Health Economics Consulting

UEA University of East Anglia

NASS

The economic cost of delayed diagnosis of axial spondyloarthritis in the UK

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act on Axial SpA

Foreword

What does delayed diagnosis of axial spondyloarthritis (axial SpA) cost the UK economy each year? The answer is £18.7 billion, according to new economic modelling commissioned by The National Axial Spondyloarthritis Society (NASS).

We already knew that diagnostic delay in axial SpA has a very real and considerable impact on people's quality of life and the impairment of their physical function. We knew that people also pay a heavy psychological price for delayed diagnosis.

We now also know that the price they pay has a very significant financial value. For someone whose symptoms start at an average age of 26, and who has an average time to diagnosis of 8.5 years, the total cumulative cost per person is £193,512. The majority of these costs are borne by the individual through lost productivity and out of pocket expenses.

These costs are startling and completely unnecessary. In June 2021, in response to our national consultation into diagnostic delay in axial Spa, we launched our Act on Axial SpA campaign which set out a route map to achieve a Gold Standard time to diagnosis of one year.

If the NASS Gold Standard was achieved this would reduce the average cost of receiving a diagnosis down to £25,798, saving individuals around £167,000.

The estimates contained in this ground-breaking research, undertaken by the University of East Anglia, are potentially conservative due to data availability and the difficulty in estimating the effect of diagnostic delay on disease progression. Consequently, the costs within the report only included those up to the point of diagnosis. The true costs, therefore, may be even higher.

We are publishing this report at a time of significant economic turmoil, with household incomes under greater pressure than at any time in a generation. In this context, the cost of waiting for a diagnosis can make the effect on someone's life even more harmful than ever.

The cost to the UK economy of delayed diagnosis in axial SpA is greater than the cost of treating the condition. The economic argument for early diagnosis is clear. The route map to achieve this has been set, and the resources to support patients and clinicians are available.

We call on parliamentarians and policy makers to apply pressure to ensure that a Gold Standard time to diagnosis is achieved which will relieve very high levels of financial, psychological, and physical suffering.

Dr Dale Webb, FRSA, FRSPH

CEO, NASS

Acknowledgments

We are grateful to Dr Dale Webb, CEO and Jill Hamilton, Head of Policy and Health Services, at the National Axial Spondyloarthritis Society (NASS) for their work in providing data to the research team at the University of East Anglia (UEA) and for their support with contacting key stakeholders. The key stakeholders included clinicians and people living with axial spondyloarthritis (axial SpA), who kindly gave the research team insights into this chronic condition. 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 over 16-year-olds. We are also indebted to Professor Karl Gaffney of the Norfolk and Norwich University Hospital (NNUH) and Dr Raj Sengupta of the Royal National Hospital for Rheumatic Diseases (RNHRD), part of the Royal United Hospitals Bath NHS Foundation Trust for providing anonymised patient data to populate the economic model for costs associated with delayed diagnosis of axial SpA.

NASS wishes to express sincere thanks to UCB for funding the Act on Axial SpA programme, which includes this research.

List of abbreviations

AS	Ankylosing spondylitis
Axial SpA	Axial spondyloarthritis
CI	Confidence Interval(s)
EMMs	Extra Musculoskeletal Manifestations, also referred to in report as co-morbidities
GDG	Guidance Development Group
GP	General Practice
HEC	Health Economics Consulting
LCI	Lower Confidence Interval
MRI	Magnetic Resonance Imaging
NASS	National Axial Spondyloarthritis Society
NICE	National Institute for Health and Care Excellence
NNUH	Norfolk and Norwich University Hospital
NVIVO	a qualitative data analysis computer software package produced
OTC	Over the Counter
PSA	Probabilistic Sensitivity Analysis
RNHRD	Royal National Hospital for Rheumatic Diseases, part of the Royal United Hospitals Bath NHS Foundation Trust
UCI	Upper Confidence Interval
UEA	University of East Anglia
UK	United Kingdom

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Executive summary

Background

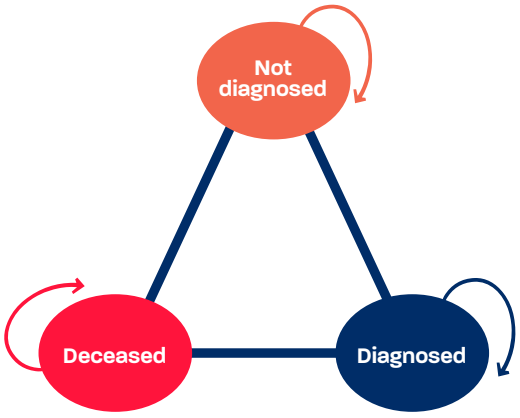
Axial spondyloarthritis (axial SpA) is an umbrella term for a form of inflammatory arthritis that affects the spine and sacroiliac joints. It includes ankylosing spondylitis (AS) or radiographic axial SpA, where changes to the sacroiliac joints or the spine can be seen on X-ray, and non-radiographic axial SpA, where X-ray changes are not present, but inflammation is visible on magnetic resonance imaging (MRI), or the patient has a range of other symptoms. Axial Spa is characterised by inflammatory pain and functional impairment and can have a devastating impact on the lives of those living with it. Onset of axial SpA typically starts between late teen years to early twenties, with an average age of symptom onset of 26[1]. This condition can have a life-long impact and long-term complications if left untreated. Diagnosis is difficult and often delayed several years after the appearance of symptoms – on average patients wait 8.5 years for a diagnosis from the moment of symptom onset[2].

Previous studies have assessed the medical and productivity costs associated with axial SpA. Treatment costs typically focus on health care costs such as medications, administration and monitoring, General practice (GP) visits, hospital admissions, management of treatment related adverse events etc. Costs borne by the patients or their caregivers, such as transportation and over-the-counter medications, or the productivity losses arising from work absence, inability to work or early mortality, particularly pre-diagnosis, have received little attention to date. Studies have focussed on costs associated with the diagnosis of axial SpA, however, there is no research on the costs incurred prior to diagnosis. Given the average delay is around 8.5 years, it is likely that considerable costs will be incurred, both societal and individual, and these will increase over longer delay periods. The analysis reported here adopts a broad societal perspective for estimating the burden of delayed diagnosis, up to the point of diagnosis for those living with axial SpA in the United Kingdom (UK), applying a comprehensive approach including out of pocket expenses, medical costs, productivity losses and broader social costs but not costs accrued after diagnosis. The current analysis does not take into consideration any costs accrued after diagnosis.

Methodology

To develop the model, a mixed method approach was taken. It included semi-structured interviews with key stakeholders (12 clinicians, 4 people living with axial SpA) to understand the experiences and impacts of delayed diagnosis and the costs incurred. Researchers also gathered survey data and data sets of anonymised patient information. Key clinical stakeholders also assisted in the validation of the model.

The model projects diagnosis progression ("Not Diagnosed" to "Diagnosed" and "Deceased") forward in time-steps with feedback loops to allow movement in states back and forth. Transition states within each time-step were constructed according to the various stages of the diagnosis process and they were used primarily to demonstrate an assessment of the costs in the time taken to a confirmed diagnosis.



The main inputs into the model included:

- the probability of patients engaging with health care services in different period from the onset of the symptom
- the probability of getting diagnosed, by gender and age group
- the sensitivity and specificity of various diagnostic strategies
- the health resources utilised
- the cost of managing the symptoms and co-morbidities
- the cost related to productivity losses
- any other parameters and costs reflecting real resources required to diagnose, confirm, treat, cope with, manage and accommodate axial SpA symptoms.

The model relied upon assumptions due to the non-availability of data, which is a limitation. There is a need for detailed records of societal costs that impact on people with axial SpA to be collated. Such data would reduce the assumptions needed and, therefore, improve the predictiveness of the model.

Results

Our modelling suggests the cost of delayed diagnosis of axial SpA, up to the point of diagnosis, is substantial and falls mainly on the individuals concerned in the form of time off work, out-of-pocket medical expenses, non-prescription (over the counter) drugs, travel costs and paid-for exercise.

These costs are higher in younger patients but remain substantial in older groups. The costs decrease each year as more people from the modelled cohort get diagnosed. With a symptom onset at the age of 26 and an average time to diagnosis of 8.5 years we estimate that the cumulative costs of delayed diagnosis per person living with axial SpA is £193,512 (CI 95%: £108,355 - £313,670).

In comparison, in younger ages with an onset at the age of 20 and an average time to diagnosis of 8.5 years, the mean cost is approximately £215,550 while with an onset at the age of 30 and an average time to diagnosis of 8.5 years the mean costs is approximately £170,800.

The total annual cost that accrues to delay prior to diagnosis in the UK is therefore estimated at £18.7 billion, based on a prevalence of 0.018 while the treatment costs have been estimated for comparison at £9.1 billion for the same proportion of population (based on an average yearly medication cost of £9,500 per patients).

Concluding remarks

The estimated cumulative costs to the individual due to delayed diagnosis of axial SpA, up to the point of diagnosis, are thus substantial. These escalate over the course of the delay and most likely cause significant burden to the health care system due to complications attributable to this delay. The results show that if diagnosed early, axial SpA can significantly reduce the financial burden for both patients (out of pocket expenses) and society (productivity losses). These savings also could offset the cost of treatment as they are of the same magnitude and in some cases significantly higher[3].

Delayed diagnosis of axial SpA carries significant societal costs due to the productivity loss. The estimated productivity costs for women are likely to be conservative as it does not account for workforce participation and unpaid work. These costs, when added to those once a diagnosis has been made, would be considerable. Health care costs are also substantial, both before and after diagnosis, and exactly what a delayed diagnosis "costs" in terms of increased and more invasive treatments is beyond the scope of this research. In addition, the out-of-pocket costs for people living with axial SpA before diagnosis are also considerable, and carry a large burden once added to out-of-pocket expenses post diagnosis.

To conclude, the results show that the early diagnosis of axial SpA can significantly reduce the financial burden for both patients (out of pocket expenses) and society (productivity losses). These savings could also offset the cost of treatment[3].

