



Aalborg Universitet

AALBORG UNIVERSITY
DENMARK

The unifying diagnostic construct of bodily distress syndrome (BDS) was confirmed in the general population

Petersen, Marie Weinreich; Schröder, Andreas; Jørgensen, Torben; Ørnbøl, Eva; Dantoft, Thomas Meinertz; Eliassen, Marie; Thuesen, Betina H; Fink, Per

Published in:
Journal of Psychosomatic Research

DOI (link to publication from Publisher):
[10.1016/j.jpsychores.2019.109868](https://doi.org/10.1016/j.jpsychores.2019.109868)

Creative Commons License
CC BY-NC-ND 4.0

Publication date:
2020

Document Version
Version created as part of publication process; publisher's layout; not normally made publicly available

[Link to publication from Aalborg University](#)

Citation for published version (APA):
Petersen, M. W., Schröder, A., Jørgensen, T., Ørnbøl, E., Dantoft, T. M., Eliassen, M., Thuesen, B. H., & Fink, P. (2020). The unifying diagnostic construct of bodily distress syndrome (BDS) was confirmed in the general population. *Journal of Psychosomatic Research*, 128, 1-7. [109868].
<https://doi.org/10.1016/j.jpsychores.2019.109868>

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- ? Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- ? You may not further distribute the material or use it for any profit-making activity or commercial gain
- ? You may freely distribute the URL identifying the publication in the public portal ?

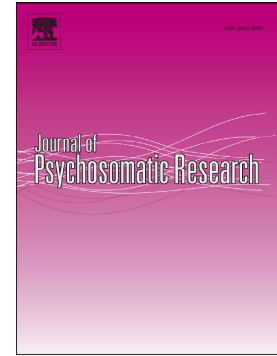
Take down policy

If you believe that this document breaches copyright please contact us at vbn@aub.aau.dk providing details, and we will remove access to the work immediately and investigate your claim.

Journal Pre-proof

The unifying diagnostic construct of bodily distress syndrome (BDS) was confirmed in the general population

Marie Weinreich Petersen, Andreas Schröder, Torben Jørgensen, Eva Ørnbøl, Thomas Meinertz Dantoft, Marie Eliassen, Betina H. Thuesen, Per Fink



PII: S0022-3999(19)30601-4

DOI: <https://doi.org/10.1016/j.jpsychores.2019.109868>

Reference: PSR 109868

To appear in: *Journal of Psychosomatic Research*

Received date: 4 June 2019

Revised date: 5 November 2019

Accepted date: 9 November 2019

Please cite this article as: M.W. Petersen, A. Schröder, T. Jørgensen, et al., The unifying diagnostic construct of bodily distress syndrome (BDS) was confirmed in the general population, *Journal of Psychosomatic Research*(2018), <https://doi.org/10.1016/j.jpsychores.2019.109868>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Title

The unifying diagnostic construct of bodily distress syndrome (BDS) was confirmed in the general population

Running head

Bodily distress syndrome in the general population

Department for the conducted paper

The Research Clinic for Functional Disorders and Psychosomatics, Aarhus University Hospital, Denmark.

Authors

Marie Weinreich Petersen¹, Andreas Schröder¹, Torben Jørgensen^{2,3,4}, Eva Ørnbøl¹, Thomas Meinertz Dantoft², Marie Eliassen², Betina H Thuesen², Per Fink¹

Author affiliations

¹ The Research Clinic for Functional Disorders and Psychosomatics, Aarhus University Hospital, Aarhus C, Denmark

² Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospital, The Capital Region of Denmark, Denmark

³ Department of Public Health, Faculty of Health and Medical Science, University of Copenhagen, Copenhagen C, Denmark

⁴ Faculty of Medicine, Aalborg University

Corresponding author:

Marie Weinreich Petersen

The Research Clinic for Functional Disorders and Psychosomatics

Aarhus University Hospital

Nørrebrogade 44, building 2C, second floor

8200 Aarhus C

Denmark

Phone: +45 7846 4628

Fax: +45 7846 4340

E-mail: mawept@rm.dk

Word count: 3833 in main text, 238 in abstract

Tables: 3

Figures: 2

Appendices: 5

References: 44

Abstract

Objectives: Bodily distress syndrome (BDS) has been shown to encompass a range of functional somatic syndromes (FSS) such as irritable bowel syndrome (IBS), fibromyalgia (FM), and chronic fatigue syndrome (CFS) in clinical samples. This study aimed to explore symptom clusters and test classification of individuals with illness similar to the BDS criteria in a general population sample. **Methods:** A stratified subsample of 1590 individuals from the DanFunD part two cohort was included. Symptoms were assessed with the Research Interview for Functional somatic Disorders, performed by trained physicians. In 44 symptoms pooled from criteria of IBS, FM, CFS, and BDS, symptom clusters were explored with explorative factor analysis. Confirmation of symptom clusters of BDS in the previously described 25- and 30-item BDS checklists was performed with confirmatory factor analysis. Classification of individuals into illness groups was investigated with latent class analysis. **Results:** Four symptom clusters (cardiopulmonary, gastrointestinal, musculoskeletal, general symptoms/fatigue) corresponding to the BDS subtypes and their corresponding FSS were identified and confirmed. A three-class model including 25 BDS items had the best fit for dividing participants into classes of illness: One class with low probability, one class with medium probability, and one class with high probability, not having ≥ 4 symptoms in all symptom clusters. **Conclusion:** The BDS concept was confirmed in the general population and constitutes a promising approach for improved FSS classification. It is highly clinically relevant being the only diagnostic construct defining the complex multi-organ type.

Key words: Bodily distress syndrome, factor analysis, functional somatic disorders, latent class analysis, somatic symptoms.

1. Introduction

Persistent physical symptoms are prevalent in general populations and medical settings (1,2). When severe, such symptoms are often disabling for individuals and costly for society (2).

