

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Health anxiety and risk of ischemic heart disease: a prospective cohort study linking the Hordaland Health Study (HUSK) with the Cardiovascular Diseases in Norway (CVDNOR) project
AUTHORS	Berge, Line; Skogen, Jens Christoffer; Sulo, Gerhard; Igland, Jannicke; Wilhelmsen, Ingvard; Vollset, Stein Emil; Tell, Grethe; Knudsen, Ann Kristin

VERSION 1 - REVIEW

REVIEWER	Henneke Versteeg Department of Cardiology, University Medical Center Utrecht, the Netherlands
REVIEW RETURNED	20-Jun-2016

GENERAL COMMENTS	<p>In this study, the authors examined the association between health anxiety and risk of ischemic heart disease using data from the community based HUSK study. Overall, the paper is interesting and well written. However, I do have some concerns:</p> <p>My main concerns regard the WI, covariate selection and interpretation of results:</p> <p>Whitely Index:</p> <p>1) I am not familiar with the Whiteley Index, but if I understand correctly from the paper this index has a potential maximum score of 70. In this study, the cut-off for the 90th percentile was a score of 31, which seems rather low. What was the score range in the highest 10% of subjects? Can subjects with a score of ≤ 50 really be qualified as suffering from health anxiety? How do the scores in this study compare to other studies using the WI? And what is the correlation between WI scores and the DSM-IV criteria for health anxiety?</p> <p>Covariates:</p> <p>2) Among the covariates I miss other comorbidities besides diabetes, like COPD, renal failure and malignancy, that can have a major influence on the results. Also, diabetes was utilized from self-report, yet I feel this data (and data on other comorbidities) can more objectively be obtained from the PAS that was used to gather CVD-related hospital admissions.</p> <p>3) I also miss information on other psychological disorders/symptoms, like general anxiety or depression, that are highly correlated with health anxiety and with IHD risk. Was this information not collected in the HUSK questionnaires?</p> <p>4) What were the HR-results for smoking, HDL cholesterol and</p>
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	<p>education? Were these associations stronger or weaker than for health anxiety?</p> <p>Interpretation of results:</p> <p>5) From Table 2 it seems that the association between health anxiety and IHD is non-significant for women when adjusting for CVD risk factors/all covariates. However, this is not mentioned in the results/discussion section.</p> <p>6) In the discussion section it is mentioned that non-participants showed a higher risk of stress related or somatoform disorders and diseases in the circulatory system. The authors should elaborate on how this influences their results.</p> <p>Minor issues:</p> <p>7) How many cases and non-cases were excluded due to an ischemic heart event in the first year after baseline?</p> <p>8) In Table 1, please state the total N for cases and non-cases.</p> <p>9) In Table 1, 5 rows with results are presented for alcohol consumption, while only 4 'options' are given in the first column.</p> <p>10) In Table 2, the * in the footnote is not represented in the table.</p>
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REVIEWER	Matthew Sunderland University of New South Wales, Australia.
REVIEW RETURNED	21-Jun-2016

GENERAL COMMENTS	<p>"Health anxiety and risk of ischemic heart disease: a prospective cohort study linking the Hordaland Health Study (HUSK) with the Cardiovascular Diseases in Norway (CVDNOR) project"</p> <p>The current study examines the risk of ischemic heart disease associated with heightened levels of health anxiety after adjustment for established CVD risk factors. The study has many strengths including: a large prospective community sample linked with extensive cardiovascular data, comprehensive assessment of health anxiety (using the Whiteley Index and various cut-offs and definitions), and outcome data measured using physician diagnosis or death certificates. This study provides evidence for the link between health anxiety and cardiovascular disease independent of additional covariates associated with CVD risk and poor lifestyles. As such, there are several implications of the current research related to the assessment and treatment of health anxiety.</p> <p>My primary concern involves whether or not the results represent specific risk of health anxiety to ischemic heart disease or whether it could be explained by heightened levels of general anxiety, panic, or depression not directly related to health anxiety. Previous evidence has demonstrated that health anxiety is highly comorbid with other anxiety and depressive disorders. Moreover, there is strong support for a relationship between general anxiety, depression, and cardiovascular disease (as outlined in the literature review). Therefore, I feel the models needs to include comorbid anxiety and depressive disorders as covariates (or a least a measure of non-specific general distress) in order to examine the specific contribution of health anxiety? I believe this would strengthen the paper, contribute more to the existing literature, and better align with the research question that was outlined in the introduction. If these measures are not available then further discussion of this issue is</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name
Henneke Versteeg

Institution and Country
Department of Cardiology, University Medical Center Utrecht, the Netherlands

Please state any competing interests or state 'None declared':
None declared.

