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Development of hand phenotypes and changes in hand pain and problems over time in older people

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INTRODUCTION

Musculoskeletal hand problems are common in the general population aged 50 years and over, with an estimated one-month prevalence for hand problems of 47% and for hand pain of 31%, with a significant impact on everyday life [7]. Women and the very old appear especially vulnerable to the effect of hand problems on their daily activities and independence [6,7,11,37]. Hand problems in older people can be due to a range of conditions, with osteoarthritis (OA) being the most frequent cause of pain and disability. In a community-based study of adults aged 50 years and over, approximately 80% of older people with hand pain attending a research clinic had radiographic change (Kellgren & Lawrence grade ≥2 in one or hand more joints [17]. However, there is little information on the course of hand pain and functional limitations in community-based and primary care samples of older people [12,14].

A study of adults consulting with hand and wrist problems in general practice, reported that the main factors that influenced a poor outcome were female gender, older age, symptom duration over 3 months and lower coping strategies [30]. However, individuals consulting for hand problems may reflect a population with more severe symptoms and therefore a study based in the general population would capture a wider range of hand symptoms severities [23]. A recent report has also highlighted the need for insights into risk factors for onset of hand problems, specifically hand OA, and for changes in symptoms over time [8].

Hand pain and problems in older adults represent a heterogeneous group of conditions with a variable presentation and prognosis [15]. Therefore, a more adaptive technique that identifies different profiles of hand pain and problems, and the ability to move between profiles over time is needed. A potential impact of this would be clinicians have more knowledge to identify the likely course of pain and functional limitations in patients presenting with hand problems, and patients at risk of poorer trajectories. The main objectives of this study were to identify sub-groups of older individuals with distinct presentations (phenotypes) of hand pain and function, investigate how these might change over a 6-year period, and explore what factors, in addition to baseline hand phenotype, are associated with long term status.

METHODS

Study Design and Population

This study was conducted using data from the North Staffordshire Osteoarthritis Project (NorStOP), a large population-based prospective cohort study described in detail elsewhere [32]. Briefly, all individuals aged 50 years and over registered with 8 local general practices were recruited through the use of a two-stage mailing process. Participants were initially mailed a 'Health Survey' (HS) questionnaire which contained information on socio-demographics, general health, physical function and bodily pain. Those who reported any hand problems, or pain in their hands in the previous 12 months were then mailed a 'Regional Pain Survey' (RPS) (if permission for further contact was given), which collected further detailed information on the hand. This process was repeated with the same HS and RPS at 3-years and 6-years follow-up. Participants that responded at all 3 time points (baseline, 3-years and 6-years) to the HS (and RPS if sent) were included in the analysis. The RPS

included detailed hand items regarding pain, function, and limitations, including the AUSCAN (Australian/Canadian Osteoarthritis Index)[1] and AIMS2 (Arthritis Impact Measurement Scale)[20].

Item selection

The selection of items for developing the model of hand phenotypes was based on previous literature [1,8,16,19], and through consultation with eight patient representatives with hand pain and problems from the Research Users Group (RUG) at Keele University. All hand-related items from the NorStOP questionnaires (HS and RPS), which included items from the AUSCAN and AIMS2 were considered potentially relevant for inclusion in the development of the model and were presented to the RUG [1,20]. RUG members, in pairs, were asked to rank the items to indicate which represented their hand condition the most. Items that were ranked in the top half by two sets of pairs or more were considered as potential items for model development using Latent Transition Analysis (LTA), see statistical analysis.

Items were dichotomised to ease interpretation. As most of the items were measured on a 5-point scale, these were dichotomised so that 0 (low) represented 'None' or 'Mild', and 1 (high) represented 'Moderate', 'Severe' or 'Extreme' pain or limitations in function. The other item, 'pain in both hands', was dichotomised into no hand pain or pain only in one hand versus pain in both hands. At each stage of the analysis, should any participant state in their HS that they had no hand pain/problems in the previous 12 months and subsequently were not sent the RPS, their responses to hand items in the RPS were imputed to be '0' (to represent 'None').

