Title

Path Analysis Models Integrating Psychological, Psycho-physical and Clinical Variables in Individuals with Tension-Type Headache

Authors

Bernard X W Liew[1] PT, PhD; María Palacios-Ceña[2] PT, PhD; Marco Scutari[3] PhD; Stella Fuensalida-Novo[2] PT, PhD; Angel Guerrero-Peral[4] MD, PhD; Carlos Ordás-Bandera[5] PT, PhD; Juan A Pareja[6] MD, PhD; César Fernández-de-las-Peñas[2] PT, PhD

Affiliations

(1) School of Sport, Rehabilitation and Exercise Sciences, University of Essex, Colchester, United Kingdom.
(2) Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine, Universidad Rey Juan Carlos, Alcorcón, Spain
(3) Istituto Dalle Molle di Studi Sull'Intelligenza Artificiale (IDSIA), Lugano, Switzerland
(4) Headache Unit, Hospital Clínico Universitario de Valladolid, Spain
(5) Department of Neurology, Hospital Rey Juan Carlos, Madrid, Spain
(6) Department of Neurology, Hospital Quirón Pozuelo, Madrid, Spain

Address for reprint requests / corresponding author:
César Fernández de las Peñas
Facultad de Ciencias de la Salud
Universidad Rey Juan Carlos
Avenida de Atenas s/n
28922 Alcorcón, Madrid, SPAIN
E-mail address: cesar.fernandez@urjc.es

Telephone number: + 34 91 488 88 84

Fax number: + 34 91 488 89 57

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Abstract

Tension type headache (TTH) is a prevalent but poorly understood pain disease. Current understanding supports the presence of multiple associations underlying its pathogenesis. Our aim was to compare competing multivariate pathway models that explains the complexity of TTH. Headache features (intensity, frequency, or duration - headache diary), headache-related disability (Headache Disability Inventory-HDI), anxiety/depression (Hospital Anxiety and Depression Scale), sleep quality (Pittsburgh Sleep Quality Index), widespread pressure pain thresholds (PPTs) and trigger points (TrPs) were collected in 208 individuals with TTH. Four latent variables were formed from the observed variables - Distress (anxiety, depression), Disability (HDI subscales), Severity (headache features), and Sensitivity (all PPTs). Structural equation modelling (SEM) and Bayesian network (BN) analyses were used to build and compare a theoretical ($\boldsymbol{model_{theory}}$) and a data-driven ($\boldsymbol{model_{BN}}$) latent variable model. The $\boldsymbol{model_{BN}}$ (root mean square error of approximation [RMSEA] = 0.035) provided a better statistical fit than $\boldsymbol{model_{theory}}$ (RMSEA = 0.094). The only path common between $\boldsymbol{model_{bn}}$ and $\boldsymbol{model_{theory}}$ was the influence of years with pain on TrPs. The $\boldsymbol{model_{BN}}$ revealed that the largest coefficient magnitudes were between the latent variables of Distress and Disability (β=1.524, P=0.006). Our theoretical model proposes a relationship whereby psycho-physical and psychological factors result in clinical features of headache and ultimately affect disability. Our data-driven model proposes a more complex relationship where poor sleep, psychological factors, and the number of years with pain takes more relevance at influencing disability. Our data-driven model could be leveraged in clinical trials investigating treatment approaches in TTH.

Keywords: Tension type headache, structural equation modelling, Bayesian network, pain.

Perspective

A theoretical model proposes a relationship where psycho-physical and psychological factors result in clinical manifestations of headache and ultimately affect disability. A data-driven model proposes a more complex relationship where poor sleep, psychological factors, and number of years with pain takes more relevance at influencing disability.

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Introduction

The Global Burden of Disease Study reported that neurological conditions represent the leading cause of disability-adjusted life-years [13]. Primary headaches are the most common pain disorders attended by neurologists in clinical practice. Tension-type headache (TTH), in particular, is probably the most common type of headache showing a worldwide prevalence of 42% [21]. The one-year prevalence of TTH has increased from 16% to 21% during the last decade [21]. Despite its prevalence, TTH is the most neglected primary headache, probably because its underlying mechanisms are not completely understood [32].

Current understanding supports several mechanisms behind the pathogenesis of TTH[50]. These mechanisms consist of pressure pain hyperalgesia [20]; psychological/emotional factors[6], sleep disorders[6], musculoskeletal impairments[3, 10], genetics[14] or humoral and immune responses [17] and can be involved in TTH at the same time in a complex matrix. The interaction between these mechanisms is different in men and women with TTH [25].

When quantifying complex multivariate pathways where variables can simultaneously depend on and influence other variables, structural equation modelling (SEM) has been the “de facto” statistical method. A conundrum in SEM occurs when the theoretical model results in a poor statistical fit [8] - how can a better alternative model be derived? Some studies using SEM manually alter the paths until the fit of the model crosses the desired threshold, a challenging task if there are many variables and paths [24]. An alternative approach is adopting a data-driven modelling approach that efficiently searches the model space and selects a pathway model that achieves the best statistical fit [5]. One such data-driven approach is Bayesian Networks (BN) [5, 37, 38]. BN emphasizes learning structural pathways directly from

data [42]. The learned structural model using BN can then be fitted using traditional SEM analysis. Using BN to learn a structural model may not only be useful when a theoretical model poorly fits the data, but it may be equally useful to statistically compare two competing pathway models. We argue that supplementing traditional theory-based approaches with data-driven approaches provide a better framework to efficiently test-explore-retest competing causal models, especially in a complex disorder such as TTH. The primary objective of this study was to understand the multivariate psychological, neuro-physiological, and clinical pain contributions to TTH. The secondary objective was to explore alternative path models using a data-driven approach and verify which models best explain the complex presentation of TTH.