Please leave your comments for the authors below

In this study, the authors examined the association between health anxiety and risk of ischemic heart disease using data from the community based HUSK study. Overall, the paper is interesting and well written. However, I do have some concerns:

My main concerns regard the WI, covariate selection and interpretation of results:

Whitley Index:

1) I am not familiar with the Whiteley Index, but if I understand correctly from the paper this index has a potential maximum score of 70. In this study, the cut-off for the 90th percentile was a score of 31, which seems rather low. What was the score range in the highest 10% of subjects? Can subjects with a score of ≤ 50 really be qualified as suffering from health anxiety? How do the scores in this study compare to other studies using the WI? And what is the correlation between WI scores and the DSM-IV criteria for health anxiety?

Response:

Score range of Whiteley Index according to percentiles is shown in the table below. The score of WI in the study population was skewed towards the left and did not display a normal distribution. Mean in the total population was 22.5 (st.dev 6.3).

Percentile Range score WI

80th	26-68
90th	31-68
95th	35-68
99th	45-68

The Whiteley Index is available in several versions, differing with regard to number of items included. The vast majority of studies on WI have investigated psychometrical properties with regard to factor structure (overview on the literature on this in ref 19 (Veddegjærde et al) in the manuscript). To our best knowledge, no established cut-off for caseness of health anxiety exists for Whitley Index. We have previously used the 90th percentile in a study on health anxiety and cancer detection (Knudsen et al: The prospective association between health anxiety and cancer detection: A cohort study linking the Hordaland Health Study (HUSK) with the Norwegian Cancer Registry, Journal of Psychosomatic Research, 2015, 148-152), and in this study, the 90th percentile was used as a compromise between prevalence estimates in previous literature and the need for sufficient statistical

power in the regression models.

We are not familiar with studies using the 14 item WI in a general population other than the HUSK Study. However, the national Survey of Mental Health and Wellbeing in Australia applied the World Mental Health version of the Composite International Diagnostic Interview (WMH-CIDI) in a general population in 2007, estimating lifetime prevalence and a current prevalence of health anxiety of 5.7% and 3.4%, respectively. Highest prevalence was found among persons aged 35-44 years, corresponding to the age of the participants in our study, with lifetime and current prevalence of 7.4% and 4.4%. (ref 23 (Sunderland et al) in our manuscript).

Health anxiety is not regarded a diagnostic entity in the current DSM or ICD-10 manuals, and the correlation with WI will therefore be difficult to elaborate on. The update from DSM-IV to DSM-V replaced the diagnose "Hypochondriasis" with two new, empirically derived diagnosis; the "Somatic symptom disorder" and the "Illness anxiety disorder", with corresponding prevalence estimates in the general population of 5-7% and 1.3-10% respectively. In ICD-10 the diagnosis "Hypochondrical disorder" is classified under the F45 chapter of "Somatoform disorders". The diagnose "Hypochondrical disorder" requires disagreement or lack of reassurance from physicians negative finding, making the diagnosis difficult to apply in population based studies. Therefore, attempts have been made to define and validate health anxiety as an abridged form of hypochondriasis, with prevalence estimates ranging from 2% to 9% in the general population (for an overview of the literature, see the introduction in Mykletun et al: Health anxiety and disability pension award: The HUSK Study, *Psychosomatic Medicine* 2009, 353-360).

With regard to the statistical power and the strenght of the associations in our study, we found a significant positive trend with increased risk of IHD by levels of health anxiety (figure 1). Further, relative to the first quintile of scores of WI, a significant increased risk of IHD was found from the second quintile in the gender adjusted models (table 3), both of these findings arguing in favor of a relative low cutoff for caseness of health anxiety.

In line with this, a study in general practice on dimensionality and scale model properties found a cutoff score of 2/3 yielding the best balance between sensitivity and specificity when using WI as a measure of hypochondriasis (Conradt et al: Dimensionality of the Whiteley Index: Assessment of hypochondriasis in an Australian sample of primary care patients. *Journal of Psychosomatic Research*, 2006, 137-143).

