BMJ Open

Is reduced heart rate variability associated with functional somatic disorders? A cross-sectional population-based study; DanFunD

Torben Jørgensen ,[1,2] Thomas Meinertz Dantoft ,[1] Marie Weinreich Petersen,[3,4] Lise Gormsen,[3,4] Matilde Winter-Jensen,[1] Per Fink,[3,4] Allan Linneberg,[1,5] Michael Eriksen Benros,[6,7] Lene Falgaard Eplov,[6] Anne Ahrendt Bjerregaard ,[1] Signe Ulfbeck Schovsbo ,[1] Louise Schouborg Brinth[8]

To cite: Jørgensen T, Dantoft TM, Petersen MW, *et al*. Is reduced heart rate variability associated with functional somatic disorders? A cross-sectional population-based study; DanFunD. *BMJ Open* 2024;**14**:e073909. doi:10.1136/bmjopen-2023-073909

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2023-073909).

Received 22 March 2023
Accepted 18 January 2024

For numbered affiliations see end of article.

Correspondence to
Dr Torben Jørgensen;
torben.joergensen@regionh.dk

ABSTRACT

Objectives It has been hypothesised that functional somatic disorders (FSD) could be initiated by sympathetic predominance in the autonomic nervous system as measured by low heart rate variability (HRV). Earlier studies on the association between HRV and FSD are small case–control studies hampered by selection bias and do not consider the great overlap between the various FSDs. The aim of the present study is to assess any associations between HRV and various FSDs and whether chronic stress confounds such an association.

Design A cross-sectional general population-based study.

Setting The Danish Study of Functional Somatic Disorders conducted 2013–2015 in 10 municipalities in the western part of Greater Copenhagen, Denmark.

Participants A total of 6891 men and women aged 18–72 years were included in the analyses after exclusion of 602 persons with missing HRV data. Various delimitations of FSD (chronic fatigue, chronic widespread pain, irritable bowel and bodily distress syndrome) were identified by validated questionnaires and diagnostic interviews. HRV parameters in time and frequency domains were calculated from successive beat-to-beat heart rate (HR) data using the 'E-motion' HR monitor device during 7 min of supine rest. Chronic stress was assessed by Cohen's self-perceived stress scale.

Outcome measures Logistic regression analyses were used to calculate possible associations between the various delimitations of FSD and HRV adjusting for chronic stress.

Results Persons with FSD had a slightly higher mean HR and lower HRV as measured by time domain parameters, whereas associations with frequency domain parameters were not consistent. Adjusting for chronic stress attenuated associations slightly.

Conclusion The study supports a sympathetic predominance in persons with FSD, which could not be entirely explained by chronic stress. However, it is not possible to conclude whether the association is a causal factor to or a consequence of FSD.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study was based on a large, unselected sample from the general population.
⇒ Functional somatic disorders (FSDs) were delimitated in different ways using well-known validated questionnaires and clinical diagnostic interviews.
⇒ Heart rate variability was calculated from internationally accepted measures.
⇒ Chronic stress was measured by use of a validated questionnaire.
⇒ Due to the cross-sectional design, we cannot determine whether the found associations are consequences or determinants of FSD.

INTRODUCTION

Functional somatic disorders (FSDs) are frequent in all medical settings and are characterised by persistent physical symptoms that cannot be better explained by other somatic or psychiatric conditions.[1] The literature comprises a great variation of various delimitations of FSD, the most used are fibromyalgia (FM) or chronic widespread pain (CWP), chronic fatigue syndrome (CFS) and irritable bowel syndrome (IBS). A well-documented huge overlap between these syndromes has led to the question whether they are distinct diseases or represent the same underlying condition.[2 3] An empirically founded diagnostic category, bodily distress syndrome (BDS), has been proposed as a unifying diagnostic approach,[4 5] a construct which has been confirmed in the general population.[6] The aetiology of FSD is considered multifactorial,[3 7] but as no consensus on biological or physiological markers have yet been identified, delimitation of the various FSD is based on the identification of

characteristic symptom patterns. This has made the question of a common biomarker as key in understanding the syndromes a challenging issue.

Heart rate variability (HRV) assesses activity in the autonomic nervous system (ANS) and reflects ANS's ability to respond to a variety of physiological as well as psychological stimuli. Heart rate (HR) of the healthy heart is not constant but oscillates in a complex and non-linear way influenced by the interplay between the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) as well as a long array of other physiological and environmental factors. Analysis of HRV is an inexpensive, non-invasive method that is based on a continuous measurement of HR and has been made increasingly accessible in the last decade through better algorithms making almost instant test results accessible. After the guidelines of HRV measurement were published in 1996,[8] HRV has been used extensively to explore the autonomic features and mechanisms of FSD.[9–11]

In a recent meta-analysis of HRV in persons with FM, IBS and CFS[12] including 85 studies it was concluded that persons with FSD showed significant lower HRV than persons without, indicating an ANS imbalance with predominance of sympathetic activity in FSD. However, all these studies are limited by a dominance of small case–control studies performed in highly specialised clinical settings, the use of a broad range of diagnostic criteria and unclear diagnostic procedure, and the lack of including various delimitation of FSD in the same study, thereby ignoring their mutual overlap.[2 10]

Chronic stress is strongly associated with FSD.[13–15] Chronic stress also disrupts the balance in the ANS between the SNS and the PNS branch. SNS and PNS have antagonistic influences on most bodily functions contributing to the homeostasis of the body[16] and a dysfunction of this balance may lead to experience of pain and fatigue, which are common symptoms observed in FSD.[17]

The aim of the present study was to examine, in a large random sample of the adult general population, various delimitations of FSD in relation to HRV and to test if chronic stress confounds such associations. It was hypothesised that persons with FSD would show a decreased variability in HR indicating a sympathetic dominance and that this possible association between HRV and FSD could indicate HRV being a mediating factor in the well-known association between chronic stress and FSD.

