RESEARCH ARTICLE

The Impact of Dyspepsia on Symptom Severity and Quality of Life in Adults with Headache

Mei-Ling Sharon Tai1*, Norbelinda Norhatta1, Khean Jin Goh1, Foong Ming Moy2, Ramanujam Sujarita3, Azman Ahmad Asraff1, Qin Zhi Lee1, Jiun Hoong Ng1, Eugene Choon Li Tan1, Sanjiv Mahadeva4

1 Division of Neurology, Department of Medicine, Faculty of Medicine, University Malaya, Kuala Lumpur, Malaysia, 2 Department of Social and Preventive Medicine, Faculty of Medicine, University Malaya, Kuala Lumpur, Malaysia, 3 Department of Primary Care, Faculty of Medicine, University Malaya, Kuala Lumpur, Malaysia, 4 Division of Gastroenterology, Department of Medicine, Faculty of Medicine, University Malaya, Kuala Lumpur, Malaysia

* sharont1990@gmail.com

Abstract

Background
Dyspepsia and headache frequently co-exist, but the clinical implication of this association is uncertain. We planned to examine the prevalence and impact of dyspepsia in adults with headache.

Methods
A cross-sectional study was conducted in a secondary care setting. Clinical, psychological and health-related quality of life (HRQOL) data were compared between subjects with headache and controls (non-headache subjects). The impact of dyspepsia was analysed further in subjects with headache alone.

Results
280 subjects (93 cases with headache and 187 matched controls) were recruited. The following baseline characteristics of subjects were as follows: mean age 45.0±17.3 years, 57.0% females and ethnic distribution—Malaysian = 45 (48.4%), Chinese n = 24 (25.8%) and Indians n = 24 (25.8%). Headache sub-types among cases with headache were as follows: tension-type headache (TTH) n = 53 (57.0%) and migraine n = 40 (43.0%). Dyspepsia was more prevalent in cases with headache compared to controls (25.8% vs 12.8%, p = 0.011), and headache was independently associated with dyspepsia (OR 2.75, 95% CI 1.39–5.43). Among cases with headache, there was a trend towards a higher prevalence of dyspepsia in those with migraine (27.5%) compared to TTH (24.5%). Subjects with headache and dyspepsia, compared to those with headache alone, had a greater severity of headache symptoms (63.67±22.85 mm vs 51.20±24.0 mm VAS, p = 0.029). Overall HRQOL scores were lower in headache subjects with dyspepsia (EQ-5D summary score
Conclusion

Dyspepsia is associated with more severe headache symptoms and results in a lower HRQOL in patients with headache.

Introduction

Headache and gastrointestinal symptoms are common in the community [1]. Previous studies have shown that the prevalence of headache in the community range from 17% to 21% [2, 3]. Similarly, upper gastrointestinal symptoms, particularly dyspepsia, have been reported to be prevalent in 24.3%–38.1% of the adult population [4]. Recent reports have suggested that these common conditions may be associated [5]. A higher prevalence of headache has been reported in adults who complained of various gastrointestinal symptoms such as reflux symptoms, diarrhoea, constipation and nausea [6]. Whilst more dyspepsia has been observed in migraine sufferers [7], a higher prevalence of migraine has been described in adults with dysmotility-like dyspepsia [5].

Several pathophysiological mechanisms have been suggested to explain the association between headache, particularly migraine, and dyspepsia. An abnormal visceral mechano-sensory vagal function [8, 9] and an excess of certain neuropeptides, have been described in both migraine and dyspepsia [10, 11]. The neuropeptide calcitonin gene-related peptide (CGRP) is known to increase during acute episodes of migraine [12]. CGRP is also an important neurotransmitter of the inhibitory sensory neuron and plays a role in visceral afferent nerve sensitization of the gastrointestinal tract, which can result in functional dyspepsia symptoms [13, 14].

Whilst the association of headache and dyspepsia is recognised, the impact of dyspepsia in patients with headache has not previously been studied. In particular, there is a paucity of data on health-related quality of life (HRQOL) consequences due to the co-existence of both conditions in a patient. We therefore conducted a study to provide more data in this area, in particular, to determine the prevalence of dyspepsia and examine its' impact on symptom severity and HRQOL in a cohort of Asian subjects with headache.

