I, Katelyn M Heraty, hereby submit this original work as part of the requirements for the degree of Master of Science in Genetic Counseling.

It is entitled:
Examining Differences in Symptoms in Individuals with Hypermobile Ehlers-Danlos Syndrome in Relation to Puberty

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Examining Differences in Symptoms in Individuals with Hypermobile Ehlers-Danlos Syndrome in Relation to Puberty

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By

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Abstract

Background:
Ehlers-Danlos syndrome hypermobile type (EDS-HT) is a connective tissue disorder characterized by excessive movement of the joints. Although inherited in an autosomal dominant pattern, 90% of diagnosed patients are female. Clinical observations have indicated that female EDS-HT patients seem to demonstrate an increase in symptoms at or around the time of puberty, whereas males often improve during this time. Based on these observations we believe that the difference in disability experienced and the discrepancy in sex prevalence may become more pronounced at puberty indicating sex hormones may be an underlying cause.

Purpose:
This study aimed to characterize the progression of symptoms in both males and females in early/pre-puberty (EPP) and late/post-puberty (LPP) and serve as the framework for further research examining the impact hormonal changes have EDS-HT symptoms.

Methods:
Ninety-one patients with a clinical diagnosis of EDS-HT, or having a first degree relative with a diagnosis and a positive Beighton score (>4) filled out questionnaires during clinic visits at CCHMC Connective Tissue Clinic. Participants were grouped into early/pre-pubertal (EPP) and late/post puberty groups (LPP) and compared on their composite scores to three questionnaires.

Results:
Females had significantly higher Functional Disability Inventory scores than males (p=0.0289). In both sexes, FDI in the LPP group was significantly higher than that of EPP by (p=0.017). When examining the FDI changes in males and females separately, we found that in females, FDI was significantly higher in the LPP group compared to the EPP group (p<0.001). Specifically, females in the LPP group were seen to have significantly higher disability related to more strenuous activities. In females, the PEDSQL quality of life score related to pain was significantly lower in the LPP group (p=0.006), suggesting that pain contributed to a lower quality of life.

Discussion:
These results indicate that the overall disability related to an individual’s symptoms increases in females with EDS-HT pre- to post-puberty. This study provides preliminary evidence that implicates the function of sex hormones in the progression of the disease state. Further longitudinal and functional studies are needed to establish evidence that hormonal changes cause increases in disability.

Keywords: Ehlers-Danlos syndrome, Joint Hypermobility syndrome, Disability, Hormones, Pain, Headaches, Functional Disability, Orthostatic Symptoms, Puberty
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BACKGROUND

Ehlers-Danlos Syndrome-Hypermobility Type (EDS-HT) is a connective tissue disorder, which leads to excessive movement of the joints (Beighton, De Paepe, Steinmann, Tsipouras, & Wenstrup, 1998; Seckin et al., 2005; Tinkle, 2008). The major diagnostic criteria for EDS-HT are joint hypermobility, soft skin with normal or only slightly increased extensibility and absence of skin or soft tissue fragility (Shirley, Demaio, & Bodurtha, 2012; Tinkle, 2008). Joint hypermobility is measured by the Beighton scale, an evaluation of nine joints. One point is given for each hypermobile joint with a minimum threshold for hypermobility of 5 and a maximum score of 9 (Shirley et al., 2012). Although it was originally thought to be a benign condition involving joint hypermobility, EDS-HT has more recently been noted to be associated with high morbidity (Hoffman Jessica, 2008; Rombaut, Malfait, De Paepe, et al., 2011; Sacheti et al., 1997; Stanitski, Nadjarian, Stanitski, Bawle, & Tsipouras, 2000). In about 10% of EDS-HT cases, a mutation in the TNXB gene is responsible and is inherited in an autosomal recessive pattern (Zweers et al., 2003). The causative gene responsible for the majority of cases has not yet been found, but it is thought to be inherited in an autosomal dominant pattern.

Despite the suspected autosomal inheritance of this condition there is a sex bias with 90% of patients diagnosed with EDS-HT being female (Shirley et al., 2012). We propose that this discrepancy in sex-specific prevalence is due to influences from sex hormones. It is common knowledge that male and female sex hormones influence each sex differently. Previous studies have found that sex hormones influence pain perception and muscle strength differently in males and females (Aloisi et al., 2007; Bhasin & Storer, 2009; Fillingim, King, Ribeiro-Dasilva, Rahim-Williams, & Riley, 2009; Trudeau, Shephard, Arsenault, & Laurencelle, 2003). Estradiol specifically, has been shown to interfere with the synthesis of collagen (Abubaker, Hebda, &
Gunsolley, 1996; Fischer & Swain, 1977, 1985; Kwan et al., 1996), which may explain why Beighton scores in females in the general population have been shown to increase around late/post-pubertal ages (Jansson, Saartok, Werner, & Renstrom, 2004). This hypothesis may also help to explain the changes in symptoms experienced by patients during times of hormonal increases such as pregnancy (Atalla & Page, 1988).

Clinical observations at Cincinnati Children’s Hospital Medical Center (CCHMC) have suggested that female EDS-HT patients demonstrate an increase in symptoms at or around the time of first menarche, whereas males’ symptoms often improve during puberty. Puberty demonstrates the largest shift in hormone activity and it is expected that differences in disability as well as the discrepancy in sex prevalence will become most pronounced at that time. We hypothesize that pubertal state and sex will determine the amount of disability experienced. This hypothesis would be best approached through longitudinal studies of hypermobile children; however, in order to justify the need to perform longitudinal studies, a cross-sectional study to support the clinical observations was employed.

Three common comorbidities of EDS-HT will be addressed in this study. These symptoms include pain, orthostatic symptoms and headaches. All of these symptoms are more prevalent in the EDS-HT population compared to the general population (Bendik et al., 2011; Gazit, Nahir, Grahame, & Jacob, 2003; Hakim & Grahame, 2004; Rombaut, Malfait, Cools, De Paepe, & Calders, 2010; Sacheti et al., 1997; Seckin et al., 2005).

Pain experienced by EDS-HT patients is described as chronic pain, which cannot typically be treated effectively with medication (Grahame, 2009), making it a major source of morbidity. Individuals with EDS-HT are known to experience pain in the shoulders, knees,
spine, and lower extremities including ankles, feet, toes and hips. The pain they experience has been found to progress over time, be associated with reduced physical activity and to have a considerable impact on the physical daily life of these patients (Sacheti et al., 1997). Up to 91% of EDS-HT patients experience chronic physical pain, compared to 30% of the general population (Hakim & Grahame, 2004).

Orthostatic symptoms include lightheadedness, headaches, dizziness and fatigue, which are associated with changes in position. The prevalence of orthostatic symptoms in the adult EDS-HT population is quoted as 78% compared to the prevalence in the general population, which is 10% (Gazit et al., 2003).

Headaches have been seen approximately three times more in individuals with EDS-HT than in controls (Rombaut et al., 2010). Migraines specifically are seen more frequently, affecting 40-75% of females with EDS-HT and 20-43% of females in the general population (Bendik et al., 2011; Hakim & Grahame, 2004).

Although there have been multiple accounts of phenotypic characterization, the mechanisms of many features of EDS-HT remains unclear. This study aims to show a large shift in disability during puberty, implicating hormonal action as a contributing mechanism. The purpose of this study is to characterize the difference in symptoms in both males and females in early/pre-puberty (EPP) compared to individuals in late/post-puberty (LPP). The primary objective of this study is to assess the association of sex and puberty with Functional Disability, caused by the combination of all an individual’s symptoms. Members of the EEP group and LPP group in each sex as well as between sexes will be compared. This will be measured using the Functional Disability Inventory as the primary outcome measure. The secondary objectives
examined the sex and puberty associations with disability experienced due to the specific symptoms of EDS-HT (pain, orthostatic symptoms and headaches) using the same comparison groups.

We hypothesized that females in the LPP group would experience more disability compared to females in the EPP group. Conversely, we expected males to have no significant difference in symptoms throughout puberty. Finally, we expected males in the LPP group to have less disability related to their symptoms than females in the LPP group.

MATERIALS & METHODS

Subjects

This study took place at Cincinnati Children’s Hospital Medical Center (CCHMC) within the Connective Tissue Clinic and was approved through the CCHMC IRB.

Participants aged 6-21 years were enrolled through their previously scheduled appointments within the connective tissue clinic between September 2013 and December 2013. To reduce referral bias, we also recruited 6-21 year old first-degree relatives of these patients through a mailing. Individuals were able to participate if they had a clinical diagnosis of EDS-HT or a first degree relative who had a diagnosis. To be included in analysis participants were required to have a Beighton score of ≥ 5. Individuals were excluded if they were not able to communicate in English, if they had a second diagnosis that also interfered with joint hypermobility and/or pain (e.g. cerebral palsy), or if there was a second diagnosis, which could have interfered with their ability to communicate their symptoms (e.g. a severe form of autism).
Informed consent was obtained for all participants by research staff. Consent and permission for participants ages 6-17 was given by their parents, those ages 11-17 also signed an assent, and individuals’ ages 18-21 gave their own consent. After the consent process, participants underwent a Beighton exam and were examined for skin findings and additional joint mobility by a physician.