METHODS

Study population

Details of the Danish Study of Functional Somatic Disorders (DanFunD) study, which comprises two cohorts (DanFunD-I and DanFunD-II), have been reported previously.[18 19] This presentation uses data from the DanFunD-II cohort, which is a random sample of the general population obtained from the Danish Central Personal Register. A total of 25 368 men and women aged 18–72 living in the western part of the Greater Copenhagen area were invited, of whom 7493 participated (29.5%) in the study between 2013 and 2015. Exclusion criteria were not being born in Denmark, not being a Danish citizen or pregnancy.

All participants were invited to fill in questionnaires on physical symptoms and mental parameters and all went through a general health examination including measurement of HRV. All examinations were performed between 08:00 and 15:00. Participants met after at least 6 hours of fasting (including intake of coffee) and were asked to abstain from smoking at least 1 hour prior to the examination. Participants were resting in supine position for at least 5 min before measurement of continuous interbeat intervals (RR intervals) between successive sinus node-derived heartbeats, which was performed using the 'E-motion' HR monitor device (eMotion HRV, Bittium, Kuopio, Finland). In concordance with current guidelines[8] measurements were performed during the last 5 min of at least 10 min supine rest with free breathing and a sampling rate of 250 Hz was chosen. Both staff and subjects were instructed to refrain from talking apart from necessary commands.

Data preparation

Analysis of HRV was performed using a standardised analysis program (Kubios V.2.0, http://kubios.uku.fi).[20] In 270 participants, RR intervals were not recorded due to technical errors or known pacemaker implant. Participants with atrial fibrillation or excessive extrasystoles defined as more than 20 ectopic beats during the 5 min sampling period were excluded from further analysis (n=100). Files with technical artefacts due to poorly attached electrodes or equipment failure were also excluded (n=232). In the remaining files (n=6891), ectopic beats were corrected using a threshold-based artefact correction algorithm,[21] thus turning the interbeat intervals into normal-to-normal (NN) intervals. Detrending was performed using smoothen priors with a lambda value of 500.[22]

Data analysis

From the NN intervals the following time domain parameters were calculated: average heart rate (mean HR); the mean of intervals between consecutive normal-to-normal heartbeats (mean NN); the SD of NN intervals (SDNN); the root mean square of successive NN differences (RMSSD); and the percentage of successive NN intervals that differ by more than 50 ms (pNN50).[8 23] SDNN was corrected for HR (cSDNN) using the formular from Monfredi.[24]

Due to the different physiological processes influencing the variability of the HR, the so-called power spectral density analysis enables us to describe the complex HRV signal as a sum of specific individual frequency components (frequency domain parameters). In the recording of instantaneous HR, three main spectral components were differentiated by non-parametric fast Fourier transformation using Welch's periodogram with a 300 s window with 50% overlap[25]: very low frequency (VLF; <0.04 Hz),

low frequency (LF; 0.04–0.15 Hz) and high frequency (HF; 0.15–0.4 Hz) components. In short-term recordings (5 min or less), total power and VLF variation have ill-defined physiological meaning and are therefore not reported.[11 20] The LF and HF variations are measured and reported both as total power (LF_{total}, HF_{total}); normalised units representing the relative values of each power component proportional to the total power (minus the VLF component) (LF_{norm}, HF_{norm}); and the ratio between LF_{total} and HF_{total} variations (LF/HF). The distribution of the time and frequency domain parameters in the population has been described earlier.[26]

Case definitions

Due to the ongoing discussion of whether FSD represents one or many diseases[3] we decided in the DanFunD study to include various delimitations of FSD in the analyses. Cases with FSD were identified with symptom lists from questionnaires, with only bothersome symptoms within the last 12 months included. Two different delimitations of FSD were applied.[27] The first delimitation constituted three classical functional somatic syndromes (as there are many different delimitations of each syndrome, we have chosen to avoid the word syndrome): chronic fatigue (CF),[28] FM/CWP[29] and irritable bowel (IB).[30] Due to overlap between the syndromes, the pure syndromes (individuals with only one type of FSD: CF_{pure}, CWP_{pure} and IB_{pure}) were included as well. The second delimitation constituted the unifying diagnosis BDS.[4 5] BDS constitutes a single/oligo-organ type including persons with symptoms from one or two of four symptom clusters and a multi-organ type (multi-BDS) comprising persons with at least four symptoms from at least three of the four symptom clusters. In the analysis, BDS total encompassed persons with either single/oligo or multi-BDS. The specific questions asked and the algorithms used have been described previously.[31] In a stratified sample (n=1590), the semi-structured Research Interview for Functional Somatic Disorders was performed by trained physicians to assess a clinical diagnosis of BDS by excluding persons with known diseases that could explain the symptoms.[32] These cases were marked as BDS interview. The prevalence of BDS assessed by interview was lower than BDS assessed by questionnaire with an overall agreement of 67%.[33]

Covariates

Chronic stress was measured by means of the internationally validated Cohen's self-perceived stress scale[34] comprising 10 questions each with five answer categories from never to very often, which are scored 0–4. The highest score will be 40 indicating the highest degree of stress. There is no international agreement of a cut-point for having chronic stress, so the scale is used as a continuous variable.