Methodology

Study subjects

A cross-sectional study was conducted in a tertiary institution, the University Malaya Medical Centre, from February 2012 until September 2012. The study was approved by the Institutional Ethics Committee of University Malaya Medical Centre. Cases consisted of subjects, aged ≥ 18 years, with headache at least once per month for more than three months attending the specialist neurology outpatient clinic. Patients with headache secondary to intracranial mass lesions and secondary headache were excluded. Patients with headache on aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs), a known history of gastroesophageal reflux or peptic ulcer disease were also excluded.

At the same time, control subjects who were age, gender and ethnicity matched with the study subjects, were recruited. They were non-related carers and friends who travelled with
patients. Written informed consent was obtained from all the study participants or their legally acceptable representatives.

Study design
All consenting subjects were interviewed with a structured questionnaire, which included information on relevant clinical and demographic parameters, details of headache characteristics, details of GI symptoms (see below), features of anxiety and/or depression (see below) and HRQOL (see below). The diagnosis of the headache was based on the International Headache Society (IHS) Criteria (ICHD III) [15]. The International Headache Society (IHS) classification, International Headache Criteria II (ICHD-III) was used to classify the headache subtypes [15]. The severity/intensity of headache symptoms was based on a visual analogue scale (VAS), which has previously been shown to be valid for this purpose [16].

Specific instruments
The presence of dyspepsia was confirmed by a locally translated and validated version of the Leeds Dyspepsia Questionnaire [17]. The LDQ is an eight item symptom-based questionnaire detailing the frequency and severity of various upper gastrointestinal symptoms [18]. The upper gastrointestinal symptoms comprise of dysphagia, belching, upper abdominal pain/discomfort, nausea, vomiting, heartburn, regurgitation, and post-prandial distension/early satiety. A score ranging from 0 to 40 can be calculated in the LDQ based on item frequency, and a cutoff of 11/40 has previously been shown to be diagnostic of significant dyspepsia in Malaysian adults [17]. The various subtypes of dyspepsia according to Rome II criteria were also documented based on the predominant symptom in the LDQ [19].

The Hospital Anxiety Depression Scale (HADS) [20] and the Hamilton Depression Scale [21] were used to assess for depression and anxiety in study subjects. The HADS consists of seven questions on anxiety and seven questions on depression, with relevant scoring for mild, moderate and severe disease. A translated version of the HADS has previously been validated and shown to be reliable in our local population [22]. The Hamilton Depression scale consists of 17 items which are rated and has relevant scores for mild, moderate and severe depression as well.

HRQOL was assessed using the EQ-5D (Euroqol). The EQ-5D comprises five questions on major domains of HRQOL, i.e. mobility, self-care, pain, usual activities and psychological status with three possible answers for each item (1 = no problems, 2 = moderate problems, 3 = severe problems) [23]. An overall utility score is calculated based on these domains, with a score ranging from 0 (worse health scenario) to a maximum of 1.0 (best health scenario). An additional visual analogue scale (VAS, scale 0–100) is used to assess general health status with 100 indicating the best health status. Malaysian English and Malaysian Malay versions of the EQ-5D were developed by the EuroQoL Group: 2005 (original developers) using their standard translation and linguistic validation process [24] and have been validated for use in Malaysia [25].

Statistical analysis
All descriptive statistics were done using Statistical Package for Social Sciences, SPSS (Version 16.0, SPSS Inc., Chicago, USA). Chi square test (or Fisher’s exact test) were used to analyse categorical data, whilst an independent sample T-test was used for continuous data analysis. Multivariate analysis was carried out to identify independent predictors of dyspepsia, using a logistic stepwise regression model. Risk associations were reported as odds ratios (OR) with a 95% confidence interval (CI). A p value of < 0.05 (two-tailed p value) was taken as statistical significance.
Results

During the study period, 93 subjects with headache and 187 controls were recruited at the specialist neurology clinic at University Malaya Medical Centre. Table 1 highlights the demographic and clinical comparisons between subjects with headache (cases) and those without headache (controls). Patients with headache and controls were matched for age (45.0±17.3 years).

