The influence of perceived stress on the onset of arthritis in women: Findings from the Australian Longitudinal Study on Women's Health

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Abstract

Background: Psychosocial factors are considered as risk factors for some chronic diseases. A paucity of research exists surrounding the role of perceived stress in arthritis onset.

Purpose: Perceived stress as a risk factor for arthritis development was explored in an ageing cohort of Australian women.

Methods: This study focused on 12,202 women from the 1946-1951cohort who completed the Australian Longitudinal Study on Women's Health surveys in 2001, 2004, and 2007. Longitudinal associations were modelled, with and without a time lag.

Results: Findings from the multivariate time lag modelling, excluding women with persistent joint pain revealed that perceived stress predicted the onset of arthritis, with women experiencing minimal and moderate/high stress levels having a 1.7 and 2.4 times greater odds of developing arthritis three years later, respectively (p's<0.001).

Conclusion: Chronically perceiving life as stressful is detrimental to future health. The findings provide support for perceived stress to be considered alongside other modifiable risk factors.

Key words: arthritis, perceived stress, risk factor, women.

Arthritis represents an ongoing public health challenge. It contributes significantly to global healthcare expenditure [1-3] and remains a major cause of disability, chronic pain and reduced health-related quality of life [1,4,5]. Estimates from epidemiological research suggest that the prevalence of arthritis is approximately 20% [6,7]. When studies are focused on middle-aged and older adults, prevalence approaches or exceeds 50% [2,5,8]. While significant progress has been made regarding disease progression, the pathogenesis of arthritis remains unclear [9,10]. Arthritis is viewed as a disease of multifactorial origin, with both genetic and environmental factors contributing to its occurrence and expression [11,12]. Prevention strategies have focused on identifying risk factors for disease development [13]. Notably, age [8,14,15], gender [16-18], and genetic predisposition [11,12,19,20] have been highlighted as risk factors for arthritis onset. In addition to these non-modifiable factors, potentially modifiable factors have been found to place individuals at an increased risk of developing both osteoarthritis (OA) and rheumatoid arthritis (RA). Specifically, in relation to OA, factors such as overweight and obesity [21], physical activity [21,22], joint trauma [23], and occupational-based repetitive joint loading [24,25] have been identified. With respect to RA, tobacco smoking [26-28] has been found to be the best established modifiable risk factor. While arthritis remains incurable, identifying additional factors that contribute to increased risk is of public health significance.

Psychosocial factors and in particular psychological stress (defined in terms of an interpersonal event such as trauma or response to an event such as stress perception) are beginning to be considered in concert with traditional risk factors (e.g. overweight and obesity, and poor nutrition) for chronic diseases other than arthritis [29-31]. Despite this increasing body of research, relatively little attention has been paid to understanding the role of psychological stress as a risk factor for arthritis onset. When the relationship between psychological stress and arthritis risk has been addressed in epidemiological studies, it has

primarily been examined in response to a specific life stressor [32-34]. The perception of stress and psychosocial processes, with control for traditional risk factors has not been undertaken.

Chronically perceiving life as stressful, has been hypothesised to be a more important factor in the stress-chronic disease process than the experience of specific life events [35]. Although primarily focused on RA subpopulations, previous research has indicated that perceived stress may play a pertinent role with regard to symptom expression [36-39] and psychological adjustment to the disease [40,41]. However, prospective evidence for the role of perceived stress in arthritis onset is limited. In a prospective population-based study focused on the relationship between childhood trauma and the onset of medically diagnosed arthritis in Canadian men and women, perceived stress was found to have a significant confounding effect on this relationship. Particularly, chronic perceived stress conferred a similar risk to experiencing multiple childhood adversities [32]. While perceived stress may be a key risk factor in arthritis onset, these findings may reflect symptom expression as opposed to disease onset. Thus, it is important to gain an understanding of the role perceived stress may play in the onset of arthritis, controlling for additional psychosocial processes (e.g. social support and mental health) that may influence the stress-chronic disease relationship in conjunction with traditional risk/protective factors for arthritis (including socioeconomic status, age, obesity, physical activity, occupation, gynaecological status). Social support, in particular has been found to have both direct and moderating effects on the stress response in arthritis populations [42-46]. As such, modelling these distinct relationships may assist in qualifying this relationship. Thus, the main aim of this study is to examine longitudinally the relationship between perceived stress and arthritis in a broadly representative cohort of ageing women. It is hypothesised that perceived stress will precede the onset of arthritis in

these women. Additionally, the hypothesis regarding personal psychosocial coping resources (i.e. social support) as a moderator of this relationship will also be tested.

Methods

Overview of the Australian Longitudinal Study on Women's Health. The Australian Longitudinal Study on Women's Health is a longitudinal cohort study assessing physical, psychological, environmental, social and economic factors in Australian women. Using self-report mailed surveys, in excess of 42,000 women were randomly recruited through the national health insurer's (Medicare Australia) database. Details of the methodological practices have been extensively reviewed in independent publications [47-49]. This project has ongoing ethical clearance from both the University of Newcastle and University of Queensland's Human Research Ethics Committees.

Sample. The focus of this study is on women from the 1946-1951 cohort who completed surveys in 2001 (survey 3), 2004 (survey 4) and 2007 (survey 5) when the diagnosis of arthritis was examined. Of the 14,099 women (aged 45-50 years) who responded to the initial invitation in 1996, 11,220 (79.6%), 10,905 (77.3%) and 10,638 (75.5%) completed the follow-up surveys in 2001, 2004 and 2007 respectively (unweighted data). These women were found to be largely representative of the original cohort with a slight over-representation of married, Australian born and tertiary educated women [47]. According to Australian Longitudinal Study on Women's Health recommendations, all cross-sectional analyses were weighted for area of residence in order to correct for the over sampling of women from rural and remote areas. As such, the weighted sample sizes at each survey comprised 11,042 (survey 3), 10,715 (survey 4) and 10,532 (survey 5). The longitudinal analysis related to those women who provided at least one data point at either survey 3, 4 or 5. Thus, the final sample for the longitudinal analysis comprised 12,202 (86.5%; unweighted data) women.

Measures

The following variables were included in analyses examining the role of perceived stress as a predictor of arthritis.

Arthritis case definition (outcome variable). 'Arthritis' was defined as those women who reported being diagnosed with, or treated for any form of arthritis in the past three years at either survey 3, 4 or 5. At surveys 3 and 4 women were asked to indicate whether they had been diagnosed or treated for 'arthritis/rheumatism'. At survey 5 however, this item was amended to reflect the major arthritis forms with separate questions relating to diagnosis or treatment of OA, RA or another form of arthritis (other arthritis). Responses were dichotomised to indicate the presence or absence of at least one form of arthritis. This method of arthritis case definition is considered a valid approach for epidemiological research [50-52]. As arthritis is considered a chronic unremitting condition, once a respondent indicated having arthritis, they were considered to have the disease thereafter.

Psychological stress. The Australian Longitudinal Study on Women's Health developed Perceived Stress Scale [53] was used to assess levels of psychological stress across ten life domains, including own health, health of a family member, money and personal relationships. Women were asked to rate how stressed they had felt in these areas within a 12 month period on a five point likert-type scale from 'not stressed at all' to 'extremely stressed'. Mean scores were aggregated into 'no stress' (mean score of 0), 'minimal stress' (scores >0 and ≤1) and 'moderate/high stress' (scores >1). This method of classification has been previously adopted [54]. This measure has shown acceptable internal consistency (Cronbach's alpha=0.70) for the 1946-1951 cohort [55] and has demonstrated convergent and discriminant validity [56,57].