Patient and public involvement

None.

Statistics

Statistical analyses were performed using R V.4.05.[35] Descriptive statistics were presented as medians and 25th–75th percentiles. Several logistic regression analyses were applied including the various FSD groups and controls as the dependent variables, and various HRV measures as primary independent variable. In the first model, analyses were adjusted for age and sex. If an interaction was found between sex and HRV measures, analyses were divided into the sex groups. In model 2 the analyses were further adjusted for self-perceived chronic stress to test whether stress could be a confounder of the association. The associations were reported as OR with 95% CIs. The ORs were based on prevalent cases, as the study is cross-sectional.

All models were assessed for linearity between log odds of outcome and HRV and compared with a spline model with optimal number of knots, based on graphical assessment. Knots were placed using the R package.[36] The models presented were all found to be linear.

RESULTS

Median age of the cohort was 54 years (44–64), and 46.1% were men. A total of 6891 persons had valid HRV measures, and of these 1166 (16.9%) fulfilled the criteria for BDS total, 633 (9.2%) for CF, 308 (4.5%) for CWP and 244 (3.5%) for IB. Median and IQR for the time and frequency domain factors in men and women is shown in table 1.

Heart rate (mean HR) was positively associated and, consequently, mean NN was negatively associated with CF, CWP, IB (except for women) and BDS (tables 2 and 3). Furthermore, SDNN, RMSSD and pNN50 were all slightly, but significantly, negatively associated with CF, CWP (except for RMSSD in men), IB (except for women) and BDS (tables 2 and 3). Compared with SDNN, the association to cSDNN was attenuated a little, but was still significantly associated with CF (men), CWP and total and single BDS. Looking at the pure delimitations, only CF_{pure} and CWP_{pure} were significantly associated positively with mean HR and negatively with mean NN (table 4). Men, but not women, with CF_{pure} were negatively associated with SDNN, RMSSD and pNN50. Persons with CWP_{pure} showed significantly lower pNN50 and as regards SDNN, cSDNN and RMSSD there was a significant negative association in women, but not in men. Person with IB_{pure} was not associated with the time domain measures.

The picture was more unclear in the frequency domain area. LF_{total} and HF_{total} showed a slightly negative association with most of the delimitations, however, few were significant (tables 2–4). LF_{norm} and HF_{norm} showed a significant association for IB_{pure}, positive for HF_{norm} and negative for LF_{norm}. For persons with multi-BDS a positive association for LF_{norm} and a negative association for HF_{norm} were seen. No association was seen between LF/HF ratio and the various delimitations. The same pattern was seen for BDS cases defined by a clinical diagnostic procedure (online supplemental table S1).

Table 1 Median and 25th–75th percentiles of time and frequency domain factors in men and women

HRV measures	Men (n=3152) Median (25th–75th percentiles)	Women (n=3739) Median (25th–75th percentiles)
Time domain factors		
Mean HR (beats/min)	61.8 (55.9–69.1)	64.8 (59.0–71.0)
Mean NN (ms)	972 (871–1080)	928 (847–1020)
SDNN (ms)	27.7 (18.8–41.7)	29.0 (19.7–41.9)
RMSSD (ms)	24.2 (15.1–39.1)	26.3 (17.1–42.5)
pNN50 (%)	3.60 (0.33–17.4)	5.03 (0.60–22.4)
Frequency domain factors		
LF_{total} (ms^2/Hz)	399 (167–934)	362 (157–788)
HF_{total} (ms^2/Hz)	193 (72.4–498)	263 (107–664)
LF_{norm} (%)	67.1 (52.3–79.6)	57.2 (40.0–72.0)
HF_{norm} (%)	32.9 (20.4–47.6)	42.7 (28.0–59.9)
LF_{total}/HF_{total} ratio (–)	2.04 (1.10–3.90)	1.34 (0.67–2.57)

The DanFunD-II cohort.
DanFunD, Danish Study of Functional Somatic Disorders; HF_{norm}, relative value of high-frequency variation; HF_{total}, high-frequency variation in total power; HRV, heart rate variability; LF_{norm}, relative value of low-frequency variation; LF_{total}, low-frequency variation in total power; LF_{total}/HF_{total}, ratio between low-frequency and high-frequency variations; Mean HR, average heart rate; Mean NN, mean of intervals of normal-to-normal heartbeats (corrected interbeat (RR) intervals); pNN50, percentage of successive NN intervals that differ by more than 50 ms; RMSSD, root mean square of successive NN differences; SDNN, SD of NN intervals.

Adjusting the associations between HRV and FSD with chronic stress attenuated the associations, but only slightly, with most of the significant findings remaining so (online supplemental tables S1–S4).