Conducting additional analyses using the 80th percentile as cutoff for caseness of health anxiety yielded a gender adjusted HR of 1.63 (95% CI:1.23, 2.16) and HR fully adjusted model of 1.38 (95% CI: 1.02, 1.86). Corresponding HRs when using the 95th percentile as cutoff was 2.05 (95% CI: 1.35, 3.12) and 1.60 (95% CI: 0.99, 2.55).

Covariates:

2) Among the covariates I miss other comorbidities besides diabetes, like COPD, renal failure and malignancy, that can have a major influence on the results. Also, diabetes was utilized from self-report, yet I feel this data (and data on other comorbidities) can more objectively be obtained from the PAS that was used to gather CVD-related hospital admissions.

Response:

First, we truly acknowledge that presence of other conditions such as for example COPD, renal failure and malignancy can be associated with increased risk of IHD in the general population. These conditions are also likely to be associated with health anxiety, and further not expected to be on the causal pathway between health anxiety and IHD, suggesting them to act as possible confounders for the association. The HUSK study was undertaken in 1997 to 1999 primarily aiming to investigate prevalence of and established risk factors for cardiovascular diseases in the general population at the time of investigation. However, as for all studies, one had to prioritize which data to collect, and therefore we not have access to valid information on all possible confounder known today, and

consequently had to select covariates based on availability of data and established risk tools, such as the Framingham risk score (reference 18 in main manuscript). Nevertheless, we recognize this as a potential weakness of the study, and have addressed it in limitation section (page 14, line 5-7):

“Finally, we did not have information on a range of additional conditions that are likely to be associated with both health anxiety and increased risk of IHD, such as for example pulmonary diseases and malignancies. As a result, residual confounding cannot be ruled out”

Second, we agree that data from PAS is more valid than self-reported information. However, use of data from PAS on for example presence of diabetes would represent an underestimation of the prevalence in the study population, as the majority of persons with diabetes type 2, the most prevalent type, only receive treatment in primary care, not covered by PAS.

3) I also miss information on other psychological disorders/symptoms, like general anxiety or depression, that are highly correlated with health anxiety and with IHD risk. Was this information not collected in the HUSK questionnaires?

Response:

Also requested by the second reviewer, we have addressed this highly relevant issue this in a post-hoc analysis in the result section. It includes data on the distribution on levels of anxiety and depression by caseness of health anxiety, as well as measures of the association between health anxiety and IHD adjusted for gender and measures of anxiety and depression (page 10, line 12-22):

“Health anxiety often exist comorbid to other psychiatric disorders, such as general anxiety and depression (23). Additionally, regarded as an anxiety disorder, health anxiety obviously shares many features with anxiety in general, and a sharp distinction between the conditions is difficult to draw. Nevertheless, in an attempt to investigate a possible specific effect of health anxiety on risk of IHD, we conducted post-hoc analyses adjusting for presence of anxiety and depression at baseline in HUSK measured by the Hospital Anxiety and Depression Scale, HADS-a and HADS-d (24). Cases with health anxiety had mean HADS-a and HADS-d of 8.01 (SE: 0.15) and 5.54 (SE: 0.16), while non-cases scored 4.27 (SE 0.04) and 2.89 (SE 0.36) respectively. HR for the association between health anxiety and IHD adjusted for gender and HADS-a was 1.65 (95% CI: 1.14, 2.38), corresponding HR adjusted for gender and HADS-d was 1.89 (95% CI: 1.33, 2.59), while HR adjusted for gender and both HADS-a and HADS-d was 1.64 (95% CI: 1.14, 2.37)”.

A sentence on this finding and its possible implications has also been added to the first paragraph of the discussion (page 12, line 8-12):

“The positive association between health anxiety and IHD was attenuated, but still remained, after adjustments for measures of anxiety and depression in post-hoc analyses, possibly suggesting an additional increased risk of IHD among persons with health anxiety beyond that explained by anxiety and depression in general.”

As stated in the revised version of the manuscript, health anxiety share many features with anxiety in general, and a sharp distinction between the conditions are difficult to draw. We therefore argue that overadjustment will be the most likely consequence of including measures of anxiety and depression in the fully adjusted model, and therefore suggest not include these measures in the main analyses.

4) What were the HR-results for smoking, HDL cholesterol and education? Were these associations stronger or weaker than for health anxiety?

