Investigating the Relationship Between Comorbid Headaches and Depression

Alex Wynd BA (Hons)

Paul R. Martin DPhil

Kathryn Gilson DPsych

Graham Meadows MD

Monash University and Griffith University

Melbourne and Brisbane

Australia

Conflict of interest statement: There are no conflicts of interest for any of the authors.

Key words: Headache, depression, Major Depressive Episode, Life History Calendar, order of onset, genetic, heritability, participant views.

Abbreviations: Depression, Major Depressive Episode as part of Major Depressive Disorder; Headaches: A subset of common primary headaches disorders; TTH: Tension-type headache; LHC, Life History Calendar; CIDI-LT, Composite International Diagnostic Interview, Lifetime Version.; PTSD, post traumatic stress disorder; BAI, Beck Anxiety Inventory; GAD, Generalised Anxiety Disorder; BDI-II, Beck Depression Inventory, 2nd edition.

Abstract

Three possibilities may explain headache and depression comorbidity: (i) Headaches cause depression; (ii) depression causes headaches; and (iii) third variables cause both. Evidence supports all three possibilities. This study sought to examine which of these three relationships has the most support. This was achieved firstly by establishing the order of onset of the most recent episode of headaches and depression, and comparing these groups on headache severity, depression heritability, and exploratory variables; and asking participants open-ended questions. Thirty participants had been diagnosed with a primary headache disorder and major depressive disorder. The order of onset was assessed using the Life History Calendar, while depression heritability was estimated upon probable depression in a parent. Although the order of onset was statistically random, it was more frequent for participants to state that depression caused headaches than the reverse. Most participants identified life events or circumstances as third variables. Intense headaches may be contributing to depression in the headaches first group, although headaches causing depression may be infrequent. Life events and circumstances may frequently be involved in both disorders. Successful headache treatment for individuals with major depressive disorder will most likely necessitate treatment of the comorbid depression.

Key words: Depression, headache, heritability, Life History Calendar, major depressive episode, order of onset.

What is already known on this topic: Comorbidity exists between headaches and depression, third variables such as genetics are involved, and there is evidence that headaches or any pain condition often has a bidirectional relationship with depression.

What this paper adds: Depression may be a more important influence in the bidirectional relationship, exceptionally, severe headache conditions may occasionally cause depression, and difficult life events may be a key third variable contributing to both conditions.

Both headaches (defined here as a subset of common primary headache disorders) and depression (a major depressive episode as part of major depressive disorder) are common and disabling conditions, with migraine by itself accounting for 1.3% of years lost due to disability (World Health Organisation [WHO], 2012a), and depression being the leading cause of disability worldwide (WHO, 2012). The most severe headache conditions, those termed chronic, occur on 15 or more days per month and have a point prevalence rate of up to 4% of the global population at any one time (WHO, 2012a). Depression affects an estimated 5% (WHO, 2012). Headachesand depression tend to coexist, with depression more common among people with headaches as well as the reverse (Breslau, Davis, & Andreski, 1991; Breslau, Davis, Schultz, & Paterson, 1994; Breslau, Lipton, Stewart, Schultz, & Welch, 2003; Juang, Wang, Fuh, Lu, & Su, 2000; McWilliams, Goodwin, & Cox, 2004; Mitsikostas & Thomas, 1999; Schur, Noonan, Buchwald, Goldberg, & Afari, 2009; Wang et al., 1999). For example, rates of depression of up to 78% have been found among chronic-migraine outpatients (Juang et al., 2000). It is critical to understand the reasons behind this comorbidity for developing effective treatments, and for limiting the severe disability of depression being further worsened by headaches. Headache and depression comorbidity could potentially be explained by the following, either in isolation or in combination:

1. Headaches cause depression.
2. Depression causes headaches.
3. A third variable causes both conditions.

Although experimental research involving manipulation of variables is necessary for drawing firm conclusions about causality, non-experimental research can be used to build evidence towards establishing a causal relationship. For example, establishing the order of onset of the two disorders is a pre-condition in identifying a causal relationship. If depression tended to follow headaches, this would suggest that headaches causing depression is possible

and is more likely than depression causing headaches. With respect to the first possibility, although any medical condition that involves frequent, intense, and disabling pain could be depressing, there is limited research evidence supporting headaches causing depression. One major longitudinal study demonstrated that migraine predicted depression at a higher rate (*OR* = 5.8) than depression predicted migraine (*OR* = 3.4) (Breslau et al., 2003). A second major longitudinal study demonstrated that depression followed migraine in 54.9% of cases (Breslau et al., 1994), implying that if headaches can cause depression, it is not always the case Retrospective studies have demonstrated a clearer tendency for depression to follow headaches, occurring in 62% (Breslau et al., 1991) and 75% (Radat et al., 2005) of comorbid cases. These studies did not include tension-type headache (TTH), so this pattern may not apply to TTH.

Other evidence which indicates that headaches may cause or contribute to depression comes with the remarkable consistency in which a broad variety of medical conditions predict the onset of depression and depressive symptoms (Dalton & Heinrichs, 2005; Nicassio & Wallston, 1992; Patten, 2001). Such conditions include arthritis, cancer, and acquired injuries, with the latter being notable because it is unlikely that third variables contributed to both acquired injuries and depression. One study found that the relationship between arthritis pain and depressive symptoms was mediated by sleep disturbance (Nicassio & Wallston, 1992). This pattern may also apply to headaches.