DISCUSSION

In this first major population-based study with specific focus on FSD, we found that persons with FSD had a slightly higher mean HR and lower HRV as measured by time domain parameters, whereas associations with frequency domain parameters were not consistent. No major differences were observed between the different delimitations of FSD. Adjusting for chronic stress attenuates the associations, but only slightly. The findings indicate a slight predominance of the SNS branch in ANS in persons with FSD.

Several meta-analyses support the findings of lower HRV in patients with various delimitations of FSD.[10 12 37] A systematic review and meta-analysis including 85 small case–control studies[12] showed a stronger association among patients with FM, but also patients with CFS and IBS showed a significant lower HRV compared with healthy controls. The meta-analysis comprised many small case–control studies (average 38 cases per study), and the authors stressed that publication bias, which is a well-known problem when making conclusions from meta-analyses of only small case–control studies, could not be excluded. This was supported by Tak *et al*,[10] where the association between FSD and HRV disappeared after correction for funnel plot asymmetry. In none of the studies it was possible to take the overlap between the various delimitations into account due to lack of this information. In the present study it did change the association—especially for IB, but the decreased power due to fewer cases must be taken into consideration.

It is generally accepted that the more high-frequent changes in HR (RMSSD, pNN50 and HF) are primarily driven by the PNS. SDNN reflects the total variability in HR and, therefore, the combined effects of both PNS, SNS and other involved systems, but SDNN and PNS, are highly and positively associated. There are more doubts as regards the LF values. Formerly, they were believed to be driven by SNS, but now they are thought to be driven by both systems.[23] Our findings of negative associations between the parameters reflecting PNS activity with most of the delimitations of FSD in the present study are, therefore, in accordance with an ANS imbalance with a predominance of sympathetic activity in these persons. It is notable, though, that both the HF and the LF are only inconsistently associated with FSD compared with the time domain parameters. There has not been a major focus on mean HR and FSD in the literature, but they were consistently positively associated in our study except for IB in women and for IB_{pure}. It is well established that persons with chronic stress have a high pulse rate[38] but adjusting for chronic stress only marginally reduced the association between FSD and mean HR.

It has been shown that HR and SDNN are associated,[39] indicating the measures of HRV are dependent on HR. It has, therefore, been argued that measures of HRV should be adjusted for HR.[24 39] A simple adjustment is not recommendable as the association is not linear. We lack further knowledge on how to adjust most HRV measures with HR, but for SDNN a correction formular has been developed in an experimental design.[24] Adjusting SDNN in the present study only attenuated the association between SDNN and FSD to a minor degree. Further studies in this area are needed.

We confirmed our hypothesis that FSD was associated with lower HRV, but the association was very weak. We could not confirm that the association was entirely explained by chronic stress. This suggests that the association shown between chronic stress and FSD[14 15] is not necessarily mediated through imbalance in the ANS; other mechanisms may be involved. Being a cross-sectional study, the shown association also could be a consequence of having FSD. The lack of major differences between the various delimitations of FSD and HRV could indicate either that the associations are a consequence of FSD or that the various delimitations represent the same disease pattern.

Table 2 Associations between chronic fatigue, chronic widespread pain, and irritable bowel and various time and frequency domain factors in men and women adjusted for age (and sex)

HRV measures (units of comparison)	Chronic fatigue (CF) (n=633)		Chronic widespread pain (CWP) (n=308)		Irritable bowel (IB) (n=244)	
	Men (n=195)	Women	Men (n=79)	Women	Men (n=63)	Women
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Time domain factors						
Mean HR (1)*	**1.029 (1.020–1.037)**†		**1.029 (1.017–1.041)**†		**1.039 (1.017–1.061)**	1.012 (0.996–1.029)
Mean NN (10)*	**0.979 (0.973–0.985)**†		**0.979 (0.971–0.988)**†		**0.974 (0.957–0.990)**	0.992 (0.981–1.003)
SDNN (1)*	**0.983 (0.974–0.993)**	**0.994 (0.989–0.999)**	**0.989 (0.982–0.997)**†		**0.979 (0.961–0.997)**	0.997 (0.990–1.004)
cSDNN	**0.996 (0.992–0.999)**	0.999 (0.997–1.001)	**0.997 (0.995–1.000)**†		0.994 (0.988–1.001)	0.999 (0.997–1.002)
RMSSD (1)*	**0.985 (0.977–0.994)**	**0.995 (0.991–0.999)**	0.999 (0.990–1.008)	**0.989 (0.982–0.997)**	**0.984 (0.969–1.000)**	0.998 (0.993–1.003)
pNN50 (1)*	**0.981 (0.970 to 0.992)**	**0.992 (0.986–0.998)**	**0.987 (0.978–0.996)**†		0.983 (0.964–1.003)	0.997 (0.988–1.005)
Frequency domain factors						
LF_{total} (10)*	**0.999 (0.998–1.000)**†		1.000 (0.999–1.002)	**0.997 (0.995–0.999)**	0.999 (0.998–1.000)†	
HF_{total} (10)*	**0.999 (0.999–1.000)**†		1.000 (1.000–1.001)	0.999 (0.997–1.000)	1.000 (0.999–1.001)†	
LF_{norm} (1)*	1.004 (0.996–1.012)	0.997 (0.992–1.002)	1.001 (0.996–1.007)†		1.001 (0.998–1.015)	0.993 (0.986–1.001)
HF_{norm} (1)*	0.996 (0.988–1.004)	1.004 (0.998–1.009)	0.999 (0.993–1.005)†		0.999 (0.985–1.012)	1.007 (0.999–1.014)
LF_{total}/HF_{total} ratio (0.1)*	0.999 (0.997–1.002)†		1.000 (0.996–1.003)†		0.998 (0.992–1.002)†	