Assessment Tools

In addition to a study examination, participants were asked to complete a composite questionnaire that included a Tanner puberty scale, the Functional Disability Inventory (FDI), the Pediatric Quality of Life Rheumatology module (PEDSQL), Orthostatic Grading Scale (OGS), and the Migraine Disability Assessment (MIDAS or PedsMIDAS).

All subparts of the questionnaire, aside from the Tanner, were selected due to the fact they evaluate disability related to specific symptoms. The Tanner puberty scale is a validated scale (Schmitz et al., 2004), which contains diagrams of genitals at different stages of puberty. Participants were asked to indicate the picture that most closely represents where they are in puberty.

A participant reported Tanner scale was used instead of a direct examination in order to allow enrollment of siblings into the study as well as to allow for longitudinal registries wherein the patient may no longer be seen in the clinic.

For males Tanner scores were used to determine EPP or LPP status. Males who indicated they fell in Tanner stages 1, 2 or 3 were characterized as EPP, whereas males who marked they were Tanner stage 4 or 5 were characterized as LPP. For females the presence or absence of menarche separated EPP from LPP individuals.
The FDI is a validated questionnaire (Walker & Greene, 1991), which consists of 15 questions that assess disability due to all one’s symptoms in multiple aspects of life using a Likert scale. A composite score is created by summing the answers to each question; a higher score indicates a greater perceived functional disability. Scores range from 0 to 60 with the general population scoring between 0 and 12 (Flowers & Kashikar-Zuck, 2011).

The PEDSQL rheumatology module is a validated (Varni et al., 2002) 22 question assessment which uses a Likert scale to evaluate the pain individuals’ experience, difficulties with daily activities due to the pain, how they cope with their treatments, their concern about their symptoms, and their comfort communicating with their physicians. A composite score for each participant is calculated by averaging their responses. A lower score indicates a lower quality of life due to pain.

The third part of the questionnaire was the OGS, which is a validated questionnaire (Schrezenmaier et al., 2005) that asks 5 questions to assess disability caused by orthostatic symptoms. These questions evaluate how frequently orthostatic symptoms occur, how severe the symptoms are, the relationship of the symptoms to the orthostatic stressor, and how the symptoms impact the daily life of the patient. A final score is calculated by summing each of the participant’s answers. Scores range from 0 to 20, with a higher score indicating further disability.

The final section of the questionnaire assessed headaches. Two different questionnaires were used depending on the participant’s age; participants under 18 years old completed the PedsMIDAS while adults 18-21 filled out the MIDAS. Both versions are validated questionnaires (Hershey et al., 2001; Stewart, Lipton, Dowson, & Sawyer, 2001) that ask five
and six questions respectively to measure the disability related to headaches in the past three months, including number of days individuals missed school/work, could not complete household tasks, and could not attend family or social gatherings. Due to differences in the forms, participants were characterized as either experiencing headaches or not.

Questionnaire Data

Demographic information including sex, age, highest amount of schooling achieved, race, ethnicity, employment status, state lived in and zip code was collected on each participant.

All data was entered into the secured REDCap database.

Data Analysis

Statistical analyses were performed using Statistical Analysis Software (SAS), version 9.3 (SAS Institute Inc., Cary, NC).

Prior to the analyses, quality of data was checked. Characteristics of the subjects were examined by sex and by puberty status. By using linear regression, the association of sex and puberty status was tested the composite scores of the primary outcome FDI, and the secondary outcomes including pain and orthostatic symptoms. To assess the sex and puberty effects on headache, we dichotomized headache scores into two groups; no headache (headache score =0) and having headaches (headache score >0). A logistic regression was then performed on the dichotomous outcome. We also examined the sex and puberty effect on the composite headache score in subjects who reported headache using linear regression. Residuals were checked for the validity of the models. A sex*puberty interaction was tested in each of the models to assess potential sex-specific puberty effects on outcomes. In addition, by using exact Wilcoxon Rank
Sum tests, we compared the scores of each of the questionnaire items between pre and post puberty when sex was stratified. This analysis enabled us to identify items that significantly affect the four final outcomes. In this study, four correlated outcomes were tested (mean Pearson correlation coefficient=0.6). A correlation adjusted Bonferroni correction ([http://www.quantitativeskills.com/sisa/](http://www.quantitativeskills.com/sisa/)) yielded a significance threshold of 0.029. We also report association reaching the threshold of 0.05, but these associations should be considered exploratory and interpreted with caution.

RESULTS:

One hundred and twelve subjects were consented for entry into the study, but 21 individuals were excluded from analysis due to: incomplete questionnaires, a secondary diagnosis affecting pain, and having multiple surgeries resulting in nonambulatory or reduced ambulatory status for an extended period of time making them substantially different that the ambulatory EDS-HT population [Figure 1]. The final study sample was made up of 91 participants (67 females and 24 males). As shown in Table 1, participants were primarily white with females in the LPP group being the majority (n=42) and males characterized as LPP being the minority (n=5). Females were slightly older and also had slightly higher Beighton score. A majority of the study sample, 70 individuals (76%) lived in OH. Of the 22 (23%) individuals who reported living outside Ohio, 21 were from the United States and one was from Canada. These 22 individuals reflect the fact that many of these patients travel far to meet their complex care needs.
**Primary Outcome**

**FDI**

To test the association of FDI with puberty and sex, we performed a linear regression with a sex*puberty interaction included. As shown in figure 2, the least square mean FDI scores in females in the EPP group, LPP group, and males in the EPP group and LPP group were 8.84 (± 2.01), 18.86 (±1.55), 5.95 (±2.31) and 9.40 (± 4.49), respectively. On average, Females had significantly higher FDI (13.85) than males (7.68) with a difference of 6.17 (p=0.0289). For the combined male and female groups, individuals in the LPP group had a significantly higher FDI (14.3) than the EPP (7.40) group by 6.73 (p=0.0170). When FDI changes in males and females were examined separately, we found that in females, FDI was significantly higher in the LPP group with a difference of 10.02 (p<0.0001), while in males, no significant change was detected though FDI tended to be higher in the LPP group as well (p=0.4940). Moreover, no statistically significant sex-specific puberty effect on FDI was detected (p=0.2470).

Upon closer examination of the specific questions in the FDI it was found there was significantly greater disability experienced by females characterized as LPP when compared to their EPP counterparts in 10 specific aspects of life [Table 2]. Six of these were associated with more strenuous activities including; walking up stairs (p=.0001), doing activities in gym class (p<0.0001), and running the length of a football field (p=0.0024) etc. Additionally females in the LPP group were also seen to have increased disability compared to their EPP counterparts in 4 non-mobile aspects of life including; riding the school bus or traveling in the car (p=0.0228), being at school all day (p=0.0006) and reading and doing homework (p=0.0068) among others.
Secondary Outcomes

Pain

In females, the least square mean of the PEDSQL, QOL related pain score in the EPP group was 72.48 (±3.20) and the LPP group had a predicted score of 61.19 (±2.50). In males the least square mean of QOL-pain was 77.45 (±3.68) in the EPP group compared to the LPP group which had a mean of 83.86 (±7.16). In females, the pain score was significantly lower in the LPP group compared to the EPP group, with a difference of 11.30 (p=0.006), suggesting that LPP females had reduced quality of life due to pain [Figure 3]. In contrast, in males, no significant changes were detected (p=0.428). Moreover, the test on the sex*puberty interaction suggested that puberty may affect pain differently in males and females (p=0.052), but did not reach statistical significance.

When examining changes in disability experienced by females in different pubertal groups it can be seen that there were 8 questions that showed a significantly lower PEDSQL QOL-pain related score in females in the LPP group compared to their EPP counterparts, indicating the LPP group had a lower quality of life due to pain symptoms [Table 3]. All questions assessing disability due to pain and hurt, as well as questions examining anxiety such as, difficulty managing illness, worrying about one’s illnesses, worrying about the side effects of medications and having difficulty explaining one’s illness to other people showed a significantly lower QOL-pain score in females in the LPP group (p<0.0500).

Orthostatic Symptoms

The least square mean for females characterized as EPP was 2.32 (± 0.71) whereas the mean for the LPP group was 7.82 (±0.57). For males the least square mean was 1.83 (± 0.83) in
the EPP group and 5.6 (±1.58) in the LPP group. In both males and females, orthostatic symptoms were significantly higher in the LPP groups. In males there was a difference of 3.77 (p=0.035), while in females, there was a difference of 5.50 (p<0.0001). No sex effect or sex-specific puberty effect on orthostatic symptoms were detected [Figure 4].

