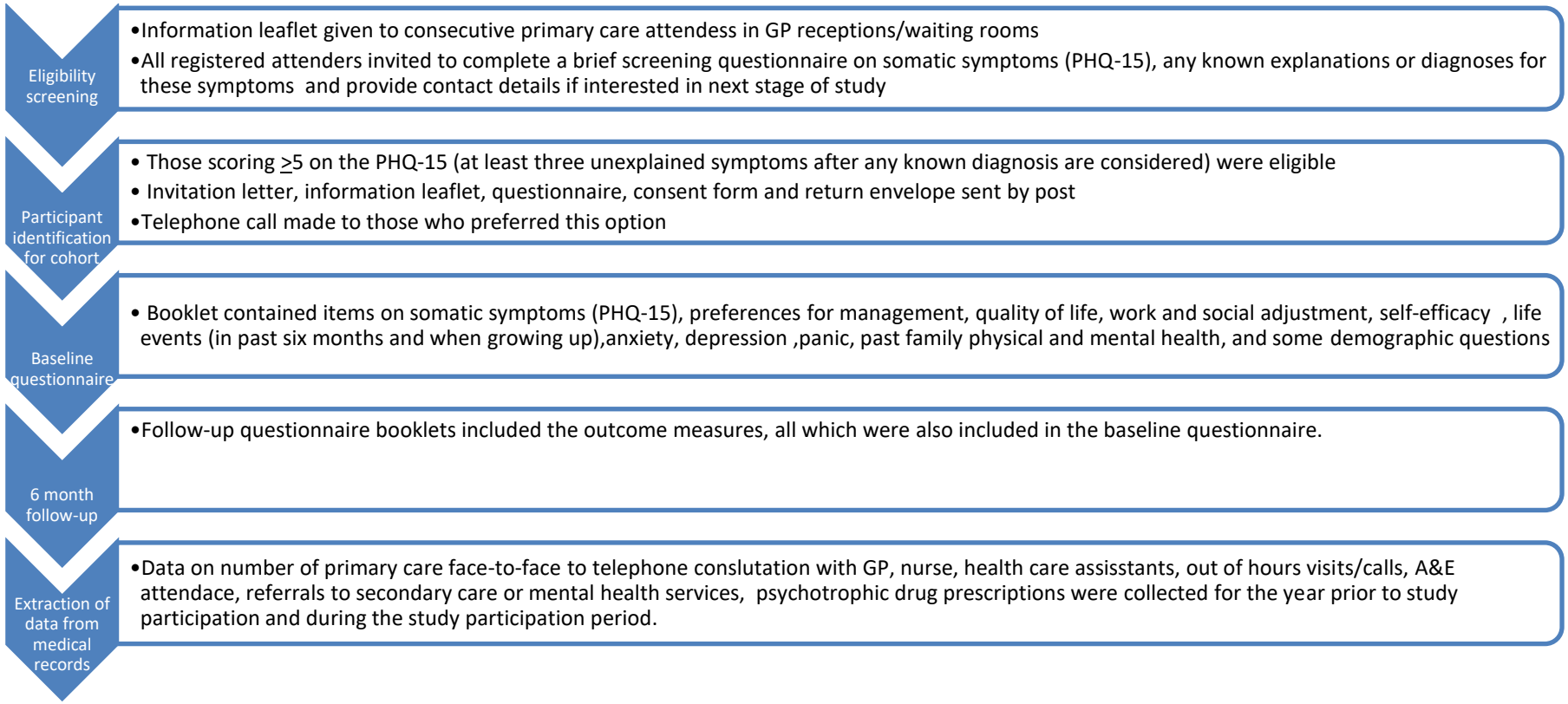
I recruited general practices with the support of the North and Central London Research Consortium (NoCLoR) Research Network. Emails were sent out to twenty research active practices in sub-urban and urban boroughs located in areas of North and Central London with study information (see Appendix 3.1 and Appendix 3.2). Recruitment took place in practices with varying levels of deprivation to ensure a variety of participant demographics and characteristics. Nine general practices located across four North and Central London boroughs agreed to participate. I decided that this was a feasible number of practices to travel to and recruit at, in the time I had available for data collection and would not place undue burden on individual practices. Based on data for year 2012/2013, Index of Multiple Deprivation (IMD) deciles of the practices included in my study range from 1 to 8 (Public Health England, 2015). IMD deciles range from one, being the most deprived, to 10, the least deprived (Public Health England, 2015). Two practices included in the study had a score of 1 (practice 6 and 8), two practices had a score of two (practice 5 and 4), two practices had a score of three (practice 7 and 3), two practices had a score of five (practice 2, 9) and one practice had a score of 8 (practice 1). Practice list sizes varied from 5,122 to 17,494 and the number of General Practitioner surgeries per day during recruitment periods ranged 1 to 8 and the number of surgeries held by nurses and health care assistants varied from 0 to 6. In addition to these, in three of the practices there was a psychologist who

carried out sessions in the practice, in two of the surgeries there was a podiatrist and in another a phlebotomist.

4.3 Study population

All adults above the age of 18 years, who were registered at one of the nine general practices and attending during the time the I was attending the practice between the study period of January to December 2013, were considered potentially eligible (see Figure 4.1). Below I describe the specific inclusion and exclusion criteria for the screening stage of the study and for the cohort study.

Figure 4.1 The diagram below shows a summary of the steps involved in identification of participants and collection of data.



4.3.1 Inclusion and exclusion criteria for the screening stage

Consecutive attenders over the age of 18 years who were registered at one of the nine general practices were eligible to complete screening questionnaires. Those who were unable to complete the questionnaires in English due to language difficulties or cognitive impairment, registered at the GP practice temporarily or planned to move away in the next six months were excluded.

4.3.2 Inclusion and exclusion criteria for the cohort study

Inclusion criteria for the cohort study were a PHQ-15 score of five or more (at least three or more symptoms), without any stated medical condition likely to fully explain their somatic symptom were considered and ability to complete the questionnaire in English. Exclusion criteria were having a medical explanation or diagnoses, which explained fully all symptoms or having a terminal illness.

4.4 Ethical considerations

Prior to the commencement of the study, I obtained ethical approval from Brent Local Research Ethics Committee. Local R&D clearence was granted from the North and Central London Research Consortium. Written informed consent was obtained from all participants, to be returned with the written questionnaire or prior to the telephone interview. In face-to-face meetings, the patient information leaflet was

sent to the participant prior to the meeting and the written consent was obtained at the meeting, prior to completing the questionnaire. The consent form also requested access to medical records. Participants were given the option to refuse to access to medical records but could continue to take part in the rest of the study. Each participant was given an identity number and all questionnaires and electronic records were anonymised. I carried out the screening at all the general practices, completed questionnaires by telephone or the face-to-face for with those who requested this and extracted all health care data from medical records. A research assistant with full clearance to access data supported with questionnaire posting and completed one telephone interview. All identifiable paper records such as consent forms were kept separately in a locked cabinet. Identifiable electronic data were stored in a secure password protected server in anonymised format. All study data were stored in accordance with the Data Protection Act 1998.

4.5 Recruitment of patients

I asked receptionists at the GP practices to give a short information leaflet to all those checking in for appointments and to inform them about the presence of a researcher in the waiting room (see Appendix 3.3). Posters were also put up in the waiting rooms (see Appendix 3.4) and leaflets left out for practice attenders to pick up to inform them of the study. I approached consecutive attenders in the waiting areas to ask whether they had read the leaflet and whether they had any queries

about the study. All waiting room attenders registered at the practice who were interested in the study were encouraged to complete the self-administered screening questionnaire to ascertain eligibility and asked to indicate their interest in being contacted regarding the next stage of the study (Appendix 3.5). I checked each screening questionnaires to ascertain eligibility and any uncertainty was discussed with the rest of the study team. I contacted those who were eligible and who had provided their contact details within two weeks, regarding the next stage of the study. When preference was indicated for contact by telephone, potential participants were contacted to arrange completion of questionnaire over the telephone or face-to-face, either at their GP surgery, their home or at a neutral venue such as the UCL campus. Participants were considered fully recruited to the study when they returned a signed consent form (see Appendix 3.8).

4.6 Stage 1: Screening

I used an initial screening questionnaire to identify potential participants (see Appendix 3.5). It consisted of the validated PHQ-15 questionnaire (Spitzer et al., 1999), which was chosen following an review of the literature (discussed in detail in section 4.9.1). The PHQ-15 is made up of fifteen questions for females and fourteen questions applicable to males, about specific body symptoms including stomach pain, back pain, headaches and trouble sleeping. Respondents are asked to rate how much they have been bothered by these somatic symptoms and are given the options not at all, a little or a lot. Additional supplementary screening questions

were included to collect information on self-reports of any known diagnoses or medical explanation for the symptoms, whether the doctor was being consulted about any of the symptoms bothering them that day, and basic socio-demographic information about age and gender. Respondents were asked to indicate their interest in the study and preferred method of being contacted (either telephone or by post) as well as to provide their contact details.

4.7 Stage 2: Cohort Study

As described in section 4.3.2, eligible and consenting participants were sent an information leaflet describing the study in detail, a questionnaire booklet (refer section 4.8.1) a consent form and return envelope, approximately within two weeks of completing the screening questionnaire. If the baseline questionnaire booklet was not returned within two weeks of being sent to the potential participant, the complete package was re-sent along with a reminder letter. The reminder letter invited the participant to complete the baseline questionnaire or to return a reply slip indicating whether they wanted to discuss the study further or were no longer interested and if possible, to give a reason for their decision. Those who did not return the questionnaire or the reply slip within the next two weeks were contacted by telephone, if they had provided their telephone contact details. If I was unable to get through to them, no messages were left to maintain confidentiality and to avoid burdening the potential participant. Up to four telephone calls were made; if these were not successful, these participants were considered to be non-respondents.

Six months after the baseline questionnaire booklet was returned, a follow-up invitation letter and questionnaire booklet was sent to the participant. The same steps as with the baseline questionnaire were taken if the follow-up questionnaire was not returned after two weeks. The original study design included six months and one year follow-up, however, due to resource and time limitations, this was revised to six months only. The questionnaire booklets used in the study will be discussed in the next section.

4.8 Questionnaire booklets

4.8.1 The baseline questionnaire booklet

The baseline questionnaire booklet that I developed was informed by the literature on UPS (see Appendix 3.9). These included studies from any settings (primary, secondary, community) and of any study design (cross-sectional or cohort studies) discussed in section 1.6 and a limited number of studies that have explored prognostic factors in primary care, presented in section 2.8; some of which met the criteria for the systematic review and some of which did not. Inclusion of possible prognostic factors was discussed with my supervisors based on their expertise as practicing GPs, in order to determine clinical relevance. Having agreed a list of potential prognostic factors, the literature was searched to identify validated, short and easy to complete questionnaires. These are listed in Table 4.1. The questionnaire booklet was designed to take no longer than thirty minutes to

complete, in order to reduce the burden on the participant. Where it was not possible to find short validated questionnaires such as for childhood trauma, some modified scales with short questions were developed and included. These will be discussed further in section 4.9.

The potential prognostic factors considered at baseline were:

1) Somatic symptom severity
2) Quality of life
3) Preferred sources of support
4) Management of symptoms
5) Work and social adjustment
6) Self-efficacy
7) Stressful life events
8) Depression
9) Anxiety
10) Panic
11) Family health during childhood (physical and mental)
12) Traumatic experiences in childhood
13) Experience of abuse a child (emotional, physical or sexual)
14) General sociodemographic questions on age, sex, education, employment, socioeconomic status/well-being, and perceived social support

4.8.2 The follow-up questionnaire booklet

I chose the predefined primary and secondary outcomes based on reference to the literature and clinical relevance. Data were collected (at six-months after baseline) on the progress of symptoms in terms of whether symptoms were still unexplained, under investigation, referred for further investigation or they had received a diagnosis (for six month questionnaire booklet please see Appendix 3.11). Validated measures were used to gather data on the following:

1) Somatic symptom score (primary outcome)
2) Quality of life (secondary outcome)
3) Depression
4) Anxiety

4.9 Instruments and questions used

The instruments and questions that have been included in the each of the questionnaire booklets are shown in Table 4.1. I first discuss the primary and secondary outcomes followed by the other baseline variables collected. These were also discussed in reference to existing studies in Chapter 1 and Chapter 2.

Table 4.1 Potential prognostic variables and measures used in my study and the questionnaires booklets they were included in.

Potential prognostic variables/ instruments or questionnaires used	Baseline questionnaire booklet	Six month follow-up questionnaire booklet
Somatic symptom severity/ PHQ-15 (Primary outcome)	X	X
Quality of life/ (SF-12)	X	X
Depression (PHQ-9)	X	X
Anxiety (GAD-7)	X	X
Panic (PHQ-PD)	X	X
Management of symptoms/ questions developed for study	X	
Social functioning/WSAS	X	
Self-efficacy/GSE	X	
Stressful life events/LTE-Q	X	
Childhood experiences/ questions developed for study	X	
Socio-demographic information including: gender, age, ethnicity, marital status, employment status, socioeconomic stuatus/well-being, education level and perceptions of social support/ questions developed for the study, ethnic categories informed from the ONS study	X	

4.9.1 The primary outcome: somatic symptom severity

Somatic symptom severity, the primary outcome of my study, is measured using the PHQ-15. The shorter PHQ-15 is a self-administered questionnaire derived from the longer Primary Care Evaluation of Mental Disorders (PRIME-MD) questionnaire (Spitzer et al., 1994). PRIME-MD is a criteria-based diagnostic instrument of mental disorders common to primary care, developed and validated in the early 1990s by Spitzer and colleagues(Spitzer et al., 1994). It included a 27 item screening tool and a follow-up structured interview with a clinician; it took up to 12 minutes to complete for patients with a mental disorder diagnosis, and was therefore considered difficult to use in busy clinical settings. This led to the development and validation of a self-administered version, the PHQ-15 (Spitzer et al., 1999; Kroenke et al., 2002). The PHQ-15 includes an initial question 'during the past 4 weeks, how much have you been bothered by any of the following problems,'; followed by fifteen questions for females and fourteen questions for males, about specific body symptoms (Appendix 4.x). These include stomach pain, back pain, headaches and trouble sleeping with options to answer 'not bothered at all' (equal to a score of 0), 'bothering a little' (equal to a score 1) or 'bothering a lot' (equal to a score 2) (Kroenke et al., 2002). It is suggested that the PHQ-15 includes 90% of the most common somatic symptoms with which people consult (Kroenke et al., 2002).

The PHQ-15 was intended to function as a continuous measure of somatic symptom severity with a potential to score from zero indicating no somatisation to 30 indicating severe somatisation. Clinical cut-off points are frequently used with 0-4

considered as minimal severity; 5-9 considered to be low severity; 10-14 considered to be moderate severity; and ≥15 high severity (Kroenke et al., 2002). In order to meet the threshold for low severity, at least three symptoms must be rated as bothersome; to meet the threshold for moderate severity a minimum of five symptoms must be rated as bothersome and at least eight symptoms to reach the threshold for high severity. The cut-off points were chosen pragmatically; however, Kroenke et al. (2002) found that the associations between increasing PHQ-15 severity and measures of construct validity did not change with these cut-off points. A moderate effect size in functional status measured using six domains of the short-form 20 (SF-20) was found when PHQ-15 somatic symptom severity increased from one severity level to the next (Kroenke et al., 2002). These cut-off points are increasingly being used in research (Mewes et al., 2008, Steinbrecher and Hiller, 2011, Korber et al., 2011). I chose to use the cut-off point of a score of ≥5, in order to exclude those with minimal severity.

Other potential screening instruments that can be used to identify participants with UPS were discussed in section 1.4.2. As I explored recent studies of UPS, I found that the use of the PHQ-15 was increasing. This is likely a result of its ease of use; being easy to understand and quick to complete. Additionally, it is reliable and validated for use in primary care and has been used effectively in longitudinal studies (Kroenke et al., 2010). In the original validation study that included 6,000 patients from general internal medicine and family practice clinics, internal consistency for the PHQ-15 was Cronbach's α of 0.80 (Kroenke et al., 2002). In

another validation study of 906 high-risk primary care patients, internal consistency was the same as in the larger study with a test-retest correlation of 0.83 when using the PHQ-15 on a continuous scale (van Ravesteijn et al., 2009).

I conducted a scoping review using the key words 'PHQ-15' and 'patient health questionnaire' along with key words for unexplained physical symptoms such as 'medically unexplained' OR 'somatic symptoms' in May 2012, to determine how frequently the PHQ-15 was being used in research, in what types of studies and in which settings. Since the publication of the first validation study of the PHQ-15, I identified 32 papers that used the PHQ-15, to identify somatic symptom severity.

These papers included several validation studies that translated the questionnaire to other languages including Korean, German and Spanish (Han et al.,2009; Körber et al.,2011; Ros Montalbán et al.,2010) were conducted in different health care settings including primary care (Burton et al., 2012; Clarke et al., 2008; Hanel et al., 2009) the general population (Rief et al., 2010), outpatient settings (Ros Montalbán et al.,2010) and more specific populations such as sick list employees (Hoedeman et al.,2009). Several intervention studies used the PHQ-15 to determine change in severity of symptoms including drug studies (Kroenke et al., 2006), it had been used in complex interventions (Burton et al., 2012; Escobar et al., 2007) and longitudinal studies to explore severity of symptoms and symptom change over time (Steinbrecher and Hiller, 2011, Jackson and Passamonti, 2005).

An updated search highlighted the growing popularity of the PHQ-15, as I identified an additional 16 papers published between June 2012 and February 2014 that used the PHQ-15 to measure severity of somatic symptoms for research. I also found that the PHQ-15 is used in clinical practice. For example the NHS programme 'Improving Access To Psychological Therapies' (IAPT) recommends that the PHQ-15 is used to assist clinical judgements in identifying patients with unexplained physical symptoms (UPS), alongside other tools that are being developed for commissioning purposes (Commissioning Support for London,2011).

High symptom severity according to the PHQ-15, with a minimum of eight symptoms and a score above fifteen is reported to likely predict clinically significant somatisation disorder (Löwe et al., 2008). Although I did not intend to identify those meeting the criteria for somatoform disorder, this reported alignment does allow for comparison of new findings with existing studies. Many items overlap with validated somatisation screening questionnaires further increasing the utility of PHQ-15 (Kroenke and Rosmalen, 2006). It is reported to be highly correlated with clinician-rated symptom counts but is more advantageous for use as it is less resource intensive, not needing clinician evaluation (Kocalevent et al., 2013; Rost et al., 2006; Interian et al., 2006). However, as the PHQ-15 does not identify the nature or cause of the symptoms, in my screening questionnaire, I included an additional question to enquire whether the participant knew of an explanation or diagnosis for their symptoms, in order to determine whether or not their somatic symptoms were unexplained. The PHQ-15 was also included in the baseline

questionnaire to determine whether the symptom score had changed following the initial screening questionnaire and chosen as the primary outcome measure for the follow-up questionnaire.

4.9.2 Secondary outcomes

4.9.2.1 Quality of life

Health related quality of life relating to functioning and well-being was measured using the validated, self-report short-form questionnaire (SF-12) (Ware et al., 1996). Based on the widely used 36 question SF-36 survey (Ware and Sherbourne, 1992), the shorter SF-12 contains only twelve questions enquiring about the impact of symptoms on the participants' lives in physical, mental and social dimensions. The scores can be coded and analysed to form two separate sub scales of physical and mental functioning. Correlation for the general population physical component summary (PSC) score for the SF-12 compared to the SF-36 was 0.905 and for the mental component summary (MCS) score was 0.938 (Ware et al.,1996). The SF-12 has been used in variety of research settings including in studies of UPS (McGorm et al., 2010; Burton et al.,2012) and is considered suitable for generic and disease specific health surveys (Ware et al.,1996). Test-retest (2-week) correlations of 0.86 and 0.77 were observed for the 12-item Physical Component Summary and the 12-item Mental Component, in the UK (Ware et al., 1996). It is included in both the baseline and follow-up questionnaires and is a secondary outcome measure.

4.9.2.2 Psychological well-being: Depression and Anxiety

Depression and generalised anxiety disorder were measured using the Patient Health Questionnaire depression module (PHQ-9) (Kroenke et al., 2001),and the generalised anxiety disorder assessment (GAD-7) (Spitzer et al., 2006) which are brief, reliable and validated questionnaires.

4.9.2.2.1 Depression

The PHQ-9 is the self-report version of the PRIME-MD diagnostic instruments (Kroenke et al., 2001). It has been translated into several languages and is widely used in research and routinely in clinical practice (Gilbody et al., 2007). It scores each of the nine DSM-IV criteria for depression on the extent to which these have bothered the respondent in the previous two weeks. The response categories are not at all (scored 0) several days (scored 1), more than half the days (scored 2) and nearly every day (scored 3). Scores of 5, 10, 15, and 20 are suggested to represent the cut-off points for mild, moderate, moderately severe and severe depression, respectively with a maximum possible score 27; although it can be used on a continuous scale as I have used in my study (Kroenke et al., 2010).

With increasing severity on the PHQ-9, worse functioning, greater symptom related difficulty, greater numbers of sick days and higher health care utilization have all been reported (Kroenke et al., 2010). In the original study of 6000 patients, at a cut-off point of $\geq$10 was suggested to be clinically significant; the sensitivity was found

to be 0.88 and the specificity 0.88. The internal validity was between Cronbach α 0.86 to 0.89 and re-test reliability was 0.84 (Kroenke et al., 2001). The PHQ-9 is considered to be a good diagnostic measure; a number of meta-analyses have compared the validity of the PHQ-9 to DSM-IV major depressive disorder diagnosis and find good rates of agreement between them (Gilbody et al., 2007; Wittkampf et al .,2007). Gilbody et al. (2007) combined findings from 14 studies with a total of 5,026 participants to validate the PHQ-9 against major depressive disorder; they report sensitivity of 0.80 (95% CI 0.71–0.87) and specificity of 0.92 (95% CI 0.88–0.95) (Gilbody et al., 2007). However, it has been suggested that a higher cut-off of ≥12 may improve the accuracy without compromising on specificity (Gilbody et al., 2007b; Kendrick et al., 2009).

4.9.2.2.2 Anxiety

The GAD-7 is a seven item scale was used to screen and measure anxiety and is similar to the PHQ-9 in terms of its response categories. It is considered to be a measure of severity; the use of a diagnostic interview is recommended to confirm a clinical disorder (Kroenke et al., 2010). Increasing scores on the GAD-7 are also associated with multiple domains of functional impairment (Spitzer et al., 2006). GAD-7 anxiety severity is calculated by assigning scores of 0, 1, 2, and 3, to the response categories of not at all, several days, more than half the days and nearly every day respectively and the total score for the seven items ranges from 0 to 21. Scores of 5, 10, and 15 represent cut-off points for mild, moderate, and severe

anxiety, respectively and once again as with the PHQ-9, it is used as a continuous measure in this study. The GAD-7 has been shown to be a valid tool for identifying patients with generalised anxiety disorder with a sensitivity of 89% and specificity of 82% at a cut-off point of ≥10 (Spitzer et al., 2006). Although developed much later than the PHQ-15 and PHQ-9, it is increasingly used in clinical practice and in research. It has shown to have good convergent validity to more established anxiety scales such as the Beck Anxiety Inventory and anxiety subscale of the symptom checklist (SCL-90) (Spitzer et al, 2006)

4.9.2.3 Health service use data collection from electronic patient medical records

Information about health care use was extracted from the participant's general practice records. Eight of the practices in the study used the electronic patient record software EMIS whilst one used InPS vision. I identified primary health care contacts as either face-to-face to telephone meetings with doctors, nurses, health care assistants or out of hours GP services. I also recorded secondary health care contacts which were secondary care referrals, mental health referrals and A&E access. I also recorded psychotropic drug prescriptions specifically antidepressants, anti-hypnotics and antipsychotics. Data were collected from twelve months prior to baseline data collection and during the period of study participation.

4.9.3 Potential prognostic factors to consider

4.9.3.1 Management of symptoms

This section included questions on management of UPS, in terms of who/what sources of support they chose to turn to and what strategies they may have used based on work by Walters and colleagues, (2008), on help seeking in populations with sub-clinical emotional disorders and emotional distress.

4.9.3.2 Social functioning

The Work and Social Adjustment Scale (WSAS) was used to measure functional impairment relating to work and social aspects (Marks, 1986). It is a short, reliable, valid measure consisting of five questions with nine categories for each response, from zero indicating no impairment at all to a score of eight indicating very severe impairment. There is a total possible score range of 40 (Mundt et al., 2002). A WSAS score above 20 suggests moderately severe or worse functional impairment, scores between 10 and 20 are associated with significant functional impairment but less severe clinical symptomatology and scores below 10 are associated with subclinical populations. It has been found to have strong psychometric properties in populations with depression, anxiety and alcohol misuse disorders with good internal consistency and positive correlation with depressive symptom severity (Mundt et al., 2002). It has been used in studies of patients with functional and UPS (Deale et al., 1997; Cella et al., 2011). A validation study of two groups of patients with chronic fatigue syndrome (CFS), one enrolled in a large randomized controlled

trial (cohort 1) and the other accessing a clinical service (cohort 2) resulted in comparable findings, supporting its acceptability as a measure of disability in both research and in everyday clinical contexts. Lower scores on the WSAS were modestly associated with better physical functioning (Cella et al.,2011).

4.9.3.3 Self-efficacy

Increasingly, self-efficacy is considered as a favourable characteristic in adapting to chronic illness. It is positively associated with quality of life, activities of daily living, social and family functioning, well-being and self-care (Scholz et al., 2002). The General Self-Efficacy (GSE) questionnaire enquires about the sense of perceived self-efficacy, optimism and self-belief with regard to personal competence to deal effectively with a variety of difficult tasks, adversity or stressful situations (Schwarzer and Jerusalem, 1995). The ten item validated questionnaire has been translated into several languages (Scholz et al., 2002). Reponses are based on a four point scale on the extent of agreement to each statement with one being no agreement at all and four being considerable agreement. The final composite score ranges from 10 to 40. It has been shown to correlate with positively with self-esteem and optimism and negatively with anxiety, depression, stress, health complaints and physical symptoms. In samples from 23 nations, Cronbach's alpha ranged from 0.76 to 0.90 with a majority greater than 0.80 (Scholz et al., 2002).

4.9.3.4 Life events

The 12 item 'list of threatening experiences' questionnaire (LTE-Q) (Brugha et al., 1985) was used to obtain information about difficult and stressful life events experienced relating to illness, death, relationships, job or financial crisis in the previous six months. It is a short and reliable questionnaire that has been recommended for use in studies relating to psychiatry, psychology and social studies, in which intervening variables such as social support, coping, and cognitive variables are of interest. The responses are binary for whether an event has happened or not and the number of events that the respondent considers are still affecting them are counted. The questionnaire does not have a cut-off point and is scored on the basis that the more life events the adult has been through, the higher the score and therefore the greater the likelihood of some form of longer term impact. In a recent study eight questions from the LTE-Q were used to determine association of stressful life events with unexplained chronic syndromes (Aggarwal et al., 2006). This study found that having one stressful life event in the previous six months was associated with having increased odds of having unexplained chronic symptoms (OR 1.5 (95% CI 1.2 to 1.9)) compared to those who had not experienced any, whilst those who had experienced between two and eight adverse events in the previous six months participants were 2.5 times (95% CI 2.0 to 3.0) more likely to be included in the group.

4.9.3.5 Panic

The PHQ- PD (Spitzer.,1999) was used to screen for panic disorder. The panic questionnaire includes an initial question that screens out those who have not experienced panic or an anxiety attack. This is followed by 14 questions with two possible responses either 'no' (0 points) and 'yes' (1 point) to be answered only by those who had experienced a recent anxiety or panic attack in the previous two weeks (Spitzer et al., 1999). The original algorithm requires the first four questions to be answered as yes, along with four or more of the following eleven questions. Due to the fairly low prevalence of panic disorder Wittkampf et al. (2011) suggests the use only the initial question in primary care; it is reported to have high sensitivity (0.71, 95% CI 0.54–0.83). For the purpose of this study, I follow this suggestion and use only the initial question in the analyses.

4.9.3.6 Childhood experiences

As discussed in section 1.6.5, studies have found that experience of illness in the family during childhood may impact on unexplained symptoms (Hotopf, 2002; Stuart and Noyes, 1999; Essau, 2007; Craig et al 1993). It has been suggested that growing up in an environment with an ill parent and exposure to help-seeking may develop a pattern of illness behaviour which focuses more on somatic symptoms and learn to use symptoms as a way in which to receive more sympathy, care and support (Mumford et al 1991; Craig et al 1993). For my study, I developed two questions that asked about family history of long-term physical and mental health

with two open ended question for participants to explain the nature of the condition and which family member was affected.

