ORIGINAL RESEARCH



Economic Burden of Itch-Related Sleep Loss in Moderate-to-Severe Atopic Dermatitis in the United Kingdom

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ABSTRACT

Introduction: Atopic dermatitis is associated with intense itch, which has been shown to cause sleep disruption that significantly impacts the lives of patients with atopic dermatitis. Despite this, little is known about its burden to the healthcare system and society. This study aimed to quantify the economic burden of itch-related sleep loss in moderate-to-severe atopic dermatitis in the UK.

Methods: A literature-based decision-analytic model was developed from a healthcare payer and societal perspective. The model quantifies the economic burden by linking the severity of itch to the number of days of sleep disruption. The model captures the direct costs of health-care resource utilization and treatment alongside the indirect costs of productivity loss from absenteeism and presenteeism at work over a 5-year time horizon. The patient population considered was patients aged \geq 15 years with

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A. J. Hirst · A. M. Fox · A. K. Suokas · Y. Yi Adelphi Values PROVE, Cheshire, England, UK moderate-to-severe atopic dermatitis and itchrelated sleep disruption.

Results: The model estimated that itch-related sleep disruption as a result of moderate-to-severe atopic dermatitis would affect an average of 821,142 people over the time horizon (2022 to 2026). This translates into an average net economic burden of £3.8 billion (£4687 per patient), with an average of 172 million days being affected by sleep disruption per year in the UK. The greatest contributor to the annual average net economic burden was productivity loss from absenteeism and presenteeism, each accounting for 34%. The direct costs (treatment costs and healthcare resource use) accounted for 32% of the net economic burden. The results showed a high and gradually increasing economic burden over the 5-year time horizon. Conclusions: Sleep disruption has a high eco-

nomic burden and reducing itch may provide substantial direct and indirect savings. Quantifying the economic burden of itch-related sleep loss may provide support for analyses to inform public health policies for treatment of atopic dermatitis, particularly within the moderate-tosevere level.

Keywords: Atopic dermatitis; Itch-related sleep disruption; Cost-of-illness model; Burden of disease; Work impairment

Key Summary Points

Why carry out this study?

Atopic dermatitis (AD) is associated with intense itch, which has been shown to cause sleep disruption that significantly impacts the daily lives of patients with AD.

Despite itch-related sleep disruption significantly impacting the daily lives of patients with AD, little is known about its burden to the healthcare system and the society.

This analysis quantified the economic burden of itch-related sleep loss in moderate-to-severe AD in the UK.

What was learned from this study?

The model estimated that itch-related sleep disruption as a result of moderate-tosevere AD would affect an average of 821,142 people between 2022 and 2026. This translates into an average economic burden of £4687 per patient.

Sleep disruption has a high economic burden and reducing itch may provide substantial direct and indirect savings.

INTRODUCTION

Atopic dermatitis (AD) is a chronic skin condition characterized by erythema, intense itching and dry, cracked, scaly skin in the folds of joints, back of the hands or scalp [1]. The condition usually begins in early infancy, with a prevalence of 11–20% in children in the UK and will often disappear before adolescence [2]. However, more recent evidence shows that, in some patients, the condition persists into adulthood, estimated to affect between 5 and 10% of all adults [2]. AD is categorized by severity as mild, moderate or severe, and the prevalence of moderate-to-severe AD (M-S AD) is estimated at 61% in the UK [3].

AD is associated with intense itch which can cause sleep disruption [4, 5]. Itch is experienced by patients with AD of all grades of severity [6], but patients with M-S AD may suffer more severe symptoms and experience inadequate treatment response and problems with dose optimization in the longer term [7]. Despite promising new treatments, itch is still the most burdensome symptom of AD [6]. Sleep disruption has been shown to have both short- and long-term health impacts, with short-term impacts ranging from headaches and abdominal pains to psychosocial issues such as emotional distress and memory and performance deficits [8]. The long-term impact has been shown to include increased risk of physical health complications including cardiovascular and metabolic disorders as well as mental disorders such as depression and anxiety [8, 9].