In females it was found that every aspect of orthostatic symptoms (frequency, severity, conditions under which they occur, activities of daily living, and standing time) lead to significantly greater disability in females in the LPP group compared to females in the EPP group (p<0.05). In males there was significantly higher disability in males in the LPP group compared to males in the EPP group related to the frequency and severity of orthostatic symptoms. Puberty seemed to have the smallest effect on activities of daily living (e.g., work, chores, dressing, bathing) in females (p=0.0134) and males (p=0.1246) in comparison to its effects on other orthostatic symptoms.

**Headaches**

Different questionnaires were used for subjects younger than 18-year old and subjects 18 or above, therefore, we separated them into these two age groups when examined the headache. Eight subjects were 18 or above, with all being post-pubertal females. In subjects below 18 year old, 73 had complete headache scores, among which 27 (37%) reported no headache at all in the past three months (headache score=0). Therefore, we dichotomized headache into two groups: no headache (score=0) vs. headache (score>0). The effect of sex and puberty on the odds of having headache was then tested. Our results supported an overall significant puberty effect (p=0.0290); in late/post puberty, the odds of having headache were 4.59 fold higher (95% CI: 1.17-17.95). In both males and females, the odds of having headache tended to be higher in the LPP groups,
though did not reach statistical significant level (data not shown). We then tested whether headache scores differ by sex or puberty in subjects who reported headache. No sex or puberty effects were detected (data not shown).

DISCUSSION

Primary Finding

FDI

The primary finding of this study was that females with EDS-HT in the LPP group experienced a greater amount of disability related to all of their symptoms compared to the EPP group. Males, on the other hand, did not show significantly higher overall disability in the LPP group. This difference in disability between different age groups expands upon a previous report by Castori et al (2010) in which he observed 21 individuals with EDS-HT, 18 of which were female, and noticed that symptoms in EDS-HT do not remain constant throughout the lifetime. Through this observation three phases seen in EDS-HT patients were classified. According to this model, the first stage is the “ligamentous laxity stage.” During this stage, children are very flexible and do not complain about muscle or joint pain. The second stage, the “pain stage,” begins in the second decade of life, during which we would expect puberty to occur. During this stage, individuals lose some hypermobility (although they remain more hyper-flexible than the general population) and begin experiencing muscle and joint pains. This pain limits their physical activity and is thought to impact their social and emotional daily life as well (Castori, Camerota, Celletti, Danese, et al., 2010; Rombaut et al., 2010). During the third stage, the “stiffness phase,” individuals experience a more limited range of joint motion.
This significantly higher amount of disability experienced solely by females in the LPP group may help to explain the sex bias in the condition which is found to be more profound in young adults and adults (Castori, Camerota, Celletti, Danese, et al., 2010; Kirk, Ansell, & Bywaters, 1967). This greater amount of disability experienced in the female LPP group may lead to females presenting to physicians and receiving a diagnosis. Alternatively, males, who do not seem to experience this significantly greater amount of disability, may never experience enough symptoms to cause them to visit a physician and receive a diagnosis. Furthermore, since this increase in symptom related disability does not occur until after females experience menarche it may play a role in the fact that females with EDS-HT are often diagnosed years after they begin experiencing symptoms (Baeza-Velasco, Gely-Nargeot, Bulbena Vilarrasa, & Bravo, 2011).

Specifically, females in the LPP group were seen to have significantly more disability related to more strenuous activity. The greatest difference in disability was shown to occur during activities in gym class (or playing sports) and walking up stairs. Disability was also found to significantly impede females in the LPP group from doing things with friends, doing chores, being up all day without resting, riding the school bus or traveling in the car, attending school all day, reading or doing homework, running the length of a football field and going shopping. No statistically significant change in disability was found to occur in walking, eating regular meals and getting to sleep and staying asleep at night. This finding was mostly supported by Rombaut et al. (2011) who assessed functional impairment in 72 females diagnosed with EDS-HT with a mean age of 40 and found that the greatest dysfunction was observed in work, recreation, home management, sleep and rest and alertness and the least dysfunction was found in eating.
Secondary Findings

Pain

The results of this study lead us to believe that the cause of the greater disability experienced by females in the LPP group compared to their EPP counterparts may be, at least in part, due to greater pain. Quality of life due to pain was found to be significantly lower in the female LPP group compared to females in the EPP group. This result expands upon previous research showing that pain in EDS-HT progresses over time, often presenting in the second decade of life and beginning to cause disability, which increased throughout time (Castori, Camerota, Celletti, Danese, et al., 2010; Sacheti et al., 1997). Other studies have found that adult females with EDS-HT experience pain, which affects their daily lives by interfering with daily activities or physical functioning (Rombaut, Malfait, De Paepe, et al., 2011; Rombaut, Malfait, De Wandele, et al., 2011; Sacheti et al., 1997; Voermans, Knoop, Bleijenberg, & van Engelen, 2010).

The first part of the PedsQL rheumatology module asks four questions about pain and aching, all four of these questions were found to be significantly more debilitating in females who fall into the LPP group compared to females in the EPP group. Interestingly, despite there being no significant difference between the EPP and LPP groups in the FDI question asking if participants have trouble getting to sleep at night and staying asleep at night, there was a significantly greater amount of disability experienced by females in the LPP group compared to the EPP group in a similar question on the PEDSQL, which asked if the participant had trouble sleeping because of pain. Previously other studies have shown that individuals with EDS have sleep related troubles due to their pain (Hoffman Jessica, 2008; Rombaut, Malfait, De Paepe, et al., 2011; Voermans et al., 2010).
Specific questions relating to worry and anxiety about their diagnosis, managing EDS-HT, the side effects from the medications, and difficulties explaining their illness to others were also found to be higher in females characterized as LPP compared to those characterized as EPP. This increase in worry and anxiety may be due to their greater disability. Based on these findings it may be beneficial for patients to have a better understanding of the progression of their disease. Moreover this finding may show us the importance of providing psychosocial counseling to patients either during puberty or directly afterwards to assess how patients are dealing with changes in symptoms.

Literature shows that joint hypermobility has been associated with fibromyalgia, a syndrome associated with chronic musculoskeletal pain (Acasuso-Diaz & Collantes-Estevez, 1998), with studies finding between 27 and 80% of individuals with fibromyalgia having hypermobility (Acasuso-Diaz & Collantes-Estevez, 1998; Gedalia, Press, Klein, & Buskila, 1993). In showing that pain increases in females at the time of puberty, we are now faced with the opportunity to intervene before the onset of chronic pain. By stabilizing the joint manifestations through physical therapy (Acasuso-Diaz & Collantes-Estevez, 1998) physicians may be able to prevent the diffuse chronic pain and stiffness typically experienced by individuals with fibromyalgia.

Orthostatic Symptoms

A significant change was found both in males or females separately when comparing EPP and LPP groups. This data is supported by other studies, which assert that in the general population orthostatic symptoms are found to be worse in post-pubertal individuals compared to
pre-pubertal (Johnson et al., 2010). This may be related to growth spurts experienced during puberty, which often precede the onset of orthostatic symptoms (Shirley et al., 2012).

Similarly to the FDI both males and females were found to be less severely affected in completing activities of daily living, which are less strenuous activities including work, chores, dressing and bathing.

*Headaches*

Disability due to headaches was also not found to have a statistically significant difference in either males or females when comparing EPP and LPP individuals. It should be noted here that a bias may exist in our headache analysis due to the way some patients filled out the questionnaire. The questionnaire asked for specific number of days patients experienced migraines or disability related to them. Some patients, predominantly more severely affected individuals, would write answers such as “most days” or “nearly always.” As there was no way of determining how many days these answers meant, this data was excluded; therefore, some of the most severely affected individuals have been excluded from analysis. Additionally a recall bias may be seen in this data since the questionnaires were asking the patient how many days in the last 3 months an individual had experienced different types of disability due to headaches. These biases may show that these questionnaires are not amenable to quantitative analysis.

*Theories Explaining Greater Disability Experienced In LPP Females*

Many mechanisms have been hypothesized for the increased prevalence of females diagnosed with EDS-HT, specifically in the young adult and adult populations (Castori, Camerota, Celletti, Grammatico, & Padua, 2010). One theory that explains this phenomenon is
hormonal changes occurring in females at puberty. Traudeau et al. 2003 found that pubertal changes lead to greater muscle strength in males and greater pain sensitivity in females; therefore, possibly causing the perception of less disability in males in the LPP group and more disability in females related to pain in the LPP group. It is hypothesized that these hormonal changes, including changes in estradiol and relaxin, and their association with collagen may be causing the increase in joint laxity (Aldabe, Ribeiro, Milosavljevic, & Dawn Bussey, 2012; Unemori & Amento, 1990), which may in turn lead to disability (Nicholas, 1970; Pacey, Nicholson, Adams, Munn, & Munns, 2010). Additionally, this may also explain the fact that Beighton scores were found to increase in late/post-pubertal aged females in previous studies (Jansson et al., 2004).

