



# The personal burden for caregivers of children with phenylketonuria: A cross-sectional study investigating time burden and costs in the UK



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## ABSTRACT

**Introduction:** Management of phenylketonuria (PKU) is mainly achieved through strict dietary control that aims to limit the intake of phenylalanine (Phe). Adherence to this diet is burdensome due to the need for specially prepared low-Phe meals and regular monitoring of Phe concentrations. A UK cross-sectional study was conducted to identify the personal time and monetary burden associated with aspects of the PKU lifestyle for caregivers of children (aged <18 years) living with PKU.

**Methods:** Caregivers of pediatric patients with PKU attending one of four specialist metabolic centers in the UK were invited to participate in a questionnaire-based survey that evaluated different aspects of PKU management that could potentially present out-of-pocket costs (OOPCs) or time burden. Medical clinicians/dietitians provided patient information on PKU severity and an assessment of blood Phe control.

**Results:** The survey was completed by 114 caregivers of 106 children having mild or moderate ( $n = 45$ ; 39%) or classical ( $n = 60$ ; 53%) PKU (severity data missing for  $n = 1$ ), among whom 8 (8%) and 87 (82%) reported poorly controlled and controlled blood Phe status, respectively; Phe control data were missing for 11 children. Dietary management of PKU incurred a median time burden of >19 h per week. OOPCs were incurred via attendance at PKU events, PKU-related equipment, and extra holiday expenditure. 21% of caregivers reduced their working hours (median 18.5 h/week) to care for their child, with a further 24% leaving their paid jobs completely.

**Discussion and conclusions:** Dietary management of PKU is associated with a considerable time burden for caregivers of pediatric patients with PKU. A personal financial burden also arises from OOPCs and lost earnings.

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## 1. Introduction

Phenylketonuria (PKU) is an autosomal recessive disorder characterized by accumulation of phenylalanine (Phe) in blood and body fluids that is caused by defective Phe hydroxylase activity (PAH, EC 1.14.16.1) [1]. PAH deficiency is classified as classical PKU (Phe > 1200  $\mu\text{mol/L}$ ), mild PKU (Phe 600–1200  $\mu\text{mol/L}$ ) or mild hyperphenylalaninaemia (Phe < 600  $\mu\text{mol/L}$ ) [2]. The incidence of PKU varies according to ethnic background. In the UK, PKU affects about 1 in every 10,000 newborns of white European ancestry [3] with around 70 babies born with PKU annually, suggesting that over 6000 people in the UK have PKU.

If left untreated, the prolonged high Phe concentrations in the blood and tissue that can occur in classical PKU can result in severe cognitive

impairment, seizures, behavioral problems and features of autism [4]. Such irreversible complications can be avoided through early treatment with a low-Phe diet from the first few weeks after diagnosis [5,6] and throughout life [4,7–9]. Pharmacological treatments are also available and currently include the synthetic formulation of tetrahydrobiopterin ( $\text{BH}_4$ ), sapropterin dihydrochloride [10], and medical food or amino acid supplements, including formulations of large neutral amino acids such as tryptophan and tyrosine [11].

Dietary treatment of PKU is achieved via a low-Phe diet that severely restricts the intake of natural protein in order to achieve control of blood Phe concentrations [12,13]. The low-Phe diet includes food that is naturally low in protein, such as fruit, some vegetables, fats and oils, as well as specially formulated low-protein products, such as low-protein flour, pastas and bread. All patients on dietary treatment require Phe-free L-amino acids, usually supplemented with additional carbohydrate, with or without fat, vitamins and minerals [14]. Adherence to dietary treatment is essential, thus careful planning, dietary supervision and monitoring are required. Adherence to this treatment regimen is considered demanding [7] and includes sourcing and purchasing speciality foods, supervising the intake of Phe-free L-amino acid supplements,

*Abbreviations:* ACBS, Advisory Committee on Borderline Substances; DLA, Disability Living Allowance; NHS, National Health Service; NRES, NHS Research Ethics Committees; OOPC, out-of-pocket cost; PAH, phenylalanine hydroxylase; Phe, phenylalanine; PKU, phenylketonuria.