Methods

Participants

A cross-sectional cohort study following the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines [54] was conducted. Consecutive individuals with headaches were recruited from an university-based hospital between January 2017 and December 2019. Diagnosis was performed following the third edition criteria of the International Classification of Headache Disorders (ICHD-III), the beta [1] or final [2] version by neurologists with more than 20 years of clinical experience in headaches. They were excluded if presented with 1, any other primary or secondary headache including medication overuse headache; 2, previous neck/head trauma; 3, cervical herniated disk on medical records; 4, systemic medical disease which modify pain perception, e.g., brain tumour, rheumatoid arthritis, polyneuropathy, fibromyalgia syndrome; 5, had received any therapy different than their usual medication intake the previous 6 months; or, 6, pregnancy. The study was approved by the Local Ethical Committees of Universidad Rey Juan Carlos (URJC 23/2018), and Hospital Rey Juan Carlos (HRJ 07/18). All participants read and signed a written consent form

prior to their participation in the study.

Evaluations were conducted when patients were headache-free and when at least one week had elapsed since the headache attack. In patients with a high frequency of headaches, i.e., chronic TTH, evaluation was conducted at least 3 days after a headache if possible or when the intensity of pain the day of the evaluation was ≤3 points on the numerical pain rate scale (NPRS). Participants were asked to avoid any analgesic or muscle relaxant 24 hours before their examination. No change was made on their regular medication treatment if taken. In fact, just 22% of the sample regularly intake amitriptyline as prophylactic medication.

Clinical Variables: Headache Diary

A 4-week diary was used to obtain features of headache attacks[43]. Accordingly, participants registered in the diary the number of days with headache in days/month (HFreq), the duration of the headache episodes in hours/day (HDura), and the intensity of pain of each headache attack (HInten) on an 11-point NPRS (0: no pain; 10: the worst unimaginable pain). In addition, they were also asked for describing the presence (or lack of) headache-associated symptoms (if existed), such as phonophobia or phonophobia, for further confirm the diagnosis of TTH [43].

Headache Disability Inventory

Headache-related disability was assessed with the Headache Disability Inventory (HDI) - a questionnaire including 25 items about the impact of headache on emotional functioning and daily activities [30]. Thirteen items evaluate the emotional burden (HDI-E, score 0 to 52), and the remaining 12 items the physical burden (HDI-P, score 0 to 48) of headache. A greater score suggests a greater headache-related burden. The HDI exhibited good test-retest reliability [31].

Psychological Variables

Anxiety and Depressive Levels

The Hospital Anxiety and Depression Scale (HADS) was used to determine the presence of anxiety/depressive symptoms. Seven items assess anxiety (HADS-A) and the other seven assess depressive (HADS-D) symptoms [55]. Each question is scored on a 4-point scale ranging from 0 to 3 points (total score of each scale 0-21 points) where a higher score indicates greater symptoms [34]. The HADS has shown good internal consistency in people with headache [34]. These items were codified as Anx and Dep in the SEM.

Sleep Quality

The Pittsburgh Sleep Quality Index (PSQI) was used to assess the quality of sleep [55]. This 24-items questionnaire evaluates sleep quality over the previous month by asking aspects such as usual bed-time, usual wake time, the number of actual hours slept, and the number of minutes to fall asleep. All questions are answered on a Likert-type scale (0–3). The total score ranges from 0 to 21 where a higher score indicates worse sleep quality (codified as sleep).

Psycho-physical Variables

Pressure pain thresholds (PPT) were assessed the temporalis muscle (trigeminal point, PPThx), cervical spine (extra-trigeminal point, PPTcx), second metacarpal, and tibialis anterior to assess widespread pressure pain sensitivity with an electronic pressure algometer (Somedic® Algometer, Sollentuna, Sweden). The mean value of PPTs over the second metacarpal and the tibialis anterior muscle was used in the analysis (remote pain-free point, PPTrm). The mean of 3 trials on each point, with a 30s resting period for avoiding temporal pain summation, was calculated. The order of assessment was randomized. Since no side-to-side differences are commonly seen, the mean of both sides for each point was used within the main analysis.

Since widespread pressure pain hyperalgesia is associated with the presence of trigger points (TrPs) [41], the total number of TrPs was calculated on each subject. Trigger points in

the temporalis, masseter, suboccipital, upper trapezius, sternocleidomastoid, and splenius capitis muscles were bilaterally explored according to international guidelines [16]: 1, presence painful spot in a palpable taut band in the muscle; 2, local twitch response on palpation of the muscle taut band; and 3, reproduction of referred pain with manual palpation.

Statistical Analysis

Packages

All analyses were performed using the R software (v4.0.2). The following packages were used: *mice*[52] for missing data pattern inspection and data imputation, *lavaan[47]* for SEM analysis, *semPlot [11]* for visualizing SEM paths, *bnlearn[48]* for BN structural learning, *SEMsens [35]* for sensitivity analysis of SEM models, and, finally, *semTools*[33] which fits a SEM model across our 20 imputed datasets and pools the statistical outputs using Rubin's rule. All codes and results are included in an online repository (https://bernard-liew.github.io/2020_cts_bn/4-TTH.html). No a priori power analysis was performed to guide the sample size determination.

Missing Data Management

The proportion of missing data ranged from 0.48% to 18.75% (**Suppl. Fig. 1)**. The number of different patterns of missing data ranged from one to 24 (Suppl. Fig. 2). Also, when comparing the baseline characteristics of individuals with and without missing data, there is no evidence that those with missing data had more severe headache symptoms (Table 1). Hence, the data was judged to be suitable for multiple imputations to be performed. Herein, we used the Multivariate Imputation by Chained Equations method [52]. The random forest method was used for imputation. We generated 20 imputed datasets using a maximum number of iterations of 30 for each imputation.

