

**Title: Factors associated with persistent unexplained physical symptoms in UK primary care attenders.**

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## How this fits in

- Most existing studies of UPS are based on meeting the criteria for severe symptomology and comorbid psychiatric disorders, with few studies conducted with primary care attenders.
- Existing guidelines developed from evidence including individuals with psychiatric disorders, hypochondriasis, hysteria or somatoform disorder and from secondary care populations or community samples are likely to have a very different illness trajectories and outcomes than for patients recruited in primary care.
- In our study about half the respondents recruited in primary care had persistent unexplained symptoms at six months follow-up.
- Female gender, poor physical well-being, more severe symptoms at onset, past history of physical abuse during childhood and current stressful circumstances such as financial difficulties were associated with higher somatic symptom severity at follow-up.

## **Abstract**

**Background:** Unexplained physical symptoms (UPS) are extremely common amongst primary care attenders but little is known about their longer-term outcome.

**Aim:** To investigate persistence of somatic symptoms at six months amongst a cohort with multiple UPS and identify prognostic factors associated with worsening symptom scores.

**Design and Setting:** Prospective longitudinal cohort study involving adults attending UK general practice between January-December 2013.

**Method:** Consecutive adults attending nine general practices were screened to identify those with at least three UPS. Eligible participants completed measures of symptom severity (measured using the Patient Health Questionnaire Somatic Symptom Module (PHQ-15)), physical and mental well-being and past health and social history and were followed-up after six months. Multivariable linear regression analysis was conducted to identify prognostic factors associated with the primary outcome, somatic symptom severity.

**Results:** Overall 245/294 (83%) provided six month outcome data. 135/245(55%) reported still having UPS, 103/245(42%) had symptoms still under investigation and only 26/245(11%) reported complete symptom resolution. Being female, higher baseline somatic symptom severity, poorer physical functioning, experience of childhood physical abuse, and perception of poor financial well-being were significantly associated with higher somatic symptom severity scores at six months.

**Conclusion:** This study has shown that at six months few have complete resolution of unexplained somatic symptoms. GPs should be made aware of the likelihood of UPS persisting and factors that make this more likely, to inform decision making and care planning. There is a need to develop prognostic tools that can predict the risk of poor outcomes.

## **Keywords**

Primary Health Care; General Practice; Unexplained Physical Symptoms; Somatic Symptoms

## **Introduction**

Unexplained physical symptoms (UPS), i.e. physical symptoms that lack obvious pathological explanations even after appropriate investigations, are common amongst primary care attenders. (1) They are associated with high morbidity, distress to patients and their families, and costs to the NHS and wider economy. (2,3) In the past, outcome studies focused on those meeting psychiatric diagnostic criteria such as the Diagnostic and Statistical Manual for Mental Disorders and not more heterogeneous primary care groups with common symptoms such as headaches, back pain, bloating, nausea and fatigue. (4) Depending on the diagnostic criteria and methods of identification their prevalence is estimated to vary from 0.8% to 79%. (1)

Primary care is often the first point of access for healthcare and doctors report difficulties with the appropriate management of patients with UPS. (5,6) Better early detection and management could reduce the burden on patients and clinicians and those requiring longer term input. (7) General Practitioners' (GP) decision making and care planning for individuals with UPS could be assisted by use of prognostic tools to predict the risk of poor outcomes like persistence of symptoms. Identification of factors associated with relevant outcomes is the key component in developing prognostic models. (8) However, little is known about outcomes over time and the factors associated with prognostic factors in primary care attenders with UPS. (9-12)

This UK based primary care study aimed at six month follow-up to:

- i) Investigate outcome in terms of persistence of UPS
- ii) Identify prognostic factors associated with somatic symptom severity, quality of life (QoL), anxiety, depression and healthcare use.

## **Method**

Design: Prospective longitudinal cohort study

### **Setting & participants**

We refer to physical symptoms of 'unknown cause' as UPS and use this term broadly to include those who reported that they had not received a clear diagnosis for their symptoms, even after consultation and investigation, as well as those who are attending for the first time with symptoms bothering them on the PHQ-15. Our definition of UPS does not imply an underlying psychological cause.