Psychosocial covariates. Cohort-specific negative life events were extracted from a modified version of the Life Event Questionnaire [58]. Women were asked to indicate whether they had experienced life events of varying severity and chronicity including a significant trauma (e.g. death of a spouse) or constant sources of stress (e.g. financial difficulties) in the previous 12 months.

Women were considered to have depression and anxiety if they reported being diagnosed with, or treated for these conditions in the past three years [59].

The abbreviated version of the Medical Outcomes Study Social Support Survey [60] was used to measure perceived social support. This version includes two items from each of the emotional/informational (e.g. "someone to share your most private worries and fears with"), tangible (e.g. "someone to take you to the doctor if you need it") and affectionate/positive social interaction subscales (e.g. "someone to turn to for suggestions about how to deal with a personal problem"). Respondents were asked to rate how often these types of support were made available to them when needed, on a five point likert-type scale from 'none of the time' to 'all of the time'. Mean scores for the scale were aggregated into 'all of the time' (scores >4 and ≤5, 'most of the time' (scores >3 and ≤4), 'some of the time' (>2 and ≤3) and 'none/little of the time' (scores ≤2). The abbreviated index has shown strong agreement with the original 19 item scale [53].

Behavioural, demographic and health-related covariates. Body Mass Index (BMI) was calculated for each participant from self-report height and weight according to the World Health Organization guidelines [61]. BMI was aggregated into four categories: 'underweight' (<18.5), 'healthy' (18.5-24.99), 'overweight' (25-29.99) and 'obese' (≥30). Items from Active Australia's National Activity Survey [62] based upon the frequency and duration of leisure-time activity in the last week was used as a measure of physical activity. Weekly

minutes were assigned a resting metabolic rate (MET) equivalent and were defined as 'nil/sedentary' (<40 MET mins/week), 'low' (>40 and <600 MET mins/week), 'moderate' (600-<1200 mins/week), and 'high' (≥ 1200 MET mins/week).

Women were also classified according to cigarettes smoked each day as a 'non-smoker', 'ex-smoker', and current smoker' using a modified version of the Australian Institute of Health and Welfare data dictionary [63]. Additional demographics included age, marital status, highest educational qualification, occupation and area of residence (categorised according to the Rural Remote and Metropolitan Areas classification system) [64]. Further, menopause status was determined on the basis of self-report menstrual bleeding [65], while current hormone replacement therapy usage was assessed in a separate question which contained dichotomous response categories (yes/no).

In conjunction with the above mentioned variables, the following disease-related covariates were also included as part of sensitivity analyses examining arthritis as a predictor of perceived stress.

Disease-related covariates. Women who reported being diagnosed with, or treated for anaemia, osteoporosis, diabetes, or cardiovascular disease in the past three years were considered to have chronic medical comorbidity. Likewise, women were considered to have comorbid somatic symptomatology if they reported experiencing fatigue, gastrointestinal problems, or headaches/migraine sometimes/often in the previous 12 months. Health service use was also assessed by the number of visits made to a general practitioner in the previous 12 months.

Statistical analyses. Chi-square analyses were employed to report differences between women who had arthritis from those that did not at each of the three surveys. Unadjusted logistic regression analyses were performed to examine the association with the arthritis-

perceived stress relationship. All univariate analyses were weighted for area (i.e. where area of residence was not included in the model) in order to correct for the oversampling of women from rural and remote areas.

Graphical representations of the relationship between perceived stress and arthritis were derived from classifying women as having prevalent, incident or no arthritis at each of the three surveys. Women who reported arthritis at survey 3 in 2001 were classified as having 'prevalent' arthritis, while women who did not report arthritis at any of the three surveys were classified as having 'no' arthritis. Women who did not report arthritis in 2001 but indicated arthritis in either of the subsequent surveys (i.e. survey 4 or 5) were classified as having 'incident' arthritis. Separate cross-sectional multinomial logistic regressions were fitted to the data, with perceived stress as the dependent variable and arthritis status, along with the psychosocial, behavioural, demographic and health-related covariates as independent variables.

The longitudinal association between perceived stress and arthritis status was examined using Generalized Estimating Equations (GEE) models with an independent correlation matrix. Models were constructed with and without a time lag (i.e. one survey period or three years) at both a univariate (weighted for area) and multivariate level. This method allowed for the examination of a temporal sequence (i.e. cause and effect) between perceived stress and arthritis onset (with psychological stress preceding arthritis diagnosis). With a slight variation to the standard GEE model, the GEE time lag model was used to examine whether psychological stress (the predictor variable) repeatedly studied over time was related to arthritis diagnosis one survey later, thus taking into account the temporal sequence of cause and effect [66].

Limited research has suggested that a delay between the onset of symptoms and the diagnosis of arthritis, particularly for OA may exist [67-69]. In order to mitigate the potential impact of possible undiagnosed arthritis on the analysis, the time lag model was also conducted on a sub-sample of women (n=10,986) excluding women without arthritis at any survey who reported experiencing joint pain 'often' at either survey 4 or 5; women with incident arthritis at survey 4 who reported experiencing joint pain 'often' at survey 3; and women with incident arthritis at survey 5 who reported joint pain 'often' at either survey 3 or 4 (n=1216).

Moreover, interaction GEE models (with and without time lags) for social support were also fitted to the data in order to test the hypothesis regarding the moderating effect of psychosocial processes on the relationship between perceived stress and arthritis.

Finally, sensitivity analyses were conducted in order to provide further support for the role of perceived stress as a predictor in the onset of arthritis. Adjusted multinomial GEE models (with and without a time lag), controlling for arthritis onset predictors and factors that impact on the arthritis experience (e.g. disease comorbidity and health service use) were conducted in order to examine the role of arthritis as a predictor of perceived stress over time.

Due to a large sample size, statistical significance was set at $p<0.005$. All analyses were conducted using the software package SPSS v.19 (SPSS Inc., Chicago, IL, USA). The graph was constructed in Microsoft Excel 2010.

Results

Sample characteristics. In 2001, a total of 2441 (22.1%) reported being diagnosed with, or treated for arthritis in the previous three years. Demographically, the majority of these women with a mean age of 52.5 (SD=1.5) years were living in partnered relationships (79.8%), resided in urban areas (69.8%), and had achieved secondary education (46. 4%) or

higher (20.1% and 17.3% for trade and tertiary education, respectively). The women however reported diverse occupations with 33.4% employed in highly skilled occupations, 30.0% in skilled occupations and 6.0% in less skilled occupations. Meanwhile, a total of 2510 women (22.7%) reported no paid employment.

At the following survey, 3,452 (32.2%) women reported being diagnosed or treated for arthritis within the following three years, while in 2007, 40.8% of women reported arthritis (n=4301). A total of 9116 women completed the question relating to arthritis diagnosis at all three surveys, with 2013 (22.1%) reporting arthritis at all three time points. An additional 965 (10.6%) and 782 (8.6%) women reported arthritis twice, or on one occasion.

A sensitivity analysis was conducted using chi-square for arthritis diagnosis between women who remained in the cohort at either of the follow-up 2004 and 2007 surveys from women who did not in order to assess for sample bias arising from attrition between each of the surveys. These comparisons revealed no significant differences in arthritis status between women who provided data at each of the time points from women who did not.

Cross-sectional associations between perceived stress and arthritis. As indicated in Table 1, women with arthritis consistently reported significantly higher prevalence estimates of moderate/high perceived stress in comparison to women without arthritis. Peak prevalence was reported in 2001 with 22.1% of women (n=536) with arthritis experiencing higher levels of perceived stress compared to only 14.2% (n=1214) of women without the disease.