Finally, one study compared individuals with chronic myofascial pain and depression to those with early onset depression alone, and found that only the latter had a significantly greater number of relatives with depression than did healthy controls (Dohrenwend, Raphael, Marbach, & Gallagher, 1999). Potentially, those with chronic myofascial pain developed a reactive form of depression low in heritability in response to their pain. The findings with arthritis and myofascial pain together suggest a second non-experimental method of building

evidence for a causal relationship, and that is through establishing systematic differences between headaches and depression based on order of onset. Certain differences, such as more severe and therefore disabling headaches tending to precede depression, with depression being less heritable and more reactive, would further suggest that the order of onset has arisen because of causality.

Overall, there is no direct evidence that headaches can cause or contribute to depression, although the above findings with headaches and other medical conditions do suggest that it is quite likely. However, the frequency and circumstances in which this would occur are unclear.

With respect to depression causing headaches, despite the first onset of depression tending to follow that of headaches as reviewed above, more direct evidence exists for this direction of relationship, some of which is of a quasi-experimental nature. Two studies that involved administering a stressful task have demonstrated how depression may exacerbate headaches via increasing both stress and pain sensitivity (Cathcart, Winefield, Lushington, & Rolan, 2009; Janke, Holroyd, & Romanek, 2004). Other studies have demonstrated how depression may worsen episodic headache disorders by contributing to medication overuse (Atasoy, Atasoy, Unal, Emre, & Sumer, 2005; Radat et al., 2005). It is therefore probable that depression can worsen headaches, but the magnitude and frequency of this relationship, and whether depression is often a primary cause of headaches, requires further exploration.

With respect to third variables causing both headaches and depression, the commonly researched factors include shared genetic factors, trauma, and stress. Shared genetics have been shown to account for between 20% and 36% of the variance between migraine and depression (Schur et al., 2009). Regarding trauma and stress, these factors have been associated with headaches and depression, although the findings have occurred within separate studies on headaches (Peterlin, Ward, Lidicker, & Levin, 2007) and depression

(Brown, Cohen, Johnson, & Smailes, 1999; Goldberg, 1994), rather than being identified as involved in both conditions within the same individuals. Trauma may contribute to both conditions via dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (Baskin & Smitherman, 2009; Peres et al., 2001). Stress in general has been shown to be the most common trigger of individual headache attacks (Martin & MacLeod, 2009), and also has a causal relationship with depression (Kendler, Karkowski, & Prescott, 1999).

Overall, shared genetics appear to explain some of the headache and depression comorbidity, at least with migraine. Trauma and stress have been consistently associated with headaches and depression separately, and a contribution to both conditions when comorbid is probable but unexplored.

This study primarily aimed to provide some preliminary non-experimental evidence with respect to whether headaches cause depression, depression causes headaches, or shared environmental variables (given that shared biological variables are established) is most tenable and common. This will be achieved through the following:

- Examining the order of onset of the most recent episode of headaches and depression.
- Assessing for differences between headaches that came before depression and headaches that came after depression (e.g., Headache severity). This is another step closer towards establishing causality after looking at the order of onset.
- Assessing whether depression that came before headaches had higher estimated heritability, with lower heritability in depression that followed headaches.

- Asking participants themselves whether they thought that one disorder caused or contributed to the other, and whether third variables had contributed to both disorders through structured, open-ended questions.

If the findings indicate that depression tends to follow headaches in the majority of cases, that headaches that precede depression tend to be more severe and therefore disabling and potentially depressing, and that most participants report that their headaches caused their depression, this would suggest that a causal relationship in this direction is likely. Alternatively, headaches tending to follow depression, and participants also stating that depression caused their headaches, would suggest that depression may often cause headaches. Finally, if depression heritability is found to be greater when headaches follow depression, this could provide support for headaches contributing to a more reactive/less heritable form of depression or a more heritable form of depression contributing to headaches. Depression heritability would therefore need to be interpreted along with the order of onset and other data rather than by itself.

A seemingly random order of onset amongst other findings may suggest that both disorders can contribute to each other, or they are not causally related to each other and shared variables such as genetics and/or life events are more important.

The study utilized a combination of in-depth case studies and quantitative analyses among a group of individuals with comorbid headaches and depression. The study used the Life History Calendar to establish the order of onset of the most recent episode of headaches and depression, which is a semi-structured interview technique shown to produce greater recall accuracy than free recall (Brown et al., 1999; Goldberg, 1994; Peterlin et al., 2007). This is important given that the reviewed longitudinal studies involved free recall every one to two years.

Given that anxiety is also frequently comorbid with both headaches (Radat & Swendsen, 2005) and depression (Kessler et al., 2008), anxiety will be included as a secondary/exploratory predictor of order of onset, along with other demographic variables.

It was hypothesized that those who experienced headaches first would tend to have more severe headaches, whereas those who experienced depression first would tend have a more endogenous (that is, a stronger genetic component) type of depression.

Method

Design

This study was exploratory and cross-sectional in nature and utilized a combination of new interview data assessing retrospective events, as well as the participants' existing data from an earlier study. Three order of onset groups were specified:

1. Headaches first. Headaches followed by depression.
2. Depression first. Depression followed by headaches.
3. Headaches/depression. Headaches and depression began at approximately the same time.

Although headache severity, and a reported diagnosis of depression in a parent (titled 'depression heritability') were included as predictors of order of onset to estimate which if any causal direction between headaches and depression was more likely (more severe headaches should be more likely to cause depression, with this depression tending to be more reactive/low in heritability) they were listed as outcome/grouping variables for the sake of conducting the ANOVA.The possibility was also left open for the groups to be compared on other exploratory variables. The primary author had full access to all data.

Participants

Forty five individuals had previously completed a study entitled ‘Headaches and Depression – Overcome Now’ (HeaD-ON), which ended inJanuary 2012. Of these individuals, thirty chose to participate in the present study. The HeaD-ON project was a randomized controlled trial examining the efficacy of a 12-week cognitive behaviour therapy (CBT) program for people with comorbid headaches and major depressive disorder (Martin et al., 2014). These participants were required to rate their headaches in a diary each waking hour, during the CBT course as well as for at least two weeks before and after the treatment program.