Despite itch-related sleep disruption significantly impacting the daily lives of patients with AD, little is known about its burden to the healthcare system or society. A previous study using the National Health and Wellness Survey (NHWS) estimated the economic and psychosocial burden of patients with M-S AD in the UK to be between £6500-£13,700 per patient in 2017 [4]. However, this study did not quantify the impact of sleep disruption within the reported economic burden, despite just over 50% of the UK sample reporting sleep difficulties as a result of M-S AD [4]. Therefore, it is important to understand the economic burden of itch-related sleep loss to support decisionmaking in AD, particularly within the M-S level. To the best of the authors' knowledge, no recent UK-based assessment has been performed to quantify the economic burden of itch-related sleep disruption in patients with M-S AD. Therefore, a de novo economic model has been developed to assess the burden of this important health problem.

The primary objective of the model is to quantify the economic burden of itch-related sleep loss in M-S AD in the UK. To do so, the model compared the total costs of patients with M-S AD who experience itch and sleep disruption to a hypothetical control group that do not experience itch or sleep disruption.

METHODS

A literature-based decision analytic model was developed in Microsoft[®] Excel from a UK healthcare payer and societal perspective. The model captures the direct costs of healthcare resource utilization (HCRU) and treatment alongside the indirect costs of productivity loss from absenteeism and presenteeism at work over a 5-year time horizon.

Patients

The model stratified the M-S AD population by prevalence of itch ranging from none to very severe, with the target population suffering from mild-to-severe itch and a hypothetical control group that did not suffer from itch, as shown in Fig. 1.

For example, in 2022, the model considered 841,698 patients aged \geq 15 with M-S AD; 96.8% (814,762) of patients had itch problems. Among them, patients with mild (175,073), moderate (298,802), severe (272,710) and very severe itch (68,177) were estimated based on the distribution of itch intensity Peak Pruritus Numerical Rating Scale (PP-NRS) points reported by Bruin-Weller et al. [7]. The associations among itch severity, sleep disruption severity [assessed by Patient Oriented Eczema Measure sleep item (POEM-SI) 0-4] and the number of days of sleep disruption in the past week (ranging from no days to every day) found by Gooderham et al. [11] were used to estimate number of patients with different severity of itch-related sleep disruption. For patients with mild, moderate and severe itch-related sleep disruption, resource utilisation, absenteeism and presenteeism were based on Girolomoni et al.[4].

A control group of the same 814,762 patients aged \geq 15 with M-S AD but without itch was assumed to assess the disease burden. Resource utilisation, absenteeism and presenteeism for patients with no sleep disruption were also based on Girolomoni et al.[4].

Model Structure

For patients with itch-related sleep problems, the model estimated the number of days affected by sleep disruption, the direct cost of treatment [drug therapy, ultraviolet (UV) light therapy and HCRU] and the indirect costs (absenteeism and presenteeism at work). The control group included the same cost categories but assumed that patients without itch-related sleep disruption did not receive any advanced drug therapy or UV light therapy for itch-related sleep problems. The model structure is presented in Fig. 2. The indirect cost of work-related impairment was calculated for the working age patients only.

The model assessed the net economic burden defined as the difference in the total costs between the two patient cohorts. The net economic burden was estimated based on the current treatment mix using a societal perspective comprising both direct and indirect costs. The model also included the flexibility to assess the net economic burden following a change in the future mix of treatments available for patients with M-S AD. Such change may occur when new therapies are made available for treating AD or when therapies become unavailable. Therefore, the ability to assess the impact of treatment mix changes is important for future research, and this feature is included in Fig. 2 for presentation purposes only.