Figure 1 shows that women with prevalent arthritis consistently reported the highest levels of moderate/high perceived stress across the three time points. The proportion of women with moderate/high levels of perceived stress were the highest across the six year study period for women with prevalent arthritis, however by 2007 these levels approached those of women with incident arthritis. In 2001, women categorised as having no arthritis reported higher

levels of minimal stress, while those with prevalent arthritis reported the least. In 2004 however, the proportion of women reporting minimal stress by women with no arthritis and incident arthritis were the same, and by 2007 all three groups were reporting similar proportions. Fewer women with prevalent arthritis reported experiencing no stress in comparison to the other two groups. However, in the follow-up surveys, the proportions of women contributing to the prevalent and incident arthritis groups were similar. Further, while women who did not report arthritis at any survey reported higher levels of moderate/high stress in comparison to no stress in 2001, the proportion of women contributing to either group were similar in 2004 and 2007.

The longitudinal relationship between perceived stress and arthritis. The longitudinal relationship between perceived stress and arthritis was examined using GEE models. As shown in Table 2, the unadjusted odds associated with arthritis significantly increased over time. Specifically, women who reported experiencing minimal stress had 1.7 (95% CI=1.5, 2.0; $p<0.001$) times greater odds of reporting arthritis than women who had experienced no stress during the study period. Likewise, women who reported moderate/high levels of perceived stress were found to have a 2.6 (95%CI=2.2, 3.0; $p<0.001$) times greater odds of reporting arthritis. When psychosocial, behavioural, demographic and health-related confounders were included in the model (see Table 3), the odds of experiencing arthritis dropped slightly with minimal stress found to be predictive of a 1.5 (95% CI=1.4, 1.8; $p<0.001$) times greater odds of the reporting of arthritis and 1.9 greater odds for those moderately to highly stressed (95% CI=1.6, 2.2; $p<0.001$).

The longitudinal relationship between perceived stress and arthritis using a time-lag approach. Findings related to the time lag analyses provided similar results to those using the GEE approach without a time lag. Notably, the odds associated with reporting arthritis increased when using this technique. Univariate associations revealed that compared to

women who experienced no stress, women who experienced minimal levels of perceived stress experienced in the previous 12 months were found to have a 1.8 times greater odds of reporting arthritis (95%CI=1.5, 2.1; p<0.001), while women who experienced moderate/high levels of perceived stress were found to have a 3.0 (95% CI=2.5, 3.6; p<0.001) times greater of odds of reporting arthritis (see Table 2). The multivariate time lag GEE model (see Table 3) indicated a 1.6 (95% CI=1.4, 1.9; p<0.001) times greater odds of reporting arthritis when experiencing minimal levels of stress compared to women with no stress. This number increased slightly when considering moderate/high levels of perceived stress (OR=2.0; 95% CI=1.7, 2.4; p<0.001).

Findings relating to perceived stress as a predictor of arthritis onset increased further, particularly in relation to moderate/high stress when the time lag model was employed following the exclusion of women with persistent joint pain. Particularly, at a univariate level (see Table 2), compared to women who experienced no stress, women with minimal levels of stress were found to have a 1.8 times greater odds of arthritis (95% CI=1.6, 2.2; p<0.001) at the following survey, while those with moderate/high stress levels resulted in a 3.7 (95% CI=3.1, 4.5; p<0.001) times greater odds of reporting arthritis three years later. At a multivariate level (see Table 3), women with minimal levels of stress reported a 1.7 (95% CI=1.5, 2.0; p<0.001) times greater odds in arthritis diagnosis at the following survey compared to women without stress. On the other hand, women with moderate/high perceived stress levels had a 2.4 (95% CI=2.0, 2.9; p<0.001) times greater odds in being diagnosed with arthritis three years later than women without stress (see Electronic Supplementary Material (ESM) Table S1 for the complete model).

Social support as a moderator of the perceived stress-arthritis relationship. Higher order multivariate interactional analyses testing social support as a moderator of the perceived

stress-arthritis relationship revealed no significant associations (all ps>0.005) for all examined models (ESM Table S2).

Sensitivity analyses. Findings from the adjusted multinomial GEE models (with and without a time lag) examining arthritis as a predictor of perceived stress also produced non-significant findings (all ps>0.005) (see ESM Table S3).

Discussion

This is the first study to examine the role of perceived stress in the onset of arthritis in an ageing cohort of Australian women. Findings from the longitudinal analyses indicate that perceived stress is a strong risk factor for arthritis, with both minimal and moderate/high levels of perceived stress contributing to the onset of arthritis three years later. Although the use of a longitudinal study design does not necessarily allow the implication of causality, the comparison of GEE models with and without a time lag component, along with the adjustment for traditional risk factors, provides some evidence towards perceived stress playing a causal role in arthritis onset.

Perceived stress may contribute to disease onset through multiple pathways. Researchers have speculated that psychological stress may influence the onset of arthritis, notably RA via neuroendocrine and immune pathways [70,71]. Dysregulation of the hypothalamic-pituitary-adrenal axis has been identified as crucial to this process [72]. McEwen and colleagues have argued that in the process of restoring allostasis (equilibrium) following psychological insult, chronic stress activation may result in cumulative changes that lead to allostatic overload, and thus a reorganisation in order to set a new equilibrium [73,74]. Chronically stressed individuals have been found to have rigid patterns of cortisol secretion, reduced cortisol variation and hypersensitisation of the nervous system [75,76]. As such, a response to decreasingly intense stimuli such as minor stressors may occur [77]. The findings of this

study support this hypothesis, with women who developed arthritis found to have greater stressor reactivity (in terms of diagnosed depression). Less evidence exists for the role of psychological stress in the onset of OA, however it has been posited that psychological stress remains a substantial contributor to cellular ageing [78-80] and thus may be a significant contributor to accrued joint degeneration through similar pathways. Others have suggested that the effects of perceived stress may be elicited via behavioural or metabolic pathways, altering health through increased engagement in adverse behaviours (e.g. poor nutrition leading to increased BMI), or through psychosocial processes (e.g. depression and poor coping), thus increasing allostatic load [81,82]. Similar pathways have been posited for conditions with chronic stress at its core [83].

The consistency in odds ratios between the multivariate models in our study suggests that women who develop arthritis chronically perceive their lives as stressful. As such, these women may have coping mechanisms that, while adaptive in the first instance, are maladaptive in the long-term. Although an under-researched phenomenon within the arthritis literature, findings from other chronic disease studies, including those with pain as a key feature support the results of this study [84,85]. Additionally, Smith et al. [86] demonstrated that perceived stress partially mediated the relationship between traumatic events and mental as well as physical health in women with fibromyalgia. The authors concluded that the findings suggested that although women with, and without the condition had relatively little difference in stress exposure, an exposure to trauma may have contributed to ongoing cognitive appraisals. As such, traumatic events may lead to long-term dysregulation of stress response systems and increased sensitivity to ongoing life demands [75,87]. Although we were unable to examine the cumulative impact of traumatic events related to abuse, arthritis was associated with the stress of having a family member/close friend with a major illness, although to a far lesser extent than perceived stress (See ESM Table S1). While the role of

allostasis would have to be examined in further prospective analyses, women in our study did show a hypersensitivity to this ongoing stressor. Further, while having functional types of social support available most of the time was found to be a modest predictor of arthritis onset in all GEE models, specific relationship sources were identified as more pertinent to arthritis onset. Notably, never being in a partnered relationship compared to those in married or de facto relationships produced similar increases in arthritis risk as experiencing low levels of chronic stress. Although further research is required in order to elucidate the complex interplay between stressors (including the impact of trauma histories), coping resources and stress appraisal, the results of this study suggest that having functional forms of social support available is ineffective in mitigating the deleterious effects of perceived stress. As such, these psychosocial factors appear to act independently in increasing arthritis risk, with perceived stress far more pertinent.