Bayesian Network (BN)

BN is a graphical modelling technique [40] that can leverage either data alone, or data combined with an expert prior knowledge to learn multivariate pathway models. Building a BN model using a data-driven approach involves two stages: 1) structure learning - identifying which arcs are present in the graphical model, and 2) parameter learning - estimating the parameters that regulate the strength and the sign of the corresponding relationships.

As previously mentioned, BN can easily include prior knowledge, sourced from the literature and experts, during the model building process. In the BN framework, prior TTH knowledge of known relationships can be included or excluded in the model by enforcing these as included and excluded arcs, respectively. Excluded arcs are always removed from the model's structure, whilst included arcs are always incorporated in the structure. Excluded arcs are those that contravene known biological or physical associations. In the current study, we enforced the following as excluded arcs:

- No arcs point to the variables of Age, Sex, and YearsP (years with pain). For YearsP, the variable reflected a historical measure, which cannot be dependent on the other variables.
- No arcs pointing from the latent variable of Disability.
- No arcs pointing to and from the variables PPTcx, PPThx, PPTrm , HInten, HDura, HFreq, HDI_E, HDI _P, Dep, Anx; as these variables were modelled as part of four latent variables (Figure 1).

In the current study, we enforced the following as included arcs:

- Arcs pointing from the latent variable to each of their observed variables, as modelled in the measurement model were enforced in the model (Figure 1).

For each of the 20 imputed datasets, we made use of model averaging to reduce the potential of including spurious relationships in the BN, using bootstrap resampling ($B = 50$) and performing structure learning on each of the resulting samples (total resamples being 1000)

using the hill-climbing (HC) algorithm. An "average" consensus model was calculated by selecting those arcs that have a frequency greater than 50% in the bootstrapped samples, a data-driven threshold estimated from the frequencies themselves to create a sparse and interpretable DAG network [49]. This DAG was again used for SEM analysis, the procedures of which have been reported in previous paragraphs – and we term this $model_{BN}$.

Structural Equation Modelling (SEM)

SEM are probabilistic models that unite multiple predictors and outcome variables in a single model, and where latent variables can also be included. First, SEM was used to assess the fit of the proposed measurement model (**Figure 1**), which defines the relationship between the observed variables, and the latent variables of Severity (intensity, duration, and frequency of the headache), Sensitivity (PPTs), Distress (depression and anxiety), and Disability (physical and emotional burden). Next, SEM was used to fit the theoretical path model ($model_{theory}$), which was informed by the literature [3, 6, 10, 18, 20, 25, 50] (**Figure 2**), and using the DAG learned from BN.

For both the measurement and path models, Maximum Likelihood was used to estimate the model's parameters, whilst the 'Huber-White' robust standard errors were used. An excellent model fit is determined when two of the four fit indices exceed the thresholds: (a root-mean-square error of approximation [RMSEA] ≤0.05; standard root mean residual [SRMR] ≤0.05; confirmatory fit index [CFI] ≥0.95; and non-normed fit index [NNFI] ≥0.95) [26]. For the estimated parameters, a more stringent P-value < 0.025 (Bonferroni correction for two SEM analyses) was considered to be statistically significant.

Sensitivity analysis

A sensitivity analysis was conducted on $model_{BN}$. to quantify the potential effect unmeasured confounding variables would have on our results, using the phantom variable [34]. A phantom variable is a latent variable without observed indicators but with mean, variance,

covariances, and paths to variables in the model set to specific values – known as sensitivity parameters. The path coefficients from the phantom variable to variables in the analytic model quantify the hypothetical relations between a potential confounder and variables in the model that could change the statistical conclusions of the model. A conclusion can be made that potential missing confounders may be present if small sensitivity parameters significantly alter the results of the model. Path coefficients with a change in value between the original $model_{BN}$ and the mean coefficient larger than 10% across all included sensitivity parameters can be considered to be sensitive to missing confounders [35]. A limitation of the implementation of the *SEMsens* package is that it can only perform sensitivity analysis on a single dataset at a time. We performed sensitivity analysis across the datasets and report the mean and SD values of the original and perturbed coefficients and percentage change in coefficient value between the original $model_{BN}$ and perturbed models.

Results

A total of 208 participants with TTH were included in the analysis. **Table 1** summarizes the descriptive characteristics of the cohort.

Measurement model

The tested measurement model and associated standardized regression weights are reported in **Figure 1**. Fit for the measurement model was excellent (RMSEA = 0.025, CFI = 0.994, SRMR = 0.043, NNFI = 0.990).

Testing and examining $model_{theory}$

The tested theoretical model and associated standardized regression weights are reported in **Figure 2**. The standard errors, 95% confidence intervals (CI) and P-values can be found in **Table 2**. The $model_{theory}$ had fit values of RMSEA = 0.094, CFI = 0.814, SRMR = 0.111, NNFI = 0.766, reflecting an inadequate model fit. Severity was significantly associated with

Disability ($\beta = 1.201, P = 0.012$), Sex was significantly associated with Distress ($\beta = 0.403, P = 0.008$), TrPs was significantly associated with Sensitivity ($\beta = -0.347, P < 0.001$), and YearsP was significantly associated with TrPs ($\beta = 0.200, P = 0.004$) (Table 2).