The effect of female sex hormones leading to excessive joint laxity leads us to propose that EDS-HT may follow a Threshold Model, in which the properties of the connective tissue determine the level of disability (Nicholas, 1970; Pacey et al., 2010). In this model, weakening of the already lax connective tissue, by actions of hormones such as estradiol and relaxin, will cause an individual to cross the threshold into disability. Conversely, factors that strengthen the connective tissue, such as testosterone, which has been shown to increase collagen formation (Fischer & Swain, 1977), will protect an individual by moving them further away from the threshold. Due to the inherent weakness in connective tissue quality, patients with EDS-HT start closer to the threshold and it is easier for them to cross the threshold into disability.

The results of our study add to these hypotheses, showing that aspects of puberty, presumably hormonal changes, not only cause a sex prevalence discrepancy, but also lead to females with EDS-HT experiencing more disability.
The short-term significance of this study lies in the ability to characterize the differences in the progression of the disorder in males and females at different pubertal statuses. This would provide physicians with a better understanding of the condition, which in turn allows them to give patients a more accurate idea of the symptoms they may experience in the future. Broadly, this study aims to establish the evidence base needed to pursue further clinical and laboratory-based experiments examining the effects hormonal changes have on the symptoms of EDS-HT. The hope is that these studies will ultimately lead to the identification of drug-targetable pathways in order to prevent disability from occurring.

**Limitations**

One limitation to this study was the limited number of males who were consented to participate in this study. Considering the literature reports a 9:1 ratio of female to male EDS-HT patients (Shirley et al., 2012), we attempted to rectify this bias by sending out mailings inviting first-degree relatives of diagnosed individuals to participate. Despite these efforts, we were only able to recruit 24 males meeting the Beighton criteria, of which only 5 were post-puberty. This limited number of post-pubertal males may have been the reason for us not finding a significant difference in any of the symptoms when comparing males and females stratified for pubertal status. A post-hoc analysis was performed which indicated that to achieve 80% power, 20 males and 20 females would be required to detect a statistically significant difference at alpha=0.05 level between male and female FDI scores post puberty.

Additionally, since the participants in this study have been referred to Connective Tissue Clinic they are not generalizable to the hypermobile population at large, many of which have never experienced enough symptoms to cause them to present for treatment.
Lastly, since this research consisted of a cross-sectional design we were not able to monitor changes throughout puberty. While we are able to draw conclusions based on significant differences between EPP and LPP groups, we are not able to pinpoint when these changes in disability occur.

Applications

Little is known about the progression of symptoms related to EDS-HT in relation to sex. This research may help give a more accurate prognosis of symptom progression throughout a patient’s lifetime. By identifying the time frame in which we would expect females to begin experiencing an increase in disability we hope to guide future researchers to examine hormonal pathways and their downstream effectors related to puberty. If the mechanism for this increase in disability is found we hope that preventative strategies and treatments can be set in place to preclude more severe symptoms.

Conclusions

Our study indicates that the overall disability related to a combination of all an individual’s symptoms is higher in late/post-puberty females compared to early/pre-puberty females with EDS-HT. Strenuous physical activity was found to be the area of life most impaired. This overall increase in disability is probably at least partially due to the lower PEDSQL QOL –pain related score seen in females in the LPP group. In order to best treat or prevent this increased disability we believe action must be taken in early/pre-puberty, especially in females.
TABLES AND FIGURES:

Figure 1:

112 individuals met the inclusion criteria and were consented into the study

21 individuals were excluded from analysis

The final study sample consisted of 91 individuals

19 EPP males
5 LPP males
25 EPP females
42 LPP females

* Twenty-one individuals were excluded, of these 9 were females, 11 were males, and one did not mark sex. One individual had an ankle injury followed by multiple surgeries resulting in nonambulatory or reduced ambulatory status for approximately four years. This was substantially different than the ambulatory EDS-HT population. Two individuals were excluded due to not filling out the Tanner or Beighton questionnaires, another was excluded due to filling out the wrong form, one individual was excluded due to having a second diagnosis of Crohn’s disease and sixteen individuals were excluded from analysis due to having a Beighton score under 5.
<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EPP</td>
<td>LPP</td>
</tr>
<tr>
<td>N</td>
<td>19 (79%)</td>
<td>5 (21%)</td>
</tr>
<tr>
<td>Age</td>
<td>9(8-11)</td>
<td>14(14-16)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>18 (94.7%)</td>
<td>4 (80.0%)</td>
</tr>
<tr>
<td>Beighton Score</td>
<td>7(6-8)</td>
<td>6(6-6)</td>
</tr>
</tbody>
</table>

Note: Age and Beighton scores are shown as median (IQR); the rest of the data is shown as N (proportion)
Table 2: FDI questions

<table>
<thead>
<tr>
<th>Activity</th>
<th>Males EPP n=19</th>
<th>Males LPP n=5</th>
<th>p</th>
<th>Females EPP n=25</th>
<th>Females LPP n=42</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walking to the bathroom</td>
<td>0(0-0)</td>
<td>0(0-0)</td>
<td>1.0000</td>
<td>0(0-0)</td>
<td>0(0-1)</td>
<td>0.1875</td>
</tr>
<tr>
<td>Walking up stairs</td>
<td>0(0-1)</td>
<td>0(0-1)</td>
<td>0.7360</td>
<td>0(0-0)</td>
<td>1(1-2)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Doing something with a friend (ex: playing a game)</td>
<td>0(0-1)</td>
<td>0(0-1)</td>
<td>1.0000</td>
<td>0(0-0)</td>
<td>1(0-2)</td>
<td>0.0025</td>
</tr>
<tr>
<td>Doing chores at home</td>
<td>0(0-0)</td>
<td>1(0-1)</td>
<td>0.1525</td>
<td>0(0-1)</td>
<td>0(0-1)</td>
<td>0.3629</td>
</tr>
<tr>
<td>Eating regular meals</td>
<td>0(0-0)</td>
<td>0(0-0)</td>
<td>0.5440</td>
<td>0(0-1)</td>
<td>0(0-1)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Being up all day without a nap or rest</td>
<td>0(0-0)</td>
<td>1(0-1)</td>
<td>0.2689</td>
<td>0(0-1)</td>
<td>2(0-3)</td>
<td>0.0206</td>
</tr>
<tr>
<td>Riding the school bus or traveling in the car</td>
<td>0(0-0)</td>
<td>0(0-0)</td>
<td>1.0000</td>
<td>0(0-1)</td>
<td>1(0-2)</td>
<td>0.0228</td>
</tr>
<tr>
<td>Being at school all day</td>
<td>0(0-1)</td>
<td>1(0-1)</td>
<td>0.4615</td>
<td>0(0-1)</td>
<td>2(0-2)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Doing the activities in gym class (or playing sports)</td>
<td>0(0-1)</td>
<td>2(0-3)</td>
<td>0.1448</td>
<td>0(0-1)</td>
<td>3(1-3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Reading or doing homework</td>
<td>0(0-0)</td>
<td>0(0-1)</td>
<td>0.5104</td>
<td>0(0-1)</td>
<td>1(0-2)</td>
<td>0.0068</td>
</tr>
<tr>
<td>Watching TV</td>
<td>0(0-0)</td>
<td>0(0-0)</td>
<td>0.2083</td>
<td>0(0-0)</td>
<td>0(0-0)</td>
<td>0.0683</td>
</tr>
<tr>
<td>Walking the length of a football field</td>
<td>0(0-1)</td>
<td>1(0-2)</td>
<td>0.1650</td>
<td>1(0-1)</td>
<td>1(0-2)</td>
<td>0.0682</td>
</tr>
<tr>
<td>Running the length of a football field</td>
<td>0(0-2)</td>
<td>2(0-2)</td>
<td>0.4745</td>
<td>1(0-3)</td>
<td>3(1-4)</td>
<td>0.0024</td>
</tr>
<tr>
<td>Going shopping</td>
<td>0(0-1)</td>
<td>0(0-1)</td>
<td>1.0000</td>
<td>0(0-1)</td>
<td>1(0-2)</td>
<td>0.0083</td>
</tr>
<tr>
<td>Getting to sleep at night and staying asleep</td>
<td>0(0-2)</td>
<td>1(0-1)</td>
<td>0.7431</td>
<td>1(0-2)</td>
<td>2(0-3)</td>
<td>0.0617</td>
</tr>
</tbody>
</table>

Note: All scores are shown as median (IQR). Difference between pre and post puberty was tested using exact Wilcoxon Rank Sum tests
Table 3: PEDSQL Quality of Life related to pain questions