Moreover, the findings from analyses with and without a time lag indicate that arthritis risk increased for women who experienced chronic depression during the study period. This finding parallels that of Magin et al. [88] who found that perceived stress and depression predicted the onset of skin disease. While the strength of the relationship between perceived stress and arthritis onset was stronger for those women with either minimal or moderate/high levels of stress, the experience of chronic depression also predicted the onset of arthritis in the time lag analyses (see ESM Table S1). As such, this finding suggests that perceived stress and depression may act through similar pathways in order to induce arthritis.

Taken together, the findings from this study have important clinical implications. Particularly, the results suggest that focusing on reducing perceived stress and poor mental health as well as increasing personal coping resources (such as increasing social networks), coupled with current modifiable preventive strategies (focused on overweight and obesity, occupational joint overload, physical activity) may prove beneficial in the reduction of

arthritis. Notably, moderate/high levels of perceived stress had a similar risk of arthritis onset to being in the highest BMI category (see ESM Table S1).

The current study must however, be considered in light of a few limitations. Firstly, this study relied upon a self-report measure of arthritis. March and colleagues [89] however, have found that self-reported physician diagnosed general arthritis has good congruency with clinically derived diagnoses. Likewise, due to the nature of the survey, we were unable to distinguish between arthritis forms. While it has been more commonly accepted that stress may play a role in the onset and exacerbation of RA due to its relationship with systemic inflammation, this study examined arthritis onset in a cohort of women transitioning from midlife to older age. It is likely that the numbers of arthritis were driven by OA. Therefore, the findings from these analyses provide the most conclusive evidence that perceived stress also plays a substantial role in the onset of OA. Additionally, 'arthritis' is a collective term used to describe a subset of conditions characterised by inflammation of tissues in or around a joint. As such, symptom intensity at onset may vary according to arthritis form with differing lag times between symptom onset and diagnosis [67-69] Thus, there is the potential for reverse causality in which individuals with undiagnosed arthritis report increasing psychological stress. Unlike the Kopec and Sayre study [32] we excluded women without arthritis with persistent joint symptoms in order to minimise this effect. While there is discordance between clinical symptomatology and radiographic evidence of OA [90,91], pain has been found to be present in approximately 75-85% of individuals with abnormalities of the knee, hips, and hands [92]. Moreover, sensitivity analyses examining arthritis as a predictor of perceived stress, controlling for factors that impact on the arthritis experience (e.g. disease comorbidity and health service use) produced non-significant findings (see ESM Table S3). Given this result, it is unlikely that reverse causality contributed to the study findings, suggesting that factors other than arthritis are responsible for increased levels of stress over the course of the

disease. Thus, the role of perceived stress as a risk factor for arthritis is of greater potential significance. This causal pathway however would require investigation in future studies. A further limitation of this study is that we examined the role of perceived stress in a cohort of women. Studies have shown gender differences in stress reactivity [93,94]. As such, these findings may not be generalisable to the development of arthritis in males.

With life expectancies increasing, addressing the burden associated with arthritis has become a key priority for governmental policy makers. The findings of this large national cohort study add to our current understanding of arthritis risk factors and highlight the importance of perceived stress in disease onset, particularly for women. Importantly, our findings indicate that chronic perceived stress has significant health consequences, with the effects of such cognitive appraisal evident years later. While further prospective research is required in order to elucidate the complex interplay between stressors, coping resources and stress appraisal, the findings provide support for perceived stress to be considered alongside other modifiable risk factors such as obesity and physical activity in public health primary prevention approaches. Moreover, these findings have implications for interventions with a cognitive-behaviour focus, namely reducing psychological stress and increasing psychosocial coping resources, in order to prevent or delay the onset of this debilitating condition in women. In doing so, this will not only reduce the economic burden associated with the disease, but also facilitate women in ageing well.

Conflict of Interest Statement

The authors have no conflict of interest to disclose.

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Table 1. Unadjusted cross-sectional analyses for perceived stress according to arthritis status during the survey periods 2001-2007[a]

	Survey 3 (2001)			Survey 4 (2004)			Survey 5 (2007)		
	Missing	**No arthritis**	**Arthritis**	**Missing**	**No arthritis**	**Arthritis**	**Missing**	**No arthritis**	**Arthritis**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
[b]**Perceived stress**									
None [ref]		696 (8.2%)	100 (4.1%)		689 (9.6%)	176 (5.1%)		637 (10.4%)	262 (6.1%)
Minimal		6626 (77.6%)	1790 (73.8%)		5520 (77.2%)	2573 (74.9%)		4845 (79.1%)	3336 (77.8%)
Moderate/high		1214 (14.2%)	536 (22.1%)		942 (13.2%)	684 (19.9%)		641 (10.5%)	688 (16.1%)
Missing	*80 (0.7%)*			*131 (1.2%)*			*123 (1.2%)*		

[a] all analyses were weighted for area of residence

[b] all associations significant ($p<0.001$)

Table 2. Unadjusted longitudinal GEE models reporting odds ratios with 95% confidence intervals (CI) for the relationship between perceived stress and arthritis during the period 2001-2007[a]

	GEE Model without a time lag		GEE Model with a time lag		GEE Model with a time lag (excluding persistent joint pain)	
	Odds ratio (95% CI)	**P Value**	**Odds ratio (95% CI)**	**P Value**	**Odds ratio (95% CI)**	**P Value**
Perceived stress						
None [ref]	—	—	—	—	—	—
Minimal	1.7 (1.5, 2.0)	<0.001	1.8 (1.5, 2.1)	<0.001	1.8 (1.6, 2.2)	<0.001
Moderate/high	2.6 (2.2, 3.0)	<0.001	3.0 (2.5, 3.6)	<0.001	3.7 (3.1, 4.5)	<0.001

[a]analyses were weighted for area of residence

Table 3. Adjusted longitudinal GEE models reporting odds ratios and 95% confidence intervals (CI) for the relationship between perceived stress and arthritis during the period 2001-2007[a]

	GEE Model without a time lag		GEE Model with a time lag		GEE Model with a time lag (excluding persistent joint pain)	
	Odds ratio (95% CI)	**P Value**	**Odds ratio (95% CI)**	**P Value**	**Odds ratio (95% CI)**	**P Value**
Perceived stress						
None	—	—	—	—	—	—
Minimal	1.5 (1.4, 1.8)	<0.001	1.6 (1.4, 1.9)	<0.001	1.7 (1.5, 2.0)	<0.001
Moderate/high	1.9 (1.6, 2.2)	<0.001	2.0 (1.7, 2.4)	<0.001	2.4 (2.0, 2.9)	<0.001

[a]adjusted for the following covariates: psychosocial (negative life events, psychiatric mood disorders, perceived social support); demographics (area of residence, age, occupation, marital status, educational attainment, time); health behaviours (physical activity, BMI, smoking); hormonal (menopause status, hormone replacement therapy use).