The DanFunD-II cohort.
In case of a significant interaction between sex and HRV results are presented for each sex.
Numbers in bold indicate significant associations.
*Numbers in parentheses indicate the unit for the OR.
†No sex difference.
cSDNN, SDNN corrected for HR; DanFunD, Danish Study of Functional Somatic Disorders; HF_{norm}, relative value of high-frequency variation; HF_{total}, high-frequency variation in total power; HRV, heart rate variability; LF_{norm}, relative value of low-frequency variation; LF_{total}, low-frequency variation in total power; LF_{total}/HF_{total}, ratio between low-frequency and high-frequency variations; Mean HR, average heart rate; Mean NN, mean of intervals of normal-to-normal heartbeats (corrected interbeat (RR) intervals); pNN50, percentage of successive NN intervals that differ by more than 50 ms; RMSSD, root mean square of successive NN differences; SDNN, SD of NN intervals.

Table 3 Associations between the BDS concept (assessed by questionnaires) and various time and frequency domain factors in men and women adjusted for age

HRV measures (units of comparison)	BDS total (n=1166)		Single BDS (n=1087)		Multi-BDS (n=79)	
	Men (n=390)	Women	Men (n=374)	Women	Men (n=16)	Women
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Time domain factors						
Mean HR (1)*	**1.028 (1.018–1.038)**	**1.016 (1.007–1.024)**	**1.019 (1.012–1.026)**†		**1.070 (1.029–1.113)**	**1.037 (1.011–1.063)**
Mean NN (10)*	**0.981 (0.974–0.988)**	**0.988 (0.982–0.994)**	**0.986 (0.982–0.991)**†		**0.941 (0.907–0.976)**	**0.975 (0.956–0.995)**
SDNN (1)*	**0.983 (0.976–0.990)**	**0.993 (0.989–0.997)**	**0.983 (0.976–0.991)**	**0.994 (0.990–0.998)**	0.970 (0.933–1.008)	**0.984 (0.968–0.999)**
cSDNN	**0.995 (0.992–0.998)**	**0.998 (0.996–0.999)**	**0.995 (0.992–0.998)**	**0.998 (0.997–0.999)**	0.995 (0.983–1.007)	0.996 (0.990–1.001)
RMSSD (1)*	**0.985 (0.979–0.992)**	**0.996 (0.992–0.999)**	**0.987 (0.980–0.993)**	**0.996 (0.993–1.000)**	**0.940 (0.896–0.985)**	**0.986 (0.973–0.999)**
pNN50 (1)*	**0.983 (0.974–0.991)**	**0.994 (0.989–0.999)**	**0.985 (0.976–0.993)**	0.995 (0.990–1.000)	**0.914 (0.843–0.990)**	0.985 (0.969–1.001)
Frequency domain factors						
LF_{total} (10)*	**0.998 (0.996–0.999)**	**0.999 (0.998–1.000)**	**0.998 (0.998–0.999)**†		0.998 (0.992–1.004)	0.998 (0.994–1.001)
HF_{total} (10)*	**0.997 (0.995–0.999)**	1.000 (0.999–1.000)	**0.998 (0.996–0.999)**	1.000 (0.999–1.000)	**0.963 (0.933–0.995)**	0.998 (0.996–1.001)
LF_{norm} (1)*	1.003 (0.998–1.009)	0.997 (0.993–1.001)	0.998 (0.995–1.002)†		**1.040 (1.006–1.075)**	1.004 (0.992–1.017)
HF_{norm} (1)*	0.997 (0.991–1.002)	1.003 (0.999–1.007)	1.002 (0.998–1.005)†		**0.962 (0.930–0.994)**	0.996 (0.983–1.009)
LF_{total}/HF_{total} ratio (0.1)*	1.000 (0.998–1.002)	0.999 (0.997–1.002)	0.999 (0.997–1.001)†		1.002 (0.997–1.007)	1.004 (0.999–1.009)

The DanFunD-II cohort.
In case of a significant interaction between sex and HRV results are presented for each sex.
Numbers in bold indicate significant associations.
*Numbers in parentheses indicate the unit for the OR.
†No sex difference.
BDS, bodily distress syndrome; cSDNN, SDNN corrected for HR; DanFunD, Danish Study of Functional Somatic Disorders; HF_{norm}, relative value of high-frequency variation; HF_{total}, high-frequency variation in total power; HRV, heart rate variability; LF_{norm}, relative value of low-frequency variation; LF_{total}, low-frequency variation in total power; LF_{total}/HF_{total}, ratio between low-frequency and high-frequency variations; Mean HR, average heart rate; Mean NN, mean of intervals of normal-to-normal heartbeats (corrected interbeat (RR) intervals); pNN50, percentage of successive NN intervals that differ by more than 50 ms; RMSSD, root mean square of successive NN differences; SDNN, SD of NN intervals.