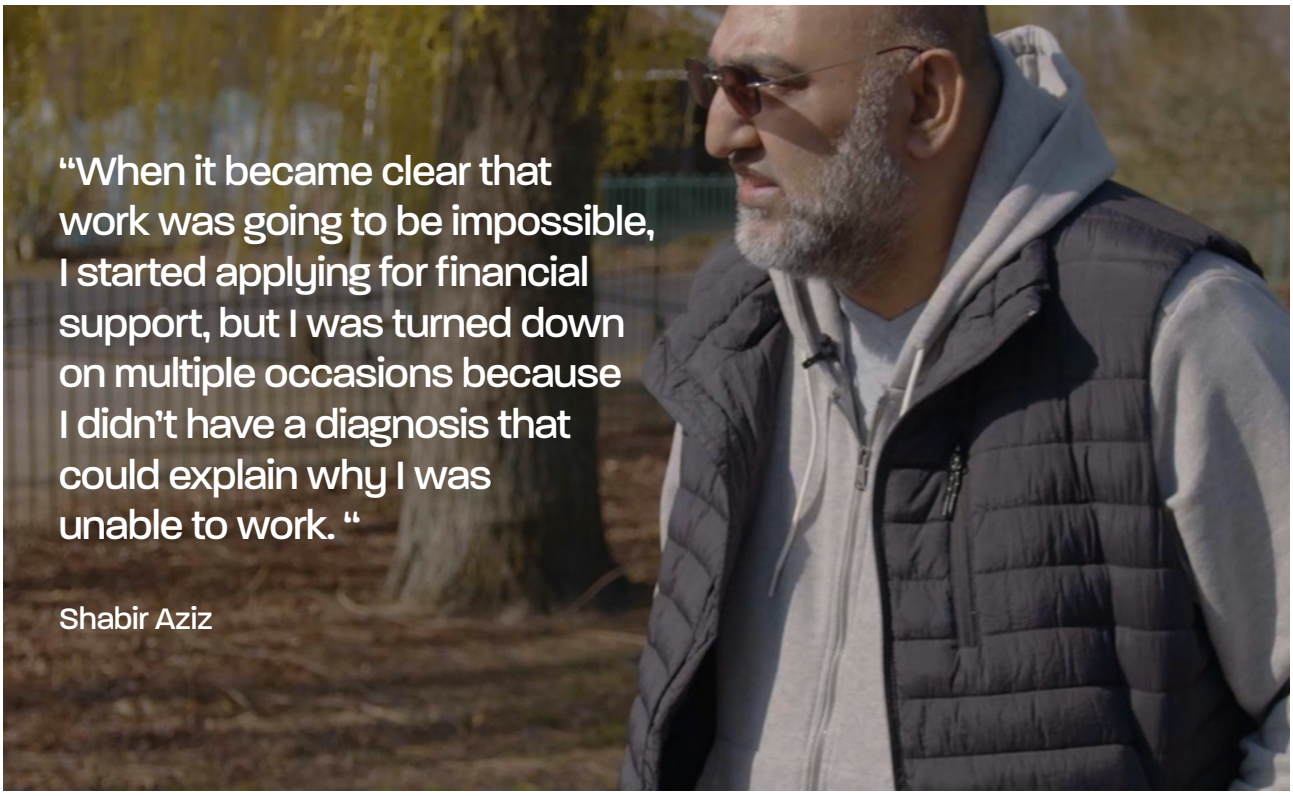
"As a family, we had to rely completely on my wife's income. We had to make heartbreaking choices between heating the house and putting food on the table."

Steve Spray

Introduction

Previous studies have assessed the medical and productivity costs associated with axial SpA. Furthermore, estimations of treatment costs typically focus on health care costs such as medications, administration and monitoring, GP visits, hospital admissions, management of treatment related adverse events etc.

However, this does not capture the costs borne by the patients or their caregivers, personal transportation, over-the-counter (OTC) medications, unpaid care costs, productivity losses arising from work absence, inability to work or early mortality. To better inform treatment decisions, the analysis reported here adopts a broader societal perspective for estimating the burden of delayed diagnosis for the people living with axial SpA in the UK.



Background

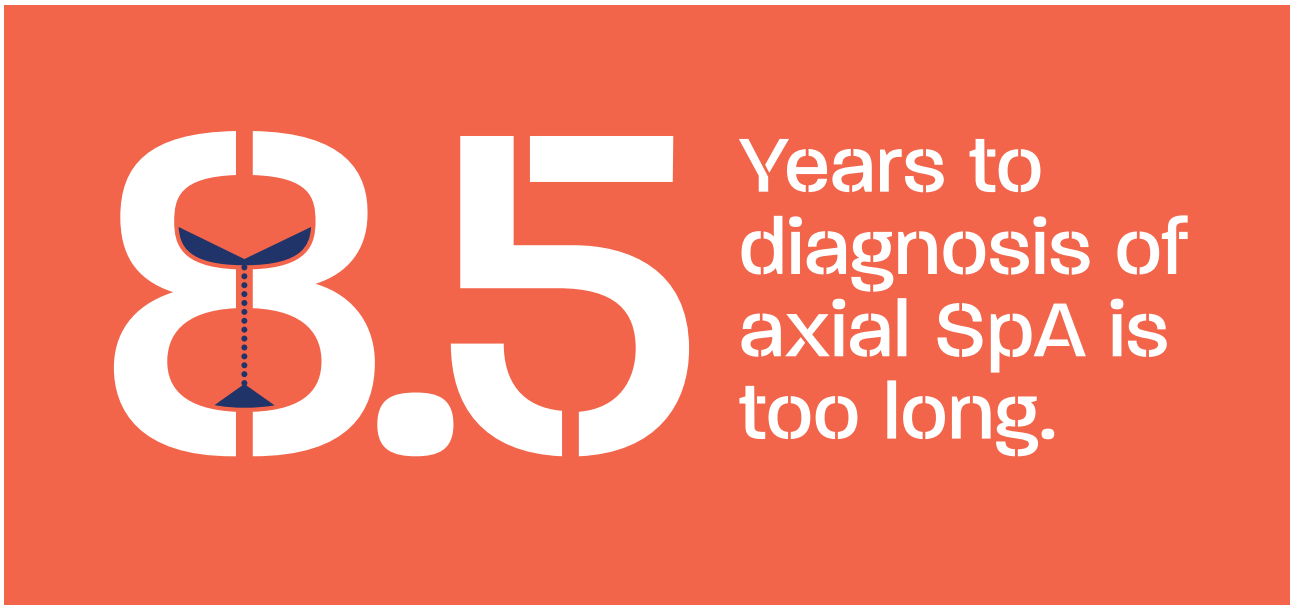
Axial SpA is an umbrella term for a form of inflammatory arthritis that affects the spine and sacroiliac joints. It includes ankylosing spondylitis (AS) or radiographic axial SpA, where changes to the sacroiliac joints or the spine can be seen on x-ray, and non-radiographic axial SpA, where x-ray changes are not present, but inflammation is visible on Magnetic Resonance Imaging (MRI), or the patient has a range of symptoms. Axial SpA is characterised by inflammatory pain and functional impairment and can have a devastating impact on the lives of those living with it. Onset of axial SpA typically starts between late teen years to early twenties, with an average age of symptom onset of 26[1].

Axial SpA is a progressive form of inflammatory arthritis which most commonly affects the spine but can also affect other joints, tendons, and ligaments. One of the key symptoms of axial SpA is back pain which comes on slowly and can last for at least 3 months. Axial SpA is characterised by periods of flare and periods when the pain and inflammation die down. Patients may initially be misdiagnosed with mechanical back pain including sports injuries. Most patients experience symptoms of pain, stiffness, and fatigue. These symptoms are likely to worsen during periods of flare. Extra Musculoskeletal Manifestations (EMMs) include inflammatory eye condition - acute anterior uveitis (22%), inflammatory bowel problems (5%) including Crohn's Disease and ulcerative colitis, and the inflammatory skin condition psoriasis (8%)[1].

The underlying disease process is that inflammation occurs at the site where ligaments or tendons attach to the bone (enthesis). The inflammation is followed by some wearing away of the bone at the site of the attachment (enthesopathy). As the inflammation reduces, healing takes place and new bone develops. Movement becomes restricted when bone replaces the elastic tissue of ligaments or tendons. Repetition of this inflammatory process leads to further bone formation and vertebrae can fuse. An estimated 25% will experience spinal fusion[4] over their lifetime but prompt diagnosis and good management reduces the risks of fusion[4,6].

The average time of delay in the UK is 8.5 years; however, it can vary between 5 and 15 years[5] and case studies from NASS reports examples of lengthier delays. The median age of onset is 26 years[1]; however, case studies suggest onset in childhood. One in two hundred people suffer from axial SpA. Women often are misdiagnosed and have a longer delay than men[6–8]. In addition to the spinal pain most often associated with axial SpA, people with the condition can also have a range of complications and co-morbidities[4]. A review noted that factors consistently reported to be associated with longer delays were lower education levels, younger age at symptom onset and absence of EMMs[9]. These diagnostic delays may result in a less favorable response to treatment and poorer outcomes, including functional impairment and quality of life[9]. Overall, delays mean worse outcomes in disease activity, fatigue, spinal mobility and radiographic damage to the spine[4]. Risk of mortality is higher for people suffering from axial SpA[10].

A recent systematic review of the literature found that people with delayed diagnosis also had a greater likelihood of depression, negative psychological impacts, work disability, worse quality of life and higher health care costs and that the disease had a significant societal impact, due to economic factors such as work disability and health care cost[11]. An estimated 10 - 40% of people must give up work and patients tend to retire 9.5 years earlier on average than the general population[12]. 3.5% of people with axial SpA report absenteeism



at work while 22% report presenteeism[13]. There are currently an estimated 220,000 people in the UK living with this painful and progressive form of inflammatory arthritis. While people wait for a diagnosis, many withdraw from socialising and find it harder to establish careers, form relationships, and start families. There have been fewer studies into the costs of lost productivity or out of pocket costs because of diagnostic delay. Other impacts are less tangible monetarily such as on patients' quality of life. Whilst a study in the UK looked at the total cost of AS and estimated it to be £19,016 per patient per year[14], timing and impact of costs (both NHS and other sources) in years leading-up to diagnosis have not been modelled.

The indirect effect of delay (through greater disease severity) has been shown potentially to double the cost to the NHS[14]. An Egyptian study found that patients with longer delay had nearly 3-times higher number of visits to the doctor prior to diagnosis, amounting to a near fourfold higher expenditure[15]. This was replicated in an Australian study, where a quarter of patients with <5-year delay incurred high treatment costs (>3000 US Dollars), compared to two thirds among those with >10-year delay[16]. Comparative UK data is unavailable.

The NICE Guideline Development Group (GDG) identified the recognition and appropriate referral of axial SpA as its key priority for original health economic analysis[17]. The group advised that delayed diagnosis is a significant issue in all spondyloarthritis, but that people with axial SpA symptoms are subject to particularly damaging delays, invariably because their symptoms are misidentified as mechanical back pain[17].

Commissioned by NASS, Health Economics Consulting (HEC) undertook the research to create a new health economics model to assess the cost of delayed diagnosis, up to the point of diagnosis of axial SpA by combining health care, out of pocket costs and productivity costs/losses.

