What is the economic burden of delayed axial spondyloarthritis diagnosis in the UK?

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Abstract

Objectives: To develop an economic model to determine the annual cost of delayed axial spondyloarthritis (axial SpA) diagnosis in the UK, adopting both National Health Service (NHS) and societal perspectives.

Methods: We developed a Markov economic model to estimate the costs of delayed axial SpA diagnosis in the UK. Model parameters were sourced from a 2016 National Axial Spondyloarthritis Society patient survey, anonymised patient level data, published literature and expert opinion. A literature defined, mixed cohort (64% male) of people assumed to have axial SpA, whose age of symptom onset was 26 years, were targeted. To assess the robustness of the results, base case and probabilistic sensitivity analyses were performed.

Results: In a simulated cohort of 1,000 patients, with a mean time to diagnosis of 8.5 years, we estimate the cumulative costs of delayed diagnosis per person living with axial SpA to be £193,512 (95% CI: 108,770 - 306,789). The costs were led by productivity losses (65.1%) and out-of-pocket expenses (31.3%) The total annual cost resulting from delayed axial SpA diagnosis in the UK has been estimated at £3.1 billion and £12.5 billion, based on a prevalence of 0.3% (Assessment of SpondyloArthritis international Society classification criteria) and 1.2% (European Spondyloarthropathy Study Group classification criteria), respectively.

Conclusion: Delayed axial SpA diagnosis carries high costs for society due to productivity losses. Early diagnosis and treatment could offer significant benefits to the patient and potentially reduce productivity losses; however, future research is needed to evaluate the long-term health economic impact.

Keywords: Axial spondyloarthritis; ankylosing spondylitis; economic evaluation; cost; delayed diagnosis; burden

Key messages:

- Estimated cumulative UK costs of delayed diagnosis per person living with axial SpA is £193,512
- Costs of delayed axial SpA diagnosis (8.5 years) are substantial for the patient and society
- Reducing the time to diagnosis in axial SpA could impact the societal economic burden

Introduction

Axial spondyloarthritis (axial SpA) is an immune-mediated inflammatory disease that predominantly affects the axial skeleton (sacroiliac joints and spine) and is typified by chronic back pain, peripheral musculoskeletal (MSK) manifestations (arthritis, enthesitis and dactylitis), and extra-musculoskeletal manifestations (EMMs; acute anterior uveitis, psoriasis and inflammatory bowel disease) [1, 2]. The term axial SpA encompasses individuals with definitive sacroiliitis on plain radiographs (radiographic axial SpA; formerly known as ankylosing spondylitis) and individuals without definitive structural damage (non-radiographic axial SpA) [1, 2]. Symptoms usually begin in early adulthood, with the median age of onset being 26 years and the majority (92%) experiencing symptoms prior to the age of 45 years [3]. Recent reports from a multi-country, prospective, observational study suggest that only 16% of patients with non-radiographic axial SpA progress to radiographic axial SpA within 5 years [4].

Typical clinical features of axial SpA include chronic back pain and stiffness; however, fatigue, sleep disturbance, negative affect and psychological distress are also frequent [5]. As a result, people living with axial SpA may experience reduced physical function, poor work outcomes [6] and worse quality of life [7]. The prevalence of axial SpA in the UK general adult primary care population is estimated to be between 0.3% (Assessment of SpondyloArthritis international Society [ASAS] classification criteria) and 1.2% (European Spondyloarthropathy Study Group [ESSG] classification criteria) [8].

The mean time to diagnosis in axial SpA in the UK is 8.5 years [9], which is higher than the worldwide mean estimates for axial SpA (6.7 years) and psoriatic arthritis (2.6 years) [10]. The reasons for diagnostic delay are complex and include: poor healthcare professional (HCP) awareness; axial SpA representing an uncommon cause of chronic lower back pain; the existence of out-dated misconceptions (e.g., axial SpA as a male disease); a lack of diagnostic criteria; misleading biomarkers; and, imaging difficulties [11]. Identifying the characteristics of individuals most at risk of diagnostic delay remains an important issue, with literature to date lacking consensus [10, 12]. Delay in the diagnosis of axial SpA may result in considerable clinical, humanistic and economic burden [13]. For example, individuals with a lengthy time to diagnosis may have worse physical function, more structural damage, a greater likelihood of depression and work disability, and higher direct and indirect healthcare costs compared to those with an earlier diagnosis [13].

The economic burden of axial SpA remains a significant issue and is largely defined by healthcare costs (e.g., healthcare visits and medical tests), societal costs (productivity losses in paid work) and patient costs (e.g., out-of-pocket expenses). A recent study in Spain found that half of patients with axial SpA used ≥25 healthcare resources (i.e., healthcare visits, emergency visits, hospital admissions and medical tests) over a 12-month period [14]. Further, in a prospective cohort study of 1,188 individuals living with axial SpA in Great Britian, 19% reported absenteeism, and 79% reported presenteeism, in the past week owing to their axial SpA [6]. In another UK-based cohort study, individuals with radiographic axial SpA (n = 570) reported missing 3.5% of their work time on average and a 21.6% impairment

of working level, which in 2014, represented an average estimated cost of £869 due to absenteeism and £7,241 due to presenteeism per year per working radiographic axial SpA patient [15]. The estimated total cost of radiographic axial SpA in the UK (in 2014) was £19,016 per patient per year, when including general practice attendance, administration and hospital costs, out-of-pocket expenses and productivity losses [15]. Indeed, multiple international studies have demonstrated the substantial cost of axial SpA [16 - 21], but few have estimated the economic burden of delayed diagnosis.