Table 4 Associations between chronic fatigue, chronic widespread pain and irritable bowel not fulfilling the criteria of the other two syndromes (pure syndromes) and time and frequency domain factors in men and women adjusted for age

HRV measures (units of comparison)	Chronic fatigue (pure) (n=439)		Chronic widespread pain (pure) (n=161)		Irritable bowel syndrome (pure) (n=134)
	Men (n=150)	Women	Men (n=48)	Women	Both sexes
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Time domain factors					
Mean HR (1)*	**1.025 (1.015–1.035)**†		**1.029 (1.017–1.041)**†		1.010 (0.992–1.028)†
Mean NN (10)*	**0.981 (0.974–0.988)**†		**0.979 (0.971–0.988)**†		0.992 (0.980–1.004)†
SDNN (1)*	**0.986 (0.976–0.996)**	0.966 (0.990–1.002)	0.996 (0.984–1.009)	**0.986 (0.977–0.995)**	0.997 (0.989–1.001)†
cSDNN	0.997 (0.993–1.000)	0.999 (0.997–1.001)	1.000 (0.996–1.005)	**0.993 (0.988–0.999)**	0.999 (0.996–1.003)†
RMSSD (1)*	**0.987 (0.978–0.996)**	0.997 (0.992–1.001)	0.999 (0.990–1.008)	**0.989 (0.982–0.997)**	0.999 (0.993–1.005)†
pNN50 (1)*	**0.981 (0.968–0.993)**	0.995 (0.988–1.002)	**0.987 (0.978–0.996)**†		0.998 (0.988–1.009)†
Frequency domain factors					
LF_{total} (10)*	**0.999 (0.999–0.9999)**†		1.000 (0.999–1.002)	**0.997 (0.995–0.999)**	0.999 (0.998–1.001)†
HF_{total} (10)*	1.000 (0.999–1.000)†		1.000 (0.999–1.001)	0.999 (0.997–1.000)	1.000 (0.999–1.001)†
LF_{norm} (1)*	1.002 (0.993–1.011)	0.994 (0.988–1.001)	1.001 (0.996–1.007)†		**0.990 (0.981–0.998)**†
HF_{norm} (1)*	0.998 (0.989–1.007)	1.006 (0.999–1.012)	0.999 (0.993–1.005)†		**1.011 (1.002–1.019)**†
LF_{total}/HF_{total} ratio (0.1)*	0.998 (0.995–1.002)†		1.000 (0.996–1.003)†		0.995 (0.987–1.002)†

The DanFunD-II cohort.
In case of a significant interaction between sex and HRV results are presented for each sex.
Numbers in bold indicate significant associations.
*Numbers in parentheses indicate the unit for the OR.
†No sex difference.
cSDNN, SDNN corrected for HR; DanFunD, Danish Study of Functional Somatic Disorders; HF_{norm}, relative value of high-frequency variation; HF_{total}, high-frequency variation in total power; HRV, heart rate variability; LF_{norm}, relative value of low-frequency variation; LF_{total}, low-frequency variation in total power; LF_{total}/HF_{total}, ratio between low-frequency and high-frequency variations; Mean HR, average heart rate; Mean NN, mean of intervals of normal-to-normal heartbeats (corrected interbeat (RR) intervals); pNN50, percentage of successive NN intervals that differ by more than 50 ms; RMSSD, root mean square of successive NN differences; SDNN, SD of NN intervals.

Strengths and limitations

The current study has several strengths. First, we included a large (n=6891) unselected sample from the general population with almost equal distribution of the two sexes. Other studies mostly involve highly selected—often female—patient samples recruited in specialised clinical setting with great risk of publication bias.[10 12] The population-based study design reduces the risk of selection bias and allows the results to be generalised to other adult populations. Second, as many different criteria to identify FSD have been proposed,[1] we included two approaches for defining FSD in our study.[27] Hence, we tried to capture the diverse nature of these conditions as both monosystematic and multisystematic. Third, we used well-known and validated symptom questionnaires for defining the various FSD. Fourth, we included an analysis based on BDS cases diagnosed by a trained clinician to assess any difference between self-report delimitation and clinical assessment in relation to HRV.

However, our study also has some limitations. First, it may be that we included cases with milder symptoms than studies on clinical samples. However, in our study, a cut-off on symptom severity was made, only including bothering symptoms in the criteria defining FSD cases. Furthermore, we included definitions of multisystematic conditions (multiorgan BDS). We therefore argue that the cases in our study were not all mild cases but also constituted individuals with symptom patterns of severe FSD. Also, a majority of mild cases might underestimate associations. Second, the response rate of 29.5% may be considered low, and even though the risk of selection bias is markedly reduced compared with clinical studies, we cannot completely rule it out. But we have previously shown that selection bias is not a major problem in the DanFunD study.[40] Third, we are dealing with a cross-sectional design and therefore cannot determine whether the findings are consequences or determinants for FSD. Prospective cohort studies are needed to further elucidate this. Fourth, although HRV reflects autonomic regulation of the heart, and not generalised autonomic control and activity, the autonomic regulation of HR will be in concordance with autonomic outflow to the rest of the body in many circumstances.[41] As IB could reflect the influence of ANS on the intestine, HRV may not be the best measure as regards IB.

CONCLUSIONS

In this first large-scale study in the area, we did find a small association between various delimitations of FSD and sign of an ANS imbalance with a predominance of sympathetic activity, which could not be entirely explained by chronic stress. The finding does support our hypothesis, but due to the cross-sectional design and that the associations were both weak and inconsistent for some of the parameters, further studies—preferably prospective studies—are needed.