Negative life events and trauma during childhood relating specifically to abuse and particularly to sexual or physical abuse have been suggested to impact on later somatization (Stuart and Noyes, 1999; Essau, 2007). Due to the long and sensitive nature of many questionnaires on trauma and abuse that are commonly used, I included only two short screening questions in the baseline questionnaire booklet. In order to build up to the sensitive question on abuse I first include a more general question that asked whether the participant had experienced any type of trauma whilst growing up and to clarify what this was. This was followed by a question about whether they had experienced any type of abuse as a child. Options for response were based on the Childhood Trauma Interview (Bernstien & Fink,1998) and included five options from never true to very often true. An option to clarify whether abuse was physical, sexual or emotional was also included. It was also emphasised that respondents could skip this question if they did not wish to answer it.

4.9.3.7 Sociodemographic information

I included sociodemographic questions on gender, age (date of birth), ethnicity, marital status, employment, perception of financial well-being, educational level and availability of social support. For ethnicity, participants were given a list of seventeen options, under five broader categories adapted from the census options

(Ethnic group, ONS). For employment options included being in paid employment, retired, unable to work due to poor health, studying, looking after family, volunteering or doing 'something else' with an option to clarify what this was.

To determine financial situation, I used a question that enquired about how well they were managing financially with options ranging from living very comfortably to finding it very difficult, on a Likert scale (Weich and Lewis, 1998). An additional question was included on perceived social support, which asked whether the participant had someone they could turn to for emotional or practical support and who this person/ people were. I used postcodes of study participants to generate Index of Multiple Deprivation (IMD) scores using GeoConvert (Geoconvert); this online tool maps postcode to IMD, 2007 scores (Noble et al., 2008). IMD provides an indication of relative socioeconomic deprivation localised to the Lower layer Super Output Area and is based on the English Indices of Deprivation and higher scores indicate higher deprivation (Noble et al., 2008).

4.10 Analysis

4.10.1 Data entry, cleaning and verification

In order to ensure consistent coding and entering of data at each stage of the study, I developed a coding booklet. I carried out the majority of data entry of anonymised data with the assistance of research assistants. Data from screening questionnaires, baseline

and follow-up questionnaire were entered into separate SPSS databases. For each stage of data entry, between 10-25% of data was randomly selected and double entered. The two versions were compared and data entry error rate was calculated for inconsistencies identified. An error rate of up to 1% was considered acceptable. For each variable I checked for outliers, tabulations and histograms. Any values that lay outside the permitted ranges were cross checked against original data and corrected as appropriate.

4.10.2 Sample size calculation

Sample size calculations were made at the start of the study to ensure that it was adequately powered to be able to detect a difference, if one exists. Traditionally for most studies, power calculations are carried out with consideration to confidence intervals (error rate), confidence level (significance) and standard deviation (variance in response). However, where studies use regression analyses or are conducted for the development of prognostic models, a rule of thumb is commonly used, that provided the primary outcome is continuous, for every independent predictor variable at least ten outcome events or cases should be included (Harrell et al., 1996; Mallet et al., 2010). This rule thumb is based on estimates of the stability of coefficient estimates for individual variables in the prognostic models (Mallet et al., 2010). Variables that contain multiple discreet options for responses (more than two responses) are considered as multiple variables and continuous responses are considered as single variables (Harrell et al., 1996).

Sample size was calculated based on the assumption that a maximum of 23 variables would be included in the model based on existing literature (Chapter 1 and Chapter 2) which also informed the development of the baseline questionnaires as discussed in 4.6 and 4.7. I decided a priori, that the primary outcome would be treated as a continuous measure, as it allows for valid analyses to be conducted with smaller sample sizes and has greater sensitivity than categorical outcomes (Mallett et al.,2010). Hence, using the rule of thumb described, I calculated that at follow-up it would be necessary for 230 participants with UPS to be present, if the model were to contain 23 variables. It was assumed that 20% would be lost to follow-up, which indicated that 287 participants would need to be recruited to the longitudinal study. Table 4.2 shows the potential predictors that will be included in the models a priori.

Table 4.2 Potential predictors that may be included in the regression models

Explanatory variables at baseline	Somatic symptom severity	Quality of life	Depression	Anxiety	Health service use
Somatic symptom severity	x	x	x	x	x
Duration of symptoms	x	x	x	x	x
Quality of life	x	x	x	x	x
Management of symptoms	x	x	x	x	x
Social functioning	x	x	x	x	x
Self-efficacy	x	x	x	x	x
Stressful life events	x	x	x	x	x
Depression	x	x	x	x	x
Panic	x	x	x	x	x
Anxiety	x	x	x	x	x
Family health during childhood	x	x	x	x	x
Traumatic experiences in childhood	x	x	x	x	x
Age	x	x	x	x	x
Sex	x	x	x	x	x
Education	x	x	x	x	x
Employment	x	x	x	x	x
Financial situation	x	x	x	x	x
Perceived social support	x	x	x	x	x
GP practice where participant was recruited	x	x	x	x	x

4.10.3 Statistical analysis

I used Stata version 12 (StataCorp, 2011) to conduct my analyses. First, for each stage of the study I produced histograms of continuous variables to visualise the data in terms of dispersion, centring and shape to check for normality (Altman, 1990). This enabled me to determine whether descriptive data should be presented as means with standard deviations (SD) or medians with interquartile range (IQR). Categorical data were explored using frequencies and percentages. I used regression analysis to explore the univariable association of baseline variables with outcome variables. This was followed by multivariable regression modelling to identify potential factors associated with outcome variables (Altman,1990). The specific methods that were in each stage of the study are described below.

4.10.3.1 Screening data

At the screening stage, somatic symptom scores and basic characteristics such as age, sex and presence of any explanations or diagnoses were summarised. Responder self-reports of explanations for symptoms were categorised into unexplained, fully explained by physical diagnoses, partially explained by a physical diagnosis (e.g. diabetes, arthritis and medicine side effects), psychological explanations (e.g. stress, anxiety or depression) and functional diagnoses (e.g. irritable bowel syndrome or chronic fatigue). Characteristics of responders were also explored stratified by symptom severity according to the previously discussed

cut-offs 0-4 (minimal severity), 5-9 (low severity), 10-14 (moderate severity) and 15≥ high severity. Results are discussed in Chapter 5.

4.10.3.2 Baseline data

At baseline, I compared the characteristics of those who returned baseline questionnaires to those who did not, using data from the screening questionnaire. This included basic characteristics such as age, sex and any explanations or diagnoses (or lack of). I then used summary statistics to describe baseline characteristics of the cohort study participants overall and stratified by gender. Results are discussed in Chapter 6.

4.10.3.3 Longitudinal study

4.10.3.3.1 Descriptive, univariable analyses and conceptual group analysis

I compared the baseline characteristics of those of those who returned follow-up questionnaires to those who did not, using summary statistics. I then explored the characteristics of those who returned questionnaires overall and stratified by gender. Univariable analyses was conducted with each of the baseline variables and the primary outcome measure somatic symptoms at six month follow-up, as well as the secondary outcome variables physical health functioning, mental health functioning, depression, anxiety and primary health care contact. In addition to exploring the baseline variables that I discussed in section 4.8.1, I also conducted

univariable analysis with practice as an independent variable. The residuals for continuous outcomes were checked for normality and all were found to be approximately normally distributed; hence, there was no need to transform any of the data.

This step was followed by conceptual group modelling, a method used to reduce number of variables included in the final multivariable analysis (Marston et al., 2007). Multivariable analyses were conducted using variables that are significantly associated with the outcome variables ($p<0.05$) and theoretically considered to be measuring similar characteristics amongst the study population. For example a conceptual group consisted of socioeconomic factors; education level, employment status, index of multiple deprivation score, and perception of financial well-being would be placed in the same conceptual group if they were significantly associated with the outcome.

4.10.3.3.2 Multivariable regression modelling

Finally, variables that showed strong significant associations ($p <0.05$) in the univariable and/or conceptual group analysis were included in the multivariable regression models (Mallet et al.,2010). I also chose to include gender and age in all multiple regression models a priori. Based on statistical reasoning, each model was also adjusted for the baseline value of the outcome variable of interest.

These models were used to determine which baseline factors were associated with the primary and/or secondary outcomes at six months follow-up. The decision making process on variables to include in modelling cannot be based on p-value alone but must identifying a meaningful difference on outcomes (Mallet et al.,2010; Lewis and Ward, 2013). The theoretical basis for the inclusion of variables in the modelling process for this study was based on prior evidence from literature and clinical judgement. All outcomes were continuous measures and so I conducted multivariable linear regression (Altman,1990). Backwards elimination was used; all identified variables included in the model and then taken out one by one starting with the one with the highest p-value and continuing until only variables with p-value of <0.05 remained (and/ or those included in the model a priori).

4.10.4 Missing data

Specific ways of handling missing data have been prescribed in several of the validated questionnaires and instruments used. For example, for the PHQ-15, PHQ-9 and GAD-7 several methods have been suggested including a 'conservative approach' to count missing responses as implying that the respondent was not bothered by the item (Kroenke et al., 2010). This method was developed based on the assumption that missing data on each of these questionnaires are generally small and less than 5% of participants (Kroenke et al., 2010). Any missing data for the questionnaires mentioned were entered as zero from the stage of data entry rather than as missing. Table 4.3 shows a summary of how missing data has been

handled. However, missing data was minimal and accounted for less than 0.5% of data at each time point. The largest amount of missing data were found in health service contacts and accounted for 2.6% of data. This included a number of participants had joined the practice less than a year before study participation or left the practice before the end of the data collection period. Another four people did not wish their medical records to be accessed.

Table 4.3 Methods of dealing with missing data on variables include in the study

Questions and instruments used	Methods of dealing with missing data	Source
Somatic symptom severity (PHQ-15)	Missing data treated as respondent did not experience that symptom and therefore scored as 'not bothered at all'	Kroenke et al., 2010
Duration of symptoms	If participant gave different dates for different symptoms, the duration for the longest bothersome symptom was included. If no data was available, it was left as missing and not imputed.	In consultation with clinical and statistics supervisors
Quality of life (SF-12)	Missing Score Estimator (also referred to as Maximum Data Recovery) feature is included in the software used. It applies a value to a missing item if at least one of the items in the scale has valid data. A scale receives a missing score only if all the items in the scale are missing. Physical and mental health component summary scores are calculated when at least seven of the eight profile scales have valid data. For PCS this must include PF and for MCS it must include MF.	QualityMetric Incorporated, 2012
Management of symptoms	If not ticked, it was assumed that specific source of support was not used.	In consultation with clinical and statistics and supervisors
Work and Social functioning (WSAS)	If a respondent selected non-applicable for question 1, or if one value is missing, then total scores were pro-rated from non-missing items.	Department of Health,2011a
General Self-Efficacy (GSE)	As long as no more than three items on the 10 item scale were missing, missing values were imputed with the mean scores of the total, from completed items as suggested by the developers of the questionnaire.	Schwarzer, 2005
List of threatening experiences (LTE-Q)	Questions focused on whether the respondent experienced the event in the previous six months, if incomplete it was assume that they did not experience that particular event	In consultation with clinical and statistics and supervisors
Depression (PHQ-9)	Missing data treated as respondent did not experience that symptom and therefore scored as 'not bothered at all'	Kroenke et al., 2010
Panic (PHQ-PD)	Missing data treated as respondent did not experience that symptom and therefore scored as 'not bothered at all'	Kroenke et al., 2010
Anxiety (GAD-7)	Missing data treated as respondent did not experience that symptom and therefore scored as 'not bothered at all'	Kroenke et al., 2010
Family health during childhood	If incomplete, left as missing, not imputed	In consultation with statistician and

		supervisors
Traumatic experiences in childhood	If incomplete, left as missing, not imputed	In consultation with statistician and supervisors
Age	Determine age from screening questionnaire or from medical records if participant had provided consent to access these	In consultation with statistician and supervisors
Sex	Refer screening questionnaire or if consent given to access medical records.	In consultation with statistician and supervisors
Education	If incomplete, left as missing, not imputed	In consultation with statistician and supervisors
Employment	If incomplete, left as missing, not imputed	In consultation with statistician and supervisors
Financial situation	If incomplete, left as missing, not imputed	In consultation with statistician and supervisors
Perceived social support	If incomplete. left as missing, not imputed	In consultation with statistician and supervisors

4.11 Summary

In this chapter, I have detailed the study design, described recruitment of participants, variables included in the questionnaires used and finally the analysis. In the next chapter, I present the results from the screening stage (see Chapter 5), followed by results of the main cohort study (Chapter 6 and Chapter 7). My findings have been presented at a number of national conferences and a paper for publication is in preparation (see Appendix 5). In Chapter 8, I draw together the findings, by comparing them to existing literature, discuss the strengths and limitations of my study, implications and areas for future research before I make my final conclusions.

Chapter 5 : **Results of screening stage**

5.0 Chapter overview

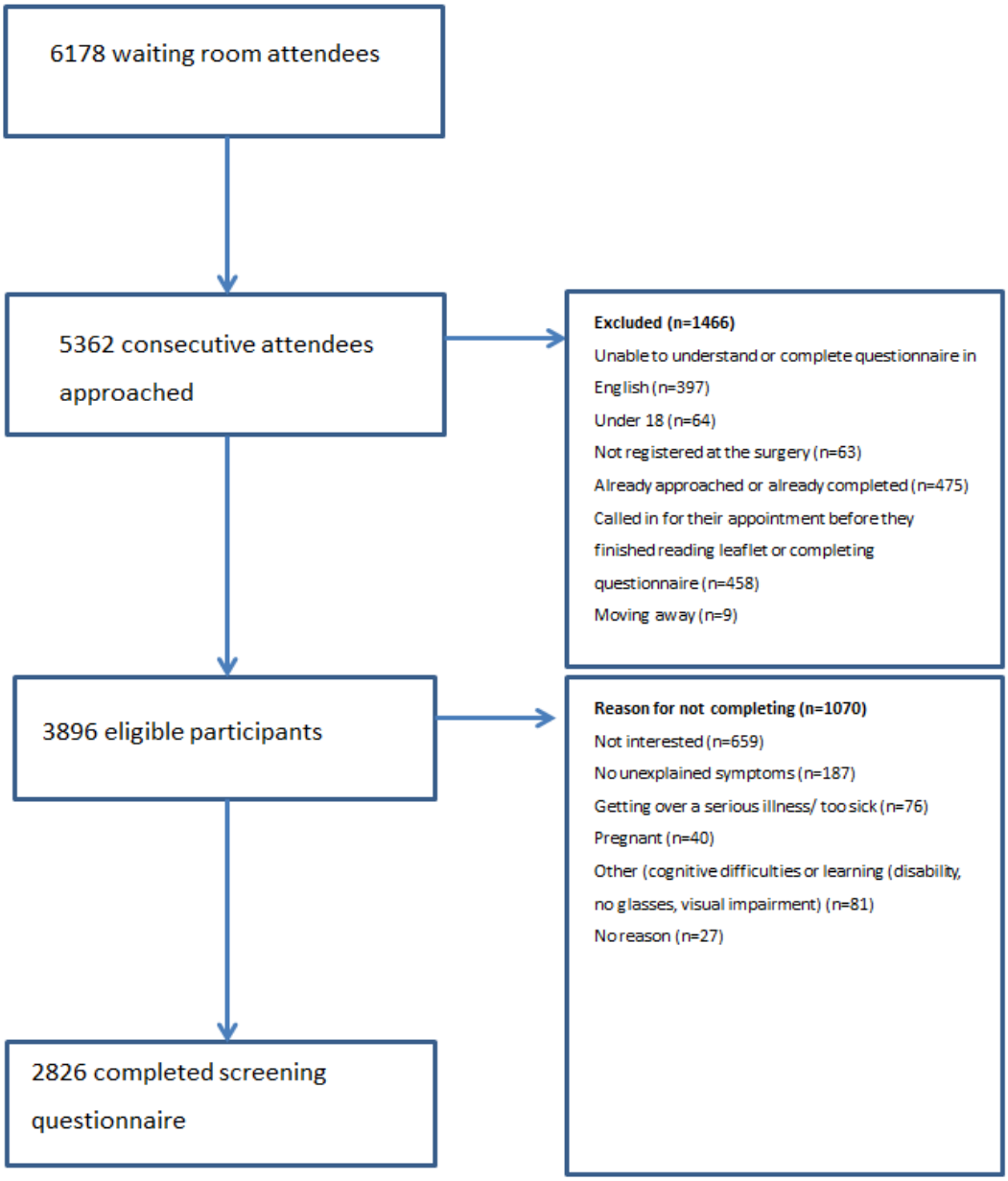
In this chapter I report results of the screening stage of the study, conducted with the main aim to identifying those who would be eligible for the longitudinal study. First, I present characteristics of the general practices where screening took place. Second, I report the characteristics of those who completed the screening questionnaires overall, by gender and symptom severity (minimal, low, moderate and high).

5.1 Results of recruitment of general practices and participants

Twenty practices from urban and suburban areas of north London were contacted; one replied to say that they were not interested, nine practices took part in the study and I received no response from the others (see section 4.2). The list sizes of these practices varied from 5122 to 17,494. Index of Multiple Deprivation score (IMD) for the practices ranged from 12 (least deprived) to 46.8 (most deprived). The number of doctors conducting surgeries during recruitment periods ranged from 2 to 10 and numbers of nurse or health care assistant clinics ranged from 0 to 6.

In the nine practices where screening was conducted, 5,614 consecutive attenders were approached and invited to complete the screening questionnaire (see Section 4.6 for details on recruitment). A note was kept of the numbers who were in attendance in the waiting rooms; in total I was able to approach 5,362/6,178 (87%) of attenders. Of these 524 were excluded, as they were unable to understand or complete the questionnaire in English, were under 18 years age or not registered at the practice. A further 458 attenders were called in for their appointment, before having a chance to finish reading the leaflet and/or complete the questionnaire and 475 reported having already received information on the study or completing the questionnaire, on a previous occasion. Out of those who were approached 1,070 declined to participate, including 187 who said the reason for this was that they had no unexplained symptoms. Therefore, 2,826/3,896 (73%) of potentially eligible attenders completed the questionnaire. Figure 5.1 shows detail on participant identification and screening, including numbers excluded or ineligible to take part in this stage of the study.

Figure 5.1 Flow diagram of entry and exclusion at screening phase.



5.2 Descriptive findings of the screening data overall

Over two-thirds of respondents who completed the screening questionnaire were female (n=1,931/2,826, 68%) and age distribution was right skewed with a median age of 42 years with interquartile range (IQR) 30 to 55 (see Table 5.1). Those who completed the questionnaires had a median PHQ-15 symptom score of 7 (IQR 4, 11), which is in the low symptom severity range on the PHQ-15. Most had at least one unexplained symptom (2,425/2,826 (86%)) and close to half had symptoms that they reported as not having any explanation or diagnosis (1,393/2,826 (49%)). Just under half of those screened provided some explanation for their symptoms (1,248/2,826, (44%)), which were categorised as shown in table 5.1. These included functional diagnoses (100/2,826 (4%)); psychological explanations (187/2,826 (7%)) and physical explanations or diagnoses (921/2,826 (33%)). When the natures of symptom experienced by the participants were explored (Table 5.2) it was found that there was a good spread of most of the 15 symptoms. Back pain (10%), pain in arms and legs (10%) and feeling tired or having little energy (12%) were the most frequently reported but more than two thirds had experienced some of the other 12 symptoms.

When characteristics of the cohort were stratified by gender, there were few differences between males and females on types of explanations given for symptoms or percentages who were consulting about their symptoms that day. The main difference between males and females was age and symptom severity. Female

(median 40 years IQR 30, 55) were younger than males (median 46 years IQR 32, 61), and had greater median symptom scores (females 8 IQR 4, 12 vs males 5 IQR 3, 9). In the next section, I provide descriptive results on the participants, stratified by symptom severity.

Table 5.1 Characteristics of all waiting room attenders who completed the screening questionnaire by total cohort and stratified by symptom severity. Results displayed as N (%) unless otherwise indicated

	Total N=2826	PHQ-15 0-4 N=891	PHQ-15 5-9 N=963	PHQ-15 10-14 N=595	PHQ-15 ≥15 N=377
Gender					
Males	873 (31%)	375 (42%)	293 (30%)	133 (22%)	72 (19%)
Female	1931 (68%)	505 (57%)	665 (69%)	459 (77%)	302 (80%)
Missing	22 (1%)	11 (1%)	5 (1%)	3 (1%)	3 (1%)
Age[†]	42 (30,55)	43 (31,59)	40 (29,55)	43 (31,59)	43 (33,53)
Consulting about symptoms today					
Yes	1073 (38%)	200 (22%)	360 (37%)	287 (48%)	226 (60%)
No	1321 (47%)	548 (62%)	471 (49%)	212 (37%)	90 (24%)
Missing	432 (15%)	143 (16%)	132 (14%)	96 (16%)	61 (16%)
One or more unexplained symptoms	2425 (86%)	628 (71%)	890 (92%)	558 (94%)	349 (93%)
Fully unexplained (no explanations for any of their symptoms)	1393 (49%)	463 (52%)	496 (52%)	286 (48%)	148 (39%)
Fully explained (explanations for all symptoms)	40 (1%)	33(4%)	4 (0%)	1 (0%)	2 (1%)
Functional diagnoses	100 (4%)	11 (1%)	27 (3%)	31 (5%)	31 (8%)
Psychological explanations or mental health diagnoses	187 (7%)	17 (2%)	69 (7%)	50 (8%)	51 (14%)
Physical explanations or health diagnoses (partial explanations or diagnosis for symptoms)	921 (33%)	163 (18%)	350 (36%)	236 (40%)	172 (46%)

[†] Median (IQR)

Table 5.2. Symptoms reported by waiting room attenders who completed the screening questionnaire by total cohort and stratified by gender. Results displayed as N(%).

Symptom	Total* N=2826	Male N=873	Female N=1,931
Stomach Pain	953 (6%)	241 (6%)	702 (6%)
Back Pain	1596 (10%)	442 (11%)	1141 (10%)
Pain in arms, legs or joints (e.g. hips, knees)	1676 (10%)	508 (12%)	1155 (10%)
Menstrual cramps or other problems with your periods [women only]	734 (5%)	9 (0%)	721 (6%)
Headache	1352 (8%)	325 (8%)	1017 (9%)
Chest pain	691 (4%)	221 (5%)	463 (4%)
Dizziness	951 (6%)	254 (6%)	691 (6%)
Fainting spells	317 (2%)	76 (2%)	239 (2%)
Feeling your heart pound or race	903 (6%)	237 (6%)	660 (6%)
Shortness of breath	975 (6%)	290 (7%)	677 (6%)
Pain or problems during sexual intercourse	367 (2%)	91 (2%)	274 (2%)
Constipation, loose bowels or diarrhea	1023 (6%)	266 (6%)	752 (6%)
Nausea, gas or indigestion	1056 (7%)	265 (6%)	784 (7%)
Feeling tired or having little energy	1939 (12%)	506 (12%)	1421 (12%)
Trouble sleeping	1485 (9%)	410 (10%)	1067 (9%)
Total symptoms reported	16018 (100%)	4141 (100%)	11764 (100%)

*Gender information missing for N=22

5.3 Comparing characteristics stratified by symptom severity

The characteristics of primary care attenders were stratified by symptom severity (see Table 5.1). Scores were stratified by PHQ-15 groups where 0-4 (891/2,826) are considered to have minimal severity, 5-9 (963/2,826) is considered to be representative of low symptom severity, 10-14 (595/2,826) of moderate severity and ≥15 (377/2,826) high severity. Scores of ≥5 are considered to represent significant symptom severity; two thirds (1935/2,826) of all those who completed the screening questionnaires scored ≥5 (see Table 5.1). Of those who scored ≥5, the half experienced low symptom severity (963/1,935, 50%) with scores between 5-9, 595 /1935 (31%) reported scores of 10-14 and 377/1,935 (19%) reported scores ≥15. Generally, the percentage of women increased as symptom severity increased but the median age of responders within each of the severity groups were similar (see Table 5.1).

All severity groups consisted of similarly high percentages who had one or more unexplained symptom (PHQ-15 5-9, 92%; PHQ-15 10-14, 94%; PHQ-15 15≥, 93%), except for the minimal severity group where fewer had at least one UPS as might be expected (PHQ-15 0-4, 71%). Similar percentages of responders whose symptoms were within the minimal and low symptom severity groups reported that their symptoms were fully unexplained (PHQ-15 0-4, 52%; and PHQ-15 5-9, 52%). However, as symptom severity increased, percentages of responders with fully

unexplained symptoms decreased (PHQ-15 10-14, 48%; and PHQ-15 ≥15, 39%) and those with functional diagnosis, psychological or partial explanations for their symptoms increased (see Table 5.1). The percentage of screening questionnaire completers who reported consulting about their symptoms that day also increased as symptom severity increased. Each severity group was explored stratified by gender; there was little variability between males and females within each of the severity groups, other than with regards to age, which consistently showed that males were older than females.

5.4 Participants considered eligible for next stage of study

Those who scored at five or more on the PHQ-15, after any explanations for their symptoms were taken to account were considered eligible for the cohort study (see section 4.7). A total of 1,632/2,826 (58%) were considered eligible for the next stage; 1,196/2,826 (42%) were eligible and also expressed interest in being contacted regarding the next stage of the study. The characteristics of those who took part in the longitudinal study will be discussed in further detail in Chapter 6.

5.5 Summary

This chapter presents findings from the first stage of the study, where consecutive waiting room attenders were invited to complete a screening questionnaire regarding their symptoms. A high proportion of those who were present in the waiting room were approached (91%) and a high proportion completed the

questionnaires (73%). The screening questionnaire completers had a median symptom severity score of 7 (IQR 4, 11); over two-thirds were female and median age was close to 40 years. Females were younger than males and had higher symptom severity.

When stratified by symptom severity, percentage of females in each group increased, as symptom severity increased. The majority of primary care attenders had at least one unexplained symptoms and close to half had symptoms that they reported as having no explanation or diagnoses (fully unexplained). Close to half of those screened also provided some explanations for their symptoms, which were categorised into partial physical, mental health or functional diagnoses. As symptom severity increased, the percentages of those who had mixed symptoms with partial physical explanations increased. Just over a third of all those screened were consulting about their symptoms that day; percentages of those who were consulting about their symptoms also increased with increasing symptom severity. Of all those considered eligible, nearly three-quarters agreed to be contacted for the longitudinal study. In the following chapter (see Chapter 6), I present the results of those took part in my cohort study.

Chapter 6 : **Baseline results of cohort study**

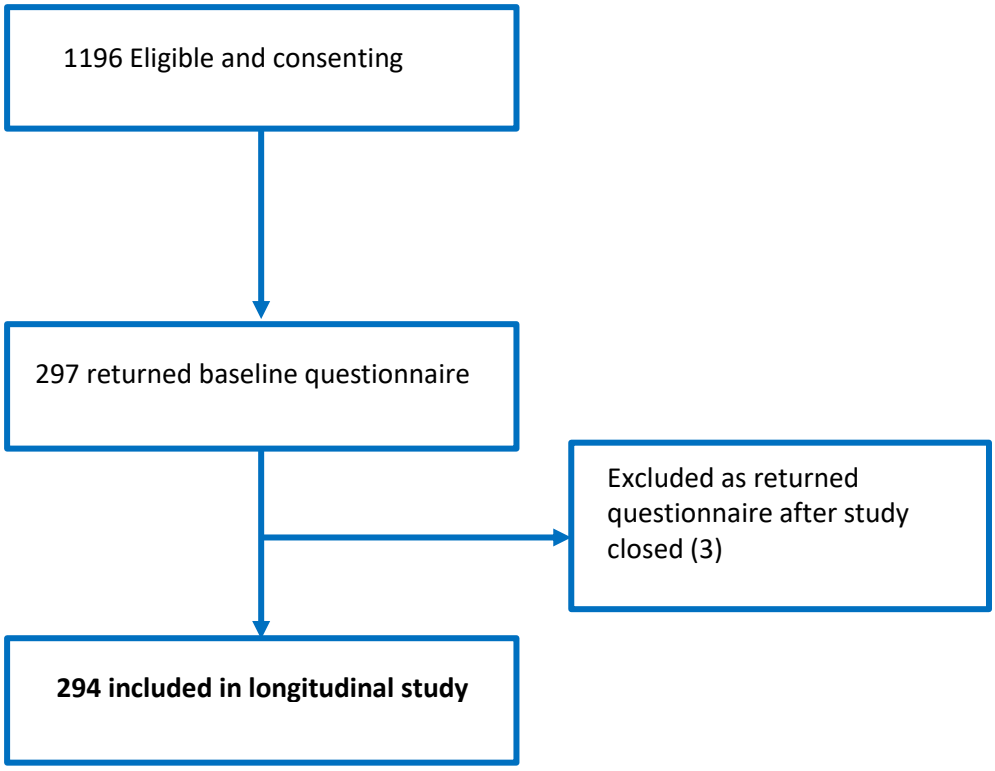
6.0 Chapter overview

In this chapter, I present the findings of my cohort study. First, I describe the characteristics of the study participants, compared to those who were eligible and expressed interest in the longitudinal study but who did not return questionnaires. This is followed by a detailed description of the study cohort with respect to the baseline sociodemographic and clinical characteristics, and the frequency of primary and secondary health care contact. I explore the cohort characteristics overall and by gender.