Response:

The gender adjusted associations between IHD and smoking, HDL cholesterol and education are presented in the table below:

Covariates HR (95% CI) for IHD, adjusted for gender only

Smoking

Never

Former

Current

(ref)

1.01 (0.68, 1.52)

2.32 (1.67, 3.21)

HDL quintiles (mg/dl)

1st (<37.0)

2nd (\geq 37.0, <43.0)

3rd (\geq 43.0, <49.5)

4th (\geq 49.5, <58.1)

5th (\geq 58.1)

4.60 (2.56, 8.27)

3.74 (2.07, 6.75)

2.49 (1.35, 4.60)

2.29 (1.23, 4.29)

(ref)

Education

Less than high school

High school

College or university

2.31 (1.61, 3.31)

1.47 (1.07, 2.02)

(ref)

Comparing the strength of the association between the covariates and IHD is challenging due to different scales of the categorical covariates. However, operationalizing both HDL and WI in quintiles (as presented in table 3) shows a possible trend of stronger association with IHD by decreasing levels of HDL when compared with the increasing strength of the association by higher levels of WI (HR 1st quintile of HDL (relative to 5th quintile): 4.60 (95% CI: 2.56, 8.27), vs HR 5th quintile of WI (relative to 1st quintile): 3.06 (95%CI: 1.89, 5.28)). The difference between these relative risks is however likely not significant due to overlapping confidence intervals.

Interpretation of results:

5) From Table 2 it seems that the association between health anxiety and IHD is non-significant for women when adjusting for CVD risk factors/all covariates. However, this is not mentioned in the results/discussion section.

Response:

We are most thankful for the thorough review, and have underlined in the result section that the associations between health anxiety and IHD for women were no longer significant after adjustments for CVD risk factors and all covariates combined (page 9, line 17-18):

“Further, the association between health anxiety and IHD was no longer significant for women after adjustments for CVD risk factors and all covariates combined.”

In accordance with this, the last sentence in the first paragraph of the discussion on gender stratified

findings has been removed.

6) In the discussion section it is mentioned that non-participants showed a higher risk of stress related or somatoform disorders and diseases in the circulatory system. The authors should elaborate on how this influences their results.

Response:

Again, we thank the reviewer for valuable comments, and have consequently added a sentence on possible underestimation of the true association due to non-participation of persons with highest risk of stress related and somatoform disorders (page 13, line 33-34):

“In general, nonparticipation represents a greater threat to the validity of results from studies estimating prevalence rather than risks, and we argue that this is a minor threat to the internal validity of our results, nevertheless, an underestimation of the true association cannot be excluded.”

Minor issues:

7) How many cases and non-cases were excluded due to an ischemic heart event in the first year after baseline?

Response:

A total of 10 participants were excluded due to hospitalizations or death of IHD the first 12 months after participation in HUSK. Among these, 2 participants had WI scores above the 90th percentile of ≥ 31 points. Mean WI among these 10 excluded participants was 24.5 (st.dev 7.4), range 17-43.

8) In Table 1, please state the total N for cases and non-cases.

Response:

This has been corrected.

9) In Table 1, 5 rows with results are presented for alcohol consumption, while only 4 'options' are given in the first column.

Response:

This was an unfortunate spelling error, and has now been corrected.

10) In Table 2, the * in the footnote is not represented in the table.

Response:

This has been corrected.

Reviewer: 2

Reviewer Name

Matthew Sunderland

Institution and Country

University of New South Wales, Australia.

Please state any competing interests or state 'None declared':

None declared.

Please leave your comments for the authors below

"Health anxiety and risk of ischemic heart disease: a prospective cohort study linking the Hordaland Health Study (HUSK) with the Cardiovascular Diseases in Norway (CVDNOR) project"

The current study examines the risk of ischemic heart disease associated with heightened levels of health anxiety after adjustment for established CVD risk factors. The study has many strengths including: a large prospective community sample linked with extensive cardiovascular data, comprehensive assessment of health anxiety (using the Whiteley Index and various cut-offs and definitions), and outcome data measured using physician diagnosis or death certificates. This study provides evidence for the link between health anxiety and cardiovascular disease independent of additional covariates associated with CVD risk and poor lifestyles. As such, there are several implications of the current research related to the assessment and treatment of health anxiety.