Understanding the economic burden of delayed diagnosis is of primary concern, with many individuals seeing multiple HCPs [22] or receiving various therapies, prior to diagnosis [23]. Further, the amplified costs associated with increased disease burden and impaired function [15] are likely to compound the economic burden of diagnostic delay, as individuals are denied timely access to advanced therapies. Mennini et al. recently explored the economic impact of diagnostic delay in Italy, although the model only considered direct costs for specialist health care services and pharmacological treatments before a diagnosis of spondyloarthritis (SpA) [24]. These data cannot be extrapolated to the UK as costs and healthcare systems vary between country. No studies have explored the direct and indirect costs of delayed axial SpA diagnosis in the UK. Thus, the objective of this study was to develop an economic model to determine the annual cost of delayed diagnosis of axial SpA, adopting the perspective of the healthcare system in the UK (National Health Service (NHS) England) and the societal perspective.

Methods

Study design

We developed a Markov economic model to understand and estimate the economic impact of delayed axial SpA diagnosis in the UK. As such, the model estimated the cumulative costs of an 8.5-year time to diagnosis, focusing on costs accrued up to the point of diagnosis. We assumed that after diagnosis, the patient will receive effective treatment, and their condition will be kept under control.

The Markov model is an analytical framework commonly used to represent stochastic processes - random processes that change over time. Markov models are frequently used in economic evaluations of healthcare interventions and suited to modelling chronic disease. The disease is defined in terms of mutually exclusive health states and individuals can move or transition between states (represented as transition probabilities) over a discrete period (Markov cycle). Estimated costs and health outcomes can be attached to states and transitions and the modelled for a patient cohort over successive cycles to estimate long-term costs and outcomes associated with a disease or intervention [25].

The model was constructed using Microsoft Excel and the analysis was reported according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement for transparency [26]. For Patient and Public Involvement and Engagement (PPIE), stakeholders / experts by experience were interviewed for their insight into axial SpA and to

help develop the economic model. Ethical approval is not required when stakeholders are asked for their input to develop the research.

Decision model structure

The Markov model captured the resources used and costs related to the diagnosis, management of symptoms, and impacts of axial SpA until the diagnosis of the disease and initiation of treatment (costs after a diagnosis were excluded). Assuming a 'Gold Standard' time to diagnosis of one year [27], the sum of costs in each consecutive cycle was estimated.

To develop the model and understand the economic impact of diagnostic delay, semi-structured interviews with key stakeholders (one general practitioner (GP), one GP/clinical commissioner, one osteopath and four people living with axial SpA) and a focus group with clinical stakeholders (two chiropractors, two physiotherapists, two first contact practitioners, one GP, one rheumatology consultant, and one osteopath) were undertaken. This PPIE was used to check that appropriate variables and parameters were added to the model.

Figure 1 presents the structure of the Markov economic model. In summary, the model has three health states. People start in the model at the undiagnosed health state and remain in that health state until they are diagnosed with axial SpA or die for any reason. Once people are diagnosed, they move into the diagnosed health state and remain in this health state, receiving treatment until they move into the dead health state.

The long-term costs associated with an axial SpA diagnosis were not modelled because they were outside the scope of the research. The model does not distinguish between radiographic axial SpA and non-radiographic axial SpA, as they share similar clinical features and most likely lie on a spectrum of the same disease entity [28].

[INSERT FIGURE 1 HERE]

Time horizon

The economic evaluation estimated costs over a lifetime horizon to accurately calculate resources used and costs related to delay in diagnosis of axial SpA. Furthermore, the model followed patients in 3-month cycles to capture any resource utilization and cost related to diagnosis at the predefined stage. The model had a lifetime horizon as diagnostic delay may span over decades and have an impact on the costs incurred (over a lifetime) [29].

Study perspective

Economic analysis was carried out using the costs collected from the NHS England perspective (to estimate direct medical costs), the societal perspective (to estimate productivity losses in paid work due to absenteeism, presenteeism and staff turnover) and

the patient perspective (to estimate out-of-pocket expenses). All costs were reported in British pounds for the years 2021-22. Costs were discounted at the standard annual rate of 3.5%, adhering to the NICE Guidelines Manual [30].

Model input parameters

Study population

To accurately calculate the cost of delayed diagnosis of axial SpA, the modelled population comprised people that we considered a priori to have axial SpA. We modelled the patient journey towards diagnosis based on the transition probabilities gathered from diverse sources. Results from the online, NASS *State of the Nation Survey* (2016), that was distributed by NASS to people living with axial SpA in the UK [31], were used as inputs for the economic modelling. Anonymised patient level data from Norfolk and Norwich University Hospital (NNUH) and Royal National Hospital for Rheumatic Diseases (RNHRD) on the patient journey to diagnosis were also utilised [9]. Secondary data sources such as the NICE NG65 model [32] and evidence from the extant literature and expert opinion were used to generate data input. Further details on the input parameters used in the model are described below and in Supplementary Table S1.

The target population comprised people whose symptom onset was 26 years old [3]. The percentage of male patients for the mixed cohort calculations was 64%, as defined in the NICE NG65 model [32]. The standardised mortality rate for male and female patients was set to 1.630 and 1.380 respectively, exposing patients to a lengthy disease burden [33]. Diagnostic sensitivity and specificity were obtained from the study developed by Van Hoeven et al. [34].