Testing and examining $model_{bn}$

The tested BN model and associated standardized regression weights are reported in **Figure 3**. The standard errors, 95% confidence intervals (CI) and P-values can be found in **Table 3**. The $model_{bn}$ had fit values of RMSEA = 0.035, CFI = 0.975, SRMR = 0.063, NNFI = 0.968, reflecting an excellent model fit. The only path common between $model_{bn}$ and $model_{theory}$ was the influence of YearsP on TrPs, with the relationship in $model_{bn}$ being $\beta = 0.237 (P < 0.001)$ (Table 3). In this model, there was no direct relationship between Severity and Disability (see Figure 3). Instead, Severity was significantly associated with Sleep ($\beta = 0.858, P = 0.007$) and Distress ($\beta = 0.818, P = 0.023$), and these latter variables acted as mediators to Disability (Figure 3).

Sensitivity analysis

Results of the sensitivity analysis can be found in **Table 4**. Based on a threshold change in the coefficient value of 10%, seven paths in $model_{BN}$ are likely to be affected by the presence of missing confounding variables. Of the seven, the path most likely to be affected include the relationship between Disability and Sleep, where their coefficients changed on average by > 20% across the sensitivity parameters (Table 4). Further, we note that the range of the perturbed coefficients spans both positive and negative values (and thus includes zero as well) for eight of the 13 paths.

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Discussion

Current understanding supports the presence of biopsychosocial associations behind the pathogenesis of TTH, which lends itself suited to be analyzed within the SEM framework. This

study applied SEM to validate and compare two candidate multivariate pathway models - a theoretical and a data-driven model, to better understand the complex interactions between psychological, neuro-physiological and clinical variables in TTH.

The $model_{theory}$ revealed a role for TrPs and Distress influencing Sensitivity (Fig. 2). The association between the number of TrPs and widespread pain sensitivity in TTH has been previously suggested[41]. The association between Sensitivity and TrPs was higher within the $model_{BN}$ (Fig. 3) than in the $model_{theory}$ (Fig. 2), but in the opposite way, i.e., Sensitivity leads to TrPs. A bidirectional association between Sensitivity (central mechanism) and TrPs (peripheral mechanism) is possible since nociception from TrPs lead to central sensitization, but central sensitization also promotes TrP pain[15]. Our findings suggest that Sensitivity and TrPs may be influenced by a common mechanism (sensitization), explaining why the TrPs and Sensitivity path exhibited a high chance of missing confounding (table 4). Further, although the presence of TrPs seems to be clear in TTH and our models support their role, their clinical relevance is still unclear[36] since just low to moderate evidence supports a positive effect of TrP treatment in TTH[12].

Interestingly, the path between years with headache predicted the number of TrPs in both models. Current knowledge of the pathogenesis of TTH suggests that this headache has a muscle component contributing to the sensitization process related to the transition from acute to chronic TTH[4]. It would be expected that patients with a longer history of pain are more prone to develop TrPs due to a temporal summation muscle nociception. Nevertheless, TrPs and years with pain path exhibited the highest chance of missing confounding (table 4).

Moderate evidence supports the presence of widespread hyperalgesia as a manifestation of sensitization in TTH, particularly in the chronic form[20]. The $model_{theory}$ showed that Sensitivity was influenced by TrPs and Distress. These findings agree with a meta-analysis reporting that baseline PPTs predict pain and disability[27]. Additionally, linear associations

between PPTs and pain and related-disability are not commonly reported in the literature[29]. Our $model_{theory}$ supports this lack of association since the association between Sensitivity and Severity was small. It has been postulated that Sensivitity reflects a neurophysiological mechanism whereas Severity represents the clinical expression of pain.

In the $model_{theory}$, we proposed that Sex influences Distress and that Distress influences Sensitivity (Fig. 2); but the $model_{BN}$ found that Sex influences Sensitivity, and that was the path to Distress but mediated by sleep quality (Fig. 3). The results of the $model_{BN}$ proposes that females exhibit lower PPTs than males, a common finding reported in the literature[45]. In fact, sex differences, not only in Sensitivity, but also in Distress, could determine specific approaches to be applied in TTH[25].

The association between stress and sleep in TTH has been previously reported[46]. The influence of sleep on Distress was more relevant in the $model_{BN}$ than in the $model_{theory}$. This effect supports previous assumptions that poor/lack of sleep is a trigger factor for headache[28]. Accordingly, the $model_{BN}$ would suggest that poor sleep plays a higher relevant role in the chronicity of TTH than theoretically expected but mediating an effect on Distress. Further, the relevance of poor sleep agrees with recent evidence supporting that sleep interventions not only improve the quality of sleep but also decrease headache frequency in TTH[51].

In the $model_{theory}$, we hypothesized that Sensitivity would influence Severity (Fig. 2). However, the $model_{BN}$ revealed that Severity was not directly influenced by any modelled factor. These results propose the relevance of headache parameters as independent features to be considered in TTH. This was also supported by the fact that Severity did not have an effect on Disability in the $model_{BN}$. One question that remains to be answered is the "cause" of Severity, since the $model_{BN}$ did not identify any variable influencing on these variables. It is possible that headache attacks are clinical features intrinsic to the disease itself than the others modelled variables.

Clinical Application

Based on the pain-stimulus responses and symptoms, TTH could be classified as a "nociplastic condition", where exaggerated responses as well as other central nervous system-derived symptomatology, e.g., poor sleep, memory problems, or mood disorders are present[22]. The current study using SEM confirms that TTH represents a multidimensional pain condition where multimodal approaches should be applied. The application of SEM revealed a complex matrix of interactions between biological and psychological variables. These variables have been identified as prognostic factors associated with less favorable outcomes from preventive medication treatments in chronic headache[44]. Emotional variables are considered modifiable risk factors of chronic conditions[46]. Accordingly, treatment of psychological or emotional factors should include cognitive behavior, education or coping strategies.