Table 1. Baseline characteristics of subjects with headache and non-headache controls.

|                          | Patients, n = 93 | Controls, n = 187 | p value |
|--------------------------|------------------|-------------------|---------|
| **Age** (mean±SD)        | 45.0±17.3        | 42.1±15.4         | 0.15    |
| **Gender** (n, %)        |                  |                   |         |
| Male                     | 40 (43%)         | 63(33.7%)         | 0.15    |
| Female                   | 53 (57%)         | 124(66.3%)        |         |
| **Ethnic group** (n, %)  |                  |                   |         |
| Malay                    | 45 (48.4%)       | 102 (54.5%)       | 0.61    |
| Chinese                  | 24 (25.8%)       | 41 (21.9%)        |         |
| Indian                   | 24 (25.8%)       | 44 (23.5%)        |         |
| **BMI** (kg/m2) (mean±SD)| 25.2±5.1         | 24.4±4.7          | 0.23    |
| **Marital status** (n, %)|                  |                   |         |
| Single                   | 21(22.6%)        | 51(27.3%)         | 0.33    |
| Married                  | 64(68.8%)        | 116(62.0%)        |         |
| Widow/widower            | 6(6.4%)          | 19(10.2%)         |         |
| Divorced                 | 2(2.2%)          | 1(0.5%)           |         |
| **Educational Level** (n, %) |                |                   |         |
| Primary                  | 5(5.4%)          | 13 (7.0%)         | 0.22    |
| Secondary                | 12(12.9%)        | 29(15.5%)         |         |
| Pre-university           | 43(46.2%)        | 70(37.4%)         |         |
| Diploma                  | 23(24.7%)        | 32(17.1%)         |         |
| Tertiary                 | 9(9.7%)          | 38(20.3%)         |         |
| **Smoking** (n, %)       |                  |                   |         |
| Yes                      | 10(10.8%)        | 13(7.0%)          | 0.003   |
| No                       | 83(89.2%)        | 174(93.0%)        |         |
| **Alcohol** (n, %)       |                  |                   |         |
| Yes                      | 0                | 5 (2.7%)          | 0.002*  |
| No                       | 93 (100%)        | 182(97.3)         |         |
| **Concomitant medical illness** (n, %) |                |                   |         |
| Cardiovascular           | 21(22.6%)        | 21 (11.2%)        | 0.036   |
| Metabolic                | 16(17.2%)        | 19(10.2%)         | 0.12    |
| Respiratory              | 14(15.1%)        | 21(11.3%)         | 0.44    |
| Renal/Genitourinary tract| 1(1.1%)          | 2(1.1%)           | 1.00    |
| Rheumatological Disease  | 3(3.3%)          | 3(1.6%)           | 0.40    |
| Dermatological Disease   | 2(2.2%)          | 4(2.2%)           | 1.00    |
| Neurological Disease     | 1(1.1%)          | 1(0.5%)           | 1.00    |
| Dyspepsia (n, %)         | 24 (25.8%)       | 24(12.8%)         | 0.011   |
| HADS-D: moderate and severe (n, %) | 11 (11.8%) | 19 (10.2%) | 0.69    |
| HADS-A: moderate and severe (n, %) | 18 (19.4%) | 32(17.1%) | 0.74    |
| Hamilton score           | 4.39±4.80        | 4.19±5.34         | 0.77    |

*Likelihood Ratio Chi-square test

doi:10.1371/journal.pone.0115838.t001
headache vs 42.1±15.4 years control, p = 0.15), gender (57% females headache vs 66.3% females controls, p = 0.15) and ethnicity (Table 1).

There were more smokers among cases (10.8% vs 7.0%) and a slightly greater amount of alcohol intake in controls (2.7% vs 0%) (Table 1). Cases with headache additionally had more co-morbidities in terms of cardiovascular (22.6% vs 11.2%) and metabolic (17.2% vs 11.2%) diseases.

**Headache characteristics**

Headache characteristics of the study subjects are shown in Table 2. Most of the patients had a headache onset at anytime of the day. About one-third of the patients had headache for ≥ 15 days in a month. In terms of lateralization of headache, most patients complained of unilateral and alternating unilateral headache. The most frequently affected area was the temporal area and approximately half had a throbbing headache. Headache sub-types were as follows: tension-type headache (TTH) n = 53 (57.0%) and migraine n = 40 (43.0%). Among the migraine sub-types, 26 (65.0%) patients had migraine without aura and 26 (65.0%) had migraine without aura. The TTH sub-type group had the following characteristics: frequent TTH n = 31 (58.5%), infrequent TTH n = 6 (11.3%) and chronic TTH n = 16 (30.2%). The mean score of the visual analogue scale (VAS) for headache was 54.4±24.2 mm. VAS for headache intensity was used for current headache symptoms. More than half of the patients took paracetamol for headache, but a significant number of patients (37.6%) also used traditional medicated oil for analgesia.