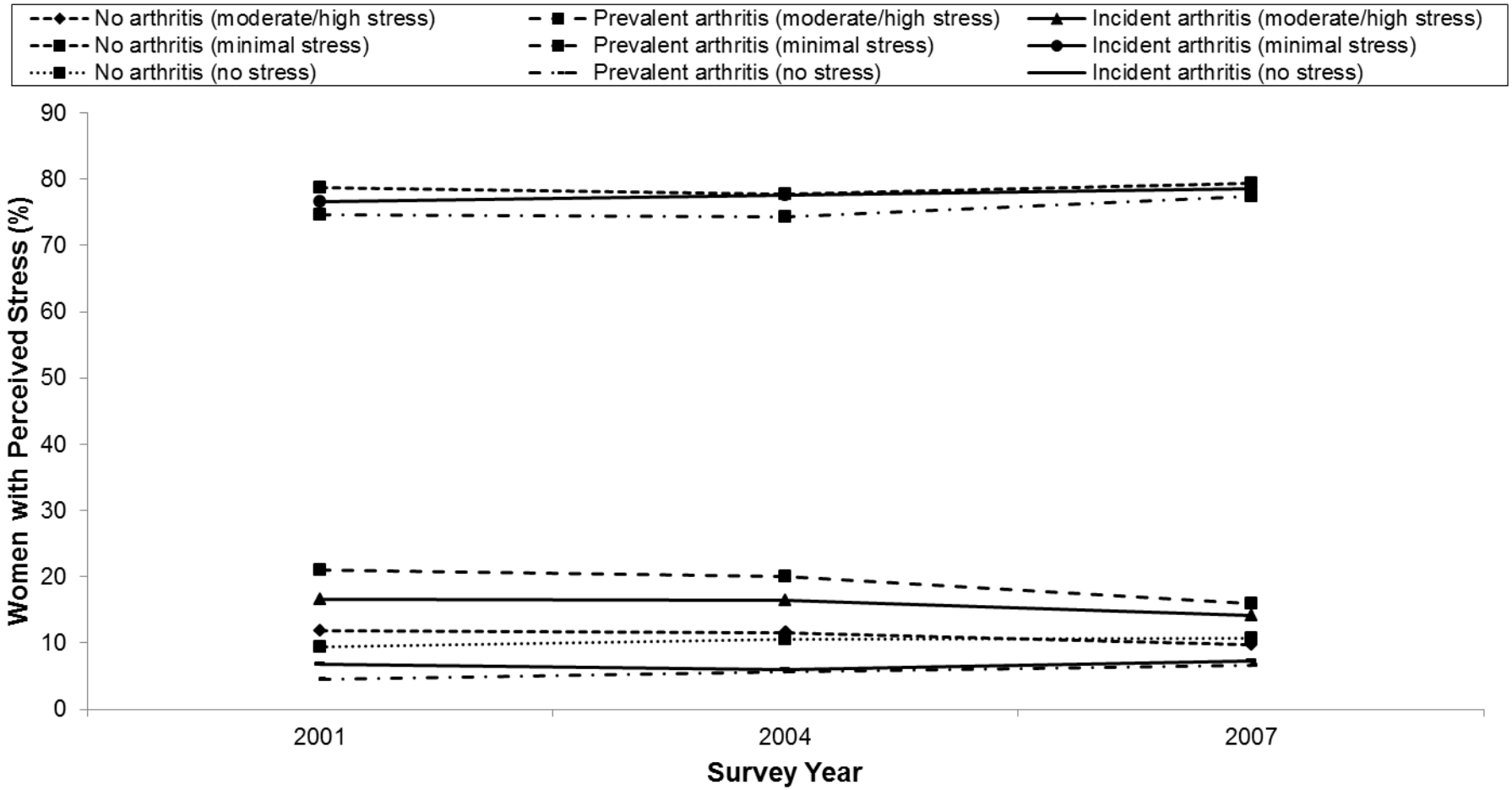

Figure 1. The relationship between arthritis and perceived stress for the 1946-1951 cohort across three time points according to prevalent, incident and no arthritis status.

Electronic Supplementary Material

Electronic Supplementary Material Table S1. Adjusted GEE models reporting odds ratios and 95% confidence intervals (CI) for the relationship between perceived stress and arthritis during the period 2001-2007

	GEE Model without a time lag		GEE Model with a time lag		GEE Model with a time lag (excluding persistent joint pain)	
	Odds ratio (95% CI)	**P Value**	**Odds ratio (95% CI)**	**P Value**	**Odds ratio (95% CI)**	**P Value**
Perceived stress						
None [ref]	—	—	—	—	—	—
Minimal	1.5 (1.3, 1.7)	<0.001	1.6 (1.4, 1.9)	<0.001	1.7 (1.4, 2.0)	<0.001
Moderate/high	1.7 (1.5, 2.1)	<0.001	1.9 (1.6, 2.3)	<0.001	2.2 (1.8, 2.7)	<0.001
Negative life events experienced within the past 12 months						
Death of a family member/close friend						
No [ref]	—	—	—	—	—	—
Yes	1.1 (1.0, 1.1)	0.172	1.0 (0.9, 1.1)	0.696	1.0 (0.9, 1.1)	0.766
Major illness of family member/close friend						
No [ref]	—	—	—	—	—	—
Yes	1.1 (1.1, 1.2)	<0.001	1.1 (1.1, 1.2)	<0.001	1.2 (1.1, 1.3)	<0.001
Interpersonal/relationship difficulties						
No [ref]	—	—	—	—	—	—
Yes	1.1 (1.0, 1.2)	0.033	1.1 (1.0, 1.2)	0.090	1.1 (1.0, 1.2)	0.106
Financial strain						
No [ref]	—	—	—	—	—	—
Yes	1.1 (1.0, 1.2)	0.041	1.1 (1.0, 1.2)	0.070	1.1 (1.0, 1.2)	0.063
Psychiatric diagnoses						

Depression						
No [ref]	—	—	—	—	—	—
Yes	1.3 (1.2, 1.5)	<0.001	1.4 (1.2, 1.6)	<0.001	1.5 (1.3, 1.7)	<0.001
Anxiety/nervous disorder						
No [ref]	—	—	—	—	—	—
Yes	1.2 (1.1, 1.4)	0.003	1.1 (0.9, 1.3)	0.208	1.2 (1.0, 1.4)	0.071
Perceived social support						
All of the time [ref]	—	—	—	—	—	—
Most of the time	1.1 (1.1, 1.2)	0.001	1.1 (1.0, 1.2)	0.003	1.2 (1.1, 1.3)	<0.001
Some of the time	1.1 (1.0, 1.2)	0.146	1.1 (1.0, 1.2)	0.122	1.1 (1.0, 1.2)	0.184
None/little of the time	1.1 (1.0, 1.3)	0.080	1.2 (1.0, 1.4)	0.025	1.2 (1.0, 1.4)	0.026
Optimistic life approach						
LOT-R	0.98 (0.97, 0.98)	<0.001	0.97 (0.96, 0.99)	<0.001	0.97 (0.96, 0.98)	<0.001
BMI						
Under weight	1.0 (0.7, 1.4)	0.776	0.9 (0.6, 1.3)	0.468	0.9 (0.6, 1.4)	0.701
Healthy weight [ref]	—	—	—	—	—	—
Overweight	1.4 (1.2, 1.5)	<0.001	1.3 (1.2, 1.5)	<0.001	1.4 (1.3, 1.5)	<0.001
Obese	2.0 (1.8, 2.2)	<0.001	1.9 (1.7, 2.2)	<0.001	2.0 (1.8, 2.3)	<0.001
Physical activity						
Nil/sedentary	1.2 (1.1, 1.3)	0.001	1.2 (1.1, 1.3)	0.005	1.3 (1.1, 1.4)	<0.001
Low	1.1 (1.0, 1.2)	0.107	1.1 (1.0, 1.2)	0.147	1.1 (1.0, 1.2)	0.140
Moderate [ref]	—	—	—	—	—	—
High	1.1 (1.0, 1.2)	0.197	1.1 (1.0, 1.2)	0.136	1.1 (1.0, 1.2)	0.107
Smoking status						
Non-smoker [ref]	—	—	—	—	—	—

