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# Burden of illness in hereditary periodic fevers: a multinational observational patient diary study

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**Key words:** colchicine resistant familial Mediterranean fever, mevalonate kinase deficiency (MKD)/hyperimmunoglobinaemia D with periodic fever syndrome (HIDS), tumour necrosis factor receptor-associated periodic syndrome (TRAPS), hereditary periodic fever (HPF), quality of life, physical, psychosocial

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Competing interests: page S33.

## ABSTRACT

**Objective.** This study aimed to characterise the burden of illness of patients with inadequately controlled hereditary periodic fevers (HPFs), during and outside of flares. It was focused on the burden to the patients and also considered the wider impact on their caregivers and families.

**Methods.** The target population was patients or caregivers of patients with clinically/genetically confirmed colchicine resistant FMF (crFMF), mevalonate kinase deficiency/hyperimmunoglobinaemia D with periodic fever syndrome (MKD/HIDS) or TRAPS, who were expected to flare at least once in a 6-month period based on patient history. Disease burden was captured during and between flares using an electronic diary (e-diary) with questions on patient functioning, emotional/social well-being and pain, using validated instruments.

**Results.** HPF-related symptoms such as fever, joint, muscle or bone pain and tiredness and fatigue were reported by patients both during and outside of a flare. The SF-10 Health Survey (SF-10v2) (paediatric patients) and SF-12 Health Survey (SF-12v2) (adult patients) showed that flares negatively impacted patients' psychosocial and physical health. Negative effect of on-flare status on health utility index score assessed by the Short-Form Six-Dimension (SF-6D) was significant only for crFMF patients. Furthermore, the Sheehan Disability Score (SDSv3) showing the on-flare status resulted in significant functional impairment in all 3 disease cohorts through assessment of impact on work/school, social and family life.

**Conclusion.** crFMF, MKD/HIDS and TRAPS negatively affected the quality of life (QoL) of adult and paediatric patients, including their physical, men-

tal, psychosocial health, and social functioning. There remains, however, a high number of unmet needs for these patients to reduce their disease burden.

## Introduction

Tumour necrosis factor receptor-associated periodic syndrome (TRAPS), familial Mediterranean fever (FMF), and mevalonate kinase deficiency (MKD)/hyperimmunoglobinaemia D with periodic fever syndrome (HIDS) are disorders of the innate immune system, which belong to a larger group of hereditary periodic fevers syndromes (HPFs), of which they are the most common (1, 2). The rarity of these diseases can result in difficulties during diagnosis due to significant clinical overlap with infectious and malignant conditions, resulting in delays of several years.

HPFs are life-long conditions, characterised by recurrent episodes of generalised systemic inflammation often manifesting as fever, fatigue, rash, and musculoskeletal pain (3-6). Symptoms present either as attacks or flares lasting from days to weeks separated by asymptomatic intervals (7), or as persistent inflammatory symptoms. Long-term complications such as amyloid-A (AA) amyloidosis can lead to kidney and other organ damage and potential organ failure (8). Current treatments aim to reduce systemic inflammation. In 2018, the results of the pivotal CLUSTER study demonstrated the crucial role of interleukin 1 (IL-1) in these HPFs, and resulted in the approval for the use of canakinumab in FMF, TRAPS and MKD/HIDS in the US and in Europe (9). Additionally, the targeting of IL-1/IL1R has also shown to be successful in other HPFs with the approval of both rilonacept and anakinra for the treat-

ment of cryopyrin-associated periodic syndromes (CAPS) patients.

These diseases usually have an early onset that can present at any time, varying from the first hours to the second decade of life (10, 11). Family members are frequently affected, adding additional impact on the quality of life (QoL) for the whole family (10, 11). While the outcome of these patients to available therapies in the real world has been described in some registries (12–14), the disease burden associated with HPFs is still poorly recognised. The early onset of disease results in impairment of QoL of parents and caregivers, due to increased need to care for their children, when compared to the general population (15, 16). The negative effect of HPFs on QoL have been linked to a number of psychological factors such as illness beliefs, coping strategies and the distribution of dependency (6). Furthermore, it has been suggested that increased educational awareness, and creating a supportive social network, may help patients to adapt to the chronic illness (6).

We designed this non-interventional multinational hereditary periodic fevers burden of illness observational patient diary study (HEROES) to address this evidence gap by collecting real-world data on the burden of illness of patients with inadequately controlled HPFs (with or without treatment with IL-1 inhibitors or other biologics). The data generated document the nature and extent of socio-economic impact on patients with crFMF, MKD/HIDS or TRAPS, during on- or off-flares and aim to better characterise the disease burden and unmet needs of these patients.

## Methods

### Study design

This study included patients from France, Germany, Israel, Turkey, USA and UK. Patient data were captured through study participant completion of an e-diary (Study design overview, Supplementary Fig. S1). E-diaries captured baseline disease burden ‘off-flare’, followed by disease burden experienced either ‘on-flare’ or ‘off-flare’ with a daily and weekly recall period. Flare status was determined by the re-

spondent and data capture varied between 2 to 6 months dependent on the flare frequency of the respondents and their willingness to remain in the study.