Formal care

Formal care use and associated costs included an estimate of annual visits to GP and physiotherapist services. The probability of comorbidities appearing within 3 months was also estimated based on an 8.5-year time to diagnosis, an assumed prevalence of specific comorbidities [35, 36] and experts' opinions. Costs were taken from the latest Personal Social Services Research Unit (PSSRU) cost publication [37].

All rates and probabilities were adjusted based on formulas to refer to the correct timeframe. All costs were inflated to 2021 values using the NHS Cost Inflation Index (NHSCII) [37] and the Treasury Green Book on the social discount rate [38]. Further details can be seen in Supplementary Table S1.

Out-of-pocket expenses

The frequency of visits to chiropractic and osteopathic services, and the use of over the counter (OTC) medications, were assumed as reported in the NASS *State of the Nation*

Survey (2016) [31]. In this survey, respondents with axial SpA were asked to recall their usage of specific medications and visits to a HCP in the last 12 months.

Based on discussions with stakeholders (patients and rheumatologists), it was assumed that individuals would self-manage pain with OTC medications. We assumed the maximum dosage allowed in the British National Formulary to estimate the monthly cost of these medications [39]. Prices for OTC medicines were obtained online from Boots Pharmacy. Patients who often purchase multiple medications monthly may obtain a prescription from their GP (regardless of their availability OTC) to control monthly costs. Therefore, the cost of the medicine was estimated so that the monthly cost did not exceed the monthly NHS prescription rate of £9.35. Our calculation also considered the availability of NHS prescription pre-payment certificates [40], so that the annual cost of the medicine does not exceed £108.10 per person.

We estimated the cost of travel to and from general, physiotherapy, osteopath, and chiropractor practices. The average travelling distance to a general practice in the UK was acquired from the Department of Transport journey time statistics [41]. The average taxi price for this travelling distance was used to estimate cost. A car (or taxi) was the presumed mode of transportation, based on the assumption that individuals might opt for a comfortable means of transportation, especially if they are experiencing some degree of pain. The same assumption was utilised to estimate the travel costs to and from osteopath and chiropractic visits. The number of GP visits during the period of diagnostic delay and the costs of non-prescribed exercise per person were based on research by Cooksey et al. [15]. Further details on the out-of-pocket expenses and their respective sources are described in Supplementary Table S1.

Productivity losses

The cost of productivity losses (absenteeism, presenteeism and staff turnover) were sourced from the Deloitte report and based on estimations for public and private sector employees [42]. Calculations were adjusted by the self-reported data on employment status and impact of disease on employment (e.g., probabilities of experiencing productivity loss) [31], and the gross median wage per hour per gender [43]. The costs and percentages of early retirement and of people requiring unpaid care assistance due to axial SpA were also included [15, 44] (see Supplementary Table S1).

Prevalence of axial SpA

To calculate the national costs of diagnostic delay, we assumed a conservative disease prevalence estimate (0.3% vs 1.2%) based on previous literature [8] and expert (rheumatologist) consultation. The NASS patient population estimate of 220,000 was also used to provide an additional estimate [45]. We assumed the UK adult population in mid-2022 as reported by the Office of National Statistics [46].

Sensitivity analysis

The NICE health technology evaluations manual sets out the parameters and how an economic analysis and probability sensitivity analysis (PSA) should be conducted [30]. To quantify the level of confidence in the analysis results, assess the impact of uncertainties around key model parameters, and increase the robustness of the results, we implemented a PSA following the NICE standard of health economics evaluation [30, 47].

PSA was done by defining parameter values using distributions rather than point estimates. PSA was carried out for all input parameters of the model, considering minimum and maximum values of the parameters using the 95% CI when the data were available or varying by ± 20%. The model was run 1,000 times, using the Monte-Carlo simulation to generate outputs that can be stored and compared to check how much the results vary from the base case. Further details about parameters, values and distributions used in the PSA are shown in Supplementary Table S1.

Results

The estimated cumulative cost of an 8.5-year time to diagnosis per person living with axial SpA (symptom onset at age 26 years) is £193,512 (95% CI: 108,770 - 306,789). Table 1 presents the annual costs related to the healthcare system, out-of-pocket expenses, and productivity losses of delayed axial SpA diagnosis. The PSA results were consistent with the deterministic results (base case) with an average cumulative cost per patient of £196,572 (95% CI: 111,830 - 309,850).

[INSERT TABLE 1 HERE]

Supplementary Figure S1 presents the average cost per year per patient and cumulative lifetime costs, and the average annual cost by decade of patients' age. Figure S1 shows the average total cost per year for different ages of symptom onset. For example, the first eight values (bars) represent the average total cost of an 8-year time to diagnosis for people whose symptom onset began at 26 years. The costs per year decrease as more people from the initial cohort/cycle are diagnosed over time (or die), thereby leaving the model.

According to the analysis by gender, men had a higher total cost than women (£187,462 vs. £182,960 – Table 2). This difference in total cost was led by the difference in productivity losses, which was higher among men (see Table 2).

[INSERT TABLE 2 HERE]

We extrapolated the results of the economic analysis to calculate the total annual cost for the entire UK population, using the cost per year of late diagnosis of axial SpA. We assumed the total number of patients in the UK estimated by NASS (220,000 patients) [44], and an axial SpA prevalence of 0.3% (ASAS classification criteria), and 1.2% (ESSG classification criteria) [8] to estimate the nationwide total annual cost. Assuming the axial SpA population in the UK estimated by NASS in 2022, the total yearly cost was approximately £4.2 billion. The total annual cost resulting from delayed axial SpA diagnosis in the UK has been estimated between £3.1 billion and £12.5 billion, based on a prevalence of 0.3% and 1.2%, respectively. Further details are described in Table 3.