Predictors of long-term hand phenotype membership

Potential baseline predictors of changes in hand phenotype membership at 6-years were selected based on existing evidence regarding their prognostic value in patients with hand problems [8,19,30]. Demographic/lifestyle factors included age, gender, living status, employment status, and social class (based on current or most recent job). In addition to this, general health factors were included, such as widespread bodily pain (ACR)[35], depression (based on the HADS)[38], body mass index (BMI), sleep problems [13], self-reported frequency of GP consultations, and self-perceived general health status (item from Short Form 12)[34]. Specific hand factors included previous hand injury, previous hand operation, excessive use of hands in hobbies or occupation, self-reported presence of nodes, pain duration over last 12 months, pain in both hands (if not included in final list of items for phenotype development), impact of hand problems compared to others of the same age and self-reported diagnosis of rheumatoid arthritis (RA). Finally, the self-reported presence of any comorbid condition (at least one of: high blood pressure, diabetes, heart or chest problems) was also used as a potential baseline predictor of phenotype membership at 6-years.

Statistical Analysis

Latent Transition Analysis

LTA was used to define distinct population sub-groups (called states, or phenotypes) based on the items relating to hand problems collected at baseline, 3-years and 6-years. The technique classifies individuals into one and only one phenotype at each time point (based on their average posterior

probability of belonging in each phenotype, described later) and determines the transition probabilities of individuals changing phenotypes between each of the time points investigated [4,5].

Model development

The main aim of the first stage of analysis was to develop a model that clustered respondents into an optimum number of phenotypes representing the most important factors of hand pain and function (including stiffness). This was performed using the following steps:

1. LTA was applied using all the items and the optimal number of phenotypes identified based on the Bayesian Information Criteria (BIC) (where a lower number is optimal [25,28], entropy (a measure of distinction and amount of overlap between the phenotypes, range 0-1 where a higher number is optimal) [5,27], size of each phenotype (>5% of the respondents should be in each phenotype in at least one time period) [26,36], and the clinical relevance and interpretation of each phenotype;
2. For the optimal number of phenotypes, each item was removed in turn (backward stepwise procedure), and the models compared on fit (BIC/ entropy) and interpretation, with the least influential item removed;
3. Steps 1 and 2 were repeated until removing further items provided no further improvement to the model.

The modelling process defines latent phenotypes for each of the time points investigated (here 3 time points), and so an assessment was made as to whether the definition for each phenotype was comparable at each time point. This would then indicate that the hand condition of an individual who remains in the same phenotype over time points could be regarded as stable. Individuals should clearly be classified into a phenotype at each time point. This was assessed using average posterior probabilities [2]. Posterior probabilities represent the probability of membership for an individual in each potential phenotype at each time point given their item scores. Participants are allocated to the phenotype for which their probability is highest. Average posterior probability (APP) for individuals allocated to a phenotype should be greater than 0.7 [2].

LTA is able to include respondents with missing data. However, for this analysis, respondents were removed from the analysis if they had missing values on more than half of the measures at any time point analysed. A sensitivity analysis was carried out using baseline and 3-year data only to investigate whether including individuals who were lost to follow-up at 6-years resulted in alternative definitions of the phenotypes at baseline and 3-years.

Phenotype characteristics

Phenotype labels were derived from the item-response probabilities for each phenotype. Item-response probabilities (range 0 to 1) reflect how likely participants in each phenotype are to respond ‘1’ (high) for each item. Therefore, a probability of ‘1.00’ for a particular item reflects that participants in that phenotype all responded high for that item. Item-response probabilities close to 0.5 reflect more uncertainty in defining phenotypes, as half of the individuals in that phenotype would be expected to respond high for that indicator, while the other half would not. Baseline characteristics of each phenotype were compared. The characteristics included demographic information (gender, age, social class, employment, cohabitation status, and marital status). In addition, general health factors were compared including HAD anxiety and depression scores, BMI, SF-12 general health and sleep

problems [13]. Each of these characteristics were compared between phenotypes, using a t-test for continuous measures, and a χ^2 (chi-squared) test for categorical/ordinal measures. Transition probabilities of movement between phenotypes from baseline to 3-years, and from 3-years to 6-years were determined.

