Level of psychosocial impairment predicts early response to treatment in vasovagal syncope

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Aim
To investigate whether levels of psychosocial impairment and psychological distress at diagnosis in those with vasovagal syncope (VVS) predict subsequent response to conventional treatment.

Methods and results
This is a prospective, observational new patient cohort study, which includes consecutive patients with head-up tilt-confirmed VVS (September 2004—March 2006). Subjects completed the Hospital Anxiety and Depression Scale, State and trait anxiety inventory, and an Adapted Syncope Functional Status Questionnaire at diagnosis and at 3 months. A total of 108 participants (mean (SD) age 52 (21) years, 70.4% were female) completed baseline assessments. Response status was ascertained for 103 individuals; 70 were responders and 33 non-responders. Eighty-three of 103 participants (81%) completed the follow-up questionnaires. At follow-up, compared with responders, non-responders reported higher levels of Impairment (P = 0.001), negative cognitions (P = 0.01), and depression scores (P = 0.006). At diagnosis those who ultimately did not respond to treatment reported significantly higher levels of Impairment (P < 0.001) and negative cognitions (P = 0.03). Those who did not respond to treatment were significantly more depressed (P = 0.001) with higher Trait anxiety scores (P = 0.007). Multivariate analysis confirmed increased impairment predicted poor response status (z = 9.82, P = 0.002) with participants being 3% more likely to be a non-responder with each 1% increase in self-reported level of impairment.

Conclusion
Higher levels of psychosocial impairment reliably predict non-response to treatment, suggesting that psychological factors have an important role in VVS. Screening individuals at diagnosis may enable identification of those at risk of non-response and delivery of targeted psychological interventions to reduce the impact of VVS and its sequelae.

Keywords
Vasovagal syncope • Impairment • Anxiety

Introduction
Vasovagal syncope (VVS) is an increased tendency towards the simple faint and is a common, relapsing, and potentially debilitating medical condition, which can impact on a sufferer’s quality of life. Psychological difficulties, such as anxiety and depression, have been reported in more than 30% of people with VVS, with chronic syncope resulting in significantly worse psychological rather than physical impairment. The measured impact and impairment related to syncope does not, however, correlate with age, number of co-morbid conditions, frequency of episodes, or injury related to syncope, but the level of reported impairment in VVS is comparable with that of other chronic diseases, such as chronic pain and rheumatoid arthritis.

Despite a greater understanding of the pathophysiology of VVS and the availability of effective non-pharmacological treatments, recent studies suggest a large proportion of VVS patients remain symptomatic. Recent cross-sectional studies from our group have confirmed that those with VVS who have not responded to treatment report higher levels of psychosocial impairment and distress. This is a considerable burden when studies suggest that approximately half of those seen in a tertiary referral centre are unresponsive to conventional treatment. Non-responders do not differ from responders on gender, age, number of months with symptoms, past history of fainting, or type of symptom (syncope or pre-syncope), but were significantly more anxious and depressed, report more fear and worry and significantly more VVS-related impairment. It is unclear whether non-response to

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treatment for VVS is attributable to greater distress and impairment, or whether these parameters have the potential at diagnosis to predict outcome or identify those who might benefit from specific behavioural interventions.

Building upon our previous work, the purpose of the current study was to enhance further our understanding of VVS and to prospectively examine those factors that may influence response to treatment. If psychological factors are predictors of treatment outcome, then this would have major implications for service delivery, including assessment, informational care, and targeted psychological interventions. Particularly considering work confirming that VVS patients have been shown to benefit from psychological therapy (cognitive behavioural therapy; CBT) that addresses VVS-related fears, misconceptions, beliefs, and behaviours.7

This longitudinal study aims to examine prospectively syncope-specific dysfunction and psychological distress at the time of diagnosis of VVS, to investigate whether the levels of psychosocial impairment, psychological distress, and syncope-specific negative cognitions at diagnosis can predict subsequent response to conventional treatment.