6.1 The longitudinal study cohort

In total, 301 participants returned questionnaires. Questionnaires were inadvertently sent to four respondents from the screening stage that were later confirmed as ineligible and removed from the longitudinal study cohort (not shown in Figure 6.1). Three of the returned questionnaires were excluded as they were received after the study closed (see Figure 6.1). The final longitudinal study sample consisted of 294/1,196 participants; this was 25% of those eligible and consenting to take part in the study.

Figure 6.1 Shows number of those: 1) eligible and consenting to be contacted; 2) that returned the baseline questionnaires; and 3) were included in the longitudinal study.



6.2 Characteristics of the study cohort vs non-responders

The study cohort was fairly similar to non-responders on all key variables including age, symptom severity, and explanations of existing diagnoses provided for symptoms (completely unexplained, partially explained by physical symptoms, functional and mental health diagnosis). Suggesting that those who returned the questionnaires, were representative in their characteristics of those all who were eligible and consented to be contacted, but did not return the questionnaires (see Table 6.1). Female study participants and non-responders were comparable on all

items explored (see Table 6.1). Males who responded were older than those who did not; median age of responders was 53 years compared to non-responders 43 years. Amongst males, a greater percentage of responders had partially explained physical symptoms (49%) compared to non-responders (29%); and a greater percentage of non-responders had completely unexplained symptoms (63%) compared to responders (40%). One can speculate that some of those who did not respond to the baseline questionnaire may have received an explanation for their symptoms following the initial visit to the doctor. Others may have been waiting for their test results or follow-up appointments and therefore felt that their symptoms were not yet unexplained and hence chose not to return the questionnaire. There may also have been a proportion of people whose symptoms subsided without the need for further investigation, tests or receiving a diagnosis. All these possibilities would suggest that those responding were perhaps most likely to be more troubled by their problems that non-responders.

In the next section, the study cohort will be described in further detail using data collected at baseline.

Table 6.1 Characteristics of study responders vs non-responders. Results displayed as: N (%) unless otherwise specified.

	Cohort study participants			Non-responders		
	Total N=294	Male N= 63 (21%)	Female N=231 (79%)	Total N=902*	Male N=225 (25%)	Female N=676 (75%)
Age (years) †	44 (32,57)	53 (36,66)	41 (31,53)	40 (30,52)	43 (30,55)	39 (30,51)
Symptom severity (PHQ-15 score)†	11 (8,14)	9 (7,13)	11 (8,14)	10 (7,17)	9 (7,12)	11 (8,14)
Consulting about symptoms today	150 (51%)	24 (38%)	126 (55%)	416 (46%)	102 (45%)	314 (46%)
Fully unexplained	159 (54%)	24 (40%)	134 (58%)	518 (57%)	141 (63%)	376 (56%)
Partially explained by physical symptoms	113 (38%)	31 (49%)	82 (35%)	318 (35%)	66 (29%)	252 (37%)
Partially explained by a functional diagnoses	17 (6%)	3 (5%)	14 (6%)	45 (5%)	8 (4%)	37 (5%)
Partially explained by a mental health diagnosis	30 (10%)	8 (13%)	22 (10%)	85 (9%)	19 (8%)	67 (10%)

† Median (IQR)

* Gender missing for 1 respondent

6.3 Baseline reporting of cohort characteristics

6.3.1 Sociodemographic characteristics

The study cohort consisted of 231/294 (79%) females and the sample was ethnically diverse; less than half of the sample was white British (125/294 (43%)). Just over half the participants were married or in a long term relationship (155/294 (53%)) and most (247/294 (84%)) reported having someone they could rely on for practical or emotional support, which included family members and friends. Close to a half of participants were in paid employment (139/294 (47%)), whilst the majority of those who were not in paid employment were either retired (36/294 (12%)), unable to work due to long term sickness or disability (35/294 (12%)), or unemployed (34/294 (12%)). The cohort included 125/294 (43%) who reported having a university degree or higher. Just over half of the cohort reported their perceived financial well-being as 'doing well' (140/294 (48%)). Mean Index of Multiple Deprivation (IMD) score for the cohort was 35 (SD 13).

Baseline characteristics stratified by gender, showed female participants to be younger than males; mean age for females was 41 years compared to 53 years for males. However on all other sociodemographic variables, female and male respondents were fairly comparable (see Table 6.2).

Table 6.2 Sociodemographic characteristics for total study cohort and by gender

Results displayed as N (%) unless otherwise indicated

Sociodemographic characteristics	Total (n=294)	Male (n=63)	Female (n=231)
Age (years)†	44 (32,57)	53 (36,66)	41 (31,53)
Ethnic group			
White (combined)	215 (73%)	44 (70%)	171 (74%)
White British	*125 (43%)*	*27 (43%)*	*98 (42%)*
White Irish	*32 (11%)*	*6 (10%)*	*26 (11%)*
White other	*58 (20%)*	*11 (17%)*	*47 (20%)*
Black	14 (5%)	2 (3%)	12 (5%)
Asian	45 (15%)	14 (22%)	31 (13%)
Mixed	10 (3%)	2 (3%)	8 (3%)
Other	9 (3%)	0 (0%)	9 (4%)
Missing	1 (0%)	1 (2%)	0 (0%)
Marital status			
Married or in a long term relationship	155 (53%)	38 (60%)	117 (51%)
Widowed, separated, divorced or single	135 (46%)	25 (40%)	110 (47%)
Missing	4 (1%)	0 (0%)	4 (2%)
Employment status			
In paid employment	139 (47%)	27 (43%)	112 (48%)
Other	153 (52%)	36 (57%)	117 (51%)
Retired	*36 (12%)*	*12 (19%)*	*24 (10%)*
Unable	*35 (12%)*	*9 (14%)*	*26 (11%)*
Unemployed	*34 (12%)*	*10 (16%)*	*24 (10%)*
Looking after family or home	*25 (9%)*	*2 (3%)*	*23 (10%)*
Full time education	*15 (5%)*	*2 (3%)*	*13 (6%)*
Doing something else	*5 (2%)*	*0 (0%)*	*5 (2%)*
Voluntary work	*3 (1%)*	*1 (2%)*	*2 (1%)*
Missing	2 (1%)	0 (0%)	2 (1%)
Education			
No qualification/GCSE/A-levels or equivalent	162 (55%)	42 (67%)	120 (52%)
Bachelor's degree / Master's Degree/ PhD or equivalent	125 (43%)	20 (32%)	105 (45%)
Missing	7 (2%)	1 (2%)	6 (3%)
Financial situation			
Doing well	140 (49%)	27 (48%)	113 (43%)
Doing badly	149 (49%)	35 (51%)	114 (56%)
Missing	289 (2%)	1 (2%)	4 (2%)

Sociodemographic characteristics	Total (n=294)	Male (n=63)	Female (n=231)
IMD score*[§]	35.1 (13.1)	38.2 (13.4)	34.3 (13.0)
Missing	10 (3%)	3 (5%)	7 (3%)
Social support available			
Yes	247 (84%)	47 (75%)	200 (87%)
No	45 (15%)	16 (25%)	29 (13%)
Missing	2 (1%)	0 (0%)	2 (1%)

Results displayed as: [†] Median (IQR), [§] Mean (SD)
*IMD = Index of Multiple Deprivation score

6.3.2 Clinical characteristics

In terms of clinical characteristics (see Table 6.3), the cohort was a moderately severe group with a mean baseline symptom severity of 11.5 (SD 4.9). As shown in Figure 6.2, symptom duration was right skewed; most participants had experienced their symptoms for over a year (212/294 (72%)) with a median duration of 36 months (IQR 15, 72). Figure 6.3 shows distribution of symptoms amongst those who reported experiencing symptoms for less than one year; the majority reported experiencing symptoms for 11 months. Physical and mental health functioning was fairly low with scores of 43.8 (SD 10.6) and 39.6 (SD 11.0) based on the SF-12 on the physical and mental health component scores (out of a potential score of 100). Median depression (9 IQR 5, 14) and mean anxiety (8.9 SD 5.8) scores fell into the to moderate severity range. Amongst the cohort, 134/294 (46%) had scores $\geq$10 on the PHQ-9 for depression and 119/294 (40%) scored $\geq$10 on the GAD-7 for anxiety; 97/294 (33%) scored $\geq$10 on their respective scales for both anxiety and depression. When a cut-off of $\geq$12 on the PHQ-9 was considered this accounted for 104/294 (35%) of the cohort.

The majority (70%) had experienced one or more stressful life events, in the previous six months with a median score of 1 (IQR 0, 2). With regard to childhood experiences, just over a third (94/294 (32%)) reported experience of poor physical health in family members whilst they were growing up and around a third (93/294 (32%)) reported experiencing traumatic events. Types of trauma included illness in family members, death of loved ones, accidents, abuse and war. Close to a third (77/294 (26%)) reported experience of childhood abuse. Further enquiry was made to the type of abuse experienced, amongst the non-mutually exclusive categories of physical, sexual and emotional abuse; most reported experience of emotional abuse (59/294 (20%)).

Figure 6.2 Symptom duration at baseline in years

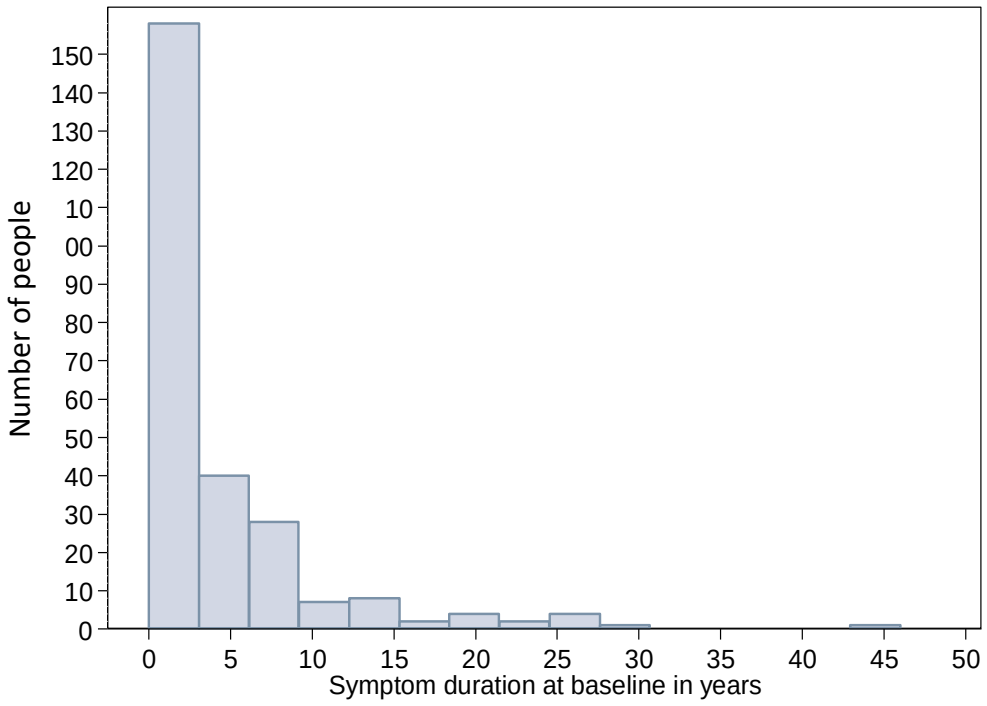
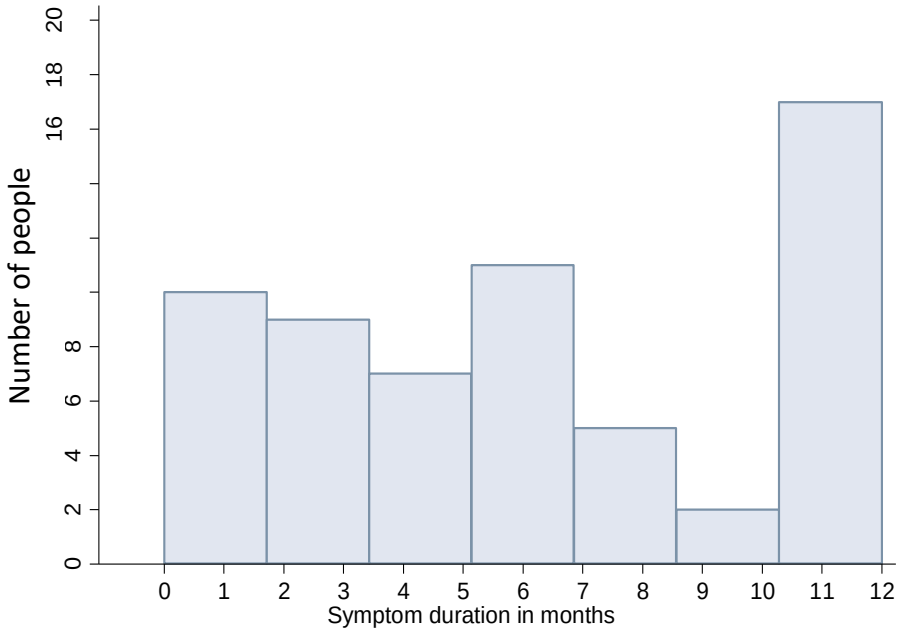


Figure 6.3 Distribution of symptom duration at baseline, amongst those experiencing symptoms for a year or less in months



Clinical variables are also shown in Table 6.3 stratified by gender. The clinical characteristics of males and females were similar. There were only a few differences with reference to experiences during childhood. For example a slightly greater percentage of males reported having experienced physical illness in family members as a child compared to females (37% vs 31% respectively), whilst more females reported having experienced mental illness in family members as a child compared to males (18% vs 8% respectively). Females also reported more sexual abuse (10% vs 3%) and experience of traumatic events (33% vs 27%).

In this chapter, the characteristics of the study cohort have been explored and reported, overall and stratified by gender. As there were few gender variations in both sociodemographic and clinical variables (see Table 6.2 and 6.3), the main analyses in this study have been conducted as a complete group without gender stratification (see Chapter 7).

Table 6.3 Clinical characteristics for total study cohort and by gender

Results displayed as N (%) unless otherwise indicated. No missing data unless otherwise indicated

Clinical characteristics	Total N=294	Male N=63	Female N=231
Baseline symptom severity (PHQ-15 score)[§]	11.5 (4.9)	11.0 (5.0)	11.7 (4.9)
Symptom duration			
<1 year	63 (21%)	14 (22%)	49 (21%)
≥1 year	212 (72%)	43 (68%)	169 (73%)
Missing	19 (6%)	0 (0%)	19 (8%)
SF-12 score*[§]			
Physical health functioning[1]	43.8 (10.6)	42.9 (10.6)	44.1 (10.6)
Mental health functioning	39.6 (11.0)	41.0 (11.1)	39.2 (11.0)
Work and social adjustment score [§]	18.7 (11.5)	19.1 (11.5)	18.5(11.5)
Missing	6	0	6
Self-efficacy score[§]	27.4 (7.4)	27.4 (7.2)	27.4 (7.4)
Missing	4	0	4
Anxiety score[§]	8.9 (5.8)	8.2 (5.8)	9.0 (5.7)
Depression score[§]	9(5,14)	9 (4,14)	9 (5,14)
Panic			
Yes	62(21%)	12 (19%)	50 (22%)
No	204(69%)	43 (68%)	161 (70%)
Missing	28(10%)	8 (13%)	20 (9%)
Stressful life events[†]	1 (0,2)	1 (1,3)	1(0,2)
Missing	3	1	2
Experienced physical illness in			

Clinical characteristics	Total N=294	Male N=63	Female N=231
family as a child			
Yes	94 (32%)	23 (37%)	71 (31%)
No	194(66%)	39 (62%)	155 (67%)
Missing	6(2%)	1 (2%)	5 (2%)
Experience mental illness in family as a child			
Yes	47(16%)	5 (8%)	42 (18%)
No	242(82%)	57 (90%)	185 (80%)
Missing	5(2%)	1 (2%)	4 (2%)
Experienced 1 or more traumatic event as child			
Yes	93(32%)	17 (27%)	76 (33%)
No	192(65%)	43 (68%)	149 (65%)
Missing	9(3%)	3 (5%)	6 (3%)
Experienced any abuse as a child			
Yes	77(26%)	16 (25%)	61 (26%)
No	204(69%)	46 (73%)	158 (68%)
Missing	13(4%)	1 (2%)	12 (5%)
Type of abuse experienced as a child**			
Physical abuse			
Yes	31(11%)	8 (13%)	23 (10%)
No	253(86%)	54 (86%)	199 (86%)
Missing	10(3%)	1 (2%)	9 (4%)
Sexual abuse			
Yes	25(9%)	2 (3%)	23 (10%)
No	259(78%)	60 (95%)	199 (86%)
Missing	10(3%)	1 (2%)	9 (4%)
Emotional abuse			
Yes	59 (20%)	13 (22%)	46 (20%)
No	225(77%)	49 (78%)	176 (76%)
Missing	10(3%)	1 (2%)	9 (4%)

*SF-12 = Short Form Health questionnaire ** Possible to tick more than one type of abuse
Results displayed as: † Median (IQR), §Mean (SD)
[1]Missing data for one male participant

6.3.3 Health service use in the year prior to study inclusion

Health care use of participants was explored for the year prior to study participation (see Table 6.4). In total, as shown the median frequency of primary care contacts was 8 (IQR 4, 12) and ranged from 1 to 54 contacts and was similar amongst males and females. Secondary care contacts were lower with median frequency of 1 (IQR 0, 2) ranging from 0 to 10. In total, 51/294 (17%) had received a prescription for antidepressants, hypnotics or antipsychotics in the year before study enrolment and there was no large difference between receipt of prescription between males and females; 14% of males received a prescription compared to 18% of females.

Table 6.4 Health service use for total study cohort and by gender in one year prior to study participation

Results are displayed as median (IQR) unless stated

Health service use	Total (n=288)	Male (n=62)	Female (n=226)
Primary health contacts *	8 (4,12)	8 (4,14)	8 (4,12)
Secondary care contacts **	1 (0,2)	1 (0,3)	1 (0,1)
Psychotropic drug prescription[¥]	51 (17%)	9 (14%)	42 (18%)

* Includes doctors, nurses, health care assistants and out of hours GP services
** Includes secondary care referrals and A&E access
[¥] Results displayed as N (%)

6.3.4 Preferences for help-seeking

The majority (217/294 (74%)) reported that they would seek help for their symptoms (see Table 6.5). Most (218/294 (74%)) reported that they would seek help from their general practitioners (GPs), the next largest source of help seeking was the internet (103/294 (30%)) followed by family (88/294 (30%)) and friends (82/294 (28%)). A few people reported turning to religious advisor (16/294 (5%)). There were no major differences in terms of preferences for sources of help seeking in terms of gender.

Table 6.5: Preferences for sources of help-seeking for total study cohort and by gender

Results displayed as N (%) unless otherwise indicated

Preferences for help-seeking	Total (N=294)	Male (n=63)	Female (n=231)
On your own	54 (18%)	14(22%)	40(17%)
Like some help	217(74%)	40(63%)	177(77%)
Unsure	21 (7%)	9(14%)	12(5%)
Missing	2(1%)	0(0%)	2(1%)
Where do you turn for help?*			
Internet	103 (35%)	20(32%)	83(36%)
Family	88(30%)	17(27%)	71(31%)
Friends	82(28%)	19(30%)	63(27%)
Religious advisor	16(5%)	3(5%)	13(6%)
GPs	218(74%)	44(70%)	174(75%)
Psychologist or counsellor	44(15%)	8(13%)	36(16%)
Complementary therapy	67(23%)	9(14%)	58(25%)
Other	33(11%)	5(8%)	28(12%)
Missing	1(0%)	0(0%)	1(0%)

*Categories are non-mutually exclusive

6.4 Summary

Data from the screening questionnaires were used to determine the representativeness of the longitudinal study cohort. Those who returned questionnaires were a representative sample of those who were eligible and consented to take part, although males who participated were older.

The baseline questionnaire data was used to explore the characteristics of the longitudinal study cohort overall and by gender. The cohort consisted of a majority of females, who were younger in age to males; as there were few other notable differences in sociodemographic and clinical variables, the main analyses in this study have been conducted as a complete group without gender stratification.

The cohort was a fairly morbid group with moderately severe somatic symptoms, depression and anxiety scores; a majority had experienced symptoms for a year or more. Most had experienced a stressful event in the previous six months. Around a third had difficult childhood experiences relating to abuse. A third reported poor health in family members and a third reported experience of traumatic events. Most accessed primary care; with a median frequency of 8 (4, 12) and preferred to turn to others, generally their GPs, for health problems. Secondary referrals were low with a median frequency of 1 (0, 2). In the next chapter, I report the characteristics of the study cohort and main results of the study.

Chapter 7 : **Follow-up results of cohort study**

7.0 Chapter overview

In this chapter, I present the main results of my study. First, I use the baseline results to compare the characteristics of the responders at follow-up to non-responders. Second, the cohort characteristics are described at follow-up. Finally, the main analyses of the study are reported with respect to factors associated with: 1) the primary outcome somatic symptom severity; and 2) the secondary outcomes (physical and mental health functioning, depression, anxiety and primary health care contact).

7.1 Characteristics of responders compared to non-responders at follow-up

At follow-up, 245/294 (83%) of questionnaires were returned. Responders and non-responders were similar in terms of gender, consisting of close to 80% females in both groups. Baseline symptom severity scores were similar between the two groups. There were only a few notable differences (Table 7.1). Compared to non-responders, responders were older (median age 45 years with IQR 33,58 vs 39 years with IQR 27,49) and reported experiencing symptoms for longer at baseline, with a median symptom duration of 36 months (IQR 17,72) compared to

24 months (IQR 14,58) amongst non-responders. There was a small difference in the two groups in median depression scores; responders scored 8 (IQR 4, 14) whilst non-responders scored 10 (IQR 6, 18). Finally fewer responders reported having experienced abuse during childhood compared to non-responders (24% vs 35%).

Table 7.1 Characteristics of responders compared to non-responders using baseline data

Results reported in N/% unless otherwise stated. No missing data unless otherwise stated.

Characteristics at baseline	Responders N=245	Non-responders N=49
Gender		
Males	52 (21%)	11 (22%)
Females	193 (79%)	38 (78%)
Age (years)†	45 (33,58)	39 (27,49)
Symptom severity scores (PHQ-15)§	11.6 (5.0)	11.5 (4.7)
Symptom duration (in months)†	36 (17, 72)	24 (14,58)
SF-12 scores§		
Physical health functioning[1]	43.5 (10.6)	45.2 (10.5)
Mental health functioning	39.9 (10.8)	38.2 (12.0)
Depression score†	8 (4,14)	10 (6,18)
Anxiety score§	8.6 (5.6)	10.0 (6.4)
Type of abuse experienced as a child		
Yes	60 (24%)	17 (35%)
No	173 (71%)	31 (63%)
Missing	12 (5%)	1 (2%)

Results displayed as: † Median (IQR), §Mean (SD)
[1]Missing data for one participant

7.2 Comparison of baseline and follow-up characteristics of those who responded at follow-up

At follow-up, the cohort was fairly impaired and clinical characteristics were similar to baseline. Somatic symptom scores at follow-up were moderately severe, with a mean score of 10.5 (SD 5.3), physically and mentally health functioning scores were 43.7 (SD 11.1) and 40.7 (SD 10.9) respectively, which were also similar to baseline scores (see Table 7.2). In the six month period from baseline to follow-up, participants made a median of 4 primary care contacts (IQR 2, 6), which was comparable to the number of contacts made in the year prior to baseline participation.

Table 7.2 Characteristics of study cohort at baseline and follow-up. Results reported in N/% unless otherwise stated. No missing data unless otherwise stated.

Characteristics of study cohort	Total N=245 Baseline	Follow-up
Somatic symptom score (PHQ-15) [§]	11.6 (5.0)	10.5 (5.3)
SF-12 scores[§]		
Physical health functioning[1]	43.5 (10.6)	43.7(11.1)
Mental health functioning[2]	39.9 (10.8)	40.7 (10.9)
Depression score[†]	8 (4,14)	8 (3,14)
Anxiety score[§]	8.6 (5.6)	7.9 (5.7)
Panic[3]		
Yes	48 (20%)	51 (21%)
No	175 (71%)	179 (73%)
Primary health care contact[†]	8 (4,13)*	4 (2,6)**
Secondary care contact[†*]	1 (0,2)*	0 (0,1)**

Results displayed as: [†] Median (IQR), [§]Mean (SD)
*In the year before starting enrolment
** In the six months from baseline participation to follow-up
[1] Missing data at baseline (N=1) and follow-up (N=2)
[2] Missing data missing at follow-up only (N=1)
[3]Missing data at baseline (N=12) and follow-up (N=15)

In self-reported outcomes of symptoms, a few (26/245 (11%)) reported being fully recovered at follow-up and close to a quarter (58/245 (24%)) reported having received a diagnosis. Just under half (103/245 (42%)) of respondents reported that they were still under investigation either by their GP or had been referred to the hospital for further investigation. However, over half (135/245 (55%)) reported their symptoms as still unexplained. Options were not mutually exclusive and participants could choose more than one.

7.3 Regression analyses

Univariable analyses were conducted with each of the baseline variables and the primary outcome, somatic symptoms severity at follow-up, as well as the secondary outcomes including physical health functioning, mental health functioning, depression, anxiety and primary health care contact. Following univariable analyses, conceptual group modelling was carried out with significantly associated variables, which were theoretically considered to be closely associated to one another. This method was described in section 4.10.3.3.1. Variables identified from univariable analyses and conceptual group analysis, as well as gender and age, which were chosen a priori, were included in the modelling process. Overall, there was no significant association between general practices and any of the outcomes, and therefore general practices were not considered in the multivariable analysis. In the following sections, each outcome will be discussed in relation to the univariable and multivariable regression analyses conducted.

7.4 Primary outcome: somatic symptom severity

7.4.1 Univariable analyses

The following tables show the coefficient estimates along with 95% confidence intervals and associated p-values for the univariable analyses carried out with the sociodemographic (Table 7.3) and clinical variables at baseline (Table 7.4), and health service use in the year prior to study participation (Table 7.5). The variable with the largest univariable association with follow-up somatic symptoms was experience of physical abuse during childhood (Table 7.4), which was associated with a 4 point increase in somatic symptom severity (95% CI 1.92 to 6.28). Other variables which were significantly associated with increased symptom severity at follow-up included not being in paid employment, a lower level of education (i.e. O-levels, GCSE, A-levels or equivalent), perception of financial well-being as doing badly, duration of symptom at baseline longer than a year, reports of wanting help to deal with their symptoms, having experienced panic in the previous two weeks, experience of a traumatic events during childhood and experience of emotional abuse during childhood.

Table 7.3 Univariable analyses of baseline sociodemographic variables with outcome variable somatic symptom severity at follow-up.

Baseline sociodemographic variables	Somatic symptom severity (PHQ-15)		
	Coefficient	95% Conf. Interval	p-value
Gender			
Male	-	-	-
Female	1.50	-0.11,3.11	0.069
Age (years)	0.01	-0.32, 0.05	0.653
Ethnicity			
White	-	-	-
Black	0.14	-3.22, 3.49	0.935
Asian	1.52	-0.32, 3.37	0.105
Other (including mixed)	1.96	-0.73, 4.66	0.153
Marital status			
Married or in a long term relationship	-	-	-
Widowed, separated, divorced or single	0.50	-0.85, 1.85	0.467
Employment status			
In paid employment	-	-	-
Not in paid employment *	2.47	1.18, 3.77	<0.001
Education			
GCSE, A-levels, up to NVQ-3 or equivalent	-	-	-
Undergraduate, Masters, higher or equivalent	-2.80	-4.10, -1.51	<0.001
Perception of financial well-being			
Doing well	-	-	-
Doing badly	3.83	2.59,5.07	<0.001
IMD**	0.05	0.00, 0.10	0.06
Social support			
No			
Yes	-0.46	-2.27,1.35	0.614

*Unemployed, retired, full time education, unable to work because of long term sick or other

** IMD=IMD = Index of Multiple Deprivation score

Table 7.4 Univariable analyses of baseline clinical variables with outcome variable somatic symptom severity.

Baseline clinical variables	Somatic symptom severity (PHQ-15)		
	Coefficient	95% Conf. Interval	p-value
Baseline Somatic symptom score	0.70	0.60 , 0.80	<0.001
Duration of symptoms at baseline			
≤1 year	-	-	-
>1 year	3.15	1.56 , 4.75	<0.001
Preference for help-seeking			
By themselves	-	-	-
Like some help	2.71	1.02 , 4.40	0.002
SF-12 score			
Physical health functioning	-0.22	-0.28 , -0.17	<0.001
Mental health functioning	-0.19	-0.25 , -0.14	<0.001
Depression score	0.37	0.28 , 0.46	<0.001
Anxiety score	0.33	0.22 , 0.44	<0.001
Panic			
No	-	-	-
Yes	2.83	1.19 , 4.47	0.001
Work and social adjustment score	0.22	0.17 , 0.27	<0.001
Self-efficacy score	-0.23	-0.31 , -0.14	<0.001
Stressful life events	0.87	0.44 , 1.30	<0.001
Experienced physical illness in family members as a child			
No	-	-	-
Yes	1.69	0.28 , 3.10	0.019
Experience mental illness in family members as a child			
No	-	-	-
Yes	1.52	-0.28 , 3.32	0.098
Experienced 1 or more traumatic event as child			
No	-	-	-
Yes	2.24	0.86 ,3.62	0.002
Experienced abuse as a child			
No	-	-	-
Yes	2.14	0.61 , 3.68	0.006
Physical Abuse as a child			
No	-	-	-
Yes	4.10	1.92 , 6.28	<0.001
Sexual abuse as a child			
No	-	-	-
Yes	2.29	-0.07 , 4.65	0.058
Emotional abuse as a child			
No	-	-	-
Yes	2.66	1.02 , 4.31	0.002

Table 7.5 Univariable analyses of health service use in the year before study participation with outcome variable somatic symptom severity at follow-up.