My primary concern involves whether or not the results represent specific risk of health anxiety to ischemic heart disease or whether it could be explained by heightened levels of general anxiety, panic, or depression not directly related to health anxiety. Previous evidence has demonstrated that health anxiety is highly comorbid with other anxiety and depressive disorders. Moreover, there is strong support for a relationship between general anxiety, depression, and cardiovascular disease (as outlined in the literature review). Therefore, I feel the models needs to include comorbid anxiety and depressive disorders as covariates (or a least a measure of non-specific general distress) in order to examine the specific contribution of health anxiety? I believe this would strengthen the paper, contribute more to the existing literature, and better align with the research question that was outlined in the introduction. If these measures are not available then further discussion of this issue is required in the discussion and limitations section of the manuscript.

Response:

Also requested by the first reviewer, we have addressed this highly relevant issue this in a post-hoc analysis in the result section, showing that adjustment for measures of anxiety and depression attenuates the association between health anxiety and IHD in the crude, gender adjusted model, yet the positive association still remains (page 10, line 12-22):

"Health anxiety often exist comorbid to other psychiatric disorders, such as general anxiety and depression (23). Additionally, regarded as an anxiety disorder, health anxiety obviously shares many features with anxiety in general, and a sharp distinction between the conditions is difficult to draw. Nevertheless, in an attempt to investigate a possible specific effect of health anxiety on risk of IHD, we conducted post-hoc analyses adjusting for presence of anxiety and depression at baseline in HUSK measured by the Hospital Anxiety and Depression Scale, HADS-a and HADS-d (24). Cases with health anxiety had mean HADS-a and HADS-d of 8.01 (SE: 0.15) and 5.54 (SE: 0.16), while non-cases scored 4.27 (SE 0.04) and 2.89 (SE 0.36) respectively. HR for the association between health anxiety and IHD adjusted for gender and HADS-a was 1.65 (95% CI: 1.14, 2.38), corresponding HR adjusted for gender and HADS-d was 1.89 (95% CI: 1.33, 2.59), while HR adjusted for gender and both HADS-a and HADS-d was 1.64 (95% CI: 1.14, 2.37)".

A sentence on this finding and its possible implications has also been added to the first paragraph of the discussion (page 12, line 8-12):

"The positive association between health anxiety and IHD was attenuated, but still remained, after adjustments for measures of anxiety and depression in post-hoc analyses, possibly suggesting an additional increased risk of IHD among persons with health anxiety beyond that explained by anxiety and depression in general."

However, the HR of the fully adjusted model for the association between health anxiety and IHD no longer reached statistical significance when including HADS-a. This is reflected in a HR of 1.33 (95%

CI: 0.90, 1.98) for the previously fully adjusted model including solely HADS-a and HR of 1.31 (95%CI: 0.88, 1.97) for the previously fully adjusted model including both HADS-a and HADS-d, while including HADS-d in the previously fully adjusted model gave HR of 1.56 (95% CI: 1.06, 2.28). We cannot rule out that our study did not have the statistical power to include adjustments for additional covariates, and as a result of underpowerment, these analyses did not reach statistical significance at 95% CI level.

As stated in the revised version of the manuscript, health anxiety share many features with anxiety in general, and a sharp distinction between the conditions are difficult to draw. We therefore argue that overadjustment will be the consequence of including measures of anxiety and depression in the fully adjusted model, and therefore suggest not presenting these results in detail in the manuscript.

VERSION 2 – REVIEW

REVIEWER	H Versteeg Dept of Cardiology, UMC Utrecht, the Netherlands
REVIEW RETURNED	21-Jul-2016

GENERAL COMMENTS	<p>I think the manuscript has improved, however I feel non-significant results are too easily put aside by the authors and should receive more attention in the discussion of results.</p> <p>According to Table 2, the association between health anxiety and IHD is no longer significant for women in the models adjusting for CVD risk factors and all variates combined. I feel this finding should be discussed. What is the difference between men and women that could explain this result?</p> <p>In their response letter, the authors state that the association between health anxiety and IHD was no longer significant in the fully adjusted model including HADS-A. However, this result was not incorporated in the manuscript as the authors feel the model is overadjusted or underpowered, yet the sample is quite big. What is the correlation between WI and HADS-A scores, is there indeed collinearity? I think these results should be presented in the manuscript and discussed in the discussion section.</p>
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REVIEWER	Matthew Sunderland UNSW Australia
REVIEW RETURNED	28-Jul-2016

GENERAL COMMENTS	The authors have satisfactorily address my concerns. Thank you.
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
 Reviewer Name
 H Versteeg
 Institution and Country
 Dept of Cardiology, UMC Utrecht, the Netherlands

Please state any competing interests or state 'None declared':
None declared

Please leave your comments for the authors below

I think the manuscript has improved, however I feel non-significant results are too easily put aside by the authors and should receive more attention in the discussion of results.