Methods

Participants

Participants were consecutive patients attending the Falls and Syncope Unit (FASS) of the Royal Victoria Infirmary, Newcastle-upon-Tyne, UK, with symptoms suggestive of VVS, where the diagnosis was subsequently diagnosed by Head-up tilt (HUT) performed in our unit. All HUT are performed using recognized protocols by experienced physicians, when HUT is positive subjects were all managed immediately in a consistent manner. Details of the diagnosis in our unit are provided to all patients verbally, followed up with a patient information sheet explaining the diagnosis and its management. All subjects with an HUT-confirmed diagnosis of VVS, who received conventional treatment, between September 2004 and March 2006, were included. Fourteen per cent of referrals to this unit are tertiary type. Our standardized treatment regimen in all newly diagnosed patients with VVS is to recommend increased fluid intake and promote counter manoeuvres, including a self-tilt training programme.8 All participants consented to the use of their information contained in clinical notes for the purposes of research. Participants for whom a response status could be ascertained ~3 months after diagnosis were included in the final data analysis.

All participants aged 16 years or over, had recently received a definite diagnoses of VVS/presyncope, confirmed by a positive HUT test accompanied with symptom reproduction were included in the study.9,10 Participants with a co-existing psychosis or cognitive impairment were excluded at the point of initial assessment by their responsible physician. Subjects who had had HUT performed prior to attending our unit.

Power calculation confirmed that a sample size of 103 would be necessary for 80% power to detect a medium effect ($d = 0.60$) if an unequal-groups design was used.12

Measures

Measures were completed at diagnosis and at follow-up (~3 months later).

Hospital anxiety and depression scale13

The Hospital anxiety and depression scale (HADS) is a 14-item measure of severity of current anxiety and depression used extensively in medical settings. Scores for each scale range from 0 to 21; higher scores indicate greater anxiety/depression. Scores fall into two categories: non-case (0–7) and clinical case (8–21).

State and trait anxiety inventory (STAI)14

This is a well-established measure of state and trait anxiety with 40 items. The State anxiety scale measures current anxiety, the Trait measuring general anxiety. Scores for each subscale range from 20 to 80, a higher score indicating greater levels of anxiety.

Adapted Syncope Functional Status Questionnaire3

The Syncope Functional Status Questionnaire (SFSQ) is a measure of quality of life for the syncope-specific population. Two subscales measure psychosocial impairment and fear/worry due to syncope. Scores are scaled to vary between 0 and 100, with higher scores representing greater impairment or more VVS-related fear and worry. The overall Syncope Dysfunction Score (SDS) is the average of the Impairment and Fear/Worry scores. Norm means scores for a group of mixed origin syncope patients are 49 ($SD = 39$), 51 ($SD = 21$), and 50 ($SD = 30$) for the Impairment and Fear/Worry subscales, and overall SDS, respectively.3

This measure was adapted for use in this study (Adapted Syncope Functional Status Questionnaire, ASFSQ). Supplementary questions were added aimed at identifying individual’s thoughts and predictions about their condition based on the information obtained from our previous work.6 These additional questions were subjected to factor analysis, from which emerged a new subscale: syncope-specific Negative Cognitions. The new measure demonstrated good internal consistency (Cronbach’s $\alpha = 0.88$, $n = 92$).

Symptom severity

The type of symptoms experienced by patients at presentation (presyncope and syncope) and the severity of symptoms (daily, weekly, monthly, and less frequently) were also recorded and subsequently included in the analysis.

Response status

Three months after diagnosis, participants’ response status was assessed by their physician. This decision was based on whether symptoms had completely disappeared or significantly reduced since diagnosis, as agreed between the physician and participant. Patients were specifically asked whether they had experienced symptoms since they had been seen in the unit, what the nature of these symptoms was (syncope or presyncope) and whether they considered their symptoms to be the same, better, or worse. If patients had experienced no symptoms or only minimal presyncope, they were considered a responder; if they had experienced any further syncope or moderate presyncope (i.e. affecting an individual’s ability to perform activities of daily living), they were considered a non-responder. Physicians were unaware of the scores obtained on the psychological measures.