Author affiliations
[1]Center for Clinical Research and Prevention, Copenhagen University Hospital – Bispebjerg and Frederiksberg, Frederiksberg, Denmark
[2]Department of Public Health, Faculty of Health and Medical Science, University of Copenhagen, Copenhagen, Denmark
[3]Research Clinic for Functional Disorders and Psychosomatics, Aarhus University Hospital, Aarhus, Denmark
[4]Department of Clinical Medicine, University of Aarhus, Aarhus, Denmark
[5]Department of Clinical Medicine, Faculty of Health and Medical Science, University of Copenhagen, Copenhagen, Denmark
[6]Copenhagen Research Centre for Mental Health – CORE, Mental Health Centre Copenhagen, Copenhagen University Hospital, Copenhagen, Denmark
[7]Department of Immunology and Microbiology, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[8]Department of Imaging and Radiology, Copenhagen University Hospital - North Zealand, Helsingør, Denmark

Acknowledgements The authors thank the participants in the DanFunD cohort and the staff behind the cohort at the Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospital, Capital Region of Denmark, for their great work in collecting and assuring data of high quality.

Contributors TJ, TMD, PF, LFE and LSB contributed to conceptualisation. TJ, PF, LFE and AL contributed to acquisition of data. TJ, LFE and PF contributed to funding acquisition. MW-J and TJ contributed to formal analysis. TJ, MW-J, TMD, MWP and PF contributed to methodology. AL, TMD and TJ contributed to project administration. TJ wrote the original draft. All authors (TJ, TMD, MWP, LG, MW-J, PF, AL, MEB, LFE, AAB, SUS, LSB) contributed to interpretation, review and editing and approved the final version to be published. TJ is the guarantor of the study.

Funding The DanFunD study was supported by TrygFonden (7-11-0213 and 117548), the Lundbeck Foundation (R155-2013-14070) and Helsefonden (22-B-0583).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Obtained.

Ethics approval This study involves human participants and was conducted in accordance with the Declaration of Helsinki. It was approved by the Ethical Committee of Copenhagen County (H-3-2011-081 and H-3-2012-0015) and the Danish Data Protection Agency (P-2020-845).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data cannot be made publicly available for ethical and legal reasons. Public availability may compromise participant privacy, and this would not comply with Danish legislation. Access to the subset of data included in this study can be gained through submitting a request to the Capital Region Knowledge Center for Data Compliance, Capital Region Denmark; cru-fp-vfd@regionh.dk. Acquisition of data is only allowed after permission to handle data has been obtained in accordance with the guidelines stated by the Danish Data Protection Agency: http://www.datatilsynet.dk/english.

ORCID iDs
Torben Jørgensen http://orcid.org/0000-0001-9453-2830

Thomas Meinertz Dantoft http://orcid.org/0000-0001-7437-7052
Anne Ahrendt Bjerregaard http://orcid.org/0000-0002-0628-5292
Signe Ulfbeck Schovsbo http://orcid.org/0000-0002-0206-8581