### Patient population

The study population was composed of patients who had clinically and/or genetically confirmed diagnosis of crFMF, MKD/HIDS or TRAPS. crFMF patients had to have documented active disease despite self-reported compliance with stable doses of colchicine, or intolerance to colchicine therapy (dosage must all be in accordance with guidelines/standard practice). Three age cohorts were included in this study: children 2–12 years old (for whom the e-diary was completed by a caregiver); adolescents 13–17 years old (for whom the e-diary was partially completed by the caregiver in areas such as socio-economic impact, whereas daily symptoms and their impact was completed by the patients themselves) and adult patients. Enrolled patients were required to have a history of clinically symptomatic flares at least once every 3 months despite treatment and to have understood and signed the study consent form (adult patients or caregivers) or study assent form (paediatric patients >7 years and <18 years). Study exclusion criteria were concomitant enrolment in an interventional clinical trial, which may, in the opinion of the investigator, have changed the real-world disease burden experienced by the patients and their families or inability of the patient to identify the start and end of a disease flare.

### Caregiver inclusion criteria

Caregiver inclusion criteria included being a caregiver of a patient ( $\geq 2$  and <18 years old) who had clinically and/or genetically confirmed diagnosis of HPF (crFMF, MKD/HIDS or TRAPS) and met all other inclusion and none of the exclusion criteria. Caregivers were required to be >18 years old and spend a minimum of 50% of their time living with the child with HPF. Caregivers with an uncontrolled psychiatric condition, very severe clinically active HPF, or those who the recruiting physician believed would be unable to provide

reliable e-diary responses for any other reason, were also excluded from this study.

### Data collection

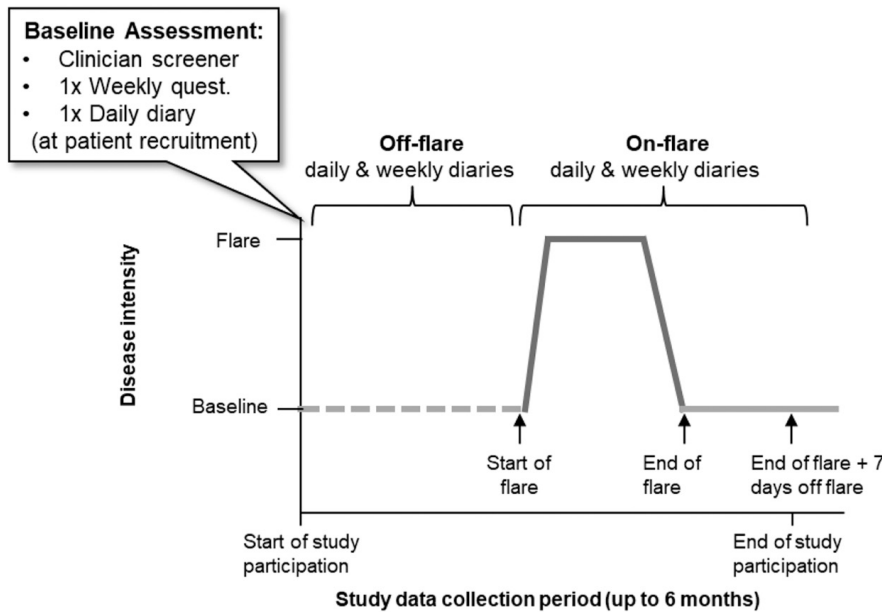
Once an interested participant was identified, the recruiting clinician confirmed his/her diagnosis and study eligibility by completing a brief clinician screener. Study assessments consisted of a clinician-completed screener and three e-diary assessments: baseline questionnaire, daily diary (24-hour recall period) and weekly diary (7-day recall period). Participants completed assessments (baseline questionnaire, daily diary off- and on-flare and weekly diary off- and on-flare) on a mobile electronic device. The same version of both diaries was completed both off- and on-flare (Fig. 1).

### Variables

Validated instruments to capture disease burden included the following: patient/parent’s global assessment of disease activity (PPGA), SF-12v2, SF-10v2 for children and SDS v3. While the SF-10v2 had not been used previously in HPF populations, it is a validated and widely published measure of paediatric QoL. It was adapted from the Child Health Questionnaire with a shorter 7-day recall period that can capture short-term fluctuations in disease burden and QoL. The PPGA was self-completed by adult or adolescent patients ( $\geq 13$  years old) and completed by caregivers for children 2–12 years old to measure patients’ overall symptom severity on- and off-flare scores.

### Data analysis

Statistical analyses were conducted on data from the intent-to-treat population. Patients were required to have a flare at least once in a 6-month period on average despite current therapy. The patient must have been considered eligible for biological therapy in the opinion of the recruiting physician, but not currently receiving any biological therapy at the start of the study or currently receiving biologic therapy off-label for HPF, but still experience a flare at least once every 6 months. Two patients did not complete the study and did not provide sufficient data to be included in subsequent



**Fig. 1.** Data collection schedule overview.

analysis. Generalised linear regression mixed models for repeated measures were used to estimate the treatment effects on the change of SDS, SF-10 and SF-12 patient reported QoL scores.