Data analysis

SPSS (version 12.0.1) was used for data analysis. All analyses were conducted at the conventional significance level of 0.05, with two-tailed tests used throughout. $\chi^2$ analysis was utilized for categorical data, and parametric statistical techniques were utilized for continuous data.15 One variable (Depression) was log-transformed.
Results

Participant cohort

One hundred and eight participants met the study criteria and consented to inclusion. Mean age was 52.3 years (SD = 20.8; range 17–85), and 70.4% were females. Patient characteristics and details of length of history and presenting symptoms are shown in Table 1. Response status was ascertained for 103 individuals; 70 were responders and 33 were non-responders. Eighty-three of the initial 103 participants (81%) completed a set of follow-up questionnaires at 3 months. No significant differences were seen in baseline characteristics at diagnosis between those whose response status is known and those for whom response status could not be determined (data not shown).

Analysis

The analysis was performed in three phases: Phase 1, to replicate our previous cross-sectional VVS studies in this prospectively recruited cohort, syncope-specific and psychological distress measures in responders to conventional treatment at 3 months were compared with non-responders. Phase 2: baseline data collected at diagnosis were interrogated between groups to determine whether differences occurred in psychological measures at diagnosis between those who ultimately responded to treatment compared with those who did not respond. Subsequently, in Phase 3, logistic regression analysis was used to ascertain the predictive value of syncope-specific impairment, symptom severity, and psychological distress measures on determining response status.

Phase 1: comparison of syncope-specific dysfunction between responders and non-responders at follow-up

To determine in this prospectively recruited cohort whether similar levels of psychological distress occurred as in our previous cross-sectional cohort, we examined follow-up data at 3 months. Follow-up questionnaires were available for 83 of the initial 103 participants. As in Gracie et al., non-responders report statistically significantly higher levels of Impairment than responders, resulting in significantly higher scores on the overall SDS. Non-responders also reported statistically significant higher levels of Negative Cognitions than responders. Differences at follow-up between responders and non-responders are shown in Table 2.

On the HADS, 50% of non-responders score in the clinical range for anxiety, and 26% for depression. In comparison, 33% of the responders score in the clinical range for anxiety, and 10% for depression. Comparisons between non-responders and responders, however, did not reach a level of statistical significance (anxiety: $\chi^2 = 1.26, P = 0.26$, depression: $\chi^2 = 2.3, P = 0.08$).

As there were significant differences between responders and non-responders at follow-up, replicating our earlier study, the measures of psychological distress and syncope-specific dysfunction were then examined to ascertain if those who respond to our standardized treatment algorithm differ significantly at the time of diagnosis on any measure to those who ultimately do not respond.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Responder</td>
</tr>
<tr>
<td>n</td>
<td>69</td>
</tr>
<tr>
<td>Length of history (mean ± SD), years</td>
<td>3.4 (3.0)</td>
</tr>
<tr>
<td>Presenting symptoms, n (%)</td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td>30 (43)</td>
</tr>
<tr>
<td>Presyncope</td>
<td>9 (13)</td>
</tr>
<tr>
<td>Both</td>
<td>30 (44)</td>
</tr>
<tr>
<td>Culprit medication, n (%)</td>
<td>6 (9)</td>
</tr>
<tr>
<td>Cardiac history, n (%)</td>
<td>4 (6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Responders and non-responders mean scores (SD) obtained on measures of Syncope-Related Dysfunction at follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Responders Mean (SD)</td>
</tr>
<tr>
<td>Impairment (ASFSQ)</td>
<td>18.4 (26.3)</td>
</tr>
<tr>
<td>Fear/Worry (ASFSQ)</td>
<td>26.1 (20.0)</td>
</tr>
<tr>
<td>Syncope Dysfunction Score (ASFSQ)</td>
<td>22.0 (19.9)</td>
</tr>
<tr>
<td>Negative Cognitions (ASFSQ)</td>
<td>23.8 (13.7)</td>
</tr>
<tr>
<td>Anxiety (HADS)</td>
<td>5.9 (3.9)</td>
</tr>
<tr>
<td>Depression*(HADS)</td>
<td>3.0 (3.5)</td>
</tr>
<tr>
<td>State Anxiety (STAI)</td>
<td>33.8 (10.4)</td>
</tr>
<tr>
<td>Trait Anxiety (STAI)</td>
<td>37.1 (11.9)</td>
</tr>
</tbody>
</table>