**Prevalence of dyspepsia in headache**

Dyspepsia was more prevalent in subjects with headache compared to non-headache controls (25.8% vs 12.8%, p = 0.011). However, dyspepsia prevalence did not differ among the major headache types (27.5% migraine vs 24.5% TTH, p = 0.81). Six patients who had migraine with aura and five patients who had migraine without aura complained of dyspepsia. (p = 0.15) There were no statistically significant differences between various types of headache and dyspepsia (p = 0.84). Similarly, dyspepsia sub-types (according to the Rome II criteria) were not different between headache categories as follows: ulcer-like (18.2% migraine vs 23.1% TTH), motility-like (36.4% migraine vs 46.1% TTH) and reflux-like (45.4% migraine vs 30.8% TTH).

The association of dyspepsia with headache was explored further in a multivariate regression model with various recognised variables (Table 3). Predictive factors for dyspepsia in our subjects were found to include headache (OR 2.75) and anxiety (OR 3.52) only, indicating a strong link between headache and dyspepsia.

**Impact of dyspepsia on headache**

Differences in the clinical severity of headache and EQ-5D parameters were explored between headache subjects with and without dyspepsia. Subjects with headache and dyspepsia had a higher VAS-pain score compared to those with headache alone (63.67±22.85 mm vs 51.20±24.00 mm VAS, p = 0.029). Table 4 highlights the differences in HRQOL domains between headache subjects with and without dyspepsia. Headache subjects with dyspepsia reported more problems with “pain/discomfort” (62.5% vs 34.8%, p = 0.029) and “anxiety” (25.0% vs 7.2%, p = 0.03) compared to those with headache alone (Table 4). Globally, subjects with headache and dyspepsia had a lower EQ-5D utility score (0.82±0.18 vs 0.90±0.16, p = 0.037) and a lower EQ-5D VAS measurement (62.08±17.50 mm vs 72.62±18.85 mm, p = 0.018) compared to subjects with headache alone.
Table 2. Headache characteristics of patients.

| Characteristics                                | n = 93 |
|-----------------------------------------------|--------|
| **TIME OF ONSET (n, %)**                      |        |
| On rising                                     | 18(19.4%) |
| Afternoon/evening                             | 30(32.3%) |
| Night                                        | 10(10.8%) |
| Anytime                                       | 35 (37.6%) |
| **FREQUENCY OF HEADACHE (n, %)**              |        |
| Every day                                     | 23(8.2%) |
| Every other day                               | 4(1.4%)  |
| Once to three times weekly                    | 16(5.7%) |
| Two to four times per month                   | 34(12.1%) |
| Once monthly                                  | 16(5.7%) |
| **NUMBER OF HEADACHE EPISODES IN A MONTH (n, %)** |    |
| Headache < 15 days/month                      | 66 (71.0%) |
| Headache ≥ 15 days/month                      | 27 (29.0%) |
| **SITE OF PAIN (n, %)**                       |        |
| Frontal                                       | 30(32.3%) |
| Temporal                                      | 31(33.3%) |
| Occipital                                     | 11(11.8%) |
| Vertex                                        | 1(1.1%)  |
| Whole head                                    | 20(21.5%) |
| **LATERALITY OF PAIN (n, %)**                 |        |
| Unilateral                                    | 29 (31.2%) |
| Bilateral                                     | 36 (38.7%) |
| Alternating unilateral                        | 26(28.0%) |
| Orbital                                       | 2(2.2%)  |
| **CHARACTER OF HEADACHE (n, %)**              |        |
| Throbbing/pulsating                           | 51(54.8%) |
| Sharp/stabbing                                | 11(11.8%) |
| Tightness/pressing                            | 29(31.2%) |
| Pricking                                      | 2(2.2%)  |
| **INTENSITY OF HEADACHE (n, %)**              |        |
| Mild                                          | 21 (22.6%) |
| Moderate                                      | 43 (46.2%) |
| Severe                                        | 29 (31.2%) |
| **TRIGGER FACTORS (n, %)**                    |        |
| Stress                                        | 55(59.1%) |
| Lack of sleep                                 | 44(47.3%) |
| Weather                                       | 30(32.3%) |
| Sun exposure                                  | 26(28%)  |
| Too much sleep                                | 16(17.2%) |
| Certain food and drinks                       | 16(17.2%) |
| Missing meal                                  | 16(17.2%) |
| Menstruation                                  | 7(7.5%)  |
| **HEADACHE SUBTYPES (n, %)**                  |        |
| Frequent TTH                                  | 31(33.3%) |
| Chronic TTH                                   | 16(17.2%) |
| Infrequent TTH                                | 6(6.5%)  |