Health service use in year before study participation	Somatic symptom severity (PHQ-15)		
	Coefficient	95% Conf. Interval	p-value
Primary health service contact	0.14	(0.06 , 0.22)	0.001
Secondary health service contact	0.17	(-0.08 , 0.43)	0.178

7.4.2 Multivariable analyses

Following conceptual group modelling, fifteen variables were identified for inclusion in the analyses. Backward selection was carried out and variables were taken out one by one starting with the one with the highest p-value and continuing until only variables with $p<0.05$ remained (and/or those included in the model a priori). Six variables remained in the final model; these were gender, age, perception of financial well-being, somatic symptom severity at baseline, physical health functioning at baseline, and experience of physical abuse during childhood (Table 7.6). Somatic symptoms severity at follow-up were on average 1.31 (95% CI 0.12 to 2.50) points higher amongst females compared to males, after adjusting for the other variables. Perception of financial well-being as doing badly was associated with a 1.90 (95% CI 0.89 to 2.91) point higher in somatic symptom scores at follow-up, compared to those who perceived that they were doing well, after adjusting for other variables. Similar findings were seen amongst those who had experience of physical abuse during childhood, with an increase in somatic symptom severity of 1.86 (95% CI 0.27 to 3.45) compared to those who had not.

Each additional point increase in symptom severity score at baseline were associated with a 0.53 (95% CI 0.42 to 0.64) point increase in symptom severity at follow-up, once adjusted for the other variables. Each additional point increase in physical health functioning at baseline were associated with a -0.10 point decrease (95% CI -0.15 to -0.04) in symptom severity at follow-up, once adjusted for other variables. For each year increase in age, follow-up symptom scores increased by a very small amount (0.01, 95% CI -0.03 to 0.04) and this association was not significant.

Table 7.6 Final multivariable model showing the association between baseline predictors and somatic symptom severity at follow-up.

Baseline predictors	**Somatic symptom severity (PHQ-15)**		
	Coefficient	**95% CI**	**p-value**
Gender			
Female	1.31	0.12, 2.50	0.031
Age (years)	0.01	-0.03, 0.04	0.559
Perception of financial well-being			
Doing well	-	-	-
Doing badly	1.90	0.89, 2.91	<0.001
Baseline somatic symptoms score	0.53	0.42, 0.64	<0.001
Physical health functioning score	-0.10	-0.15, -0.04	0.001
Experience of physical abuse during childhood			
No	-	-	-
Yes	1.86	0.27, 3.45	0.022

7.5 Secondary outcomes

7.5.1 Quality of life: physical health functioning

7.5.1.1 Univariable analyses

Physical health functioning was explored using the physical component score (PCS) of the short-form questionnaire (SF-12) which measures quality of life (health functioning). Univariable analysis of baseline variables with the outcome physical health functioning showed that employment status had the strongest association with physical health functioning at follow-up (see Appendix 4.1). This variable was associated with a reduction of -7.69 points (95% CI -10.35 to -5.04) in physical health functioning score, suggesting an increase in impairment amongst those who reported not being in paid employment compared those who were in employment. The experience of physical abuse during childhood was associated with a -7.65 point reduction (95% CI -12.50 to -2.79) in physical health functioning score at follow-up (Appendix 7.1). Other baseline variables which showed significant associations with physical health functioning included duration of somatic symptoms at baseline, which suggested that those who had symptoms for longer than a year had poorer physical health functioning and greater impairment at follow-up (-7.29, 95% CI -10.59 to -3.99). Perceived financial well-being reported as doing badly was associated with a point reduction of -6.46 (95% CI -9.16 to -3.74) in physical health functioning score compared to those who reported doing well financially. Help-seeking preferences for support from others were

associated with a -5.93 point reduction (95% CI -9.40 to -1.46) in physical functioning score at follow-up.

Both greater primary health care contact (-0.60, 95% CI -0.84 to -0.44) and secondary health care contact (-0.92, 95% CI -1.45 to -0.40) were associated with greater impairment at follow-up (see Appendix 7.1). However, average rate of secondary care referrals was low with median 0 (IQR 0, 1), and therefore, it has not been included in any of the multivariable models, even when statistically significant.

Factors associated with better physical health functioning at follow-up included education, where higher education which was strongly associated with a 7.84 (95% CI 5.17 to 10.50) point increase in physical health functioning score, compared to those with A- levels or less. Being female was associated with a 2.34 point increase in physical health functioning score, suggesting less impairment at follow-up.

7.5.1.2 Multivariable analysis

Sixteen variables were included in the full multivariable model. The final model included the following variables: gender, age, somatic symptom score at baseline, physical functioning at baseline and primary care use in the year before study recruitment (see Table 7.7). Higher somatic symptom scores at baseline were associated with lower physical functioning scores at follow-up (-0.30, 95% CI -0.51

to -0.09). There was a positive association between physical health functioning score at baseline and at follow-up, with every point increase in baseline score being associated with a 0.61 point increase in the score at follow-up (95% CI 0.51 to 0.72). Higher primary health service use in the year before study enrolment was associated with lower physical functioning scores at follow-up, after controlling for all other variables. Older age was associated with decreased physical functioning, after adjusting for all other variables.

Table 7.7 Final multivariable model showing the association between baseline predictors and physical health functioning at follow-up.

Baseline predictors	Physical health functioning (PCS)		
	Coefficient	95% CI	p-value
Gender			
Female	0.83	-1.47, 3.13	0.479
Age (years)	-0.08	-0.15, -0.02	0.014
Somatic symptom score	-0.30	-0.51, -0.09	0.005
Baseline physical health functioning score	0.61	0.51, 0.72	<0.001
Primary health service contact	-0.18	-0.31, -0.04	0.011

7.5.2 Quality of life: mental health functioning

7.5.2.1 Univariable analyses

Mental health functioning was explored using the mental component score (MCS) of the short-form questionnaire (SF-12) which measures quality of life (health functioning). Univariable analysis of baseline variables showed a large association between mental health functioning and physical (-7.83, 95% CI -12.58 to -3.08), sexual (-7.79, 95% CI -12.65 to -2.94) and emotional abuse (-6.71, 95% CI -10.17 to -3.26) at follow-up (see Appendix 4.2). Other variables including panic (-7.64, 95% CI-11.07 to -4.21), financial perception of doing badly (-5.95, 95% CI -8.62 to -3.28), preference for health seeking reported as wanting help (-5.20, 95% CI-8.71 to -1.69), traumatic experiences as a child (-3.89, 95% CI -6.84 to -0.93), primary health care contact at baseline (-0.22, 95% CI -0.39 to -0.04), not being in paid employment (-3.47, 95% CI-6.21 to -0.73) and not being in a relationship were all associated with lower mental health functioning at follow-up. Baseline variables associated with increased mental health functioning at follow-up included higher mental health functioning (0.58, 95% CI 0.48 to 0.69), higher physical health functioning (0.15, 95% CI 0.02 to 0.28) and greater self-efficacy at baseline (0.59, 95% CI 0.41 to 0.76).

7.5.2.2 Multivariable analysis

Eighteen variables were included into the full multivariable model. Following backwards selection, the final model included the following variables: gender, age,

mental health functioning and depression (see Table 7.8). Each unit increase in mental health functioning score at baseline was associated with 0.40 point (95% CI 0.27 to 0.54) increase in mental health functioning score at follow-up and each unit increase in depression score at baseline was associated with a -0.45 point decrease (95% CI -0.67 to -0.23) in mental health score at follow-up.

Table 7.8 Final multivariable model showing the association between baseline predictors and mental health functioning follow-up.

Baseline predictors	Mental health functioning (MCS)		
	Coefficient	95% CI	p-value
Gender			
Female	-2.47	-5.18, 0.25	0.075
Age (years)	-0.21	-0.09, 0.48	0.543
Baseline mental health functioning score	0.40	0.27, 0.54	<0.001
Depression score	-0.45	-0.67,-0.23	<0.001

7.5.3 Depression

7.5.3.1 Univariable analyses

As with the mental health functioning outcomes (section 7.5.2.1), variables physical (4.64, 95% CI 1.92 to 7.35), sexual (3.38, 95% CI 0.46 to 6.30) and emotional abuse during childhood (3.74, 95% CI 1.71 to 5.77) had some of the largest individual associations with depression score at follow-up (Appendix 4.3). Other variables which were associated with depression scores at follow-up included panic (4.54, 95% CI 2.56 to 6.51) financial perception of doing badly (4.46, 95% CI 2.89 to 6.03), preference for help seeking reported as wanting help (3.49, 95% CI 1.42 to 5.56), experience of traumatic experience as a child (1.93,

95% CI 0.20 to 3.67), not being in paid employment (3.36, 95% CI 1.76 to 4.95), duration of somatic symptoms at baseline (2.66, 95% CI 0.63 to 4.69) and stressful life events in the previous six months (1.11, 95% CI 0.57 to 1.64). Those who had attained higher education had a lower depression scores compared to those with A-levels or less. Higher physical health functioning (-0.20, 95% CI-0.27 to -0.13) and mental health functioning scores (-0.33, 95% CI -0.40 to -0.26) at baseline were associated with a reduction in depression score. Finally, better self-efficacy was associated with a reduction in depression scores (-0.45, 95% CI -0.55 to -0.36).

7.5.3.2 Multivariable analysis

As shown in Table 7.9, after a modelling process which started with sixteen variables, the final model included the following variables: gender, age, somatic symptom severity, depression score and self-efficacy score. Somatic symptom score at baseline was associated with a 0.16 point (95% CI 0.03 to 0.30) increase in depression score at follow-up after adjusting for other variables. Depression score at baseline was associated with a 0.54 point (95% CI 0.42 to 0.65) increase in depression scores. Better self-efficacy was found to be protective, with a 0.18 decrease in depression scores for each point increase in self-efficacy at baseline.

Table 7.9 Final multivariable model showing the association between baseline predictors and depression at follow-up.

Baseline predictors	Depression score (PHQ-9)		
	Coefficient	95% CI	p-value
Gender			
Female	0.79	-0.64, 2.23	0.277
Age (years)	0.02	-0.02, 0.05	0.339
Somatic symptom score	0.16	0.03, 0.30	0.016
Baseline Depression score	0.54	0.42, 0.65	<0.001
Self-efficacy score	-0.18	-0.27, -0.09	<0.001

7.5.4 Anxiety

7.5.4.1 Univariable analyses

Findings of the univariable analyses are shown in Appendix 4.4. Those who reported having experienced panic in the two weeks prior to baseline questionnaire had the highest association with anxiety at follow-up, with a 3.77 point (95% CI 2.02 to 5.52) increase in anxiety scores. Experience of any abuse during childhood (2.01, 95% CI 0.36 to 3.68) as well as physical (3.22, 95% CI 0.84 to 5.59), sexual (2.19, 95% CI 0.36 to 4.73) and emotional abuse (2.90, 95% CI 1.12 to 4.67) were also associated with increased anxiety scores at follow-up (Appendix 7.4).

Other baseline variables which were significantly associated with anxiety score included financial perception of doing badly (2.50, 95% CI 1.09 to 3.91), preferring help from others for managing symptoms (2.14, 95% CI 0.33 to 3.95), somatic symptoms that had lasted a year or more at baseline (2.22, 95% CI 0.47 to 3.97)

and experience of mental illness in family members as a child (1.98, 95% CI 0.03 to 3.92). There was a -0.10 point (95% CI -0.16 to -0.03) reduction in anxiety scores for every point increase in physical health functioning score at baseline and a -0.24 point (95% CI -0.30 to -0.18) reduction in anxiety scores for each point increase in mental health functioning score at baseline. Higher self-efficacy scores were also associated with decreased anxiety scores at follow-up (-0.28, 95% CI -0.37 to -0.19).

7.5.4.2 Multivariable analysis

Sixteen variables were included in the multivariable model following conceptual group analysis, in addition to gender and age included a priori. Following backwards elimination, five variables remained in the model (see Table 7.10). For every point increase in baseline depression score, follow-up anxiety score increased by 0.20 (95% CI 0.06 to 0.34) once adjusted for all other variables. For each point increase in baseline anxiety, follow-up anxiety increased by 0.44 points (95% CI 0.27 to 0.61).

Table 7.10 Final multivariable model showing the association between baseline predictors with anxiety at follow-up.

Baseline predictors	Anxiety score (GAD-7)		
	Coefficient	95% CI	p-value
Gender			
Female	0.55	-0.85, 1.96	0.437
Age (years)	0.02	-0.01, 0.06	0.227
Depression score	0.20	0.06, 0.34	0.007
Baseline anxiety score	0.44	0.27, 0.61	<0.001

7.5.5 Primary health care contacts

Primary health care contacts included general practitioner, nurse, health care assistant and out of hours services contact.

7.5.5.1 Univariable analyses

Univariable analyses showed that primary health care contact at follow-up had the largest association with employment status (Appendix 4.5). There were on average 2.27 (95% CI 1.21 to 3.33) higher primary health care contacts amongst those who were not in paid employment compared to those who were in paid employment. A 2.13 unit (95% CI 0.79 to 3.47) increase in health service contact was found amongst those who reported experiencing emotional abuse during childhood compared to those who had not. Having experienced any type of abuse (1.31, 95% CI 0.07 to 2.56) was also associated with greater primary health care use. A 0.70 point (95% CI 0.40 to 1.10) increase in primary health care contact was observed for every ten years increase in age.

Other variables positively associated with primary health care contact included baseline symptom severity score (0.19, 95% CI 0.09 to 0.30), depression score (0.13, 95% CI 0.05 to 0.21) and work and social adjustment score (0.10, 95% CI 0.05 to 0.15). Higher number of baseline primary health care contacts (0.41, 95% CI 0.35 to 0.46) and secondary health care contacts (0.85 95% CI 0.66 to 1.05) in the year before study enrolment were associated with greater primary health care contacts at follow-up.

Variables which showed a significant negative association with and a reduction in primary health care contact at follow-up were higher education level (-1.77, 95% CI -2.87 to -0.67), as well as higher baseline physical health functioning scores (-0.14, 95% CI -0.19 to -0.92), mental health functioning scores (-0.05 95% CI -0.09 to 0.00) and higher self-efficacy (-0.10 95% CI -0.17 to -0.02).

7.5.5.2 Multivariable analysis

Following conceptual group modelling, twelve variables were included in the modelling process. Finally, four variables including those which were chosen a priori remained in the model. There was a 1.28 unit (95% CI 0.26 to 2.32) increase in health care contact amongst those who reported having experienced emotional abuse during childhood compared to those who had not, after adjusting for the other variables. Each unit increase in primary health care contact in the year before study enrolment was associated with a 0.40 unit increase in primary health care contact at follow-up (95% CI 0.34 to 0.45) (see Table 7.11).

Table 7.11 Final multivariable model showing the association between baseline predictors and primary health care contacts at follow-up.

Baseline predictors	Primary health care contacts		
	Coefficient	95% CI	p-value
Gender			
Female	-0.57	-1.60, 0.46	0.274
Age (years)	0.01	-0.02, 0.04	0.568
Experience of emotional abuse during childhood			
No	-	-	-
Yes	1.28	0.26, 2.32	0.015
Primary health care contact*	0.40	0.34, 0.45	<0.001

*In the year before study enrolment

7.6 Summary

Following screening of nearly 3,000 patients in primary care, 1,196 eligible participants were invited to take part in the cohort study. This chapter reports the main results of those who took part in the longitudinal study. My study cohort included 294 participants at baseline and follow-up response rate was high. Although responders and non-responders were fairly similar, there were a few differences; responders were older, had experienced symptoms for a longer duration at baseline, had slightly lower median depression scores and fewer reported having experienced childhood abuse compared to non-responders. The cohort remained impaired at follow-up; over half reported that their symptoms were still unexplained. On average, somatic symptoms scores were moderately severe, and physical and mental health functioning was poor.

A number of sociodemographic and clinical baseline variables were significantly associated with the primary outcome somatic symptoms severity, following univariable analyses. These included: perception of financial well-being; baseline symptoms; poor physical and mental health functioning; anxiety; depression; number of stressful life events; and historic variables relating to childhood experiences such as physical illness in family members, trauma and abuse.

Multivariable analysis identified being female, higher baseline somatic symptom severity, worse physical health functioning, perception of financial well-being as doing badly and experience of physical abuse during childhood as significantly associated with higher somatic symptom severity at follow-up. Although age was included a priori, there was no significant association at follow-up.

All final multivariable models for the secondary variables included several similar baseline variables. These are summarised in Table 7.12. For all secondary outcomes the baseline measure of the same variable was associated with its follow-up severity, after adjusting for all other variables. For example, poor physical health functioning at baseline was associated with poor physical health functioning at follow-up, and higher baseline depression scores were associated with higher depression at follow-up.

The final multivariable models for physical health functioning and depression included baseline somatic symptoms scores. All final models for depression, anxiety and mental health functioning included baseline depression score. Health

service use in the year before study participation was included in the final models for physical health functioning and health service use at follow-up. Additionally, self-efficacy at baseline remained in the final models for depression, and emotional abuse in childhood in the final model for primary health care contacts at follow-up. Age and gender were included a priori in all models, however only age showed a significant association with one of the outcomes, physical health functioning. I discuss the meaning and implications of these findings in Chapter 8.

Table 7.12 Summary of baseline predictors which were significantly associated with each of the outcomes in multivariable analyses

Baseline variables	Primary outcome	Secondary outcomes				
	Somatic symptom severity	Physical health functioning	Mental health functioning	Depression	Anxiety	Primary health care contact
Female	x					
Age (years)		x				
Perception of financial well-being as doing well	x					
Somatic symptom score	x	x		x		
Mental Health Functioning score			x			
Physical Health Functioning score	x	x				
Self-efficacy score				x		
Anxiety score					x	
Depression score			x	x	x	
Experienced physical abuse during childhood	x					
Experienced emotional abuse during childhood						x
Primary care health service contacts in year prior to study participation		x				x

Chapter 8 : **Discussion**

8.0 Chapter overview

In this final chapter of my thesis, first I summarise the main results of my study and compare my findings to existing literature. I then discuss the methodological strengths and limitations of the research. Finally, the clinical and policy implications of the findings, as well as the scope for future research will be explored

8.1 Summary of findings

In this study, I examined the outcome of UPS in primary care attenders and identified prognostic factors associated with somatic symptom severity at six months follow-up. To achieve this, first, I systematically reviewed previous research on UPS. The review found that a few studies focused on primary care attenders in the UK with UPS, highlighting the need for my research.

I screened nearly 3,000 attenders in nine general practices in North and Central London for UPS. Most respondents reported at least one unexplained symptom and about half had no explanation or diagnoses for any of their symptoms. From this sample, those with multiple somatic symptoms were recruited to participate in a cohort study.

The study cohort was largely made up of women, around half were educated to a high level and reported that they were 'doing well' financially. On average, at baseline the cohort had moderately severe somatic symptoms; their quality of life relating to physical and mental health functioning was poor. Average anxiety and median depression scores were within the range for moderate severity. Although, using a cut-off of $\geq$10 on their respective scales, less than half of responders had clinically significant anxiety or depression, and around a third had comorbid depression and anxiety. A third of responders fell into the range of clinical significance at a higher cut-off of $\geq$12. In the year prior to study enrolment, the cohort had frequently accessed health care with a median of eight consultations to primary care.

At six months follow-up, scores for all the outcome measures were similar to baseline scores demonstrating poor recovery; only one in ten reported being fully recovered. Over half of the cohort reported that their symptoms were still unexplained and just under half said that were still under investigation. One quarter reported having received a diagnosis for at least some of their symptoms.

Multivariable analysis indicated a significant association between higher somatic symptom severity at six months and several baseline variables: being female, perception of doing poorly financially, higher baseline somatic symptom severity, poorer physical health and experience of childhood physical abuse. Several baseline

factors were significantly associated with each of the secondary outcomes. There was a clear dichotomy between baseline variables associated with the physical outcomes (somatic symptom severity and physical health functioning) and psychological outcomes (mental health functioning, depression and anxiety). Physical health functioning at follow-up had a similar trend to the primary outcome; high baseline somatic symptom scores were associated with poor physical health functioning at follow-up. With each of the psychological outcomes there was a similar association; poor mental health functioning, and higher depression and anxiety at baseline were associated with poor mental health functioning, and higher depression and anxiety at follow-up. Greater self-efficacy was associated with a better outcome for depression at follow-up. Only reports of emotional abuse in childhood and health care contacts in the year prior to the study were associated with primary health use at follow-up.

8.2 Relating findings to existing literature

In this section I discuss the findings from the screening stage of my study and the cohort study with existing literature. The following areas will be explore in detail: prevalence of somatic symptoms in GP attenders; characteristics of the cohort; outcomes of UPS; factors associated with somatic symptom severity at follow-up; and factors associated with secondary outcomes at follow-up.

8.2.1 Prevalence of somatic symptoms in GP attenders

The severity of somatic symptoms amongst those screened in my study is comparable to other primary care attender studies in which the same measure was used in Germany, USA and Australia (Steinbrecher and Hiller, 2011; Kroenke et al., 2002; Clarke et al, 2008). There are only a few studies that have explored prevalence of UPS in primary care in the UK. These are difficult to compare due to the use of different definitions and methods to identify those with UPS (Peveler et al 1997; Duddu et al 2008; Morriss et al., 2012). The proportion of those with five or more symptoms, amongst those who completed screening questionnaires in my study were similar to that of another primary care attender study in the UK, which explored persistence based on abridged somatisation (Peveler et al., 1997).

Most of the people screened in my study had at least one unexplained symptom, which is slightly higher than percentages confirmed by GPs as having at least one unexplained symptom amongst consecutive primary care attenders, in Germany (Steinbrecher et al., 2011). However, they do compare favourably to those whose symptoms lacked a clear medical explanation but where the nature of the symptoms were considered ambiguous, in the same study (Steinbrecher et al., 2011). Numbers with UPS in my study also compare closely to percentages who reported experiencing at least one symptom in the past seven days in a recent population based study in New Zealand (Petrie et al., 2014).

Two thirds of the respondents at both the screening stage and in my cohort study, were women, in line with the higher rates of general practice consultation amongst women compared to men amongst various studies, including those on UPS (Barsky et al., 2001; Green and Pope, 1999; Vedsted and Christensen, 2005; Hippisley-Cox and Vinogradova,2009; Taylor et al.,2012; Mayor,2015). Younger and working aged men are less likely to attend primary care (Patel et al 2003; Vadsted and Christensen, 2005; Wang et al., 2013) and gaps in consultation rates between genders are greatest between the ages of 16 and 60 years (Wang et al., 2013).

At the screening stage, fewer than may be expected indicated that a mental health or functional diagnoses underlined their symptoms, in comparison to research on prevalence of mental illness such as depression or anxiety, and functional syndromes such as irritable bowel syndrome amongst general practice attenders in the UK (King et al., 2008; Canavan et al., 2014). It is possible that some respondents did not want to admit to a mental illness; however, in another study amongst consecutive primary care attenders at ten general practices in the UK, similar percentages were given psychological explanations for their symptoms, by GPs (Taylor et al.,2012). With regard to the low report of functional diagnoses such as irritable bowel syndrome or chronic fatigue, some may have considered these diagnoses to be unsatisfactory and so reported their symptoms as unexplained.

A third of those screened reported consulting their GP about their bothersome symptoms. There are several possibilities for this finding. Although, it is said that 90% of the most common somatic symptoms with which people consult are covered by the PHQ-15, it is possible that some consulted with the remaining 10% of symptoms that were not included (Kroenke et al., 2002). It is, however, more likely, that some were attending the surgery for other reasons such as: routine appointments, to monitor existing chronic illness; health checks, to test for risk of chronic illnesses; to obtain contraceptives; for screening (e.g. smear tests); or for lifestyle advice (e.g., services such as stop smoking) (Kontopantelis et al 2015).

8.2.2 Characteristics of the cohort

The sociodemographic characteristics of the cohort were comparable to the population of the four London boroughs from which the sample was recruited, in terms of ethnicity and education (Office for National Statistics, 2011). Over half of the respondents reported their marital status as either married or in a long-term relationship compared to just over a third, in the four boroughs included in the study (i.e. married or in a civil partnership) (Office for National Statistics, 2011). The higher rate in my study could be explained by the inclusion of those in long-term relationships, regardless of legal status.

More of the cohort was economically inactive compared to the population of London in 2011 (Greater London Authority, 2013). This is likely when sampling from

general practice population who are more likely to be sick and older than the general population. Participants' perceptions of financial well-being, were on average worse compared to figures reported in both the UK and in London (Self et al., 2013).

Finally, a major difference in the study participants compared to the general population in the four boroughs was the high level of perceived social support reported by them. This is interesting as London is considered to be one of the loneliest places in Europe and the UK; in one report, up to 52% of people in London reported feeling lonely (ComRes, 2013). Although loneliness is a subjective experience and some may feel lonely even in the company of friends and family. However, some of the boroughs from which GP practices were recruited also have some of lowest rates of marriage in the UK (Office for National Statistics, 2011). Based on these multiple sources of evidence, it is likely that that levels of social support identified in my study may be higher than amongst the actual population from which the sample was drawn. In contrast to my study, other research has suggested that perceived presence of social support may act as protective factor against physical morbidity (Reblin and Uchino, 2008).

My study cohort had somatic symptom scores within the range for moderate severity on the PHQ-15; suggesting that on average they experienced at least five or more unexplained symptoms (Kroenke et al., 2010). This, as previously mentioned,

is comparable to the diagnostic criteria 'abridged somatisation' (Peveler et al., 1997). On average, the number of symptoms reported amongst my cohort is much lower than primary care attenders who met the criteria for DSM-IV diagnosis of undifferentiated somatoform disorder, who on average experienced 10 physical symptoms (De Waal et al., 2008). Most of my study cohort also had fairly chronic symptoms, having experienced symptoms for over a year and on average close to three years.

Physical and mental health functioning scores based on the SF-12 suggest that on average my study cohort were moderately functionally impaired and likely to experience a poor quality of life. Physical functioning scores in my study were similar to those with limiting long-term illness in the UK and also comparable to those with respiratory disease and cancer, whilst their mental health functioning scores were similar to those with clinical depression (Booker and Sacker, 2011). The average physical and mental health functioning scores amongst my cohort were comparable to average scores amongst those identified by Creed et al. (2012) as having high symptom severity[6].

Scores on the work and social adjustment scale for my study cohort were comparable to those with mild and persistent depression-dysthymia reported amongst primary care patients recruited from 42 GP practices, across the UK

[6] This study was discussed in detail in the systematic review in chapter 2.

(McMahon et al., 2012) and considered to be in the range associated with significant functional impairment but less severe clinical symptomology (Mundt et al., 2002). These scores suggest that functioning amongst my cohort was fairly poor.

Lower mean and median levels of anxiety and depression were found in my study compared to scores suggested to be clinically significant at a cut off of ≥10 (Spitzer et al., 2006; Kroenke et al., 2002). Scores were also lower compared to primary care attenders with somatisation disorder (Löwe et al., 2008) and those with medically unexplained symptoms in primary care, in the UK (Duddu et al., 2008). Comorbid depression and anxiety rates reported amongst those with UPS vary (see section 1.6.3). The percentages in my study with anxiety and/or depression scores considered clinically relevant, are fairly consistent with past reports of populations with similar symptom counts (Kroenke, 2003). They are however higher than prevalence estimates reported more recently, amongst primary care attenders diagnosed with somatoform disorder in Germany (Steibrecher et al. 2011). Childhood experiences such as deprivation, traumatic experiences, family illness and abuse have been commonly reported amongst adults with UPS, these were discussed in detail in 1.6.5. Such experiences were common in my study; I found that more females reported experience of sexual abuse compared to males, in line with previous findings (Edwards et al., 2003). Where different types of abuse have been explored, emotional abuse has been identified as the most frequently

reported type of abuse (Edwards et al., 2003; Radford et al., 2011) and this was also the case in my study.

Primary care consultation rates amongst my study cohort in the year prior to study participation were higher than average national rates reported in the UK between 2008 and 2009, based on 496 practices (Hippisley-Cox and Vinogradova,2009). My findings are slightly higher than those reported by Taylor et al., (2012), amongst consecutive primary care attenders in the UK, determined to have UPS by their GPs; however their rate is based on GP contact alone, whilst my study included GP, nurse, HCA or out of hours contact. The average frequency of primary care consultation in my study was comparable to a control group of another large UK primary care study, who were older than 61 years; this study compared the rates of consultation between those with severe mental illness and a matched control group (Kontopantelis et al., 2015).