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planning daily Phe consumption, preparing low-Phe meals (often involving additional cooking), monitoring Phe intake, and attending clinic visits [15]. Blood tests are conducted by parents at home usually with the following frequency: weekly for children aged  $\leq 5$  years and between twice monthly and monthly for children  $\geq 6$  years [15]. Thus, the many aspects of PKU management appear time-consuming for caregivers who manage the PKU lifestyle on top of regular childcare. PKU has already been shown to impact a caregiver's life and even their ability to continue regular work responsibilities [16], with 11% of parental caregivers in one survey reporting they had to stop paid work and 20% reporting that they had to change jobs [17].

The cost of PKU to the National Health Service (NHS) is well documented; retrospective database analyses estimated that Phe-free L-amino acids and low-protein foods are responsible for around 60% and 10%, respectively, of the total NHS costs for managing a patient with PKU [5]. Appropriate reimbursement of special PKU dietary products and L-amino acids via subsidized Advisory Committee on Borderline Substances (ACBS) prescriptions and financial help schemes, such as the Disability Living Allowance (DLA), Carers Allowance and Family Fund, are important in helping to reduce the financial burden on caregivers. Fortunately, in the UK, many products are available on prescription (free for under 16 s) and the DLA is considered an essential income source for many families with a child with PKU [18].

Given that living with PKU impacts caregivers' lives and that the time-consuming nature of PKU remains unknown in a UK population, we conducted a cross-sectional study to quantify the personal time and monetary burden for caregivers of children (aged  $< 18$  years) living with PKU in the UK.

## 2. Methods

### 2.1. Study participants

This cross-sectional study was designed to assess the personal time burden and out-of-pocket-costs (OOPCs) for caregivers (usually parents) of children living with PKU. The study was conducted through four NHS metabolic care clinics in the UK. National ethics approval was obtained via the NHS Research Ethics Committees (NRES) and hospital research and development departments. One hundred and ninety-five caregivers were included via four NHS specialist metabolic dietitians from Birmingham Children's Hospital, the Bristol Royal Hospital for Children, St Luke's Hospital in Bradford, and Evelina Children's Hospital in London, between September 2012 and March 2013. Caregivers of early and continuously treated pediatric patients were invited to participate in this study, and informed parental consent was obtained. Children gave assent when their age and understanding was appropriate. Confidentiality was maintained by assigning numerical codes to individual patient data sets. Caregivers were asked to complete a questionnaire, and on its return a voucher worth £15 was sent.

### 2.2. Questionnaire items

The data were collected via a caregiver-reported questionnaire evaluating the different aspects of the PKU lifestyle that could potentially present an OOPC or a time burden to caregivers of pediatric PKU patients. The questionnaire was developed for use in two studies, one in The Netherlands, published in 2013 [19] and the current study in the UK population. In brief, the questionnaire was based on: a) the published literature on aspects of PKU management that may pose a financial or time burden on patients or caregivers; b) the insights from interviews with six PKU specialists, to ensure that all relevant items were captured regarding the lifestyle aspects related to the time and cost burden of PKU [19]. The resulting questionnaire was piloted with four caregivers who provided additional feedback. The questionnaire collected background information on the child or children with PKU.

Caregivers were asked about their time and costs spent on 'Social Life', 'Health and Work' and 'The PKU Diet'. The 'Health and Work' section included the Short Form Health & Labour Questionnaire [20], a pre-validated questionnaire that investigates the impact of a disorder on a respondent's employment. Respondents provided answers using weekly and monthly recall periods. In addition to the respondent's questionnaire, consent was asked for the child's dietician or treating specialist to report in an addendum on the disorder severity and control status of the child with PKU. Disease status was recorded as 'Mild', 'Moderate' or 'Classical' (determined by diagnostic blood Phe concentration [i.e. Mild  $< 600$   $\mu\text{mol/L}$ , Moderate  $> 600$ – $1200$   $\mu\text{mol/L}$ , Classical  $> 1200$   $\mu\text{mol/L}$  and Phe tolerance and stability of blood Phe control) and control status recorded as 'Controlled' or 'Uncontrolled' (determined by blood Phe concentrations based on the previous 3 months Phe concentrations). Blood Phe within the controlled Phe range for  $\geq 70\%$  of the time was considered good control. If the respondents did not permit access to the child's blood Phe concentration data, the expert opinion of the child's dietician's was used for disease and control status.