Baseline predictors of 6-year phenotype membership

To explore baseline predictors of 6-year phenotype membership in individuals most likely to seek health care, participants classified into a phenotype representing no hand problems at baseline were first removed. Factors significantly associated with 6-year phenotype from univariable analyses were taken forward into a multivariable multinomial logistic regression.

Sensitivity analysis

Restricting phenotype sample size to a minimum of 5% of participants may potentially prevent additional clinically meaningful groups being identified. In light of this, a sensitivity analysis was performed relaxing this criterion and exploring the impact of this on the identification of further hand phenotypes.

Mplus version 7.11 and STATA version 13.1 were used for analysis [22,31]. A *p*-value of <0.05 was considered statistically significant.

RESULTS

Of the original 26,129 individuals contacted, 18,497 (71%) responded to the baseline health survey (*Supplementary figure 1*), those who did not respond tended to be male and younger [21]. 5,751 (22.0% of those invited to the study) responded at all 3 time points (baseline, 3-years and 6-years), with 5,617 (21.5% of those invited) participants providing sufficient data to be included in the analysis. 3,308 (58.9% of responders) reported hand problems at baseline or at least one follow-up time point. The participants that did not respond at all time points were more likely to be female (56.5% versus 54.0%) and older (mean age 67.8 (SD=10.6) versus 62.6 (SD=8.2)).

Model development

From the 40 items (listed in *Supplementary figure 2*) included in the questionnaire at each time point 11 remained following review and ranking by the RUG. The optimum model had 5 phenotypes of hand pain/problems. Removing items that did not improve the model fit or distinction between phenotypes resulted in a model based on 8 items (*Table 1*). The definition of each phenotype remained stable for each time point (baseline, 3-years, 6-years), and there was a high probability of individuals being classified in their allocated phenotype (all average posterior probabilities≥0.85). A sensitivity analysis on just baseline and 3-years data (therefore including those that did not respond at 6-years) provided a similar model to using everyone available at 6-years.

Phenotype characteristics

The definitions of each of the phenotypes were based on the item-response probabilities displayed in *Table 2*. The first phenotype (which contained 77% of the population at baseline) was characterised by low probabilities for all of the items, and as such was labelled ‘least affected’. Individuals in the second phenotype (4.3% at baseline) had probability >0.70 of responding high on the pain items, and

were therefore labelled ‘high pain’. The third phenotype (5.8%) was characterised by high probabilities for three functional items (gross functional difficulty), and was labelled ‘poor gross function’. The fourth group (6.8%) were affected by both pain and problems with gross function, and were labelled ‘high pain & poor gross function’. The final group (6.3%) had large probabilities of responding high to all of the items in the model, and were therefore labelled ‘severely affected’.

Participants in the ‘least affected’ and ‘high pain’ phenotypes were more likely to be male, younger, married, have less anxiety and depression and have (or previously had) a high managerial/ professional job compared to the other phenotypes (*Table 3*), however those in ‘least affected’ were less likely to have ‘widespread pain’ compared to those in ‘high pain’. Participants in the ‘severely affected’ phenotype represented a population with more health concerns (higher anxiety, depression, more sleep problems, poorer self-reported general health) along with a larger proportion of females, those that live alone and older aged compared to the other phenotypes.

Transitions between time points

There were high levels of stability (remaining in the same phenotype) between baseline and 3-years for individuals in the ‘least affected’ (87% remained in this phenotype), and ‘severely affected’ (68%) phenotypes at baseline (*Table 4*). The largest transitions were seen from individuals moving from ‘high pain’ at baseline into the ‘least affected’ phenotype at 3-years (42% transitioning). The largest proportion of individuals moving into ‘severely affected’ was from ‘high pain and poor gross function’ (21% transitioning). 33% of those with poor gross function but not high pain at baseline, developed high pain as well at 3-years. Transition probabilities were similar from 3 to 6-years (*Table 4*).