Patients received electronic reminders on the e-diary device to encourage completion and minimise missing data. Despite this, it was possible that during a flare the intensity of disease

may have prevented participants from completing the diary every day. The generalised linear regression mixed model used in this study removed only the time point containing the missing value, all remaining data was retained for analysis. Adjusted regression models were performed on on-flare and off-flare measures. Patients' age, gender, disease conditions and time were used as the covariates, and patients' flare status as exposure variables. A total of 44 models were created and the means of each sub-scale of the three QoL measures (SDS, SF-10 and SF-12) were calculated and compared between patients off-flare and on-flare period. Patient-reported disease burden was reported as least square mean with standard error. The analysis was conducted using SAS-9.4. The significance level for the analysis was 0.05.

*Ethics*

This study complies with the Declaration of Helsinki. The locally appointed ethics committee has approved the re-

**Table I.** Patient and caregiver characteristics. Characteristics for colchicine resistant FMF (crFMF), mevalonate kinase deficiency (MKD)/hyperimmunoglobulinaemia D with periodic fever syndrome (HIDS) patients and their caregivers.

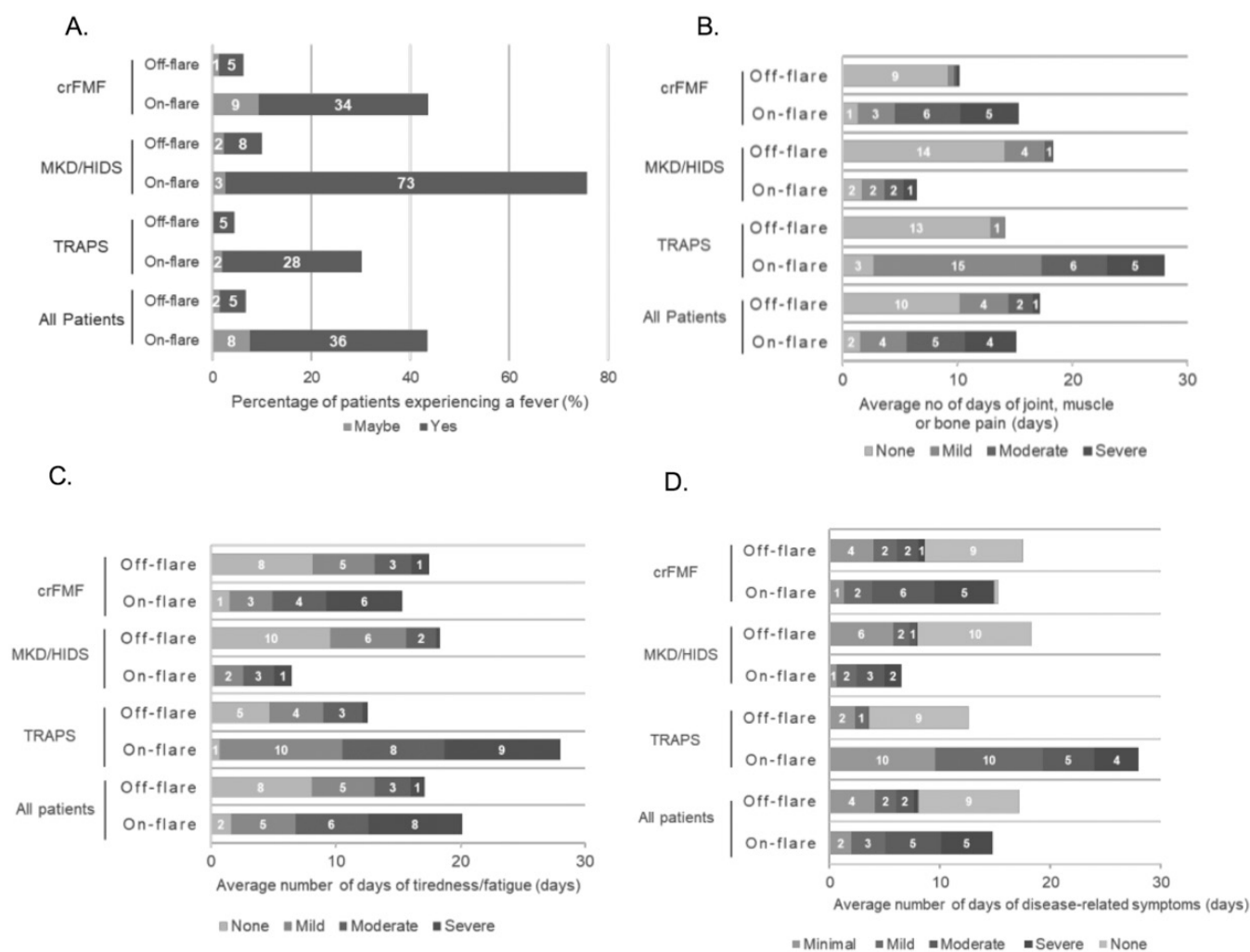
Variable	FMF n (%)	MKD/ HIDS n (%)	TRAPS n (%)	HPFs n (%)
<b>Patients</b>				
Total patients	57 (75.0)	12 (15.8)	7 (9.2)	76 (100.0)
Patient's gender				
Male	19 (33.3)	4 (33.3)	4 (57.1)	27 (35.5)
Female	38 (66.7)	8 (66.7)	3 (42.9)	49 (64.5)
Patient's age cohort				
Child (2-12)	20 (35.1)	9 (75.0)	1 (14.3)	30 (39.5)
Adolescent (13-17)	9 (15.8)	1 (8.3)	1 (14.3)	11 (14.5)
Adult (18+)	28 (49.1)	2 (16.7)	5 (71.4)	35 (46.1)
Patient's age at baseline[mean years (SD)]	21.6 (15.8)	9.9 (8.9)	25.3 (12.9)	20.1 (15.2)
Age at first symptoms (years)*	4.5 (5.8)	2.2 (3.3)	6.1 (6.0)	4.3 (5.6)
Age at diagnosis (years)**	8.4 (9.6)	5.8 (6.0)	17.8 (16.9)	8.8 (10.2)
Age at first treatment (years)***	8.5 (9.3)	6.3 (6.1)	22.7 (23.4)	8.7 (10.0)
Patient reported number of flares experienced in last 12 months [median (SD)]	12.0 (15.6)	12.0 (7.9)	6.0 (7.3)	12.0 (14.2)
Patient reported average length of flare (days) [median(SD)]	3.0 (3.9)	4.5 (1.4)	7.0 (4.5)	3.0 (3.7)
<b>Caregivers</b>				
Total caregivers	29 (100.0)	10 (100.0)	2 (100.0)	41 (100.0)
Caregiver's gender				
Male	8 (27.6)	1 (10.0)	2 (100.0)	11 (26.8)
Female	21 (72.4)	9 (90.0)	0 (0.0)	30 (73.2)
Caregiver's age (years) [mean age (SD)]	38.6 (5.6)	36.6 (7.0)	41.5 (9.2)	38.2 (6.1)
Caregiver working full time	10 (34.5)	4 (40.0)	2 (100.0)	16 (39.0)
Caregiver working part time	13 (44.8)	3 (30.0)	0 (0.0)	16 (39.0)