MODEL INPUTS

Demographic, Epidemiological, Treatment and Cost Data

Age-stratified population data (Table 1) were sourced from the Organization for Economic Co-operation and Development (OECD) [10]. Prevalence data were retrieved from an international, cross-sectional, web-based survey, measuring AD severity using the Patient Oriented Eczema Measure (POEM) instrument [3, 10]. The M-S AD population was stratified by itch severity (from none to very severe) based on the Peak Pruritus Numerical Rating Scale (PP-NRS) obtained from the prospective

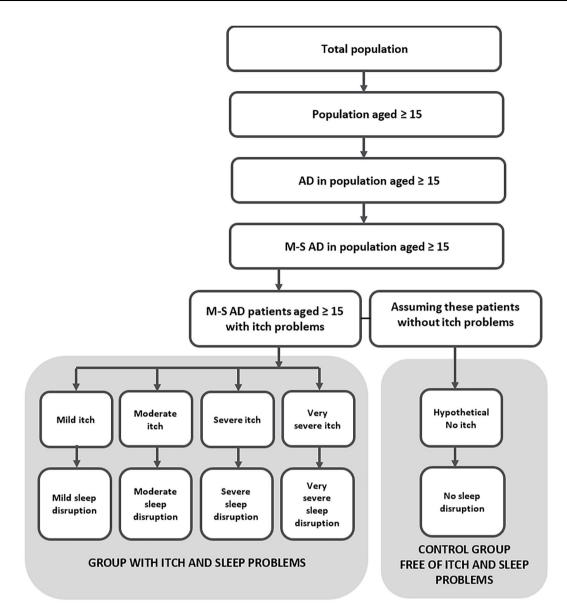


Fig. 1 Patient flow diagram. AD atopic dermatitis, M-S AD moderate-to-severe atopic dermatitis

observational European Prospective Observational Study in Patients Eligible for Systemic Therapy for Atopic Dermatitis (EUROSTAD) study [7]. The median days of sleep disruption, based on the POEM sleep item (POEM-SI) associated with each PP-NRS category, were obtained from a study by Gooderham et al.[11].

Treatment utilization (Table 1) was sourced from the EUROSTAD study of patients with M-S AD and concerned systemic and topical drugs and UV light therapy [7]. Within the model, treatment duration was assumed to be 1 year unless the therapy was approved for a shorter time period, which is often the case for managing flare-ups of AD. For drugs that are not currently approved for treatment of M-S AD in the UK and used off-label, the treatment schedule for similar indications such a psoriasis, per approved labelling, was used in the economic model.

The direct cost of treatments and HCRU (Table 1) were obtained from publicly available UK sources [12, 13]. The indirect cost of work impairment was estimated by calculating the

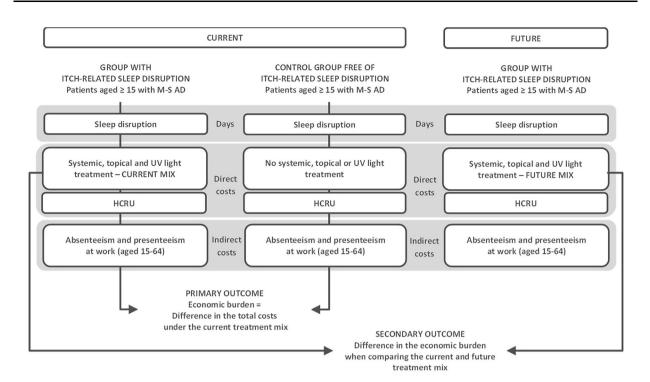


Fig. 2 Model structure. UV ultraviolet B, HCRU healthcare resource use, AD atopic dermatitis, M-S AD moderateto-severe atopic dermatitis

salary costs, equivalent of the percentage of work time affected by sleep disruption [4], based on the average annual salary sourced from the OECD [14]. All direct and indirect costs were inflated to 2022 prices and extrapolated to 2026 costs by adjusting for population growth and considering medical cost and wage inflation.

Full details including the treatment schedules and treatment costs are presented as supplementary material.