Ex-smoker	1.2 (1.1, 1.3)	0.001	1.2 (1.1, 1.3)	<0.001	1.2 (1.1, 1.3)	0.001
Current smoker	1.0 (0.9, 1.2)	0.496	1.0 (0.9, 1.2)	0.502	1.1 (0.9, 1.2)	0.490
Age						
	1.09 (1.06, 1.12)	<0.001	1.08 (1.05, 1.11)	<0.001	1.07 (1.04, 1.11)	<0.001
Marital status						
Married/de facto [ref]	—	—	—	—	—	—
Separated/divorced/widowed	1.0 (0.9, 1.1)	0.862	1.0 (0.9, 1.1)	0.720	1.0 (0.9, 1.2)	0.675
Never married	1.6 (1.2, 2.0)	<0.001	1.6 (1.2, 2.1)	<0.001	1.5 (1.2, 2.0)	0.002
Area of residence						
Urban [ref]	—	—	—	—	—	—
Rural/remote	1.0 (0.9, 1.1)	0.620	1.0 (0.9, 1.1)	0.446	1.0 (1.0, 1.1)	0.379
Educational attainment						
Tertiary/post graduate [ref]	—	—	—	—	—	—
Trade/diploma	1.1 (1.0, 1.3)	0.133	1.1 (0.9, 1.2)	0.393	1.1 (0.9, 1.3)	0.246
School/higher school certificate	1.0 (0.9, 1.2)	0.817	1.0 (0.9, 1.1)	0.978	1.0 (0.9, 1.2)	0.606
No formal education	1.2 (1.0, 1.4)	0.014	1.2 (1.0, 1.4)	0.027	1.3 (1.1, 1.6)	0.003
Occupation						
Highly skilled [ref]	—	—	—	—	—	—
Skilled	1.0 (0.9, 1.2)	0.396	1.0 (0.9, 1.2)	0.465	1.0 (0.9, 1.2)	0.640
Less skilled	1.1 (0.9, 1.3)	0.432	1.2 (1.0, 1.4)	0.048	1.2 (1.0, 1.5)	0.029
No paid employment	1.4 (1.3, 1.6)	<0.001	1.4 (1.2, 1.5)	<0.001	1.4 (1.3, 1.6)	<0.001
Menopause status						
Pre/peri-menopause	0.9 (0.8, 1.0)	0.009	1.0 (0.9, 1.1)	0.459	1.0 (0.9, 1.1)	0.490
Post-menopause [ref]	—	—	—	—	—	—
Surgical menopause	1.4 (1.3, 1.5)	<0.001	1.4 (1.3, 1.6)	<0.001	1.4 (1.3, 1.6)	<0.001

HRT use						
No [ref]	—	—	—	—	—	—
Yes	1.2 (1.1, 1.3)	<0.001	1.3 (1.2, 1.4)	<0.001	1.3 (1.2, 1.5)	<0.001

Note: time was entered as a within subjects variable and as a predictor

Electronic Supplementary Material Table S2. Adjusted longitudinal GEE interaction models (social support) for the relationship between perceived stress and arthritis during the period 2001-2007

	GEE Model without a time lag		GEE Model with a time lag		GEE Model with a time lag (excluding persistent joint pain)	
	Odds ratio (95% CI)	**P Value**	**Odds ratio (95% CI)**	**P Value**	**Odds ratio (95% CI)**	**P Value**
Perceived stress						
None [ref]	—	—	—	—	—	—
Minimal	1.5 (1.3, 1.8)	<0.001	1.6 (1.3, 1.9)	<0.001	1.6 (1.3, 1.9)	<0.001
Moderate/high	1.7 (1.3, 2.1)	<0.001	1.7 (1.3, 2.2)	<0.001	1.9 (1.5, 2.6)	<0.001
Perceived social support						
All of the time [ref]	—	—	—	—	—	—
Most of the time	1.2 (0.9, 1.7)	0.159	1.0 (0.7, 1.4)	0.976	1.0 (0.7, 1.4)	0.832
Some of the time	1.2 (0.7, 2.0)	0.505	1.5 (0.8, 2.6)	0.172	1.3 (0.7, 2.3)	0.426
None/little of the time	0.6 (0.3, 1.2)	0.174	0.6 (0.3, 1.2)	0.150	0.6 (0.3, 1.2)	0.153
Perceived stress x social support						
None x all of the time [ref]	—	—	—	—	—	—
None x most of the time	—	—	—	—	—	—
None x some of the time	—	—	—	—	—	—
None x none/little of the time	—	—	—	—	—	—
Minimal x all of the time	—	—	—	—	—	—
Minimal x most of the time	0.9 (0.7, 1.2)	0.542	1.2 (0.8, 1.7)	0.428	1.2 (0.9, 1.8)	0.263
Minimal x some of the time	0.9 (0.5, 1.5)	0.666	0.7 (0.4, 1.3)	0.243	0.8 (0.4, 1.5)	0.535
Minimal x none/little of the time	1.8 (0.9, 3.4)	0.079	2.0 (1.0, 4.0)	0.060	2.1 (1.0, 4.5)	0.050
Moderate/high x all of the time	—	—	—	—	—	—

Moderate/high x most of the time	1.0 (0.7, 1.4)	0.938	1.2 (0.8, 1.8)	0.394	1.3 (0.8, 2.1)	0.223
Moderate/high x some of the time	1.0 (0.6, 1.7)	0.929	0.8 (0.5, 1.6)	0.580	1.0 (0.5, 1.9)	0.959
Moderate/high x none/little of the time	1.9 (1.0, 3.8)	0.059	2.3 (1.1, 5.0)	0.027	2.3 (1.0, 5.2)	0.041
Negative life events experienced within the past 12 months						
Death of a family member/close friend						
No [ref]	—	—	—	—	—	—
Yes	1.1 (1.0, 1.1)	0.172	1.0 (0.9, 1.1)	0.695	1.0 (0.9, 1.1)	0.763
Major illness of family member/close friend						
No [ref]	—	—	—	—	—	—
Yes	1.1 (1.1, 1.2)	<0.001	1.1 (1.1, 1.2)	<0.001	1.2 (1.1, 1.3)	<0.001
Interpersonal/relationship difficulties						
No [ref]	—	—	—	—	—	—
Yes	1.1 (1.0, 1.2)	0.036	1.1 (1.0, 1.2)	0.099	1.1 (1.0, 1.2)	0.117
Financial strain						
No [ref]	—	—	—	—	—	—
Yes	1.1 (1.0, 1.2)	0.041	1.1 (1.0, 1.2)	0.073	1.1 (1.0, 1.2)	0.068
Psychiatric diagnoses						
Depression						
No [ref]	—	—	—	—	—	—
Yes	1.3 (1.2, 1.5)	<0.001	1.4 (1.2, 1.6)	<0.001	1.5 (1.3, 1.7)	<0.001
Anxiety/nervous disorder						
No [ref]	—	—	—	—	—	—
Yes	1.2 (1.1, 1.4)	0.002	1.1 (1.0, 1.3)	0.195	1.2 (1.0, 1.4)	0.066
Optimistic life approach						
LOT-R	0.98 (0.97, 0.98)	<0.001	0.97 (0.96, 0.99)	<0.001	0.97 (0.96, 0.98)	<0.001