Percentages may not be a total of 100 due to rounding

\*n=3 participants could not recall the age at which they/their patient first started experiencing symptoms;

\*\*n=5 participants could not recall the age at which they/their patient was diagnosed;

\*\*\*n=6 patients have not received any treatment for their condition, n=5 participants could not recall the age at which they/their patient initiated treatment.



**Fig. 2.** Symptoms colchicine resistant FMF (crFMF), mevalonate kinase deficiency (MKD)/hyperimmunoglobulinaemia D with periodic fever syndrome (HIDS) and tumour necrosis factor receptor-associated periodic syndrome (TRAPS) patients experienced as a result of their disease.

Patients were asked if they had experienced A) fever, B) joint muscle or bone pain, C) tiredness or fatigue, and D) how they persevered during their daily diaries either “on-flare” or “off-flare”; some patients were unsure if they had a fever and these patients reported “maybe”. Joint muscle or bone pain, tiredness or fatigue and overall severity of disease are reported as average number of days during this study. The values shown are to the nearest full day.

search protocol and informed consent was obtained from the study subjects (or their legally authorised representative).

## Results

A total of 76 patients were enrolled in the study; the highest represented cohort was crFMF, with 57 patients (75%), followed by 12 (16%) patients with MKD/HIDS and 7 (9%) patients with TRAPS (Table I). Females represented 64.5% of all patients/caregivers enrolled in this study. Thirty children, 11 adolescents, and 35 adult patients were enrolled in this study. Forty-one caregivers completed the e-diary on behalf of children/adolescents in the study. The patient and caregiver char-

acteristics are summarised in Table I and current treatments are outlined in Supplementary Table S1.

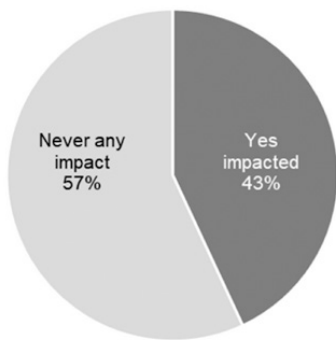
Patients with MKD/HIDS presented with symptoms at an earlier age (2.2 years) than those with crFMF (5.8 years) and TRAPS (6.1 years). The median number of patient-reported flares in the previous 12 months was 12 for patients with crFMF and MKD/HIDS, whereas patients with TRAPS had the least average number of flares per year with a median of 6 flares a year. The length of flares experienced by patients was longest in TRAPS patients with a median of 7 days, while crFMF and MKD/HIDS patients reported a median of 3 days and 4.5 days per flare, respectively.