Linking Itch-Related Sleep Disruption with HCRU and Work Impairment

To link itch-related sleep disruption to HCRU and work impairment, data inputs were combined from different studies identified through a targeted literature review conducted during the conception of this project. The targeted literature review screened 500 articles which identified 19 papers relevant to the UK (Table 2) [4, 7, 11]. For example, the prevalence of itch, based on the PP-NRS, was linked to the severity of sleep disruption using the POEM sleep item scores through published estimates (Table 2) [7, 11]. This allowed the severity of sleep disruption to be linked to HCRU and work impairment [4]. The collated data were mapped to each patient within the model. For example, the Gooderham 2021[11] study (N = 391) was used to allocate a NTIS score to the AD groups in the Bruin-Weller 2021 [7] study (N = 308). The median NTIS score was then linked to the % of work impairment in the Gooderham 2021 [11] study. Following on from this, the data were then linked up with those from the Girolomoni 2021[4] study (*N* = 1014), which reported work productivity and healthcare resource use by selfreported sleep difficulties (none, mild, moderate and severe).

Sensitivity and Scenario Analysis

Deterministic one-way sensitivity analyses (SA) were performed by varying parameters in the base case by \pm 20%.

Three scenario analyses were carried out to explore key areas of uncertainty. The first

data inputs	
Parameter	Input values
Demographic data	
Total population [10]	67,844,183
Population aged 15 or over of total population [10]	81.4%
Percentage of working age of those aged 15 or over [10]	76.8%
Prevalence of AD [3]	2.5%
Prevalence of M-S AD [3]	61.0%
Average population growth rate 2023–2026 [10]	0.4%
Treatment mix and use for itch-rel	ated sleep loss
Patients receiving therapy [15]	8.0%
Systemic drug therapy [7]	92.9%
Dupilumab [7]	19.6%
Cyclosporine [7]	39.2%
Methotrexate [7]	23.1%
Corticosteroid* [7]	17.8%
Azathioprine [7]	5.6%
Topical drug therapy [7]	81.8%
Corticosteroid [‡] [7]	80.6% (203 patients out of 252)**
Emollient [§] [7]	48.0% (121 patients out of 252)**
Calcineurin inhibitor [¶] [7]	29.4% (74 patients out of 252)**
UV light therapy[7]	1.6%
HCRU costs	
Physician visit (outpatient) [12]	£133
Emergency care visit [12]	£149
Average length hospitalization [16]	£1,966
Salary data	
Annual average salary [14]	£39,163

Table 1 Summary of demographic, treatment use and	cost
data inputs	

Table 1 continued

Parameter	Input values
Population aged 15 or over of total population [10]	81.4%
<i>UV</i> ultraviolet B, <i>HCRU</i> healthe atopic dermatitis, <i>M-S AD</i> mod dermatitis *Systemic corticosteroid was assume based on NICE [17] [‡] Topical corticosteroid was assume based on NICE [17] [§] Emollient was assumed to be Avee based on NICE [16] [¶] Calcineurin inhibitor was assumed on NICE [16] **The percentage was re-calculated b patients who received topical drug	derate-to-severe atopic ned to be prednisolone d to be betamethasone no cream or equivalent to be tacrolimus based pased on the number of

explored the impact of excluding indirect costs to quantify the economic burden of itch-related sleep loss in M-S AD from the payers perspective. The second scenario excluded presenteeism from the indirect costs which assumed zero productivity from workers who were impaired by sleep disruption. The final scenario assessed the impact of lower HCRU by applying alternative data from a National Institute for Health and Care Excellence (NICE) (2018) health technology assessment (HTA) for dupilumab [18].

Ethical Approval

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Base Case Analysis

Results for the base case are presented in Table 3. The model estimated that itch-related sleep disruption as a result of M-S AD would affect an average of 821,142 people over the

Itch severity and score range [7] based on PP-NRS score	None (0)	Mild (≥ and < 4		Moderat and < 7)	•		ere (≥ 7 < 9)	Very severe (≥ 9)
Patients with M-S AD	3.2%	20.8%		35.5%		32.4	%	8.1%
Severity of sleep disruption due to itch [11]		None	* Mild*	Mode	rate*	Severe [†]	Very severe [†]
Median number of days with sleep disruption	in the p	oast week	0.0	1.5	3.5		5.5	7.0
Severity of sleep difficulty [4]	N	one*	Mil	d*	Moder	ate*	Sev	ere ^{e†}
HCRU in the past 6 months								
Number of physician visits	9.	2	10.0)	12.2		14.3	3
Number of emergency room visits	0.	6	0.6		0.7		1.1	
Number of hospitalizations	0.	4	0.5		0.5		0.4	
Work impairment in the past seven days								
Absenteeism (% of work time missed)	21	1.5%	23.0)%	25.4%		29.4	4%
Presenteeism (% of time at work affected)	45	5.5%	47.9	9%	55.9%		59.4	4%