[INSERT TABLE 3 HERE]

Discussion

Many UK studies have demonstrated the high cost of axial SpA post diagnosis [15, 16, 19]. However, the time to diagnosis in the UK is estimated at 8.5 years [9] and is associated with a significant clinical, humanistic and economic burden [13]. Here, we estimate that the cumulative costs of delayed diagnosis per person living with axial SpA to be £193,512. We assume that after diagnosis, the patient will receive effective treatment, and their condition will be kept under control. In particular, the costs were led by productivity losses (£125,916) and out-of-pocket expenses (£60,563). The total annual cost resulting from delayed axial SpA diagnosis in the UK is estimated at £3.1 billion and £12.5 billion, based on a prevalence of 0.3% and 1.2%, respectively. To the best of our knowledge, this is the first economic evaluation study estimating the annual cost of delayed axial SpA diagnosis in the UK, adopting both NHS (UK) and societal perspectives.

Our results indicate that the cost of delayed axial SpA diagnosis is significant, with the majority falling on the patient and society. Indeed, results suggest that by delaying the diagnosis of axial SpA in a mixed cohort of people presumed to be living with axial SpA and with an age of symptom onset of 26 years, productivity losses and out-of-pocket expenses represent 65.1% and 31.3% of the total annual costs, respectively. These results corroborate with post diagnosis economic studies (mainly radiographic axial SpA), whereby total costs were dominated by productivity losses, informal care by family and/or out-of-pocket expenses, instead of direct healthcare costs [15, 17, 19, 20, 21]. Our model did not estimate costs beyond the point of diagnosis. However, given that productivity losses account for a large proportion of the total costs, and delayed diagnosis is associated with increased risk of becoming work disabled [48], we posit that reducing time to diagnosis will lead to overall costs savings and better patient outcomes. Future models could consider both pre- and post-diagnosis costs. Data pertaining to the costs of diagnostic delay are sparse, posing a challenge to between-study comparison. However, a recent study estimated that in the 3 years prior to a SpA diagnosis, the cost to examine and manage 38,232 new patients in Italy

between 2010 and 2013 was over €5.4 million [24]. This study highlights a significant economic burden pre-diagnosis, but it is limited in not considering indirect costs (e.g., productivity losses and out-of-pocket expenses) and utilising International Classification of Diseases (ICD) codes that include diagnoses such as spinal enthesopathy [24]. Other studies have demonstrated that those with longer time to diagnosis have worse economic outcomes than those with shorter time [49, 50]. Our study is the first to comprehensively model the potential costs of a lengthy time to diagnosis in axial SpA on the healthcare system, individuals with axial SpA, and society. Strategies such as HCP education, dispelling axial SpA myths, public awareness campaigns, establishing local referral pathways and utilising digital solutions in primary care, may be important for reducing diagnostic delay [11] and in turn, the economic burden prior to a diagnosis.

An interesting finding was the gender difference observed in costs prior to a diagnosis of axial SpA. Our results indicate than men have greater total costs, led by a higher burden of productivity losses. A possible reason for this difference might be work participation and pay inequalities in the UK. However, there may be "hidden" costs in the productivity losses, potentially due to childcare needs when managing a flare. It should be noted that healthcare costs and out-of-pocket expenses were marginally higher in women than in men. Women report longer diagnostic delays than men, which may be due to physician bias or gender differences in disease manifestation [22]. Previous research has also indicated that women report more visits to HCPs prior to a diagnosis [22] and a greater use of alternative therapies [22, 51]. Such findings may be consistent with increased healthcare costs and out-of-pocket expenses for women. More research is needed determine the unmet needs of females and the potential economic inequalities.

Model strengths and limitations

This is the first economic model developed to estimate the annual cost of delayed axial SpA diagnosis in the UK, adopting both NHS and societal perspectives. Most studies have assessed the economic burden of those diagnosed with axial SpA [16 - 21], overlooking the cost accumulated before diagnosis. A Markov model is an efficient, parsimonious, and accurate method for modelling disease or process progression over time [52]. Notably, NICE has previously used Markov modelling to estimate the costs and utility of being correctly identified as having SpA and having the disease missed [32]. Our model incorporated input parameters derived from a diverse range of data sources and considered potential productivity losses and out-of-pocket expenses, which have often been neglected in the extant literature. Additionally, our model differentiated economic burden by gender and adds to the growing body of research highlighting gender differences in the patient journey to diagnosis [22].

Our study has some limitations. The model was based on limited available data and requires validation using real-world data to ensure its accuracy and reliability. The lack of prolonged follow-up data and existing literature on physiotherapy visits necessitated the extrapolating of survey data over a one-year period to estimate physiotherapy costs across the entire

duration of the model. This approach may have led to an overestimation of costs and should be addressed in future economic models. Further, costs pertaining to absenteeism, presenteeism and staff turnover were calculated based on the average annual costs of public and private sector employees [42]. Data from a national registry would have provided a more precise reflection of these parameters.

The estimated time to diagnosis is based on data from a decade ago [9]. Despite encouraging findings from a recent UK study reporting an average time to diagnosis of between five and six years [53], the sample is small, derived from two specialist centres and may not reflect the national average. The model also used self-report data from individuals completing the NASS *State of the Nation Survey* (2016) [31], which may be subject to recall bias and somewhat hinder the validity of the results. For example, the frequency of OTC medication use was based on data from a survey completed by individuals who self-reported a diagnosis of axial SpA and may underestimate the use of OTC medication as they are currently receiving more advanced and targeted therapies. There remains uncertainty regarding referral strategies, however our model used high quality research to gather diagnostic sensitivity and specificity [34].