(Continued)
Discussion

This study has affirmed several observations between dyspepsia and headache. Compared to non-headache controls, subjects with headache had a significantly higher prevalence of dyspepsia. Among subjects with headache, a higher prevalence of dyspepsia (27.5%) was observed among those with migraine in this study. Our findings appear to concur with previous reports demonstrating a particular predilection for dyspepsia among patients with migraine (up to 60% in the study by Kurth et al) [7]. A higher frequency of smoking and co-morbidities, known risk factors for dyspepsia [26], among subjects with headache may have resulted in more dyspepsia. However, we performed a multivariate regression analysis which demonstrated an independent association between dyspepsia and headache. This association between

Table 2. (Continued)

| Characteristics                        | n = 93 |
|----------------------------------------|--------|
| Migraine without aura                  | 26(28%)|
| Migraine with aura                     | 14(15.1%)|
| MEDICATION USED TO RELIEVE HEADACHE (n, %) |        |
| Acute treatment                         |        |
| Paracetamol                             | 61 (65.6%)|
| Tramadol                                | 5 (5.4%) |
| Ergotamine                              | 5 (5.4%) |
| Sumatriptan                             | 3 (3.2%) |

doi:10.1371/journal.pone.0115838.t002

Table 3. Multivariate analysis of predictors of dyspepsia.

| Factors    | Dyspepsia | Unadjusted OR | 95% CI | Adjusted OR | 95% CI | p value |
|------------|-----------|---------------|--------|-------------|--------|---------|
|            | Yes (n = 48) | No (n = 232)  |        |             |        |         |
| Age        | (n, %)     |               |        |             |        |         |
| < 50 years | 33 (18.9)  | 142 (81.1)    | 1.00   | 1.00        |        |         |
| ≥ 50 years | 15 (14.3)  | 90 (85.7)     | 0.71   | 0.37–1.40   | 0.66   | 0.32–1.40 | 0.28 |
| Gender     | (n, %)     |               |        |             |        |         |
| Male       | 16 (15.5)  | 87 (84.5)     | 1.00   | 1.00        |        |         |
| Female     | 32 (18.1)  | 145 (81.9)    | 1.20   | 0.62–2.31   | 1.63   | 0.79–3.37 | 0.19 |
| Smoking    | (n, %)     |               |        |             |        |         |
| No         | 45 (17.5)  | 212 (82.5)    | 1.00   | 1.00        |        |         |
| Yes        | 3 (13.0)   | 20 (87.0)     | 0.71   | 0.20–2.48   | 0.79   | 1.67–7.44 | 0.001|
| Alcohol    | (n, %)     |               |        |             |        |         |
| No         | 48 (17.5)  | 227 (82.5)    | 1.00   | 1.00        |        |         |
| Yes        | 0 (0)      | 5 (100)       | NA     | NA          | 1.67   | 0.79–3.37 | 0.19 |
| Anxiety    | (n, %)     |               |        |             |        |         |
| No         | 29 (12.6)  | 201 (87.4)    | 1.00   | 1.00        |        |         |
| Yes        | 19 (39.1)  | 31 (61.9)     | 4.37   | 2.16–8.85   | 3.52   | 1.67–7.44 | 0.001|
| Depression | (n, %)     |               |        |             |        |         |
| No         | 37 (14.8)  | 213 (85.2)    | 1.00   | 1.00        |        |         |
| Yes        | 11 (36.7)  | 19 (63.3)     | 3.33   | 1.47–7.57   | 2.41   | 0.99–5.91 | 0.05 |
| Headache   | (n, %)     |               |        |             |        |         |
| No         | 24 (12.8)  | 163 (87.2)    | 1.00   | 1.00        |        |         |
| Yes        | 24 (25.8)  | 69 (74.2)     | 2.36   | 1.36–4.44   | 2.75   | 1.39–5.43 | 0.004|

doi:10.1371/journal.pone.0115838.t003
headache and dyspepsia was independent of the presence of anxiety and depression, well recognised associations for both these conditions [27–30].

The impact of dyspepsia on symptom severity in headache is a novel finding in this study. Headache subjects with dyspepsia had more severe symptoms compared to those cases without dyspepsia. A possible explanation may be due to a heightened common pathophysiological mechanism, such as visceral sensitisation, which may lead to more severe symptoms in cases with dual pathology compared to just headache alone.