Table 2 Linking itch-related sleep disruption to healthcare resource use and work impairment

HCRU healthcare resource utilization, *PP-NRS* Peak Pruritus-Numerical Rating Scale, *M-S AD* moderate-to-severe atopic dermatitis

*Categories None, Mild and Moderate for "sleep disruption" and "sleep difficulty" were assumed to match

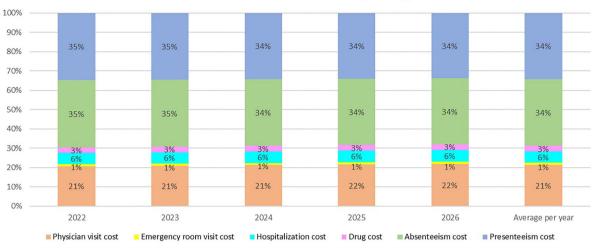
[†]Category "Severe" for "sleep difficulty" was assumed equivalent to the combined categories "Severe" and "Very severe" for "sleep disruption"

Burden of itch associated with sleep disturbance*	2022	2023	2024	2025	2026	Average burden per year
Number of M-S AD patients with itch	814,762	817,940	821,130	824,332	827,547	821,142
Total number of days with itch- related sleep disruption	170,849,217	171,515,529	172,184,439	172,855,959	173,530,097	172,187,048
Total costs for patients with itch- related sleep problems	£20,945,154,321	£21,725,890,486	£22,537,140,704	£23,380,163,966	£24,256,274,184	£22,568,924,732
Total costs for patients with no itch- related sleep problems	£17,386,665,127	£18,028,198,356	£18,694,496,651	£19,386,567,972	£20,105,463,663	£18,720,278,354
Total cost difference: net economic burden	£3,558,489,194	£3,697,692,130	£3,842,644,053	£3,993,595,993	£4,150,810,521	£3,848,646,378
Total cost difference per patient	£4,368	£4,521	£4,680	£4,845	£5,016	£4,687

Table 3 Economic burden of itch-related sleep disruption

M-S AD moderate-to-severe atopic dermatitis

*Results are presented as the average per year



Economic burden contributions by cost type

Fig. 3 Net economic burden by cost type

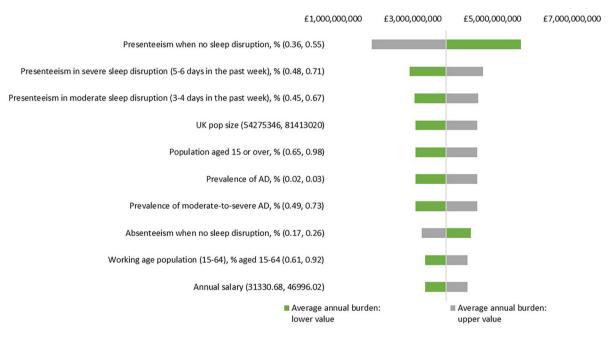


Fig. 4 Net economic burden in one-way sensitivity analyses. AD atopic dermatitis

5-year time horizon (2022 to 2026). This translates into an average net economic burden of £3.8B (£4687 per patient) from a societal perspective, with an average of 172 million days being affected by sleep disruption per year in the UK. The greatest contributor to the annual average net economic burden was productivity loss from absenteeism and presenteeism, each accounting for 34.0% (Fig. 3). This was followed by physician visit costs contributing to 21% of the average net economic burden and hospitalization costs at 6.0%. Drug costs and