According to Table 2, the association between health anxiety and IHD is no longer significant for women in the models adjusting for CVD risk factors and all variates combined. I feel this finding should be discussed. What is the difference between men and women that could explain this result?

Response:

We thank the reviewer for emphasizing this finding, and agree that it was too lightly discussed in the previous version. We believe that the most likely explanation for the gender difference is the relatively young age of the participants in our study. At group level, women develop IHD approximately a decade later than men, resulting in fewer events among women in our young cohort, corresponding to larger confidence intervals and a non-significant association in this group when all covariates are included in the fully adjusted model. However, as we found no significant interaction by gender, and as there are, to the best of our knowledge, no reports in the literature on effect modification by gender in the association between anxiety and IHD/cardiovascular diseases, we argue the results should be interpreted with caution. The following section summarizes our reflection on the finding on page 13, line 25-34.

“In the gender stratified analyses in table 2, the association between health anxiety and IHD was no longer significant for women after adjustments for established CVD risk factors. This finding must be interpreted with caution, as no significant gender interaction was found. Further, no previous studies on the prospective association between anxiety and risk of IHD or cardiovascular diseases have, to the best of our knowledge, found evidence of effect modification by gender (8, 9, 25). In the general population, women develop IHD one decade later in life compared to men (28). Thus, our findings are likely explained by the expected low event rate of IHD for women in this relatively young cohort of participants followed from their forties into early sixties, resulting in wider confidence intervals and non-significant associations when including numerous covariates in the more adjusted models”.

In their response letter, the authors state that the association between health anxiety and IHD was no longer significant in the fully adjusted model including HADS-A. However, this result was not incorporated in the manuscript as the authors feel the model is overadjusted or underpowered, yet the sample is quite big. What is the correlation between WI and HADS-A scores, is there indeed collinearity? I think these results should be presented in the manuscript and discussed in the discussion section.

Response:

As requested by the reviewer, the non-significant estimates of the fully adjusted model including measures of anxiety have now been added to the section presenting this post-hoc analysis in the result section (page 12, line 14-18):

“However, adding measures of anxiety to the fully adjusted model outlined in table 2 and 3 resulted in a no longer significant association between health anxiety and IHD, evident from a HR of 1.33 (95% CI: 0.90, 1.98) for the fully adjusted model in addition to adjustments for HADS-a and HR of 1.31 (95% CI: 0.88, 1.97) for the fully adjusted model in addition to adjustments for both HADS-a and HADS-d. Including adjustments of HADS-d only to the previously fully adjusted model yielded a HR of 1.56 (95% CI: 1.06, 2.28).”

Additionally, we present estimates of the correlation between WI and HADS-a, and HADS-d (page 12, line 9-10), suggesting that collinearity between WI and HADS are unlikely.

“Pearson’s correlation coefficient between WI and HADS-a and Hads-d were 0.48 ($p=0.00$) and 0.37 ($p=0.00$), respectively.”

However, the size of this correlation indicates an overlap between the measures of WI and HADS-a, possibly due to difficulties discriminating between health anxiety and anxiety in general. We therefore argue in the discussion section that including HADS-a in the main models in this study will increase the risk of overadjustments (page 14, line 31-36 and page 15, line 1-3).

“Finally, a sharp distinction between health anxiety and other psychiatric conditions is challenging to draw, as health anxiety often exists comorbid to other psychiatric disorders (23), and, regarded an anxiety disorder, obviously shares many features of anxiety in general. To reduce the risk of overadjustments, we decided against including measures of anxiety and depression in the main model of this study as symptoms of health anxiety correlate to a large extent with symptoms of these conditions. This is particularly evident for anxiety in general, reflected in the relatively strong correlation between WI and HADS-a likely explaining the no longer significant finding between health anxiety and IHD when including measures of anxiety in the fully adjusted model.”

Reviewer: 2

Reviewer Name
Matthew Sunderland

Institution and Country
UNSW Australia.

Please state any competing interests or state ‘None declared’:
None declared.

Please leave your comments for the authors below
The authors have satisfactorily address my concerns. Thank you.