Disease-associated symptoms while

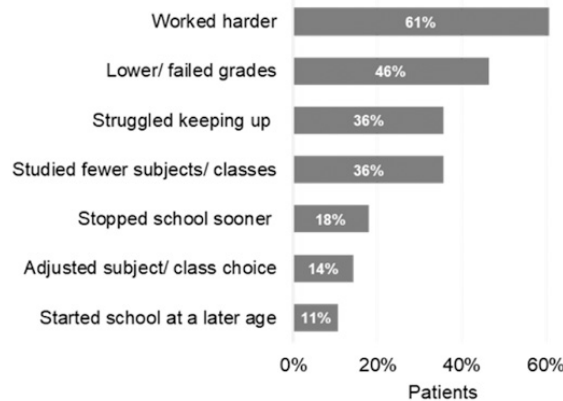
in the presence and absence of a flare are reported in Figure 2. On-flare fever was reported most frequently in 73% of MKD/HIDS patients, followed by 34% of crFMF and 28% of TRAPS patients (Fig. 2A). Patients reported joint, muscle or bone pain more frequently when on-flare, with severe pain reported for an average of 5 days per flare for both crFMF and TRAPS patients and for one day for MKD/HIDS patients (Fig. 2B). The duration of joint, muscle or bone pain experienced when on-flare was highest among TRAPS patients, where it was experienced an average of 26 days during the study (Fig. 2B; the areas of body pain and other symptoms are detailed in Supplementary Table S2). Tiredness or fatigue was fre-



**A. HPF impact on education**

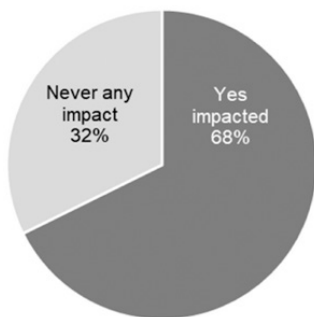


**How HPF impacted their education**

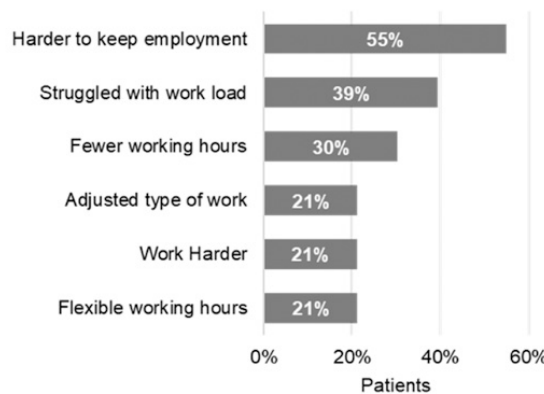


**B.**

**HPF having impact on work achievement**



**How HPF impacted their work achievement**



**Fig. 3.** The impact of colchicine resistant FMF (crFMF), mevalonate kinase deficiency (MKD)/hyperimmunoglobinaemia D with periodic fever syndrome (HIDS) and tumour necrosis factor receptor-associated periodic syndrome (TRAPS) on the education and employment of patients.

Baseline surveys completed by patient/caregiver believed that the patients disease affected their **A)** education or **B)** employment. This was reported as a percentage based on the number of patients enrolled in this study. Patients who reported their/their child's education/employment was impacted by the disease were then asked what type of impact the disease had. This was reported as a percentage based on the total number of patients who confirmed an impact of the disease.

quently reported both on- and off-flare, with the highest number of days among on-flare TRAPS patients (Fig. 2C). Tiredness or fatigue was also reported off-flare, ranging from an average of 9 days by crFMF patients, 8 days by MKD/HIDS patients and 7 days by TRAPS patients.

Severe disease-related symptoms lasted for an average of 5, 2 and 4 days for crFMF, MKD/HIDS and TRAPS patients, respectively (Fig. 2D). crFMF patients also reported a higher number of days with moderate severity of symptoms (6 days), when compared to TRAPS (5 days) and MKD/HIDS (3 days). On-flare TRAPS patients showed disease-related symptoms of variable severity (ranging from mild to severe) for the longest duration (27 days). While patients were off-flare, only crFMF patients reported severe disease-related symptoms. Furthermore, in the off-flare setting, among patients experiencing minimal to severe

disease, symptoms were reported by crFMF and MKD/HIDS patients with an average of 8 and 9 days, respectively, compared to only a 3-day average for TRAPS patients.

In terms of disease impact on daily activities, 28 (43%) paediatric patients reported that their education/schooling was negatively affected (Fig. 3A). The most frequently reported impacts were the need to work harder than their peers (17 patients, 61%), followed by lower or failed grades because of their disease (13 patients, 46%), the struggle to keep up with their peers (10 patients, 36%) and the need to compromise by studying fewer subjects or taking fewer classes (10 patients, 36%). Furthermore, parents and caregivers not working full-time additionally reported that their reason was at least partially due to their child's condition (Table I, Suppl. Table S3). Twenty-one (68%) adult patients reported their disease had a negative impact on their work achievement