Statistically significant results are shown in bold.

*aNorms for a group of syncope of mixed origin participants$^3$ $n = 22$, *b$n = 59$.

*Norms from a group of cancer patients ($n = 573(16))$.

*Norms from a group of working age adults without psychological diagnosis.$^{14}$

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Table 3  Responders and non-responders mean scores obtained on measures of Syncope-Related Dysfunction and emotional distress measures at diagnosis

<table>
<thead>
<tr>
<th>Measure</th>
<th>Responders (n = 69) mean (SD)</th>
<th>Non-responders (n = 32) mean (SD)</th>
<th>P-value</th>
<th>Standard Norms Mean (SD)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impairment (ASFSQ)</td>
<td>23.3 (27.8)</td>
<td>54.42 (35.3)</td>
<td>&lt;0.001</td>
<td>49 (39)</td>
</tr>
<tr>
<td>Fear/Worry (ASFSQ)</td>
<td>33.4 (22.8)</td>
<td>36.01 (24.8)</td>
<td>0.02</td>
<td>51 (21)</td>
</tr>
<tr>
<td>Syncope Dysfunction Score (ASFSQ)</td>
<td>28.6 (21.9)</td>
<td>44.14 (24.7)</td>
<td>0.002</td>
<td>50 (30)</td>
</tr>
<tr>
<td>Negative Cognitions (ASFSQ)</td>
<td>26.6 (15.7)</td>
<td>35.1 (18.5)</td>
<td>0.03</td>
<td>N/A</td>
</tr>
<tr>
<td>Anxiety (HADS)</td>
<td>6.6 (3.8)</td>
<td>9.4 (5.3)</td>
<td>0.01</td>
<td>5.4 (4.1)*</td>
</tr>
<tr>
<td>Depression* (HADS)</td>
<td>2.8 (2.7)</td>
<td>6.1 (5.0)</td>
<td>0.001</td>
<td>3.0 (3.0)*</td>
</tr>
<tr>
<td>State Anxiety (STAI)</td>
<td>36.1 (10.7)</td>
<td>43.3 (17.2)*</td>
<td>0.05</td>
<td>35.2 (10.6)*</td>
</tr>
<tr>
<td>Trait Anxiety (STAI)</td>
<td>35.9 (9.4)</td>
<td>44.1 (13.7)*</td>
<td>0.007</td>
<td>34.8 (9.2)*</td>
</tr>
</tbody>
</table>

Statistically significant results are shown in bold.

*Norms for a group of syncope of mixed origin participants. **n = 51, *n = 28, and *n = 50.
*Norms from a group of cancer patients (n = 573). **Norms for a group of working age adults without psychological diagnosis.

Phase 2: comparing measures of syncope-specific dysfunction between responders and non-responders at diagnosis

At the time of diagnosis, 71% of participants were females, and the mean age was 52.7 years (SD = 20.6). There were no statistically significant differences in gender ($\chi^2 = 0.27, P = 0.61$) or age ($P = 0.42$) between those who subsequently responded to treatment and those who did not. Differences between mean scores on the original and additional subscales of the ASFSQ and distress measures at diagnosis are shown in Table 3. Non-responders reported significantly higher levels of Impairment resulting in a significantly higher overall SDs. On the new measure of Negative Cognitions, non-responders reported higher levels than responders.