Project outline

Aims and objectives

The key objective of this research was the development of an economic model to determine the cost to society and the UK economy culminating in a total cost per patient with axial SpA for each year of delay, up until the point of confirmed diagnosis. NASS commissioned the research as part of the Act on Axial SpA campaign aiming to reduce diagnostic delay through a Gold Standard time to diagnosis of one year. The research showing the economic and financial cost adds to the already established physical, psychological, and emotional impact that waiting for a diagnosis cause, often resulting in worse patient outcomes.

The main objectives include:

- the gathering of opinions from medical experts and people living with axial SpA
- the investigation of the current body of literature and previous models developed in this area
- the estimation of the medical cost, productivity losses and other out of pocket expenses related to delayed diagnosis of axial SpA in the UK
- the estimation of the cumulative costs and costs per year of the delayed diagnosis per patient
- the estimation of the cumulative costs and costs per year of the delayed diagnosis per gender.

Key stakeholders

Key stakeholders who were consulted to provide background information, feedback for development and the quality control of the project outcomes were:

- clinicians including primary care and secondary care clinicians
- people living with axial SpA including NASS.

Project management

The project was designed and conducted by the University of East Anglia's HEC research team with discussion and guidance from the NASS team including members of the Medical Advisory Board and other key stakeholders.

Design

Mixed methods included qualitative input from clinicians and people living with axial SpA as guidance for the development of the model and an economic Markov model was developed to determine a total cost per patient per year of delay.

Methodology

To develop the model, a mixed methods approach was taken. It included semi-structured interviews with key stakeholders (experts by experience - 12 clinicians, 4 people living with axial SpA) to understand the experiences and impacts of delayed diagnosis and the costs incurred. These experiences were used to check that suitable variables and parameters were added to the model and cross-checked against other data sources. Key clinical stakeholders also assisted in validation of the model.

HEC considered the best way to model the potential cost and established that a Markov Chain model process was the most effective in representing the NASS Act on Axial SpA campaign aiming to drive down the time to diagnosis.

A Markov model is an analytical framework that is frequently used in decision analysis for dynamic systems where it is assumed that future states do not depend on past states/ nodes in the model representing events that occurred before them. This model shows all possible states as well as the transitions, rate of transitions and probabilities between them. Markov models are accurate and efficient for modelling disease progression over time without over-complication[18]. They can be visually inspected for programming errors and tested straightforwardly for replication.

The Markov model process also has some limitations including non-retention of patient history and fixed length cycles. Non-retention of patient history means that Markov models are memoryless in the sense that they require specific current state to determine statistics about its future and they are not dependent on previous nodes of the model. These limitations can be addressed using a combination of time-dependent transition probabilities and distinct disease states as it was used in this model to assess misdiagnosed cases and co-morbidities.

The model was built using the latest version of Microsoft Excel. Markov models use a series of inter-related steps (or cycles) to determine an outcome at a predetermined stage e.g., a measurable number of progressive cases until diagnosis. Cycles can be represented in a Markov by referring to the period over which the probability of transitions are applied in the model. Cycle duration can be pre-specified; and in this study we have used 3-month duration cycles to capture any probable resource use or cost.

The model projects diagnosis process forward in time-steps to allow movement in states back and forth. The model captured symptoms and impacts of axial SpA leading up to that diagnosis and before initiation of treatment. Assuming the one-year maximum 'gold standard' time to diagnosis, the sum of costs prior to this in each consecutive cycle was estimated.

The original model was devised to estimate the costs for people who are not yet diagnosed. The model utilised a cohort who are suspected to have axial SpA, it has a 3-month cycle length and a lifetime time horizon. The lifetime horizon was chosen as there were cases where delayed diagnosis spanned over decades and had an impact on the costs incurred over a patient's lifetime. The model adopts a patient perspective for productivity and out of pocket costs and an NHS perspective for medical costs, in line with the section 7 of NICE Guidelines Manual[19].

The main inputs into the model included:

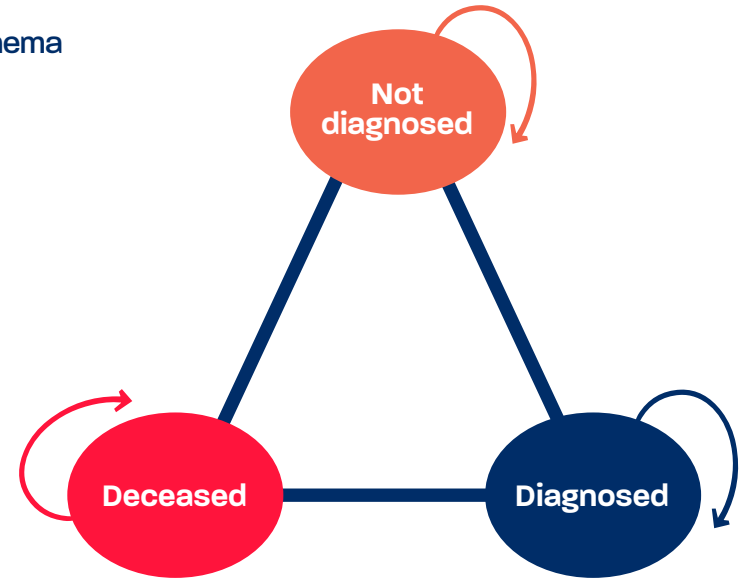
- the probability of people living with axial SpA to engage with health care services in different period from the onset of the symptoms
- the probability to get diagnosed, per gender and age group
- the sensitivity and specificity of various diagnostic strategies
- the health resources utilised
- the cost of managing the symptoms and co-morbidities
- the cost related to productivity losses
- any other parameters and costs reflecting real resources required to diagnose, confirm, treat, cope with, manage and accommodate axial SpA symptoms.

Data input sources used included anonymised diagnosed patient data with the pathways they followed pre-diagnosis shared under strict confidentiality data sharing agreement from the secondary health units participating in the project, 2016 NASS survey data, and data from published literature. Cost data were collected from national sources and research into axial SpA, NHS unit costs reports, and productivity related reports. Interviews with people with axial SpA and clinicians provided valuable insight into the condition. Specific data sources and references have been provided in various relevant sections within this report. The economic model has been validated by experts in the field to ensure accurate representation of actual events.

Figure 1 provides a schematic depiction of the model structure. It shows the stages modelled in terms of its ability to categorise people into true-positive and true-negative diagnoses (with complementary probabilities of false-negative and false-positive diagnoses, respectively). True positive cases refer to positive axial SpA diagnoses, conditioned on truly being positive, and true negative cases refer to negative diagnoses, conditioned on truly being negative. The long-term costs associated with people who have been diagnosed with axial SpA was not modelled as this was beyond the scope of the research.

In reflection of the lack of diagnostic accuracy evidence, the model did not distinguish between radiographic and non-radiographic axial SpA as initial symptoms have general similar clinical characteristics[20]. For this report the data used are described in the sections below and in the Appendices.

Figure 1: Model schema



Model inputs

HEC's Markov model captures resources and impacts related to axial SpA leading up to that diagnosis and before initiation of treatment. The inputs consist of:

- axial SpA epidemiological data: prevalence, mortality
- the probability of people living with axial SpA to engage with health care services
- the probability of people living with axial SpA to get diagnosed
- the sensitivity and specificity of various diagnostic strategies
- the health resources utilised: GP, and physiotherapist utilisation in terms of diagnosis and co-morbidities management
- out of pocket expenses for managing the symptoms: over the counter medication costs, chiropractor and osteopath costs, travel expenses, expenses on non-prescribed exercise
- costs related to productivity losses and any other parameters: absenteeism, presenteeism and staff turnover expenses, productivity losses from leaving a job, working fewer hours, unpaid care assistance and early retirement.

All rates and probabilities were adjusted based on formulas to refer to the correct timeframe while all costs were inflated to 2021 values using the NHS Cost Inflation Index (NHSCII) and the Treasury Green Book[21] on the social discount rate.

Semi-structured interviews

To inform the research team and gather information about potential model inputs, semi-structured interviews were conducted with key stakeholders (experts by experience): three clinicians - a GP, a GP/ clinical commissioner, and an osteopath- and four people living with axial Spa.

Table 1 shows the people living with axial SpA were selected to represent age and gender differences and variation in the delay to diagnosis.

Table 1: Patients with axial SpA

Stakeholder pseudonym	Gender	Age	Age of first symptoms	Years to diagnosis
Jane	Female	43	8	35
Mary	Female	56	28	24
Kyle	Male	34	14	17
Saba	Male	53	21	25

A focus group was conducted with nine clinicians associated with the treatment of axial SpA to gather further information about the condition. The composition of this group is shown in Table 2.

Table 2: Focus group with clinical stakeholders

Clinical speciality	Number of stakeholders
Chiropractor	2
GP	1
Physiotherapist	2
Rheumatology Consultant	1
Osteopath	1
First Contact Practitioners	2

Interviews were thematically analysed following the stages developed by Braun and Clarke[22] to provide information on symptoms, journey to diagnosis, costs associated with treatment from the NHS and private sources, societal and productivity costs. Transcripts were coded by one researcher (Stephanie Howard Wilsher) and checked by another researcher (Oyewumi Afolabi) using NVIVO 12, a specialist qualitative research tool.

The information gathered during the interviews and focus groups were used by the research team to understand more about the lived experience of axial SpA, and to check that suitable variables and parameters were added to the model.

Ethical approval is not required when stakeholders are asked for their input to help develop the research, however, all participants were asked if anonymised quotes could be used in research outputs.

Recruitment of stakeholders

NASS contacted all key stakeholders and asked for volunteers to take part in the research. Interviewees contacted the UEA research team to organise dates and times for the interviews. NASS organised the focus group for clinicians that was steered by the UEA research team.

Data collection

Interview guides were developed for the people living with axial SpA (Appendix 1) and clinicians (Appendix 2). The interviews with stakeholders were recorded via MS Teams and digital recorder. The automatic transcription provided on MS Teams was checked for accuracy against the two recordings.

Data input for the model was generated from several sources. The report and results from a 2016 survey data collected by NASS from patients with diagnosed axial SpA was shared with researchers at the UEA. Key parameters and estimates from this survey 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 patients journey to diagnosis was also made available to the researchers. Secondary data sources used to generate

input includes data from the NICE NG65 Spondyloarthritis Guideline as well as evidence from published literature.

Population data

We considered that to accurately calculate the costs of delayed diagnosis of axial SpA, the modelled population should be comprised by people that we consider a priori that have axial SpA and we model their journey towards diagnosis based on the transition probabilities gathered from various sources (NICE NG65 model, NASS survey data, published literature evidence as well as user inputs).