### 2.3. Data analysis

The time burden and OOPCs for caregivers of pediatric patients with PKU were assessed in: a) the overall study population; b) subgroups related to PKU severity and Phe concentration control status. Patients with mild or moderate PKU were grouped together and compared with those with classical PKU, and patients who successfully controlled their Phe concentrations were compared with those who were 'uncontrolled'. Analyses were performed on the available data; therefore, the sample number for each analysis varies depending on the outcome of interest. Outcomes were continuous variables (time and OOPCs) and were described in terms of medians and ranges.

## 3. Results

### 3.1. Study population characteristics

From November 2012 to March 2013, 195 caregivers of children diagnosed with PKU were invited to take part in the study. Of these, 114 surveys were completed and returned, with each survey representative of one pediatric patient. All patients were under the age of 18 years, the majority had classical PKU, and  $> 90\%$  of those for whom control status was known were considered to have controlled PKU (Table 1). Of the patients,  $> 90\%$  were treated with a low-Phe diet ( $n = 106$ ) and special

**Table 1**  
Characteristics of PKU patients.

Caregivers invited to participate, n	195
Survey completed and returned, n	114
Median age of PKU patients, years (range)	7 (1–17)
Patients treated with low-Phe diet, n (%)	106 (93.0)
Patients treated with low-protein foods, n (%)	108 (94.7)
Patients taking Phe-free L-amino acid supplements, n (%)	87 (76.3)
PKU severity, n (%) <sup>a</sup>	
Mild ( $< 600$ $\mu\text{mol/L}$ )	8 (7.5)
Moderate (Phe 600– $\leq 1200$ $\mu\text{mol/L}$ )	37 (34.9)
Classical ( $> 1200$ $\mu\text{mol/L}$ )	60 (56.6)
Unknown	1 ( $< 1$ )
Control status of PKU, n (%) <sup>a</sup>	
Controlled/uncontrolled	87 (82.1)
Unknown <sup>b</sup>	8 (7.5)
	11 (10.4)

Phe, phenylalanine; PKU, phenylketonuria.

<sup>a</sup> Analysis based on all patients treated with a low-Phe diet ( $n = 106$ ); control status determined from the previous 3 months Phe concentrations.

<sup>b</sup> Respondents answered 'don't know' to the question 'Do you know what your PKU child's maximum daily recommended number of 'exchanges' is (their level of protein intake), as recommended by their doctor or dietician that they should try not to exceed?'

low-protein foods ( $n = 108$ ), and  $>75\%$  ( $n = 87$ ) took Phe-free L-amino acid supplements (Table 1).

### 3.2. The time burden and out-of-pocket-costs of caregivers

Fig. 1 illustrates the median hours per week spent on activities related to managing aspects of PKU care, including ordering special food and Phe-free L-amino acid supplements, dietary management (baking, cooking, supervising the diet), taking blood Phe samples, organizing food for patient social events (e.g. parties, food for school, after school activities, visiting friends' homes), or attending PKU-related events. Dietary management was the most time-consuming activity (median 19.3 h; range 0–79 h per week; median 3 h per day). Fig. 2 shows that a large proportion of dietary management time was spent on cooking and meal preparation (median 7 h; range 0–28 h per week) and supervising Phe intake, including the intake of Phe-free L-amino acids (median 3.5 h; range 0–21 h per week). In addition to standard dietary management time and day-to-day cooking, caregivers described on a median of twice each month (range 0–31 days per month) they would pre-prepare special food for their child for social events (Fig. 1). Such events typically required a median of 42 min per week (range 0–3 h) in preparation time.

Severity of PKU and control of blood Phe concentrations did not markedly influence the time spent on dietary management (Table 2), with the overall median weekly time spent on dietary management being 19.3 h.

Most caregivers indicated no expense on Phe-free L-amino acid supplements, due to their availability via free prescription for patients younger than 16 years in the UK. Caregivers did identify PKU-specific OOPCs for holidays, such as extra luggage required for L-amino acid supplements, special low protein food and equipment (median £30; range £0–£3150 per year), and for attending PKU events including overnight stay and travel costs (median £40; range £0–£1020 per year). In addition, caregivers spent a one-off median amount of £150 (range £0–£1110) on PKU-specific equipment for food preparation (e.g. bread makers, bread-slicing machines, blenders and electronic digital scales). In general, neither severity nor control of PKU substantially influenced OOPCs, although the majority of caregivers of patients with controlled PKU reported no holiday-related costs specific to PKU (Fig. 3).