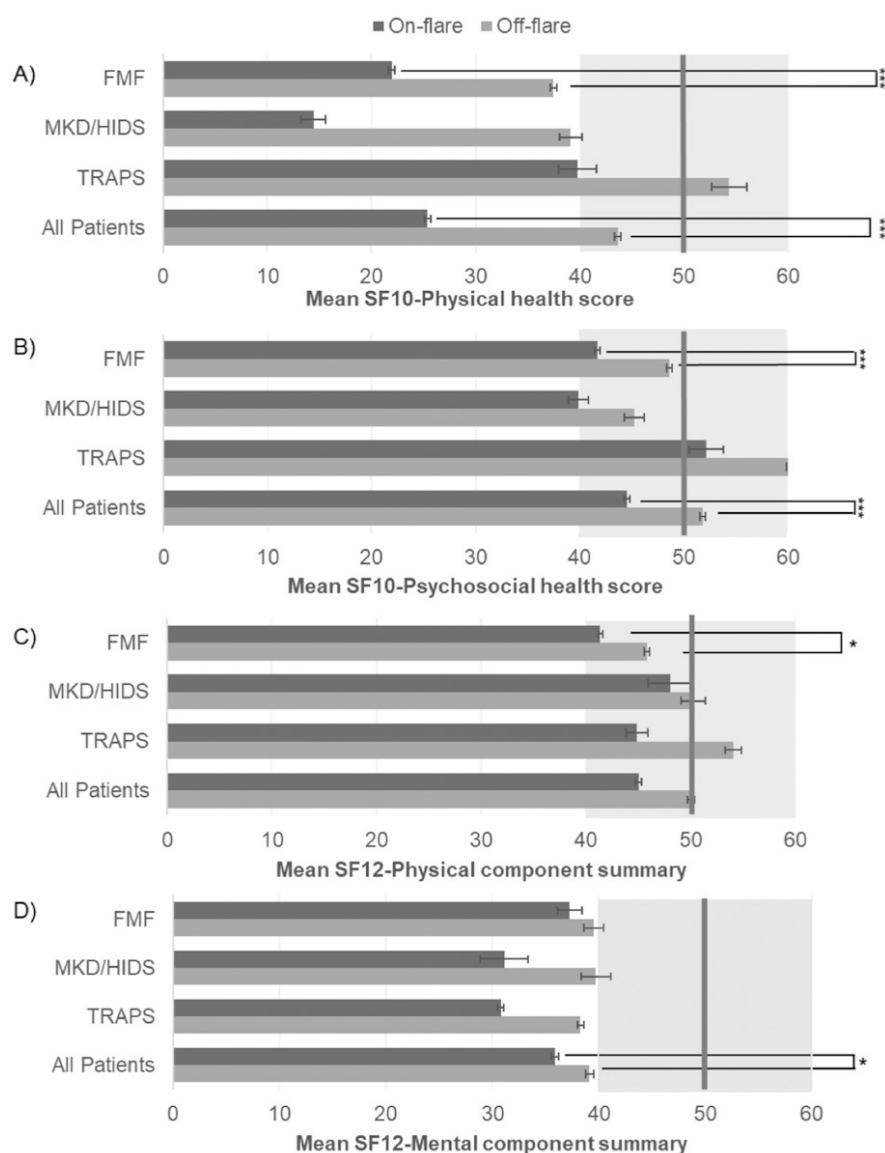
(Fig. 3B), with the most frequently reported impact being their ability to keep employment (17 patients, 55%). Patients also frequently reported that they struggled with workload (13 patients, 39%) and needed to work fewer hours (10 patients, 30%).

In the SF-10 survey, the physical health score, comprising questions relating to physical activity, energy, movement and pain, showed a statistically significant difference ( $p < 0.0001$ ) between on- and off-flare for crFMF, as well as overall for all patients combined (Fig. 4A). There are a limited patient numbers for both MKD/HIDS and TRAPS cohorts, therefore the probability value for these cohorts is not shown. MKD/HIDS and crFMF patients showed a considerably worse mean score while experiencing a flare when compared to the normed population score (mean of 50 and a standard deviation of 10). Overall, patients showed a lower mean score when experiencing a flare which

shows poorer physical health associated with flare.

The TRAPS patients mean off-flare score (54.4) was within the normal physical health score, however, when experiencing a flare, it fell marginally outside of this range (39.8). In the SF-10 survey, the psychosocial health score, which covers friendships, social participation and related emotional issues, the largest difference between being on- and off-flare was in TRAPS patients ( $9.3 \pm 4.6$ ), followed by crFMF ( $7.0 \pm 1.6$ ) and then MKD/HIDS ( $5.3 \pm 1.5$ ). However, this was highly significant for the crFMF ( $p < 0.001$ ) patient cohort. Due to the small number of patients, the probability values for the MKD/HIDS and TRAPS cohorts are not shown (Fig. 4B). The SF-10 psychosocial health for all disease cohorts fell within the standard deviation boundary of the normal population score, except for MKD/HIDS during on-flare, where the mean was marginally outside of this range (39.8).

The SF-12v2 physical component showed a significant difference between the on-flare and off-flare score in crFMF patients ( $4.4 \pm 2.0$ ;  $p = 0.0333$ ) (Fig. 4C). The difference between on-flare and off-flare scores for MKD/HIDS patients was minimal (2.2) and showed a large range across patients giving a standard error of the mean (SEM) of 8.5, suggesting that scores were variable among patients. The scores for all cohorts both on- and off-flare fell within the score range of the normal population. The mental component, however, showed that scores for all cohorts regardless of flare status were outside the normed population range (on-flare: crFMF 37.2, MKD/HIDS 31.1, TRAPS 30.8; off-flare: crFMF 39.5, MKD/HIDS 39.8, TRAPS 38.3) (Fig. 4D). The mental component scores during a flare were lower than off-flare for all cohorts. The cohort with the largest difference between on-flare and off-flare scores was MKD/HIDS (8.6), followed by TRAPS (7.5) and then crFMF (6.1). The scores of each individual component of the SF-12 survey are outlined for crFMF, MKD/HIDS, TRAPS and all HPF patients in Supplementary Figures S2-5.