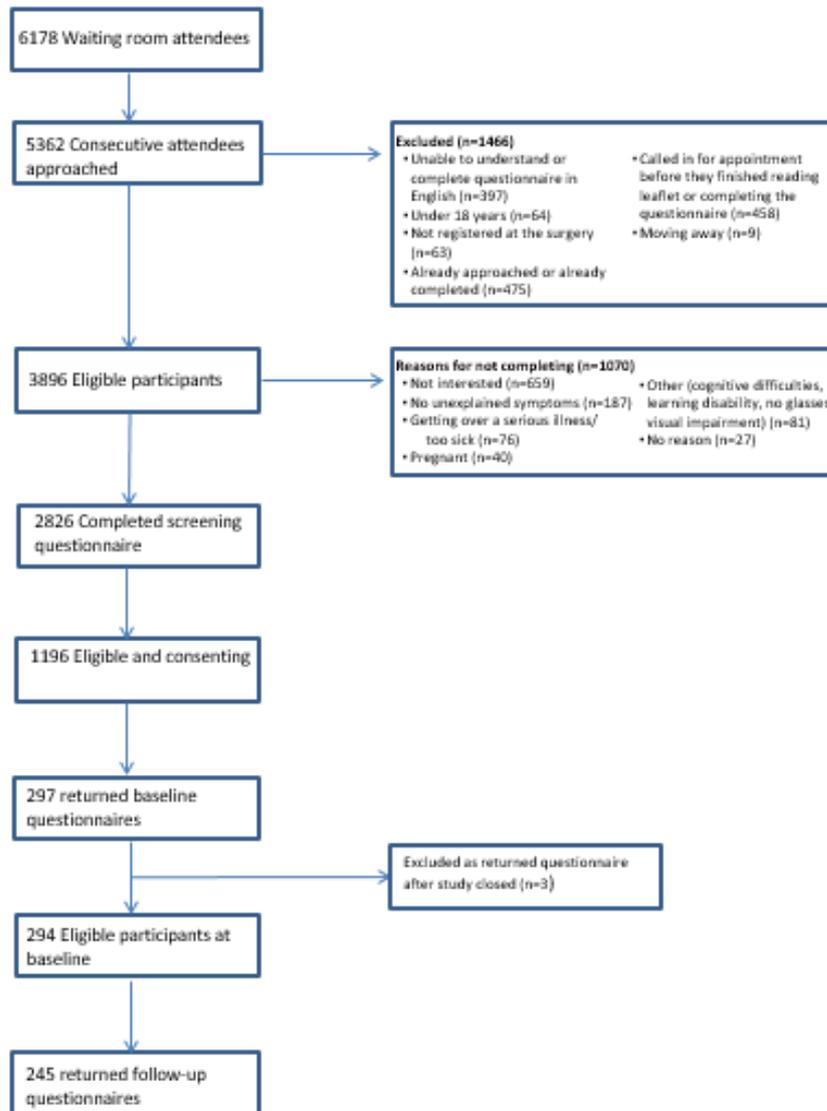
Over an 11 month period (January 2013 to December 2013) waiting room attendees aged 18 years and over, at nine general practices in north and central London, were invited to complete a screening questionnaire. We excluded people not registered at the practice, planning to move away in the next six months or unable to understand and complete the questionnaire in English. Those with a medical explanation/ diagnoses that fully explained their symptoms or those with a terminal illness were also excluded.

**Sampling:**

Consecutive attendees were screened and those meeting the eligibility criteria recruited to the main study.

<Figure 1>

Figure 1: Screening and recruitment of study cohort.



### **Phase 1: Screening**

Participants completed the Patient Health Questionnaire Somatic Symptom Module (PHQ-15); a self-administered questionnaire that includes 90% of common presenting somatic symptoms. (13,14) Fifteen questions for females and fourteen for males about specific body symptoms follow a question 'During the past 4 weeks, how much have you been bothered by any of the following problems?' A score is calculated based on answers 'not bothered at all' [0], 'bothered a little' [1] or 'bothered a lot' [2] (15). Clinical cut-off points are frequently used with a score of 0-4 considered as minimal severity (at least three symptoms); 5-9 considered to be low severity (at least five symptoms); 10-14 considered to be moderate severity (at least eight symptoms); and  $\geq 14$  high severity (15). Those who had seen the doctor before for their symptoms, as well as those seeing the doctor for the first time, who had at least three symptoms and scored five or above on the PHQ-15 were considered eligible as at this stage their symptoms were considered 'unexplained'."