### 3.3. Effect of PKU on the working lives of caregivers

Caregivers were questioned about any changes in their employment that they could specifically attribute to PKU. Fifty-two of 106 (49%)

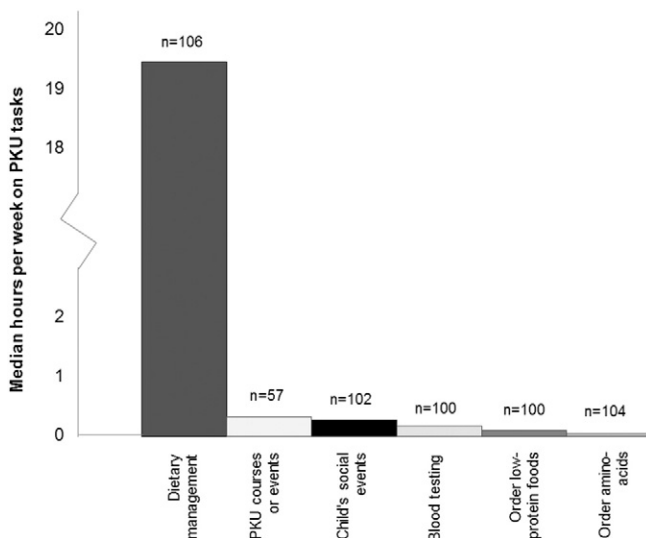


Fig. 1. Median hours spent per week on PKU management tasks. PKU, phenylketonuria.

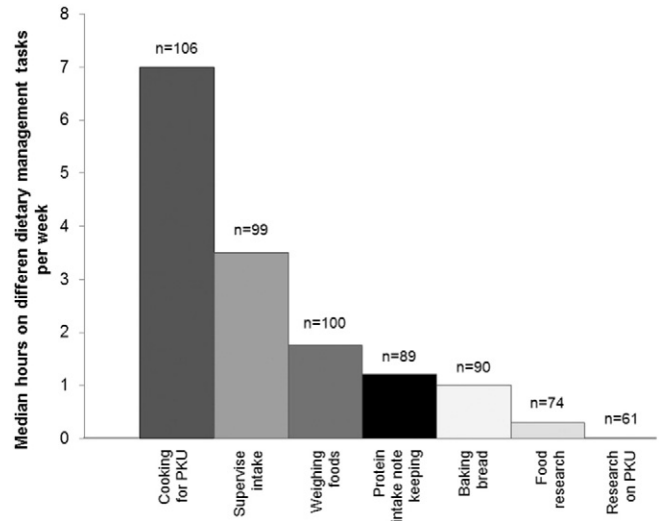


Fig. 2. Median hours spent per week on different aspects of the dietary management of PKU. PKU, phenylketonuria.

caregivers indicated changes in their working pattern due to their children having PKU (Table 3).

Of the 52 caregivers who reported a change in their working pattern, 48% (25 caregivers) stopped paid work completely; 42% (22 caregivers) reduced their number of working hours in their current job or took another job to allow fewer hours; 10% (5 caregivers) changed jobs to better suit their schedule while maintaining their number of working hours. Overall, there was a median reduction of 18.5 working hours per week, taking into account only the 27 caregivers who stayed in work, but not the 25 who left paid employment. In most cases the reason was to personally care for their child with PKU, but the impact on some respondents' employment was due to the treatment regimen being too time-consuming to manage alongside their current working pattern.