Despite every effort to include the most pertinent costs related to diagnostic delay, some costs (e.g., caregiver costs or talking therapies for mental health) could not be included within the model due to a lack of available data and therefore the economic burden may be higher than estimated. This study did not stratify costs by disease severity, which is a potential area for future research. Additionally, including time-dependent probabilities or a patient-level simulation relying on risk equations that accounts for age could enhance future research. The data availability and the project scope did not allow for further investigation.

Conclusion

Delayed axial SpA diagnosis carries significant societal costs due to productivity losses. The financial burden for people living with axial SpA (out-of-pocket expenses) is also substantial. Our findings will assist national decision makers to understand the substantial economic burden of diagnostic delay. Early diagnosis and treatment could offer significant benefits to the patient and potentially reduce productivity losses; however, further research is needed to evaluate the long-term health economic impact. Improving public and healthcare community awareness of the signs and symptoms of axial SpA and establishing local referral pathways may be important for reducing diagnostic delay and relieving some of the associated economic burden.

Acknowledgements

We are grateful to the clinicians and people living with axial SpA, who kindly gave their insights into this chronic condition and helped inform the development of the economic model. We are grateful to the National Institute for Health and Care Excellence (NICE) for

providing us with their model, developed to assess the economic costs of diagnosis and monitoring of axial SpA in people over 16 years old.

Funding

This work was supported by UCB Pharma Ltd [Grant number: UK-N-DA-RH-2100001].

Conflict of interest statement

FZ, GX, SHW, OA and RF declare no conflicts. CC has received consulting/speaker fees from AbbVie, Novartis, Galapagos, Gilead and Bristol Myers Squibb. RS has been sponsored to attend regional, national and international meetings by UCB, AbbVie, Novartis and Lilly. He has received honoraria for speaking and attended advisory boards with Pfizer, AbbVie, Biogen, BMS, Lilly, Novartis, UCB. He has received grants from UCB, BMS, AbbVie and Novartis. KG has received meeting expenses from AbbVie, Lilly, Roche, Novartis, Pfizer and UCB; honoraria or consultancy fees from Novartis, AbbVie, UCB, Lilly and Pfizer; participated in speaker's bureau for Novartis, UCB, AbbVie and Lilly; obtained grant support from NASS, Versus Arthritis, AbbVie, Alfasigma, Pfizer, UCB, Novartis, Eli Lilly, Medacpharma, Celltrion, Janssen and Biogen; and, is a shareholder of Rheumatology Events. DW, JE, TI, CC and JH received institutional grant funding from AbbVie, Biogen, Janssen, Lilly, Novartis and UCB.

Data availability statement

The data underlying this article may be shared on request to the corresponding author.

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Tables/Figures

Table 1. Base case and probabilistic sensitivity analysis results of delayed axial SpA diagnosis (8.5-year time to diagnosis) classified by cost category

Cost per category	Base case (%)	PSA (%)
Healthcare system, £ (95% CI)	£7,032.74	£7,048.38
	(5,549.66 - 9,285.47)	(5,565.30 - 9,301.11)
	(3.5%)	(3.6%)
Out-of-pocket expenses, £ (95% CI)	£60,563.04	£67,875.70
	(32,561.78 - 115,978.53	(39,874.44 - 123,291.20)
	(31.3%)	(34.5%)
Productivity losses, £ (95% CI)	£125,916.27	£121,648.16
	(70,658.27 - 181,525.29)	(66,390.16 - 177,257.20)
	(65.1%)	(61.9%)
Total, £ (95% CI)	£193,512.04	£196,572.24
	(108,769.71 - 306,789.30)	(111,829.90 - 309,849.50)

Note. PSA: probabilistic sensitivity analysis. CI: confidence interval.

Table 2. Base case and probabilistic sensitivity analysis results of delayed axial SpA diagnosis (8.5-year time to diagnosis) classified by gender and cost category

	Female	
Cost per category	**Base case (%)**	**PSA (%)**
Healthcare system, £ (95% CI)	£8,556.80	£8,571.38
	(6,268.82 - 11,981.16)	(6,283.40 - 11,995.74)
	(4.7%)	(4.7%)
Out-of-pocket expenses, £ (95% CI)	£54,734.77	£58,650.46
	(26,960.32 - 106,102.19)	(30,876.01 - 110,017.88)

	(29.9%)	(32.2%)
Productivity losses, £ (95% CI)	£119,668.90	£115,039.41
	(63,264.07 - 178,269.09)	(58,634.58 - 173,639.60)
	(65.4%)	(63.1%)
Total, £ (95% CI)	£182,960.47	£182,261.25
	(96,493.20 - 296,352.44)	(95,793.99 - 295,653.22)
	Male	
Cost per category (95% CI)	**Base case (%)**	**PSA (%)**
Healthcare system, £ (95% CI)	£7,775.60	£7,812.16
	(5,373.88 - 11,490.44)	(5,388.46 - 11,505.02)
	(4.7%)	(4.2%)
Out-of-pocket expenses, £ (95% CI)	£53,255.48	£55,814.57
	(25,151.42 - 98,164.18)	(27,710.51 - 100,723.27)
	(28.4%)	(30.1%)
Productivity losses, £ (95% CI)	£126,431.03	£121,778.53
	(68,867.49 - 186,270.02)	(64,214.99 - 181,617.52)
	(67.4%)	(65.7%)
Total, £ (95% CI)	£187,462.11	£185,405.25
	(99,392.79 - 295,924.63)	(97,313.96 - 293,845.81)

Note. PSA: probabilistic sensitivity analysis. CI: confidence interval.