Respondents were asked to provide any known explanation or diagnosis for their symptoms to determine which symptoms were unexplained from their perspective. These were discussed and a booklet of diagnoses that could potentially explain symptoms was developed, in consultation with practising GPs (IN, MB, KW). The booklet was iteratively updated until no further additions to explanations were identified, which allowed for consistency in inclusion/exclusion. This information was used to in the descriptive analysis to categorise respondents' symptoms as unexplained; fully explained by physical diagnoses; or partially explained by a physical diagnosis (e.g. diabetes and medicine side effects), psychological explanations (e.g. stress, anxiety or depression) or functional diagnoses (e.g. irritable bowel syndrome or chronic fatigue).

### **Phase 2: Main cohort study**

Potentially eligible participants were sent a postal questionnaire at baseline, followed by two reminders. Options for completion were post, telephone or face-to-face. Baseline responders were sent a follow-up questionnaire at six months and asked to indicate whether their symptoms: had resolved; were still under investigation; been diagnosed; or were still considered unexplained. Both questionnaires included measures of relevant prognostic factors (see table 1).

<Insert Table 1>

### **Outcome measurements**

The primary outcome was somatic symptom severity score, measured using the PHQ-15.

Data were also collected on secondary outcomes: QoL was measured using the mental and physical health components of the 12 item Medical Outcome Survey Short Form Questionnaire (SF-12); (15) depression and generalised anxiety disorder were measured using the Patient Health Questionnaire depression module (PHQ-9); (16) and the generalised anxiety disorder assessment (GAD-7); (17) number of primary healthcare contacts in the year before study recruitment and during the study period (either face-to-face or telephone) with doctors, nurses, healthcare assistants or out of hours GP services were obtained from patients' medical records.

### **Statistical analysis**

First, univariable analysis was conducted to determine the association of baseline variables with outcomes using Stata version 12. (18) This was followed by conceptual group modelling, a method used to reduce number of variables included in the main modelling. (19) 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. This was carried out to avoid potential collinearity in the main modelling process as well as ensuring the main modelling was not over fitted by including too many explanatory variables for the number of observations. Those variables that remained would then be included in the main multivariable modelling procedure, after which backwards elimination was carried out, starting with the largest p-value and continuing until only variables with  $p < 0.05$  remained (and/ or were included in the model a priori). All models were adjusted for baseline outcome variable, including baseline PHQ-15; age and sex were included a priori. Results reported are from mutually adjusted models.

### **Missing data**

Guidance on correcting missing data for each of the scales and measures was used. For the PHQ-15, PHQ-9 and GAD-7 we used a conservative approach of assuming the respondent was not bothered by the item. (21) Missing data was minimal and accounted for less than 0.5% of data at each time point.

### **Results**

Baseline characteristics: 1,632/2,826 (58%) of those who had completed the screening questionnaire were potentially eligible for the next stage of the study; whilst 1,196/2,826 (42%) also gave their

contact details, allowing them to be followed up with the baseline questionnaire. Baseline questionnaires were returned by 294/1,196 (25% of those screened), excluding three who sent back questionnaires after the study had closed.

The majority were female (231/294 (79%)) and median age was 44 (Interquartile range (IQR) 32, 57) years. The sample was ethnically diverse, less than half white British (125/294 (43%)) and representative of the practice populations. At baseline, responders were asked about duration of their symptoms, most had experienced symptoms for over a year. On average, they had moderately severe physical symptom scores and poor physical and mental health functioning based on the SF-12. One third of responders fell into the range of clinically significant comorbid depression and anxiety at a cut-off of  $\geq 10$  on the PHQ-9 and GAD-7. Other clinical characteristics are shown in Table 2. Baseline responders had similar characteristics to eligible non-responders who had consented to be contacted after screening (1,196/2,826 (42%)). However, male responders when compared to male non-responders were older (53 years IQR 36, 66 vs 43 years IQR 30,55) and more reported symptoms that were partially explained by a diagnosis (49% vs 29%).

<Insert Table 2>

*Outcomes at six months:* The follow-up rate was high (245/294 (83%)). Responders (n=245) were slightly older (45 years IQR 33,58 vs 39 years (IQR 27,49) than non-responders (n=49), had experienced symptoms for longer (36 months SD 17,72 vs 24 months SD 14,58) and with lower median baseline PHQ-9 scores (8 IQR 4, 14 vs 10 IQR 6, 18). Otherwise, they were similar in all other respects. At six months follow-up, mean scores for all outcome measures were similar to the baseline scores indicating poor recovery; only 11% (26/245) reported full recovery; 24% (58/245) had received a diagnosis for at least some of their symptoms; 42% (103/245) reported being still under investigation (by GP/specialist), and 55% (135/245) continued to have unexplained symptoms. These categories were not mutually exclusive.