Within the various medical specialties, the classification and delimitation of conditions characterized by persistent physical symptoms that cannot be assessed with clinical or paraclinical tests have shown to be inconsistent: Within the general medicine tradition, they are addressed as e.g. non-cardiac chest pain (cardiology), irritable bowel syndrome (IBS) (gastroenterology), fibromyalgia (FM) (rheumatology), and chronic fatigue syndrome (CFS) (infectious diseases); diagnoses that are often summarized under the label functional somatic syndromes (FSS) (3). Within psychiatry, these syndromes are mainly covered by the somatoform disorder diagnoses (SFD) defined by the World Health Organization International Classification of Diseases (ICD)-10, or by somatic symptom disorder (SSD) defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 (2,4-6). Studies have shown a great overlap of these different diagnoses indicating that they may belong to the same family of disorders instead of being distinct entities (3,4,6,7). To accommodate this, the diagnostic construct, bodily distress syndrome (BDS), was developed in a sample of primary care patients and patients from neurological and internal medicine departments (4,7). Here, symptoms were assessed with a modified version of Schedules of Clinical Assessment in Neuropsychiatry (SCAN) (8). BDS consists of four symptom clusters; a cardiopulmonary (CP) cluster, a gastrointestinal (GI) cluster, a musculoskeletal (MS) cluster, and a general symptoms/fatigue (GS) cluster. It comprises a single/oligo-organ type, i.e. ≥ 3 symptoms from one or two of the symptom clusters or ≥ 4 symptoms across symptom clusters, and a multi-organ subtype, i.e. having ≥ 3 symptoms from at least three of the symptom clusters (4,7). BDS thus comprises a unifying concept, i.e. it eliminates the problematic overlaps of the medical specialty-specific FSS by identifying both a distinct multi-organ type and a single/oligo-organ type depending on number of affected organ systems in the patient. The BDS construct has been verified in a primary care sample where cases were assessed with self-reported patient questionnaires (5,9). This analysis confirmed the symptom clusters as well as the single/oligo-organ type; now defined as having ≥ 4 self-reported symptoms from one or two of the symptom clusters or ≥ 4 self-

reported symptoms across symptom clusters, and the multi-organ subtype defined as having ≥ 4 self-reported symptoms from at least three of the symptom clusters. Unlike the SFD and the SSD but in accordance with the various definitions for FSS, no emotional or behavioral symptoms are part of the diagnostic criteria.

BDS has shown to be prevalent in different settings in Denmark (7,10-12) and to encompass a great part of the present diagnostic constructs, both within selected patient samples (7,13) and in the general population (10). Further, the European research network EURONET-SOMA has drafted the term functional somatic disorders (FSD) as an umbrella classification of the various FSS and BDS (14). BDS has showed to be applicable in different settings, and an adapted version of the diagnosis, *bodily stress disorder*, has been included in the primary care version of the ICD-11 draft for the mental disorder chapter (15) and included in primary care studies (16,17). Of note, the bodily stress disorder diagnosis uses only the terminology of the BDS concept but has different diagnostic criteria.

To date, the diagnostic construct of BDS has not yet been scientifically verified in the general population. This is a further necessary step in finally accepting BDS as a diagnostic construct (18).

This study was based on a stratified sub-sample from the adult Danish population and aimed to 1) explore symptom clusters in symptoms pooled from criteria of IBS, FM, CFS, as well as BDS, 2) confirm established symptom clusters of BDS in symptom lists equivalent to the 25- and 30-item BDS checklists (9), and 3) investigate the classification of individuals as to the BDS criteria.

The following hypotheses were made: 1) Symptom clusters consistent with subtypes of BDS and the corresponding FSS would reveal in symptoms pooled from criteria of IBS, FM, CFS, and BDS, 2) symptom clusters from the previously described 25- and 30-item BDS checklists would be confirmed, and 3). individuals would be divided into three groups similar to the BDS criteria

2. Method

2.1. Participants and data collection

We included a stratified subsample from the Danish Study of Functional Disorders (DanFunD) part two cohort (n=7493) (19) (Fig 1). Participants filled in questionnaires with measures of BDS and health anxiety, among others. Every tenth participant together with all high scores on the BDS checklist (9) or Whiteley-7 scale (20) were invited to participate in a diagnostic interview (n=2450). A total of 1590 (64.9%) participants agreed to participate and were included in the study. Of those, 796 were high scores and 794 were randomly selected of whom 187 also showed to be high scores.

Figure 1 around here

2.2. Measurements

Symptoms were assessed with the newly developed Research Interview for Functional somatic Disorders (RIFD), a semi-structured interview originally developed from the modified version of SCAN for use in epidemiological research (21). Interviews were conducted by telephone, and all interviewers were family physicians trained in conducting both SCAN and RIFD.

Of relevance for this study, RIFD included symptoms for assessing three common FSS: IBS (22), FM (23), and CFS (24), together with symptoms defining BDS (7,9). The interviewer had the possibility to state whether a whole symptom cluster could be explained by other organic conditions or if it was part of a FSD. All items were dichotomous. Some of the symptoms for FSS and BDS were identically or almost identically named. A correlation matrix was performed, and answers from identically named items and items with a correlation above 0.75 were collapsed and analyzed as one item. We collapsed the answers for 26 items. Thus, in total, we included 44 symptoms pooled from criteria of IBS, FM, CFS, and BDS (Appendix A).

2.3. Analyses

Basic statistical analyses were performed with Stata 15.0 for Windows (25). Age and sex were compared between the high score group and the randomly selected group with a two-sample t-test and χ^2 -test, respectively. For these analyses, the group of 187 randomly selected participants who also showed to be high

scores were excluded. Factor analyses and latent class analysis (LCA) were performed in Mplus version 8.0 (26).

2.3.1. Exploring symptom clusters in symptoms of IBS, FM, CFS, and BDS

Exploratory factor analysis (EFA) with oblique Geomin rotation and WLSMV¹ estimation (26) was applied on all 44 dichotomous items. The number of factors in the EFA was determined by the number of eigenvalues above one, at least three items with high loadings on the respective factor, and potentials for the models to be interpretable and render clinical meaning. Indicators of a good model fit were a Root Mean Square Error of Approximation (RMSEA) <0.05, a Comparative fit Index (CFI) and a Tucker-Lewis fit Index (TLI) >0.95, and a Standardized Root Mean square Residual (SRMR) <0.08 (27). Values of the χ^2 -test were also reported, but as this may tend to be sensitive to sample size, model fit values from this test were not taken into consideration in the final model fit assessment (26).

2.3.2. Can we confirm established symptom clusters of BDS?

In order to confirm the four BDS symptom clusters established in different medical settings, two confirmatory factor analyses (CFA) with WLSMV¹ estimation (26) were performed: One CFA on the 30-item BDS checklist derived from the original work by Fink et al. (4) and one CFA on the 25-item BDS checklist from the additional work by Budtz-Lilly et al. (9).

Indicators of good fit to the models were a RMSEA <0.05, a CFI and TLI >0.95, and a SRMR <0.08 (27).

2.3.3. Classification of individuals into illness groups similar to the BDS criteria

Four different LCAs with WLSMV¹ estimation (26) were performed. They all included five dichotomous variables derived from the symptom four clusters of BDS and one group with ≥ 4 symptoms across all symptom clusters. In the first model, we included the BDS criteria by Budtz-Lilly et al. (≥ 4 symptoms in a cluster and ≥ 4 symptoms across clusters) (9) on 25 items. In a second model, we included the BDS criteria by Fink et al. (≥ 3 symptoms in a cluster and ≥ 4 symptoms across clusters) (4) on 30 items. In a third model,

¹ Weighted least square parameter estimates using a diagonal weight matrix with standard errors and mean and variance adjusted chi-square test statistic that uses a full weight matrix.

we included the BDS criteria by Budtz-Lilly et al. (≥ 4 symptoms in a cluster and ≥ 4 symptoms across clusters) (9) on all 44 items. In a fourth model, we included the BDS criteria by Fink et al. (≥ 3 symptoms in a cluster and ≥ 4 symptoms across clusters) (4) on all 44 items.