Baseline predictors of 6-year phenotype membership

After exclusion of those in the ‘least affected’ group at baseline (remaining n=1,025), in the multivariable model (of variables that were significant at the univariable stage), females were significantly more likely to be in the ‘severely affected’ than least affected phenotype at 6-years (adjusted relative risk ratio (RRR)= 1.82, 95% Confidence Interval= (1.18, 2.82)), while being male was significantly associated with membership in the ‘high pain’ state (RRR=0.54 (CI: 0.29, 0.97)). In addition to this, individuals with sleep problems, presence of nodes, chronic pain duration, pain in both hands and widespread pain at baseline were more likely to be in more severe hand phenotypes at 6-years *(Table 5*).

Sensitivity analysis

Relaxing the minimum 5% phenotype sample size criterion expanded the LTA model to a 6 phenotype model (*Supplementary Table 1*). This additional phenotype (1.8% of the analysis population) had large item-response probabilities for the poor gross function indicators (>0.82), and small for two of the three pain indicators (<0.20), which reflected a sample of individuals with poor gross function and pain squeezing objects. However, 3 of the 8 indicators had item-response probabilities of around 0.4 which suggested they did not help to define this phenotype. Therefore, the 5 phenotype LTA model of *Table 2* was preferred.

DISCUSSION

This exploratory study has identified five phenotypes of hand pain and functional limitations from a population-based sample of older people. Item selection was informed by opinions of older

individuals with hand problems. These phenotypes indicate that in general, individuals with functional hand problems are more likely to deteriorate over time whereas those with hand pain only are more likely to see an improvement in the future. However, once individuals reach the 'severely affected' phenotype (with high probabilities of hand pain and functional limitation) they were less likely to see change over time (stability>68% at each transition point). An exploratory analysis of predictors of long term phenotypes suggests that those in the 'severely affected' phenotype at 6-years were more likely to have baseline widespread bodily pain, nodes, and difficulties sleeping, after adjusting for baseline hand phenotype membership.

Strengths and Limitations

The technique of LTA used in this study has some direct benefits for use in musculoskeletal research. The information required for creating the phenotypes was based on a small set of key pain and function items that can be gathered by self-report questionnaires. In addition to this, the approach of LTA permits individuals to have different profiles of a condition, in this study, levels of pain or types of functional difficulty. LTA allows individuals to change membership phenotype over time and moves away from presumptions that disease progression advances linearly. There is no universally agreed approach for determining necessary sample size, but generally a sample of 200 is needed to perform a reliable basic LTA [5]. This study was therefore of sufficient size to generate reliable results. A limitation of LTA is that there is no gold standard approach to deciding on the number of states. In a sensitivity analysis, we assessed a model with 6 phenotypes, but found the additional phenotype to have similarities with another phenotype ('high pain and poor gross function') but with some of the items having item-response probabilities around 0.4 suggesting uncertainty in the definition of this new phenotype.

A large proportion of baseline respondents did not respond at all the specified time points, and as such were not able to be included in the analysis. It is possible that adults with more severe hand problems or poorer general health were more likely to be lost to follow-up. Although our sensitivity analysis using baseline and 3-year data showed similar phenotype definitions/transitions, this lost to follow-up may have led to an underestimation of the burden and proportion of people with severe hand pain and problem phenotypes in the population. Further, the items analysed in this study were restricted to those collected in the original NorStOP study, and as such, there could be other elements of hand problems that have not been considered, which could alter the profiles of the hand phenotypes, such as Parkinson's disease which was not collected in the NorStOP questionnaires. As this is a population-based cohort measured at 3-year intervals, it is difficult to be certain what might happen to individuals between the assessment time points and the role any treatment may have had in the course of hand problems.

Relationship with current literature

It is likely that many of the individuals reporting pain and functional difficulty in this study had hand OA. Analysis of a subgroup of participants within NorStOP with additional hand investigations, found that of those with hand pain (n=623), radiographic OA (in one or more joints) was present in 78% (n=485) [18]. That study also showed that other hand conditions were less common (e.g. carpal tunnel syndrome, trigger finger, tenosynovitis) and that these were equally distributed across those with and without radiographic change [18]. As previous research in a primary care based sample with hand problems has demonstrated that demographic, physical and psychosocial factors are more strongly associated with hand pain and function outcomes than medical diagnosis [29], we assume that the

absence of diagnostic information is unlikely to have greatly influenced the resulting functional phenotypes in this study.