## 4. Discussion

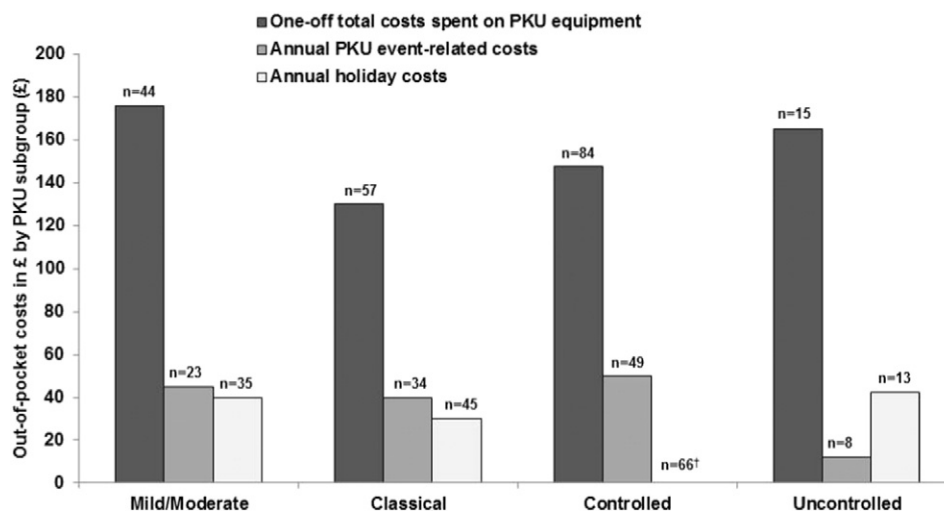
This is the first UK study that examines the time and cost burden, in detail, of managing children with PKU, although a previous study by Guest et al. reported on costs and resource use of adults with PKU over their lifetime [5]. However, the population in our study consisted of children and adolescents who were closely managed and their PKU was generally well controlled, whereas the study by Guest et al. included all PKU patients in the Health Improvement Network. Our study demonstrates a high burden on the working capacities of caregivers and a large time burden due to the treatment regimen. The questionnaire used in this study collected information on time taken up by dietary management and cooking in addition to normal childcare, in order to distinguish the time specifically related to management of PKU and not just looking after the child in general. Organizing, preparing and cooking low phenylalanine meals (in addition to regular meals for the rest of the family) were the most time-consuming tasks. The magnitude of the dietary time burden (a median of 19 h per

Table 2

Median hours spent per week on dietary management per PKU subgroup.

PKU subgroup	Median time spent per week (hours)
Mild/moderate ( $n = 45$ )	20.5
Classical ( $n = 60$ )	17.7
Controlled ( $n = 87$ )	19.7
Uncontrolled ( $n = 16$ )	17.3

PKU, phenylketonuria. Mild/moderate  $\leq 1200 \mu\text{mol/L}$ . Classical  $> 1200 \mu\text{mol/L}$ . Control status determined from previous 3 months of Phe concentrations.



**Fig. 3.** Median out-of-pocket-costs\* per PKU subgroup. PKU, phenylketonuria. \*Not including Phe-free L-amino acid supplements/low-protein specialist foods available on UK NHS free prescription for under-16 year olds. †Value was £0.

week) was interpreted as significant time effort from the caregivers to manage a child with PKU. A similar study performed in the Netherlands also illustrated the time-consuming nature of the PKU diet, which represented an extra time burden of 1 h and 24 min for caregivers per day [19]. Although this time is only half of that reported in this UK study, this might reflect the difference between these countries in the time generally spent preparing food. One survey reported the average time spent cooking an evening meal in the UK was 32 min [21], compared with >2 h in the Netherlands [22]; it is possible that the limited time spent cooking by many of the UK population is a consequence of them eating more convenience foods. Furthermore, the additional time stated in food preparation for when a child socializes outside of the home (visiting friends for example) demonstrates that appropriate low-protein food is unlikely to be available in many social situations. This causes a time-burden stress for caregivers of PKU, who have to constantly liaise with other families as well as school and nursery teachers to keep them informed and supervise appropriate dietary management.

The management time and OOPCs of caregivers with children who have controlled PKU and uncontrolled PKU was similar. It was assumed that those who are not in control of their PKU might not be adhering to a specialist diet and, thus, are spending less money and time on PKU than patients who are controlled. However, the similarities between the controlled and uncontrolled groups perhaps suggest that dietary management is not the only factor that impacts disorder control, even though few patients in the study had uncontrolled PKU. This study demonstrated little financial burden of PKU in the UK, where Phe-free L-amino acids and low-protein products are reimbursed by the NHS. By contrast, in the Netherlands caregivers purchased low protein foods, which substantially increased their OOPCs [19].