All models were evaluated by several model fit statistics (28,29). For information criteria, Akaike's Information Criteria (AIC), the Bayesian Information Criteria (BIC), the Sample-size estimated BIC, the Consistent AIC (CAIC), and the Approximated Weight of Evidence (AWE) were used. For all these measures, the lowest value indicates the optimal number of classes. Also, Chi-Square fit statistics for binary data were used to evaluate the overall fit of the models. A Chi-square P-value above 0.05 indicated an acceptable fit. Entropy was used to evaluate the model's capacity to separate individuals into classes. An entropy above 0.8 indicated an acceptable separation (30). Finally, the models were evaluated on their clinical interpretation and the management and transparency of class assignment.

2.3.4. Subanalyses

EFA were performed within each subgroup of participants, (randomly selected individuals and high scores). The 187 participants that were randomly selected but also showed to be high scores were included and analyzed with both subgroups.

EFA, CFA and LCA were performed 1) within each sex and 2) only including symptoms that could not be better explained by other organic conditions.

2.4. Ethical considerations

Written informed consent was obtained from each participant before participation in the study. The study was approved by the Ethical Committee of Copenhagen County (Ethics Committee: KA-2006-0011; H-3-2011-081; H-3-2012-0015) and the Danish Data Protection Agency.

3. Results

The mean age of the 1590 participants was 51.9 years (SD: 13.1); 59.3% were women. Prevalence of each symptom ranged from 5.5% to 42.8%; most prevalent were the MS symptoms (Appendix A). No differences

were found between the two subgroups according to age ($t(1401)=-0.64$, $p=0.53$), but there were significantly more women in the high score group compared to the group of randomly selected individuals (64.5% vs. 48.9%, $\chi^2(1)=34.0$, $p<0.0001$).

3.1. Exploring symptom clusters in symptoms of IBS, FM, CFS, and BDS

In the EFA, seven eigenvalues greater than one and a model with five factors including at least three distinct items with loadings ≥ 0.5 was revealed (Appendix B).

The items *regurgitations*, *burning sensation in the chest or upper part of the stomach/epigastrium* and *heartburn* loaded ≥ 0.5 on both a fifth factor characterizing an upper GI factor and a factor with the other gastrointestinal items. Hence, it was reasonable to conclude that a four-factor model characterized by CP symptoms, GI symptoms, MS symptoms, and GS/fatigue symptoms as in the original studies on BDS also applied here (Table 1). In both models, the items *regurgitations* and *heartburn* were difficult to place; they loaded ≥ 0.5 in more than one factor. Factor correlations between factors in the four-factor model ranged from 0.36 to 0.52.

Table 1 around here

3.2. Can we confirm established symptom clusters of BDS?

Both original four-factor models of BDS were confirmed with good fit to the observed model (Table 2).

Table 2 around here

3.3. Classifications of individuals into illness groups similar to the BDS criteria

The LCA applied on a pool of 25 symptoms and BDS criteria by Budtz-Lilly et al. (9) revealed a three-class model with acceptable capacity of classification (Entropy=0.95) and model fit ($\chi^2(14)=16.3$, $p=0.30$). It constituted one class with 0% probability of having ≥ 4 symptoms in any symptom cluster, one class with 8-45% probability of having ≥ 4 symptoms in all symptom clusters, and one class with 63-89% probability of having ≥ 4 symptoms in all symptom clusters. The two latter classes also had 100% probability of fulfilling the criteria of ≥ 4 symptoms across clusters (Fig 2A).

The LCA applied on a pool of 30 symptoms and BDS criteria by Fink et al. (4) also showed a three-class model. The model constituted one class with 0-7% probability of having ≥ 3 symptoms in any symptom cluster, one class with 17-62% probability of having ≥ 3 symptoms in all symptom clusters, and one class with 73-100% probability of having ≥ 3 symptoms in all symptom clusters. The two latter classes had 100% probability of fulfilling the criteria ≥ 4 symptoms across clusters (Fig 2B). Classification capacity was high (Entropy= 0.948), however, the model fit was not acceptable ($\chi^2(14)=39.6$, $p=0.0003$).

Figure 2 around here

Two additional LCA were performed on all 44 items. The first model included the BDS criteria by Budtz-Lilly et al. (9) (4 symptoms within a cluster and ≥ 4 symptoms across clusters). This model revealed a four-class solution consisting of one class with 0% probability of having ≥ 4 symptoms in any symptom cluster (class size: 39.6%) and one class with 57-97% probability of having ≥ 4 symptoms in all symptom clusters (class size: 8.6%). The two other classes constituted one class with 12-48% probability of having ≥ 4 symptoms in all symptom clusters (class size: 32.8%) and one class primarily characterized by 100% probability of having ≥ 4 symptoms in the MS cluster (class size: 18.9%). The three latter classes also had 100% probability of fulfilling the criteria of ≥ 4 symptoms across clusters. This model had an acceptable model fit ($\chi^2(8)=7.32$, $p=0.50$) but lacked classification capacity (Entropy=0.78).

The second model included the BDS criteria by Fink et al. (4). This model also revealed a four-class solution consisting of one class with 0-6% probability of having ≥ 3 symptoms in any symptom cluster (class size: 39.6%) and one class with 39-78% probability of having ≥ 3 symptoms in all symptom clusters (class size: 32.4%). The two other classes constituted one class primarily characterized by 94% probability of having ≥ 3 symptoms in the MS cluster (class size: 20.3%) and one class primarily characterized by 100% probability of having ≥ 3 symptoms in the GI cluster (class size: 7.7%). The three latter classes also had 100% probability of fulfilling the criteria of ≥ 4 symptoms across clusters. This model had a poor model fit ($\chi^2(8)=25.2$, $p=0.001$) but acceptable classification capacity (Entropy=0.87).

From these LCAs and the clinical interpretation and size of each class, we found the most suitable model to be the model including 25 symptoms and criteria by Budtz-Lilly et al. (9). This model constituted three classes of individuals that differ on several characteristics, indicating different disease load (Table 3).

Table 3 around here

3.4. Subanalyses

None of the results from the subanalyses led to questioning of the results from the main analyses on the whole sample, and it could be concluded that these results were not due to participants selection (Appendix C), sex (Appendix D) or symptom etiology (Appendix E).

4. Discussion

4.1. Principal findings

We studied 44 symptoms pooled from criteria of IPS, FM, CFS, and BDS. By means of EFA, we identified four *symptom clusters*: A CP cluster, a GI cluster, a MS cluster, and a GS cluster. The four-factor models of BDS were furthermore confirmed whether using the previous reported 25-item BDS symptom checklist (9) or the 30-item BDS symptom checklist (4).