**Fig. 4.** SF-10 and SF-12 scores of patients both “on” and “off-flare”.

Data calculated using adjusted regression model. SF-10 for colchicine resistant FMF (crFMF), mevalonate kinase deficiency (MKD)/hyperimmunoglobulinaemia D with periodic fever syndrome (HIDS) and tumour necrosis factor receptor-associated periodic syndrome (TRAPS) patients who were 18 years or under covers two scores: A) Physical Summary Score (PHS) which covers physical activity, energy, movement, and pain, and B) the Psychosocial Summary Score (PSS) which covers friendships, social participation, and related emotional issues. For both summary scores, higher values indicate more favourable physical or psychosocial functioning. SF-12 for patients 18 years and over covers two scores: C) physical and D) mental health component. The dark grey vertical line at 50 represents the average normed population score; the surrounding lighter grey box from 40-60 represents the standard deviation. All scores are shown as an average with error bars for FMF and all patients combined represent SEM. Patient numbers for MKD/HIDS and TRAPS were too few to report SEM and  $p$ -values.  $p \leq 0.05$ ; \*\*\* $p \leq 0.001$ .

The health utility index score of the patients in this study were assessed by Short-Form Six-Dimension (SF-6D). Scores when patients were on-flare were consistently lower than off-flare scores across all cohorts. This was statistically significant for crFMF patients ( $p = 0.03$ ).  $p$ -values are not shown for MKD/HIDS patients due to the limited

patient numbers (Fig. 5A). The functional impairment of patients was determined by the SDS, which assessed three inter-related domains work/school, social and family life, using the adjusted regression model (Fig. 5B). All 3 patient cohorts showed a significant increase in functional impairment when patients were experiencing a flare

compared to off-flare state. TRAPS patients showed the largest difference with a mean of -39.9, while the mean difference for MKD/HIDS and crFMF was -34.7 and -18.9 ( $p < 0.0001$ ), respectively.

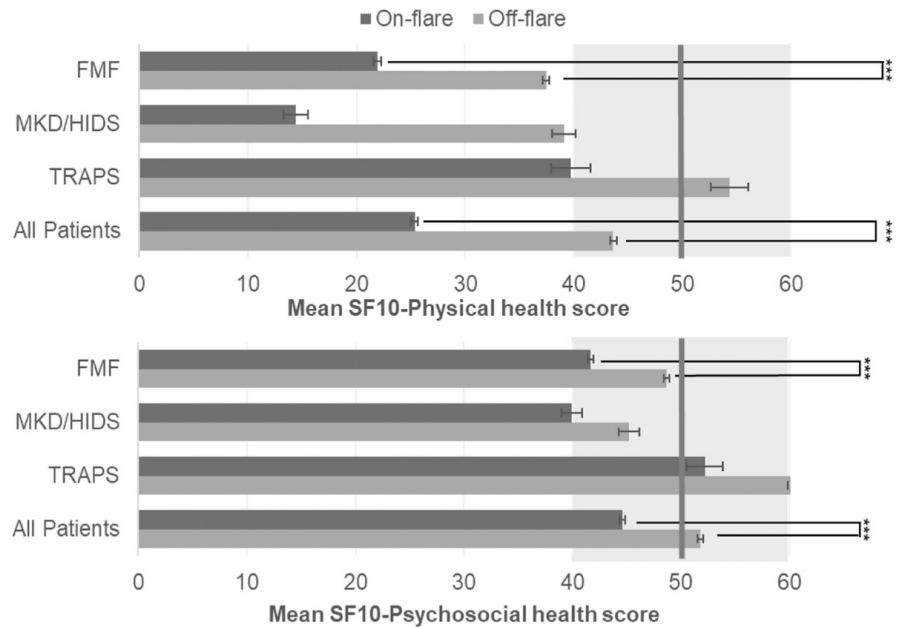
**Discussion**

HEROES is the first international study to document the nature and extent of the socio-economic burden experienced by crFMF, MKD/HIDS and TRAPS patients and their families. Previous studies have separately assessed the QoL of FMF (16-19), MKD/HIDS (20-22) and TRAPS patients (23, 24) regardless of flare status.

HEROES is the first global longitudinal patient-reported disease burden study, stratifying disease burden according to flare status, with validated instruments, although not specifically for HPFs. We found that flares have a statistically significant negative impact on patients' and caregivers' physical, mental/psychosocial health and social functioning, and that HPFs negatively impact patients' education and work achievements, leading to both a reduced QoL and increased socio-economic burden as a result of the disease.