A key finding of this study was that nearly half of all caregivers reported an impact on their job of having a child with PKU. Ninety percent of the caregivers who reported this either stopped working completely or reduced their working hours. This contrasts with a study of children

with PKU in Lithuania, in which only 30% of parents reported changing their working situation due to their child's condition, with only 11% stopping work completely [17]. This might reflect the close management of the children in our study, concerns about the ability of caregivers in nurseries or child minders to take care of children with PKU, or a lack of close family support available to caregivers. PKU management appears to be associated with lost earnings, which has an important impact on the financial status of caregivers. In the UK, families with a child with PKU can apply for DLA; the highest carer claim rate to date is £82.30 per week [23]. There are three rates of DLA benefit (high, medium and low), and discussions with the dietitians revealed that most families are on the middle rate of DLA (£55.10), with the high rate only exceptionally justified because of overnight care (and an additional carer's allowance may be awarded to low income families) [23]. Considering that over 19 h are spent per week on dietary management alone, we believe that there is a significant cost in the working time relinquished by caregivers. At the UK minimum wage rate, a reduction of 19.29 h per week equates to £120 of missed earnings, which is more than double the middle DLA rate, although low-income families can also apply for the carer's allowance. The gap grows further when considering those who have earning potential above the minimum wage rate. It is, thus, essential that families continue to have access to the DLA and that Phe-free L-amino acids and low-protein foods continue to be available on ACBS prescription, with the cost paid by the NHS. If financial help is not maintained for PKU-affected families, dietary management of the disorder may become unaffordable, with adverse effects on blood Phe control and, ultimately, on cognitive outcome.

Caregivers of children with classical PKU would be expected to commit more time and money to managing the disorder than caregivers of children with mild/moderate disorder, as the more severe disorder requires a stricter diet. However, our results indicated that the time spent on management of PKU was high, irrespective of severity. These results contradict the results from the Netherlands study, which were in line with the assumption that children with classical PKU require more time for dietary management [19]. Because the overall time spent cooking the evening meal in the UK is around a quarter of the time spent in the Netherlands, any additional time commitment required to prepare a Phe-restricted diet would be perceived as high, regardless of the severity of the disorder. Furthermore, few caregivers of poorly controlled PKU patients responded to this present survey, so the results may not be applicable to a larger population.

This discrepancy is also reflected in the lower time burden reported in the UK for ordering and acquiring low-protein foods or amino acid

**Table 3**

Changes in employment attributable to being a caregiver for a paediatric patient with PKU.

Employment change	Proportion of caregivers (%) <sup>a</sup>
Changed job	4.7
Reduced working hours	20.8
Stopped work	23.6
No change in employment status	50.9

PKU, phenylketonuria.

<sup>a</sup> n = 106.

supplements. In the UK, specialist food companies run home delivery services that contact caregivers and adult patients directly to check their stock of some low-protein foods and L-amino acid supplements. Therefore, this service minimizes the time families have to spend organizing supplies of these products.

Limitations of this study include the potential for bias due to data being collected from only 114 of the 195 caregivers invited to participate; it is possible that the decision to participate was associated with factors that might influence the responses given. The majority of participants were recruited via one clinic, based in Birmingham, and the median age of 7 years for patients included in the study suggests that the sample included younger, rather than older, PKU patients, and a limited number of caregivers of uncontrolled patients responded to the survey. Furthermore, there was potential variability between centers when determining control status (controlled versus uncontrolled), and the PKU classification of mild, moderate or classical is only an indication of severity, as mutation analyses are not performed in the UK. We also set out to infer a correlation between responses and a family's socioeconomic status (as measured through household earnings); however, an accurate analysis was difficult as many respondents chose not to provide income data for privacy reasons. Lastly, this was not a controlled study.

## 5. Conclusion

Dietary management of PKU is associated with a considerable time burden for caregivers of pediatric patients with PKU. Furthermore, a personal financial burden also arises from OOPCs and lost earnings. Although this was not a controlled study, it does reflect the real-world situation; robust controlled studies are required to validate the findings.

## Authors' disclosures

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## Authors' contributions

TAS, JvL and AM contributed to the conception, design and execution of this study, as well as the data analysis and interpretation. TAS developed the questionnaire, and AM and TAS were involved in the recruitment of respondents. All authors contributed to data interpretation and review of the manuscript and approved the final manuscript.

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