The best fitting model for dividing *participants* into different classes of illness was the model by Budtz-Lilly et al. (9). In an LCA including 25 symptoms corresponding to the 25-items BDS symptom checklist (9), participants were divided into three classes that, after clinical interpretation, could be understood as one class with healthy participants (i.e. no BDS), one class with single/oligo-organ BDS, and finally, a class with multi-organ BDS.

4.2. Comparison with existing literature

The identified four-factor model of symptom clusters from the current study has been found independently of assessment method both in studies including patient samples (4,5,7,9,31-34) and studies including unselected general population samples (35,36).

In accordance with the present study, previous studies in clinical patient samples have also shown that these symptom clusters can be used for a diagnostic classification, dividing individuals into three different classes of illness (4,5,7,9). We found the same four symptom factors and the same three LCA classes as the original studies by Fink et al. (4) and Budtz-Lilly et al. (9), both in our main analysis including all symptoms regardless of etiology and in our subanalysis only including symptoms that could not be attributed to other medical conditions. However, studies from other research groups are inconsistent in how to define individuals with or without illness. In a population-based study of 964 individuals, Rosmalen et al. (36) concluded on the basis of four LCAs that a two-class model had the best fit for dividing individuals into classes of illness. However, they based the LCAs on the 23 most prevalent and non-gender specific symptoms and one of their primary aims was to test if a symptom count and a cut-off could be used for a categorical diagnosis of somatization. Hence, their aims and the before interpretation of results may not be comparable to our study. In a primary care study on major somatoform disorders by Kroenke et al. (37), they identified three symptom clusters of MS/fatigue, GI, and CP by EFA in a 13-symptom checklist which is similar to our results. However, they recommended a simple symptom count for differentiating between groups with and without illness. A cut-off of seven symptoms was made, however this was not based on LCA methods but on calculation of sensitivity, specificity, and predictive values of various symptom thresholds for multi-somatoform disorders. Finally, in a study by Lacourt et al. (38) including 394 individuals with reported functional somatic symptoms, cluster analysis was used on 47 items, exploring three cluster solutions. This study identified the same four symptom clusters as in the current study, and these clusters differed on total symptom score. They found the solution, dividing individuals into two clusters of illness, to have the best fit. However, their sample size was small and they chose the two-cluster solution on the basis of its discriminative ability.

Our results from the LCA including all 44 symptoms indicate that when establishing a simple symptom count cut-off, the number of symptoms has to be taken into account; the more symptoms included, the lower the probability gets of falling into classes presumably interpreted as "healthy". This is underlined by our results where the size of the class with low probability of having ≥ 4 symptoms in any of the symptom clusters decreases with increasing size of symptom pool. The approach of using symptom counts on a pre-

defined symptom checklist may be practical in large-scale epidemiological studies where distinction between "disease" and "no disease" is sought, but it may be of little value in clinical practice for diagnosing patients with FSD. Here, a symptom pattern recognition such as the BDS construct may be more appropriate (5).

Other studies on large population-based samples where the group of individuals with severe disease is large enough to be detected, support our classification of individuals (39-41). These studies, one of them conducted on the whole DanFunD baseline cohort (39), identified one class with no symptoms, multiple classes with few, specific symptoms, and one class with all symptoms. Hence, even though these studies identify a larger number of classes than in the current study, their results do not conflict with ours but may be attributed to methodological differences: All have used LCA on obtained symptoms contrary to the current study in which we have used the information from the factor analyses on symptom clustering into organ systems. Using only five dichotomous variables in the LCAs may have limited the number of classes that could be estimated, and this may account for the difference in obtained number of classes compared to the other studies. From a clinical point of view a simpler model with fewer classes may be more applicable to differentiate between patients and their management.

4.3. Strengths and limitations

A major strength of the current study is the large sample of 1590 participants who completed the interview. Furthermore, symptoms were obtained through clinical diagnostic interviews performed by family physicians that were all trained in conducting the specific interview. This ensured valid presence of each symptom. Also, the included sample was drawn from a large Danish general population sample, making it less prone to selection bias than the patient samples in which BDS until now has been investigated (4,7,9). Finally, we addressed recent symptoms that had been present within the last 12 months, which may have reduced the risk of recall bias compared to using life-long symptoms (42,43).

However, some limitations also need to be addressed: First, we included a stratified subsample why a risk of selection bias cannot be excluded. However, as we did not obtain any major difference by analysing subgroups, nothing indicated that this stratification has influenced the results. Second, we included all symptoms regardless of etiology. Yet, the results was not changed in the sub analysis only including

symptoms that could not be better explained by other organic conditions. Third, our data included a high number of symptoms (n=44) relative to a rather small sample (n=1590), and therefore we could not include individual symptoms in the LCA which limits direct comparison with other studies (9,36,39-41). Fourth, the different analyses were depending on the input of symptoms and criteria. Thus, there may be other important symptom clusters that were not detected in the current study, e.g. urogenital or temporomandibular/jaw clusters (4). Even though our classes from the LCAs differed in number of fulfilled criteria rather than type of specific criteria, including additional symptom factors might have increased the number of classes in the LCAs.

4.4. Clinical implications

Our study provides further empirical support of the clustering of symptoms into a CP type, a GI type, an MS type, and a GS/fatigue type as defined by the BDS criteria. We have further shown that symptoms of IBS, FM, and CFS were aligned in the same symptom specific clusters as the BDS clusters. This supports studies on BDS and the previous findings that BDS as a unifying construct may encompass the various FSS (4,7,10). From a clinical as well as a research point of view, this indicates that the BDS concept may be used instead of the several specialty-specific FSS, making it easier to communicate between medical specialties and clinical management. Furthermore, the current verification of the BDS concept in a sample from an unselected general population supports that BDS is not an artefact of medical specialization.

In a previous study, we have argued that the BDS construct provides the opportunity of distinguishing between mono- and multi-syndromic individuals which may be of paramount importance in clinical management as the latter group constitute complex patients with severe need of treatment. This group is not delimited and may be neglected in current approach the various FSS categories induce (10,44). The current study and its results support the diagnostic construct of BDS and its use in not only selected patient samples but also in a sample derived from the general population.

Acknowledgements

This work was supported by grants to the first author from the Danish foundations The Lundbeck Foundation [grant number R155-2013-14070]; TrygFonden [grant number 7-11-0213]; Helsefonden [grant number 17-B-0082]; and Aase og Ejnar Danielsens Fond [grant number 10-001993].

The authors would like to thank members of the DanFunD steering committee, Senior consultant MD PhD Lene Falgaard Epløv, MSc PhD Susanne Brix Pedersen, and MD PhD Michael Eriksen Benros.