BMI						
Under weight	0.9 (0.7, 1.3)	0.756	0.9 (0.6, 1.3)	0.456	0.9 (0.6, 1.4)	0.683
Healthy weight [ref]	—	—	—	—	—	—
Overweight	1.4 (1.2, 1.5)	<0.001	1.3 (1.2, 1.5)	<0.001	1.4 (1.3, 1.5)	<0.001
Obese	2.0 (1.8, 2.2)	<0.001	1.9 (1.8, 2.2)	<0.001	2.1 (1.8, 2.3)	<0.001
Physical activity						
Nil/sedentary	1.2 (1.1, 1.3)	<0.001	1.2 (1.1, 1.3)	0.005	1.3 (1.1, 1.4)	<0.001
Low	1.1 (1.0, 1.2)	0.104	1.1 (1.0, 1.2)	0.145	1.1 (1.0, 1.2)	0.144
Moderate [ref]	—	—	—	—	—	—
High	1.1 (1.0, 1.2)	0.192	1.1 (1.0, 1.2)	0.137	1.1 (1.0, 1.2)	0.108
Smoking status						
Non-smoker [ref]	—	—	—	—	—	—
Ex-smoker	1.2 (1.1, 1.3)	0.001	1.2 (1.1, 1.3)	<0.001	1.2 (1.1, 1.3)	0.001
Current smoker	1.0 (0.9, 1.2)	0.501	1.0 (0.9, 1.2)	0.501	1.0 (0.9, 1.2)	0.494
Age						
	1.09 (1.06, 1.12)	<0.001	1.08 (1.05, 1.11)	<0.001	1.07 (1.04, 1.11)	<0.001
Marital status						
Married/de facto [ref]	—	—	—	—	—	—
Separated/divorced/widowed	1.0 (0.9, 1.1)	0.854	1.0 (0.9, 1.1)	0.717	1.0 (0.9, 1.2)	0.670
Never married	1.6 (1.2, 2.0)	<0.001	1.6 (1.2, 2.1)	<0.001	1.5 (1.2, 2.0)	0.003
Area of residence						
Urban [ref]	—	—	—	—	—	—
Rural/remote	1.0 (0.9, 1.1)	0.611	1.0 (0.9, 1.1)	0.439	1.0 (1.0, 1.1)	0.374
Educational attainment						
Tertiary/post graduate [ref]	—	—	—	—	—	—

Trade/diploma	1.1 (1.0, 1.3)	0.144	1.1 (0.9, 1.2)	0.411	1.1 (0.9, 1.3)	0.259
School/higher school certificate	1.0 (0.9, 1.2)	0.844	1.0 (0.9, 1.1)	0.957	1.0 (0.9, 1.2)	0.630
No formal education	1.2 (1.0, 1.4)	0.014	1.2 (1.0, 1.4)	0.025	1.3 (1.1, 1.6)	0.003
Occupation						
Highly skilled [ref]	—	—	—	—	—	—
Skilled	1.0 (0.9, 1.2)	0.393	1.0 (0.9, 1.2)	0.459	1.0 (0.9, 1.2)	0.619
Less skilled	1.1 (0.9, 1.3)	0.427	1.2 (1.0, 1.4)	0.047	1.2 (1.0, 1.5)	0.027
No paid employment	1.4 (1.3, 1.6)	<0.001	1.4 (1.2, 1.5)	<0.001	1.4 (1.3, 1.6)	<0.001
Menopause status						
Pre/peri-menopause	0.9 (0.8, 1.0)	0.009	1.0 (0.9, 1.1)	0.464	1.0 (0.9, 1.1)	0.493
Post-menopause [ref]	—	—	—	—	—	—
Surgical menopause	1.4 (1.3, 1.5)	<0.001	1.4 (1.3, 1.6)	<0.001	1.4 (1.3, 1.6)	<0.001
HRT use						
No [ref]	—	—	—	—	—	—
Yes	1.2 (1.1, 1.3)	<0.001	1.3 (1.2, 1.4)	<0.001	1.3 (1.2, 1.5)	<0.001

Note: time was entered as a within subjects variable and as a predictor

Electronic Supplementary Material Table S3. Adjusted multinomial GEE models (with no stress as the reference category) for the impact of arthritis on perceived stress during the period 2001-2007, controlling for onset predictors, chronic conditions and health service use

	GEE Model without a time lag				GEE Model with a time lag			
	Minimal stress		Moderate/high stress		Minimal stress		Moderate/high stress	
	Odd Ratio (95%CI)	P Value	Odd Ratio (95%CI)	P Value	Odd Ratio (95%CI)	P Value	Odd Ratio (95%CI)	P Value
Arthritis								
No [ref]	—	—	—	—	—	—	—	—
Yes	1.2 (1.1, 1.4)	0.008	1.2 (0.9, 1.6)	0.144	1.2 (1.0, 1.4)	0.024	1.2 (0.9, 1.5)	0.203
Negative life events experienced within the past 12 months								
Death of a family member/close friend								
No [ref]	—	—	—	—	—	—	—	—
Yes	1.0 (0.8, 1.1)	0.681	0.9 (0.7, 1.2)	0.610	0.9 (0.8, 1.0)	0.119	0.7 (0.6, 1.0)	0.023
Major illness of family member/close friend								
No [ref]	—	—	—	—	—	—	—	—
Yes	2.4 (2.1, 2.8)	<0.001	4.6 (3.7, 5.7)	<0.001	1.5 (1.3, 1.8)	<0.001	2.5 (2.0, 3.1)	<0.001
Interpersonal/relationship difficulties								
No [ref]	—	—	—	—	—	—	—	—
Yes	3.2 (2.4, 4.3)	<0.001	10.3 (7.0, 15.1)	<0.001	1.7 (1.3, 2.1)	<0.001	3.4 (2.5, 4.7)	<0.001

Financial strain								
No [ref]	—	—	—	—	—	—	—	—
Yes	1.9 (1.6, 2.2)	<0.001	3.7 (2.9, 4.9)	<0.001	1.3 (1.1, 1.6)	0.001	1.9 (1.5, 2.5)	<0.001
Psychiatric diagnoses								
Depression								
No [ref]	—	—	—	—	—	—	—	—
Yes	2.0 (1.4, 2.8)	<0.001	4.1 (2.6, 6.6)	<0.001	1.8 (1.3, 2.6)	0.001	3.0 (1.9, 4.7)	<0.001
Anxiety/nervous disorder								
No [ref]	—	—	—	—	—	—	—	—
Yes	2.5 (1.7, 3.7)	<0.001	5.3 (3.1, 9.2)	<0.001	1.4 (1.0, 2.2)	0.085	2.4 (1.5, 4.1)	0.001
Perceived social support								
All of the time [ref]	—	—	—	—	—	—	—	—
Most of the time	1.6 (1.4, 1.8)	<0.001	3.0 (2.4, 3.8)	<0.001	1.5 (1.2, 1.7)	<0.001	2.2 (1.7, 2.8)	<0.001
Some of the time	2.1 (1.7, 2.7)	<0.001	6.2 (4.5, 8.5)	<0.001	1.7 (1.4, 2.2)	<0.001	3.0 (2.2, 4.2)	<0.001
None/little of the time	1.2 (0.9, 1.5)	0.175	4.2 (2.9, 6.1)	<0.001	1.2 (0.9, 1.6)	0.259	2.7 (1.8, 4.3)	<0.001
Life approach								
LOT-R	0.94 (0.92, 0.95)	<0.001	0.82 (0.80, 0.85)	<0.001	0.94 (0.93, 0.96)	<0.001	0.87 (0.85, 0.90)	<0.001
BMI								
Under weight	0.9 (0.5, 1.5)	0.603	0.9 (0.4, 2.0)	0.796	0.9 (0.4, 1.6)	0.635	1.0 (0.5, 2.0)	0.986
Healthy weight [ref]	—	—	—	—	—	—	—	—