In addition to an impact on symptom severity, we have demonstrated that dyspepsia resulted in a lower HRQOL in subjects with co-existing headache and dyspepsia. Both headache and dyspepsia, on their own, have been reported to be associated with a lower HRQOL among sufferers in the community [26, 31]. It is not entirely surprising then, that the combination of both conditions in adults, as opposed to just headache alone, would result in a greater HRQOL impairment. Examining the specific domains of HRQOL within the EQ-5D instrument, it is apparent that greater problems of “pain” and “anxiety” were reported in adults with co-existing dyspepsia and headache, compared to those with headache alone. Although not conclusive, it can be assumed that an increased headache symptom severity and possible psychological disturbance may have contributed to the lower HRQOL in subjects with dyspepsia and headache.

A previous large endoscopy-based study examined the association between dyspepsia and migraine [5]. Among 378 patients with dyspepsia and 310 controls, Meucci et al showed no difference in the prevalence of migraine. However, they were able to observe a greater prevalence of migraine among subjects with motility-like dyspepsia, compared to ulcer-like and reflux-like dyspepsia. Our study did not demonstrate a similar association between headache and dyspepsia sub-types for several possible reasons. We included various types of headache in this study, and not just migraine. The proportion of subjects with migraine alone was fewer than in Meucci’s study, which may have lead to a Type II statistical error in our findings. Finally, our definitions of dyspepsia may have differed. The inclusive definition of dyspepsia used in the LDQ, which include symptoms of GERD as well, may appear to conflict with the Rome process [32]. However, the Rome definition of dyspepsia, and its requisite of excluding any symptoms

| Table 4. HRQOL differences between headache with and without dyspepsia. |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| EQ-5D (n, %) | Headache and dyspepsia (n = 24) | Headache alone(n = 69) | p value |
| **Mobility** | | | |
| No problem | 20(83.3%) | 63(91.3%) | 0.28 |
| Problem | 4(16.7%) | 6(8.7%) | 0.28 |
| **Self-caring** | | | |
| No problem | 24(100%) | 65(94.2%) | 0.57 |
| Problem | 0 | 4(5.8%) | 0.57 |
| **Activities** | | | |
| No problem | 22(91.7%) | 65(94.2%) | 0.65 |
| Problem | 2(8.3%) | 4(5.8%) | 0.65 |
| **Pain or discomfort** | | | |
| No problem | 9(37.5%) | 45(65.2%) | 0.029 |
| Problem | 15(62.5%) | 24(34.8%) | 0.029 |
| **Anxiety** | | | |
| No problem | 18(75%) | 64(92.8%) | 0.03 |
| Problem | 6(25%) | 5(7.2%) | 0.03 |
| **EQ-5D VAS** | 62.08±17.50 | 72.62±18.85 | 0.018 |
| **EQ-5D score** | 0.82±0.18 | 0.90±0.16 | 0.037 |

doi:10.1371/journal.pone.0115838.t004

Impact of Dyspepsia on Headache
of GERD, has been criticised for excluding many patients with genuine FD in both Asian [33] and non-Asian communities [34]. It has even less applicability for uninvestigated dyspepsia in the community, where both reflux symptoms and epigastric pain commonly coexist.

There were several limitations to this study. The study was conducted in a secondary care setting, with the selection bias of subjects with more severe symptoms or greater anxiety, leading to an increased health-care seeking behaviour. Hence, the findings from this study may not be relevant to adults with less complicated headache residing in the community. However, due to the structure of the health-care system in urban Malaysia, many patients are able to consult specialists in secondary/tertiary institutions without prior primary care visitation [1]. Hence, it is likely that some of the subjects recruited in this study may be representative of headache cases in the community. Several important factors which may have been relevant to the development of dyspepsia, such as dietary intake and H. pylori infection, were not measured in this study.

Conclusion

We conclude that dyspepsia is strongly associated with headache, particularly in cases with migraine. Compared to cases without dyspepsia, headache cases with dyspepsia have more severe symptoms and a lower HRQOL. The impact of dyspepsia in headache has clinical implications – i.e. treatment of dyspepsia (and its’ underlying causes) may improve HRQOL in such patients.

Supporting Information

S1 Data. Data for the study. (XLS)

Author Contributions

Conceived and designed the experiments: MLST SM KJG NN. Performed the experiments: MLST NN AAA QZL JHN. Analyzed the data: SM MLST NN FMM. Contributed reagents/materials/analysis tools: RS ECLT. Wrote the paper: MLST SM NN.