Conflicts of interest

None.

5. References

- (1) Eliassen M, Kreiner S, Ebstrup JF, Poulsen CH, Lau CJ, Sloth-Jørgensen S, et al. Somatic Symptoms: Prevalence, Co-Occurrence and Associations with Self-Perceived Health and Limitations Due To Physical Health - A Danish Population-Based Study. *PLoS One* 2016 Mar 1;11(3):e0150564.
- (2) Henningsen P, Gundel H, Kop WJ, Lowe B, Martin A, Rief W, et al. Persistent Physical Symptoms as Perceptual Dysregulation: A Neuropsychobehavioral Model and Its Clinical Implications. *PsychosomMed* 2018 Jun;80(5):422-431.
- (3) Wessely S, Nimnuan C, Sharpe M. Functional somatic syndromes: one or many? *The Lancet* 1999 Nov 9;354(9182):936-939.
- (4) Fink P, Toft T, Hansen MS, Ornbøl E, Glesen F. Symptoms and syndromes of bodily distress: an exploratory study of 978 internal medical, neurological, and primary care patients. *PsychosomMed* 2007 Jan;69(1):30-39.
- (5) Budtz-Lilly A, Schröder A, Rank MT, Fink P, Vestergaard M, Rosendal M. Bodily distress syndrome: A new diagnosis for functional disorders in primary care? *BMC Fam Pract* 2015 Dec 15;16(1):180.
- (6) Rief W, Isaac M. The Future of Somatoform Disorders: Somatic Symptom Disorder, Bodily Distress Disorder or Functional Syndromes? *Curr Opin Psychiatry* 2014;27(5):315-319.
- (7) Fink P, Schröder A. One single diagnosis, bodily distress syndrome, succeeded to capture 10 diagnostic categories of functional somatic syndromes and somatoform disorders. *J PsychosomRes* 2010;68(5):415-426.
- (8) Cambridge University Press. WHO-SCAN: Schedules for Clinical Assessment in Neuropsychiatry, Version 2.1. Available at: <http://whoscan.org/introduction/>. Accessed January 10th, 2016.
- (9) Budtz-Lilly A, Fink P, Ornbøl E, Vestergaard M, Moth G, Christensen KS, et al. A new questionnaire to identify bodily distress in primary care: The 'BDS checklist'. *J PsychosomRes* 2015 Jun;78(6):536-545.
- (10) Petersen M, Schröder A, Jørgensen T, Ørbøl E, Dantoft T, Eliassen M, et al. Irritable bowel, chronic widespread pain, chronic fatigue and related syndromes are prevalent and highly overlapping in the general population: DanFunD. Submitted. *Scientific Reports* 2019.

- (11) Petersen MW, Schroder A, Jorgensen T, Ornbol E, Dantoft TM, Eliassen M, et al. Prevalence of functional somatic syndromes and bodily distress syndrome in the Danish population: the DanFunD study. *Scand J Public Health* 2019 Aug 14;1403494819868592.
- (12) Budtz-Lilly A, Vestergaard M, Fink P, Carlsen AH, Rosendal M. Patient characteristics and frequency of bodily distress syndrome in primary care: a cross-sectional study. *Br J Gen Pract* 2015 Sep;65(638):e617-23.
- (13) Tschudi-Madsen H, Rodevand LN, Boymo Kaarbo M, Granan LP. Chronic Widespread Pain in a tertiary pain clinic: classification overlap and use of a patient generated quality of life instrument. *Scand J Pain* 2018 Nov 22.
- (14) Weigel A, Husing P, Kohlmann S, Lehmann M, Shedden-Mora M, Toussaint A, et al. A European research network to improve diagnosis, treatment and care for patients with persistent somatic symptoms: Work report of the EURONET-SOMA conference series. *J PsychosomRes* 2017 Jun;97:136-138.
- (15) Lam TP, Goldberg DP, Dowell AC, Fortes S, Mbatia JK, Minhas FA, et al. Proposed new diagnoses of anxious depression and bodily stress syndrome in ICD-11-PHC: an international focus group study. *Fam Pract* 2013 Feb;30(1):76-87.
- (16) Goldberg DP, Reed GM, Robles R, Bobes J, Iglesias C, Fortes S, et al. Multiple somatic symptoms in primary care: A field study for ICD-11 PHC, WHO's revised classification of mental disorders in primary care settings. *J PsychosomRes* 2016 Dec;91:48-54.
- (17) Fortes S, Ziebold C, Reed GM, Robles-Garcia R, Campos ME, Reis-Jorfer E, et al. Studying ICD-11 Primary Health Care bodily stress syndrome in Brazil: do many functional disorders represent just one syndrome? *Rev Bras Psiquiatr* 2018 Oct 11.
- (18) Kendell RE. Clinical validity. *PsycholMed* 1980 Feb;19(1):45-55.
- (19) Dantoft T, Ebstrup J, Linneberg A, Skovbjerg S, Madsen A, Mehlsen J, et al. Cohort description: The Danish Study of Functional Disorders. *Clin Epidemiol* 2017;5:127-139.
- (20) Fink P, Ornbol E, Toft T, Sparle KC, Fosholm L, Olesen F. A new, empirically established hypochondriasis diagnosis. *Am J Psychiatry* 2004 Sep;161(9):1680-1691.
- (21) Petersen MW, Schroder A, Jorgensen T, Ornbol E, Dantoft TM, Eliassen M, et al. RIFD - A brief clinical research interview for functional somatic disorders and health anxiety. *J PsychosomRes* 2019 Apr 2.
- (22) Kay L, Jorgensen T. Redefining abdominal syndromes. Results of a population-based study. *Scand J Gastroenterol* 1996 May;31(5):469-475.
- (23) White KP, Harth M, Speechley M, Ostbye T. Testing an instrument to screen for fibromyalgia syndrome in general population studies: the London Fibromyalgia Epidemiology Study Screening Questionnaire. *J Rheumatol* 1999 Apr;26(4):880-884.
- (24) Chalder T, Berelowitz G, Pawlikowska T, Watts L, Wessely S, Wright D, et al. Development of a fatigue scale. *J PsychosomRes* 1993;37(2):147-153.
- (25) StataCorp. *Stata Statistical Software: Release 15.* : College Station, TX: StataCorp LLC; 2017.
- (26) Muthén L, Muthén B. *Mplus User's Guide. Eighth Edition.* Los Angeles, CA: Muthén & Muthén; 1998-2017.
- (27) Hu L, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Structural Equation Modeling: A Multidisciplinary Journal* 1999 01/01;6(1):1-55.