The age of the onset of the symptoms was set to 26 years old[1], while the percentage of the male patients for the mixed cohort calculations were set to 64% in accordance with the NICE NG65 Axial SpA model. Standardised Mortality Rate for male and female patients was set to 1.630 and 1.380 respectively[23]exposing patients to a prolonged burden of disease. Whether this is associated with excess mortality is still uncertain. Radiation therapy for AS has previously been shown to increase mortality. The present study investigated standardised mortality ratios, causes of death and survival predictors in a large regional cohort of patients with AS. Method: A total of 677 patients with AS followed at our hospital since 1977 were matched by gender, age and postal area to three controls from the general population and standardised mortality rates (SMRs).

Condition-related parameters used in the model, including the probability of engaging with formal care and the probability of diagnosis are presented in Table 3 and Appendix 3.

"There's lots of confounders and lots of tricky things. People come in and say they've got back pain for lots of different reasons, not just because they've got back pain. There's lots of reasons, economic reasons, to seek certain medicines as well. You've got to try and filter those ones out and try and work out what the agenda really is."

General Practitioner

Table 3: Population parameters

Model Parameters	Value	Source
Cohort size	1000	Model Setting
Cycle length (in years)	0.25	
Model iterations	1000	
Discount rate (costs)	0.035	Attema et al., 2018[24]
Population starting age	26.00	Boel et al., 2022[1]
Sex (% male)	0.64	NICE NG65 Model
Model time horizon (years)	74.00	Model Setting

Formal care utilisation and costs

Formal care utilisation and the associated costs included an estimation of the yearly visits to the GP and physiotherapist services. It also estimated the 3-month probability of co-morbidities appearance based on the 8.5-year time to diagnosis prevalence of the specific co-morbidities[25]. Costs were collected from the Personal Social Services Research Unit's (PSSRU) latest cost publication[26]. Table 4 summarises the parameters used in the model and their respective sources.

Table 4: Formal care utilisation and costs

Variable Category / Name	Value	Source
Health Utilisation Costs		
Physiotherapist (in the past 12 months)		
Hospital based specialist rheumatology physiotherapist	0.654	NASS survey, 2016
NHS community-based physiotherapist	0.150	
Private community-based physiotherapist	0.108	
NASS group physiotherapist	0.287	
Other	0.057	
Physiotherapist visits frequency	1.27	Expert Opinion
Hospital Physiotherapist Costs		
Physiotherapist specialist (Band 6)	£ 52.00	PSSRU, 2021[26]
Physiotherapist specialist (advanced) (Band 7)	£ 63.00	
Physiotherapist principal (Band 8)	£ 72.00	
Physiotherapist consultant (Band 8b)	£ 85.00	
Average cost	£ 68.00	Calculated
Community Physiotherapist Costs		
Physiotherapist (Band 5)	£ 41.00	PSSRU, 2021
Physiotherapist specialist (Band 6)	£ 54.00	
Physiotherapist specialist (advanced) (Band 7)	£ 65.00	
Physiotherapist principal (Band 8)	£ 75.00	
Physiotherapist consultant (Band 8b)	£ 88.00	
Physiotherapist consultant (Band 8b)	£ 64.60	

Table continues next page

GP and A&E Costs		
GP costs per visit (15 min consultation)	£ 63.82	PSSRU 2021
GP visits per year	6.92	Cooksey et al., 2015[14]
A&E visits	0.87	Expert Opinion
A&E cost per visit	£182.19	PSSRU, 2021
Admin costs per patient per consultation	£24.58	
Co-morbidities Parameters		
Co-morbidities Proportions		
Co-morbidities presentation 3-month probability	0.500	Martindale et al 2015[25]
Chronic back pain	0.050	
Episodic iritis (Iritis: a type of uveitis known as anterior uveitis)	0.120	
Psoriasis	0.043	
Inflammatory bowel disease	0.026	
Depression (delay ≥7 years)	0.040	Fitzgerald et al 2017[27]
Depression (delay<7 years)	0.024	
Co-morbidities Treatment Costs (Annual)		
Chronic back pain	£1341.27	NHS reference cost 2019/2020
Uveitis	£123.05	Ocular Immunology and Uveitis Foundation[28]
Psoriasis	£3007.31	NHS reference cost 2019/2020
Inflammatory bowel disease	£3323.93	NHS reference cost 2019/2020
Depression	£1857.62	Average cost between CBT models. Morriss et al 2019[29]72 (44.7%

Out of pocket expenses

Out of pocket expenses calculations include an estimation of the utilisation and cost of chiropractor and osteopath services as well as the over the counter (OTC) medication proportion, as reported in the NASS 2016 survey of 2,827 NASS members. Moreover, we have also included the non-prescribed exercise costs per person as they were described in Cooksey (2015)[14].

Estimates of the use of OTC pain management medication as well as visits to osteopaths, chiropractors and private physiotherapists were obtained from NASS survey (2016) data. The survey was shared with axial SpA patients, and respondents were asked to recall their usage of specific medications and visits in the last 12 months. It was assumed that the use of the above will approximately be the same as prior to getting a diagnosis of axial SpA. It should be noted that this assumption is very conservative as patients with an official diagnosis have access to better and improved treatment and as such reports on the use of OTC pain medication might be lower than it was pre-diagnosis. It is relatively common for patients to consult/visit an osteopath and/or a chiropractor prior to diagnosis as a means of pain management. The frequency of visits and percentage of survey respondents that reported using either one or both is presented in Table 5. Chiropractor and osteopath costs per session were calculated as the average of the reported costs by the NHS[30,31].

In addition, HEC estimated the cost of travel to and from GP, physiotherapist, chiropractor, and osteopath practices. The average travelling distance to a general practice (GP) in the UK was obtained from the Department of Transport journey time statistics and the average taxi price for the estimated distance was used. The presumed mode of transportation to these appointments was via a car (taxi), based on the assumption that individuals might be experiencing some degree of pain and would opt for a comfortable means of transport. The number of doctor's visits during delay period, was obtained from the research by Cooksey et al[14].

The same assumption was adopted to calculate travel cost for osteopath and chiropractor visits.

The type of OTC medication and frequency of use was obtained from the NASS survey data (see Table 5). Based on discussion with stakeholders, it was assumed that individuals self-managing pain with medication will do so using the maximum allowable dosage which was obtained from the British National Formulary and used to estimate required monthly supply. Prices for OTC drugs were obtained online from Boots Pharmacy. It is not unusual for patients who purchase multiple drugs monthly to obtain a prescription for this from their GP (regardless of their availability OTC) as a means of controlling monthly cost. Taking this into consideration, the drug cost to everyone was estimated such that monthly cost does not exceed NHS monthly prescription charge of £9.35. Our calculation also factored in the availability of NHS prescription prepayment certificates[32] such that annual drug cost does not exceed £108.10 per person.

Table 5: Out of pocket expenses

Out of Pocket Expenses	Value	Source
Chiropractor Visits		
Proportion of people that had visited a chiropractor	0.433	NASS, 2016
Proportion of people that had visited a chiropractor before diagnosis	0.791	
Proportion of people visiting a chiropractor more than once a week	0.040	
Proportion of people visiting a chiropractor weekly	0.313	
Proportion of people visiting a chiropractor fortnightly	0.213	
Proportion of people visiting a chiropractor monthly	0.120	
Proportion of people visiting a chiropractor less than once a month	0.315	
Chiropractor cost per visit	£ 55.00	Chiropractic - NHS
Osteopath Visits		
Proportion of people that had visited an osteopath	0.359	NASS, 2016
Proportion of people that had visited an osteopath before diagnosis	0.737	
Proportion of people visiting an osteopath more than once a week	0.009	
Proportion of people visiting an osteopath weekly	0.336	
Proportion of people visiting an osteopath fortnightly	0.216	
Proportion of people visiting an osteopath monthly	0.133	
Proportion of people visiting an osteopath less than once a month	0.306	
Osteopath cost per visit	£ 47.50	Osteopathy - NHS

Medication Parameters		
Medication Proportion		
NSAIDs e.g., ibuprofen, Anadin extra etc	0.240	NASS, 2016
Topical anti-inflammatory gels, creams, or sprays	0.220	
Rubefacients: heat rubs, sprays, and gels e.g Deep Heat Rub	0.120	
Paracetamol	0.430	
Aspirin	0.050	
Co-codamol e.g., Solpadine	0.100	
Glucosamine and/or Chondroitin	0.060	
Natural medicines (herbal remedies) e.g., Turmeric, Willow Bark etc.	0.090	
No medicine	0.340	
Others	0.060	
Over the Counter Medication Costs (3 months) Per Person		
NSAIDs e.g., ibuprofen, Anadin extra etc	£ 2.60	Boots Pharmacy[33] (Price checked 18/5/2022) BNF British National Formulary Calculated average
Topical anti-inflammatory gels, creams, or sprays	£ 1.58	
Rubefacients: heat rubs, sprays, and gels	£ 1.76	
Paracetamol	£ 6.14	
Aspirin	£ 2.81	
Co-codamol e.g., Solpadine	£ 2.28	
Glucosamine and/or Chondroitin	£ 0.42	
Natural medicines (herbal remedies) e.g., Turmeric etc.	£ 1.07	
Others	£ 1.07	
Other Costs per person		
Non-NHS exercise cost	£ 31.57	Cooksey et al., 2015

Productivity losses

Productivity losses include the cost of absenteeism, presenteeism and staff turnover, as estimated for public and private sector by the Deloitte report[34] (Appendix 4) adjusted by the data on the employment status, the impact of axial SpA on employment of the patients and the gross medial wage per hour per gender (Tables 6, 7 & 8).

Table 6: Employment status

Employment	Percentage	Source
Full-time	0.352	NASS, 2016
Part-time	0.166	
No employment (in education)	0.008	
No employment (full-time parent)	0.020	
No employment (retired)	0.290	
No employment (due to health issues)	0.164	

Table 7: Impact of AS on employment

Impact of AS on Employment	Percentage	Source
No impact	0.086	NASS, 2016
Work fewer hours	0.098	
Go to work when not well	0.274	
Do less physical work	0.145	
Decreased job satisfaction	0.104	
Not preferred job	0.053	
Job not best use of skills	0.040	
Had to change occupation	0.082	
Left a job	0.119	

Table 8: Gross median wage (per hr)

Gross Median Wage (per hr)	Full-time	Part-time	Source
ALL	£15.65	£10.64	ONS[35]
Male	£16.25	£10.45	
Female	£14.87	£10.71	

HEC also considered the costs of early retirement percentages due to axial SpA for patients above and unpaid care assistance need percentage below the age of 50 years old, 64.9% and 30.4% respectively 14 (Table 9 & 10).