8.2.3 Outcomes of UPS

Over half of the participants in my cohort reported that their symptoms were still unexplained at follow-up, indicating chronicity. This refutes the suggestion by Olde Hartman et al. (2009) that symptoms are transient and that a majority of patients will improve over time; this was not so in my study. Only 10% of my study cohort reported that their symptoms had resolved; this is much lower than rates of

resolution amongst consecutive primary care attenders at three month follow-up, found by Jackson and Passamonti (2005) in the USA. Over half of my study cohort reported symptoms were still unexplained at six months. My finding is comparable to the rates of persistence reported amongst primary care attenders meeting diagnostic criteria for somatoform disorders, somatisation disorder and abridged somatisation, at between six and twelve months follow-up (Steinbrecher and Hiller, 2011; De Gutch et al., 2004; Gureje and Simon, 1999).

8.2.4 Factors associated with symptom severity at follow-up

Higher baseline somatic symptom severity was associated with increased severity at follow-up; suggesting that greater severity at baseline is likely to be associated with worse outcome at follow-up. This is supported by other studies in which baseline symptom severity is associated with symptom severity, persistence of symptoms or presence of unexplained symptoms/somatoform disorders and less recovery at follow-up (Tomenson et al 2013; Jackson and Passamonti 2005; van der Windt et al.,2008; Hilbert et al., 2010; Steinbrecher and Hiller, 2011; Creed et al., 2012).

Women in my study were likely to have higher symptom severity compared to men at follow-up, when other variables were adjusted for (including baseline somatic symptoms). This finding is consistent with other literature; women experience a greater number of physical symptoms, more frequently and have a greater

symptom burden (Kroenke and Spitzer, 1998; Barsky et al., 2001; Tomenson et al., 2013). Studies in primary care also report that being female is associated with persistence of UPS and high symptom severity over time (De Gucht et al., 2004; Verhaak et al., 2006; Koch et al., 2009).

Perception of financial well-being as doing poorly was associated with an increase in symptom severity at follow-up, compared to those who perceived their financial well-being as doing well. Although an individual may be educated to a high level and be in full time employment, indicating a high socioeconomic status, they may yet not meet their expectations in terms of income and standard of living (Montpetit et al., 2015). In such instances, perception of financial well-being can provide valuable insight into an individual's outlook and perspective. Financial stress in particular has been associated with poorer psychological well-being (Montpetit et al., 2015) as well as the onset and maintenance of common mental health disorders (Weich and Lewis, 1998) and depression (King et al., 2006) over a 12 month period. There are two possible explanations for the association of financial stress with symptom severity over time. First, although wealth may not directly promote well-being, it may act as a buffer against some difficult events and poor financial well-being may create additional difficulties during periods of poor health (Smith et al., 2005). Second, regardless of income or education status, those who perceive their situation positively may have a generally more positive outlook on their living

situation as well as their physical health; such individuals may be better at developing coping strategies to deal with their symptoms (Falvo, 2013).

In my study, higher scores for physical health functioning at baseline were associated with a small but significant decrease in somatic symptom scores at follow-up. This suggests that those with better physical functioning at baseline are more likely to experience improvement in their symptom severity. Other primary care studies have found similar results, which suggests that greater functional disability and poor physical health are associated with the persistence of UPS or high somatic symptoms scores at 12 month follow-up (Steinbrecher and Hiller, 2011; Creed et al., 2012). These studies were discussed in detail in section 2.9.2.

Finally, those who had experienced physical abuse in childhood reported an increase in somatic symptom severity at follow-up, compared to those who did not report experience of abuse. This suggests that childhood physical abuse may have a long term impact on physical health. Increased rates of somatic symptoms such as back pain, headaches, pelvic pain, frequent tiredness, depression anxiety, functional syndromes (e.g., Irritable Bowel Syndrome, Chronic Fatigue Syndrome), and medically unexplained symptoms have all been reported amongst those who experienced childhood abuse (Kamiya et al., 2015). In a longitudinal study in primary care, Creed et al. (2012) found that psychological abuse but not physical abuse was associated with the persistence of a high level of somatic symptoms.

Childhood physical abuse has been reported to be predictive of poorer physical and mental health (Springer et al., 2009) and persistence of UPS (Barsky et al.,1994; Waldinger et al.,2006; Van Boven et al., 2011). This association may be due to a poor lifestyle (i.e alcohol consumption or risk taking behaviour) relating to poor coping (Springer et al 2003). Past experiences may also influence how symptoms are perceived; they may be mediated through pathways such as immune system sensitisation, endocrine dysregulation and abnormal proprioception and impact on individuals' help-seeking behaviour (Van Ravenzwaaij et al., 2010).

Age was not associated with an increase in symptom severity. Reports of whether UPS are more common amongst younger or older people vary (Morriss et al., 2012; Escobar et al., 1998; Verhaak et al.,2006). My findings are supported by Steinbrecher and Hiller (2011), who also found that age did not show a significant association with persistence of medically unexplained symptoms and somatoform disorders in primary care attenders. Creed et al., (2011), however, suggests that higher reports amongst younger people may be influenced by the use of diagnostic criteria (for example for somatoform disorder, the DSM-IV criteria require symptoms occurring before age 30). Furthermore, for older people, difficulties of recall as well as the natural increase in physical symptoms with age may make identification of medically unexplained symptoms difficult (Hilderink et al.,2015)

8.2.5 Factors associated with secondary outcomes

8.2.5.1 Physical health functioning

Higher somatic symptom scores suggestive of greater symptom burden were associated with poor physical health functioning and recovery at six months follow-up. Many authors have also found that UPS, symptom severity and total number of symptoms are associated with greater physical impairment in cross-sectional and longitudinal studies (Katon et al 1991; Kroenke et al., 2002; Barsky et al., 2006; Jackson and Kroenke, 2006; Koch et al., 2007; Zonneveld et al., 2009; Hansen et al., 2011; Creed et al., 2012; Tomenson et al., 2013). As might be expected, poorer physical health functioning at baseline is likely to be associated with poorer recovery of physical health functioning at follow-up, implying that recovery may be limited over six months; similar findings were reported by Hansen et al. (2011) in their primary care study over 24 month follow-up.

A greater number of primary health contact in the year prior to study participation was associated with poor physical health functioning. It is plausible that those who have greater symptom burden and poorer physical functioning at baseline access more health care but may not experience recovery over time. In my study, older age was also associated with poor physical functioning and may be due to a natural decline in physical health functioning as people get older; this is consistent with previous findings (Henchoz et al., 2008; Hilderlink et al., 2013).

8.2.5.2 Mental health functioning, depression and anxiety

Poorer baseline mental health functioning and greater depression and anxiety were associated with less recovery of psychological well-being at follow-up. Other studies have found similar associations among people with UPS (Koch et al., 2009). This persistence in poor psychological well-being may also be a result of the prolonged nature of recovery from depression and anxiety, which may take a long time or not at all, in some people (Boland and Keller, 2002; Terre et al 2003; Tylee and Haddad, 2007; McMohn et al.,2012).

Baseline somatic symptom scores were associated with higher depression scores at follow-up (after adjusting for baseline depression); others have reported similar findings amongst primary care attenders with UPS (Kisely and Simon, 2006; Kroenke et al., 1994). This relationship is likely to be bi-directional. It is possible that participants presenting with somatic symptoms but with underlying depression get worse over the follow-up, if it is not recognised and managed appropriately (Kamphuis et al.,2012). For others, the high symptom burden and uncertainty of their UPS may lead to depression as a result of poor coping. Higher self-efficacy at baseline was independently associated with lower depression scores; this suggests that self-efficacy is associated with better recovery, potentially acting as a protective factor (Maciejewski et al.,2002).

Several studies have shown that somatic symptoms are associated with increased health care use as well as increased health care costs (Tomenson et al 2013; de Waal et al., 2008; Hilbert et al., 2010; Hansen et al., 2011; Zonneveld et al., 2013). I found that greater primary care contacts in the year before study enrolment was associated with higher primary care use at follow-up; this association has been reported in previous primary care studies in patients with UPS (Blankenstein,2001; Hilbert et al 2010). It is possible that people who consume higher levels of health care may have greater levels of health anxiety or other comorbidities which are reflected in their continued high frequency of health care use at over time (Hilbert et al., 2010).

I found childhood emotional abuse was associated with increased primary care use in adults. This is in line with numerous studies that have reported that childhood physical, sexual, psychological or emotional abuse may result in long-term health consequences (Springer et al 2003; Arnow, 2004;Norman et al., 2012). Childhood abuse has been suggested to have impact on adult health through emotional, behavioural, social, and cognitive pathways that can result in poor mental health well-being, poor lifestyle and engaging in harmful activities (Kendall-Tackett et al., 2002); which may explain high health care use over time.

8.3 Strengths and limitations

8.3.1 Study design

Cohort studies are useful for studying a group of participants who are at risk of a specific outcome and following them over time to explore the outcome of interest. I considered the use a prospective cohort study design the most suitable to address the aims of my research, i.e. to: 1) investigate the outcome of UPS at six months follow-up, amongst adult primary care attenders; and 2) to identify prognostic factors associated with persistence of somatic symptom severity, quality of life, anxiety, depression and health care use. There are disadvantages associated with cohort studies. One of the main disadvantages is its resource intensive nature in terms of the time required to set up and follow-up the cohort (Sedgwick, 2013). In order to identify a population of a suitable sample size, recruitment for my study it took place over eleven months.

An alternative sampling method that could have been used is population based sampling (i.e. contacting all people in a defined population using electoral lists or GP registers). This method may have increased the representativeness of the sample and thus increased the external validity of the findings (Mann,2003). Conversely, this method could also have potentially resulted in higher non-response rates (Gordis,2014). Electronic medical records could also have been used for identification of participants by developing an algorithm to identify UPS or through

GP identification. However it is likely to have resulted in under identification of cases because of the differences in recording symptoms and diagnoses (Morriss et al., 2012); additionally, this would identify a sample based on the general practitioner's judgment.

Postal questionnaires were used as the main source of data collection rather than another method (e.g., semi-structured interviews) due to the time and resource restrictions. An option of face-to-face or telephone questionnaire completion was offered to participants but few took this up. A possible alternative (or addition) to postal questionnaires is the use of online questionnaires, which are less resource intensive regarding data entry. However, at the inception of this study, resources to securely collect identifiable data for a longitudinal study in this way were not available.

A number of methods such as structured diagnostic interviews, structured screening questionnaires, clinician or researcher identification or medical records can be used in research to identify patients. Their benefits and drawbacks were discussed in section 1.4. However, I chose to use patient self-reports because they reflect the patients' beliefs and perceptions, without the influence or interpretation of their GP. Self-reported symptoms are crucial to understanding needs and help-seeking behaviour. However, as they rely on the patients understanding of their diagnosis/explanation and their ability to recall it is possible that there may be

biased by inaccurate reporting. Nevertheless, the patients' understanding, perceptions and belief of whether their symptoms are unexplained are more likely to offer an accurate picture of the level of burden, frequency of consultation and other health care use (Sumathipala et al., 2008) irrespective of any diagnosis or physiological explanations that a general practitioner may have recorded in the person's medical notes. Therefore in my study the use of self-reported data was an extremely valuable method of identification of patients in studies of UPS and it offered a more meaningful patient oriented insight into burden of the problem to the patient and their help-seeking behaviours.

The outcomes in this study were explored over six months, rather than a longer duration. Short term outcome is important as it provides an indication of whether symptoms are self-limiting over that period of time. A few studies have explored outcomes over six months and report similar rates of persistence of UPS but higher rates of recovery than my study (De Gucht et al.2004; Arnold et al., 2006).

8.3.2 Setting

People with UPS are known to make up a large proportion of those attending primary care. Therefore, general practice was deemed the best setting to capture this population. In terms of feasibility, this setting provided access a large number of people who had symptoms that were bothering them. Furthermore, the

exploration of outcomes of a population attending primary care is valuable as it can provide information on the scale of the problem, prognosis in this setting and potentially aid in determining how best to intervene in the management of patients.

An important strength of my study is the inclusion of nine general practices with differing levels of deprivation. However, these practices may not be representative of other general practices in the UK; practices were recruited through a research network which identified them as being as research active. In some practices, I was approached by doctors and practice managers who had a special interest in this area of study. Their interest in the area may have reflected on the patient experiences within the practice, in relation to management of UPS. The research active nature of the practice may have also resulted in research fatigue amongst the patients which may explain the relatively high dropout rate from the screening to baseline questionnaire. Additionally, due to time and resource restrictions only general practices in London were included thus the generalisability of the findings is limited.

8.3.3 Response rates and representativeness

Only 25% of those who were eligible at the screening stage of the study, and who expressed interest to take part in the longitudinal study returned baseline

questionnaires. Recruitment from primary care is acknowledged to be increasingly difficult, particularly in the UK. King et al. (2006) achieved higher response rates at 44% by approaching attenders in general practices in the UK, for a study on the natural course and outcome of depression. However, a more recent cohort study in primary care, which included GP practices from London and North West England, found that the response rate varied depending on the type of long term condition, the region in which the practice was located and by practice deprivation score (Peters et al., 2014). Average response rates for all long term conditions were 38%, but were as low as 30% (Peters et al., 2014). Based on these findings, decreasing response rates may reflect a trend that is occurring over time.

It has been suggested in the past that in order to obtain a representative sample from the target population, a response rate of 70% or above is required (Patel et al., 2003). However, one of the strengths of my study is that those who returned baseline questionnaires were comparable to non-responders in terms of clinical characteristics, which suggests that despite the high dropout, the findings are likely to be comparable to a larger study population with similar characteristics to the responders. There were only a few differences, with non-responders being more likely to be male and younger. This appears to be common in many primary care studies (Patel et al., 2003).

Another strength of this study is the high response rate (83%) at six month follow-up. At follow-up responders were similar to non-responders except that they were slightly older than non-responders, reported experiencing symptoms for longer at baseline, had lower median depression scores and reported lower levels of abuse during childhood. This suggests that responders may have been experiencing more chronic symptom burden but less underlying psychological morbidity.

As I conducted screening at all practices myself, it is likely that there is very little variation in how the study was presented to participants. It is important to acknowledge that my style of communication regarding the study may have changed with increasing familiarly and confidence over the 11 month period, although every attempt was made to ensure consistency.

Whilst the study was ongoing, due to the low response rates in participation in the cohort study it was necessary to make some changes to the study design in order to reach the target sample size. In consultation with my research supervisors, clinicians and other experts in primary care, as well as with reference to literature on response rates, three changes were made. The amendments were approved by the local research ethics committee and applied to the last three practices included in the study. A £10 voucher was provided per questionnaire as to compensate for time and inconvenience. The colour of the envelopes used was changed from brown manila to white envelopes. An invitation printed on the letter head from the

general practice to which eligible participants were registered at was also used. This made no difference to the response rate and similar numbers responded to the baseline questionnaires as in the earlier practices.

With consideration to the participation rates and non-response rates, the findings of my study are likely to be generalisable to a middle-aged, female population who have symptoms for longer at baseline, who are less likely to be suffering from depression and less likely to have experience abuse in childhood. Hence, it is important to be cautious about the generalisability of these findings when extrapolating results to dissimilar populations.

8.3.4 Inclusion and exclusion criteria

A potential limitation of the study is that those who were unable to complete the questionnaire in English were excluded. This was due to time and resource constraints. In spite of this, a fairly diverse population was accessed with 27% reporting their ethnicity as Black, Asian, or Mixed. Within those who reported their ethnicity as White, a further 11% reported their ethnicity as White Other.

Another potential limitation was the exclusion of those with impaired cognitive ability or learning difficulties; however, only a minority of people stated this as a reason for not completing the questionnaire. It is difficult to know whether those

who expressed a lack of interested in the study and did not want to complete the screening questionnaire actually had underlying cognitive or learning difficulties or were unable to read or understand the questionnaire, which they did not want to reveal.

8.3.5 Identification of participants

The PHQ-15, a self-report measure, was used to determine the extent of symptom severity. Those who were considered eligible were identified as having at least three UPS, and a score of five or more, after any explanations or diagnoses offered for the symptoms were considered. Patient self-reports of symptoms and their understanding of explanations may have resulted in a different population to those who would have been identified by their doctors or by using patient notes. On the other hand, it is very possible that some people were not aware of their diagnosis, were unable to recall their diagnosis, did not understand a diagnosis, or did not feel that their diagnosis or explanation provided an adequate explanation for their symptoms. There may also have been some participants who were screened, who received a diagnosis after their first consultation and therefore decided not to return the baseline questionnaire.

Those identified as meeting the threshold for inclusion were based on my judgement in consultation with my three clinical supervisors, who are practising

GPs. Efforts were taken to ensure consistency through development of a coding list of potential diagnoses that explained symptoms on the PHQ-15. This list was revised iteratively in discussion with my clinical supervisors, as I came across new diagnoses or explanations or when any uncertainty occurred. However, this subjective judgement may have led to some bias and may reduce the reliability of the study in terms of participant identification. It is possible that some of the participants may have had some explanation or diagnosis which clinicians would consider to be adequate or reasonable and therefore not considered unexplained or even partially unexplained.

8.3.6 Sources of error

8.3.6.1 Measurement

Strengths of all the measures used in the study were discussed in section 4.9, however, some limitations warrant mention. First, the PHQ-15 does not identify whether the symptoms are unexplained. Therefore, I included a question to the screening questionnaire, which allowed participants to report whether they had an explanation for their symptoms, and if so what this explanation was. However, I did not enquire about each of the symptoms separately and it is possible that some participants only reported explanations for some of their symptoms.

The measures for depression (PHQ-9) and anxiety (GAD-7) are also widely used in clinical practice and research (Kroenke et al 2010). Scores of 10 are considered to be clinically relevant and facilitate the diagnosis of major depressive disorder, although some suggest that in primary care higher cut-offs of 12 or even 14, may increase accuracy (Kendrick et al., 2009; Mitchell et al., 2016). The GAD-7 is a measure of severity; although as scores increase the likely presence of anxiety disorder increases, a clinical interview is necessary to determine the presence of an anxiety disorder (Kroenke et al., 2010). The SF-12, which was used to measure physical and mental health functioning; it has been suggested that there are may be a bias with self-reported scores being consistently lower than when the measure is interviewer administered (Busjica et al., 2011).

A number of existing questionnaires were adapted and some new ones were developed for the purposes of this study. These included questions about childhood experiences, abuse, and self-management. For example, many validated questionnaires on childhood abuse were long and potentially too intrusive for a postal questionnaire therefore questions were reduced and adapted in consultation with my supervisors. This may have decreased the sensitivity and specificity of these measures, which may have impacted my findings. I also developed new questions on the availability of social support and to enquire about preferences for management of symptoms.

It was also noted that due to a typographical error in development of the questionnaire a running page header was incorporated in the questionnaire booklet, which asked the respondent to “please check that all questions were answered before turning the page”. This was despite the clearly stated statement within the body of the questionnaire, that those who did not want to answer questions on abuse could skip the question. This error may have inadvertently made some participants refrain from returning the questionnaire.

8.3.7 Sources of Bias

There are a number of biases that can occur in cohort studies that must be considered. These include selection and information bias.

8.3.7.1 Selection bias

Selection bias results from the impact of non-participation, non-response and loss to follow-up on how results are interpreted and the generalisability of the findings (Gordis, 2014). Although I aimed to screen consecutive patients, it is possible that this did not always happen, especially during busier times at each practice. Also, there may be some bias due to the fact that different demographics may be more likely to attend the surgery at certain times, for example, those who are working may be more likely to attend evening appointments. The impact of this bias was minimised by attending morning, afternoon and evening sessions. It was not

possible to obtain details of those who did not take part in the screening stage of the study other than brief reasons for non-participation. This is discussed in the next section.

8.3.7.2 Information bias

Information bias can result when: the quality or extent of information obtained for exposed participants is different to those who are unexposed; the assessor who determines the disease status is aware of the exposure status; or due to preconceptions which may result in unintentional biases to the analyses of data (Gordis, 2014). Due to the prospective nature of the study, information on exposure was collected prior to assessing the outcome using self-report questionnaires, thus minimising the potential for bias in assessment of exposures. Unintentional biases being introduced to the analysis of data was minimised by developing a statistical analysis plan prior to the data collection where it was decided that variables included in the multivariable models would be based on theoretical considerations and on statistical testing.

Another source of potential bias may have occurred during the collection of outcome data and data entry as I was not blinded to the details of the participants. Although this is a potential weakness, there was no other way to do this as the sole researcher for the study. In order to minimise this potential bias during data entry

from misclassification or by error, data was double checked at each stage. Between 10-25% of the data at each stage of the study was double entered by an independent person. There were minimal errors found; at each stage this was less than 1% and therefore such bias is unlikely.

8.3.8 Missing data

Missing data can introduce potential bias into a study and needs to be dealt with using an appropriate statistical method depending on how much is missing and the reason why it may be missing. In section 4.10.4, I discussed in detail the way in which missing data was handled with reference to guidance literature for the individual items used. As my study had very little missing data, both in terms of loss to follow-up and missing data in individual questions it was not necessary to use statistical methods to impute the data.

8.3.9 Chance: sample size and power

The study sample size was determined using a rule of thumb commonly used for determining sample size of prognostic studies, as discussed in section 4.10.2. Even after loss to follow-up, there was the potential to include up to 24 continuous variables in the model, provided there was no missing data. In order to ensure that each model was sufficiently powered, consideration was given to the amount of missing data and number of variables reduced using theoretical decisions and

conceptual group analysis. However, due to the large sample size and the numbers of variables that were carefully considered in each model, there can be reasonable confidence that the findings are not due to chance.

8.3.10 Confounding

Another important factor that must be considered is confounding; variables may directly or indirectly correlate with both the independent variable and outcome variable and contribute to false positive findings (Gordis, 2014). Potential variables associated with the primary outcome were carefully considered with reference to the literature and consideration of clinical value. For prospective cohort studies there is the potential to collect information on a wide range of potentially confounding variables. Although stringent efforts were taken to ensure that models were adjusted for potential confounding, it is possible that some confounding variables might not have been considered i.e., unmeasured confounding. For example, other comorbidities or long-term conditions with clear diagnoses (other than depression and anxiety), and current experience of abuse were not adjusted for.

8.4 Clinical, research and policy implications

The meaning of the study findings and the clinical and policy implications will be discussed in the following sections in relation to findings from the systematic literature review, the screening study, and the cohort study.

Past studies on UPS have used various terminologies and diagnostic criteria, thereby including participants with varying degrees of symptom severity and clinical characteristics. This means that it is difficult to determine what factors might be relevant to the majority of patients with UPS in primary care. It is therefore important to be clear about how UPS are defined in order to ensure that research carried out is applicable to the majority of those attending primary care as well as to identify best practice for managing these patients.

My study found that UPS are extremely common in primary care. It may be useful to screen frequently attending patients as a routine practice to detect potential patients with UPS and to engage with them before their symptoms become persistent or worse requiring further input. My findings also indicated that just under half of those screened reported some explanation for their symptoms; the majority of these were physical explanations. It is important to recognise that UPS can occur alongside existing medical diagnoses, increasing the level of burden and distress. The new developments to the DSM-5 are based along this line of thinking,

take into consideration symptom burden regardless of whether symptoms are explained or not (Dimsdale et al., 2013). It may therefore be beneficial for doctors to be taught to recognise and manage UPS alongside diagnosed disease or illness accordingly. Additionally, it may be useful to consider the development of more systematic and consistent ways to identify patient with such mixed explained and unexplained symptoms, for both clinical and research purposes.

A few participants reported psychological and functional explanations for their physical symptoms and some provided functional syndromes as explanations. This indicates that some individuals may be accepting of explanatory models that consider psychological explanations whilst for others a label is important. Tailoring explanations about their UPS to individual patients based on their explanatory models may be useful for doctors and beneficial to patients.

The percentage of those who reported planning to consult their GP about their UPS on the day of screening was relatively small and increased as symptom severity increased; this suggests that there may be a significant number with milder symptoms who are managing their symptoms themselves. Therefore, it may be advisable to identify those likely to have a poor outcome earlier in the process and manage them appropriately to prevent a chronic course.

I found that my study cohort was functionally impaired; with moderately severe somatic symptoms and that the majority had experienced symptoms for longer than one year. This study confirms the presence of patients with underlying psychological morbidity, but also that a large number of patients in primary care who are functionally impaired may not necessarily be suffering from comorbid depression and anxiety. Different management approaches may need to be considered for these two groups of patients.

At follow-up, my study cohort continued to be symptomatic and functionally impaired; over half reported that their symptoms were still unexplained, and physical and mental health functioning was poor. This suggests that for many, UPS may not be transient and that many will continue to be impaired over time. Therefore, it is vital that individuals are managed appropriately in the long term, to reduce the burden on themselves, health care resources and the wider economy. It may be useful to take an approach to health care advocated for other long term conditions, by engaging with the patient, involving them in decisions about their care and supporting self-management as well as providing emotional, psychological and practical support (Coulter et al 2013).

Preferences for support in my study were more often from general practitioners. This was closely followed by the internet and family and friends. There may be value

in considering management strategies that connect general practice with validated online resources and developing existing resources further.

Based on the current findings, baseline symptom severity is a good indication of how the patient will progress over a six-month period. This should be taken into consideration by general practitioners, policy makers and health service planners, as well as in research when developing interventions. A fairly high proportion of study participants were still receiving investigations at the follow-up stage and it is important for doctors to be aware that continuing investigations can perpetuate symptoms rather than resolve them, as well as lead to a number of iatrogenic consequences (Page and Wessley, 2003).

The results of my study suggest that a relatively small range of identifiable predictors are associated with adverse outcomes over time, within my study cohort. It may be beneficial for general practitioners to explore the role of current and past context within the life of the patient in managing symptoms. Management strategies both at the early stages and over time can consider addressing symptom burden, current physical and mental health, recent stressful life-events and historical factors such as abuse.

Importantly, this thesis makes a valuable contribution to informing the guidance mentioned in chapter 1.11 titled ‘Guidance for health professionals on medically

unexplained symptoms' developed by Chitnis and Colleagues (2014). Due to the scarcity of studies of primary care attenders with UPS, the evidence used in this guidance focussed on people with psychiatric disorders, hypochondriasis, hysteria or somatoform disorder as well as on those seen in secondary care or recruited from the community rather than primary care. As previously discussed in this thesis, these populations are likely to differ from primary care attenders. The findings from my study will inform the guidance based on data from a UK primary care population with UPS.

The guidance suggests that '75% remains unexplained at 12 months'; my findings suggest that this figure may be lower, I found that 55% continue to experience UPS at 6 month follow up. The document further suggests that UPS are more likely to be common amongst women and those who have experience of physical abuse and that there was no preponderance of these symptoms in any specific age group. My work supports these suggestions and additionally identified potential risk factors such as poor financial situations (which may be a proxy for current stressful situation) and poor physical health functioning (proxy for poor physical health).

The guidance states that around 30% (10-80%) have an associated psychiatric disorder; I found that around a third have associated depression and anxiety. This leaves us with a considerable proportion of people with UPS that do not have clinical significant depression and anxiety. My study provides evidence that

patients often present with unexplained symptoms alongside explained symptoms. I found that 33% of those who were screened at baseline had symptoms that were explained by a physical diagnosis alongside their UPS. Finally, the guidance suggests that patients should be reassured that long-term improvement may occur without providing an estimate of recovery. In my study I found that 11% of people report recovery at six months.

8.5 Future research

This study explored participant outcomes over a six month period, but it may be useful to explore outcomes over a longer period. Additionally, the majority of those participating in this study reported baseline symptoms that had been present for over a year; therefore, it would be useful to explore those attending general practice with symptoms for the first time and identify prognostic factors which can predict those whose symptoms will remain unexplained. However, such a study would need a large sample size as a proportion of people are likely to receive an organic diagnosis. The time required to confirm that a symptom is unexplained would mean that the study would require a long follow-up period.

This study identified a number of prognostic factors associated with somatic symptom severity, such as quality of life, depression, anxiety and primary health care use. However, it does not have an adequate sample size to conduct confirmatory prognostic model analysis. Future research can take further the

factors identified in this study to develop a prognostic model from a new study cohort and then validate it in an external cohort (see section 3.1). This would involve the identification of a new sample of primary care attenders with adequate follow up over an appropriate time frame to develop a prognostic model that would then be validated in another longitudinal cohort of primary care attenders

Finally, future research would benefit from the inclusion of qualitative methodologies. Semi-structured individual interviews and focus groups could be employed to further explore patients' perspectives on UPS. The use of such methods would be particularly useful in helping us to understand in greater depth at which point patients decide to see their doctor and what influences this decision.

8.6 Conclusion

To my knowledge, this is the first study carried out on primary care attenders in the UK, who were recruited based on the severity of their somatic symptom and their self-reported presence of UPS, to explore outcomes of UPS and prognostic factors associated with symptom severity.