It is generally presumed that hand problems in older people are either stable or only progress with more unfavourable outcomes. However, this work has highlighted that while many individuals did remain stable, modest transitions were seen amongst all phenotypes. A large proportion of individuals moved from 'high pain' to 'least affected' (>42%), and even in the more severe phenotype, approximately 30% did transition to other phenotypes. These findings are similar to other trajectory work in other OA locations such as knee and hip [3,24,33]. These studies found that groups of individuals did indicate signs of improvement in their OA condition over the study period. One additional benefit of the LTA method used in this study is that it is possible to see in which phenotypes changes are more likely to be expected. Our study found that individuals with functional problems were less likely to improve compared to those with pain only.

There have been limited studies on predictors of the long-term course of hand pain and problems. A previous study in all adults (>18 years) consulting with hand and wrist problems found that factors such as female gender, long symptom duration at presentation, and certain psychosocial factors were predictive of a poorer outcome at 12 months [30], similar to the findings in this study. More broadly, a systematic review identified that female gender, age, occupation, pain levels, and personal opinions about hand pain have been shown to be cross-sectionally associated with severity of hand function limitation and hand pain [23]. These findings are similar to the factors we identified in this study. While previous state membership was in most cases the strongest predictor of current state, in addition to the factors listed above, we also found sleep problems, presence of nodes and bilateral hand pain to be strong predictors of having a more severe hand problem at long-term (6-year) follow-up.

Implications

This exploratory work has defined phenotypes of hand problems, based on self-report answers to brief pain and functional items. In addition, it provides evidence that there is movement between some phenotypes. While individuals presenting with pain and no functional issues are less likely to get worse over time, and some will improve, there is less likelihood of improvement into less severe phenotypes once a member of the more severely affected group. While this study was exploratory, we have found some evidence that clinicians, particularly those based in primary care, should be aware that those with nodes, sleep problems and longer duration appear to have an increased risk of worsening hand conditions and may benefit from earlier intervention. In addition, clinicians should be more concerned about older adults consulting with poor hand function, as our study has found that they appear to have less chance of recovery and may benefit from self-management approaches including occupational therapy, joint protection, ergonomic aids and advice [9,10].

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Competing interests

The authors declare that they have no competing interests.

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Table 1: Development of optimal model of hand phenotypes using Latent Transition Analysis.

Optimal no. of phenotypes using 11 items	Number of phenotypes		BIC		Entropy	Smallest sample size at baseline	
	2		88,703		0.980	21.2%	
	3		80,537		0.956	10.1%	
	4		78,665		0.913	8.2%	
	5		**77,613**		**0.910**	**5.8%**	
	6		77,080		0.901	4.3%	
Removal of items	Removal stage	Number of items	Item removed	Number of phenotypes	BIC after removal	Entropy after removal	Smallest sample size at baseline
	1	11	-	5	77,613	0.910	5.8%
	2	10	Pain in both hands	5	66,059	0.941	4.6%
	3	9	Morning stiffness	5	58,505	0.941	4.5%
	4	**8**	**Pain at rest**	**5**	**51,902**	**0.941**	**4.2%**
	5	7	Difficulty opening a jar	5	46,879	0.928	3.4%
Optimal no. of phenotypes using 8 items	Number of phenotypes		BIC		Entropy	Smallest sample size at baseline	
	2		59,747		0.979	20.3%	
	3		53,897		0.954	9.6%	
	4		52,644		0.947	5.6%	
	5		**51,902**		**0.941**	**4.2%**	
	6		51,904		0.935	1.8%	

Footnote: BIC- Bayesian Information Criterion, lower score implies a more optimal model.