<table>
<thead>
<tr>
<th>Question</th>
<th>Males</th>
<th>Females</th>
<th>p</th>
<th>Males</th>
<th>Females</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>I ache or hurt in my joints and/or muscles</td>
<td>50 (50-50)</td>
<td>50 (0-75)</td>
<td>0.7919</td>
<td>50 (25-50)</td>
<td>25 (0-50)</td>
<td>0.0025</td>
</tr>
<tr>
<td>I hurt a lot</td>
<td>75 (50-100)</td>
<td>75 (25-100)</td>
<td>0.8083</td>
<td>75 (50-100)</td>
<td>50 (25-75)</td>
<td>0.0129</td>
</tr>
<tr>
<td>I have trouble sleeping because of pain or aching in my joints and/or muscles</td>
<td>75 (75-100)</td>
<td>100 (100-100)</td>
<td>0.2680</td>
<td>75 (50-100)</td>
<td>50 (25-75)</td>
<td>0.0122</td>
</tr>
<tr>
<td>I feel stiff in the morning or when I sit too long</td>
<td>100 (50-100)</td>
<td>75 (75-75)</td>
<td>0.8939</td>
<td>75 (50-100)</td>
<td>50 (13-75)</td>
<td>0.0008</td>
</tr>
<tr>
<td>It is hard to turn on water faucets</td>
<td>100 (100-100)</td>
<td>100 (100-100)</td>
<td>1.0000</td>
<td>100 (100-100)</td>
<td>100 (75-100)</td>
<td>0.1476</td>
</tr>
<tr>
<td>It is hard to turn door handles</td>
<td>100 (100-100)</td>
<td>100 (100-100)</td>
<td>0.5776</td>
<td>100 (100-100)</td>
<td>100 (75-100)</td>
<td>0.1120</td>
</tr>
<tr>
<td>I have trouble eating with a fork and knife</td>
<td>100 (50-100)</td>
<td>100 (100-100)</td>
<td>0.2561</td>
<td>100 (100-100)</td>
<td>100 (75-100)</td>
<td>0.3445</td>
</tr>
<tr>
<td>It is hard to write or draw with a pen or pencil</td>
<td>75 (50-100)</td>
<td>100 (100-100)</td>
<td>0.1012</td>
<td>100 (50-100)</td>
<td>75 (50-100)</td>
<td>0.3776</td>
</tr>
<tr>
<td>I have trouble carrying my school books</td>
<td>100 (75-100)</td>
<td>100 (75-100)</td>
<td>1.0000</td>
<td>75 (50-100)</td>
<td>50 (25-100)</td>
<td>0.4056</td>
</tr>
<tr>
<td>My medicine makes me feel sick</td>
<td>100 (100-100)</td>
<td>100 (100-100)</td>
<td>1.0000</td>
<td>100 (75-100)</td>
<td>100(75-100)</td>
<td>0.1040</td>
</tr>
<tr>
<td>My PT or daily exercise hurts</td>
<td>100 (25-100)</td>
<td>100 (75-100)</td>
<td>0.5124</td>
<td>75 (50-75)</td>
<td>50 (25-100)</td>
<td>0.9091</td>
</tr>
<tr>
<td>It is hard to be responsible for my medicines or physical therapy</td>
<td>100 (38-100)</td>
<td>100 (75-100)</td>
<td>0.7189</td>
<td>100 (50-100)</td>
<td>75 (50-100)</td>
<td>0.1405</td>
</tr>
<tr>
<td>It is hard to manage my illness</td>
<td>100 (50-100)</td>
<td>100 (100-100)</td>
<td>0.7853</td>
<td>100 (50-100)</td>
<td>50 (25-75)</td>
<td>0.0148</td>
</tr>
<tr>
<td>I get scared when I have to have blood tests</td>
<td>50 (50-100)</td>
<td>100(75-100)</td>
<td>0.1330</td>
<td>50 (0-100)</td>
<td>50 (25-100)</td>
<td>0.8410</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>75 (IQR)</td>
<td>50 (IQR)</td>
<td>75 (IQR)</td>
<td>50 (IQR)</td>
<td>0.2468</td>
</tr>
<tr>
<td>----------------------------------------------------------------</td>
<td>--------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
<td>---------</td>
</tr>
<tr>
<td>I get scared about having needle sticks/shots</td>
<td>63 (0-100)</td>
<td>100 (75-100)</td>
<td>0.2652</td>
<td>75 (0-100)</td>
<td>50 (0-100)</td>
<td>0.8084</td>
</tr>
<tr>
<td>I get scared when I have to go the doctor</td>
<td>75 (75-100)</td>
<td>100 (100-100)</td>
<td>0.0761</td>
<td>75 (50-75)</td>
<td>75 (50-100)</td>
<td>0.2702</td>
</tr>
<tr>
<td>I worry about the side effects from medicines</td>
<td>100 (100-100)</td>
<td>100 (100-100)</td>
<td>1.0000</td>
<td>100 (100-100)</td>
<td>75 (50-100)</td>
<td>0.0064</td>
</tr>
<tr>
<td>I worry about whether or not my medicines are working</td>
<td>100 (75-100)</td>
<td>100 (75-100)</td>
<td>0.8880</td>
<td>100 (75-100)</td>
<td>75 (50-100)</td>
<td>0.1272</td>
</tr>
<tr>
<td>I worry about my illness</td>
<td>100 (50-100)</td>
<td>75 (75-75)</td>
<td>0.4029</td>
<td>75 (50-100)</td>
<td>50 (25-75)</td>
<td>0.0057</td>
</tr>
<tr>
<td>It is hard for me to tell the doctors and nurses how I feel</td>
<td>75 (50-100)</td>
<td>75 (50-75)</td>
<td>0.7520</td>
<td>75 (50-100)</td>
<td>50 (50-100)</td>
<td>0.3882</td>
</tr>
<tr>
<td>It is hard for me to ask the doctors and nurses questions</td>
<td>75 (50-100)</td>
<td>75 (75-100)</td>
<td>0.7768</td>
<td>75 (50-75)</td>
<td>75 (25-100)</td>
<td>0.7651</td>
</tr>
<tr>
<td>It is hard for me to explain my illness to other people</td>
<td>75 (50-100)</td>
<td>50 (50-50)</td>
<td>0.3874</td>
<td>75 (50-100)</td>
<td>50 (25-100)</td>
<td>0.0304</td>
</tr>
</tbody>
</table>

Note: All scores are shown as median (IQR). Difference between pre and post puberty was tested using exact Wilcoxon Rank Sum tests
Table 4: OSG

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th></th>
<th>Females</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EPP</td>
<td>LPP</td>
<td>p</td>
<td>EPP</td>
</tr>
<tr>
<td>n=19</td>
<td>n=5</td>
<td></td>
<td>n=25</td>
<td>n=42</td>
</tr>
<tr>
<td>Frequency of orthostatic symptoms</td>
<td>0 (0-1)</td>
<td>1 (1-1)</td>
<td>0.012</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>Severity of orthostatic symptoms</td>
<td>0 (0-1)</td>
<td>2 (2-3)</td>
<td>0.001</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>Conditions under which orthostatic symptoms occur</td>
<td>0 (0-1)</td>
<td>1 (0-2)</td>
<td>0.1508</td>
<td>1 (0-1)</td>
</tr>
<tr>
<td>Activities of daily living</td>
<td>0 (0-0)</td>
<td>1 (0-1)</td>
<td>0.0785</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>Standing time</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
<td>1</td>
<td>0 (0-0)</td>
</tr>
</tbody>
</table>

Note: All scores are shown as median (IQR). Difference between pre and post puberty was tested using exact Wilcoxon Rank Sum tests.
**Figure 2:** This figure shows the least square mean of FDI score ± SE for males and females in early/pre-puberty and late/post-puberty.
Figure 3: This figure shows the least square mean of QOL-pain score ± SE for males and females in early/pre-puberty and late/post-puberty.
Figure 4: This figure shows the least square mean of OSG score $\pm$ SE for males and females in early/pre-puberty and late/post-puberty.