My study has found that primary care attenders with UPS are functionally impaired and around half remain symptomatic and functionally impaired at six months. Several prognostic factors were associated with somatic symptom severity at six

months. These were: being female, higher baseline somatic symptom severity, poorer physical health functioning, perception of poor financial well-being and experience of childhood physical abuse. Future work should determine whether these findings are maintained over longer periods. The value of developing prognostic prediction models based on factors identified in this study should also be explored.

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Appendix 1

Appendix 1.1 Past diagnostic categories relating to UPS

DSM-IV Somatoform disorders	ICD-10 Somatoform disorders
Somatisation Disorder History of physical complaints beginning before age 30 years occurring over several years , resulting in treatment being sought or a significant impairment of functioning/ not fully explained following appropriate investigation by a known general medical/ physical condition or in excess. Not intentionally produced or feigned. Symptoms from following areas: 1) Four pain symptoms and a history of pain related to at least four different sites or functions 2) Two gastrointestinal symptoms and a history of at least two gastrointestinal symptoms other than pain 3) One sexual symptom and a history of at least one sexual or reproductive symptom other than pain 4) One pseudo-neurological symptom with a history of at least one symptom or deficit suggesting a neurological condition not limited to pain.	**Somatisation disorder** A) A history of at least two years complaints of multiple and variable physical symptoms that cannot be explained by any detectable physical disorders. Known physical disorders or social disability do not explain the severity, variety, extend or persistence. B) Preoccupation with the symptoms causes persistent distress repeated seeking (three or more) of consultations or sets of investigations with medical practitioner/persistent self-medication/ or multiple consultations with local healers C) Persistent refusal to accept medical advice that there are no adequate physical causes except for short periods or during/ immediately after medical investigations. D) A total of six or more symptoms from the group gastro-intestinal symptoms, genito-urinary symptoms, skin and pain symptoms, with symptoms occurring in at least two separate groups E) Symptoms not restricted to any schizophrenic or related disorders, or any mood or affective disorders.
Undifferentiated Somatoform Disorder One or more physical complaints with duration of at least 6 months. After appropriate investigation symptoms, cannot be fully explained by a known general medical condition, direct effect of a substance/ or when related to a medical condition, physical complaints and functional impairment (social/ occupational) is in excess of expected (from the history, physical examination or laboratory findings) and clinically distressing. Disturbances not accounted for by any other mental disorder	**Undifferentiated Somatoform Disorder** Criteria C and B for somatization disorder are incompletely filled. A) A history of at least two years complaints of multiple and variable physical symptoms that cannot be explained by any detectable physical disorders. Known physical disorders or social disability do not explain the severity, variety, extend or persistence. Duration of disorder is at least 6 months. C) Persistent refusal to accept medical advice that there are no adequate physical causes except for short periods or during/

DSM-IV Somatoform disorders	ICD-10 Somatoform disorders
Symptoms not intentionally produced or feigned (fictitious disorder or malingering)	immediately after medical investigations. E) Symptoms not restricted to any schizophrenic or related disorders, or any mood or affective disorders.
Conversion Disorder • One or more symptoms or deficits which affect voluntary motor or sensory function that suggest a neurological or other general medical condition. • Causes clinically significant distress and impairment in all areas of functioning or warrants medical evaluation • Initiation or exacerbation of symptoms are preceded by conflicts or other stressors • Symptoms or deficit not produced or feigned/ Not explained by a general medical condition or effect of substances after appropriate investigation • Symptoms or deficit not limited to pain and does not occur exclusively during course of somatization disorder	
Pain Disorder • Associated with psychological factors • Associated with both psychological factors and a general medical condition	**Persistent Somatoform Pain Disorder**
Hypochondriasis Preoccupation with fear or idea that one has a serious disease based on the persons' misinterpretation of bodily symptoms, which persists despite appropriate investigation and reassurance. Causes clinically significant distress and duration of disturbance is at least 6 months. Preoccupation not explained by GAD, OCD, PD, Major depressive episode, separation anxiety of somatoform disorder.	**Hypochondriacally Disorder** Persistent belief of at least 6 months' duration of the presence of a maximum of two serious physical diseases of which at least one must be named by the patient or persistent preoccupation with a presumed deformity or disfigurement Preoccupation with beliefs and symptoms causes distress or interference with personal functioning and results in seeking treatment Refusal to accept that there is no physical cause for the symptoms or physical abnormality.
Body Dysmorphic Disorder	-
Somatoform Disorder Not Otherwise Specified (NOS) Somatoform disorders which do not meet criteria for any specific somatoform	Other/ Unspecified Somatoform Disorder Any other disorders or sensation, function and behaviour not due to physical disorders, which are not mediated

DSM-IV Somatoform disorders	ICD-10 Somatoform disorders
disorder	through the autonomic nervous system, which are limited to specific systems or parts of the body, and which are closely associated in time with stressful events or problems.
	Somatoform Autonomic Dysfunction Symptoms presented by the patients as if they were due to physical disorder of a system or organ that largely or completely under autonomic innervation and control such as the cardiovascular, gastrointestinal, respiratory. Complaints are based on objective signs or autonomic arousal such as palpitations, sweating, flushing Secondly there are subjective complaints of non-specific or changing nature such as fleeting aches and pains, sensations of burning, feeling of bloated or distended.

Appendix 1.2 Changes to diagnostic categories

DSM-V Somatic Symptom and Related Disorder **Somatic Symptom Disorder** A. One or more somatic symptoms that are distressing or result in significant disruption of daily life B. Excessive thoughts, feelings, or behaviours related to the somatic symptoms or associated health concerns as manifested by at least one of the following: 1. Disproportionate and persistent thoughts about the seriousness of one's symptoms. 2. Persistently high level of anxiety about health or symptoms. 3. Excessive time and energy devoted to these symptoms or health concerns. C. Although any one somatic symptom may not be continuously present, the state of being symptomatic is persistent (typically more than 6 months). Specify if: With predominant pain (previously pain disorder Specify if: Persistent: A persistent course is characterized by severe symptoms, marked impairment, and long duration (more than 6 months). Specify current severity: Mild: Only one of the symptoms specified in Criterion B is fulfilled. Moderate: Two or more of the symptoms specified in Criterion B are fulfilled. Severe: Two or more of the symptoms specified in Criterion B are fulfilled, plus there are multiple somatic complaints (or one very severe somatic symptom).
Illness Anxiety Disorder Specify whether: care seeking type, care avoidance type
Conversion Disorder (Functional Neurological Symptom Disorder Specific symptom type: With weakness of paralysis; with abnormal movement; with swallowing symptoms; with speech symptom; with attacks or seizures; with anaesthesia or sensory loss; with special sensory symptoms
Psychological factors affecting other medical conditions Specific current severity: Mild, Moderate, Severe, Extreme
Factitious Disorder (includes Factitious Disorder Imposed on Self, Factitious Disorder Imposed on Another) Specify Single episode/ recurrent
Unspecified somatic symptom and related disorder Other specified somatic symptom related disorder

Appendix 2

Appendix 2.1 Key words and terms for UPS used in literature search

Key words and phrases for unexplained symptoms
Somatoform Disorders
Psychosomatic Medicine
Somatisation
Somatoform.mp
(non organic$ or nonorganic)
(unexplain$ adj1 medical$)
((non specific or nonspecific) adj3 (symptom$ or problem$ or condition$ or complain$)).ti,ab.
(unexplain$ adj3 (symptom$ or problem$ or condition$ or complain$)).ti,ab.
((unexplain$ or inexplain$ or nonspecific or non specific) adj3 (health$ or medical$ or physical$) adj3 (symptom$ or problem$ or condition$ or complain$)).ti,ab.
(frequent$ adj1 attender$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

Appendix 2.2 Key words and terms for UPS used in literature search

Key terms and phrases for primary care
(primary adj2 (care or healthcare)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
(community adj2 (care or healthcare)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
exp General Practice/
Primary Health Care/
exp general practitioners/ or exp physicians, family/ or exp physicians, primary care/
general practitioners.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
family adj1 physician$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
(general adj1 practitioner$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
(primary adj2 (care or healthcare)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
general practice.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
GP.mp.
((family or community or district or practice or general *) and (doctor or physician or practitioner*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
physicians, family/ or physicians, primary care/

Appendix 2.3 Studies short listed for full text screening but excluded from the systematic review

Reference/ country	Cohort recruited for an intervention	Restricted population*	Other reason/ further details
Arnold et al., 2006/ Netherlands	X	X	
Blankenstein et al., 2001/ Netherlands.	X	X	
Cape et al., 2001/ UK		X	
Craig et al., 1993/UK		X	Prior to 1994- an criteria to study
De Gucht et al 2004/ Netherlands		X	
De Waal et al., 2008/ Netherlands	X		
Downes-Grainger et al., 1998/ UK		X	
Frostholm et al., 2007/ Denmark	X		
Gureje and Simon al., 1999/ 15 sites in 14 countries (WHO Mental Health Study).		X	
Hansen et al., 2011/ Denmark			
Hansen et al., 2011/ Denmark	X		
Hilbert et al., 2010/ Germany	X		
Jackson and Passamnoti,2005 /USA	X		
Frostholm et al., 2007	X		
Koch et al., 2009/ Netherlands	X		Based on one primary illness complaint
Kisely and Simon, 2006/ 15 sites in 14 countries (WHO Mental Health Study).		X	
Kooiman et al., 2004/ Netherlands	X		Based on outpatients with Alexithymia

Reference/ country	Cohort recruited for an intervention	Restricted population*	Other reason/ further details
Ladwig et al.,/ Germany			Data from population based study on MONICA (monitoring trends and determinants on cardiovascular diseases)
Mewes et al., 2008/ Germany			Not a longitudinal study and Not based on primary care population.
Rosmalan et al., 2010/ Netherlands			A population-based cohort study which screened and included people with high micro-albuminuria and cardiovascular diseases
Salmon et al., 2009/ UK			Not a longitudinal study. Focus also different to aim of literature review
Speckens et al., 1996/ Netherlands			Included patients identified in out-patient clinics
Taylor et al., 2012/ UK			Specific focus to explore role of insecure attachment amongst frequent attenders
Van den Berg et al., 2009/ Netherlands		X	Participants recruited after a traumatic experience (disaster)
Van Boven et al., 2011/ Netherlands		X	Based on single illness episodes
Van der Windt., et al 2008/Netherlands			Not a longitudinal study
Verhaak and Tijhuis, 1994/ Netherlands		X	Patients recruited specifically after a disaster
Veerkhak et al., 2006/ Netherlands			Based on symptom clusters- Pain, Irritable Bowel Syndrome, Fatigue, Depression, Anxiety

*includes populations with somatoform disorders, somatisation, single illness episodes and/or populations with psychiatric morbidity.

Appendix 2.4 Summary of potential prognostic factors to consider from excluded studies

Reference/ Country	Reason for exclusion from systematic review	Definition (criteria used)	Number enrolled/ duration of Follow-up	Outcome and Direction of significant association
Blankenstien, 2001/ Netherlands	Data from two studies with identical designs that were testing two interventions for somatisation	Somatisation (DSM-III-R)	376 (Baseline) 339 (2 years)	**Predictors of better subjective health (adjusted)** -Baseline subjective health status(adjusted OR 1.03 p<0.001) -Social support (adjusted OR=1.03 p=0.05) **Higher health care visits** -Baseline health care visits (adjusted OR=1.02 p=0.04) -Social support (adjusted OR=0.95 p=0.002)
Craig et al 1993/ UK	Based on population with emotional disorder and recent physical symptoms	Somatisers (DSM-III-R)	184 (BL) 153 (2 years)	**Predictors of somatisation in adults** -Childhood illness (OR=3.97 95% CI 1.81 to 8.72) -Lack of care (OR=3.96 95% CI 1.5 to 10.33)
De Gucht et al 2002/ Netherlands	Focus on those with alexithymia and neuroticism, extreme personality dimensions.	Somatisation disorder (SD) (DSM-III-R/DSM-IV)/MUS	377 (BL) 318/377 (6 months) 6months	**Increase in number of MUS** -Negative affect (OR=1.78 95% CI 1.33 to 2.39 -Positive affect (OR=0.71 95% CI 0.54 to 0.94 **Symptom persistence or recurrence** -Females (OR=2.29 95% CI 1.14 to 4.62 -High negative affect (OR= 2.77 95% CI 1.46-5.27 -Difficulty identifying feelings (dimension of alexithymia) (OR=1.08 95% CI 1.02-1.14
De Waal et al 2008/ Netherlands	Participants were followed up for a period of six months in order to identify those eligible for participation in a CBT trial.	SD (DSM-IV)	404 high-risk sample and 83 low risk sample.	**FP-consultation rate** (adjusted**)** -Undifferentiated SD (IRR= 1.3 95% CI 1.1–1.7) -Somatic morbidity score Intermediate (5-8) (IRR=1.2 95% CI 1.0 to 1.4) High score (≥9) (IRR=1.6 95%1.3 to 1.9) -Depressive disorders (IRR= 1.5 95% CI 1.0 to 2.3)

Reference/ Country	Reason for exclusion from systematic review	Definition (criteria used)	Number enrolled/ duration of Follow-up	Outcome and Direction of significant association
				-Anxiety disorders (IRR=0.9 95% 0.7 to 1.4)
Gureje and Simon, 1999	Inclusion of participants based on presence of psychiatric morbidity	Abridged somatization/ Somatic symptom Index	1596 met the criteria for SSI at baseline. 522/1071 met criteria at FU/12 months	**Persistence of abridged somatisation** (adjusted) -Self-rated poor overall health (OR 1.82 95% CI 1.32 to 2.52) -Moderate/severe occupational disability (OR 1.55 95% CI 1.17-2.06) **Emergence of new somatoform disorder** -Self-rated poor health (OR=2.26 95% CI 1.61 to 3.19 p) -Depression (OR=1.62 95% CI 1.10 to 2.37)
Hansen et al 2011 Denmark	Data from a large prospective intervention study	MUS and Functional diagnosis/ ICD-10/ GP rated	1728 (550 included in self-reported health analysis & 670 included in health service costs analysis)	**Predictors of poor physical health** (adjusted) - GP rated MUS (OR=0.56 95% CI 0.32 to 0.98) - ≥ 4 symptoms (OR=5.35 95% CI 2.28 to 12.56) **Predictors of good physical health** (adjusted) - Education (>basic school) (OR=0.20 95% CI 0.07 to 0.57) **Predictors of poor mental health (adjusted)** -MUS GP rated (OR 1.90 95% CI 1.00 to 3.58) - > 4 symptoms (OR 2.17 95% CI 1.02 to 4.59 p=0.04) **Predictors of good mental health** (adjusted) Education (>basic school) (OR=0.68 95% CI 1.02 to 4.59) **Predictors of high primary health care use** -Female gender (OR=2.63 95% CI 1.4 to 4.9) **Predictors of high total health care costs** -High users of health care (OR=5.56 95% CI 3.21 to 9.50) -Female (OR=3.34 95% CI 1.92 to 5.81) ->4 symptoms (OR=2.82 95% CI 1.11 to 7.16)
Hilbert at el 2010 Germany	Part of an intervention study	MUS/ SD (DSM-IV)	127/6 months	**Symptom severity** (adjusted) -Duration of relationship (B=0.08 SE 0.05) -Baseline symptom severity (B=0.68 SE 0.09) -Baseline health care use (B=0.01 S.E 0.00)

Reference/ Country	Reason for exclusion from systematic review	Definition (criteria used)	Number enrolled/ duration of Follow-up	Outcome and Direction of significant association
				Health care use (adjusted) -Baseline health care use (B=0.56 S.E 0.06)
Jackson and Passamonti, 2005 USA	Cohort established for an intervention.	Physical symptoms/multi-somatoform disorder	500/ 3 months and	**Symptom resolution at 3 months** - Shorter symptom duration at presentation (p<0.001) -No immediate post-visit worry (RR: 1.41, 95% CI: 1.02 to 1.92), -Baseline functional status (p=0.002) -Multi-somatoform disorder (RR= 0.70, 95% CI 0.51 to 0.96) -Symptom resolution at 2 weeks (RR=2.6%, 95% CI 2.1 to 3.3)
Frostholm et al 2007/Denmark-Aarhus county	Cohort established for intervention	MUS/ GP rated	1785 229 with MUS/ 3 months	**Mental health** (adjusted) - 1 Illness perceptions (b=-0.3 95% CI -4.1 to 3.5) -2 Illness perceptions (b=-0.9 95% CI -6.7 to 4.9) -3 Illness perceptions (b=-2.7 95% CI -8.2 to 2.8) **Physical health** (adjusted) -1 Illness perceptions (b=-2.0 95% CI -4.7 to 0.6) -2 Illness perceptions (b=-5.7 95% CI -10.3 to -1.1) -3 Illness perceptions (b=-2.9 95% CI -6.0 to 0.3)
Kisely & Simon 2006	Inclusion of participants based on presence of psychiatric morbidity	MUS/ CIDI diagnostic interview/ Patient report and interviewer rated	3201 (2198 with at least one medically unexplained symptom) / 12 month	**Psychiatric case based on GHQ** (adjusted) - MUS (OR 1.05 95% 1.02-1.08) **Psychiatric case based on CIDI** (adjusted) - MUS (OR 1.13 95% ci 1.1 to 1.2) **Generalised anxiety** (adjusted) - MUS (OR 1.07 95% 1.03 to 1.1) **Depression** (adjusted) -MUS (OR 1.06 95% 1.02 to 1.1) **Physical disability** (adjusted) -MUS (OR 1.12 95% 1.1 to 1.15) **Social disability (GSDS)** (adjusted) - MUS (OR 1.06 95% 1.03 to 1.9)

Reference/ Country	Reason for exclusion from systematic review	Definition (criteria used)	Number enrolled/ duration of Follow-up	Outcome and Direction of significant association
				Prescribed psychotropic (adjusted) - MUS (OR 1.06 95% 1.02 to 1.1) **>4 Clinic visits** (adjusted) - MUS (OR 1.05 95% 1.03 to 1.09)
Koch et al 2009 Netherlands	Part of a randomised controlled trial and based on a single main illness complaint	Unexplained complaints (included fatigue, musculoskeletal and abdominal)/ GP identified	444 /12 months	**Remission of unexplained symptoms** -Male (OR= 0.6 95% CI 0.4–0.8) -Abdominal complaints (OR=0.5 95% CI 0.3–0.8) **Persistence of unexplained symptoms** -Musculoskeletal complaints (OR2.3; 95% CI 0.81–1.76) **Unfavourable course, mental health functioning** -Presence of psychosocial factors such as stress, depression or anxiety (B=-5.02 95% CI -6.90 to -3.15) -Presence of complaints >6 months before presentation B=-2.81 95% ci -4.88 to -0.74 **Favourable course of mental health functioning** -Musculoskeletal complaints (B=5.45 95% CI 3.00 to 7.90) -Self-perceived quality of life (B=0.16 95% CI 0.11 to 0.21) -Passage of time b= 0.37 (per month 95% 0.29 to 0.45) **Unfavourable course, physical functioning** **-**Older age (B=-0.10 95% CI -0.14 to -0.05) -Musculoskeletal complaints (B=-4.65 95% CI -6.70 to -2.60) -Psychological factors (b=1.96 95% CI 0.45 to 3.46) -Presence of previous episodes (b=-2.04 95% CI -3.71 to -0.38) **Positive course, physical functioning** -Abdominal complaints (B=0.39 95% CI -1.80 to 2.59) -Self-perceived quality of life at baseline (0.13 95% CI 0.08 to 0.17) -Passage of time (b=0.3 per month 95% CI 0.22 to 0.36)

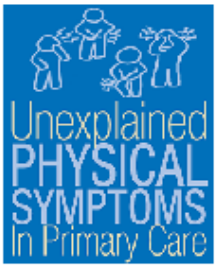
Reference/ Country	Reason for exclusion from systematic review	Definition (criteria used)	Number enrolled/ duration of Follow-up	Outcome and Direction of significant association
				-Establishment of explanation (b=1.11 95% CI 0.06 to 2.16)
Van Boven et al (2011)/ Netherlands	Symptom episodes	Unexplained symptoms/ somatoform disorder/ PHQ-15 (excluding menstrual and sexual symptoms)	16,000 symptom episodes/ 3 months	**Anxiety episode within three months** Somatoform symptom episode 'palpitations' tripled the risk of anxiety post-test Disturbances in sleep doubled risk of anxiety **Depressive disorder within three months** Not raised by somatoform symptom Episodes of lower back complaint decreased risk of depression by half

Appendix 3 : Recruitment and study Material

Appendix 3.1 GP Recruitment Email

University College Medical School
Research Department of Primary Care and Population Health

Upper 3rd Floor Royal Free Hospital
Rowland Hill Street, London NW3 2PF
Phone: Tel: 0207 794 0500 Ext 38527
E-mail: kethakie.sumathipala.11@ucl.ac.uk



We would like to invite your practice to take part in this exciting new study on 'Unexplained Physical Symptoms in Primary Care.' This is a research project undertaken as a part of a PhD, funded by the NIHR School for Primary Care Research and University College London.

Unexplained physical symptoms cost the NHS around £3 billion, approximately 10% of the annual NHS spending for the working population. This increases to over £14 billion when other cost such as sickness absence is taken to account. This study will aim to determine the natural course, morbidity and health care use in patients with unexplained physical symptoms in primary care, over one year. Knowledge of the characteristics of those who are at risk of poor outcome and those with a greater chance of a more favorable outcome should provide a better understanding of the best course of action for individual patients and provide patients with a better idea of what to expect.

The study will:

- Identify potential participants from general practice waiting rooms from between 4-8 practices in North and Central London with significant somatic symptoms using a short screening questionnaire.
- Eligible participants will be sent information about the study and invited to take part. If they are interested, written consent will be obtained, including for access to their medical records, to check that no diagnosis has been made for these symptoms.
- Participants will be invited to complete a baseline questionnaire
- Participants will be followed up with short questionnaires at six months and one year to determine the outcome of their symptoms
- Identify the course that unexplained symptoms take over a year and factors that are predictive of a good or poor outcome.

If you would like further information please contact: Ms Kethakie Sumathipala, Researcher Tel: 0207 794 0500 Ex 38821; E-mail: kethakie.sumathipala.11@ucl.ac.uk. If I am unable to answer your queries, I will pass these across the Professor Irwin Nazareth, Professor of Primary Care and Population Science, Department of Primary Care and Population science email: i.nazareth@ucl.ac.uk

This study is funded by UCL and NIHR School for Primary Care Research
GP invitation email V3 27.09.12

NHS National Institute for Health Research
REC ref: 12/LO/1885

Appendix 3.2 GP Recruitment Information Leaflet

University College Medical School
Research Department of Primary Care and Population Health

Upper 3rd Floor Royal Free Hospital
Rowland Hill Street, London NW3 2PF
Phone: Tel: 020 7 794 0500 Ext 38527
E-mail: kethakie.sumathipala.11@ucl.ac.uk

PRACTICE INFORMATION SHEET

We would like to invite your practice to take part in our research study. This leaflet explains why the research is being done and what it would involve for you. Please ask us if anything is unclear or if you would like more information. Thank you for taking the time to read this.

What is the purpose of this study?

Up to a third of people attending primary care have physical symptoms that are not explained even after examination and investigation. These symptoms can be distressing for patients and their families, difficult for GPs to manage and account for high levels of service use and investigation costs. It is estimated that the annual additional cost to UK health services is around £3 billion, approximately 10% of the annual NHS spending for the working age population. This increases to around £14 billion when other costs such as sickness absence area taken to account. Up to half such patients are thought to experience spontaneous resolution of their symptoms but a significant proportion continues to experience distressing symptoms and require ongoing care. Little is known about the course of unexplained physical symptoms or about the specific factors that may determine the outcome of patients over time, particularly in primary care. Knowledge of the characteristics of those who are at risk of poor outcomes and those with a greater chance of a more favorable outcome should provide a better understanding of the best course of action for individual patients. This study will aim to determine the natural course, morbidity and the health care use in patients with unexplained physical symptoms in primary care over one year.

Who is organising and funding this research?

This is a research project undertaken as a part of a PhD funded by NIHR School of Primary Care Research and University College London. It is being carried out by Kethakie Sumathipala and supervised by a team of GPs from University College London, Professor Irwin Nazareth (chief investigator), Dr Marta Buszewicz and Dr Kate Walters,

What would the study involve for my practice/my patients?

The study aims to recruit around 360 patients with unexplained physical symptoms from a number of practices in North and Central London. We would ask your practice to help us in the first stage of the study which will be identifying patients with unexplained symptoms.

We will use a short screening questionnaire. This will include the patient health questionnaire somatic symptom module (PHQ-15) and some basic socio-demographic questions, as well as a reply slip for patient contact details and preferred way of contact.

We have identified three methods for the initial eligibility screening:

1) The receptionist will hand out patient information leaflet and screening questionnaire to patients checking in for their appointments. A researcher will be present on site to answer any questions. The practice will be reimbursed for receptionists' time.

2) The receptionist will hand out patient information leaflets to patients checking in for their appointments. In addition leaflets will be placed in the waiting room for people to pick up. The researcher will then approach patients who were given or picked-up the leaflet to answer any questions that they may have and to invite them to complete a screening questionnaire.

3) In the unlikely event that the waiting room methods of recruitment result in lower than anticipated recruitment rates, we will use practice database searches to inform postal recruitment. We will design these database searches using appropriate read codes to identify people who have attended within the last month, with either unexplained symptoms or multiple symptoms, from their electronic records. Practice GPs will be asked to exclude any patients who they think are unsuitable to contact. We will ask your

practice to send out information leaflets and screening questionnaire with a stamped addressed reply envelope, which we will supply, to all potentially suitable patients above the age of 18 years. Patients will be asked to reply directly to the research team if they are interested in taking part in the study. **The practice will be reimbursed for all database search and postal costs.**

What are the possible benefits of taking part?

Findings from this study will be used in the development of a prognostic tool to assist GP decision making about care for patients with unexplained symptoms.

What are the possible disadvantages of taking part?

In the unlikely event data base searchers are needed to assist in the recruitment of participants, we will request that your practice complete database searches using appropriate read codes, to identify potentially eligible participants and send out postal screening questionnaires. This will take up time for the GP but you will be fully reimbursed for your time and other costs.

What will happen to the results of the research study?

The findings will be written up and shared with a variety of audiences via newsletters and peer reviewed scientific journals, as well as presentations at local and national conferences. Your practice and patients will not be identified in any publication or presentation.

Who has reviewed the study?

The study has been reviewed by Brent local research ethics committee and been given full ethical approval.

If we are interested in taking part, what should we do next?

If you/your practice is interested in taking part, please contact Kethakie Sumathipala (details on the next page). We are very happy to answer any questions you may have and give further details by telephone, e-mail or in person, for example at a practice meeting.

Contact for Further Information

If you would like any further information, please contact the researcher Kethakie Sumathipala on 0207 794 0500 Ex 38821; E-mail: kethakie.sumathipala.11@ucl.ac.uk; or Research Department of Primary Care and Population Health, University College London, Royal Free Campus, Rowland Hill Street, London NW3 2PF

The **Chief Investigator of this study Professor Irwin Nazareth, he can be contacted on Email:** i.nazareth@ucl.ac.uk or Research Department of Primary Care and Population Health, University College London, Royal Free Campus, Rowland Hill Street, London NW3 2PF

Thank you for considering taking part in this study. ***Your help with this study would be greatly appreciated.***

This study is funded by UCL and NIHR School for Primary Care Research

NHS National Institute for Health Research

Appendix 3.3 Patient Information Leaflet

NEXT STAGE

1. If you have 3 or more significant symptoms which may be unexplained, you will be sent an information leaflet explaining the study further.

2. If you are happy to participate further, you will be asked to complete the baseline questionnaire booklet. You can complete this by yourself or a researcher can complete it with you either over the telephone or in person at a location convenient to you. It should take around 30 minutes

3. We will send you a further questionnaire to complete after six months and one year. These will take 15 minutes to complete.

4. We will send all participants a summary with the key findings at the end of the study.

If you would like any further details please contact the researcher Kethakie Sumathipala.
0207 794 0500 Extension: 38821

University College London Medical School
Upper 3rd Floor Royal Free Hospital
Rowland Hill Street
London NW3 2PF

kethakie.sumathipala.11@ucl.ac.uk

WHO IS CARRYING OUT THIS STUDY?

This research is being undertaken as a part of a PhD research project by Kethakie Sumathipala. It is supervised by a team of doctors from University College London. It involves several local GP practices. It is funded by the National Institute for Health Research School of Primary Care Research and University College London.

Please remember that you do not have to take part and you can change your mind at any time. It will not affect you care in any way.

Participation information sheet short V7 5.11.12

Participant Information Leaflet

Unexplained PHYSICAL SYMPTOMS In Primary Care

Did you know

up to a third of all people seen by GPs have symptoms that can't be explained, even after thorough examination & investigation!

UCL NHS
National Institute for Health Research

We are conducting a study to investigate and to understand how unexplained physical symptoms progress over time. For this study to give us the valuable information we are looking for, we need your help!

WHAT ARE UNEXPLAINED PHYSICAL SMYPTOMS?