Table 2: Proportions of individuals in each phenotype and phenotype characteristics.

n= 5,617	Least affected	High pain	Poor gross function	High pain & poor gross function	Severely affected
Baseline Item-Response Probabilities					
Pain when turning objects	0.001	0.733	0.125	0.915	0.977
Pain when squeezing objects	0.004	0.818	0.156	0.960	0.989
Pain when gripping objects	0.006	0.763	0.146	0.865	0.973
Difficulty opening a new jar	0.005	0.228	0.728	0.897	1.000
Difficulty carrying a full pot	0.005	0.091	0.631	0.820	0.993
Difficulty wringing out a dishcloth	0.002	0.180	0.445	0.787	0.988
Difficulty doing-up buttons	0.001	0.038	0.172	0.238	0.917
Difficulty turning taps on	0.000	0.013	0.093	0.161	0.889
Proportion in each phenotype					
Baseline (Time 1)	0.768	0.043	0.058	0.068	0.063
3-years (Time 2)	0.721	0.059	0.047	0.095	0.079
6-years (Time 3)	0.702	0.057	0.046	0.094	0.101

Table 3: Baseline characteristics of hand phenotypes.

Baseline variable (n=5,617, unless stated) (n(%), unless stated)		Least affected	High pain	Poor gross function	High pain & poor gross function	Severely affected	p-value
Observations (n= 5,617)		4,338	224	307	394	354	
Age (mean (SD))		62.4 (8.2)	62.1 (7.4)	64.2 (8.1)	63.3 (7.9)	64.4 (8.1)	<0.001
Gender	Female	2167 (50)	96 (43)	241 (79)	266 (68)	261 (74)	<0.001
Live Alone (n=5,408)	Yes	752 (18)	29 (14)	60 (20)	85 (22)	94 (28)	<0.001
Marital Status (n= 5,574)	Married	3,238 (75)	178 (80)	218 (71)	279 (71)	214 (61)	<0.001
	Separated	45 (1)	3 (1)	3 (1)	3 (1)	3 (1)	
	Divorced	272 (6)	10 (5)	24 (8)	29 (7)	36 (10)	
	Widowed	457 (11)	17 (8)	41 (13)	59 (15)	78 (22)	
	Cohabiting	85 (2)	4 (2)	8 (3)	8 (2)	7 (2)	
	Single	207 (5)	11 (5)	12 (4)	14 (4)	11 (3)	
Employment Status (n= 5,482)	Employed	1740 (41)	92 (42)	78 (26)	88 (23)	44 (13)	<0.001
	Ill	184 (4)	13 (6)	28 (9)	55 (14)	77 (23)	
	Retired	1915 (45)	96 (43)	163 (55)	188 (49)	187 (55)	
	Unemployed	54 (1)	6 (3)	1 (0)	7 (2)	0 (0)	
	Housewife	233 (6)	5 (2)	25 (8)	33 (9)	21 (6)	
	Other	117 (3)	9 (4)	4 (1)	10 (3)	9 (3)	
Social Class (n= 5,335)	Higher Managerial/ Professional	1,093 (27)	66 (30)	75 (26)	77 (21)	51 (16)	<0.001
	Intermediate	1,114 (27)	52 (24)	81 (28)	94 (25)	78 (24)	
	Routine/ Manual	1,925 (47)	100 (46)	136 (47)	202 (54)	191 (57)	
[a]Anxiety (mean (SD)) (n= 5,527)		5.9 (3.9)	6.1 (4)	7.0 (4)	7.5 (4)	8.9 (5)	<0.001
[a]Depression (mean (SD)) (n= 5,528)		3.5 (3.0)	3.9 (3)	4.6 (3)	5.3 (4)	6.7 (4)	<0.001
[b]ACR widespread pain (n=5,617)		706 (16)	105 (47)	141 (46)	227 (58)	246 (70)	<0.001
BMI (mean (SD)) (n= 5,468)		26.6 (4.1)	26.9 (4)	27.1 (5)	27.9 (6)	28.0 (5)	<0.001
Self-reported general health, SF12 (n=5,562)	Excellent	287 (7)	9 (4)	4 (1)	8 (2)	3 (1)	<0.001
	Very good	1,428 (33)	43 (19)	67 (22)	53 (14)	22 (6)	
	Good	1,853 (43)	116 (52)	139 (46)	168 (43)	103 (30)	
	Fair	659 (15)	53 (24)	84 (28)	133 (34)	153 (44)	
	Poor	73 (2)	2 (1)	9 (3)	25 (7)	68 (20)	
GP visits for anything (n= 5,593)	Very often	41 (1)	1 (1)	5 (2)	7 (2)	15 (4)	<0.001
	Often	475 (11)	35 (16)	67 (22)	82 (21)	90 (26)	
	Occasionally	2251 (52)	126 (56)	166 (54)	239 (61)	218 (62)	
	Seldom	949 (22)	33 (15)	50 (16)	41 (11)	21 (6)	
	Hardly ever	606 (14)	29 (13)	18 (6)	20 (5)	8 (2)	
[c]Trouble falling asleep (n= 5,522)	No	1999 (47)	86 (39)	98 (33)	109 (28)	78 (22)	<0.001
	Some nights	1896 (45)	113 (51)	160 (53)	212 (55)	162 (46)	
	Most nights	368 (9)	23 (10)	42 (14)	67 (17)	109 (31)	
[c]Wake up in the night (n= 5,515)	No	871 (21)	34 (15)	35 (11)	29 (8)	19 (5)	<0.001
	Some nights	2356 (55)	121 (55)	144 (48)	200 (52)	146 (42)	
	Most nights	1023 (24)	67 (30)	125 (41)	157 (41)	186 (53)	
[c]Trouble staying asleep (n= 5,445)	No	1618 (39)	68 (31)	77 (26)	65 (17)	51 (15)	<0.001
	Some nights	1987 (47)	113 (51)	142 (48)	208 (55)	150 (44)	
	Most nights	603 (14)	40 (18)	77 (26)	108 (28)	138 (41)	
[c]Non-restorative sleep (n= 5,509)	No	1903 (45)	86 (39)	80 (26)	88 (23)	58 (17)	<0.001
	Some nights	1896 (45)	104 (47)	170 (56)	196 (51)	160 (46)	
	Most nights	451 (11)	33 (15)	53 (18)	103 (27)	128 (37)	