Similarly, SEM also revealed that muscle TrPs play a relevant role in both path models. Management of these impairments should include tissue-based impairment strategies (bottom-up) such as manual therapy, exercise or dry needling. A recent Delphi study concluded that the top therapeutic strategies used by physical therapist for managing headaches consisted of upper cervical spine mobilisations, therapeutic exercises of the cervical spine and lifestyle advices[9].

Current findings suggest that management of TTH should include a multi-model program consisting of targeting musculoskeletal disorders (manual therapy), central nervous excitability (neuroscience education), psychological factors (cognitive behaviour or copying strategies) and include advises on healthy lifestyles (physical activity)[19]. These interventions should be adapted to the clinical presentation of each patient since the influence of each of the identified variables in the current study will be unique. As concluding remark, our data-driven model

could be leveraged in clinical trials investigating treatment approaches in TTH, for instance, targeting first sleep and cognitive/emotional factors as earlier as possible at the beginning of the disease to reduce excitability of the central nervous system.

Strengths and Limitations

The biggest limitation of this study was that the cross-sectional nature precludes the ability to disentangle between-subjects from within-subjects relationships. For example, cross-sectional analysis cannot distinguish whether Distress is associated with Disability because whenever people feel distressed results in Disability (a within-subjects effect) or because people who are on average distressed tend to have greater Disability (a between-subjects effect). Given that temporal precedence is a key requirement for determining causality, causal inference based on this study should be made with caution.

Based on our sensitivity analysis residual or unmeasured confounding variables cannot be rejected. These unmeasured confounding variables can substantially impact the model by introducing spurious arcs between the observed variables. For example, the fact that several ranges of perturbed coefficients in Table 4 contain the value zero implies the possibility that the corresponding arcs do not correspond to statistically significant effects. Furthermore, given that the ranges include both positive and negative coefficients suggests the possibility that the direction of the effects may be incorrectly estimated even for arcs that are not spurious. The model averaging technique for learning Bayesian networks described in the Methods addresses the former concern in part by removing arcs we cannot establish with a sufficient degree of confidence, but it has limited power in addressing the latter because bootstrapping is likely to preserve any systematic effects arising from confounding. Techniques for reducing the effects of confounding in bootstrap have been proposed in the literature[39] but they require strong assumptions on the causal structure linking the observed and the unobserved variables that are not appropriate to investigations in which we wish to discover the structure from data. As an

alternative, a combination of multiple imputations and causal discovery algorithms, could be used to detect possible sources of confounding, albeit at a significant computational cost[23]. Further, network models learned by causal discovery algorithms that can address confounding have less power and are markedly more complicated to interpret as they use several different types of arcs to express confounded and unconfounded relationships[7]. Although SEM allows for the estimation of numerous associations simultaneously, it comes at a cost of making many assumptions (linearity, distributional, and no-confounding) across all paths - which make it challenging to verify. Alternative mediation analysis approaches with greater modelling flexibility and better ability for causal identification assumptions, may be more suitable when the research question focuses on testing a few associations[53].

The strength of this paper is that it synergizes the strengthening of two complementary statistical approaches to help us better understand the pathophysiology of a complex disorder. Nevertheless, limitations in relation to the sample should be also considered. First, the sample was recruited from different university-based headache centers; therefore, they may be not representative of the general population. Second, the impact of medication was not considered. Third, it should be noted that the scores of some of the variables, e.g., anxiety/depression, were low; therefore, it is possible that the influence of these factors may be different in individuals experiencing higher levels. Finally, we just explored static psycho-physical outcomes, i.e., PPTs, but not other such as conditioned pain modulation (CPM) or temporal summation (TS). We do not currently know if these other sensitivity variables would show different associations.

Conclusion

This study compared two pathway models that quantified the multivariate relationships in TTH. Our theoretical model proposes a relationship whereby psycho-physical and psychological factors result in clinical features of headache and ultimately affect disability. Our data-driven

model proposes a complex relationship where poor sleep, psychological factors, and number of years with pain takes more relevance at influencing disability. Our data-driven model could be leveraged in clinical trials investigating treatment approaches in TTH, for instance, targeting first sleep and cognitive/emotional factors as earlier as possible at the beginning of the disease to reduce excitability of the central nervous system.

Legend of Figures

Figure 1: Measurement model with standardized regression coefficients. Abbreviations: Anx: Hospital Anxiety and Depression Scale, anxiety subscale; Dep: Hospital Anxiety and Depression Scale, depression subscale; PPTcx: pressure pain threshold cervical spine; PPThx: pressure pain threshold temporalis muscle; PPTrm: pressure pain threshold at remote region (mean of second metacarpal and tibialis anterior); HDura: headache duration; HFreq: headache frequency; HInten: headache intensity; HDI_E: Headache Disability Inventory, emotional subscale; HDI_P: Headache Disability Inventory, physical subscale

Figure 2: Directed acyclic graph of theoretical model with standardized regression coefficients. Nodes shaded grey are latent variables. Observed variables of latent variables not included to reduce visual clutter, but its associated coefficients can be found in Table 2. Abbreviations: YearsP: number of years with headache; TrPs: trigger points

Figure 3: Directed acyclic graph of Bayesian Network model with standardized regression coefficients. Nodes shaded grey are latent variables. Observed variables of latent variables not included to reduce visual clutter, but their associated coefficients can be found in Table 3. Abbreviations: YearsP: number of years with headache; TrPs: trigger points

Legend of Supplementary Figures

Supplementary Figure 1: Proportion of missing data for the variables of the study. Red colour means "good" missing data (<5%). Green colour means "OK" missing data (<20%). Anx: Hospital Anxiety and Depression Scale, anxiety subscale; Dep: Hospital Anxiety and Depression Scale, depression subscale; PPTcx: pressure pain threshold cervical spine; PPThx: pressure pain threshold temporalis muscle; PPTrm: pressure pain threshold at remote region (mean of second metacarpal and tibialis anterior); HDura: headache duration; HFreq: headache frequency; HInten: headache intensity; HDI_E: Headache Disability Inventory, emotional subscale; HDI_P: Headache Disability Inventory, physical subscale; Sleep: Pittsburgh Sleep Quality Index; yearsP: years with headache; TrPs: trigger points.