Table 3. Nationwide total cost of delayed axial SpA diagnosis based on prevalence estimates

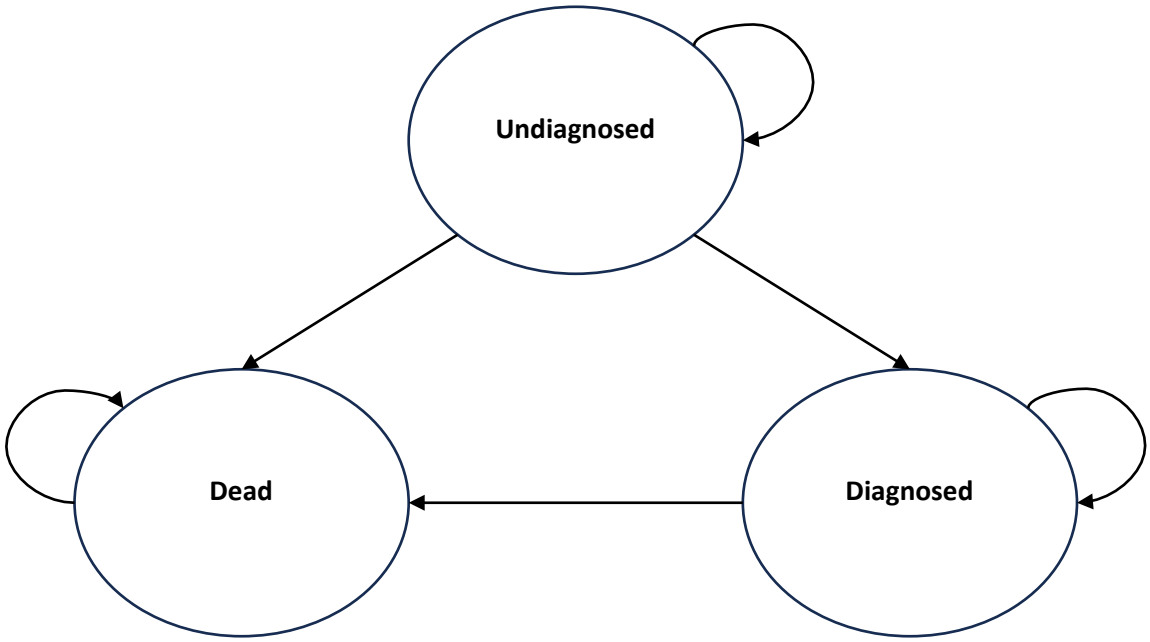
Total cost	**Base case**	**PSA**
Modelled, £ (95% CI)	£23,104.17	£24,025.06
	(14,568.52 - 36,950.02)	(15,489.41 - 37,870.91)
NASS axial SpA pop*, £ (95% CI)	£4,236,794,775	£4,431,645,007
	(2,703,455,437 - 6,595,614,347)	(2,898,305,669 - 6,790,464,579)
UK adult pop (0.3% prevalence), £ (95% CI)**	£3,115,805,703	£3,259,101,637
	(1,988,163,769 - 4,850,518,822)	(2,131,459,703 - 4,993,814,756)
UK adult pop (1.2% prevalence), £ (95% CI)**	£12,463,222,813	£13,036,406,549
	(7,952,655,079 - 19,402,075,288)	(8,525,838,815 - 19,975,259,024)

Note. 83.4% remaining undiagnosed per year. PSA: probabilistic sensitivity analysis. CI: confidence interval. NASS: National Axial Spondyloarthritis Society. Axial SpA: axial spondyloarthritis. Pop: population.

* NASS patient population estimate: 220,000 [44]

** UK adult population (2022): 53,930,490 [45]

Figure 1. Markov economic model



Alt text: A Markov economic model diagram with state transition oval-shaped nodes labelled - 'Undiagnosed', 'Diagnosed' and 'Dead'. Each node is connected by arrows indicating possible transitions between states. The 'Undiagnosed' state has a self-loop and transitions to both 'Diagnosed' and 'Dead.' The 'Diagnosed' state also has a self-loop and a transition to 'Dead.' The 'Dead' state has a self-loop but no outgoing transitions.