The HeaD-ON project used the following inclusion criteria: Diagnosed with a primary headache disorder according to International Headache Society (IHS) guidelines (Headache Classification Subcommittee of the International Headache Society, 2004); six or more headache days per month; a minimum headache chronicity of 12 months; a stable pattern of headache symptoms over the last six months; a primary diagnosis of Major Depressive Disorder using the Composite International Diagnostic Interview 2.1 Auto Lifetime Version (CIDI-LT) (World Health Organization Collaborating Centre for Mental Health and Substance Abuse, 1997), and a score on the Beck Depression Inventory (BDI-II) (Beck, Steer, & Brown, 1996) of 14 or more; a stable pattern of medication use over the last one month; and aged 18 years and over. The HeaD-ON project applied the following exclusion criteria to participants: Diagnosed with secondary headache disorders, at risk of self-harm as a consequence of severe depression or for other reasons, poor English or intellectual disability, and medical conditions with overriding treatment requirements.

Procedure

Participants consented to the HeaD-ON Research Manager to be invited via phone and/or or email to participate in a related study. Both the first phone/email contact and interviews took place between July 2011 and January 2012. All participants read and signed a

consent form, and when they concluded their participation they were provided with a A$20 gift voucher. This research project was approved by the Monash University Human Research Ethics Committee.

Materials

The Life History Calendar.

The Life History Calendar (LHC) (Freedman, Thornton, Camburn, Alwin, & Young-demarco, 1988) was used to assess the order of onset of headaches and depression' (order of onset), which focused on the order of onset of the most recent episode of depression and headaches.. The LHC can be administered as a structured or semi-structured interview. The LHC leads to greater recall accuracy than free recall by requesting people to describe the context of a particular time, thus forming contextual memory cues (Freedman et al., 1988). Studies have shown increased quality and accuracy of recall with the LHC when compared to other structured questionnaires (Belli, Shay, & Stafford, 2001; Yoshihama, Gillespie, Hammock, Belli, & Tolman, 2005). Although a longitudinal study using a continual diary record is ideal, these are often timely and expensive. Moreover, many longitudinal studies involve recall each one to two years rather than a continual diary record. The LHC is an adaptable template and style, with the researcher specifying the topics, time intervals, and degree of structure (Freedman et al., 1988). In this case, the topics chosen to act as memory cues were suburb of residence and living arrangement, relationship status, travel, children, and occupation. A sample question was: 'To begin with, let's talk about where you lived during the first/second (*choose one*) half of (year). In what town or city did you live in the first/second (*choose one)* half of (year)?' Headaches were defined to participants as 'six or more headache days per month', and depression was defined for participants as 'depressed mood or loss of pleasure for most of the time for at least two weeks, resulting in significant distress or impairment in activities.' Given that all symptoms of depression were not

assessed, depression in this context refers to a probable major depressive episode. For both headaches and depression, participants were requested to separately rate the severity from 0 (*no headaches/depression*), to 10 (~~*the worst possible headaches/depression*~~). When rating their headaches, participants were requested to take into account the average intensity, duration, and frequency of their headaches. These data were then recorded on the LHC for both the researcher and participant to see, beginning from the present and proceeding chronologically into the past.

In this case six-month intervals were chosen, which balanced precision with time constraints. Depending on the response, the LHC analysis continued until a six-month block was identified when only one of the disorders was present, indicating the order of onset. If headaches and depression began in the same six-month block they were allocated to the headaches/depression group. This was expected to be unusual, given that a major longitudinal study found that only 1.2% of comorbid migraine and depression cases had started in the same year (Breslau et al., 1994).

Demographics.

Demographic information was derived from data from the HeaD-ON study and the LHC.

Depression Heritability.

Depression heritability was assessed by noting the presence of depression in at least one parent. The probability of children developing a psychiatric disorder that a parent also had provides an approximate indication of the heritability of the disorder for a particular individual (Weissman et al., 2006). Although this method is unable to separate the influence of shared environment from genetics, the role of shared environment in the familial transmission of depression appears to be much less than that of genetics, except with children (McGuffin, Katz, Watkins, & Rutherford, 1996; Rice, Harold, & Thapar, 2002). To assess for

the current or past presence of depression in parents, participants were asked whether either of their parents had been diagnosed with depression by a general practitioner or mental-health professional.

Headache Severity.

Headache severity was measured using a diary within the HeaD-ON study. The diary involved participants rating the intensity of their headaches each hour by choosing from six options ranging from 0 (*no headache*) to 5 (*an intense incapacitating headache*). This method is regarded as the gold standard in measuring headache severity (Andrasik, Lipchik, McCrory, & Wittrock, 2005) .

Three headache variables were created based on diary data from the two weeks prior to beginning treatment in the HeaD-ON study:

- Headache severity.This was created by averaging the participants' intensity ratings, including ratings of 0, forming a composite measure taking into account headache frequency, duration, and intensity.
- Headache duration. This was the total number of hours of headaches.
- Headache intensity. The mean intensity of headaches,excluding ratings of 0.

Open-Ended Questions.

Participants were asked six open-ended questions about the relationship between their headaches and MDE, which focused mainly on the topics of influence, causality, initial onset, and third variables. All responses were audio-recorded. The questions were as follows:

1. To begin with, why do you think that your headaches became problematic for you?
2. In what ways do you think that your headaches and depression are, or were, related to each other?
3. Which began first?