Overweight	1.0 (0.9, 1.1)	0.982	1.1 (0.9, 1.4)	0.483	0.9 (0.8, 1.1)	0.274	1.0 (0.8, 1.2)	0.826
Obese	1.0 (0.9, 1.2)	0.947	1.1 (0.9, 1.5)	0.364	1.2 (1.0, 1.5)	0.026	1.4 (1.0, 1.9)	0.031
Physical activity								
Nil/sedentary	0.9 (0.7, 1.0)	0.105	0.9 (0.6, 1.2)	0.502	0.9 (0.7, 1.1)	0.196	1.0 (0.7, 1.4)	0.948
Low	1.0 (0.9, 1.2)	0.833	1.0 (0.8, 1.3)	0.916	1.0 (0.9, 1.2)	0.791	1.0 (0.8, 1.4)	0.736
Moderate [ref]	—	—	—	—	—	—	—	—
High	0.8 (0.7, 0.9)	0.001	0.7 (0.5, 0.9)	0.016	0.9 (0.7, 1.0)	0.074	0.9 (0.7, 1.2)	0.342
Smoking status								
Non-smoker [ref]	—	—	—	—	—	—	—	—
Ex-smoker	1.2 (1.1, 1.4)	0.003	1.7 (1.3, 2.1)	<0.001	1.3 (1.1, 1.5)	0.001	1.7 (1.3, 2.1)	<0.001
Current smoker	1.3 (1.1, 1.6)	0.014	1.9 (1.4, 2.7)	<0.001	1.2 (1.0, 1.5)	0.102	1.9 (1.4, 2.6)	<0.001
Age								
	0.94 (0.91, 0.98)	0.005	0.86 (0.80, 0.93)	<0.001	0.96 (0.93, 0.99)	0.011	0.84 (0.80, 0.89)	<0.001
Marital status								
Married/de facto [ref]	—	—	—	—	—	—	—	—
Separated/divorced/widowed	1.0 (0.9, 1.3)	0.664	1.1 (0.8, 1.5)	0.586	1.0 (0.8, 1.3)	0.806	1.1 (0.8, 1.6)	0.395
Never married	0.7 (0.5, 1.0)	0.069	0.6 (0.3, 1.1)	0.103	0.8 (0.5, 1.2)	0.264	0.8 (0.4, 1.6)	0.510
Area of residence								
Urban [ref]	—	—	—	—	—	—	—	—
Rural/remote	0.9 (0.8, 1.0)	0.096	0.7 (0.6, 0.9)	0.003	0.9 (0.8, 1.1)	0.295	0.7 (0.6, 0.9)	0.001

Educational attainment								
Tertiary/post graduate [ref]	—	—	—	—	—	—	—	—
Trade/diploma	0.6 (0.5, 0.7)	<0.001	0.4 (0.3, 0.6)	<0.001	0.7 (0.5, 0.8)	0.001	0.5 (0.3, 0.7)	<0.001
School/higher school certificate	0.5 (0.4, 0.6)	<0.001	0.3 (0.2, 0.5)	<0.001	0.6 (0.5, 0.7)	<0.001	0.4 (0.3, 0.6)	<0.001
No formal education	0.4 (0.3, 0.5)	<0.001	0.2 (0.1, 0.3)	<0.001	0.5 (0.4, 0.6)	<0.001	0.4 (0.2, 0.6)	<0.001
Occupation								
Highly skilled [ref]	—	—	—	—	—	—	—	—
Skilled	0.9 (0.7, 1.0)	0.078	0.7 (0.6, 1.0)	0.039	0.9 (0.8, 1.1)	0.279	0.9 (0.7, 1.2)	0.395
Less skilled	0.6 (0.5, 0.7)	<0.001	0.3 (0.2, 0.5)	<0.001	0.6 (0.5, 0.8)	0.001	0.6 (0.4, 0.9)	0.008
No paid employment	0.6 (0.5, 0.7)	<0.001	0.4 (0.3, 0.5)	<0.001	0.7 (0.5, 0.8)	<0.001	0.5 (0.4, 0.6)	<0.001
Menopause status								
Pre/peri-menopause	1.0 (0.9, 1.2)	0.992	1.0 (0.7, 1.3)	0.822	0.9 (0.8, 1.1)	0.442	1.0 (0.8, 1.3)	0.968
Post-menopause [ref]	—	—	—	—	—	—	—	—
Surgical menopause	0.9 (0.8, 1.1)	0.242	1.0 (0.8, 1.3)	0.837	0.9 (0.7, 1.0)	0.112	1.0 (0.7, 1.3)	0.782
HRT use								
No [ref]	—	—	—	—	—	—	—	—
Yes	1.1 (0.9, 1.2)	0.297	1.2 (0.9, 1.6)	0.128	1.1 (1.0, 1.3)	0.093	1.2 (1.0, 1.6)	0.105
Chronic conditions								
Anaemia								
No [ref]	—	—	—	—	—	—	—	—

Yes	1.3 (1.0, 1.6)	0.064	1.0 (0.6, 1.5)	0.830	1.2 (0.9, 1.6)	0.163	1.3 (0.8, 1.9)	0.285
Osteoporosis								
No [ref]	—	—	—	—	—	—	—	—
Yes	1.0 (0.7, 1.3)	0.887	1.0 (0.6, 1.7)	0.976	1.1 (0.8, 1.6)	0.540	1.7 (1.0, 2.7)	0.043
Diabetes								
No [ref]	—	—	—	—	—	—	—	—
Yes	0.7 (0.5, 1.0)	0.027	0.9 (0.5, 1.4)	0.576	0.6 (0.4, 0.9)	0.005	0.6 (0.3, 1.0)	0.067
Cardiovascular disease								
No [ref]	—	—	—	—	—	—	—	—
Yes	1.1 (0.9, 1.3)	0.205	1.0 (0.8, 1.3)	0.896	0.9 (0.8, 1.1)	0.545	0.9 (0.7, 1.2)	0.390
Somatic symptoms								
Fatigue								
Never/rarely [ref]	—	—	—	—	—	—	—	—
Sometimes/often	2.2 (1.9, 2.6)	<0.001	4.9 (3.9, 6.1)	<0.001	1.9 (1.6, 2.2)	<0.001	3.4 (2.7, 4.2)	<0.001
Gastrointestinal problems								
Never/rarely [ref]	—	—	—	—	—	—	—	—
Sometimes/often	1.5 (1.3, 1.7)	<0.001	2.1 (1.7, 2.6)	<0.001	1.4 (1.2, 1.6)	<0.001	1.7 (1.4, 2.1)	<0.001
Headache/migraine								
Never/rarely [ref]	—	—	—	—	—	—	—	—
Sometimes/often	1.3 (1.3, 1.7)	<0.001	1.5 (1.2, 1.9)	<0.001	1.3 (1.1, 1.5)	0.001	1.5 (1.2, 1.9)	<0.001

Health service consultations								
None [ref]	—	—	—	—	—	—	—	—
Once or twice	1.2 (1.0, 1.4)	0.042	1.1 (0.7, 1.6)	0.687	1.2 (1.0, 1.5)	0.074	1.2 (0.8, 1.8)	0.372
Three or four times	1.5 (1.2, 1.8)	<0.001	1.5 (1.0, 2.3)	0.047	1.4 (1.1, 1.8)	0.002	1.7 (1.1, 2.6)	0.009
Five or six times	1.9 (1.5, 2.4)	<0.001	2.5 (1.6, 3.9)	<0.001	1.6 (1.2, 2.1)	<0.001	2.3 (1.5, 3.6)	<0.001
Seven or more times	2.6 (1.9, 3.5)	<0.001	4.2 (2.5, 7.0)	<0.001	1.9 (1.4, 2.7)	<0.001	2.9 (1.7, 4.9)	<0.001

Note: time was entered as a within subjects variable and as a predictor