Supplementary Figure 2:

Missing data patterns. Column-wise labels are the variables included in the analysis. Left row-wise labels reflect the number of participants with a missing data pattern. Right row-wise labels reflect the number of missing variables. The blue cell indicates no missing data, the red cell indicates missing data. **Abbreviation:** Anx: Hospital Anxiety and Depression Scale, anxiety subscale; Dep: Hospital Anxiety and Depression Scale, depression subscale; PPTcx: pressure pain threshold cervical spine; PPThx: pressure pain threshold temporalis muscle; PPTrm: pressure pain threshold at remote region (mean of second metacarpal and tibialis anterior); HDura: headache duration; HFreq: headache frequency; HInten: headache intensity; HDI_E: Headache Disability Inventory, emotional subscale; HDI_P: Headache Disability

Inventory, physical subscale; Sleep: Pittsburgh Sleep Quality Index; yearsP: years with headache; TrPs: trigger points.

Figures

Figure 1

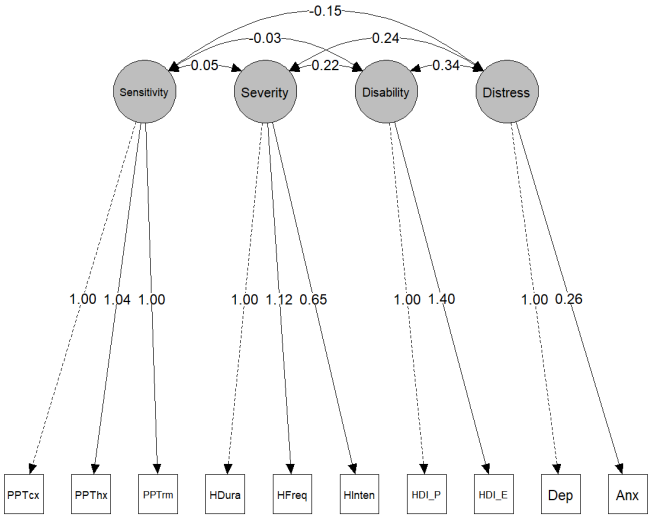


Figure 2

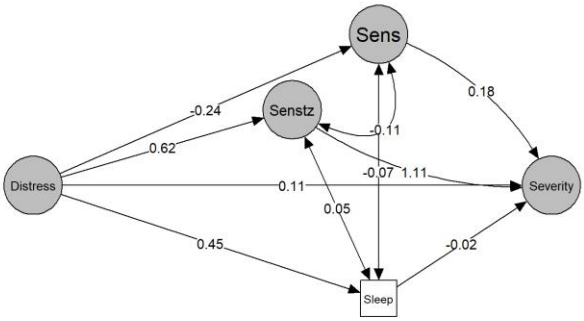
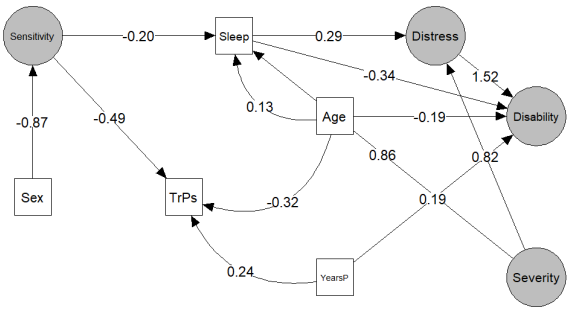
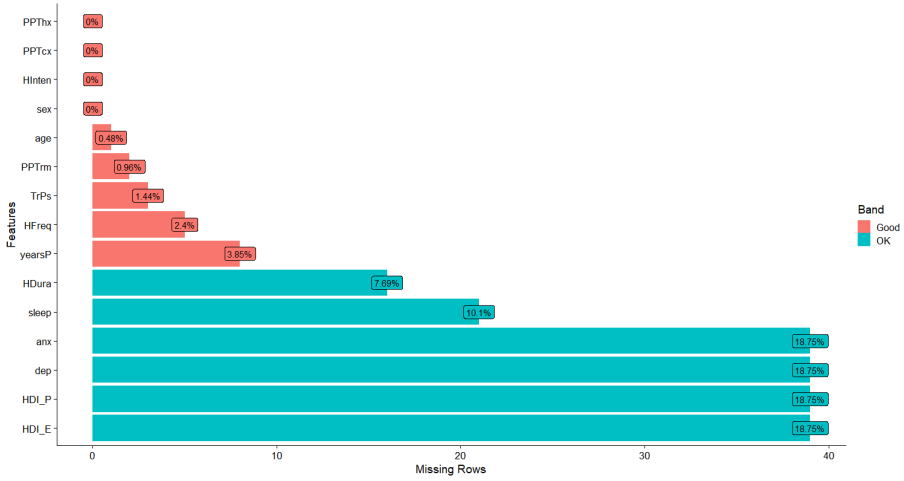