4. Did one cause the onset of the other?
5. Does, or did, fluctuation in the status of one problem affect the status of the other?
6. Was there anything else in your life that you think triggered or worsened both your headaches and depression?
7. Are there other kinds of relationships between these two problems that we have not covered?

Depression Levels.

These were measured by the BDI-II (Beck et al., 1996).

Anxiety Levels and Diagnoses.

Level of anxiety was obtained from the BAI (Beck & Steer, 1993), and anxiety diagnoses were obtained from the CIDI-LT. Data for both of these variables were obtained from HeaD-ON.

Headache Diagnoses.

Headache diagnoses within HeaD-ON were obtained from a structured interview based on the International Classification of Headache disorders, second edition (Headache Classification Subcommittee of the International Headache Society, 2004).

Statistical Analyses

Statistical analyses were conducted using IBM SPSS Statistics 20. A one-way between subjects analysis of variance (ANOVA) was used to compare the three headache variables across order of onset, and a Pearson's chi-square test to examine the relationship between the dichotomous variable depression heritability and order of onset. A compromise power analysis, using G-Power 3.1.9.2 revealed that the sample size of 30 had a 96% chance of detecting a large effect size of 0.80 , an 84% chance of detecting a medium effect size of 0.50, and a 59% chance of detecting a small effect size of 0.20 (Cohen, 1988) within an ANOVA. The Pearson's chi-square test required minimum expected cell frequencies of five.

A screening correlation matrix between the three headache variables and order of onset was undertaken to determine which if any headache variable would best differentiate the groups.

There was no missing data. Diagnosis of depression in one or more parents was coded as 0, representing the existence of a diagnosis, and 1, representing no diagnosis, coded in this manner because no diagnosis was expected to be more common in the headache first group. With regards to order of onset, the codes were 0 (*depression first*), 1 (*headaches first*), and 2 (*headaches/depression*).

Descriptive statistics are presented as raw figures and column percentages for categorical information, and mean plus standard deviation for continuous data. The following variables were subject to exploratory analyses to assess whether they could differentiate the three order of onset groups: (a) Depression levels as measured by the BDI-II; (b) Anxiety levels as measured by the BAI; (c) number of comorbid anxiety diagnoses; (d) Headache Diagnosis Type; and (e) age of participants. When the primary predictors of order of onset - headache severity variables and depression heritability, are added to these, this equates to seven predictors with an individual alpha level of $p = .007$ to maintain a family wise alpha rate of $p = .05$.

The ANOVA results include a report of the *F* statistic, relationship to criterion *p* value, effect size as R^2, and Gabriel's post-hoc comparisons. Post-hoc rather than planned comparisons were chosen because there were no hypotheses for the headaches/depression group, and Gabriel's method was chosen because it is ideal when sample sizes differ slightly between groups (Field, 2009).

Results

Descriptive Statistics, Exploratory Analyses, and Screening Correlations

The sample consisted of 18 women and 12 men (M_{age} = 42.43 years, SD_{age} = 13.58). Of the 45 participants contacted via phone, 30 chose to participate in the current study, yielding a response rate of 66.67%. Of those who did not participate, eight verbally declined to participate, four were not contactable, and three agreed to participate but did not attend the appointment.

Table 1 lists data for demographics, headache variables, depression variables, headache diagnoses, and participant views derived from open-ended questions, both in total and separately across the three groups.

Insert Table 1 about here

A chi-square goodness-of-fit test revealed that the numbers of participants in each of the three order of onset groups were not significantly different from each other, χ^2 (2) = .80, p = .67.

Of the five exploratory ANOVA analyses, only an ANOVA of BAI scores was significant, with BAI scores lower in the headaches/depression group (13.33) than in the headaches first group (26.75) and the depression first group (24.80), $F(2, 27) = 6.49$, p = .005, R^2 = .32.

A correlation matrix was undertaken between the three headache-severity measures and order of onset, and is presented in table 2. Given that order of onset was coded as an ordinal variable, Spearman's correlation was used for non-parametric data.

Insert Table 2 about here

Table 2 revealed that only headache intensity correlated significantly with order of onset. Therefore, headache intensity was chosen to be included in the ANOVA.

ANOVA Assumptions and Analysis

An ANOVA requires that standard assumptions of parametric tests should not be violated (Field, 2009). Inspection of the data revealed that these assumptions were met. The ANOVA analysis revealed that mean intensity varied significantly between order of onset, $F(2, 27) = 8.04$, $p = .002$, with $R^2 = .37$.. Gabriel post-hoc analyses revealed that experiencing headaches first was associated with more intense headaches compared to both experiencing depression first, $p = .001$, and when compared to experiencing headaches and depression simultaneously, $p = .001$.

Depression Heritability

Only 7 out of 30 participants stated that one or more of their parents had received a diagnosis of depression, meaning that all expected frequencies in the order of onset groups were below five, hence making a chi-square test for goodness-of-fit untenable. A Fisher's Exact Probability test was therefore used instead, and demonstrated that parental depression was not significantly different between the three order of onset groups, $p = .26$.

Open-Ended Questions

Responses for questions 2-6 were effectively categorised into a small number of groups, and hence could be described in quantitative terms. For example, with question 3, which assessed the first ever onset of headaches and depression, participants either stated that headaches arose first or that depression arose first, which were coded as 0 and 1, respectively. For this question, participants could also have stated that both disorders arose simultaneously, but none did. Questions 1 and 7 could not readily be separated into groups, and so some unique relationships identified by participants are described for these questions.

Aseries of chi-square tests from the relevant table 1 data revealed that it was significantly more common for participants to identify a relationship between headaches and depression than not to, χ^2 (1) = 22.53, $p < .001$; to state that depression caused headaches rather than headaches caused depression, χ^2 (1) = 19.20, $p < .001$ and more common to identify life events or circumstances as third variables than to not identify any third variable or to identify other variables as third variables, χ^2 (1) = 26.13, $p < .001$.