In the absence of a flare, patients also frequently reported several disease-related symptoms including pain and tiredness, thereby suggesting that their disease negatively impacts their lives outside of symptomatic flare periods. Indeed, several painful manifestations were reported outside of a flare period by patients. These non-flare-related symptoms often go undetected by the treating physician, as they do not fall into frameworks of the various type of the attacks or are reported as constitutional symptoms. Remission tends to be perceived as time free of symptoms and these painful manifestations often are unreported by patients or reported by physicians as fibromyalgia. This study is particularly noteworthy for having patients report on their symptoms directly, bypassing the physician barrier, thus allowing clearer insight into the suffering of these patients.

By assessing the physical and emotional status of children using the SF-10 survey, our data show that HPFs have



**Fig. 5.** SF-6D Health utility index score and Sheehan disability scores of patients with colchicine resistant FMF (crFMF), mevalonate kinase deficiency (MKD)/hyperimmunoglobulinaemia D with periodic fever syndrome (HIDS) and tumour necrosis factor receptor-associated periodic syndrome (TRAPS). SF-6D focuses on seven of the eight health domains covered by the SF-36v2™ health survey, only the general health domain is not included. The statistical difference between “on” and “off-flare” was calculated using an adjusted regression model. The SDS is an assessment of the functional impairment in three inter-related domains: work/school, social and family life. The mean of these three areas are represented as a percentage and are calculated using adjusted regression model.

† When a value was missing as not applicable, the average of the remaining two components was measured. Error bars represent SEM for FMF, and all patients combined. Patient numbers for MKD/HIDS and TRAPS were too few to report SEM and  $p$ -value.  $p \leq 0.05$ ,  $***p \leq 0.001$ .

a negative impact on patients' physical health, which is in line with previously published results (6, 25). We extend this knowledge by highlighting that QoL varies as a function of flare status. As expected, the development of a flare further decreased the physical health significantly for crFMF patients. The QoL of adult patients, quantified using the SF-12 survey, showed that, unlike paediatric patients and previously published results (6, 17, 18, 26), their mean physical impact score fell within the averaged range of the healthy population both on- and off-flare. However, for crFMF patients, the occurrence of a flare significantly reduced the physical health scores.

Interestingly, HPFs had a larger impact on the mental/psychosocial QoL of adult patients when compared to children, whose paediatric patient scores fell within the expected range of the normal population, whereas adult SF-12 scores fell outside of the normal population. The occurrence of a flare

further decreased the mental/psychosocial health score of both adult and children, in line with previously published results for FMF (16-18, 27), MKD/HIDS (20-22) and TRAPS (23, 24).

When assessing the socio-economic impact associated with the disease, our study shows HPFs negatively impact patients' education (<18-year-olds) and professional life (>18-year-olds). Paediatric patients have reported that despite their best efforts to perform in school by working harder, they still struggle to keep up with their peers as a result of their disease. Adult patients most frequently reported impact on work was their challenge to maintain employment. This likely has a financial impact not only on patients but also on their family and dependents. As reported in the literature, improved disease management can lead to symptomatic control and positively impact employment and education. Van der Hilst *et al.* (2008) reported the impact of MKD/HIDS on job discharge and

unemployment (20). Furthermore, in Erbis *et al.* study of autoinflammatory diseases, schooling was an unmet need identified by 90% of patients enrolled in the study (27). Of the 78 children, adolescents and adults in this study, 63% of patients reported missing 3 days or more per month of school or work, and 25% of patients reported missing 5 days or more (27). This data highlights the need for improved treatment management for HPF patients. Kone-Paut *et al.* have shown improved physical, emotional, and social well-being in cryopyrin-associated periodic syndrome patients who are treated with IL-1 blockade (28).

This study has limitations, including the limited number of patients per cohort. While the crFMF cohort was well represented (total of 57 patients), only 12 MKD/HIDS and 7 TRAPS patients were enrolled in this study, therefore limiting the statistical significance of their measured disease burden. The lower prevalence of these syndromes compared to crFMF likely led to lower enrolment rates (1, 2). Furthermore, the study inclusion criteria may have further limited enrolment as patients were required to have experienced clinically symptomatic flares at least once every 3 months, despite current treatment, thereby excluding patients with better controlled or milder symptoms. While limiting the generalisability of our findings to the overall HPF population, this study highlights the disease burden of a distinct sub-population of patients with a moderate-to-severe form (patients who experience a flare at least once in a 3-month period) of the disease with a high unmet need, in line with study objectives. In addition, selection bias existed as patients with continuous inflammation without overt flares were excluded from this study. The compliance of patients to treatment was also not verified by a dedicated questionnaire. Disease activity was also reliant on patient self-reporting (AIDAI grid was not used). Moreover, this study did not include healthy controls. However, where possible, normed population scores were used for validated instruments.

In conclusion, the HEROES study re-

ports that crFMF, MKD/HIDS and TRAPS negatively affect work/school, social and family life as well as QoL in both adults and paediatric patients. This data confirms previously published results (6, 16-24), and provides additional key insights into QoL changes based on flare status. Quantification of QoL stratified by flare status highlights the negative impact of the disease on patients' physical, mental/psychosocial health and social functioning, which has not been previously reported. Furthermore, HPF had a negative impact on work/school, social and family life. These insights may help physicians and healthcare providers to tailor treatment decisions for inadequately controlled HPF patients, considering their circumstances and disease severity in order to reduce disease activity and flare burden.

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#### Competing interests

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