Following univariable and conceptual group modelling, fifteen variables were included in the modelling to identify prognostic factors associated with symptom severity scores at follow-up. Backward selection was carried out until six variables remained in the final model (Table 3). Being female, higher baseline somatic symptom severity, experience of childhood physical abuse, perception of financial well-being as poor and poorer baseline physical functioning were significantly associated with higher somatic symptom severity scores at six months. Adjusted somatic symptom severity score at follow-up was on average 1.31 (95% CI 0.12 to 2.50) points higher amongst females (Table 3). Depression and anxiety scores were not independently associated with adverse outcome after adjusting for baseline somatic symptom severity.

<Insert Table 3>

All final multivariable models for the secondary variables included a fairly narrow range of baseline variables associated with physical outcomes (somatic symptom severity and physical health functioning) and psychological outcomes (mental health functioning, depression and anxiety) respectively, summarised in Table 3. For all secondary outcomes the baseline measure of the same variable was associated with its follow-up severity, after adjusting for all other variables. Most factors followed an expected association; e.g. greater self-efficacy was associated with lower depression scores and better outcome at follow-up. The only factors associated with higher primary health care use at follow-up were emotional abuse in childhood and higher health care contacts in the year prior to the study.

## **Discussion**

### **Summary:**

In our study, primary care attendees with three or more unexplained symptoms had poor quality of life but only a third had associated significant symptoms (above diagnostic thresholds) of depression or anxiety. Attendees were likely to continue to be symptomatic at six month follow-up; more than half reported UPS at six months (55%); close to half (42%) were still under investigation (by GP or specialist); and few (11%) described themselves as fully recovered. Prognostic factors associated with higher somatic symptom severity at follow-up included: being female, higher baseline somatic symptom severity, poorer physical health functioning, perception of poor financial well-being and experience of childhood physical abuse.

### **Strengths and limitations**

To our knowledge, this is the first UK study of primary care attendees with self-reported UPS recruited on the basis of severity of their somatic symptoms, in which the outcomes of their UPS were explored as well as the prognostic factors associated with their persistence. Self-reported symptoms are crucial to understanding patients' needs and help-seeking behaviour. However, as they rely on the patients' understanding of their diagnosis/explanation and their recall, it is possible that there may be some bias. Nevertheless, we believe that the patients' understanding and perceptions are likely to offer valuable understanding of the level of burden, frequency of consultation and other healthcare use.

Nine general practices with differing levels of deprivation and high ethnic diversity were included, increasing the potential for wider generalisability of our findings to the UK population. The characteristics of responders and non-responders were reasonably similar on key variables and

attrition at follow-up was low (17%), suggesting the findings are likely to be generalisable to a wider population, although potentially less applicable to younger men.

The majority of measures used were validated and reliable, but existing questionnaires were adapted in a few cases. For example, validated questionnaires on childhood abuse are long and potentially too intrusive for a postal questionnaire, so questions were reduced and adapted. This may have decreased the sensitivity and specificity of these measures, which may have impacted on the findings. Efforts were taken to ensure that models were adjusted for potential confounding; however, it is possible that there was some impact of unmeasured and unknown confounding variables such as other comorbidities and current experience of abuse. The study was powered for the primary outcome, somatic symptom severity. Although exploration of the secondary outcomes provides an indication of possible associations, they must be interpreted with caution.

### **Comparison with existing literature**

Comparison with the existing literature is difficult as most existing UPS research has included heterogeneous populations meeting psychiatric diagnostic classifications such as somatoform disorder, who comprise a very small proportion of those attending primary care. (1, 22 ) A review of studies that included populations with both somatoform disorders and hypochondriasis concluded that many unexplained symptoms are transient and that the majority of patients will improve over time (10). In contrast, we found that over half of primary care attenders, who may be anticipated to have potentially less morbidity, reported their symptoms as still unexplained at follow-up. This is line with comparatively more recent studies which have reported that around half continue to be burdened by their symptoms, albeit these studies include populations meeting the criteria for somatoform disorders (11) or bodily distress syndrome (BDS), which is diagnosis of functional disorders rather than symptoms (12). Only 11% in our study reported their symptoms as resolved; this is also much lower than rates of resolution amongst consecutive primary care attenders at three month follow-up, reported by Jackson and Passamonti (2005) in the USA, although they did not distinguish between those with explained and unexplained symptoms. (9)