- For females:
  - Early/Pre-puberty: $n=25$, Mean = 7.0, SE = 0.5
  - Late/Post-puberty: $n=42$, Mean = 8.5, SE = 0.3
  - $p<0.0001$

- For males:
  - Early/Pre-puberty: $n=19$, Mean = 4.0, SE = 0.4
  - Late/Post-puberty: $n=5$, Mean = 5.0, SE = 0.6
  - $p=0.035$


Appendix A

The Physician performed Belighton scoring and Physical Examination


**Beighton Scoring and Physical Examination**

**Beighton Exam:**

<table>
<thead>
<tr>
<th>Joint</th>
<th>Finding</th>
<th>+/-</th>
</tr>
</thead>
<tbody>
<tr>
<td>left little (fifth) finger</td>
<td>passive dorsiflexion beyond 90°</td>
<td></td>
</tr>
<tr>
<td>right little (fifth) finger</td>
<td>passive dorsiflexion beyond 90°</td>
<td></td>
</tr>
<tr>
<td>left thumb</td>
<td>passive dorsiflexion to the flexor aspect of the forearm</td>
<td></td>
</tr>
<tr>
<td>right thumb</td>
<td>passive dorsiflexion to the flexor aspect of the forearm</td>
<td></td>
</tr>
<tr>
<td>left elbow</td>
<td>hyperextends beyond 10°</td>
<td></td>
</tr>
<tr>
<td>right elbow</td>
<td>hyperextends beyond 10°</td>
<td></td>
</tr>
<tr>
<td>left knee</td>
<td>hyperextends beyond 10°</td>
<td></td>
</tr>
<tr>
<td>right knee</td>
<td>hyperextends beyond 10°</td>
<td></td>
</tr>
<tr>
<td>forward flexion of trunk with knees full extended</td>
<td>palms and hands can rest flat on the floor</td>
<td></td>
</tr>
</tbody>
</table>

**Skin Findings:**

Presence stria                          | Yes / No                        |
Presence of bruises                     | Yes / No                        |
If yes approximate size of bruising     | cm                             |
Hyperextensible skin                    | Yes / No                        |

**Physical Findings:**

Shoulders:

Reverse Namaste                         | Yes / No                        |

Jaw:

Can open more than 40mm                 | Yes / No                        |

**Family History:**

Family History:

Suspected                                | Yes / No                        |
Confirmed                                | Yes / No                        |
Appendix B

The Questionnaire

*Different questionnaires were given based on a participant’s age and sex. For this manuscript all of the questionnaires have been compiled into a single document and are marked as to which participant population fills out each page (Page that do not indicate a sex or age range are filled out by all participants)
Demographics

Please indicate your sex:

☐ Male
☐ Female

Please indicate your age: __________

What grade are you in (if not in school please mark n/a): __________

If you marked n/a above please indicate the highest amount of schooling you have achieved:

☐ Completed some of high school
☐ Graduated high school or GED
☐ Completed some of college
☐ Graduated from an associate or trade program
☐ Graduated with a bachelors degree
☐ Completed some of a masters program
☐ Graduated with a masters degree

Please indicate your race (Select all that apply):

☐ Caucasian
☐ African American
☐ Asian
☐ Hawaiian/Pacific Islander
☐ Native American/Alaskan native
☐ Other

If other please indicate ______

Please select your ethnicity:

☐ Hispanic
☐ Non-Hispanic

Are you currently employed outside of the home:

☐ Too young to work
☐ Yes, part time
☐ Yes, full time
☐ No, I work from home
☐ No, I am not currently employed
(Demographics Continued)

☐ Prefer not to answer

In what state do you currently live? ____________

What is your zip code? ____________

If you do not live in the United States please indicate what country you live in
Tanner Stage:
Place a check in the box by the number that most nearly describes you currently.

☐ 1  The preadolescent breast consists of a small, elevated nipple with no significant underlying breast tissue. The preadolescent has no pubic hair except for a fine "peach fuzz" body hair.

☐ 2  There is elevation of the breast and nipple as a small mound; the areola begins to enlarge. There is sparse growth of long, slightly darkened, downy hair mostly along the labia. This hair is usually straight or only slightly curled.

☐ 3  There is further enlargement and elevation of the breast and areola (with no separation of their contours). The areola begins to darken in color. The pubic hair becomes darker, coarser, and curlier. It now grows sparsely over the mons.

☐ 4  There is projection of the areola and nipple to form a secondary mound. The hair grows in more densely. It becomes as coarse and curly as in the adult, but there is not as much of it.

☐ 5  In the mature adult breast, there is projection of the nipple only. The mature adult has the classic coarse and curly pubic hair that extends onto the inner thighs.
Tanner Stage:
Place a check in the box by the number that most nearly describes you currently.

☐ 1 There is no pubic hair (except for a fine peach fuzz similar to that on the belly and elsewhere) and the penis and testicles are in the same proportions as in childhood.

☐ 2 There is sparse growth of long, slightly darkened, pubic hair at the base of the penis. The testicles begin to get larger, and the scrotum begins to get a reddened and altered texture. The penis may grow slightly or not at all.

☐ 3 The pubic hair gets darker, coarser, and curlier. It begins to spread over the pubic bone. The testicles continue to enlarge and the scrotal texture becomes more like that of an adult. The penis gets longer.

☐ 4 The pubic hair grows to cover the base of the penis and begins to grow on the upper part of the scrotum. The hair gets darker, coarser, and curlier. The scrotal skin gets darker as the testicles continue to grow. The penis continues to grow longer, and gets wider. The glans, or head, of the penis becomes much more prominent.

☐ 5 The pubic hair has spread to the inside of the thighs. The scrotum, testicles, and penis grow to their final adult size and shape.
Females:

Have you started to have periods?

☐ Yes
☐ No

If you answered yes above, how old were you when you had your first period? _____________

Have you had a growth spurt?

☐ I have not had a growth spurt
☐ I am currently having a growth spurt
☐ I have already had a growth spurt
☐ I do not know

39
**Functional Disability Inventory**  
**Parent Form**

When people are sick or not feeling well it is sometimes difficult for them to do their regular activities. In the past two weeks, would your child have had any physical trouble or difficulty doing these activities?

<table>
<thead>
<tr>
<th>No Trouble</th>
<th>A Little Trouble</th>
<th>Some Trouble</th>
<th>A Lot of Trouble</th>
<th>Impossible</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Walking up stairs.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
| 3. Doing something with a friend.  
(For example, playing a game.) | 0 | 1 | 2 | 3 | 4 |
| 4. Doing chores at home. | 0 | 1 | 2 | 3 | 4 |
| 5. Eating regular meals. | 0 | 1 | 2 | 3 | 4 |
| 6. Being up all day without a nap or rest. | 0 | 1 | 2 | 3 | 4 |
| 7. Riding the school bus or travelling in the car. | 0 | 1 | 2 | 3 | 4 |

*Remember, you are being asked about difficulty due to physical health.*

| 8. Being at school all day. | 0 | 1 | 2 | 3 | 4 |
| 9. Doing the activities in gym class (or playing sports). | 0 | 1 | 2 | 3 | 4 |
| 10. Reading or doing homework. | 0 | 1 | 2 | 3 | 4 |
| 11. Watching TV. | 0 | 1 | 2 | 3 | 4 |
| 12. Walking the length of a football field. | 0 | 1 | 2 | 3 | 4 |
| 13. Running the length of a football field. | 0 | 1 | 2 | 3 | 4 |
| 14. Going shopping. | 0 | 1 | 2 | 3 | 4 |
| 15. Getting to sleep at night and staying asleep. | 0 | 1 | 2 | 3 | 4 |

40
### Functional Disability Inventory

**Child and Adolescent Form**

When people are sick or not feeling well it is sometimes difficult for them to do their regular activities. In the past two weeks, would you have had any physical trouble or difficulty doing these activities?

<table>
<thead>
<tr>
<th></th>
<th>No Trouble</th>
<th>A Little Trouble</th>
<th>Some Trouble</th>
<th>A Lot of Trouble</th>
<th>Impossible</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Walking to the bathroom.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Walking up stairs.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Doing something with a friend. (For example, playing a game.)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Doing chores at home.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Eating regular meals.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. Being up all day without a nap or rest.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. Riding the school bus or traveling in the car.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

**Remember, you are being asked about difficulty due to physical health.**

<table>
<thead>
<tr>
<th></th>
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<tr>
<td>8. Being at school all day.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9. Doing the activities in gym class (or playing sports).</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10. Reading or doing homework.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11. Watching TV.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>12. Walking the length of a football field.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>13. Running the length of a football field.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>14. Going shopping.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>15. Getting to sleep at night and staying asleep.</td>
<td>0</td>
<td>1</td>
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</table>
When people are sick or not feeling well, it is sometimes difficult for them to do their regular activities. Now, I'm going to read you a list of activities. I want to know if you would have had any physical trouble or difficulty doing these activities during the past two weeks. You will have five answers to choose from (no trouble, a little trouble, some trouble, a lot of trouble, and impossible).

In the past two weeks, would you have had any physical trouble or difficulty...?

<table>
<thead>
<tr>
<th>No Trouble</th>
<th>A Little Trouble</th>
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<td>6. Being up all day without a nap or rest.</td>
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<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. Traveling in a car or other vehicle.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

*Remember, you are being asked about difficulty due to physical health.*

| 8. Being at school or work all day. | 0 | 1 | 2 | 3 | 4 |
| 9. Playing sports, going to the gym, or exercising | 0 | 1 | 2 | 3 | 4 |
| 10. Reading or concentrating. | 0 | 1 | 2 | 3 | 4 |
| 11. Watching TV. | 0 | 1 | 2 | 3 | 4 |
| 12. Walking the length of a football field. | 0 | 1 | 2 | 3 | 4 |
| 13. Running the length of a football field. | 0 | 1 | 2 | 3 | 4 |
| 14. Going shopping. | 0 | 1 | 2 | 3 | 4 |
| 15. Getting to sleep at night and staying asleep. | 0 | 1 | 2 | 3 | 4 |
At what age did you begin to notice disability due to the combination of symptoms?