References

1. Tai ML, Jivanadham JS, Tan CT, Sharma VK (2012) Primary headache in the elderly in South East Asia. J Headache Pain 13: 291–297. doi: 10.1007/s10194-012-0434-9 PMID: 22422347
2. Lebedeva ER, Olesen J, Osipova VV, Volkova LI, Tabeeva GR, et al. (2013) The Yekaterinburg headache initiative; an interventional project, within the Global Campaign against headache, to reduce the burden of headache in Russia. J Headache Pain 14(1):101. doi: 10.1186/1129-2377-14-101 PMID: 24367919
3. Yu SY, Cao XT, Zhao G, Yang XS, Qiao XY, et al. (2011) The burden of headache in China: validation of diagnostic questionnaire for a population-based study. J Headache Pain 12(2):141–6. doi: 10.1007/s10194-011-0336-2 PMID: 21452008
4. Mahadeva S, Goh KL (2006) Epidemiology of functional dyspepsia: a global perspective. World J Gastroenterol 12(17):2661–6. PMID: 16718749
5. Meucci G, Radaelli F, Prada A, Bortoli A, Crotta S, et al. (2005) Increased Prevalence Of Migraine In Patients With Uninvestigated Dyspepsia Referred For Open-Access Upper Gastrointestinal Endoscopy. Endoscopy 37(7):622–5. doi: 10.1055/s-2005-870251 PMID: 16010605
6. Aamodt AH, Stovner LJ, Hagen K, Zwart JA (2008) Comorbidity of headache and gastrointestinal complaints. The Head-HUNT Study. Cephalalgia 28:144–151. doi: 10.1111/j.1468-2982.2007.01486.x PMID: 18197684
7. Kurth T, Holtmann G, Neufang-Hüber J, Gerken G, Diener HC (2006) Prevalence of unexplained upper abdominal symptoms in patients with migraine. Cephalalgia 26:506–510. doi: 10.1111/j.1468-2982.2005.01076.x PMID: 16674758
10. Tajti J, Uddman R, Edvinsson L (2001) Neuropeptide localization in the 'migraine generator' region of the human brainstem. Cephalalgia 21:96–101. doi: 10.1046/j.1468-2982.2001.00140.x PMID: 11422090

11. Kaneko H, Mitsuma T, Uchida K, Furusawa A, Morise K (1993) Immunoreactive-somatostatin, substance P, and calcitonin gene-related peptide concentrations of the human gastric mucosa in patients with nonulcer dyspepsia and peptic ulcer disease. Am J Gastroenterol 88:898–904. PMID: 7684883

12. Edvinsson L (2001) Calcitonin gene-related peptide (CGRP) and the pathophysiology of headache: therapeutic implications. CNS Drugs 15:745–5314. doi: 10.2165/00023210-200115100-00001 PMID: 11602001

13. Arakawa T, Uno H, Fukuda T, Higuchi K, Kobayashi K, et al. (1997) New aspects of gastric adaptive relaxation, reflex after food intake for more food: involvement of capsaicin-sensitive sensory nerves and nitric oxide. J Smooth Muscle Res 33:81–8. doi: 10.1540/jsmr.33.81 PMID: 9533819

14. Plourde V, St-Pierre S, Quirion R (1997) Calcitonin gene-related peptide in viscerosensitive response to colorectal distension in rats. Am J Physiol 273:G191–6. PMID: 9252526

15. Headache Classification Committee of International Headache Society (IHS) (2013) The International Classification of Headache Diorders 3rd Edition (beta version). Cephalalgia 33(9): 629–808. doi: 10.1177/0333102413485658 PMID: 23771276

16. Lucas C, Romatet S, Mekies C, Allaf B, Lanteri-Minet M (2012) Stability, responsiveness, and reproducibility of a visual analog scale for treatment satisfaction in migraine. Headache 52(6):1005–18. doi: 10.1111/j.1526-4610.2012.02157.x PMID: 22568456

17. Mahadeva S, Chan WK, Mohazmi M, Sujairi R, Goh KL (2011) Validation study of the Leeds Dyspepsia Questionnaire in a multi-ethnic Asian population. J Gastroenterol Hepatol 26(11):1669–76. doi: 10.1111/j.1440-1746.2011.06806.x PMID: 21649731