Table S1. Input parameters

Model parameters	Value	95% LCI	95% UCI	Distribution	Source
Global parameters					
Population starting age (years)	26	-	-	-	[1]
Discount rate (%)	3.5	-	-	-	[2]
Sex (% male)	64	57.9	70.1	Beta	[3, 4]
Resource use – Physiotherapist in the past 12 months					
Hospital-based specialist rheumatology physiotherapist	0.654	0.626	0.682	Dirichlet	[5]
NHS community-based physiotherapist	0.150	0.129	0.171	Dirichlet	[5]
Private community-based physiotherapist	0.108	0.090	0.127	Dirichlet	[5]
NASS group physiotherapist	0.287	0.261	0.315	Dirichlet	[5]
Other	0.057	0.044	0.072	Dirichlet	[5]
Frequency/proportion - Physiotherapist visits					
People visiting a physiotherapist more than once a week	0.040	0.023	0.061	Dirichlet	Experts' opinion, [5]
People visiting a physiotherapist weekly	0.313	0.268	0.359	Dirichlet	Experts' opinion, [5]
People visiting a physiotherapist fortnightly	0.213	0.174	0.254	Dirichlet	Experts' opinion, [5]
People visiting a physiotherapist monthly	0.120	0.090	0.154	Dirichlet	Experts' opinion, [5]
People visiting a physiotherapist less than once a month	0.315	0.270	0.361	Dirichlet	Experts' opinion, [5]
GP visits per year	6.92	5.56	8.32	Lognormal	[6]
A&E visits	0.870	0.814	0.916	Lognormal	Experts' opinion, [6]
Delay between the development of symptoms and presentation to NHS - Proportion of people presenting in each period					
0-3 months	0.240	0.201	0.281	Dirichlet	[5]
3-6 months	0.122	0.093	0.154	Dirichlet	[5]
6 months – 1 year	0.187	0.151	0.225	Dirichlet	[5]
1 year – 5 years	0.237	0.198	0.278	Dirichlet	[5]
5 years+	0.214	0.177	0.254	Dirichlet	[5]
Proportion of people diagnosed in each period					
0-3 months	0.091	0.066	0.120	Dirichlet	[5]
3-6 months	0.105	0.078	0.135	Dirichlet	[5]
6 months – 1 year	0.107	0.080	0.138	Dirichlet	[5]
1 year – 3 years	0.158	0.125	0.193	Dirichlet	[5]
3 years – 5 years	0.080	0.056	0.107	Dirichlet	[5]
5 years – 7 years	0.066	0.045	0.091	Dirichlet	[5]
7 years – 10 years	0.087	0.062	0.115	Dirichlet	[5]
10 years+	0.306	0.264	0.350	Dirichlet	[5]

Proportions – Comorbidities					
Comorbidities presentation at 3-months	0.050	0.039	0.050	Beta	[7]
Chronic back pain	0.050	0.039	0.053	Beta	[7]
Uveitis	0.120	0.116	0.122	Beta	[7]
Psoriasis	0.043	0.030	0.045	Beta	[7]
Inflammatory bowel disease	0.026	0.021	0.028	Beta	[7]
Depression (delay ≥7 years)	0.043	0.039	0.045	Beta	[8]
Depression (delay <7 years)	0.024	0.018	0.027	Beta	[8]
Proportions - Out of Pocket Expenses					
People who had visited a chiropractor	0.433	0.402	0.464	Dirichlet	[5]
People visiting a chiropractor more than once a week	0.217	0.198	0.282	Dirichlet	[5]
People visiting a chiropractor weekly	0.445	0.423	0.478	Dirichlet	[5]
People visiting a chiropractor fortnightly	0.213	0.174	0.254	Dirichlet	[5]
People visiting a chiropractor monthly	0.120	0.090	0.154	Dirichlet	[5]
People visiting a chiropractor less than once a month	0.315	0.270	0.361	Dirichlet	[5]
People who had visited an osteopath	0.359	0.329	0.390	Dirichlet	[5]
People visiting an osteopath more than once a week	0.009	0.002	0.022	Dirichlet	[5]
People visiting an osteopath weekly	0.336	0.286	0.389	Dirichlet	[5]
People visiting an osteopath fortnightly	0.216	0.173	0.262	Dirichlet	[5]
People visiting an osteopath monthly	0.133	0.098	0.172	Dirichlet	[5]
People visiting an osteopath less than once a month	0.306	0.257	0.357	Dirichlet	[5]
Proportion - Medication					
NSAIDs e.g. ibuprofen, Anadin extra etc	0.240	0.224	0.256	Dirichlet	[5]
Topical anti-inflammatory gels, creams, or sprays	0.220	0.205	0.235	Dirichlet	[5]
Rubefacients: heat rubs, sprays, and gels) e.g. Deep Heat Rub	0.120	0.108	0.132	Dirichlet	[5]
Paracetamol	0.430	0.412	0.448	Dirichlet	[5]
Aspirin	0.050	0.042	0.058	Dirichlet	[5]
Co-codamol e.g. Solpadeine	0.100	0.089	0.111	Dirichlet	[5]
Glucosamine and/or Chondroitin	0.060	0.052	0.069	Dirichlet	[5]
Natural medicines (herbal remedies)	0.090	0.080	0.101	Dirichlet	[5]
Others	0.060	0.052	0.069	Dirichlet	[5]
Proportion - Employment status					
Full-time	0.352	0.330	0.374	Dirichlet	[5]
Part-time	0.166	0.149	0.184	Dirichlet	[5]
No employment (in education)	0.008	0.005	0.013	Dirichlet	[5]