Did you begin noticing this disability before or after you started menstruating?

- □ Before
- □ After
- □ I have not started menstruating yet
- □ I do not experience symptoms
- □ I am a male (not applicable)
Self-report Orthostatic Grading Scale

The following test asks about "orthostatic symptoms" which means feeling faint, dizzy or light headed upon standing or sitting up.

How many times do you experience faintness in a three month time span:
0-3 times 4-6 times 7-9 times

1. Frequency of orthostatic symptoms
   0 I never or rarely experience orthostatic symptoms when I stand up
   1 I sometimes experience orthostatic symptoms when I stand up
   2 I often experience orthostatic symptoms when I stand up
   3 I usually experience orthostatic symptoms when I stand up
   4 I always experience orthostatic symptoms when I stand up

2. Severity of orthostatic symptoms
   0 I do not experience orthostatic symptoms when I stand up
   1 I experience mild orthostatic symptoms when I stand up
   2 I experience moderate orthostatic symptoms when I stand up and sometimes have to sit back down for relief
   3 I experience severe orthostatic symptoms when I stand up and frequently have to sit back down for relief
   4 I experience severe orthostatic symptoms when I stand up and regularly faint if I do not sit back down

3. Conditions under which orthostatic symptoms occur
   0 I never or rarely experience orthostatic symptoms under any circumstances
   1 I sometimes experience orthostatic symptoms under certain conditions, such as prolonged standing, a meal, exertion (eg, walking), or when exposed to heat (eg, hot day, hot bath, hot shower)
   2 I often experience orthostatic symptoms under certain conditions, such as prolonged standing, a meal, exertion (eg, walking), or when exposed to heat (eg, hot day, hot bath, hot shower)
   3 I usually experience orthostatic symptoms under certain conditions, such as prolonged standing, a meal, exertion (eg, walking), or when exposed to heat (eg, hot day, hot bath, hot shower)
   4 I always experience orthostatic symptoms when I stand up; the specific conditions do not matter

4. Activities of daily living
   0 My orthostatic symptoms do not interfere with activities of daily living (eg, work, chores, dressing, bathing)
   1 My orthostatic symptoms mildly interfere with activities of daily living (eg, work, chores, dressing, bathing)
   2 My orthostatic symptoms moderately interfere with activities of daily living (eg, work, chores, dressing, bathing)
3 My orthostatic symptoms severely interfere with activities of daily living (e.g., work, chores, dressing, bathing).
4 My orthostatic symptoms severely interfere with activities of daily living (e.g., work, chores, dressing, bathing). I am bed or wheelchair bound because of my symptoms.

5. Standing time
0 On most occasions, I can stand as long as necessary without experiencing orthostatic symptoms.
1 On most occasions, I can stand more than 15 minutes before experiencing orthostatic symptoms.
2 On most occasions, I can stand 5-14 minutes before experiencing orthostatic symptoms.
3 On most occasions, I can stand 1-4 minutes before experiencing orthostatic symptoms.
4 On most occasions, I can stand less than 1 minute before experiencing orthostatic symptoms.

At what age did you begin to notice symptoms of POTS (symptoms include faintness, lightheadedness or dizziness upon standing or sitting up)?

Did you begin noticing symptoms of POTS before or after you started menstruating?

☐ Before
☐ After
☐ I have not started menstruating yet
☐ I do not experience symptoms
☐ I am a male (not applicable)
1. Please rate how much pain you think your child is having at the present time by placing a mark somewhere on the line.

Not hurting
No discomfort
No pain

Hurting a whole lot
Very uncomfortable
Severe Pain

2. Please rate how severe the worst pain your child had in the past week (7 days) by placing a mark somewhere on the line.

Not hurting
No discomfort
No pain

Hurting a whole lot
Very uncomfortable
Severe Pain
Please mark an X on the exact place where you think your child is having pain now. If there is more than one painful place, mark them '1', '2', '3', etc., starting with the most painful place as '1'.
**PedsQL™**

Rheumatology Module

Version 3.0

PARENT REPORT for YOUNG CHILDREN (ages 5-7)

---

**DIRECTIONS**

Children with a rheumatic illness sometimes have special problems. On the following page is a list of things that might be a problem for your child. Please tell us how much of a problem each one has been for your child during the past ONE month by circling:

0 If it is never a problem
1 If it is almost never a problem
2 If it is sometimes a problem
3 If it is often a problem
4 If it is almost always a problem

There are no right or wrong answers. If you do not understand a question, please ask for help.

---

In the past ONE month, how much of a problem has your child had with ...

---

PedsQL 3.0 - Parent (5-7) Rheumatology

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### PAIN AND HURT (problems with...)

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
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</tr>
</thead>
<tbody>
<tr>
<td>1. Aches in joints and/or muscles</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Having a lot of pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Trouble sleeping because of pain or aching in joints and/or muscles</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Feeling stiff in the morning or when he/she sits too long</td>
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<td>3</td>
<td>4</td>
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### DAILY ACTIVITIES (problems with...)

<table>
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>1. Difficulty turning on water faucets</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Difficulty turning door handles</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Trouble eating with a fork and spoon</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Difficulty writing or drawing with a pen or pencil</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Difficulty carrying school books</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### TREATMENT (problems with...)

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</thead>
<tbody>
<tr>
<td>1. Medicines making him/her feel sick</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Physical therapy or daily exercise causing pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Getting anxious about having blood drawn</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Getting anxious about having needle sticks/shots</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Getting anxious about going to the doctor</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### WORRY (problems with...)

<table>
<thead>
<tr>
<th></th>
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<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Worrying about side effects from medicines</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Worrying about whether or not medicines are working</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Worrying about his/her illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### COMMUNICATION (problems with...)

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Difficulty telling the doctors and nurses how he/she feels</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Difficulty asking the doctors or nurses questions</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Difficulty explaining his/her illness to other people</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
**PedsQL™**

**Pediatric Pain Questionnaire™**

*Parent of Child Form (8-12 years of age)*

| Name: | |
| Date: | Record Number: |

What words would you use to describe your child's pain or hurt?

| |
| |

1. Please rate how much pain you think your child is having at the present time by placing a mark somewhere on the line.

- [ ] Not hurting
- [ ] No discomfort
- [ ] No pain
- [ ] Hurting a whole lot
- [ ] Very uncomfortable
- [ ] Severe Pain

2. Please rate how severe the worst pain you think your child had in the past week (7 days) by placing a mark somewhere on the line.

- [ ] Not hurting
- [ ] No discomfort
- [ ] No pain
- [ ] Severe Pain
Please mark an X on the exact place where you think your child is having pain now. If there is more than one painful place, mark them ‘1’, ‘2’, ‘3’, etc., starting with the most painful place as ‘1’.
PedsQL™
Rheumatology Module
Version 3.0

PARENT REPORT for CHILDREN (ages 8-12)

DIRECTIONS

Children with a rheumatic illness sometimes have special problems. On the following page is a list of things that might be a problem for your child. Please tell us how much of a problem each one has been for your child during the past ONE month by circling:

0 if it is never a problem
1 if it is almost never a problem
2 if it is sometimes a problem
3 if it is often a problem
4 if it is almost always a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

In the past ONE month, how much of a problem has your child had with...
# PAIN AND HURT (problems with...)

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<td>3. Difficulty being responsible for medicines or physical therapy</td>
<td>0</td>
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<td>4. Difficulty managing his/her illness</td>
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<tr>
<th></th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Difficulty telling the doctors and nurses how he/she feels</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Difficulty asking the doctors or nurses questions</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Difficulty explaining his/her illness to other people</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
Name: ____________________________

Date: __________ Record Number: __________

What words would you use to describe your pain or hurt?

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

1. Put a mark on the line that best shows how you feel now. If you have no pain or hurt, you would put a mark at the end of the line by the happy face. If you have some pain or hurt, you would put a mark near the middle of the line. If you have a whole lot of pain or hurt, you would put a mark by the sad face.

Not hurting
No discomfort
No pain

Hurtling a whole lot
Very uncomfortable
Severe Pain

2. Put a mark on the line that best shows what was the worst pain you had this week. If you had no pain or hurt this week, you would put a mark at the end of the line by the happy face. If you had some pain or hurt, you would put a mark by the middle of the line. If the worst pain you had was a whole lot of pain, you would put a mark by the sad face.