Table 9: Early retirement

Early Retirement	Value	Source
Patients granted early retirement	0.001	Cobilinschi et al., 2017[36]
Early retirement below 30 per delay period	0.068	
Early retirement 40-50 per delay period	0.298	
Early retirement above 50 per delay period	0.634	
Early retirement cost per patient per quarter	£ 2026.75	Cooksey et al., 2015

Table 10: Unpaid care

Unpaid Care	Value	Source
Cost of unpaid assistance at mean wage (3-month Age < 50)	£ 490.00	Cooksey et al., 2015[14]
Cost of unpaid assistance for health care visits at mean wage (3-month Age < 50)	£ 38.27	
Cost of unpaid assistance at mean wage (3-month Age > 50)	£ 1041.45	
Cost of unpaid assistance for health care visits at mean wage (3-month Age > 50)	£ 63.41	

UK Economy: Paying a high price

NASS

Delay to diagnosis of axial SpA costs the UK economy

£18.7 billion

per year

#WaitingCosts

8.5 Years to diagnosis is NOT OK. Time to act.

Average time to diagnosis from symptom onset is **8.5 years**

26

Affects the **young** with average age of symptom onset of **26**

£187k

Waiting for an axial SpA diagnosis costs each person an average of **£187k**

One year costs less...

A Gold Standard time to diagnosis would save the UK economy

£167k

per person

www.actonaxialspa.com

Funded by: UCB Inspired by patients. Driven by science.

In partnership with: NHS Royal United Hospitals Bath NHS Foundation Trust; NHS Norfolk and Norwich University Hospitals NHS Foundation Trust

act on Axial SpA

Results

Cost of delayed diagnosis deterministic and probabilistic results

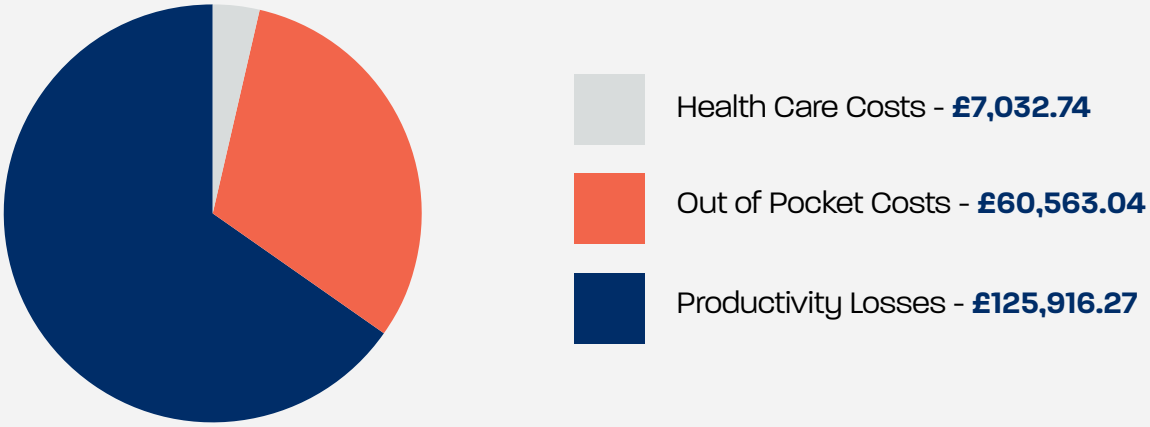
Mixed Cohort (based on NG65 model parameters around presentation to health care and diagnosis)

Based on a mixed cohort of people assumed to be living with axial SpA, with an onset of the symptoms at the age of 26, a diagnostic sensitivity and specificity based on Van Hoeven (2015)[37] >=1.0 and productivity losses based on the average presenteeism, absenteeism and staff turnover cost of both public and private sector (Appendix 4 - Presenteeism Absenteeism and Turnover per employee per sector and per region) the model predicts that the cumulative costs for a delayed diagnosis of 8.5 years are £193,512. Table 11 presents the breakdown of these cost to health care costs, out of pocket expenses and productivity losses.

Table 11: Deterministic costs

Cost Category	Deterministic Costs
Health Care Costs	£ 7,032.74
Out of Pocket Costs	£ 60,563.04
Productivity Losses	£ 125,916.27
Total	£ 193,512.04

Figure 2 : Deterministic results per cost category



As it shown in Figure 2 the productivity losses account for the 65.18% of the total costs followed by the out-of-pocket expenses which account for the 31.16%, almost a third of the total expenditure.

To quantify the level of confidence in the output of the analysis, in relation to uncertainty in the model inputs and increase the robustness of the outcome we have implemented a Probabilistic Sensitivity Analysis (PSA) in accordance with the NICE standard of health economics evaluation[19,38]. PSA is a technique used in economic modelling that allows the quantification of the level of confidence in the output of the analysis, in relation to uncertainty in the model inputs. There is usually uncertainty associated with input parameter values of an economic model, which may have been derived from clinical trials, observational studies or in some cases expert opinion. In the probabilistic analysis, these parameters are represented as distributions around the point estimate instead of a single value as in deterministic analysis, which can be summarised using a few parameters (such as mean and standard deviation for a normal distribution). Different distributions are used as more appropriate for different types of variable metrics supported by evidence from source studies and a set of input parameter values is drawn by random sampling from each distribution, and the model is 'run' many times (typically 1,000 to 10,000) to generate outputs which can be stored and analysed. Table 12 presents the distributions that we have used for different variables.

Table 12: Distribution per variable metric

Variable	Distribution
Probabilities	BETA
Population Proportions	DIRICHLET (multivariate generalization of the beta distribution)
Costs	GAMMA
Mortality Rate and Medical Visits	LOGNORMAL

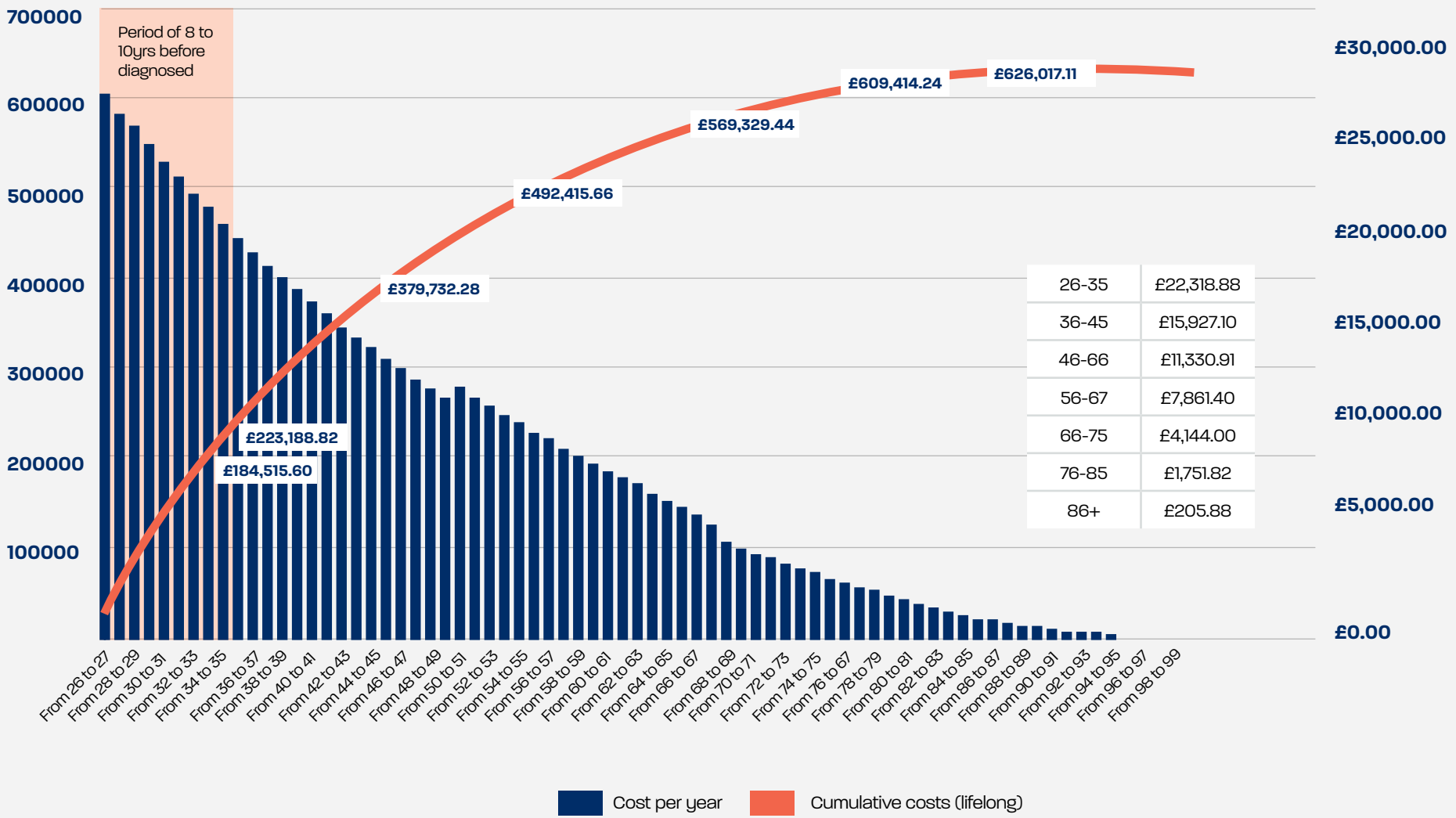
The outputs of probabilistic sensitivity analysis are consistent with the deterministic base case (Table 11) with the average cumulative cost per patient of 1000 model iterations to be £196,565.89 with a 95% confidence interval (CI) between £108,354.71 and £313,670.53. Figure 3 presents the lifelong per year costs, the cumulative costs as well an average calculation of the cost per year per decade of patients' age.

The cost per year decreases as more people from the initial cohort/cycle get diagnosed with time thus exiting the model.

Table 13: Probabilistic results

Cumulative Costs Accrued (8.5 years delay)				
	Deterministic	**Probabilistic**	**LCI (95%)**	**UCI (95%)**
Health Care Costs	£ 7,032.74	£7,003.98	£5,455.21	£9,387.00
Out of Pocket Costs	£ 60,563.04	£68,467.18	£35,773.27	£115,306.74
Productivity Losses	£ 125,916.27	£119,929.82	£67,126.22	£188,976.78
Total	**£ 193,512.04**	**£195,400.99**	**£108,354.71**	**£313,670.53**

Figure 3: Cost per year and cumulative costs (lifelong)



The cost per year of delayed diagnosis for the whole UK assuming axial SpA prevalence lies between 0.3% and 1.8%[39] yet no such data exist for axial spondyloarthritis. Following clinical review, it was agreed to use the 0.3% prevalence for the results and as such the other prevalence results were used for comparison only.