- (28) Schreiber J,B., Nora ,Amaury, Stage F,K., Barlow E,A., King ,Jamie. Reporting Structural Equation Modeling and Confirmatory Factor Analysis Results: A Review. *The Journal of Educational Research* 2006;99;6:323-338.
- (29) Nylund K,L., Asparouhov ,Tihomir, MuthÃ©n B,O. Deciding on the Number of Classes in Latent Class Analysis and Growth Mixture Modeling: A Monte Carlo Simulation Study. *Structural Equation Modeling: A Multidisciplinary Journal* 2007;14;4:535-569.
- (30) Celeux G, Soromenho G. An Entropy Criterion for Assessing the Number of Clusters in a Mixture Model. *Journal of Classification* 1996;13:195-212.
- (31) Nimmuan C, Rabe-Hesketh S, Wessely S, Hotopf M. How many functional somatic syndromes? *J Psychosom Res* 2001 Oct;51(4):549-557.
- (32) Withoft M, Fischer S, Jasper F, Rist F, Nater UM. Clarifying the latent structure and correlates of somatic symptom distress: A bifactor model approach. *Psychol Assess* 2016 Jan;28(1):107-115.
- (33) Claassen-van Dessel N, van der Wouden JC, Dekker J, Rosmalen JGM, van der Horst HE. The cross-sectional relation between medically unexplained physical symptoms (MUPS) and the Cortisol Awakening Response. *J Psychosom Res* 2017 Aug;99:130-136.
- (34) Tsai CH. Factor analysis of the clustering of common somatic symptoms: a preliminary study. *BMC Health Serv Res* 2010 Jun 10;10:160-6963-10-160.
- (35) Withoft M, Hiller W, Loch N, Jasper F. The latent structure of medically unexplained symptoms and its relation to functional somatic syndromes. *Int J Behav Med* 2013 Jun;20(2):172-183.
- (36) Rosmalen JG, Tak LM, de Jonge P. Empirical foundations for the diagnosis of somatization: implications for DSM-5. *PsycholMed* 2011 Jun;41(6):1133-1142.
- (37) Kroenke K, Spitzer RL, deGruy FV,3rd, Syme Dale R. A symptom checklist to screen for somatoform disorders in primary care. *Psychosomatics* 1998 May-Jun;39(3):253-272.
- (38) Lacourt T, Houtveen J, van Doormer L. "Functional somatic syndromes, one or many?" An answer by cluster analysis. *J Psychosom Res* 2013 Jan;74(1):6-11.
- (39) Eliassen M, Schröder A, Fink P, Kiehlner S, Dantoft T, Poulsen C, et al. A step towards a new delimitation of functional somatic syndromes: A latent class analysis of symptoms in a population-based cohort study. *J Psychosom Res* 2018;108:102-117.
- (40) Kato K, Sullivan PF, Pedersen NL. Latent class analysis of functional somatic symptoms in a population-based sample of twins. *J Psychosom Res* 2010 May;68(5):447-453.
- (41) Eliassen M, Jorgensen T, Schroder A, Dantoft TM, Fink P, Poulsen CH, et al. Somatic symptom profiles in the general population: a latent class analysis in a Danish population-based health survey. *Clin Epidemiol* 2017 Aug 23;9:421-433.
- (42) Kroenke K, Spitzer RL, deGruy FV,3rd, Hahn SR, Linzer M, Williams JB, et al. Multisomatoform disorder. An alternative to undifferentiated somatoform disorder for the somatizing patient in primary care. *Arch Gen Psychiatry* 1997 Apr;54(4):352-358.
- (43) Simon GE, Gureje O. Stability of somatization disorder and somatization symptoms among primary care patients. *Arch Gen Psychiatry* 1999 Jan;56(1):90-95.

(44) Frølund Pedersen H, Holsting A, Frostholm L, Rask C, Jensen JS, Høeg MD, et al. "Understand your illness and your needs": Assessment-informed patient education for people with multiple functional somatic syndromes. *Patient Education and Counseling* 2019 Available online 17 April 2019.

Journal Pre-proof

Figure 1:

Figure legend: Flow of study participants.

Figure caption: Abbreviations: BDS=bodily distress syndrome

Figure 2:

Figure legend: Conditional probabilities of individuals fulfilling criteria of bodily distress syndrome given class.

Figure captions: A: Analyses including the bodily distress syndrome (BDS) criteria by Budtz-Lilly et al. (9) made on 25 items. B: Analyses including the BDS criteria by Fink et al. (4) made on 30 items. Vertical axis: Probabilities of individuals in the respective class to fulfill the criteria stated in the horizontal axis.

Percentages stated after each class report size of the class. Abbreviations: BDS=bodily distress syndrome; CP=cardiopulmonary; GI=gastrointestinal; MS= musculoskeletal; GS=general symptoms/fatigue; 4 symp. across=at least four symptoms across organ systems.

Figure 1.

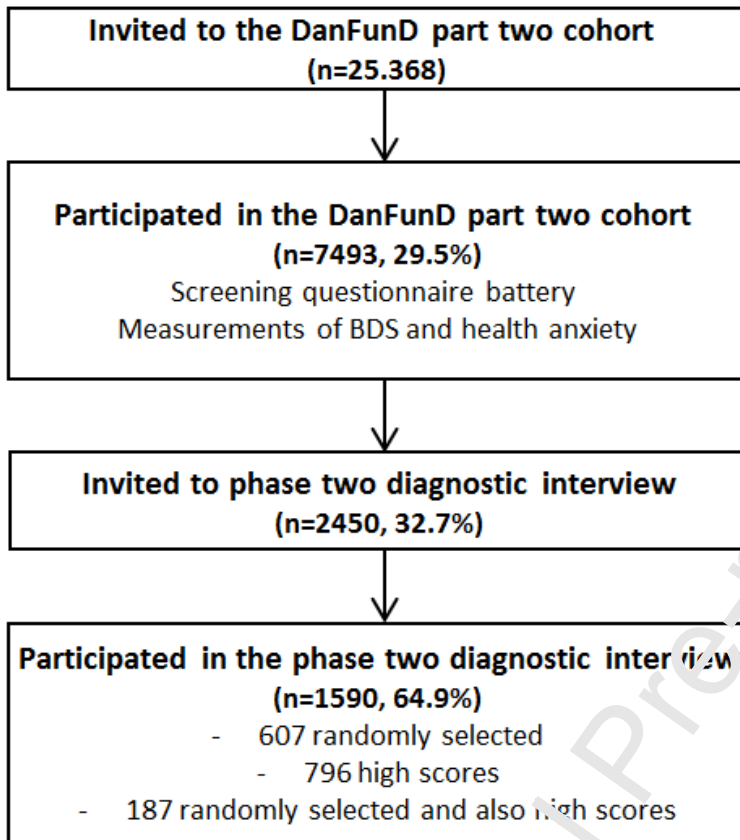


Figure 2.