Not hurting
No discomfort
No pain

Hurtling a whole lot
Very uncomfortable
Severe Pain
Please mark an X on the exact place where you are having pain now. If there is more than one painful place, mark them '1', '2', '3', etc., starting with the most painful place as '1'.
DIRECTIONS

Teens with a rheumatic illness sometimes have special problems. Please tell us how much of a problem each one has been for you during the past ONE month by circling:

0 if it is never a problem
1 if it is almost never a problem
2 if it is sometimes a problem
3 if it is often a problem
4 if it is almost always a problem

There are no right or wrong answers. If you do not understand a question, please ask for help.
In the past ONE month, how much of a problem has this been for you ...

### Pain and Hurt (problems with...)

<table>
<thead>
<tr>
<th>Problem</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I ache or hurt in my joints and/or muscles.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. I hurt a lot</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. I have trouble sleeping because of pain or aching in my joints and/or muscles</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. I feel stiff in the morning or when I sit too long</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### Daily Activities (problems with...)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. It is hard to turn on water faucets</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. It is hard to turn door handles</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. I have trouble eating with a fork and knife</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. It is hard to write or draw with a pen or pencil</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. I have trouble carrying my school books</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### Treatment (problems with...)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. My medicines make me feel sick</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. My physical therapy or daily exercise hurts</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. It is hard to be responsible for my medicines or physical therapy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. It is hard to manage my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. I get scared when I have to have blood tests</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. I get scared about having needle sticks/shots</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. I get scared when I have to go the doctor</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### Worry (problems with...)

<table>
<thead>
<tr>
<th>Worry</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I worry about the side effects from medicines</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. I worry about whether or not my medicines are working</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. I worry about my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### Communication (problems with...)

<table>
<thead>
<tr>
<th>Communication</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. It is hard for me to tell the doctors and nurses how I feel</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. It is hard for me to ask the doctors and nurses questions</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. It is hard for me to explain my illness to other people</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
At what age did you begin to notice chronic pain? ________________

Did you begin noticing chronic pain before or after you started menstruating?

☐  Before
☐  After
☐  I have not started menstruating yet
☐  I do not experience symptoms
☐  I am a male (not applicable)
PedMIDAS

Headache Disability.

The following questions try to assess how much the headaches are affecting day-to-day activity. Your answers should be based on the last three months. There are no "right" or "wrong" answers so please put down your best guess.

1. How many full school days of school were missed in the last 3 months due to headaches?

2. How many partial days of school were missed in the last 3 months due to headaches (do not include full days counted in the first question)?

3. How many days in the last 3 months did you function at less than half your ability in school because of a headache (do not include days counted in the first two questions)?

4. How many days were you not able to do things at home (i.e., chores, homework, etc.) due to a headache?

5. How many days did you not participate in other activities due to headaches (i.e., play, go out, sports, etc.)?

6. How many days did you participate in these activities, but functioned at less than half your ability (do not include days counted in the 5th question)?

Total PedMIDAS Score

Headache Frequency

Headache Severity

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The Migraine Disability Assessment Test

The MIDAS (Migraine Disability Assessment) questionnaire was put together to help you measure the impact your headaches have on your life. The information on this questionnaire is also helpful for your primary care provider to determine the level of pain and disability caused by your headaches and to find the best treatment for you.

INSTRUCTIONS
Please answer the following questions about ALL of the headaches you have had over the last 3 months. Select your answer in the box next to each question. Select zero if you did not have the activity in the last 3 months.

1. On how many days in the last 3 months did you miss work or school because of your headaches?

2. How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches? (Do not include days you counted in question 1 where you missed work or school.)

3. On how many days in the last 3 months did you not do household work (such as housework, home repairs and maintenance, shopping, caring for children and relatives) because of your headaches?

4. How many days in the last 3 months was your productivity in household work reduced by half or more because of your headaches? (Do not include days you counted in question 3 where you did not do household work.)

5. On how many days in the last 3 months did you miss family, social or leisure activities because of your headaches?

Total (Questions 1-5)

A. On how many days in the last 3 months did you have a headache? (If a headache lasted more than 1 day, count each day.)

B. On a scale of 0 - 10, on average how painful were these headaches? (where 0 = no pain at all, and 10 = pain as bad as it can be.)

Scoring: After you have filled out this questionnaire, add the total number of days from questions 1-5 (ignore A and B)

<table>
<thead>
<tr>
<th>MIDAS Grade</th>
<th>Definition</th>
<th>MIDAS Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Little or no disability</td>
<td>0-5</td>
</tr>
<tr>
<td>II</td>
<td>Mild disability</td>
<td>6-10</td>
</tr>
<tr>
<td>III</td>
<td>Moderate disability</td>
<td>11-20</td>
</tr>
<tr>
<td>IV</td>
<td>Severe disability</td>
<td>21+</td>
</tr>
</tbody>
</table>

Please give the completed form to your clinician.

This survey was developed by Richard B. Lipton, MD, Professor of Neurology, Albert Einstein College of Medicine, New York, NY, and Walter F. Stewart, MPH, PhD, Associate Professor of Epidemiology, Johns Hopkins University, Baltimore, MD.
At what age did you begin to notice you had recurrent headaches? __________

Did you begin noticing recurrent headaches before or after you started menstruating?

☐ Before
☐ After
☐ I have not started menstruating yet
☐ I do not experience symptoms
☐ I am a male (not applicable)
Joint Dislocation Questionnaire

The joint dislocation survey was designed to assess the disability experienced by individuals due to joint dislocations. It looks at the effect joint dislocations has on the daily life (including activities, school, and work). This data will be collected and analyzed.

Joint dislocations are considered an injury to a joint, a place multiple bones come together, in which the ends of your bones are forced from their normal positions. This injury temporarily deforms and immobilizes your joint and may cause sudden and severe pain.

Please list any sports/physical activates (competitive or recreational) that you participate in and include an estimate of how often you perform these activities a month:

<table>
<thead>
<tr>
<th>Activity:</th>
<th>How many days per month:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1.) In the past three months indicate how many times you have dislocated each joint
   a. Right kneecap
      0 times 1-3 times 4-6 times 7-9 times 10 or more times
   b. Left kneecap
      0 times 1-3 times 4-6 times 7-9 times 10 or more times
   c. Right shoulder
      0 times 1-3 times 4-6 times 7-9 times 10 or more times
   d. Left shoulder
      0 times 1-3 times 4-6 times 7-9 times 10 or more times
   e. Right elbow
      0 times 1-3 times 4-6 times 7-9 times 10 or more times
   f. Left elbow
      0 times 1-3 times 4-6 times 7-9 times 10 or more times
   g. Right knee
h. Left knee
   0 times  1-3 times  4-6 times  7-9 times  10 or more times

i. I have not dislocated any joint within the past three months

2.) Of the joints you have dislocated within the past three months indicate which ones have required a medical professional to put the joint back into place
   a. Kneecap
      Right  Left  Both
   b. Shoulder
      Right  Left  Both
   c. Elbow
      Right  Left  Both
   d. Knee
      Right  Left  Both

   e. I have not dislocated any joint within the past three months

3.) In your lifetime indicate how many times you have dislocated each joint
   a. Right kneecap
      0 times  1-3 times  4-6 times  7-9 times  10 or more times

   b. Left kneecap
      0 times  1-3 times  4-6 times  7-9 times  10 or more times

   c. Right shoulder
      0 times  1-3 times  4-6 times  7-9 times  10 or more times

   d. Left shoulder
      0 times  1-3 times  4-6 times  7-9 times  10 or more times

   e. Right elbow
      0 times  1-3 times  4-6 times  7-9 times  10 or more times

   f. Left elbow
      0 times  1-3 times  4-6 times  7-9 times  10 or more times
g. Right knee
   0 times 1-3 times 4-6 times 7-9 times 10 or more times

h. Left knee
   0 times 1-3 times 4-6 times 7-9 times 10 or more times

i. I have not dislocated any joint in my lifetime

4.) How many days in the last three months did you miss family, social, or leisure activities because of a joint dislocation?
   0 days 1-3 days 4-6 days 7-9 days 10 or more days

5.) Circle the number, with 0 being does not interfere, and 10 being completely interferes, that describes how, during the past three months have joint dislocations interfered with your:

a.) General activity
   (does not interfere) 0 1 2 3 4 5 6 7 8 9 10 (completely interferes)

b.) Mood
   0 1 2 3 4 5 6 7 8 9 10

c.) Walking ability
   0 1 2 3 4 5 6 7 8 9 10

d.) Normal work (includes both outside the home and housework)
   0 1 2 3 4 5 6 7 8 9 10

e.) Relations with other people
   0 1 2 3 4 5 6 7 8 9 10

f.) Sleep
   0 1 2 3 4 5 6 7 8 9 10

g.) Enjoyment of life
   0 1 2 3 4 5 6 7 8 9 10

At what age did you begin to notice recurrent joint dislocations _______?

Did you begin noticing joint dislocations before or after you started menstruating?

☐ Before
☐ After
☐ I have not started menstruating yet
☐ I do not experience symptoms
☐ I am a male (not applicable)