Parameter	Average annual burden: lower input value	Average annual burden: upper input value
Presenteeism when no sleep disruption, % (0.36, 0.55)	£5,718,801,479	£1,978,491,277
Presenteeism in severe sleep disruption (5–6 days in the past week), % (0.48, 0.71)	£2,929,959,772	£4,767,332,984
Presenteeism in moderate sleep disruption (3–4 days in the past week), % (0.45, 0.67)	£3,047,890,374	£4,649,402,383
UK population size (54,275,346, 81,413,020)	£3,078,917,103	£4,618,375,654
Population aged 15 or over, % (0.65, 0.98)	£3,078,917,103	£4,618,375,654
Prevalence of AD, % (0.02, 0.03)	£3,078,917,103	£4,618,375,654
Prevalence of moderate-to-severe AD, % (0.49, 0.73)	£3,078,917,103	£4,618,375,654
Absenteeism when no sleep disruption, % (0.17, 0.26)	£4,462,170,348	£3,235,122,408
Working age population (15–64), % aged 15–64 (0.61, 0.92)	£3,319,567,296	£4,377,725,461
Annual salary (£31,330.68, £46,996.02)	£3,319,567,182	£4,377,725,291

Table 4 Average annual burden with the lower and upper value of the parameter based on the sensitivity analysis

AD atopic dermatitis

Table 5 Scenario analysis

Scenario	Average annual burden	% Change from base case burden
Base case	£3,848,646,378	0%
Healthcare system perspective (excluding presenteeism and absenteeism)	£1,203,250,965	- 69%
Indirect costs excluding presenteeism	£2,527,387,074	- 34%
Lower HCRU by applying alternative data from the NICE (2018) HTA for dupilumab [18]	£3,466,294,269	— 10%

HCRU healthcare resource use, *NICE* National Institute for Health and Care Excellence, *HTA* health technology assessment emergency visits were the lowest contributors at 3.0% and 1.0%, respectively. Overall, the indirect costs accounted for 68.0% and the direct costs for 32.0% of the net economic burden.

One-Way Sensitivity Analysis Results

One-way sensitivity analysis results are presented in Fig. 4 and Table 4 for the ten most impactful parameters. The results show that the net economic burden was most affected by productivity loss from presenteeism in both patient cohorts. Regarding the costs of presenteeism for patients with no itch-related sleep disruption, such results suggest that other types of health issues in M-S AD, such as pain, discomfort and mental health impacts, may cause problems. The net economic burden was also affected by the size of the population and prevalence of AD.

Scenario Analysis

Three scenarios were tested on the base case net economic burden and the results are presented in Table 5. Testing the model perspective and inclusion of presenteeism reduced the financial burden by 69% and 34% respectively. The third scenario showed when lower HCRU (aligned with data from NICE HTA for dupilumab [18]) was applied and, as a result, the net economic burden was reduced by 10%.

DISCUSSION

Context in the Real World

Itch-related sleep disruption represents a significant health burden in AD, yet little is known about the economic impact of this important comorbidity. This study is unique in that it is, to the researchers' knowledge, the first model to estimate the economic burden of itch-related sleep disruption in M-S AD in the UK. The purpose of the study was to quantify the incremental economic burden caused by itch-related sleep disruption in M-S AD in terms of days disrupted with sleep loss, the direct costs of treatment and healthcare resource utilization, and the indirect cost of absenteeism and presenteeism at work. The model measured the economic burden over a 5-year time horizon and assessed the costs adjusted for population growth and inflation.

The results showed a high and gradually increasing economic burden associated with itch-related sleep disruption in M-S AD over the 5-year time horizon, and the average annual net economic burden per patient was estimated at £4687. The indirect cost of presenteeism and absenteeism was the highest contributor (68%) to the net economic burden. The scenario analyses demonstrated the importance of model perspectives, assumptions and cost components in influencing the calculations.