18. Moayyedi P, Duffett S, Braunholtz D, Mason S, Richards ID, et al. (1998) The Leeds dyspepsia questionnaire: a valid tool for measuring the presence and severity of dyspepsia. Aliment Pharmacol Ther 12: 1257–62. doi: 10.1046/j.1365-2036.1998.00404.x PMID: 9882035

19. Talley NJ (1991) Non-ulcer dyspepsia: myths and realities. Aliment Pharmacol Ther. 5 Suppl 1:145–62. PMID: 1888833

20. Zigmond AS, Snaith RP (1983) The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand; 67:361–370. doi: 10.1111/j.1600-0447.1983.tb09716.x PMID: 6880820

21. Bech P, Allerup P, Gram LF, Reisby N, Rosenberg R, et al. (1981) The Hamilton depression scale. Evaluation of objectivity using logistic models. Acta Psychiatr Scand 63(3):290–9. doi: 10.1111/j.1600-0447.1981.tb00676.x PMID: 7015793

22. Fatt QK, Atiya AS, Heng NC, Beng CC (2007) Validation of the hospital anxiety and depression scale and the psychological disorder among premature ejaculation subjects. Int J Impot Res 19:321–5 doi: 10.1038/sj.ijir.3901528 PMID: 17136103

23. Brooks R, Rabin R, De Charro F (2005) The measurement & valuation of health status using EQ-5D: A European perspective. Evidence from the Euroqol BIO MED Research Program. Quality of Life Research 14(2):571–573.

24. Herdman M, Fox-Rushby J, Rabin R, Badia X, Selai C (2003) Producing other language versions of the EQ-5D. In: The measurement and valuation of health status using EQ-5D: A European perspective. Edited by Brooks R RR, de Charro F: Kluwer Academic Publishers.

25. Mahadeva S, Wee HL, Goh KL, Thumboo J (2009) The EQ-5D (Euroqol) is a valid generic instrument for measuring quality of life in patients with dyspepsia. BMC Gastroenterol 12:9.20. doi: 10.1186/1471-230X-9-20 PMID: 19284606

26. Mahadeva S, Yadav H, Rampal S, Everett SM, Goh KL (2010) Ethnic variation, epidemiological factors and quality of life impairment associated with dyspepsia in urban Malaysia. Aliment Pharmacol Ther 31(10):1141–51. doi: 10.1111/j.1365-2036.2010.04270.x PMID: 20175766

27. Beghi E, Allais G, Cortelli P, D’Amico D, De Simone R, et al. (2007) Headache and anxiety-depressive disorder comorbidity: the HADAS study. Neurological Science 28 Suppl 2:S217–9. doi: 10.1007/s10072-007-0780-6 PMID: 17508174

28. Beghi E, Bussone G, D’Amico D, Cortelli P, Cevoli S, et al. (2010) Headache, anxiety and depressive disorders: the HADAS study. Journal of headache and pain 11(2):141–50. doi: 10.1007/s10194-010-0187-2 PMID: 20108021
29. Hartono JL, Mahadeva S, Goh KL (2012) Anxiety and depression in various functional gastrointestinal disorders: do differences exist? J Dig Dis 13:252–7. doi: 10.1111/j.1751-2980.2012.00581.x PMID: 22500787

30. Mahadeva S, Goh KL (2011) Anxiety, depression and quality of life differences between functional and organic dyspepsia. J Gastroenterol Hepatol 26 Suppl 3:49–52. doi: 10.1111/j.1440-1746.2011.06656.x PMID: 21443710

31. Guitera V, Muñoz P, Castillo J, Pascual J (2002) Quality of life in chronic daily headache: A study in a general population. Neurology 58(7):1062–1065. doi: 10.1212/WNL.58.7.1062 PMID: 11940693

32. Drossman DA (2006) The functional gastrointestinal disorders and the Rome III process. Gastroenterology 130:1377–90. doi: 10.1053/j.gastro.2006.03.008 PMID: 16678553

33. Manabe N, Haruma K, Hata J, Imamura H, Kamada T, et al. (2010) Clinical characteristics of Japanese dyspeptic patients: is the Rome III classification applicable? Scand J Gastroenterol 45:567–72. doi: 10.3109/00365521003592663 PMID: 20408773

34. van Kerkhoven LA, Laheij RJ, Meineche-Schmidt V, Veldhuyzen-van Zanten SJ, de Wit NJ, et al. (2009) Functional dyspepsia: not all roads seem to lead to rome. J Clin Gastroenterol 43:118–22. doi: 10.1097/MCG.0b013e31815591f7 PMID: 18719513