Figure 3



Supplementary figure 1



Supplementary figure 2

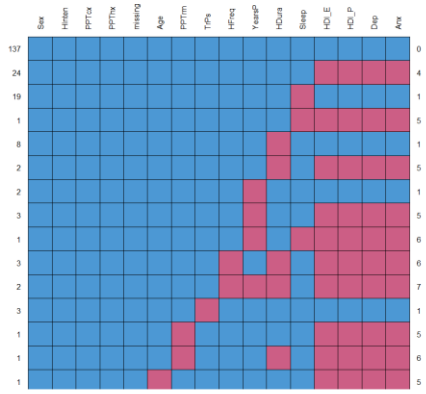


Table 1: Descriptive characteristics of cohort

Variables	No missing (n = 137)	With missing (n = 71)	Total (n = 208)	P value
Male (n, %)	39(28.47)	20(28.17)	59(28.37)	0.964
Female (n, %)	98(71.53)	51(71.83)	149(71.63)	0.964
Age (years)	47.21(14.22)	39.86(13.47)	44.72(14.37)	< 0.001
Years with headache	10.78(11.67)	9.38(10.3)	10.34(11.25)	0.415
Headache intensity (NPRS, 0.10)	6.31(2.86)	5.67(2.13)	6.1(2.65)	0.097
Headache duration (hours)	7.21(4.53)	7.91(3.87)	7.41(4.35)	0.308
Headache frequency (days/month)	17.28(9.16)	15.88(10.05)	16.82(9.45)	0.325
Trigger points	6.69(3.7)	5.06(3.46)	6.15(3.69)	0.003
HDI-E (0-52)	20.15(13.5)	14.44(11.1)	19.07(13.24)	0.028
HDI-P (0-48)	23.71(12.67)	18.94(9.53)	22.8(12.26)	0.047
Sleep (0-21)	8.24(4.62)	7.38(3.69)	8.01(4.39)	0.237
HADS-D (0-21)	8.38(4.32)	5.97(4.54)	7.92(4.45)	0.005
HADS-A (0-21)	10.15(4.75)	8.84(4.12)	9.91(4.66)	0.153
PPT head (kPa)	182.2(77.66)	316.11(177.44)	227.91(136.61)	< 0.001
PPT cervical (kPa)	194.32(81.62)	249.99(106.64)	213.32(94.46)	< 0.001
PPT remote (kPa)	320.02(135.35)	383.04(173.47)	341.13(151.74)	0.005

Categorical variable of gender analysed via Chi-Square test, whilst all other variables analysed via linear regression with missing (no/yes) as independent variable.

Abbreviations. NPRS: Numerical pain rating scale; HDI-E: Headache Disability Inventory, emotional subscale; HDI-P: Headache Disability Inventory, physical subscale; Sleep: Pittsburgh Sleep Quality Index; HADS-A: Hospital Anxiety and Depression Scale, anxiety subscale; HADS-D: Hospital Anxiety and Depression Scale, depression subscale; PPT: Pressure pain thresholds

Table 2: Parameter estimates for the model theory

DV	IV	Coef	SE	LB	UB	Pval	Sig	type
Disability	HDI_P	0.672	0.109	0.457	0.885	0.000	s	LV
Disability	HDI_P	1.000						LV
Distress	Anx	0.323	0.295	-0.254	0.899	0.275	ns	LV
Distress	Dep	1.000						LV
Sensitivity	PPThx	1.036	0.077	0.885	1.188	0.000	s	LV
Sensitivity	PPTrm	1.021	0.078	0.869	1.174	0.000	s	LV
Sensitivity	PPTcx	1.000						LV
Severity	HFreq	1.187	0.336	0.527	1.843	0.000	s	LV
Severity	HInten	0.704	0.280	0.158	1.254	0.012	s	LV
Severity	HDura	1.000						LV
Disability	Severity	1.201	0.476	0.264	2.133	0.012	s	Reg
Disability	Sleep	0.068	0.127	-0.180	0.315	0.593	ns	Reg
Distress	YearsP	-0.009	0.028	-0.063	0.046	0.753	ns	Reg
Distress	Sex	0.403	0.150	0.107	0.697	0.008	s	Reg
Sensitivity	TrPs	-0.347	0.070	-0.485	-0.209	0.000	s	Reg
Sensitivity	Distress	-1.890	0.899	-3.650	-0.123	0.036	ns	Reg
Severity	Sensitivity	-0.006	0.077	-0.159	0.145	0.936	ns	Reg
Severity	Age	0.064	0.052	-0.037	0.165	0.216	ns	Reg
Sleep	Severity	0.953	0.452	0.069	1.837	0.035	ns	Reg
TrPs	YearsP	0.200	0.069	0.065	0.334	0.004	s	Reg
TrPs	Sex	0.348	0.167	0.018	0.677	0.038	ns	Reg

Abbreviations: DV: dependent variable (or latent variable); IV: independent variable (or observed variable); Coef: standardized coefficients; SE: standard error; LB: 2.5% lower bound of 95% confidence interval; UB: 97.5% upper bound of 95% confidence interval; Pval = p value; Sig = significance; LV: latent variable analysis; Reg: regression analysis; Anx: Hospital Anxiety and Depression Scale, anxiety subscale; YearsP: number of years with headache; Dep: Hospital Anxiety and Depression Scale, depression subscale; TrPs: trigger points; PPTcx: pressure pain threshold cervical spine; PPThx: pressure pain threshold temporalis muscle; PPTrm: pressure pain threshold at remote region (mean of second metacarpal and tibialis anterior); HDura: headache duration; HFreq: headache frequency; HInten: headache intensity; HDI_E: Headache Sisability Inventory, emotional subscale; HDI_P: Headache Disability Inventory, physical subscale; Sleep: Pittsburgh Sleep Quality Index