Table 14: Nationwide costs based on axial SpA prevalence of 0.3%

Total Cost (Prevalence 0.3%)	Model	NASS Estimation (UK)*	Model Prevalence (UK)**
Deterministic	£23,104.17	£4,236,794,775.00	£3,115,805,703.35
Probabilistic	£24,025.06	£4,405,665,904.58	£3,239,996,195.59
LCI	£14,568.52	£2,671,545,836.70	£1,964,696,945.87
UCI	£36,950.02	£6,775,818,896.15	£4,983,044,089.37

% remaining undiagnosed per year 0.834
***NASS Estimation** 220,000 patients
****UK Adult Population (2022)** 53,930,490

Table 15: Nationwide costs based on axial SpA prevalence of 1.8%

Total Cost (Prevalence 1.8%)	Model	NASS Estimation (UK)*	Model Prevalence (UK)**
Deterministic	£23,104.17	£4,236,794,775.00	£18,694,834,220.08
Probabilistic	£24,025.06	£4,405,665,904.58	£19,439,977,173.56
LCI	£14,568.52	£2,671,545,836.70	£11,788,181,675.23
UCI	£36,950.02	£6,775,818,896.15	£29,898,264,536.23

% remaining undiagnosed per year 0.834
***NASS Estimation** 220,000 patients
****UK Adult Population (2022)** 53,930,490

Male cohort (based on NASS 2016 parameters around presentation to health care and diagnosis)

Based on a male cohort of people which a priori we consider as people living with axial SpA, with an onset of the symptoms at the age of 26, a diagnostic sensitivity and specificity based on Van Hoeven[40] >=1.0 and productivity losses based on the average presenteeism, absenteeism and staff turnover cost of both public and private sector, the model predicts that the cumulative costs for a delayed diagnosis of 8.5 years are £187,298.36. Table 16 presents the breakdown of these cost to health care costs, out of pocket expenses and productivity losses.

Table 16: Deterministic costs

Cost Category	Deterministic Costs
Health Care Costs	£7,815.52
Out of Pocket Costs	£53,051.81
Productivity Losses	£126,431.03
Total	£187,298.36

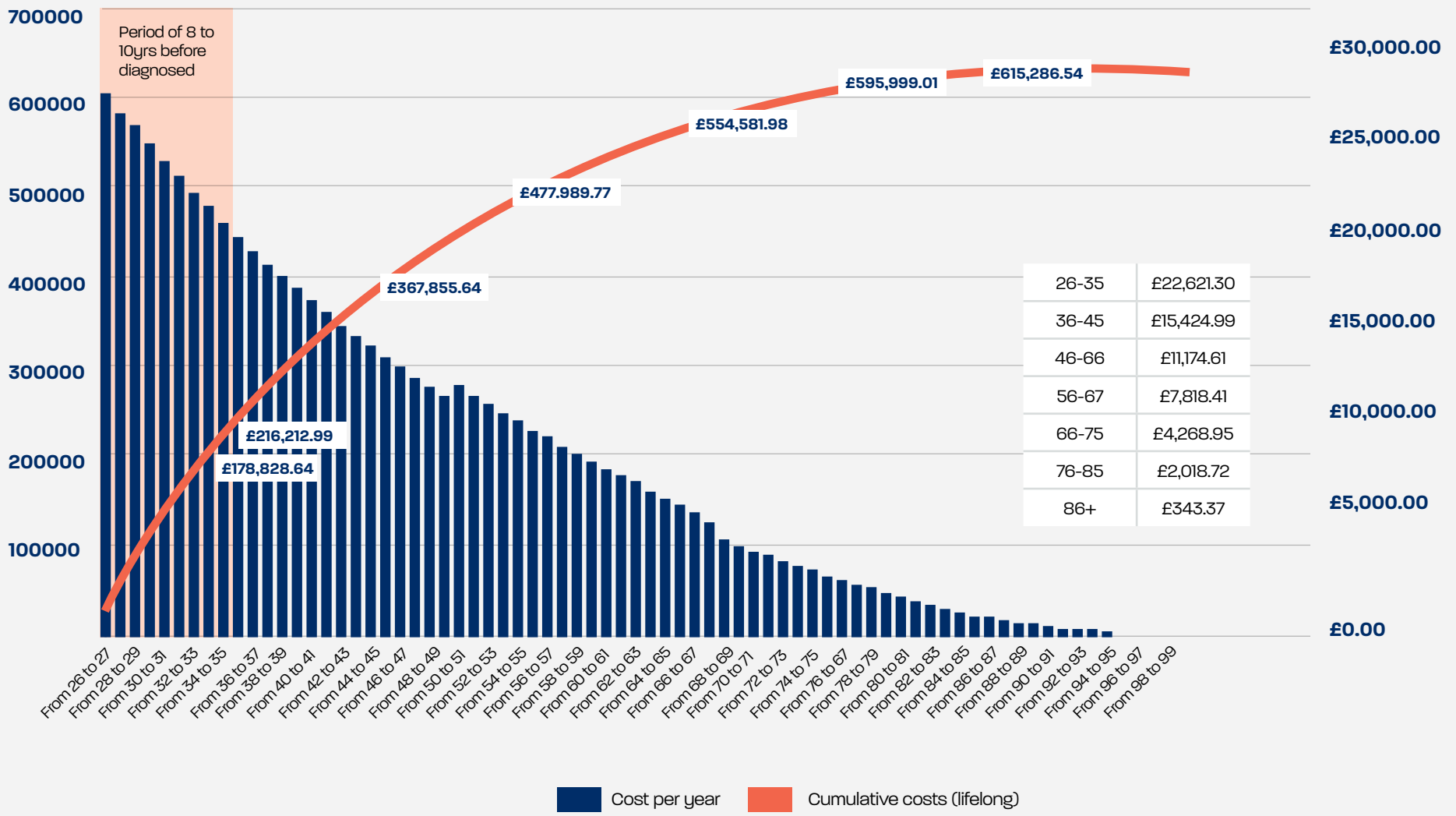
As is shown in Figure 2 the productivity losses account for the 67.50% of the total costs followed by the out-of-pocket expenses which account for the 28.32%, almost a third of the total expenditure.

The outputs of probabilistic sensitivity analysis are consistent with the deterministic base case (Table 17) with the average cumulative cost per patient of 1000 model iterations to be £181,410.04 with a 95% confidence interval (CI) between £99,392.79 and £295,924.63. Figure 4 presents the lifelong annual costs, the cumulative costs as well an average calculation of the cost per year per decade of patients' age. The costs per year are decreasing as more people from the initial are getting diagnosed a time passes and thus, they exit the model.

Table 17: Probabilistic results

Cumulative Costs Accrued (8.5 years delay)				
	Deterministic	Probabilistic	LCI (95%)	UCI (95%)
Health Care Costs	£7,775.60	£7,812.16	£5,373.88	£11,490.44
Out of Pocket Costs	£53,255.48	£55,814.57	£25,151.42	£98,164.18
Productivity Losses	£126,431.03	£121,778.53	£68,867.49	£186,270.02
Total	£187,462.11	£185,405.25	£99,392.79	£295,924.63

Figure 4: Male cohort cost per year and cumulative costs (lifelong)



Extrapolating the results based on the cost per year of delayed diagnosis for the whole UK assuming axial SpA prevalence around between 0.3% and 1.8%[39]yet no such data exist for axial spondyloarthritis.

Table 18: Nationwide costs based on axial SpA prevalence of 0.3%

Total Cost (Prevalence 0.3%)	Model	NASS Estimation (UK)*	Model Prevalence (UK)**
Deterministic	£22,373.47	£4,102,800,657.03	£1,474,770,360.96
Probabilistic	£22,821.07	£4,184,880,613.10	£1,504,274,374.58
LCI	£13,388.65	£2,455,183,100.35	£882,526,734.74
UCI	£35,009.15	£6,419,906,933.51	£2,307,664,753.21

% remaining undiagnosed per year 0.834
***NASS Estimation** 220,000 patients
****UK Male Population (2022)** 26,360,000

Table 19: Nationwide costs based on axial SpA prevalence of 1.8%

Total Cost (Prevalence 1.8%)	Model	NASS Estimation (UK)*	Model Prevalence (UK)**
Deterministic	£22,373.47	£4,102,800,657.03	£8,848,622,165.75
Probabilistic	£22,821.07	£4,184,880,613.10	£9,025,646,247.45
LCI	£13,388.65	£2,455,183,100.35	£5,295,160,408.42
UCI	£35,009.15	£6,419,906,933.51	£13,845,988,519.25

% remaining undiagnosed per year 0.834
***NASS Estimation** 220,000 patients
****UK Male Population (2022)** 26,360,000

Female cohort (based on NASS 2016 parameters around presentation to health care and diagnosis)

Based on a female cohort of people which a priori we consider as people living with axial SpA, with an onset of the symptoms at the age of 26, a diagnostic sensitivity and specificity based on Van Hoeven (2015)[40] >=1.0 and productivity losses based on the average presenteeism, absenteeism and staff turnover cost of both public and private sector, the model predicts that the cumulative costs for a delayed diagnosis of 8.5 years are £182,960.47.

Table 20 presents the breakdown of these cost to health care costs, out of pocket expenses and productivity losses.

Table 20: Deterministic costs

Cost Category	Deterministic Costs
Health Care Costs	£8,556.80
Out of Pocket Costs	£54,734.77
Productivity Losses	£119,668.90
Total	£182,960.47