Symptoms that cannot be explained by a general medical condition, even after thorough examination and investigation by a doctor are referred to as unexplained physical symptoms. Examples of such physical symptoms can include:

- Dizziness
- Headaches
- Shortness of breath
- Constipation, diarrhoea, nausea,
- Pain (for example back, stomach, arms, legs, joints or chest)
- Feeling tired
- Or any other bothersome symptoms

WHY IS THIS STUDY BEING CARRIED OUT?

Research suggests that in some people unexplained symptoms resolve but in others they may get worse over time. We want to see if we can predict when they are likely to get better and when they will probably get worse over time. This study will provide a better understanding of such unexplained physical symptoms and help GPs to provide appropriate information and care.

WHY ARE YOU BEING INVITED TO TAKE PART?

Today we are asking everyone above the age of 18 years, who is registered at this surgery to fill in a brief questionnaire about their symptoms. We hope to identify a group of people who experience physical symptoms that are bothersome for them but for which they have not been given a medical explanation.

Unexplained physical symptoms can have a negative impact on the quality of life of a person, as much as any known illness.

WHAT WILL HAPPEN TODAY?

We will invite you to fill out a short questionnaire on your bodily symptoms, how much they impact your life, whether you have seen a doctor about them and whether you have been given medical reason for any symptoms. You will not be required to take any medication or undergo any investigation as a part of the study.

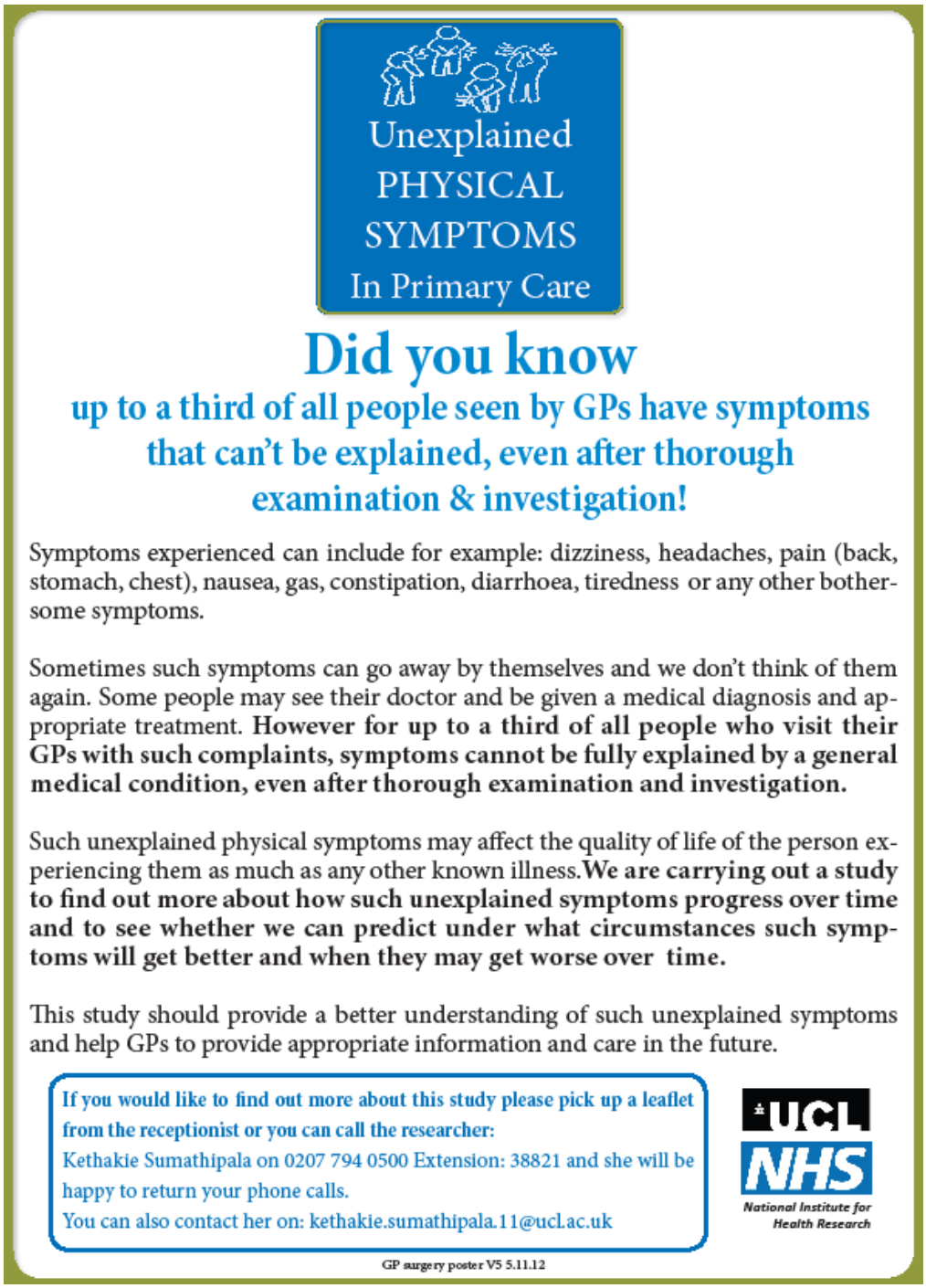
Please can you:

1. Complete the two page short questionnaire and return to reception or hand back to the researcher.

2. Provide us with your contact details, consent to be contacted regarding the next stage of the study and indicate how you prefer to be contacted (either by telephone or post).

Please turn the leaflet to find out more about what the next stages of the study will involve.

Appendix 3.4 Information used in General Practices



Unexplained
PHYSICAL
SYMPTOMS
In Primary Care

Did you know

up to a third of all people seen by GPs have symptoms that can't be explained, even after thorough examination & investigation!

Symptoms experienced can include for example: dizziness, headaches, pain (back, stomach, chest), nausea, gas, constipation, diarrhoea, tiredness or any other bothersome symptoms.

Sometimes such symptoms can go away by themselves and we don't think of them again. Some people may see their doctor and be given a medical diagnosis and appropriate treatment. **However for up to a third of all people who visit their GPs with such complaints, symptoms cannot be fully explained by a general medical condition, even after thorough examination and investigation.**

Such unexplained physical symptoms may affect the quality of life of the person experiencing them as much as any other known illness.**We are carrying out a study to find out more about how such unexplained symptoms progress over time and to see whether we can predict under what circumstances such symptoms will get better and when they may get worse over time.**

This study should provide a better understanding of such unexplained symptoms and help GPs to provide appropriate information and care in the future.

If you would like to find out more about this study please pick up a leaflet from the receptionist or you can call the researcher:
Kethakie Sumathipala on 0207 794 0500 Extension: 38821 and she will be happy to return your phone calls.
You can also contact her on: kethakie.sumathipala.11@ucl.ac.uk

UCL
NHS
National Institute for Health Research

GP surgery poster V5 5.11.12

Appendix 3.5 Screening questionnaire

Participant number ☐☐☐

Bodily Symptoms Questionnaire

We are conducting a survey of people visiting their GP today, to identify how many unexplained physical symptoms people experience. Please read the accompanying information sheet that will explain the purpose of the questionnaire further.

Please fill the questionnaire below if you are:

- Above the age of 18 years
- Are registered at the GP surgery you are visiting today and do not plan to change GP in the next six months

During the ***past 4 weeks***, how much have you been bothered by any of the following problems

Please tick one box for each of the problems	Not bothered at all	Bothered a little	Bothered a lot
Stomach pain	☐	☐	☐
Back pain	☐	☐	☐
Pain in your arms, legs, or joints (knees, hips, etc.)	☐	☐	☐
Menstrual cramps or other problems with your periods [Women only]	☐	☐	☐
Headaches	☐	☐	☐
Chest pain	☐	☐	☐
Dizziness	☐	☐	☐
Fainting spells	☐	☐	☐
Feeling your heart pound or race	☐	☐	☐
Shortness of breath	☐	☐	☐
Pain or problems during sexual intercourse	☐	☐	☐
Constipation, loose bowels, or diarrhoea	☐	☐	☐
Nausea, gas, or indigestion	☐	☐	☐
Feeling tired or having low energy	☐	☐	☐
Trouble sleeping	☐	☐	☐

PLEASE TURN OVER THE PAGE

Participant number ☐☐☐

1. Have you been given a medical reason for any of your symptoms by your doctor?

Yes ☐ No ☐

2 a) If yes, please state which symptom this was and what diagnosis you were given

Symptom 1 _____ Diagnosis _____

Symptom 2 _____ Diagnosis _____

Symptom 3 _____ Diagnosis _____

Symptom 4_____ Diagnosis _____

2b) Are you attending the GP about any of these symptoms today? Yes ☐ No ☐

Please fill in the brief information so that we can know a little bit more about you

Gender: Female ☐ Male ☐ Age: _____

THANK YOU FOR TAKING THE TIME TO COMPLETE THIS QUESTIONNARE.

We would like to contact you regarding the next stage of the study described in the accompanying information leaflet. Please complete the reply form below, if you are happy to be contacted.

Are you happy for us to contact you in the next two weeks? Yes ☐ No ☐

I would like to receive the study information and questionnaire by post ☐

I would like to discuss the study on the telephone with the researcher ☐

The best time to contact me is _____

If you are happy to be contacted please provide us with your name, address and your telephone number

Name _____

Telephone number _____

Address

House number/name_____Road_____

Town/City _____

Post code: _____

PLEASE RETURN THIS TO THE BOX AT THE RECEPTION OR TO THE RESEARCHER.

Appendix 3.6 Study invitation letter to eligible and consenting patients from screen stage

University College Medical School
Research Department of Primary Care and Population Health
Upper 3rd Floor Royal Free Hospital
Rowland Hill Street, London NW3 2PF
Phone: Tel: 0207 794 0500 Ext 38527
E-mail: kethakie.sumathipala.11@ucl.ac.uk

Unexplained PHYSICAL SYMPTOMS In Primary Care

Dear ,

Thank you for your interest in this study on *Unexplained Physical Symptoms in Primary Care* and for completing the eligibility questionnaire at your GP surgery on the [Date]. We would like to invite you to take part in the next stage of our study.

The aim of this study is to understand how unexplained physical symptoms progress in people over time and to find out if it is possible to predict when such symptoms are likely to get better and when they may get worse. **We need your help to carry out this study.** Taking part will involve filling out three questionnaires over the next year. In total these should take about one hour of your time. The questionnaire enclosed today will take about **30 minutes to complete**.

Before you decide whether to take part, please read carefully the enclosed information leaflet that will give you further details about this study. If you have any questions or would like to discuss the study please do not hesitate to contact me on 0207 794 0500 Ext 38527 and I will be happy to return your call.

If you would like to part in the study, please complete the consent form and questionnaire enclosed and return using the pre-paid envelope. If your stated preference for being contacted by telephone, I will be in touch with you shortly.
Thank you for taking the time to read about this study.

Yours Sincerely,
Kethakie Sumathipala

This study is funded by UCL and NIHR School for Primary Care Research

NHS National Institute for Health Research

Appendix 3.7 Patient information leaflet

Upper 3rd Floor Royal Free Hospital
Rowland Hill Street, London NW3 2PF
Phone: Tel: 0207 794 0500 Ext 38527
E-mail: kethakie.sumathipala.11@ucl.ac.uk

UCL

Unexplained PHYSICAL SYMPTOMS In Primary Care

PARTICIPANT INFORMATION LEAFLET

PhD RESEARCH PROJECT

We are conducting a study to find out more about the outcome of unexplained physical symptoms in primary care. We would like to see whether it is possible to predict when such symptoms get better and when they get worse over time.

This leaflet will give more details about the study we are conducting. Before you decide whether you would like to take part we would like you to explain why we are carrying out the research, why we are asking you to take part and what will happen if you get involved, as well as information about how we are carrying out the study.

We suggest that you take your time to read through the information sheet and if you wish, talk to your friends or family about the study and your participation. If you would like the researcher Kethakie Sumathipala to go through the information sheet with you or have any questions, please contact her on 0207 794 0500 Ex 38821 and she will be happy to return your call to discuss any concerns.

Thank you for reading this

Why are we doing the study?

This study is funded by UCL and NIHR School for Primary Care Research

NHS
National Institute for Health Research

Some people experience distressing physical symptoms which cannot be clearly explained by a general medical condition, even after they have had a thorough examination and any relevant investigations. Pain, headaches, dizziness, shortness of breath, constipation, diarrhoea, nausea, pain (for example back, stomach, arms, legs, joints or chest) or feeling tired are some common unexplained physical symptoms but there may be other bothersome symptoms as well. Up to a third of people seen by GPs have such symptoms. These symptoms can have a negative effect on the quality of life of the person experiencing them, as much as any other known illness. There is not much completed research about the outcomes of such unexplained symptoms. Although evidence suggests that some peoples' symptoms get better and others get worse, we don't know how to predict which category people are likely to fall into. This lack of understanding about who may improve or not means that people are left not knowing what to expect about how their symptoms may progress. We also don't know what people do for themselves to help improve their symptoms. **This study is designed to increase our understanding so that doctors and patients know what to expect and when further help is likely to be needed.**

Why are you asking me to take part?

We are asking you to take part as when you completed the initial questionnaire you suggested; 1) that you have some symptoms that bothered you; 2) you did not state a known medical diagnosis for your symptoms.

Do I have to take part?

It is up to you to decide to join the study. Please go through this information sheet carefully as it describes the study and what would happen if you take part. If you have any questions, please contact the researcher either by telephone, email or post. She will call you back and discuss any questions that you may have, with you. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

What will happen if I take part?

If you are happy to take part in the study, we will ask you to complete a questionnaire booklet which will take 30 minutes to complete. We are hoping to find out how peoples' symptoms progress over time, so we will ask you to complete a further questionnaire in six months and then in one year's time. These two should take about 15 minutes each to complete. As this study is carried out over time, it is referred to as a 'prospective longitudinal study'. You can

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complete these questionnaires by yourself and post back to us. If you prefer, you can complete it with the researcher over the telephone or in person at your home, your GP surgery or at the researcher's office, whichever is most convenient for you. If you meet us at a location outside your home, we will reimburse your travel expenses. We will also request your permission to check your GP medical notes, so that we can see any diagnoses and treatments which your doctor may have advised for your symptoms.

What are the possible disadvantages and risks of taking part?

There are no risks to taking part in the study. Some of the questions in the first booklet are of a potentially sensitive nature and there are several sections to complete. You don't have to complete the whole questionnaire at once. You can take your time to answer the questions and leave any sections blank if they are distressing for you.

What are the benefits of taking part?

The information we get from this study will help improve the understanding of unexplained physical symptoms and provide better care for people with such symptoms in the future.

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept securely and will have your name and address removed so that it will not be traceable back to you. The questionnaires you complete will be identified using a unique ID code. Identifiable material such as the consent form you sign will be kept securely under lock and key. Information stored on the computer will be encrypted and password protected. Any information that is identifiable to you will only be accessed by authorised persons, in this case the researcher and her supervisors. The encrypted study master files will be retained securely UCL for 20 years from the end of the study in accordance with the records retention schedule and will be disposed of securely following this period. Access to records is strictly regulated. If we would like to use any anonymised information which you have provided in future studies, we will obtain permission for this from the Research Ethics Committee.

What if there is a problem or something goes wrong?

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If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated by members of staff due to your participation in the research, National Health Service or UCL complaints mechanisms are available to you. Please ask the researcher if you would like more information on this. This study does not involve an intervention which means we will not ask you to take any medication or undergo and investigations as a part of this study. However in the unlikely event that you are harmed by taking part in this study, compensation may be available. If you suspect that the harm is the result of the sponsor's (University College London) or the hospital's negligence, then you may be able to claim compensation. After discussing with the researcher, please make the claim in writing to Dr Irwin Nazareth who is the Chief Investigator for the research and is based at University College Medical School, Hampstead. The Chief Investigator will then pass the claim to the Sponsor's Insurers, via the Sponsor's office. You may have to bear the costs of the legal action initially, and you should consult a lawyer about this.

What happens to the results?

Our findings will also be published in an academic journal and presented at relevant conferences in order to ensure that other patients and people working in the health service are aware of them. No information that you have provided will be identifiable to you. We hope that our findings from the study will help to improve understanding about unexplained physical symptoms and will allow doctors to better address patients' needs. A leaflet with the results of the study will be developed and sent to you for your information.

Who is carrying out the study?

This is a research project undertaken as a part of a PhD by Kethakie Sumathipala, who is being supervised by a team of academic GPs from University College London. It involves a number of local GP practices including your GP surgery. It is funded by the National Institute for Health Research, School of Primary Care Research. We will follow ethical and legal practice and any information which is collected about you during the course of the research will be kept strictly confidential. No information will be exchanged with your GP without your consent.

Please continue to see your GP as needed and follow any advice given.

This study is funded by UCL and NIHR School for Primary Care Research

NHS National Institute for Health Research

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by London Brent Research Ethics Committee (REF: 12/LO/1885)

If you would like further details please contact Kethakie Sumathipala on 0207 794 0500 Ex 38821 and she will phone you back. Professor Irwin Nazareth, the Chief Investigator of this study can be contacted at the postal address found at the top of this letter.

Your help with this study would be greatly appreciated

This study is funded by UCL and NIHR School for Primary Care Research

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Health Research

Appendix 3.8 Consent form

University College Medical School
Research Department of Primary Care and Population Health

Upper 3rd Floor Royal Free Hospital
Rowland Hill Street, London NW3 2PF
Phone: Tel: 0207 794 0500 Ext 38821
E-mail: kethakie.sumathipala.11@ucl.ac.uk

Consent Form

Study Number: Centre Number: Participant Reference Number for study:

Name of Chief Investigator: Professor Irwin Nazareth/ Researcher Kethakie Sumathipala

Please initial as appropriate each statement	Yes	No
1. I confirm that I have read the information sheet dated **25.09.2012(Version 7)** for the above study and have had the opportunity to ask questions and have had these answered satisfactorily.	☐	☐
2. I understand that my participation is voluntary and I am free to withdraw consent at any time, without giving a reason, without my medical care being affected.	☐	☐
3. I confirm that the researcher may have access to my medical notes to confirm my diagnoses and treatment relating to my symptoms.	☐	☐
4. I understand that relevant sections of my medical notes collected during the study may be looked at by responsible & authorised personnel from the study. I give permission for these individuals to have access to my records.	☐	☐
5. I understand that anonymised data collected may be looked at by responsible representatives from the sponsor (UCL) for the purposes of monitoring and auditing to ensure that the study is being conducted properly. I give permission for these individuals to have access to relevant information.	☐	☐
6. I agree to take part in the above study.	☐	☐

Name of participant (Print)	Signature of participant	Date
Name of Chief Investigator/ Researcher	Signature	Date

This study is funded by UCL and NIHR School for Primary Care Research

NHS National Institute for Health Research

Appendix 3.9 Baseline questionnaire

REC REC:12/LO/1885

BASELINE QUESTIONNAIRE

Participant study number _____
Date _____

Thank you for taking part in this study

This study aims to understand how unexplained physical symptoms progress over time and to get an idea of the characteristics of people whose symptoms may resolve and those whose symptoms may get worse.

For this study to be successful and give us the valuable information we are looking for, **we need your help**. We would be grateful if you could take the time to fill in this booklet. Each of the sections covers a different area and there is an explanation at the beginning of each of the sections. A few of the questions do overlap but we ask you to fill them all in as each question is important and especially chosen as they may impact on the experience of living with unexplained physical symptoms.

Please do not be put off by the number of questions as most of them are very straightforward. You do not have to fill in the booklet in one go. If you want you can take a break and come back to it later. It should take you no longer than 30 minutes to complete. All of the information you provide is confidential.

REC REC:12/LO/1885

Please send the completed booklet back to us using the stamped addressed envelope provided

If you need to contact us, please do so using the details provided.

University College Medical School
Research Department of Primary Care and Population Health

Upper 3rd Floor Royal Free Hospital
Rowland Hill Street, London NW3 2PF
Phone: Tel: 0207 794 0500 Ext 38821
E-mail: kethakie.sumathipala.11@ucl.ac.uk

This study is funded by NIHR School for Primary Care Research and University College London

Participant number ☐☐☐

PHQ-15

The following questions ask about your symptoms

1. During the *past 4 weeks*, how much have you been bothered by any of the following problems

	Not bothered at all	Bothered a little	Bothered a lot
a. Stomach pain	☐	☐	☐
b. Back pain	☐	☐	☐
c. Pain in your arms, legs, or joints (knees, hips, etc.)	☐	☐	☐
d. Menstrual cramps or other problems with your periods [Women only]	☐	☐	☐
e. Headaches	☐	☐	☐
f. Chest pain	☐	☐	☐
g. Dizziness	☐	☐	☐
h. Fainting spells	☐	☐	☐
i. Feeling your heart pound or race	☐	☐	☐
j. Shortness of breath	☐	☐	☐
k. Pain or problems during sexual intercourse	☐	☐	☐
l. Constipation, loose bowels, or diarrhoea	☐	☐	☐
m. Nausea, gas, or indigestion	☐	☐	☐
n. Feeling tired or having low energy	☐	☐	☐
o. Trouble sleeping	☐	☐	☐

2. Overall, how long have you being experiencing these symptoms?

Years _____ Months _____

Please check you have answered all the questions and turn to the next page

The following questions are about how you manage your symptoms

When someone faces a problem or a distressing experience relating to their health, they may turn to different people for advice, information, treatment, or general support. These may include, for example, their friends and family, their GP, alternative or complementary therapists, mental health professionals, clergy or the internet.

1. **How do you prefer to deal with your symptoms?**

Please tick one box

a. On your own ☐ Like some help for your symptoms ☐ Unsure ☐

2. **If you have ticked that you would like the help of others, who would you turn to?**
Please tick as many as which apply to you.

a. The internet ☐
b. Family ☐
c. Friends ☐
d. Religious or spiritual advisors ☐
e. Your GP ☐
f. A counsellor or psychotherapist ☐
g. Complementary therapists such as: massage, aromatherapy or homeopathy ☐
h. Other ____ ☐

3. **Have you used any other strategies to help cope with your symptoms.** Please list **as many things** as you think are relevant.

Please check you have answered all the questions and turn to the next page

SF-12

Your health and well-being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

For each of the following questions, please tick the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
b	Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3

Please check you have answered all the questions and turn to the next page

3. **During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. **During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. **During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Please check you have answered all the questions and turn to the next page

6. **These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...**

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a	Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	Have you felt downhearted and low?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Please check you have answered all the questions and turn to the next page

The following statements refer to how you feel your health has impacted on your abilities in work and day-to-day activities

0 refers to no impairment at all and 8 to severely impaired. Please *circle the number* which you feel best describes your situation.

1. Because of the way I feel, my ability to work is impaired

0= Not at all impaired	0 1 2 3 4 5 6 7 8	8= Severely impaired

2. Because of the way I feel, my home management (cleaning, tidying, shopping, cooking, looking after home or children, paying bills) is impaired

0= Not at all impaired	0 1 2 3 4 5 6 7 8	8= Severely impaired

3. Because of the way I feel, my social leisure activities involving other people (such as parties, outings, visits, dating, home entertainment, cinema) are impaired

0= Not at all impaired	0 1 2 3 4 5 6 7 8	8= Severely impaired

4. Because of the way I feel, my private leisure activities done alone (such as reading, watching TV, gardening, craft work, walking, sewing) are impaired

0= Not at all impaired	0 1 2 3 4 5 6 7 8	8= Severely impaired

5. Because of the way I feel, my ability to form and maintain close relationships with others, including those I live with is impaired

0= Not at all impaired	0 1 2 3 4 5 6 7 8	8= Severely impaired

Please check you have answered all the questions and turn to the next page

SELF-EFFICACY

The following statements are about how you feel about your ability to deal with different situations that you may face.

1 refers to no agreement at all, whilst 4 refers to considerable agreement. Please *circle the number* to show the extent to which you agree with each of the statements.

1. I can always manage to solve difficult problems if I try hard enough

1=Not true at all	1	2	3	4	4= Exactly true

2. If someone opposes me, I can find the means and ways to get what I want

1=Not true at all	1	2	3	4	4= Exactly true

3. It is easy for me to stick to my aims and accomplish my goals

1=Not true at all	1	2	3	4	4= Exactly true

4. I am confident that I could deal efficiently with unexpected events

1=Not true at all	1	2	3	4	4= Exactly true

5. Thanks to my resourcefulness, I know how to handle unforeseen situations

1=Not true at all	1	2	3	4	4= Exactly true

6. I can solve most problems if I invest the necessary effort

1=Not true at all	1	2	3	4	4= Exactly true

7. I can remain calm when facing difficulties because I can rely on my coping abilities

1=Not true at all	1	2	3	4	4= Exactly true

8. When I am confronted with a problem, I can usually find several solutions

1=Not true at all	1	2	3	4	4= Exactly true

9. If I am in trouble, I can usually think of a solution

1=Not true at all	1	2	3	4	4= Exactly true

10. I can usually handle whatever comes my way

1=Not true at all	1	2	3	4	4= Exactly true

Please check you have answered all the questions and turn to the next page

The following three sets of questions are about your emotions

Our emotions play a very important part in how we experience things. This set of questions are designed to help us to understand how you feel. Please don't take too long over your replies; your immediate reaction to each item will probably be more accurate than thinking a lot about your answers

GAD-7 BASELINE

For each statement, please give the answer that comes closest to the way you have been feeling.

Please tick one box for each statement **1. Over the last 2 weeks, how often have you been bothered by the following problems?**	Not at all	Several days	More than half the days	Nearly every day
a) Feeling nervous, anxious or on edge	☐	☐	☐	☐
b) Not being able to stop or control worrying	☐	☐	☐	☐
c) Worrying too much about different things	☐	☐	☐	☐
d) Trouble relaxing	☐	☐	☐	☐
e) Being so restless that it is hard to sit still	☐	☐	☐	☐
f) Becoming easily annoyed or irritable	☐	☐	☐	☐
g) Feeling afraid as if something awful might happen	☐	☐	☐	☐

Please check you have answered all the questions and turn to the next page

PHQ-9 BASELINE

Please tick one box for each statement **1. Over the last 2 weeks, how often have you been bothered by any of the following problems?**	Not at all	Several days	More than half the days	Nearly every day
a) Little interest of pleasure in doing things?	☐	☐	☐	☐
b) Feeling down, depressed or hopeless?	☐	☐	☐	☐
c) Trouble falling or staying asleep or sleeping too much?				
d) Feeling tired or having little energy?	☐	☐	☐	☐
e) Poor appetite or overeating	☐	☐	☐	☐
f) Feeling bad about yourself- or that you are a failure or have to let yourself or your family down?	☐	☐	☐	☐
g) Trouble concentrating on things, such as reading the newspaper or watching television?	☐	☐	☐	☐
h) Moving or speaking so slowly that other people could have noticed? Or- the opposite- being so fidgety or restless that you have been moving around a lot more than usual?	☐	☐	☐	☐
i) Thoughts that you would be better off dead, or hurting yourself in some way?	☐	☐	☐	☐

1b. **How difficult have these problems listed in the question above made it for you to do your work, take care of things at home, or get along with other people? Please tick *one* of the following.**

a. Not difficult at all ☐ b) Somewhat difficult ☐ c) Very difficult ☐ d) Extremely difficult ☐

Please check you have answered all the questions and turn to the next page

PHQ-PANIC

1. In the last 2 weeks, have you had an anxiety attack - suddenly feeling fear or panic?

Please tick one box
Yes ☐ No ☐ (If you answered no, you can skip the rest of question 1a and 1b on this page and continue with on to the next set of questions.)

*Please tick **one box** for each questions*	YES	NO
a. Has this ever happened before	☐	☐
b. Do some of these attacks come suddenly out of the blue; that is, in situations where you don't expect to be nervous or uncomfortable?	☐	☐
c. Do these attacks bother you a lot or are you worried about having another attack?	☐	☐
d. Were you short of breath	☐	☐
e. Did your heart race, pound, or skip?	☐	☐
f. Did you have chest pain or pressure?	☐	☐
g. Did you sweat?	☐	☐
h. Did you feel as if you were choking?	☐	☐
i. Did you have hot flashes or chills?	☐	☐
j. Did you have nausea or an upset stomach, or the feeling that you were going to have diarrhea?	☐	☐
k. Did you feel dizzy, unsteady, or faint?	☐	☐
l. Did you feel tingling or numbness in parts of your body?	☐	☐
m. Did you tremble or shake?	☐	☐
.n. Were you afraid you were dying?	☐	☐

1b. **How difficult have these problems listed in the question above made it for you to do your work, take care of things at home, or get along with other people? Please tick *one* of the following.**

a. Not difficult at all ☐ b) Somewhat difficult ☐ c) Very difficult ☐ d) Extremely difficult ☐

12

Please check you have answered all the questions and turn to the next page

LIFE EVENTS

The next set of questions enquires about any difficult events in your life in the last six months.

Please tick any / each box which applies to you over ***the past 6 months*** only.