Although at baseline a third of our cohort had clinically significant scores for depression and anxiety, neither depression nor anxiety independently predicted persistent somatic symptoms at follow-up. However, a few existing studies based on primary care attenders with psychiatric morbidity have reported persistent somatic symptoms at between six and twelve months follow-up. (11,24,25)

Our finding that greater overall symptom severity at baseline is associated with worse outcome at follow-up is consistent with previous research, although those studies also included populations meeting a variety of different inclusion criteria. (9-12, 26, 27, 30) 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. (13, 9, 30) As in our study, a recent review by Tomenson et al (2013) where secondary analysis was conducted on studies from four different sites, reported that somatic symptom score was a better predictor of follow-up health status and health care use than UPS. (30)

As in many other studies, we found that women were likely to have higher symptom severity compared to men at follow-up, even after adjusting for other variables including baseline somatic symptoms. (28-30) Worse functional disability and poor physical health at baseline are reported to be associated with the persistence of UPS or high somatic symptoms scores at 12 month follow-up. (11, 12) Physical abuse in childhood was associated with an increase in somatic symptom severity at follow-up, suggesting that childhood physical abuse may have a long-term impact on physical health, similar to reports in other studies. (31-35)

### **Implications for research and/or practice**

This study suggests that for many patients in primary care with several bothersome UPS, their symptoms may not be transient and that around half will continue to be affected over time. Baseline symptom severity was found to be a good indicator of how patients are likely to progress over a six-month period and can be helpful in considering prognosis by GPs and policy makers, as well as in future research.

A fairly high proportion of our study participants were still undergoing investigations at six months follow-up and there have been concerns that ongoing investigations may perpetuate symptoms, with a number of potential iatrogenic consequences. (36) It is vital that individuals are managed appropriately in the long term, to reduce the burden on themselves, healthcare resources and the wider economy. It may be useful to take an approach to health care advocated for other long term conditions in engaging with the patient, involving them in decisions about their care and supporting self-management, as well as providing emotional, psychological and practical support. (37) Management strategies used by GPs both initially and over time should consider addressing factors

such as symptom burden, current physical and mental health, recent stressful life-events and historical factors such as abuse.

A high percentage of patients with UPS in primary care were functionally impaired with high somatic symptom scores but only a third of the cohort had comorbid depression and anxiety. Our findings support assertions that UPS should not be assumed to be of psychological aetiology amongst heterogeneous primary care attenders (9,38) and accompanying psychological morbidity may not be a key to prognosis in primary care attendees.

This study adds value to the area of UPS amongst primary care attendees by providing an evidence base for existing guidance which has until now been predominantly based on research in heterogenous populations with UPS closely aligned to psychiatric morbidity and located in a wide range of settings including secondary care. (39)

## **Conclusion**

This study found that around half of primary care attenders with multiple UPS remained symptomatic at six months, the majority did not have significant psychiatric morbidity and only around a tenth described themselves as fully recovered. Several prognostic factors were associated with higher somatic symptom severity at six months: being female, higher baseline somatic symptom severity, poorer physical health functioning, perception of poor financial well-being and experience of childhood physical abuse.

**Table 1: Potential prognostic factors considered at baseline, scales and measures used for data collection and outcome variables explored.**