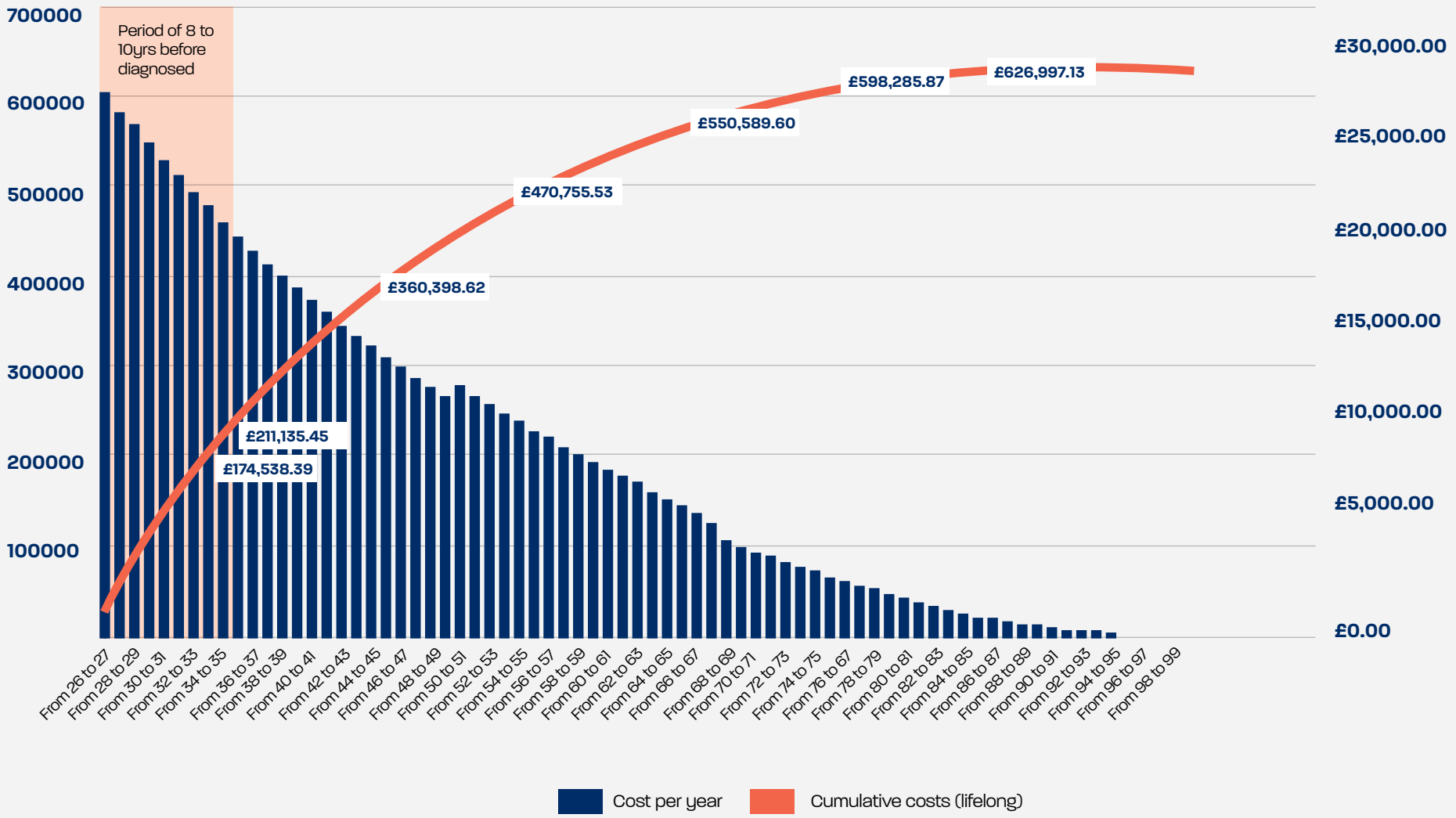
As it shown in Figure 2 the productivity losses account for the 65.46% of the total costs followed by the out-of-pocket expenses which account for the 29.8%, almost a third of the total expenditure.

The outputs of probabilistic sensitivity analysis are consistent with the deterministic base case (Table 21) with the average cumulative cost per patient of 1000 model iterations to be £181,410.04 with a 95% confidence interval (CI) between £96,493.20 and £296,352.44. Figure 5 presents the lifelong per year costs, the cumulative costs as well an average calculation of the cost per year per decade of patients' age. The costs per year are decreasing as more people from the initial are getting diagnosed a time passes and thus, they exit the model.

Table 21: Probabilistic results

Cumulative Costs Accrued (8.5 years delay)				
	Deterministic	Probabilistic	LCI (95%)	UCI (95%)
Health Care Costs	£8,556.80	£8,571.38	£6,268.82	£11,981.16
Out of Pocket Costs	£54,734.77	£58,650.46	£26,960.32	£106,102.19
Productivity Losses	£119,668.90	£115,039.41	£63,264.07	£178,269.09
Total	£182,960.47	£182,261.25	£96,493.20	£296,352.44

Figure 5: Female cohort cost per year and cumulative costs (lifelong)



Extrapolating the results based on the cost per year of delayed diagnosis for the whole UK assuming an axial SpA prevalence around between 0.3% and 1.8%[39]yet no such data exist for axial spondyloarthritis.

Table 22: Nationwide costs based on axial SpA prevalence of 0.3%

Total Cost (Prevalence 0.3%)	Model	NASS Estimation (UK)*	Model Prevalence (UK)**
Deterministic	£21,837.84	£4,004,577,543.93	£1,475,993,810.60
Probabilistic	£22,449.71	£4,116,781,419.31	£1,517,349,540.08
LCI	£13,384.42	£2,454,407,850.83	£904,637,444.72
UCI	£34,869.28	£6,394,256,987.73	£2,356,773,875.33

% remaining undiagnosed per year 0.834
***NASS Estimation** 220,000 patients
****UK Female Population (2022)** 27,028,955

Table 23: Nationwide costs based on axial SpA prevalence of 1.8%

Total Cost (Prevalence 1.8%)	Model	NASS Estimation (UK)*	Model Prevalence (UK)**
Deterministic	£21,837.84	£4,004,577,543.93	£8,855,962,863.60
Probabilistic	£22,449.71	£4,116,781,419.31	£9,104,097,240.47
LCI	£13,384.42	£2,454,407,850.83	£5,427,824,668.29
UCI	£34,869.28	£6,394,256,987.73	£14,140,643,251.98

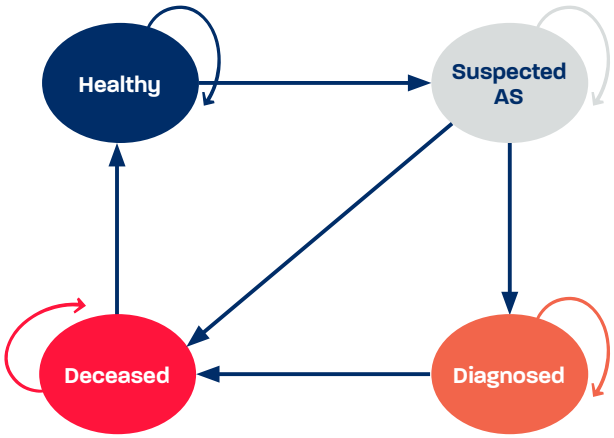
% remaining undiagnosed per year 0.834
***NASS Estimation** 220,000 patients
****UK Female Population (2022)** 27,028,955

Discussion

Apart from calculating the costs associated with delayed diagnosis of axial SpA, the model can be used as a predictive and planning tool for policy makers. This will help to understand and monitor health needs and the related costs of current and future axial SpA cases in the general population; based on the prevalence of axial SpA or on the sensitivity and specificity of various diagnostic strategies.

In this case the model schema changes to represent that we start with a healthy cohort and the transition stages are represented in Figure 6. This approach is useful for health care policy makers to examine the impact of the condition but due to the small prevalence of the condition the starting point from a cohort that we a priori consider that it suffers from axial SpA will provide more accurate results.

Figure 6: Healthy cohort model schema



Study limitations

Our efforts were focused on providing an accurate as possible calculation of the costs of delayed diagnosis of axial SpA. There are some limitations in the study however that can be addressed in future research. These limitations include:

- Assumptions regarding the yearly prevalence of co-morbidities. Attempts made to address this from data from the pragmatic literature review and experts' opinion expressed during the interview. We adhered to a conservative approach with an assumed incidence per year of co-morbidities among a proportion of the population
- Large discrepancies in prevalence and health care visits data reported in literature. To address this issue, we consulted with experts and as evident in the results of this report we used multiple calculation showing the impact of a conservative and a more realistic prevalence estimate (0.3% vs 1.8%) of the nationwide expected costs
- Assumptions about the over-the-counter medication quantity per patient per year (maximum prescribed quantity used). Initially the BNF values were used but after consultation from medical experts we decided to follow the current market values, as being more realistic
- Assumption that frequency of OTC medication usage and visits to health professionals will be the same as those reported in the survey obtained from diagnosed people living with axial SpA
- Absenteeism, presenteeism and staff turnover were calculated based on the average yearly costs for employees in the public and private sector
- As the focus of this research was on the total costs accrued at a pre-diagnosis stage the calculations do not include any costs after the point of diagnosis.

Model strengths

HEC considered among other alternatives (decision tree model structure, hybrid model and discreet event simulation modelling) that a Markov Chain model process was the most effective in representing the NASS Act on Axial SpA campaign aiming to drive down the time to diagnosis. These models show all possible states as well as the transitions between the model stages in a transparent and intuitive manner. Markov models are accurate and efficient for modelling disease or process progression over time without over-complication[18]. They can be visually inspected for programming errors and tested straightforwardly for replication.

This is the first time a model has been created to encompass costs associated with delayed diagnosis, up to the point of diagnosis of axial SpA. Much of the previous research has covered medical costs and productivity losses of those diagnosed with axial SpA, thus missing out the costs accrued before diagnosis, that can have a large impact on individuals, their family and society. Apart from the costs calculation per year of delayed diagnosis the model can provide a planning tool to help monitor what is expected to happen if we follow a healthy population based on the prevalence of axial SpA.

An important finding is the gender differences in the costs incurred by people living with axial SpA before diagnosis. Men experience higher productivity loss, which may be due to the work and pay inequalities in the UK, or that women have caring duties during their mid-twenties. People living with axial SpA may need help to manage when they have a flare up, which might include childcare – resulting in "hidden" costs in the productivity losses for women. In addition, women incurred higher health care costs and out-of-pocket expenses. Delayed diagnosis in women, tend to be longer

than in men, mainly due to the complex presentation of symptoms[41], hence their visits to the GP and other medical services are likely to increase. In addition, research evidence shows women are more likely to try alternative medicines to relieve the symptoms[42].

This model considers all the potential productivity losses arising from the burden of the condition like, absenteeism, presenteeism staff turnover and early retirement that were not included together in previous research. It is thus a more complete and comprehensive approach and a solid foundation for further future research.

Model limitations

The model was developed based on available data, which was mostly limited. For example, there are no national registers for people with axial SpA, as there are for people living with cancer. These would be helpful to accurately assess productivity losses, absenteeism, early retirement for people with axial SpA. Furthermore, frequency of use of over-the-counter medication was based on survey data from people with axial SpA. This might be an underestimation as people already diagnosed with axial SpA are on targeted treatment and are likely to use less over-the-counter pain medications. In addition, there are costs that are not easily valued and therefore, not included in the model. The stakeholders - people living with axial SpA interviewed for their insight into these costs, showed several examples of costs that are not available, such as care giver costs, costs to cover care that a person living axial SpA would normally have to spend.

A similar model was created for the use of chemotherapy in breast cancer[43]. This study showed that society costs amounted to over £141 million, more than half the total cost.

To address the parameter uncertainty, we have implemented a Probabilistic Sensitivity Analysis (PSA). Parameter uncertainty is defined as the uncertainty in the estimates of different inputs such costs and probabilities, and alternatively can be referred as the sampling variation in the input parameters of the model. As it was afore mentioned, Probabilistic Sensitivity Analysis (PSA) is one of the most common approaches to characterising parameter uncertainty and to show how uncertainty in input parameters influence the key outputs of the economic evaluation.