In their responses to the open-ended questions, the 15 participants who did not identify headaches as significantly impacting on their depression described headaches as either having no impact on their mood, causing temporary distress, arousing irritation or annoyance, or as a mild or secondary contributor towards their depression. When participants observed headaches as contributing towards their depression, they almost always stated that this was because headaches had interfered with important life activities, such as their career or social lives. The three participants who stated that headaches had caused their depression believed that this was because their headaches were so severe that they ruined multiple aspects of their lives. In contrast, participants who believed that depression had caused their headaches commonly stated that depression had made them more sensitive to stress, which in turn triggered headaches. Two participants saw alternative relationships between their depression and headaches, such as (a) depression leading to insomnia, which then led to increased headaches, and (b) depression leading to increased substance use which then led to increased headaches.

As stated in table 1, 93% of participants believed that some form of relationship existed between their headaches and depression, but they were not significantly more likely to specify one direction of relationship over another. Despite most participants stating that their headaches and/or depression contributed to each other, 47% stated that neither was the sole or even primary cause of the other disorder developing. It was rare for participants to

report that their headaches caused their depression, with only three participants stating this. Two out of these three participants were in the headaches first group, and one was in the headaches/depression group.

Out of the 90% of participants who believed that a third variable had contributed to both their headaches and depression, 96% identified life events as the third variable. Examples of life events included being bullied at work, death of a family member, and moving to another country. One participant noticed that a stressful workplace had contributed to headaches and depression, but that the headaches had also worsened the depression. Other participants identified other third variables either solely or in addition to life events as contributing to both disorders. These included hormones, identified by two participants; another psychiatric disorder, identified by two participants; a medical illness, identified by one participant; self-esteem issues, identified by one participant; and medication, identified by one participant.

In contrast to the main order of onset variable, which assessed the order of onset of the most recent episode of headaches and depression and which included many individuals identifying headaches and depression as beginning at approximately the same time (headaches/depression), there were no participants who described this with the initial onset of headaches and depression. Exactly half of participants listed headaches as arising first and half listed depression first. The former order of onset variable as identified by the LHC did not guarantee the perceived direction of influence reported by participants, with four out of the eight headaches first group stating that headaches had no influence over their depression.

Discussion

This study examined the relationship between headaches and depression utilizing a unique combination of the Life History Calendar (LHC) to improve recall accuracy, and in-

depth case study data.The primary aim of the study was to provide evidence related to whether a causal relationship between headaches and depression existed, and if so, what, if any, direction of causality is more probable. It was hypothesized that the headaches first group would have higher headache severity, and that the depression first group would have higher estimated depression heritability Support for these hypotheses would be consistent with more severe headaches causing depression; and a more endogenous form of depression causing headaches and a more reactive form of depression resulting from headaches.

Before examining the results for these hypotheses, it must first be noted that based on the LHC, it was equally likely for the most recent episode of headaches to have arisen either before, or after, or at the same time, as depression. By itself, this data would suggest that both headaches and depression can contribute to each other or that third variables are contributing to both conditions. Regarding the hypotheses, headache intensity was found to be higher in the headache first group than in the other two groups. This is consistent with more severe headaches causing depression in the headaches first group via greater disability,, with good evidence existing that the primary impact of pain on depression is via disability (Nicassio & Wallston, 1992).. Despite the above support for headaches contributing to depression, there was less support from participants themselves. Only three participants believed that headaches had caused their depression (two of whom were in the headaches first group), and another three believed that a ‘headache to depression relationship only’ existed without identifying causality. There were, however, another 10 participants who identified headaches as contributing to depression as part of a bidirectional relationship. The tentative conclusion may be that headaches are more likely to contribute to depression when they are more intense and disabling, but this is by no means certain, and headaches acting as a primary cause of depression may not be common. For many people, headaches will not have a substantial impact on their mood. This conclusion rests heavily on the accuracy of participant insight and

memory. However, it is consistent with the current study's finding that only 8 out of 30 participants were classified as headaches first. It is also consistent with previous research demonstrating that although headaches and a variety of medical conditions are associated with a greater than average chance of future depression, most people with these medical conditions do not develop depression (Breslau et al., 2003; Dalton & Heinrichs, 2005; Nicassio & Wallston, 1992; Patten, 2001).

The second possibility was that depression causes headaches. Hypothesis number two was not supported, in that depression heritability was not higher in the depression first group. Based on this finding, it would appear that headaches are not more likely to follow and therefore result from more endogenous forms of depression, although the method by which heritability was estimated has limitations to be discussed. Despite this finding, within the open-ended questions participants described depression as causing or contributing to headaches significantly more frequently than for the reverse, with 13 participants stating that depression caused their headaches, and with 22 participants identifying depression as contributing to headaches in either a unidirectional or bidirectional manner. The finding is consistent with aforementioned studies demonstrating how depression can increase headache frequency by leading to greater stress and pain sensitivity (Cathcart et al., 2009; Janke et al., 2004). However, the finding is inconsistent with research demonstrating headaches tending to have arisen first in comorbid cases (Radat et al., 2005; Schur et al., 2009). This difference may arise partly because these studies defined headache onset as when a headache diagnosis was first met, whereas this study looked at the most recent episode of headaches, defined as six or more headache days per month. The current study suggests that, based on participants' views, depression may frequently cause or exacerbate the onset of problematic headaches, more so than the reverse. A finding that depression is more likely to be involved in comorbid headaches than the reverse is consistent with depression now being the leading cause of

disability worldwide (WHO, 2012) , thus potentially tending to have broader and more negative life impacts on an individual than most medical conditions.