Comparison with Other Studies

Evidence concerning the economic burden of M-S AD in the UK is limited. Only one contemporary economic assessment was identified in the mild-to-moderate AD population. Toron et al. (2021) reported the projected total drug and HCRU costs associated with 33,749 patients with mild-to-moderate AD were ϵ 294 million (this converts to £252 million) and the total productivity loss ϵ 1.3 billion (this converts to £1.1 billion) [19].

In comparison, the economic burden of itchrelated sleep disruption in 821,142 patients with M-S AD reported in the current study estimated the drug and HCRU costs as £4.4B (non-itch group £3.4B) and the productivity loss at £16.5B (non-itch group £14B) in 2022. This difference in cost could initially be attributed to the total number of patients; these higher costs can also be explained by differences in parameterization and cost calculations. First. the current study assessed a more severely affected patient population in terms of AD and itch-related sleep disruption, both of which were associated with higher treatment and HCRU use. For example, for physician visits, the current model used 9.2 to 14.3 visits over 6 months [4] compared to an average of 5.6 visits per year for mild-to-moderate patients in the Toron et al. (2021) publication [19]. Second, Toron et al. (2021) considered the employment rate in the UK while the current study valued productivity loss for all working age patients using the annual average salary [19]. This approach combines employment and use of average absenteeism and presenteeism. Taking this approach may be more reflective of the total population rather than the employed population as employment rate is implicitly captured.

Strengths and Limitations

The model has a strength of using publicly available data to estimate the direct and indirect cost burden of disease caused by sleep disruption which has not previously been estimated to the authors' knowledge. The literature used within the model was based on a targeted search of the literature. Furthermore, the model has the flexibility to be easily adapted to other countries or markets with the appropriate use of local data inputs and assumptions. Finally, the model allows for comprehensive sensitivity analyses, including scenarios based on changes in AD treatment options and mixes.

While using publicly available data is a key strength of the analysis, it also provides a key challenge. First, no published data were identified that could directly link itch and sleep in M-S AD to HCRU, treatment use and work productivity. Instead, the model was built by linking separate studies to establish these connections [4, 7, 11]. While this approach was novel, the studies differed in methodology and patient cohorts potentially introducing bias into the analysis. Second, there were data gaps in terms of treatment duration and dosing schedules for drugs that were used off-label. Finally, the model did not capture the impact of comorbidities known to be associated with sleep disruption, such as anxiety and depression, on HCRU and treatment use. Overall, building a de novo economic model with limited data was necessary to develop the model however may have resulted in bias being introduced in the economic burden. Given the limitations associated with the data, further research is recommended to advance the linking of itch-related sleep disruption in M-S AD and its impact on direct and indirect costs of illness.

CONCLUSION

A model was built to quantify the economic burden of itch-related sleep disruption in M-S AD in the UK. The results showed a high and gradually increasing economic burden over the 5-year time horizon. The greatest individual cost component was productivity loss due to absenteeism and presenteeism. The model perspective, assumptions, cost components and data sources influenced the magnitude of the economic burden. In conclusion, this economic model provides an estimate that shows the indirect cost associated with itch and resulting sleep disruption in patients with M-S AD carries a substantial financial burden. Quantifying the economic burden of itch-related sleep loss may provide support for analyses to inform public health policies for treatment of AD, particularly within the M-S level.

Author Contributions. All authors contributed to the study conception and design. Material preparation, data sourcing and analysis were performed by Alex Hirst, Aimée M Fox, Anu K Suokas and Yunni Yi. The first draft of the manuscript was written by Anu K Suokas and all authors commented on previous versions of the manuscript. Evangeline J Pierce, Russel T Burge, Alex J Hirst, Aimée M Fox, Anu K Suokas and Yunni Yi read and approved the final manuscript.

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Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Conflict of Interest. Adelphi Values PROVE were contracted by Eli Lilly to conduct and report this research. Evangeline J Pierce is an employee of Eli Lilly. Russel T Burge is an employee of Eli Lilly. Alex J Hirst, Aimée M Fox and Yunni Yi are employees of Adelphi Values PROVE. Anu K Suokas was affiliated to Adelphi Values PROVE at time of study and is now an employee of RJW&partners.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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