Footnote: ACR- American College of Rheumatology; BMI- Body Mass Index; GP- General Practitioner.

[a]: Hospital Anxiety and Depression Scale.[37]

[b]: 'widespread pain' defined by the ACR widespread pain developed by Wolfe et al., 1990.[34]

[c]: Jenkins et al., sleep scale.[13];

Table 4: Transitional probabilities for each phenotype for baseline to 3-years, and 3-years to 6-years.

Latent transition probabilities (n= 5,617)					
3-years Baseline	Least affected	High pain	Poor gross function	High pain & poor gross function	Severely affected
Least affected	**0.867**	0.049	0.026	0.040	0.018
High pain	0.417	**0.384**	0.027	0.151	0.021
Poor gross function	0.244	0.031	**0.274**	0.329	0.122
High pain & poor gross function	0.207	0.037	0.094	**0.452**	0.211
Severely affected	0.134	0.006	0.059	0.117	**0.684**
6-years 3-years	Least affected	High pain	Poor gross function	High pain & poor gross function	Severely affected
Least affected	**0.868**	0.048	0.023	0.038	0.023
High pain	0.481	**0.262**	0.031	0.173	0.053
Poor gross function	0.284	0.000	**0.351**	0.273	0.091
High pain & poor gross function	0.222	0.076	0.089	**0.416**	0.198
Severely affected	0.177	0.000	0.034	0.057	**0.733**

Table 5: Multivariable baseline predictors of 6-year hand phenotype membership[a].