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

**Table 2: Baseline clinical characteristics of the study cohort**

Clinical characteristics	Total N=294	Male N=63	Female N=231
<b>Baseline symptom severity (PHQ-15 score)<sup>§</sup></b>	11.5 (4.9)	11.0 (5.0)	11.7 (4.9)
<b>Symptom duration</b>			
<1 year	63 (21%)	14 (22%)	49 (21%)
≥1 year	212 (72%)	43 (68%)	169 (73%)
Missing	19 (6%)	0 (0%)	19 (8%)
<b>SF-12 score<sup>*§</sup></b>			
Physical health functioning <sup>1</sup>	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)
<b>Work and social adjustment score<sup>§</sup></b>	18.7 (11.5)	19.1 (11.5)	18.5(11.5)
Missing	6	0	6
<b>Self-efficacy score<sup>§</sup></b>	27.4 (7.4)	27.4 (7.2)	27.4 (7.4)
Missing	4	0	4
<b>Anxiety score<sup>§</sup></b>	8.9 (5.8)	8.2 (5.8)	9.0 (5.7)
<b>Depression score<sup>§</sup></b>	9(5,14)	9 (4,14)	9 (5,14)
<b>Panic</b>			
Yes	62(21%)	12 (19%)	50 (22%)
No	204(69%)	43 (68%)	161 (70%)
Missing	28(10%)	8 (13%)	20 (9%)
<b>Stressful life events<sup>†</sup></b>	1 (0,2)	1 (1,3)	1(0,2)
Missing	3	1	2
<b>Experienced physical illness in family as a child</b>			
Yes	94 (32%)	23 (37%)	71 (31%)
No	194(66%)	39 (62%)	155 (67%)
Missing	6(2%)	1 (2%)	5 (2%)
<b>Experience mental illness in family as a child</b>			
Yes	47(16%)	5 (8%)	42 (18%)
No	242(82%)	57 (90%)	185 (80%)
Missing	5(2%)	1 (2%)	4 (2%)
<b>Experienced 1 or more traumatic event as child</b>			
Yes	93(32%)	17 (27%)	76 (33%)
No	192(65%)	43 (68%)	149 (65%)
Missing	9(3%)	3 (5%)	6 (3%)
<b>Experienced any abuse as a child</b>			
Yes	77(26%)	16 (25%)	61 (26%)
No	204(69%)	46 (73%)	158 (68%)
Missing	13(4%)	1 (2%)	12 (5%)
<b>Type of abuse experienced as a child**</b>			
Physical abuse			

<b>Clinical characteristics</b>	<b>Total N=294</b>	<b>Male N=63</b>	<b>Female N=231</b>
Yes	31(11%)	8 (13%)	23 (10%)
No	253(86%)	54 (86%)	199 (86%)
Missing	10(3%)	1 (2%)	9 (4%)
<b>Sexual abuse</b>			
Yes	25(9%)	2 (3%)	23 (10%)
No	259(78%)	60 (95%)	199 (86%)
Missing	10(3%)	1 (2%)	9 (4%)
<b>Emotional abuse</b>			
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)

<sup>1</sup>Missing data for one male participant

**Table 3: Summary of baseline predictors which were significantly associated with each of the outcomes in multivariable analyses. Coefficients are also given for female gender and age which were included in all models a priori.**

Baseline variables	Primary outcome Somatic symptom severity			Physical health functioning			Mental health functioning			Secondary outcomes Depression			Anxiety			Primary health care contact		
	Coefficient	95% CI	P-value	Coefficient	95% CI	P-value	Coefficient	95% CI	P-value	Coefficient	95% CI	P-value	Coefficient	95% CI	P-value	Coefficient	95% CI	P-value
<b>Female</b>	1.31	0.12, 2.50	0.031	0.83	-1.47, 3.13	0.479	-2.47	-5.18, 0.25	0.075	0.79	-0.64, 2.23	0.277	0.55	-0.85, 1.96	0.437	-0.57	-1.60, 0.46	0.274
<b>Age (years)</b>	0.01	-0.03, 0.04	0.559	-0.08	-0.15, -0.02	0.014	-0.21	-0.09, 0.48	0.543	0.02	-0.02, 0.05	0.339	0.02	-0.01, 0.06	0.227	0.01	-0.02, 0.04	0.568
<b>Perception of financial well-being as doing badly</b>	1.90	0.89, 2.91	<0.001															
<b>Somatic symptom score</b>	0.53	0.42, 0.64	<0.001	-0.30	-0.51, -0.09	0.005				0.16	0.03, 0.30	0.016						
<b>Mental Health Functioning score</b>							0.40	0.27, 0.54	<0.001									
<b>Physical Health Functioning score</b>	-0.10	-0.15, -0.04	0.001	0.61	0.51, 0.72	<0.001												
<b>Self-efficacy score</b>										-0.18	-0.27, -0.09	<0.001						
<b>Anxiety score</b>													0.44	0.27, 0.61	<0.001			
<b>Depression score</b>							-0.45	-0.67, -0.23	<0.001	0.54	0.42, 0.65	<0.001	0.20	0.06, 0.34	0.007			
<b>Experienced physical abuse during childhood</b>	1.86	0.27, 3.45	0.022															
<b>Experienced emotional abuse during childhood</b>																1.28	0.26, 2.32	0.015
<b>Primary care health service contacts in year prior to study participation</b>				-0.18	-0.31, -0.04	0.011										0.40	0.34, 0.45	<0.001

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