Responders ($n = 59$) mean score on the Fear/Worry subscale reduced from 33.6 (SD = 23.8) at diagnosis to 26.1 (SD = 20.0) at follow-up ($P = 0.02$). While non-responders ($n = 21$) mean score on the Fear/Worry subscale increased from 33.1 (SD = 24.4) at diagnosis to 37.4 (SD = 28.7) at follow-up ($P = 0.42$).

Non-responders reported significantly higher levels of clinical case range scores for depression (34%), than responders (7%); ($\chi^2 = 10.1, P = 0.001$), but not anxiety, non-responders (59%), and responders (42%) ($\chi^2 = 1.99, P = 0.159$).

Phase 3: do psychological factors predict response status?

As differences between eventual responders and non-responders have been found at diagnosis, some at statistical significance, the next stage of analysis involved logistic regression to determine the potential predictive value of measures of syncope-related psychosocial impairment, psychological distress, and symptom severity and frequency.

A test of the model with Impairment and Trait anxiety scores as potential predictors of response-status against the age and gender model was statistically reliable, $\chi^2 = 19.6$ (df = 4, $n = 76$), $P = 0.001$, indicating that the predictors, as a set, reliably distinguished between responders and non-responders. This model correctly classified 75% of cases overall, which is an improvement of the model controlling for age and gender that correctly classified 64.5% of cases overall. The positive and negative predictive values are 72.2 and 75.9%, respectively. Only Impairment score reliably predicted response status at a statistically significant level, $z = 9.82, P = 0.002$ (Table 4).

In this model, increased level of Impairment predicts poor response status with participants being 3% more likely to be a non-responder with each 1% increase in self-reported level of impairment.

Table 4 Logistic regression analysis of response status as a function of Impairment and Trait Anxiety

<table>
<thead>
<tr>
<th>Variables</th>
<th>B</th>
<th>Wald test (z-ratio)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.02</td>
<td>0.02</td>
<td>0.9</td>
</tr>
<tr>
<td>Gender</td>
<td>0.08</td>
<td>0.02</td>
<td>0.9</td>
</tr>
<tr>
<td>Impairment</td>
<td>0.03</td>
<td>9.8</td>
<td>0.002</td>
</tr>
<tr>
<td>Trait Anxiety</td>
<td>0.02</td>
<td>0.8</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Statistically significant results are shown in bold.

Discussion

Psychosocial factors including impairment, anxiety, depression, specific illness-related beliefs, predictions, fears, and worries interact with long-term conditions affecting outcome. Previous research has suggested a link between psychological distress and recurrent syncope.2,6,16,17 The direction of a possible causal relationship between psychological distress, psychosocial impairment, and response to treatment has been unclear. Studies confirm that VVS is associated with impaired quality of life; however, whether the severity of this impairment is related to syncope burden...
remains unclear. Here, we found that people who do not respond to conventional treatment report higher levels of syncope-specific impairment negative, unhelpful illness beliefs, and psychological distress at the point of diagnosis than those who experience fewer or no syncope following treatment, supporting a model in which syncope, psychosocial impairment, illness beliefs, and distress may exist within a vicious cycle. Furthermore, high levels of self-reported psychosocial impairment at the time of diagnosis appear to predict non-response to treatment in a sample of VVS patients, replicating findings of psychosocial factors being predictive of outcome in populations with other long-term conditions: angina, back pain, and COPD.

Trait Anxiety was also found to be a reliable predictor of response status when considered without Impairment scores. It is conceivable that responders have adopted a more confident approach in not allowing the symptoms associated with VVS to interfere with their lives—something that could be explained by lower levels of trait anxiety. At diagnosis, subsequent responders and non-responders report very similar levels of Fear/Worry (mean scores 33.4 and 33.1, respectively). As expected, however, those participants who responded to treatment at 3 months reported significantly less syncope-specific fear and worry at follow-up than they did at diagnosis. Conversely, the non-responders report higher levels of Fear/Worry at follow-up than they did at diagnosis. Fear and worry about the consequences of VVS may develop the longer subjects are left undiagnosed/ unrecognized or untreated. If this was the case, there could be further impact on the level of impairment and psychological distress being experienced if the VVS symptoms remain unchanged.