The final possibility was that a third variable contributed to both conditions. Third variables were commonly identified by participants and hence received solid support. Only three participants did not identify any third variable. Life events were by far the most common third variable identified, although this encompassed a broad range of factors ranging from severe trauma to work stress. As reviewed earlier, trauma and abuse have been shown to separately contribute to depression and headaches in distinct populations, but the current findings suggest that factors such as these may indeed contribute to both conditions within the same individual. Related to this finding is that 40% of the sample met a current or past post-traumatic stress disorder (PTSD) diagnosis, demonstrating that some of the life events identified may be traumatic events serious enough to result in long-term psychological changes. A possibility is that the perceived relationship between trauma and both headaches and depression is mediated by PTSD or PTSD-like symptoms, or whether trauma independently contributes to all three conditions. Other studies of individuals with headaches have also shown significant elevations in rates of PTSD among those with headaches (Leung et al., 2013; Merikangas et al., 1995), with rates of PTSD of up to 30.3% identified (Merikangas et al., 1995). Rates of PTSD may be even higher in individuals who have both depression and headaches.

A final potential third variable identified was anxiety, as measured by the BAI. These scores were classed in the moderate range in the overall sample, but in the mild range in the headaches/depression group (significantly less than the other two groups). In addition, 87% of the sample had at least one anxiety disorder. Anxiety disorders in general have been shown to predict both depression and headaches (Baskin, Lipchik, & Smitherman, 2006; Kessler et al., 2008; Schur et al., 2009), and in cases with all three conditions, the order of onset tends to

be anxiety arising first (Karakurum et al., 2004).Anxiety is generally closely associated with both headaches and depression, but the current findings suggest that anxiety may be less important when there is a close temporal relation between headaches and depression as was found in the headaches/depression group.

This study was limited by a basic method of assessing depression heritability inasking participants about depression diagnoses in their parents. The rate of reported depression diagnoses in parents may have been low because of lack of participant knowledge, and because depression is often undiagnosed. Direct diagnostic interviews with parents would likely have yielded more accurate results. Another limitation is that this sample actively sought and received psychological treatment, and hence the findings may only generalize to individuals with both conditions who are motivated towards receiving such treatment. This sample would likely have more insight than average into psychosocial contributors to their headaches and depression,; and may also have been more likely to see their depression as primary, given that depression is a more common and well known focus of psychological treatment than is headaches. Additionally, the study was also limited by its sample size, with sub-groups that were at times too small to have sufficient statistical power for comparisons.

This study sought to build evidence for possible causal relationships between headaches and depression through examining the order of onset, comparing headache severity and depression heritability based on order of onset, and through case studies. Although both headache intensity and anxiety differed based on order of onset, the richest information was from participants themselves.. The order of onsetmay provide some useful information as to which condition is more likely to be primary and hence give some guide to treatment priority. Evidence from case studies, but not other order of onset data, suggests that it is more common for depression to be influencing headaches than the reverse. With regards to headache treatment, it may therefore be essential to screen for and treat comorbid depression.

The exploratory finding with anxiety is consistent with research demonstrating the importance of anxiety in headaches and depression, and this study additionally suggests that anxiety may be of particular importance when headaches precede depression and when depression precedes headaches rather than them arising at the same time. This study also found the Life History Calendar to be a user-friendly and time-effective manner of determining order of onset.

Future research could use these exploratory findings to guide power calculations for a larger and more definitive study. A validated, structured or semi-structured recall instrument, like the Life History Calendar as used in this study, or a longitudinal design using a continual diary record, could be used. A more comprehensive method of assessing heritability of depression, such as by utilizing a twins study or by directly diagnosing an individual's wider family, and also examining heritability of headaches would all be beneficial. The latter could also take into account the genetic overlap between headaches and depression. Isolating the treatment of each condition (as much as possible) through, for example, specific CBT for headaches or depression separately, or medication, and measuring the impact on both conditions, could potentially be an effective and more conclusive way of investigating causality.

Abbreviations

Headaches: A subset of common primary headaches disorders; Depression, Major Depressive Episode as part of Major Depressive Disorder; TTH: Tension-type headache; HPA: hypothalamic–pituitary–adrenal; CIDI-LT, Composite International Diagnostic Interview, Lifetime Version; BDI-II, Beck Depression Inventory, 2nd edition; LHC, Life History Calendar; PTSD, post-traumatic stress disorder; BAI, Beck Anxiety Inventory.

Competing Interests

All authors declare that they have no competing interests.

Author Contributions

AW concept and design, drafting of article, data collection and analysis. PM concept and design, editing of manuscript. KG methodology design and editing of manuscript. GM methodology design and editing of manuscript.

Funding

The ‘Headaches and Depression – Overcome Now’ (HeaD-ON) study on which the present study was based was funded by Beyond Blue and the National Health and Medical ResearchCouncil, Australia.

References

Andrasik, F., Lipchik, G. L., McCrory, D. C., & Wittrock, D. A. (2005). Outcome measurement in behavioral headache research: headache parameters and psychosocial outcomes. *Headache, 45*(5), 429-437. doi: 10.1111 /j.1526-4610.2005.05094.x

Atasoy, H. T., Atasoy, N., Unal, A. E., Emre, U., & Sumer, M. (2005). Psychiatric comorbidity in medication overuse headache patients with pre-existing headache type of episodic tension-type headache. *European Journal of Pain, 9*(3), 285-291. doi:10.1016/j.ejpain.2004.07.006

Baskin, S. M., Lipchik, G. L., & Smitherman, T. A. (2006). Mood and anxiety disorders in chronic headache. *Headache, 46*(Suppl 3), S76-S87. doi:10.1007/s10072-009-0071-5

Baskin, S., & Smitherman, T. A. (2009). Migraine and psychiatric disorders: Comorbidities, mechanisms, and clinical applications. *Neurological Sciences, 30* (Suppl 1), S61-S65. doi: 10.1007/s10072-009-0071-5

Beck, A. T., & Steer, R. A. (1993). *Beck Anxiety Inventory Manual*. San Antonio, TX: Psychological Corporation.