REFERENCES

1 Burton C, Fink P, Henningsen P, *et al*. Functional somatic disorders: discussion paper for a new common classification for research and clinical use. *BMC Med* 2020;18:34.
2 Petersen MW, Schröder A, Jørgensen T, *et al*. Irritable bowel, chronic widespread pain, chronic fatigue and related syndromes are prevalent and highly overlapping in the general population: DanFunD. *Sci Rep* 2020;10:3273.
3 Wessely S, Nimnuan C, Sharpe M. Functional somatic syndromes: one or many? *Lancet* 1999;354:936–9.
4 Fink P, Toft T, Hansen MS, *et al*. Symptoms and syndromes of bodily distress: an exploratory study of 978 internal medical, neurological, and primary care patients. *Psychosomatic Medicine* 2007;69:30–9.
5 Budtz-Lilly A, Fink P, Ørnbøl E, *et al*. A new questionnaire to identify bodily distress in primary care: the "BDS checklist." *J Psychosom Res* 2015;78:536–45.
6 Petersen MW, Schröder A, Jørgensen T, *et al*. The unifying diagnostic construct of bodily distress syndrome (BDS) was confirmed in the general population. *J Psychosom Res* 2020;128:109868.
7 Schröder A, Sharpe M, Fink P. Medically unexplained symptom management. *Lancet Psychiatry* 2015;2:587–8.
8 Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task force of the European Society of Cardiology and North American Society of pacing and electrophysiology. *Circulation* 1996;93:1043–65.
9 Laborde S, Mosley E, Thayer JF. Heart rate variability and cardiac vagal tone in psychophysiological research - recommendations for experiment planning, data analysis, and data reporting. *Front Psychol* 2017;8:213.
10 Tak LM, Riese H, de Bock GH, *et al*. As good as it gets? A meta-analysis and systematic review of methodological quality of heart rate variability studies in functional somatic disorders. *Biol Psychol* 2009;82:101–10.
11 Meeus M, Goubert D, De Backer F, *et al*. Heart rate variability in patients with fibromyalgia and patients with chronic fatigue syndrome: a systematic review. *Semin Arthritis Rheum* 2013;43:279–87.
12 Ying-Chih C, Yu-Chen H, Wei-Lieh H. Heart rate variability in patients with somatic symptom disorders and functional somatic syndromes: a systematic review and meta-analysis. *Neurosci Biobehav Rev* 2020;112:336–44.
13 Deary V, Chalder T, Sharpe M. The cognitive behavioural model of medically unexplained symptoms: a theoretical and empirical review. *Clinical Psychology Review* 2007;27:781–97.
14 Martinez-Lavin M. Biology and therapy of fibromyalgia. Stress, the stress response system, and fibromyalgia. *Arthritis Res Ther* 2007;9:216.
15 Petersen MW, Carstensen TBW, Frostholm L, *et al*. High perceived stress and low self-efficacy are associated with functional somatic disorders: the DanFunD study. *Clin Epidemiol* 2023;15:407–19.
16 Read S, Grundy E. Allostatic load – a challenge to measure multisystem physiological dysregulation. *National Centre for Research Methods Working Paper* 2012:1–9.
17 Cohen H, Neumann L, Kötler M, *et al*. Autonomic nervous system derangement in fibromyalgia syndrome and related disorders. *Isr Med Ass J* 2001;3:755–60.
18 Dantoft TM, Ebstrup JF, Linneberg A, *et al*. Cohort description: the Danish study of functional disorders. *Clin Epidemiol* 2017;9:127–39.
19 Jørgensen T, Dantoft TM, Weinreich Petersen M, *et al*. Examine the public health impacts of functional somatic disorders using the DanFunD study. *Scand J Public Health* 2022;50:988–94.
20 Tarvainen MP, Niskanen J-P, Lipponen JA, *et al*. Kubios HRV--heart rate variability analysis software. *Comput Methods Programs Biomed* 2014;113:210–20.
21 Lippman N, Stein KM, Lerman BB. Nonlinear predictive interpolation. A new method for the correction of ectopic beats for heart rate variability analysis. *JElectrocardiol* 1993;26 Suppl:14–9.
22 Tarvainen MP, Ranta-aho PO, Karjalainen PA. An advanced detrending method with application to HRV analysis. *IEEE Trans Biomed Eng* 2002;49:172–5.
23 Shaffer F, Ginsberg JP. An overview of heart rate variability metrics and norms. *Front Public Health* 2017;5:258.
24 Monfredi O, Lyashkov AE, Johnsen A-B, *et al*. Biophysical characterization of the underappreciated and important relationship between heart rate variability and heart rate. *Hypertension* 2014;64:1334–43.
25 Welch P. The use of fast Fourier transform for the estimation of power spectra: a method based on time averaging over short, modified periodograms. *IEEE Trans Audio Electroacoust* 1967;15:70–3.
26 Brinth LS, Jørgensen T, Mehlsen J, *et al*. Normative values of short-term heart rate variability in a cross-sectional study of a Danish population. The DanFunD study. *Scand J Public Health* 2022:14034948221124020.
27 Petersen MW, Schröder A, Eliasen MH, *et al*. Three different approaches to delimitation of functional somatic disorders: DanFunD. *J Psychosom Res* 2021;145:110475.
28 Chalder T, Berelowitz G, Pawlikowska T, *et al*. Development of a fatigue scale. *J Psychosom Res* 1993;37:147–53.
29 White KP, Harth M, Speechley M, *et al*. Testing an instrument to screen for fibromyalgia syndrome in general population studies: the London fibromyalgia epidemiology study screening questionnaire. *J Rheumatol* 1999;26:880–4.
30 Kay L, Jørgensen T. Redefining abdominal syndromes. Results of a population-based study. *Scand J Gastroenterol* 1996;31:469–75.
31 Petersen MW, Schröder A, Jørgensen T, *et al*. Prevalence of functional somatic syndromes and bodily distress syndrome in the Danish population: the DanFunD study. *Scand J Public Health* 2020;48:567–76.
32 Petersen MW, Schröder A, Jørgensen T, *et al*. RIFD - A brief clinical research interview for functional somatic disorders and health anxiety. *J Psychosom Res* 2019;122:104–11.
33 Petersen MW, Ørnbøl E, Dantoft TM, *et al*. Assessment of functional somatic disorders in epidemiological research: self-report questionnaires versus diagnostic interviews. *J Psychosom Res* 2021;146:110491.
34 Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav* 1983;24:385–96.
35 R Core Team. *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing, 2021.
36 Harrell FE. Regression modelling strategies. 2020. Available: https://cran.r-project.org/package=rms
37 Liu Q, Wang EM, Yan XJ, *et al*. Autonomic functioning in irritable bowel syndrome measured by heart rate variability: a meta-analysis. *J Dig Dis* 2013;14:638–46.
38 van Kraaij AWJ, Schiavone G, Lutin E, *et al*. Relationship between chronic stress and heart rate over time modulated by gender in a cohort of office workers: cross-sectional study using wearable technologies. *J Med Internet Res*;22:e18253.
39 Sacha J. Interaction between heart rate and heart rate variability. *Noninvasive Electrocardiol* 2014;19:207–16.
40 Schovsbo SU, Dantoft TM, Thuesen BH, *et al*. Social position and functional somatic disorders: the DanFunD study. *Scand J Public Health* 2023;51:225–32.
41 Hayano J, Sakakibara Y, Yamada M, *et al*. Diurnal variations in vagal and sympathetic cardiac control. *Am J Physiol* 1990;258:H642–6.