In this study, three clinical measures have been further validated on a VVS population. The ASFSQ, the STAI, and the HADS demonstrated good reliability. A new measure of Negative Cognitions specific to VVS has been validated for this population. These measures can be used to screen for psychological disability, distress and negative cognitions in clinical practice, and could be used to inform psychological treatment.

At follow-up, 50% of non-responders scored in the clinical range for anxiety and 26% were in the clinical range for depression compared with responders (33% clinical range for anxiety and 10% for depression) (comparable with the findings of Shaffer et al.). While not statistically significant, this is clinically important. Anxiety and depression are prognostic of poor outcome in many long-term conditions, and screening and treatment in VVS are certainly warranted.

As level of syncope-induced psychosocial impairment has been shown to be a reliable predictor of non-response to treatment, screening at the point of diagnosis could allow clinicians seeing patients with VVS to identify those patients who are less likely to respond to treatment. Staff in syncope units could be equipped and trained to elicit patient’s specific fears and predictions about their condition to ensure that the patients have realistic expectations and information about VVS. A wide-range of self-management advice may also be indicated, such as training in the use of applied tension. We would strongly recommend to clinicians managing patients with VVS that if a patient presents with a level of depression and/or anxiety that reaches a level of caseness, and/or a level of impairment score >50% than this study confirms that referral to an appropriately qualified therapist may be indicated. This is particularly important when it is considered that the benefits of cognitive-behavioural therapy have been demonstrated for people with treatment-resistant VVS but further research is essential to study its efficacy, particularly in an area of physical health where reports of psychological intervention are not widely reported.

This study has several limitations. First, self-report measures are open to bias and misinterpretation, but the subjective experience of having VVS is crucial in determining the validity of the hypotheses. Importantly, the measures utilized in this study have previously demonstrated good psychometric properties that have been confirmed in this study. Secondly, determination of response status was at the discretion of the responsible physician following assessment of the participant and what participants self-reported. Although there is agreement between physicians that successful response to treatment is defined as a complete or significant reduction in VVS symptoms, the possibility of differing opinions cannot be dismissed. Thirdly, specific co-morbidities that might contribute to psychological distress (such as diabetes and cardiac disease) were not controlled for, except for psychosis and cognitive impairment. In addition, the impact of psychological distress on treatment adherence has been documented for other chronic conditions, such as diabetes. Although this was not addressed in this study, non-adherence may have contributed to non-response. Finally, the follow-up period for this study is short; this is particularly important considering the randomness of VVS recurrence and clustering of events over time. We believe that our findings need to be reproduced in a large series of well-characterized patients’ followed up for longer periods of time.

Interestingly, frequency and severity of symptoms was not predictive of response to treatment; this is in keeping with previous studies suggesting that syncope-induced impairment has no relationship to response to treatment.

In conclusion, this study has ascertained that higher levels of psychosocial impairment may reliably predict early non-response to treatment, suggesting that psychological factors have an important role in VVS. Patients who did not respond to treatment were also found to have higher levels of fears and worries and negative cognitions, and higher levels of depression and anxiety at diagnosis, with a clinically significant number remaining in the clinical case range for both anxiety and depression at their 3 month follow-up. Screening individuals at diagnosis may enable identification of those at risk of non-response, and psychological interventions, from targeted information and eliciting/responding to misconceptions, to cognitive behaviour therapy reducing the impact of VVS and its sequelae.

Conflict of interest: B.F. performed this work as part of her Doctorate in Clinical Psychology in Newcastle University. None of the authors have any conflicts on interest to declare.

References