No employment (full-time parent)	0.020	0.014	0.027	Dirichlet	[5]
No employment (retired)	0.290	0.269	0.311	Dirichlet	[5]
No employment (due to health issues)	0.164	0.147	0.181	Dirichlet	[5]
Proportion - Impact of AS on employment					
No impact	0.086	0.073	0.099	Dirichlet	[5]
Work fewer hours	0.098	0.084	0.112	Dirichlet	[5]
Go to work when not well	0.274	0.253	0.295	Dirichlet	[5]
Do less physical work	0.145	0.129	0.161	Dirichlet	[5]
Decreased job satisfaction	0.104	0.090	0.118	Dirichlet	[5]
Not preferred job	0.053	0.043	0.064	Dirichlet	[5]
Job is not the best use of skills	0.040	0.032	0.050	Dirichlet	[5]
Had to change occupation	0.082	0.070	0.096	Dirichlet	[5]
Left the job	0.119	0.104	0.134	Dirichlet	[5]
Proportion - Early Retirement					
Patients granted early retirement	0.001	0.000	0.002	Beta	[9]
Early retirement below 30 per delay period	0.068	0.062	0.074	Beta	[9]
Early retirement 40-50 per delay period	0.298	0.287	0.354	Beta	[9]
Early retirement above 50 per delay period	0.634	0.584	0.659	Beta	[9]
Diagnostic strategy – Sensitivity and Specificity					
Van Hoeven et al. (2015) (Sensitivity)	0.926	0.866	0.970	Beta	[10]
Van Hoeven et al. (2015) (Specificity)	0.390	0.348	0.434	Beta	[10]
Costs - Hospital Physiotherapist					
Physiotherapist specialist (Band 6)	£52.00	£46.80	£57.20	Gamma	[11]
Physiotherapist specialist (advanced) (Band 7)	£63.00	£56.70	£69.30	Gamma	[11]
Physiotherapist principal (Band 8)	£72.00	£64.80	£79.20	Gamma	[11]
Physiotherapist consultant (Band 8b)	£85.00	£76.50	£93.50	Gamma	[11]
Costs - Community Physiotherapist					
Physiotherapist (Band 5)	£41.00	£36.90	£45.10	Gamma	[11]
Physiotherapist specialist (Band 6)	£54.00	£48.60	£59.40	Gamma	[11]
Physiotherapist specialist (advanced) (Band 7)	£65.00	£58.50	£71.50	Gamma	[11]
Physiotherapist principal (Band 8)	£75.00	£67.50	£82.50	Gamma	[11]
Physiotherapist consultant (Band 8b)	£88.00	£79.20	£96.80	Gamma	[11]
Costs - GP and A&E					
GP Costs per Visit (15 min consultation)	£63.82	£57.44	£70.20	Gamma	[11]
A&E cost per visit	£182.19	£163.97	£200.41	Gamma	[12]

Admin costs per patient per consultation	£24.58	£22.12	£27.04	Gamma	[12]
Cost - Annual Comorbidities Treatment					
Chronic back pain	£917.09	£881.69	£935.37	Gamma	[12]
Uveitis	£3,123.05	£3,067.87	£3,183.16	Gamma	[13]
Psoriasis	£3,007.31	£2,889.43	£3,123.13	Gamma	[12]
Inflammatory bowel disease	£3,323.93	£3,267.54	£3,486.25	Gamma	[12]
Depression	£1,857.62	£1,679.34	£2,004.54	Gamma	[14]
Cost – Chiropractic Visit					
Chiropractic cost per visit	£55.00	£50.00	£60.00	Gamma	[15]
Cost - Osteopath Visit					
Osteopath cost per visit	£47.50	£42.00	£52.50	Gamma	[16]
Over the counter medication costs (3 months) per person					
NSAIDs e.g. ibuprofen, Anadin extra etc	£6.49	£4.11	£7.84	Gamma	[17, 18], Boots UK Ltd
Topical anti-inflammatory gels, creams, or sprays	£5.95	£4.79	£6.39	Gamma	[17, 18], Boots UK Ltd
Rubefacients: heat rubs, sprays, and gels) e.g. Deep Heat Rub	£4.60	£1.76	£6.01	Gamma	[17, 18], Boots UK Ltd
Paracetamol	£7.20	£7.08	£7.44	Gamma	[17, 18], Boots UK Ltd
Aspirin	£0.68	£0.45	£0.78	Gamma	[17, 18], Boots UK Ltd
Co-codamol e.g. Solpadeine	£2.70	£2.49	£2.78	Gamma	[17, 18], Boots UK Ltd
Glucosamine and/or Chondroitin	£0.32	£0.29	£0.44	Gamma	[17, 18], Boots UK Ltd
Natural medicines (herbal remedies)	£1.07	£1.01	£1.58	Gamma	[17, 18], Boots UK Ltd
Others	£1.07	£0.92	£1.12	Gamma	[17, 18], Boots UK Ltd
Cost - early retirement					
Early retirement cost per patient per quarter	£2,026.75	£1,998.69	£2,103.22	Gamma	[6]
Cost - Unpaid care					
Cost of unpaid assistance at mean wage (3 months Age < 50)	£490.00	£488.59	£493.71	Gamma	[6]
Cost of unpaid assistance for health care visits at mean wage (3 months Age < 50)	£38.27	£36.79	£39.28	Gamma	[6]
Cost of unpaid assistance at mean wage (3 months Age > 50)	£1,041.45	£982.43	£1,119.94	Gamma	[6]
Cost of unpaid assistance for health care visits at mean wage (3 months Age > 50)	£63.41	£61.15	£64.00	Gamma	[6]
Cost - Gross median wage (per hour)					
Full-time – All	£15.65	£9.29	£19.63	Gamma	[19]
Part-time – All	£10.64	£6.89	£15.88	Gamma	[19]
Full-time – Male	£16.25	£13.08	£19.56	Gamma	[19]
Part-time – Male	£10.45	£4.73	£13.78	Gamma	[19]
Full-time – Female	£14.87	£9.44	£18.82	Gamma	[19]
Part-time – Female	£10.71	£5.82	£12.66	Gamma	[19]

Cost – Presenteeism, absenteeism, and staff turnover					
Presenteeism	£1,685.27	£1,516.50	£1,853.50	Gamma	[20]
Absenteeism	£427.99	£422.73	£431.27	Gamma	[20]
Staff turnover	£318.06	£314.82	£321.18	Gamma	[20]

Note. NHS, National Health Service; NASS, National Axial Spondyloarthritis Society; GP, general practitioner; A&E, Accident and Emergency; NSAID, Non-Steroidal Anti-Inflammatory Drug; AS, ankylosing spondylitis.

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