Table 3: Parameter estimates for model Bayesian network

DV	IV	Coef	SE	LB	UB	Pval	Sig	type
Disability	HDI_P	0.796	0.084	0.631	0.960	0.000	s	LV
Disability	HDI_P	1.000						LV
Distress	Anx	0.296	0.117	0.068	0.524	0.012	s	LV
Distress	Dep	1.000						LV
Sensitivity	PPThx	1.036	0.078	0.883	1.189	0.000	s	LV
Sensitivity	PPTrm	1.023	0.078	0.870	1.176	0.000	s	LV
Sensitivity	PPTcx	1.000						LV
Severity	HFreq	1.261	0.326	0.626	1.900	0.000	s	LV
Severity	HInten	0.713	0.326	0.074	1.351	0.029	ns	LV
Severity	HDura	1.000						LV
Disability	YearsP	0.187	0.067	0.055	0.319	0.005	s	Reg
Disability	Age	-0.188	0.063	-0.312	-0.063	0.003	s	Reg
Disability	Sleep	-0.336	0.272	-0.869	0.197	0.217	ns	Reg
Disability	Distress	1.524	0.553	0.439	2.607	0.006	s	Reg
Distress	Severity	0.818	0.360	0.112	1.524	0.023	s	Reg
Distress	Sleep	0.293	0.096	0.105	0.482	0.002	s	Reg
Sensitivity	Sex	-0.866	0.176	-1.212	-0.520	0.000	s	Reg
Sleep	Sensitivity	-0.197	0.077	-0.349	-0.046	0.011	s	Reg
Sleep	Age	0.131	0.065	0.004	0.257	0.043	ns	Reg
Sleep	Severity	0.858	0.318	0.237	1.484	0.007	s	Reg
TrPs	Sensitivity	-0.492	0.072	-0.634	-0.350	0.000	s	Reg
TrPs	YearsP	0.237	0.060	0.119	0.354	0.000	s	Reg
TrPs	Age	-0.321	0.059	-0.435	-0.206	0.000	s	Reg

Abbreviations: DV: dependent variable (or latent variable); IV: independent variable (or observed variable); Coef: standardized coefficients; SE: standard error; LB: 2.5% lower bound of 95% confidence interval; UB: 97.5% upper bound of 95% confidence interval; Pval = p value; Sig = significance; LV: latent variable analysis; Reg: regression analysis; Anx: Hospital Anxiety and Depression Scale, anxiety subscale; YearsP: number of years with headache; Dep: Hospital Anxiety and Depression Scale, depression subscale; TrPs: trigger points; PPTcx: pressure pain threshold cervical spine; PPThx: pressure pain threshold temporalis muscle; PPTrm: pressure pain threshold at remote region (mean of second metacarpal and tibialis anterior); HDura: headache duration; HFreq: headache frequency; HInten: headache intensity; HDI_E: Headache Sisability Inventory, emotional subscale; HDI_P: Headache Disability Inventory, physical subscale; Sleep: Pittsburgh Sleep Quality Index

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Table 4: Sensitivity analysis of model developed using Bayesian network across imputed datasets. Values represent the mean (one standard deviation) across the imputed datasets.

DV	IV	Original coefficient	Mean perturbed coefficient	Min perturbed coefficient	Max perturbed coefficient	% Change
Disability	Sleep	-0.295 (0.03)	-0.223 (0.027)	-0.906 (0.039)	0.743 (0.026)	24.653 (2.058)
Sensitivity	Sex	-0.447 (0.079)	-0.364 (0.065)	-0.45 (0.07)	-0.197 (0.204)	18.422 (6.024)
Sleep	Severity	0.402 (0.086)	0.464 (0.069)	-0.554 (0.227)	1.282 (0.172)	15.466 (16.948)
TrPs	YearsP	0.237 (0.015)	0.272 (0.013)	-0.259 (0.095)	0.929 (0.119)	14.972 (2.965)
Sleep	Sensitivity	-0.178 (0.048)	-0.202 (0.038)	-0.831 (0.159)	0.329 (0.161)	13.483 (7.197)
TrPs	Age	-0.322 (0.066)	-0.288 (0.053)	-0.324 (0.072)	-0.194 (0.232)	10.696 (5.338)
Distress	Severity	0.583 (0.001)	0.521 (0.008)	-0.541 (0.002)	1.546 (0.036)	10.365 (1.762)
TrPs	Sensitivity	-0.432 (0.021)	-0.47 (0.02)	-1.066 (0.021)	0.016 (0.015)	8.664 (1.584)
Disability	Distress	0.965 (0.02)	1.001 (0.027)	0.225 (0.202)	1.984 (0.071)	7.527 (8.673)
Distress	Sleep	0.422 (0.03)	0.415 (0.036)	-0.106 (0.156)	1.017 (0.102)	6.036 (3.016)
Disability	YearsP	0.196 (0.004)	0.206 (0.005)	-0.303 (0.005)	0.806 (0.005)	5.783 (0.685)
Disability	Age	-0.199 (0.005)	-0.19 (0.013)	-0.275 (0.015)	-0.143 (0.154)	4.364 (3.396)
Sleep	Age	0.126 (0.012)	0.124 (0.014)	0.026 (0.053)	0.183 (0.159)	2.83 (4.833)

Abbreviations: DV: dependent variable; IV: independent variable; Anx: Hospital Anxiety and Depression Scale, anxiety subscale; YearsP: number of years with headache; Dep: Hospital Anxiety and Depression Scale, depression subscale; TrPs: trigger points; PPTcx: pressure pain threshold cervical spine; PPThx: pressure pain threshold temporalis muscle; PPTrm: pressure pain threshold at remote region (mean of second metacarpal and tibialis anterior); HDura: headache duration; HFreq: headache frequency; HInten: headache intensity; HDI_E: Headache Sisability Inventory, emotional subscale; HDI_P: Headache Disability Inventory, physical subscale; Sleep: Pittsburgh Sleep Quality Index

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