Future research

A systematic literature review, if one could have been in the scope of the budget, would have been useful but we are not convinced it would have changed our main findings and conclusion to any significant degree. However, there is a need for collection of more detailed records of societal costs that impact people living with axial SpA to be established. Such data would reduce the assumptions needed and, therefore, improve the predictiveness of the model. In addition, research needs to address the issues of psychological effects of such a long-term condition[11].

Although information gathered from the stakeholders, especially those living with axial SpA, was not used in the model, the experiences of these four people, and other research, raised questions on the assumption of symptoms beginning in the mid-twenties. Symptoms beginning in childhood and teenage years would further increase the burden on those living with axial SpA and their families. There may be also educational needs and costs[9] to factor into any future model and extension of the health care model may show that earlier interventions may reduce societal and individual costs across the life course. Further research is needed to assess the issues presented by children and women to develop better diagnostics and reduce the delays to diagnosis[6–8,17].

Concluding remarks

Delayed diagnosis of axial SpA carries significant societal costs due to the productivity losses. The estimated productivity costs for women are likely to be conservative. These costs when added to those once a diagnosis has been made, would be considerable. Health care costs are also substantial, both before and after diagnosis, and exactly what a delayed diagnosis "costs" in terms of increased and more invasive treatments is yet to be researched. In addition, the out-of-pocket costs for people living with axial SpA before diagnosis are also considerable, and carries a large burden once added to out-of-pocket expenses post diagnosis.

To conclude, the results show that the early diagnosis of axial SpA can significantly reduce the financial burden for the patients (out of pocket expenses) and the society (productivity losses). These savings also could offset the cost of treatment as they are of the same magnitude and in some cases significantly higher[3].

There is a further need for detailed records of societal costs that impact on people living with axial SpA to be collated. Such data would reduce the assumptions needed and, therefore, improve the predictiveness of the model.

8.5 Years to diagnosis of axial SpA is too long.

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Appendices

1. Interview guide – patients

The National Axial Spondyloarthritis Society (NASS) has asked the Health Economics Consulting- (HEC) from the University of East Anglia to model the health and societal costs of delayed diagnosis of this condition. We thank you for agreeing to help us.

We have looked at the research and drawn out what we think needs to be included in the model, but we need to make sure the information is correct and that we have covered everything.

All the information you provide will only be seen by the research team at UEA and used to develop the cost model. However, would you agree to us using anonymised quotes in the report, conference presentation and publication in a research journal?

Please be aware that you can refuse to answer any question and can withdraw from the interview at any time. Are you happy to proceed?

1. When do you think your symptoms for axial SpA started?
2. Could you describe them? (Back pain/sexual/urinary/psoriasis/bowel/ psychological)
3. How were your symptoms managed in the interim?

- pain medications
- exercise
- physiotherapy

4. When did you receive a diagnosis?
5. How long did it take to get a diagnosis?
6. How many years have you spent in self-management?
7. How many health care appointments (GP, hospital) did you have before getting the diagnosis?
8. How many specialties were you referred to before you were finally diagnosed?

   - What specialties were you referred to?

- What did this mean in terms of:

  - Misdiagnoses
  - Time off work
  - Travel costs
  - Prescription costs - number of prescriptions per year
  - Any other costs – appliances, complementary therapies, exercise

- How has AS affected:

  - Your daily living – help paid/unpaid
  - Work – did you change your job
  - Sick leave
  - Family life – childcare
  - Income
  - Retirement

- Do you feel you have any long-term health problems possibly due to delayed diagnosis from AS?

  - Spine/limbs
  - CVD

Can you think of anything else to add to the model? Thank you for the information – would you be willing to help further by checking that we have covered all costs?

2. Focus group guide – clinicians

The National Axial Spondyloarthritis Society (NASS) has asked Health Economics Consulting (HEC) from the University of East Anglia to model the health and societal costs of delayed diagnosis of axial spondyloarthritis (axial SpA). We thank you for agreeing to help us.

We have looked at the research and drawn out what we think needs to be included in the model, but we need to make sure the information is correct and that we have covered everything.

All the information you provide will only be seen by the research team at UEA and used to develop the cost model. However, with your permission we would like to use anonymised quotes in the report, conference presentation and publication in a research journal - Y/N

Housekeeping: confidentiality, one person to speak at any time

Please introduce yourselves with your name, job title and your main interest in axial SpA

- **We want to explore the patient journey to diagnosis**
  - How is axial SpA diagnosed?
  - Do you see any differences in presentation of axial SpA in females?
  - How would you approach diagnosing axial SpA in people of different ages?
  - What are the common prescribed drugs used for treatment prior to diagnosis?

- **How many GP/hospital appointments are they likely to have before a diagnosis is made?**
  - At each point of NHS service
  - How long does it take to move through the system?
  - Reasons for any delays – apart from covid – costs?
  - ED attendance
  - Staff involved – NHS costs
  - Patient costs – travel, prescription
  - Sick leave, changes in work/retirement/ lifestyle

- **What are is the likelihood of long-term physical health problems due to delayed diagnosis?**
  - Long-term health costs
  - Are there any data sets that would help us develop the economic model?

3. Disease-related parameters model inputs

Delay Between Development of Symptoms and Presentation to NHS		
Proportion of People Presenting in Each Period		
0-3 months	0.240	NICE NG65 Model
3-6 months	0.122	
6 months - 1 year	0.187	
1 year - 5 years	0.237	
5 years +	0.214	
Proportion of People Presenting in Each Period		
0-3 months	0.091	NICE NG65 Model
3-6 months	0.105	
6 months - 1 year	0.107	
1 year - 3 years	0.158	
3 year - 5 years	0.080	
5 year - 7 years	0.066	
7 year - 10 years	0.087	
10 years +	0.306	
Diagnostic Strategy Sensitivity and Specificity		
Van Hoeven (2015) >=1.0 (Sens)	0.926	Van Hoeven et al., 2015b[40]
Van Hoeven (2015) >=1.0 (Spec)	0.390	
Van Hoeven (2015) >=1.5 (Sens)	0.747	
Van Hoeven (2015) >=1.5 (Spec)	0.576	
Van Hoeven (2015) >=2.0 (Sens)	0.411	
Van Hoeven (2015) >=2.0 (Spec)	0.824	
Van Hoeven (2015) >=2.5 (Sens)	0.284	
Van Hoeven (2015) >=2.5 (Spec)	0.882	

Diagnostic Strategy Sensitivity and Specificity		
Van Hoeven (ASAS) >=1 (Sens)	0.997	
Van Hoeven (ASAS) >=1 (Spec)	0.186	
Van Hoeven (ASAS) >=2 (Sens)	0.997	
Van Hoeven (ASAS) >=2 (Spec)	0.601	
Van Hoeven (ASAS) >=3 (Sens)	0.669	
Van Hoeven (ASAS) >=3 (Spec)	0.864	
Van Hoeven (ASAS) >=4 (Sens)	0.304	
Van Hoeven (ASAS) >=4 (Spec)	0.964	
Van Hoeven (ASAS) >=5 (Sens)	0.094	Van Hoeven et al., 2015a[37]
Van Hoeven (ASAS) >=5 (Spec)	0.988	
Van Hoeven (ASAS) >=6 (Sens)	0.028	
Van Hoeven (ASAS) >=6 (Spec)	0.996	
Van Hoeven (SSB27) >=1 (Sens)	0.997	
Van Hoeven (SSB27) >=1 (Spec)	0.289	
Van Hoeven (SSB27) >=2 (Sens)	0.641	
Van Hoeven (SSB27) >=2 (Spec)	0.661	
Van Hoeven (SSB27) >=3 (Sens)	0.271	

Diagnostic Strategy Sensitivity and Specificity		
Van Hoeven (SSB27) >=3 (Spec)	0.889	
Braun (2013): >=1 (Sens)	0.991	
Braun (2013): >=1 (Spec)	0.026	
Braun (2013): >=2 (Sens)	0.972	
Braun (2013): >=2 (Spec)	0.073	
Braun (2013): >=3 (Sens)	0.935	
Braun (2013): >=3 (Spec)	0.267	
Braun (2013): >=4 (Sens)	0.860	Braun et al., 2013[44]
Braun (2013): >=4 (Spec)	0.634	
Braun (2013): >=5 (Sens)	0.533	
Braun (2013): >=5 (Spec)	0.953	
Braun (2013): Buttock OR HLA B27 (Sens)	0.897	
Braun (2013): Buttock OR HLA B27 (Spec)	0.403	
Braun (2013): 2-step (Sens)	0.804	
Braun (2013): 2-step (Spec)	0.754	
Braun (2011) >=2 (Sens)	0.965	
Braun (2011) >=2 (Spec)	0.172	
Braun (2011) >=3 (Sens)	0.788	
Braun (2011) >=3 (Spec)	0.464	
Braun (2011) >=4 (Sens)	0.478	Braun et al., 2011[45]
Braun (2011) >=4 (Spec)	0.861	
HLA B27: alone (Sens)	0.683	
HLA B27: alone (Spec)	0.848	
“Refer everybody” (Sens)	1.000	
“Refer everybody” (Spec)	0.000	

4. Presenteeism absenteeism and turnover per employee per sector and per region

Presenteeism Absenteeism and Turnover per employee per sector	Cost	Source
Public sector weighted average	£1,716.00	Deloitte, 2020[34]
Private sector weighted average	£1,652.00	
Average cost per employee (public and private sector)	£1,684.00	
Finance insurance and real estate	£3,521.02	
Information & communication	£2,533.77	
Professional services	£2,404.63	
Transport, distribution, and storage	£2,302.70	
Retail and wholesale	£1,412.04	
Hotels, catering, and leisure	£785.00	
Other private services	£1,615.36	
Public administration, defense, social security	£2,176.22	
Health	£1,818.68	
Education	£1,487.82	
Other Public Services	£1,888.59	

Region	Absenteeism	Presenteeism	Staff Turnover	Source
London	£427.99	£1,685.27	£318.06	Deloitte, 2020
SouthWest	£323.39	£1,237.00	£226.27	
Yorkshire and the Humber	£293.51	£1,175.10	£233.74	
Scotland	£324.46	£1,146.28	£233.74	
South East	£289.24	£1,161.22	£228.40	
East	£314.85	£1,154.82	£195.32	
Wales	£296.71	£1,138.81	£226.27	
East Midlands	£287.10	£1,151.62	£209.19	
North East	£305.25	£1,118.53	£209.19	
North West	£311.65	£1,095.05	£185.71	
West Midlands	£306.32	£1,086.51	£181.44	

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