(n=1,025)		Least Affected	High Pain	Poor Gross Function	High Pain & Poor Gross Function	Severely Affected
Gender	Female	1.00	**0.54 (0.29,0.97)**	1.24 (0.70,2.19)	1.44 (0.97,2.15)	**1.82 (1.18,2.82)**
Age	50-64	1.00	1.00	1.00	1.00	1.00
	65-74	1.00	0.77 (0.33,1.80)	0.97 (0.49,1.93)	0.86 (0.52,1.42)	0.80 (0.47,1.38)
	75+	1.00	0.25 (0.05,1.23)	0.35 (0.12,1.02)	0.49 (0.24,1.02)	0.91 (0.45,1.85)
Employment Status	Retired	1.00	1.00	1.00	1.00	1.00
	Employed	1.00	1.80 (0.80,4.07)	0.93 (0.44,1.95)	1.16 (0.68,1.97)	0.78 (0.42,1.42)
	Other	1.00	1.38 (0.55,3.48)	0.84 (0.39,1.82)	1.29 (0.74,2.22)	0.92 (0.52,1.65)
Social Class	Higher managerial/ Professional	1.00	1.00	1.00	1.00	1.00
	Intermediate	1.00	0.83 (0.39,1.75)	**0.44 (0.22,0.88)**	0.76 (0.46,1.26)	0.72 (0.41,1.26)
	Routine/ Manual	1.00	0.63 (0.32,1.26)	**0.54 (0.29,0.97)**	0.68 (0.43,1.07)	0.87 (0.53,1.45)
Widespread Pain		1.00	1.39 (0.78,2.46)	1.13 (0.67,1.88)	1.07 (0.74,1.55)	1.21 (0.81,1.80)
Body Mass Index (BMI) per unit increase		1.00	1.04 (1.00,1.09)	0.97 (0.92,1.02)	1.00 (0.74,1.55)	1.00 (0.96,1.03)
Any sleep problems[b]		1.00	0.66 (0.36,1.20)	1.28 (0.77,2.14)	**1.54 (1.06,2.22)**	1.46 (0.98,2.17)
Self-perceived general health	Good/ Very Good/ Excellent	1.00	1.00	1.00	1.00	1.00
	Poor/ Fair	1.00	0.56 (0.28,1.11)	0.79 (0.44,1.43)	0.74 (0.48,1.12)	1.47 (0.95,2.27)
Self-reported nodes		1.00	1.65 (0.92,2.96)	1.62 (0.96,2.72)	**1.53 (1.06,2.23)**	**2.24 (1.49,3.34)**
Previous 12 month duration	Less than 3 months	1.00	1.00	1.00	1.00	1.00
	3 months +	1.00	1.32 (0.72,2.40)	1.07 (0.63,1.81)	**1.65 (1.11,2.45)**	1.42 (0.91,2.20)
Hand pain in both hands		1.00	0.78 (0.44,1.38)	1.06 (0.63,1.80)	**1.69 (1.14,2.49)**	**1.79 (1.16,2.75)**
Impact of hand problems compared to people same age	Very well/ well	1.00	1.00	1.00	1.00	1.00
	Fair/ poor/ very poorly	1.00	1.74 (0.84,3.63)	**2.32 (1.27,4.23)**	1.09 (0.69,1.73)	1.28 (0.80,2.03)
Time 1 state	High Pain	1.00	1.00	1.00	1.00	1.00
	Poor Gross Function	1.00	**0.17 (0.1,0.5)**	**10.0 (4.0,25.5)**	**2.06 (1.2,3.5)**	**3.44 (1.6,7.4)**
	High Pain & Poor Gross Function	1.00	0.44 (0.2,0.9)	**4.69 (1.8,12.2)**	**2.65 (1.6,4.4)**	**5.25 (2.5,10.9)**
	Severely Affected	1.00	**0.14 (0.1,0.5)**	2.32 (0.7,7.5)	1.43 (0.8,2.7)	**18.15 (8.4,39.1)**

Footnote: All factors in the table are adjusted for each other, and were significant (p<0.05) in the univariable analyses.

[a] Estimates are Relative Risk Ratio (RRR), with 95% Confidence Intervals. All estimates are adjusted for each predictor listed in the table along with baseline state.

[b] 'sleep problems' defined as at least one response of 'on most nights' to the four items in the Jenkins et al., 1988.[13] scale (items in *Table 2*).

[c]'widespread pain' defined by the ACR widespread pain developed by Wolfe et al., 1990.[34]