Figure 2A

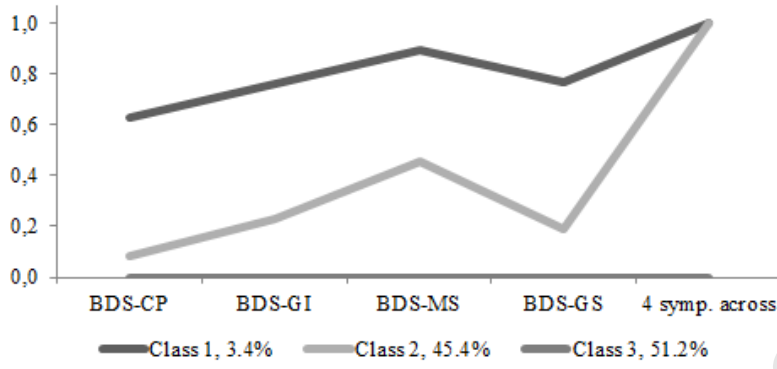


Figure 2B

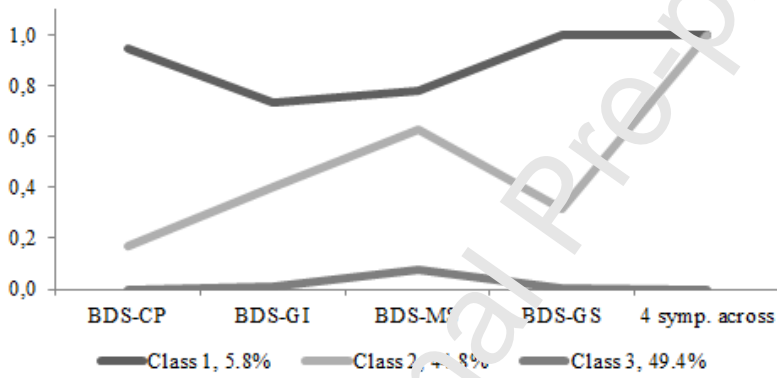


Table 1: Exploratory factor analysis with oblique geomin rotation on 44 symptoms (n=1590)

	Factor 1	Factor 2	Factor 3	Factor 4
Cardiopulmonary symptoms (CP)				
Palpitations or heart pounding	0.91	<-0.00	-0.08	0.03
Precordial discomfort	0.90	-0.03	-0.12	0.06
Breathlessness without exertion	0.82	-0.10	-0.07	0.11
Hyperventilation	0.81	-0.04	0.02	-0.01
Hot or cold sweats	0.74	0.02	0.04	0.15
Trembling or shaking	0.72	0.03	-0.09	0.27
Dry mouth	0.65	-0.03	0.09	0.21
Churning in stomach	0.65	0.18	-0.15	0.24
Flushing or blushing	0.57	0.14	0.07	0.14
Gastrointestinal symptoms (GI)				
Frequent, loose bowel movements	-0.07	0.96	0.05	0.03
Diarrhea	-0.09	0.94	-0.17	0.07
<i>Abdominal pain</i>	<i>0.03</i>	<i>0.86</i>	<i>-0.07</i>	<i>0.09</i>
<i>Feeling bloated, full of gas, distended/Distension</i>	<i>0.03</i>	<i>0.88</i>	<i>-0.06</i>	<i>0.11</i>
<i>Regurgitations</i>	<i>0.60</i>	<i>0.69</i>	<i>0.04</i>	<i>-0.40</i>
<i>Altering stool form</i>	<i>-0.05</i>	<i>0.99</i>	<i>0.01</i>	<i>0.03</i>
<i>Nausea</i>	<i>0.08</i>	<i>0.83</i>	<i>0.00</i>	<i>0.27</i>
<i>Vomiting</i>	<i>-0.01</i>	<i>0.49</i>	<i>0.07</i>	<i>0.19</i>
<i>Burning sensation in the chest or upper part of the stomach/epigastrium</i>	<i>0.38</i>	<i>0.83</i>	<i>0.11</i>	<i>-0.22</i>
<i>Borborygmi</i>	<i>0.06</i>	<i>0.85</i>	<i>-0.08</i>	<i>0.09</i>
<i>Heartburn</i>	<i>0.62</i>	<i>0.65</i>	<i>0.07</i>	<i>-0.45</i>
Musculoskeletal symptoms (MS)				
Pain in arms or legs	0.01	<-0.00	0.99	<0.00
Muscular aches or pains	<0.00	<0.00	0.82	0.15
Joint pain	0.09	0.05	0.85	-0.08
Feeling of paresis in arms or legs	0.01	-0.23	0.66	0.21
Pain moving from one place to another	0.05	0.08	0.62	0.06
Unpleasant numbness or tingling sensations	-0.01	0.09	0.68	0.18
<i>Back ache/Pain in chest or back</i>	<i>0.07</i>	<i><0.00</i>	<i>0.63</i>	<i>0.17</i>
Pain in muscles, bones or joints lasting at least one week	-0.02	0.01	0.94	0.01
Pain in shoulders, arms or hands	0.05	<0.00	0.83	0.09
Pain in legs or feet	0.05	<-0.00	0.88	-0.06
Pain in the neck	-0.07	0.05	0.45	0.32
General symptoms (GS)				
Headache	0.11	0.13	0.09	0.52
Dizziness	0.24	0.09	0.08	0.46
<i>Concentration difficulties/Difficulties concentration</i>	<i>0.15</i>	<i>0.02</i>	<i><0.00</i>	<i>0.85</i>
<i>Fatigue/Problems with tiredness</i>	<i>0.14</i>	<i>0.05</i>	<i>0.07</i>	<i>0.87</i>
<i>Memory difficulties/Memory difficulties</i>	<i>0.15</i>	<i>-0.05</i>	<i>0.02</i>	<i>0.86</i>
Need to rest more	0.11	0.04	0.06	0.86
Feel sleepy or drowsy	0.07	0.06	0.03	0.87
Problems starting things	0.04	0.04	0.08	0.86
Lack of energy	0.04	0.02	0.10	0.89
Less strength in muscles	-0.13	-0.02	0.29	0.85
Feel weak	-0.07	<0.00	0.25	0.85
Make slips of the tongue when speaking	0.04	0.01	<-0.00	0.91
Difficulties finding the right words	0.04	0.02	-0.02	0.90

Factor loadings >0.3 are shown in **bold**.

Factor (F) correlations: F1 and F2: 0.43; F1 and F3: 0.42; F1 and F4: 0.52; F2 and F3: 0.36; F2 and F4: 0.46; F3 and F4: 0.40.

Tests of model fit: Root Mean Square Error of Approximation=0.05; Comparative fit Index=0.99, Tucker-Lewis fit Index=0.99, Standardized Root Mean square Residual=0.05.

Answers to symptoms written in italic letters have been collapsed because of high correlations.