Beck, A. T., Steer, R. A., & Brown, J. K. (1996). *Manual for the Beck Depression Inventory-II*. San Antonio, TX: Psychological Corporation.

Belli, R. F., Shay, W. L., & Stafford, F. P. (2001). Event History Calendars and Question List Surveys: A Direct Comparison of Interviewing Methods. *Public Opinion Quarterly, 65*(1), 45-74. doi: 10.1086/320037

Breslau, N., Lipton, R. B., Stewart, W. F., Schultz, L. R., & Welch, K. M. (2003). Comorbidity of migraine and depression: investigating potential etiology and prognosis. *Neurology, 60*(8), 1308-1312. doi: 10.1212/01.wnl.0000058907.41080.54

Breslau, N., Davis, G. C., & Andreski, P. (1991). Migraine, psychiatric disorders, and suicide attempts: An epidemiologic study of young adults. *Psychiatry Research, 37*(1), 11-23. doi: 10.1016/0165-1781(91)90102-U

Breslau, N., Davis, G. C., Schultz, L. R., & Paterson, E. L. (1994). Migraine and Major Depression: A Longitudinal Study. *Headache: The Journal of Head and Face Pain, 34*(7), 387-393. doi: 10.1111/j.1526-4610.1994.hed3407387.x

Brown, J., Cohen, P., Johnson, J. G., & Smailes, E. M. (1999). Childhood abuse and neglect: Specificity and effects on adolescent and young adult depression and suicidality. *Journal of the American Academy of Child & Adolescent Psychiatry, 38*(12), 1490-1496. doi: 10.1097/00004583-199912000-00009

Cathcart, S., Winefield, A. H., Lushington, K., & Rolan, P. (2009). Effect of mental stress on cold pain in chronic tension-type headache sufferers. *The Journal of Headache and Pain, 10*(5), 367-373. doi: 10.1007/s10194-009-0131-5

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences* (2nd ed.). Hillsdale: Lawrence Erlbaum.

Dalton, E. J., & Heinrichs, R. W. (2005). Depression in multiple sclerosis: a quantitative review of the evidence. *Neuropsychology, 19*(2), 152-158. doi: 10.1037/0894-4105.19.2.152

Dohrenwend, B. P., Raphael, K. G., Marbach, J. J., & Gallagher, R. M. (1999). Why is depression comorbid with chronic myofascial face pain? A family study test of alternative hypotheses. *Pain, 83*(2), 183-192. doi: 10.1016/S0304-3959%2899%2900100-1

Field, A. (2009). *Discovering Statistics Using SPSS* (2nd ed.). London: SAGE Publications.

Freedman, D., Thornton, A., Camburn, D., Alwin, D., & Young-demarco, L. (1988). The life history calendar: a technique for collecting retrospective data. *Sociological Methodology, 18*, 37-68. Retrieved from http://www.jstor.org.ezproxy.lib.monash.edu.au/journals/00811750.html

Goldberg, R. T. (1994). Childhood abuse, depression, and chronic pain. *The Clinical Journal of Pain, 10*(4), 277-281. doi: 10.1097/00002508-199412000-00006

Headache Classification Subcommittee of the International Headache Society. (2004). The International Classification of Headache Disorders: 2nd edition. *Cephalalgia, 24*(Suppl 1), 9-

160. Retrieved from http://www.onlinelibrary.wiley.com.ezproxy.lib.monash.edu.au/doi/10.1111/cha.2004.24.issue-s1/issuetoc

Janke, E., Holroyd, Kenneth A., & Romanek, K. (2004). Depression increases onset of tension-type headache following laboratory stress. *Pain, 111*(3), 230-238. doi: 10.1016/j.pain.2004.06.007

Juang, K., Wang, S., Fuh, J., Lu, S., & Su, T. (2000). Comorbidity of Depressive and Anxiety Disorders in Chronic Daily Headache and Its Subtypes. *Headache: The Journal of Head and Face Pain, 40*(10), 818-823. doi: 10.1111/j.1526-4610.2000.00148.x

Karakurum, B., Soylu, O., Karatas, M., Giray, S., Tan, M., Arlier, Z., & Benli, S. (2004). Personality, depression, and anxiety as risk factors for chronic migraine. *International Journal of Neuroscience, 114*(11), 1391-1399. doi: 10.1080/00207450490476002

Kendler, K. S., Karkowski, L. M., & Prescott, C. A. (1999). Causal relationship between stressful life events and the onset of major depression. *The American Journal of Psychiatry, 156*(6), 837-848. Retrieved from http://www.ajp.psychiatryonline.org

Kessler, R. C., Gruber, M., Hettema, J. M., Hwang, I., Sampson, N., & Yonkers, K. A. (2008). Co-morbid major depression and generalized anxiety disorders in the National Comorbidity Survey follow-up. *Psychological Medicine, 38*(3), 365-374. Doi: 10.1017/S0033291707002012

Leung, S. K., Lee, Antoinette, M., Chiang, V. C. L., Lam, S. K., Kuen, Y. Wai, & Wong, D. F. K. (2013). Culturally sensitive, preventive antenatal group cognitive–behavioural therapy for Chinese women with depression. *International Journal of Nursing Practice, 19*, 28-37. doi: 10.1111/ijn.12021

Martin, P. R., Aiello, R., Gilson, K., Meadows, G. N., Reece, J., & Milgrom, J. Cognitive behavior therapy for co-morbid migraine and/or tension-type headache and major depressive disorder. Manuscript submitted for publication.