1.	Yes	No
a. You yourself suffered a serious illness, injury, or an assault.	☐	☐
b. A serious illness, injury, or assault happened to a close relative.	☐	☐
c. Your parent, child, or spouse died.	☐	☐
d. A close family friend or another relative (e.g. aunt, cousin, grandparent) died.	☐	☐
e. You had a separation due to marital difficulties.	☐	☐
f. You broke off a steady relationship.	☐	☐
g. You had a serious problem with a close friend, neighbor, or relative.	☐	☐
h. You became unemployed or you were seeking work unsuccessfully for more than one month.	☐	☐
i. You were sacked from your job.	☐	☐
j. You had a major financial crisis.	☐	☐
k. You had problems with the police and a court appearance.	☐	☐
l. Something you valued was lost or stolen.	☐	☐

Please check you have answered all the questions and turn to the next page

CHILDHOOD EXPERIENCES

The following statements are about the health of your close family when you were growing up.

1. When I was growing up, a close family member suffered from a significant physical illness…

Please tick one box a.☐ **Yes** b.☐ **No** (If no please go to question 2)

1a. If yes, please explain the illness and say which family member(s) were affected.

_____

_____

2. When I was growing up, a close family member suffered from a significant mental illness…

Please tick one box a.☐ **Yes** b.☐ **No** (If no please go to question 3)

2a. If yes, please explain the illness and say which family member(s) were affected…

_____

_____

The following questions ask about possible negative experiences in your life while you were growing up. If you find them too distressing to answer you can leave the question unanswered.

3. When I was growing up, I had a traumatic experience (for example involved in a major accident, the victim of crime, death of a loved one)

Please tick one box ☐ **Yes** b.☐ **No** (If no please go to question 4)

3a. If yes, please explain the traumatic event.

_____

_____

4. I believe I was abused as a child

Please tick one box

a. Never true ☐ b. Rarely true ☐ c. Sometimes true ☐ d. Often true ☐ Very often true ☐

(If never true please skip question 4b and go to page 14)

4b. If yes, please tick which of these apply…

Please tick as many as which apply to you

Physical abuse ☐ Sexual abuse ☐ Emotional abuse ☐

Please check you have answered all the questions and turn to the next page

GENERAL INFORMATION ABOUT YOU

The first set of questions concerns general information about you

1. **Are you?** (please tick one box) ☐Male ☐ Female

2. **What is your date of birth?** __ __day __ __ month 19__ __year

3. **How would you describe your ethnic group?** *(please tick one box)*

a) White

1) White- British ☐
2) White- Irish ☐
3)White- Other (please specify) ☐
_____

b) Black or Black British

1) Black-Caribbean ☐
2) Black- African ☐
3) Black-other ☐

c) Asian or Asian British

1) Indian ☐
2) Bangladeshi ☐
3) Pakistani ☐
4) Chinese ☐
5) Other (please specify) ☐
_____

d) Mixed

1) White and black Caribbean ☐
2) White and black African ☐
3) White and Asian ☐
4) Any other mixed background ☐
(please specify)_____

e) Other

1) Arab ☐
2) Any other ethnic group ☐
(please specify)_____

4. **What is your current marital status?** *(please tick one box)*

a) Married ☐
b) Widowed ☐
c) Separated ☐
d) In a long term relationship ☐
e) Single ☐

Please check you have answered all the questions and turn to the next page

5. **What is your current employment status?** *(please tick one box)*

a) In paid employment or self-employment ☐

b) Unemployed and looking for work ☐

c) Retired ☐

d) Full-time education ☐

e) Unable to work because of long-term sickness or disability ☐

f) Looking after family or home ☐

g) Doing something else, please specify ☐

_____

h) Voluntary work ☐

6. **How well would you say you are managing financially these days?**

(please circle one as appropriate)

1	2	3	4
Living very comfortably	Doing alright	Finding it difficult	Finding it very difficult

7. **Please read the list of qualifications and tick only your highest qualification so far.**

a) O-levels/ GCSE/A-levels or equivalent ☐

b) Bachelor's degree (BA or BSc)/ Master's Degree (MA or MSc or PGCE) ☐

c) No qualifications ☐

d) Higher degree (PhD or equivalent ☐

e) Other qualifications (please specify): ☐

_____

Now we would like you to think about your partner, family, friends and neighbours. By family we mean those who live with you as well as those who live elsewhere.

8. Do you have someone you can turn to when you need any practical help or emotional support? *Please tick one box* a.☐ **Yes** b.☐ **No**

8a. If yes, please explain your relationship to them. For example this could be friend, neighbour, mother, father, sibling, partner, husband, wife, children or other relative.

Please check you have answered all the questions and turn to the next page

REC REC:12/LO/1885

THANK YOU FOR COMPLETING IN THIS BOOKLET.

If you have any further comments you wish to make please do so below.

Participant number ☐☐☐

Appendix 3.10 Six month follow-up invitation letter

Upper 3rd Floor Royal Free Hospital
Rowland Hill Street, London NW3 2PF
Phone: Tel: 0207 794 0500 Ext 38821
E-mail: kethakie.sumathipala.11@ucl.ac.uk

UCL

Date

Dear (insert name),

Thank you for your interest in this study *on Unexplained Physical Symptoms in Primary Care* and for completing the baseline questionnaire booklet. We would like to invite you to complete the follow-up questionnaire booklet enclosed. As you may remember, the aim of this study is to understand how unexplained physical symptoms progress in people over time and to find out if it is possible to predict when such symptoms are likely to get better and when they may get worse. We need your help to carry out this study. It is important for us to find out how your symptoms have progressed, even if you feel that they no longer bother you or you have received an explanation for your symptoms, as this would be an important finding for the follow-up. This questionnaire booklet should take you about 15 minutes to complete.

If you have any questions or would like to discuss the study please do not hesitate to contact me on 0207 794 0500 Ext 38821 and I will be happy to return your call. If you have already said that you would prefer to be contacted by telephone, I will be in touch with you shortly.

Please complete the questionnaire enclosed and return using the pre-paid envelope. I will be sending you a high-street voucher worth £10 to thank you for taking the time to complete the follow-up questionnaire.

Thank you for taking the time to take part in this study.

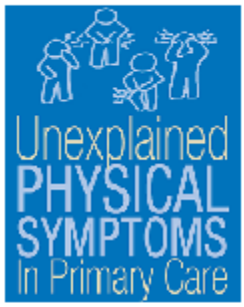
Yours Sincerely,

Kethakie Sumathipala

This study is funded by UCL and NIHR School for Primary Care Research

NHS National Institute for Health Research

Appendix 3.11 Six month follow-up questionnaire



Six months follow-up questionnaire

Participant study number _____

Date _____

Thank you for taking part in this study

This study aims to understand how unexplained physical symptoms progress over time and to get an idea of the characteristics of people whose symptoms may resolve and those whose symptoms may get worse.

For this study to be successful and give us the valuable information we are looking for, **we need your help.** As you may remember, you completed a questionnaire about your physical symptoms six months ago. We would be grateful if you could take the time to fill in this booklet. **It is important for us to find out how your symptoms have progressed, even if you feel that they no longer bother you or you have received an explanation for your symptoms, as this would be an important finding for the follow-up.** Each of the sections covers a different area and there is an explanation at the beginning of each of the sections. A few of the questions do overlap but we ask you to fill them all in as each question is important and especially chosen as they may impact on the experience of living with unexplained physical symptoms.

Please check you have answered all the questions and turn to the next page

Please do not be put off by the number of questions as most of them are very straightforward. You do not have to fill in the booklet in one go. If you want, you can take a break and come back to it later. It should take you around 15 minutes to complete. All of the information you provide is confidential.

If you need to contact us, please do so using the details provided.

Please send the completed booklet back to us using the stamped addressed envelope provided

University College Medical School
Research Department of Primary Care and Population Health

Upper 3rd Floor Royal Free Hospital
Rowland Hill Street, London NW3 2PF
Phone: Tel: 020 7 794 0500 Ext 38821
E-mail: kethakie.sumathipala.11@ucl.ac.uk

This study is funded by NIHR School for Primary Care Research and University College London

Please check you have answered all the questions and turn to the next page

PHQ-15

The following questions ask about your symptoms

1. **During the *past 4 weeks*, how much have you been bothered by any of the following problems**

	Not bothered at all	Bothered a little	Bothered a lot
a. Stomach pain	☐	☐	☐
b. Back pain	☐	☐	☐
c. Pain in your arms, legs, or joints (knees, hips, etc.)	☐	☐	☐
d. Menstrual cramps or other problems with your periods [Women only]	☐	☐	☐
e. Headaches	☐	☐	☐
f. Chest pain	☐	☐	☐
g. Dizziness	☐	☐	☐
h. Fainting spells	☐	☐	☐
i. Feeling your heart pound or race	☐	☐	☐
j. Shortness of breath	☐	☐	☐
k. Pain or problems during sexual intercourse	☐	☐	☐
l. Constipation, loose bowels, or diarrhoea	☐	☐	☐
m. Nausea, gas, or indigestion	☐	☐	☐
n. Feeling tired or having low energy	☐	☐	☐
o. Trouble sleeping	☐	☐	☐

Please check you have answered all the questions and turn to the next page

1 a. Six months ago, you informed us that you had some symptoms that were not fully explained. Please tick one of the options regarding the state of your current symptoms. *Please tick as many as which apply to you.*

a. My symptoms are completely resolved ☐	b. I am still under investigation by my GP ☐
c. I have been referred to the hospital for further tests and investigation ☐	d. My symptoms are still unexplained ☐
e. I have now received a diagnosis ☐ Please write what your diagnosis is _____	

The following questions are about how you manage your symptoms

When someone faces a problem or a distressing experience relating to their health, they may turn to different people for advice, information, treatment, or general support. These may include, for example, their friends and family, their GP, alternative or complementary therapists, mental health professionals, clergy or the internet.

1. How do you prefer to deal with your symptoms?

*Please tick **one** box*

a. On your own ☐ Like some help for your symptoms ☐ Unsure ☐

2. If you have ticked that you would like the help of others, who would you turn to?
*Please **tick as many** as which apply to you.*

f. The internet ☐
g. Family ☐
h. Friends ☐
i. Religious or spiritual advisors ☐
j. Your GP ☐
k. A counsellor or psychotherapist ☐
l. Complementary therapists such as: massage, aromatherapy or homeopathy ☐
h. Other ____ ☐

3. **We would like you to tell us about any other strategies which you have used to help cope with your symptoms.** Please list **as many things** as you think are relevant.

4

Please check you have answered all the questions and turn to the next page

SF-12

Your health and well-being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

For each of the following questions, please tick the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
b	Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3

Please check you have answered all the questions and turn to the next page

3. **During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. **During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. **During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. **These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>...**

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a	Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	Have you felt downhearted and low?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
1. ☐	2. ☐	3. ☐	4. ☐	5. ☐

The following three sets of questions are about your emotions

Our emotions play a very important part in how we experience things. This set of questions is designed to help us to understand how you feel. Please don't take too long over your replies; your immediate reaction to each item will probably be more accurate than thinking a lot about your answers

GAD-7

For each statement, please give the answer that comes closest to the way you have been feeling.

Please tick ***one box*** *for each statement* **Over the last 2 weeks, how often have you been bothered by the following problems?**	Not at all	Several days	More than half the days	Nearly every day
a) Feeling nervous, anxious or on edge	☐	☐	☐	☐
b) Not being able to stop or control worrying	☐	☐	☐	☐
c) Worrying too much about different things	☐	☐	☐	☐
d) Trouble relaxing	☐	☐	☐	☐
e) Being so restless that it is hard to sit still	☐	☐	☐	☐
f) Becoming easily annoyed or irritable	☐	☐	☐	☐
g) Feeling afraid as if something awful might happen	☐	☐	☐	☐

PHQ-9

*Please tick **one box** for each statement* **1. Over the last 2 weeks, how often have you been bothered by any of the following problems?**	Not at all	Several days	More than half the days	Nearly every day
a) Little interest or pleasure in doing things?	☐	☐	☐	☐
b) Feeling down, depressed or hopeless?	☐	☐	☐	☐
c) Trouble falling or staying asleep or sleeping too much?	☐	☐	☐	☐
d) Feeling tired or having little energy?	☐	☐	☐	☐
e) Poor appetite or overeating	☐	☐	☐	☐
f) Feeling bad about yourself- or that you are a failure or have to let yourself or your family down?	☐	☐	☐	☐
g) Trouble concentrating on things, such as reading the newspaper or watching television?	☐	☐	☐	☐
h) Moving or speaking so slowly that other people could have noticed? Or- the opposite- being so fidgety or restless that you have been moving around a lot more than usual?	☐	☐	☐	☐
i) Thoughts that you would be better off dead, or hurting yourself in some way?	☐	☐	☐	☐

1b. **How difficult have these problems listed in the question above made it for you to do your work, take care of things at home, or get along with other people? Please tick *one* of the following.**

a. Not difficult at all ☐ b) Somewhat Difficult ☐ c) Very Difficult ☐ d) Extremely Difficult ☐

PHQ-PANIC

1. In the last 2 weeks, have you had an anxiety attack - suddenly feeling fear or panic?
*Please tick **one box***

Yes ☐ No ☐ (If you answered no, you can skip the rest of question 1a and 1b on this page and continue to the last page of the booklet).

*Please tick **one box** for each questions*	YES	NO
a. Has this ever happened before	☐	☐
b. Do some of these attacks come suddenly out of the blue; that is, in situations where you don't expect to be nervous or uncomfortable?	☐	☐
c. Do these attacks bother you a lot or are you worried about having another attack?	☐	☐
d. Were you short of breath	☐	☐
e. Did your heart race, pound, or skip?	☐	☐
f. Did you have chest pain or pressure?	☐	☐
g. Did you sweat?	☐	☐
h. Did you feel as if you were choking?	☐	☐
i. Did you have hot flashes or chills?	☐	☐
j. Did you have nausea or an upset stomach, or the feeling that you were going to have diarrhea?	☐	☐
k. Did you feel dizzy, unsteady, or faint?	☐	☐
l. Did you feel tingling or numbness in parts of your body?	☐	☐
m. Did you tremble or shake?	☐	☐
n. Were you afraid you were dying?	☐	☐

1b. **How difficult have these problems listed in the question above made it for you to do your work, take care of things at home, or get along with other people? Please tick *one* of the following.**

a. Not difficult at all ☐ b) Somewhat Difficult ☐ c) Very Difficult ☐ d) Extremely Difficult ☐

THANK YOU FOR COMPLETING THIS BOOKLET.

If you have any further comments you wish to make please do so below.

Appendix 4

Appendix 4.1 Table showing results from univariable analyses of baseline variables with physical health function score (SF-12) at follow-up

Baseline variables	Coefficient	95% CI	p-value
Female	2.34	-1.02 to 5.75	0.170
Age (Median/IQR)	-0.22	-0.31 to -0.14	0.00
Ethnicity			
White	-	-	-
Black	1.18	-5.90 to 8.25	0.743
Asian	-3.51	-7.40 to 0.37	0.076
Other (including mixed)	-2.59	-8.26 to 3.10	0.372
Marital status			
In a relationship (Married/ In a long term relationship)	-	-	-
Other (Widowed, separated, single)	-1.25	-4.11 to 1.61	0.389
Employment status			
In paid employment	-	-	-
Not in paid employment	-7.69	-10.35 to -5.04	<0.001
Education			
O-levels, GCSE, A-levels or equivalent	-	-	-
Undergrad, masters or higher or equivalent	7.84	5.17 to 10.50	<0.001
Finance			
Doing well	-	-	-
Doing badly	-6.46	-9.16 to -3.74	<0.001
IMD	-0.10	-0.21 to 0.00	0.06
Preference for dealing with symptoms			
Alone	-	-	-
With help from others	-5.93	-9.40 to -2.46	0.001
Baseline symptom severity (PHQ-15)	-0.87	-1.13 to -0.60	0.00
Duration of symptoms at baseline	-7.29	-10.59 to -3.99	<0.001
SF-12 scores			
Mental health functioning	0.16	0.03 to 0.28	0.018
Physical functioning	0.76	0.67 to 0.85	<0.001
Depression	-0.59	-0.79 to -0.39	<0.001
Anxiety	-0.41	-0.65 to -0.16	0.001
Panic	-2.69	-6.30 to 0.91	0.142
Work and social adjustment	-0.48	-0.59 to -0.37	0.00
Self-efficacy	0.37	0.19 to 0.56	0.00
Stressful life events	-1.65	-2.57 to -0.73	<0.001
Experienced physical illness in family			

Baseline variables	Coefficient	95% CI	p-value
members as a child			
No	-	-	-
Yes	-3.87	-6.86 to -0.88	0.011
Experience mental illness in family members as a child			
No	-	-	-
Yes	0.09	-3.70 to 3.88	0.964
Experienced 1 or more traumatic event as child			
No	-	-	-
Yes	-5.36	-8.28 to -2.43	<0.001
Experience abuse			
No	-	-	-
Yes	-2.95	-6.28 to 0.36	0.080
Type of abuse experienced			
Physical Abuse	-7.65	-12.50 to -2.79	0.002
Sexual Abuse	-2.00	-7.06 to 3.04	0.434
Emotional Abuse	-4.80	-8.28 to -1.21	0.009
Primary health care contacts	-0.60	-0.84 to -0.44	0.001
Secondary care contacts	-0.92	-1.45 to -0.40	0.001

Appendix 4.2 Table showing results from univariable analyses of baseline variables with mental health function score (SF-12) at follow-up

Baseline variables	Coefficient	95% CI	p-value
Female	-3.34	-6.65 to -0.03	0.048
Age	0.03	-0.05 to 0.11	0.458
Ethnicity			
White	-	-	-
Black	6.40	-0.55 to 13.35	0.071
Asian	-1.61	-5.43 to 2.21	0.418
Other (including mixed)	-3.11	-8.70 to 2.47	0.273
Marital status			
Married or in a long term relationship	-	-	-
Widowed, separated, single	-3.21	-5.95 to -0.48	0.022
Employment status			
In paid employment	-	-	-
Not in paid employment	-3.47	-6.21 to -0.73	0.013
Education			
O-levels, GCSE, A-levels or equivalent	-	-	-
Undergraduate, masters or higher or equivalent	2.35	-0.48 to 5.18	0.103
Finance			
Doing well	-	-	-
Doing badly	-5.95	-8.62 to -3.28	<0.001
Indices of multiple deprivation	-0.08	-0.18 to 0.03	0.166
Baseline symptom severity (PHQ-15	-0.80	-1.05 to -0.54	<0.001
Duration of symptoms at baseline			
<1 year	-	-	-
>1 year	-2.69	-6.13 to 0.75	0.124
Preference for help seeking			
By my-self	-	-	-
Like some help	-5.20	-8.71 to -1.69	0.004
Mental	0.58	0.48 to 0.69	<0.001
Physical	0.15	0.02 to 0.28	0.025
Depression	-0.88	-1.06 to -0.70	<0.001
Anxiety	-0.91	-1.12 to -0.70	<0.001
Panic	-7.64	-11.07 to -4.21	<0.001
Work and social adjustment	-0.42	-0.52 to -0.31	<0.001
Self-efficacy	0.59	0.41 to 0.76	<0.001

Baseline variables	Coefficient	95% CI	p-value
Stressful life events	-1.42	-2.32 to -0.52	0.002
Experienced physical illness in family members as a child			
No	-	-	-
Yes	-0.85	-3.71 to 2.00	0.557
Experience mental illness in family members as a child			
No	-	-	-
Yes	-3.28	-6.99 to 0.43	0.083
Experienced 1 or more traumatic event as child			
No	-	-	-
Yes	-3.89	-6.84 to -0.93	0.010
Experience abuse			
No	-	-	-
Yes	-5.45	-8.67 to o-2.24	0.001
Physical Abuse	-7.83	-12.58 to -3.08	0.001
Sexual Abuse	-7.79	-12.65 to -2.94	0.002
Emotional Abuse	-6.71	-10.17 to -3.26	<0.001
Social support			
No	-	--	-
Yes	1.11	-2.70 to 4.92	0.565
Primary health service use	-0.22	-0.40 to -0.04	0.015
Secondary health service use	-0.22	-0.75 to 0.31	0.408

Appendix 4.3 Table showing results from univariable analyses of baseline variables with depression (PHQ-9) at follow-up

Baseline variables	Coefficient	95% CI	p-value
Female	1.04	-0.97 to 3.05	0.311
Age	0.01	-0.04 to 0.06	0.816
Ethnicity			
White	-	-	-
Black	-1.11	-5.31 to 3.10	0.605
Asian	0.12	-2.19 to 2.43	0.918
Other (including mixed)	1.59	-1.78 to 4.97	0.353
Marital status			
Married or in a long term relationship	-	-	-
Widowed, separated, single	1.34	-0.31 to 2.99	0.110
Employment status			
In paid employment	-	-	-
Not in paid employment	3.36	1.76 to 4.95	<0.001
Education			
O-levels, GCSE, A-levels or equivalent	-	-	-
Undergrad, masters or higher or equivalent	-2.95	-4.58 to -1.32	<0.001
Finance			
Doing well	-	-	-
Doing badly	4.46	2.89 to 6.03	<0.001
IMD	0.06	0.00 to 0.13	0.055
Dealing with symptoms			
By my-self	-	-	-
Prefer help	3.49	1.42 to 5.56	0.001
Duration of symptoms	2.66	0.63 to 4.69	0.010
Baseline symptom severity (PHQ-15)	0.59	0.44 to 0.74	<0.001
SF-12 scores			
Physical	-0.20	-0.27 to -0.13	<0.001
Mental	-0.33	-0.40 to -0.26	<0.001
Depression	0.70	0.61 to 0.79	<0.001
Anxiety	0.71	0.60 to 0.83	<0.001
Panic	4.54	2.56 to 6.51	<0.001
Work and social adjustment	0.30	0.23 to 0.36	<0.001
Self-efficacy	-0.45	-0.55 to -0.36	<0.001
Stressful life events	1.11	0.57 to 1.64	<0.001
Experienced physical illness in family members as a child			
No	-	-	-

Baseline variables	Coefficient	95% CI	p-value
Yes	0.96	- 0.80 to 2.73	0.283
Experience mental illness in family members as a child			
No	-	-	-
Yes	1.69	-0.54 to 3.92	0.136
Experienced 1 or more traumatic event as child			
No	-	-	-
Yes	1.93	0.20 to 3.67	0.029
Experience abuse			
No	-	-	-
Yes	2.65	0.75 to 4.54	0.007
Physical Abuse	4.64	1.92 to 7.35	0.001
Sexual Abuse	3.38	0.46 to 6.30	0.024
Emotional Abuse	3.74	1.71 to 5.77	<0.001
Social support	4.94	1.14 to 8.74	0.186
Primary health care contacts	0.22	0.12 to 0.33	<0.001
Secondary health care contacts	0.21	-0.11 to 0.53	0.191

Appendix 4.4 Table showing results from univariable analyses of baseline variables with anxiety (GAD-7) at follow-up

Baseline variables	Coefficient	95% CI	p-value
Gender	0.86	-0.88 to 2.61	0.330
Age	0.01	-0.04 to 0.05	0.777
Ethnicity			
White	-	-	-
Black	0.5	-3.14 to 4.15	0.787
Asian	0.22	-1.78 to 2.22	0.828
Other (including mixed)	1.61	-1.31 to 4.54	0.279
Marital status			
Married/ In a long term relationship)	-	-	-
Widowed, separated, single)	-0.07	-1.50 to 1.36	0.926
Employment status			
In paid employment	-	-	-
Not in paid employment	1.37	-0.06 to 2.79	0.061
Education			
O-levels, GCSE, A-levels or equivalent	-	-	-
Undergrad, masters or higher or equivalent	-0.88	-2.33 to 0.57	0.234
Finance			
Doing well	-	-	-
Doing badly	2.50	1.09 to 3.91	0.001
IMD	0.00	-0.05 to 0.06	0.871
Preference for dealing with symptoms			
By myself	-	-	-
Help from others	2.14	0.33 to 3.95	0.021
Duration of symptoms at baseline	2.22	0.47 to 3.97	0.013
Baseline symptom severity (PHQ-15)	0.44	0.30 to 0.57	<0.001
SF-12 scores			
Physical	-0.10	-0.16 to -0.03	0.003
Mental	-0.24	-0.30 to -0.18	<0.001
Depression	0.50	0.41 to 0.59	<0.001
Anxiety	0.62	0.52 to 0.72	<0.001
Panic	3.77	2.02 to 5.52	<0.001
Work and social adjustment	0.20	0.14 to 0.25	<0.001
Self-efficacy	-0.28	-0.37 to -0.19	0.00
Stressful life events	0.81	0.34 to 1.28	0.001
Experienced physical illness in			

family members as a child			
No	-	-	-
Yes	0.66	-0.89 to 2.20	0.404
Experience mental illness in family members as a child			
No	-	-	-
Yes	1.98	0.03 to 3.92	0.047
Experienced 1 or more traumatic event as child			
No	-	-	-
Yes	1.07	-0.46 to 2.59	0.169
Experience abuse			
No	-	-	-
Yes	2.01	0.36 to 3.68	0.017
Physical Abuse	3.22	0.84 to 5.59	0.008
Sexual Abuse	2.19	-0.36 to 4.73	0.092
Emotional Abuse	2.90	1.12 to 4.67	0.001
Social support	-1.13	-3.08 to 0.82	0.255
Primary health care	0.18	0.09 to 0.27	<0.001
Secondary health care	0.29	0.02 to 0.56	0.036

Appendix 4.5 Table showing results from univariable analysis of baseline predictors with primary health care contact

Baseline Predictors	Coefficient	95% CI	p-value
Female	-1.11	-2.42 to 0.21	0.099
Age	0.07	0.04 to 0.11	<0.001
Ethnicity			
White	-	-	-
Black	0.39	-2.26 to 3.03	0.773
Asian	-0.04	-1.58 to 1.51	0.963
Other (including mixed)	0.34	-1.87 to 2.56	0.761
Marital status			
Married/ In a long term relationship	-	-	-
Widowed, separated, single	0.58	-0.52 to 1.68	0.299
Employment status			
In paid employment	-	-	-
Not in paid employment	2.27	1.21 to 3.33	<0.001
Education			
O-levels, GCSE, A-levels or equivalent	-	-	-
Undergrad, masters or higher or equivalent	-1.77	-2.87 to -0.67	0.002
Finance			
Doing well	-	-	-
Doing badly	0.96	-0.13 to 2.06	0.085
Index of multiple deprivation	0.00	-0.04 to 0.04	0.968
Preference for dealing with symptoms			
Myself	-	-	-
Like some help	1.39	-0.00 to 2.79	0.051
Symptom duration at baseline	0.04	-1.28 to 1.36	0.948
Baseline symptom severity (PHQ-15	0.19	0.09 to 0.30	<0.001
SF-12 scores			
Physical	-0.14	-0.19 to -0.92	<0.001
Mental	-0.05	-0.09 to -0.00	0.046
Depression	0.13	0.05 to 0.21	0.001
Anxiety	0.08	-0.01 to 0.18	0.085
Panic	1.60	0.25 to 2.95	0.020
Work and social adjustment	0.10	0.05 to 0.15	<0.001
Self-efficacy	-0.10	-0.17 to -0.02	0.011
Stressful life events	0.21	-0.15 to 0.57	0.253

Experienced physical illness in family members as a child			
No			
Yes	0.31	-0.86 to 1.49	0.598
Experience mental illness in family members as a child			
No			
Yes	-0.65	-2.12 to 0.83	0.390
Experienced 1 or more traumatic event as child			
No			
Yes	0.54	-0.64 to 1.72	0.371
Experience abuse			
No			
Yes	1.31	0.07 to 2.56	0.039
Physical Abuse	1.62	-0.17 to 3.42	0.075
Sexual Abuse	1.39	-0.60 to 3.37	0.170
Emotional Abuse	2.13	0.79 to 3.47	0.002
Social support	-0.71	-2.23 to 0.82	0.361
Primary health care use at baseline	0.41	0.35 to 0.46	<0.001
Secondary health care use at baseline	0.85	0.66 to 1.05	<0.001

Appendix 5

Appendix 5.1 Dissemination of findings:

- A longitudinal cohort study to identify prognostic factors associated with outcome in primary care attendees with unexplained physical symptoms. To be presented at the 45th Annual Conference for the Society of Academic Primary Care, Dublin, *July 2016.*

- Preferences for sources of support for management of symptoms amongst primary care attendees with unexplained physical symptoms. To be presented at the 45th Annual Conference for the Society of Academic Primary Care, Dublin, *July 2016.*

- Prognostic factors associated with persistence of somatic symptoms: findings from a longitudinal cohort study of unexplained physical symptoms in primary care, NIHR School for Primary Care Research Annual Showcase, Oxford, *September 2015.*

- Unexplained physical symptom severity in patients attending nine general practices in London: a cross-sectional study, 44th Annual Conference for the Society of Academic Primary Care, Dublin, *July 2015.*

- Self-reported somatic symptom explanations and attributions: cross-sectional findings from the screening phase of an on-going longitudinal cohort study on unexplained physical symptoms in primary care, NIHR School for Primary Care Research Annual Showcase, Oxford, *September 2014.*

Appendix 5.2 Paper in preparation

- A prospective cohort study to determine prognostic factors associated with outcomes in primary care attenders with unexplained physical symptoms.