Table 2: Goodness of fit parameters from the confirmatory factor analyses

Model	RMSEA	95% CI		CFI	TLI	SRMR	χ^2	df	p
BDS^a , Budtz-Lilly et al (9)	0.039	0.036	0.042	0.978	0.975	0.069	922.245	269	<0.0001
BDS^b , Fink et al (4)	0.034	0.032	0.036	0.978	0.977	0.073	1130.37	399	<0.0001

Abbreviations: RMSEA=Root Mean Square Error of Approximation; CI=Confidence Interval; CFI=Comparative Fit Index; TLI=Tucker-Lewis fit Index; χ^2 =Likelihood Ratio Test; df=degrees of freedom, p=p-value.

Bold: Indicates a good fit between the specified model and the observed model in the data.

Factor (F) correlations: ^aF1 and F2: 0.51; F1 and F3: 0.49; F1 and F4: 0.64; F2 and F3: 0.42; F2 and F4: 0.57; F3 and F4: 0.57. ^bF1 and F2: 0.55; F1 and F3: 0.49; F1 and F4: 0.68; F2 and F3: 0.42; F2 and F4: 0.56; F3 and F4: 0.57.

Loading range: ^aF1: 0.80-0.89; F2: 0.79-0.92; F3: 0.65-0.94; F4: 0.75-0.97. ^bF1: 0.77-0.89; F2: 0.58-0.92; F3: 0.64-0.93; F4: 0.75-0.97.

Table 3: Characteristics of individuals in classes from the latent class analysis on 25 items and criteria of having ≥ 4 symptoms in a symptom cluster or ≥ 4 across symptom clusters

	Class 1	Class 2	Class 3
Class size; n (%)	814 (51.2)	732 (45.4)	44 (3.4)
Weighted prevalence^a; % (95% CI)	73.6 (71.1-75.9)	25.0 (22.7-27.5)	1.4 (1.0-2.0)
Women; %	51.2	67.1	77.3
Age; mean (SD)	52.3 (13.2)	51.4 (13.0)	53.1 (12.0)
Self-perceived health^b; %			
Poor	6.5	38.9	52.3
Good	93.1	60.7	45.5
NA	0.4	0.4	2.3
Impaired by symptoms^c; %	2.8	33.9	77.3
NA	83.8	27.2	4.6
Years with symptoms^c; median (IQR)	0 (0-2)	6 (1-18)	14 (5-21)
NA	90.4	44.0	11.4
Physical comorbidity^d; %	42.0	80.9	75.0
NA	0	0	0
Mental comorbidity^e; %	2.8	15.4	36.4
NA	0	0	0

^a Prevalence of each class weighed back to the whole DanFunD sample

^b One self-reported question from the 12-item Short Form Health Survey (20)

^c A global assessment through the interview (20)

^d Assessed through the interview: At least one of the following: Diabetes, asthma, joint disease, heart disease, hypertension, pulmonary disease, other conventionally-defined physical condition (20)

^e Assessed through the interview: At least one of the following: Major depressive disorder from the 10th International Classification of Disease (31), panic attacks, social phobia, generalized anxiety (20)

Abbreviations: Symp.=symptom; SD=standard deviation; IQR=inter-quartile range; NA=not accessible.

Highlights

- The Bodily distress syndrome (BDS) construct can be used in general populations
- Four symptom clusters corresponding to the BDS subtypes were identified and confirmed
- Participants were divided into three classes of illness severity
- BDS constitutes a promising approach for classification of functional somatic disorders

Journal Pre-proof

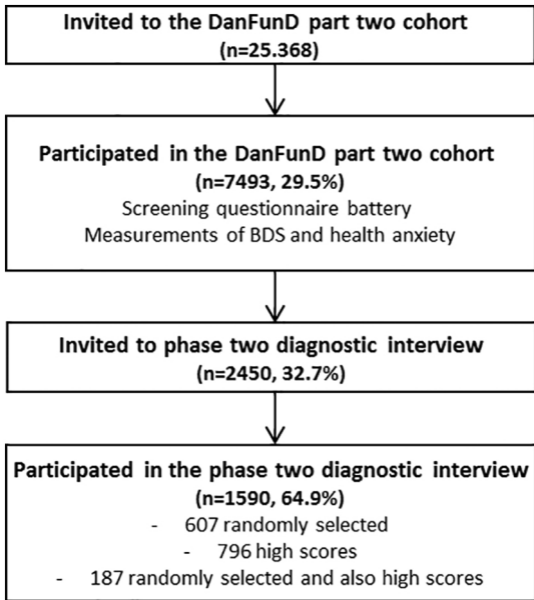


Figure 1

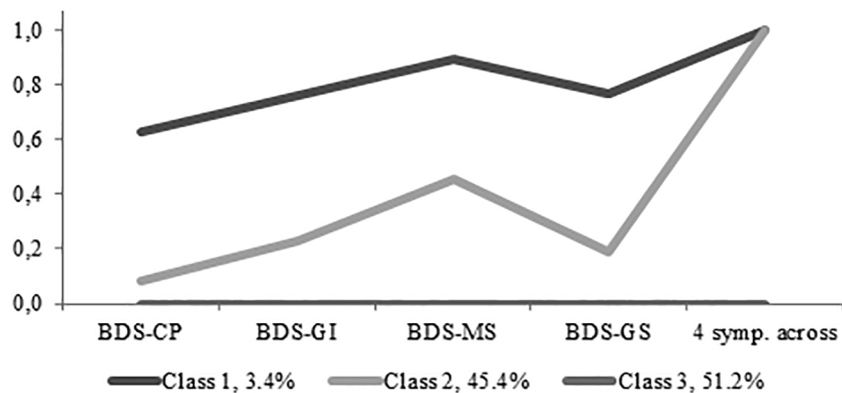
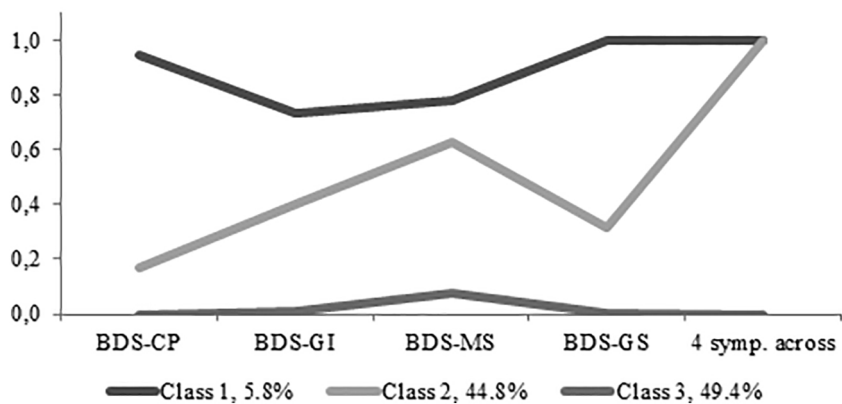
A*B*

Figure 2