Martin, P. R., & Macleod, C. (2009). Behavioral management of headache triggers: Avoidance of triggers is an inadequate strategy. *Clinical Psychology Review, 29*(6), 483-495. doi: http://dx.doi.org/10.1016/j.cpr.2009.05.002

McGuffin, P., Katz, R., Watkins, S., & Rutherford, J. (1996). A hospital-based twin register of the heritability of DSM-IV unipolar depression. *Archives of General Psychiatry, 53*(2), 129-136. Retrieved from http://archpsyc.jamanetwork.com.ezproxy.lib.monash.edu.au/ article.aspx? =497534

McWilliams, L. A., Goodwin, R D., & Cox, B. J. (2004). Depression and anxiety associated with three pain conditions: results from a nationally representative sample. *Pain, 111*(1–2), 77-83. doi: 10.1016/j.pain.2004.06.002

Merikangas, K. R., Stevens, D. E., Merikangas, J. R., Katz, C. B. S., Glover, V., Cooper, T., & Sandler, M.. (1995). Tyramine conjugation deficit in migraine, tension-type headache, and depression. *Biological Psychiatry, 38*(11), 730-736. doi: 10.1016/0006-3223(95)00045-3

Mitsikostas, D. D., & Thomas, A. M. (1999). Comorbidity of headache and depressive disorders. *Cephalalgia, 19*(4), 211-217. doi: 10.1046/j.1468-2982.1999.019004211.x

Nicassio, P. M., & Wallston, K. A. (1992). Longitudinal relationships among pain, sleep problems, and depression in rheumatoid arthritis. *Journal of Abnormal Psychology, 101*(3), 514-520.

Patten, S. B. (2001). Long-term medical conditions and major depression in a Canadian population study at waves 1 and 2. *Journal of Affective Disorders, 63*(1-3), 35-41. doi: 10.1016/S0165-0327%2800%2900186-5

Peres, M., Sanchez del Rio, M., Seabra, M., Tufik, S., Abucham, J., Cipolla-Neto, J., . . . Zukerman, E. (2001). Hypothalamic involvement in chronic migraine. *Journal of Neurology, Neurosurgery & Psychiatry, 71*(6), 747-751. doi: 10.1136/jnnp.71.6.747

Peterlin, B., Ward, T., Lidicker, J., & Levin, M. (2007). A Retrospective, Comparative Study on the Frequency of Abuse in Migraine and Chronic Daily Headache. *Headache: The Journal of Head and Face Pain, 47*(3), 397-401. Retrieved from http://web.b.ebscohost.com.ezproxy.lib.monash.edu.au/ehost/detail?sid=2ddca8c4-7447-45c0-9e3b-f15698cadaee%40sessionmgr114&vid=1&hid=128&bdata=JnNpdGU9ZWhvc3QtbGl2ZSZzY29wZT1zaXRl#db=s3h&AN=24350256

Radat, F., Creac'h, C., Swendsen, J. D., Lafittau, M., Irachabal, S., Dousset, V., & Henry, P. (2005). Psychiatric comorbidity in the evolution from migraine to medication overuse headache. *Cephalalgia, 25*(7), 519-522. doi: 10.1111/j.1468-2982.2005.00910.x

Rice, F., Harold, G. T., & Thapar, A. (2002). Assessing the effects of age, sex and shared environment on the genetic aetiology of depression in childhood and adolescence. *Journal of Child Psychology & Psychiatry & Allied Disciplines, 43*(8), 1039-1051. doi: 10.1111/1469-7610.00231

Schur, E. A., Noonan, C., Buchwald, D., Goldberg, J., & Afari, N. (2009). A Twin Study of Depression and Migraine: Evidence for a Shared Genetic Vulnerability. *Headache: The Journal of Head and Face Pain, 49*(10), 1493-1502. doi: 10.1111/j.1526-4610.2009.01425.x

Stam, A., de Vries, B., Janssens, A., Vanmolkot, K., Aulchenko, Y., Henneman, P., . . . Terwindt, G. (2010). Shared genetic factors in migraine and depression: Evidence from a genetic isolate. *Neurology, 74*(4), 288-294. doi: 10.1212/WNL.0b013e3181cbcd19

Wang, S., Liu, H., Fuh, J., Liu, C., Wang, P., & Lu, S. (1999). Comorbidity of headaches and depression in the elderly. *Pain, 82*(3), 239-243. doi: 10.1016/S0304-3959(99)00057-3

Weissman, M. M., Wickramaratne, P., Nomura, Y., Warner, V., Pilowsky, D., & Verdeli, H. (2006). Offspring of depressed parents: 20 years later. *American Journal of Psychiatry, 163*(6), 1001-1008. doi: 10.1176/appi.ajp.163.6.1001

World Health Organisation. (2012). Depression. Retrieved from http://www.who.int/mediacentre/factsheets/fs369/en/

World Health Organisation. (2012). Headaches. Retrieved from http://www.who.int/mediacentre/factsheets/fs277/en/

World Health Organisation Collaborating Centre for Mental Health and Substance Abuse. (1997). *Composite International Diagnostic Interview: CIDI-Auto, Version 2.1 (computer program)*. Geneva: WHOshihama, M., Gillespie, B., Hammock, A. C., Belli, R. F., & Tolman, R. M. (2005). Does the Life History Calendar Method Facilitate the Recall of

Intimate Partner Violence? Comparison of Two Methods of Data Collection. *Social Work Research, 29*(3), 151-163. doi: 10.1093/swr/29.3.151