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Psychosocial risk factors, pre-motor symptoms, and first-time hospitalization with Parkinson's Disease: a prospective cohort study

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Abstract

Background—Experimental studies support a link between stress and development of parkinsonian symptoms, but prospective population studies are lacking. The aim of the current study is to determine the effects of several psychosocial factors on risk of Parkinson's disease (PD) as well as identify potential pre-motor symptoms for PD in a large prospective cohort study.

Methods—In 1991–1993, a total of 9955 women and men free of PD from the Copenhagen City Heart Study, were asked about major life events, economic hardship, social network, impaired sleep, and vital exhaustion. The participants were followed for first-time hospitalization with PD in nationwide registers until 2011.

Results—Vital exhaustion was associated with a higher risk of PD hospitalization in an exposure dependent manner ($p_{\text{trend}}=0.001$), with high vs. low vital exhaustion being associated with a hazard ratio of 2.50 (95% CI: 1.28–4.89). A slightly higher risk of PD hospitalization (HR=1.49; 95% CI: 0.87–2.56) was suggested in participants with impaired sleep at baseline. No more than weak associations were observed for economic hardship, major life events or inadequate social network in the current study.

Conclusions—Overall, the hypothesis that psychosocial risk factors affect the risk of PD is not supported. The results, however, suggests that vital exhaustion may be a pre-motor marker of the neuro-degenerative process eventually leading to motor-symptoms and clinical PD. Vital exhaustion may be useful for screening aimed at early detection and when considering disease-modifying therapies in people at high risk of clinical PD.

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Disclosure of conflict of interests

None

Contributions

AC contributed to the conception and design of the study, the analyses and interpretation of data, and drafting of the article. BR, EP and NHR contributed to the conception and design of the study and critically revised the article. NHR is the guarantor of the present study. All authors have read and approved submission of the manuscript.

Keywords

Burnout; family relations; life change events; prospective studies; Parkinson's disease; sleep disorders; social support; stress; psychological

INTRODUCTION

Psychological stress has the capacity to affect several vital body systems including neuroendocrine and immunologic processes and can lead to dysregulated levels of e.g. glucocorticoids, dopamine and glutamate in centers of the brain implicated in Parkinson's Disease pathology (PD).[1] Elevated levels of these neurotransmitters may be neuro-toxic and possibly increase the susceptibility of dopaminergic neurons to damage and cell death – a cardinal element in PD.[1, 2] However, prospective population studies addressing the relation between psychosocial stress and PD onset are virtually non-existent. An exception is a large Danish record-linkage study, in which no support of an effect of major life events on the development of PD was found.[3] Risk avoidance behavior in pre-clinical PD sufferers may, however, have affected the results.[4] PD mortality has also been studied in British male prisoners of war in Japan during World War II.[5] Even though this study did not find elevated mortality-rates from PD, results from an extreme survivor population may not transfer to the general male population.

Within recent years it has been suggested that PD may start in the peripheral nervous system with autonomic dysfunctions preceding motor symptoms.[1, 6] While motor symptoms are central for clinical diagnosis, they are often not present until PD has progressed substantially.[6] Identification of pre-motor symptoms may be a prerequisite for development and testing of disease-modifying treatments targeting early PD. While not definitive, several early markers have been proposed including sleep impairment, rapid eye movement (REM)-sleep behavior disorder, loss of a sense of smell/taste, constipation, and depressive symptoms.[7–16] Large cohort studies that address pre-motor symptoms prior to PD are needed to provide prospective data.[8] In this study, we aim to determine the effects of a range of psychosocial factors including major life events, economic hardship, structural and functional aspects of social networks on first-time hospitalization with PD, as well as examine two potential pre-motor symptoms for PD i.e. vital exhaustion and sleep impairment in a large prospective cohort study with 20 years of follow-up.

MATERIALS AND METHODS

Study population

The Copenhagen City Heart Study (CCHS) is a longitudinal cohort study initiated in 1976. An age-stratified random sample of 14,223 women and men residing in Copenhagen attended the first examination in 1976–1978, including a physical examination and a comprehensive questionnaire. At subsequent waves the entire original sample and new individuals were invited and additional assessments were performed for both new and continuing participants. The local ethics committee has approved the study protocol. Informed consent was obtained from all participants. A detailed description of the CCHS has been published elsewhere.[17] A total of 10,135 (61% response rate) participated in the third wave in 1991–1993, in which a comprehensive list of psychosocial factors was assessed. The third wave is therefore the baseline for the current study. Participants with previous hospitalization for PD (n=13), or with missing information on any of the covariates (n=167) were excluded, leaving 9955 participants eligible for analyses.

Psychosocial risk factors

The psychosocial risk factors included: *major life events in childhood* (long-term disease in parents, being placed in care outside the home, serious family conflicts, parents' long-term unemployment, and serious economic problems in childhood); *major life events in work life* (job loss, serious conflicts with colleagues, supervisors or charges, not being promoted, and not achieving educational goals); *major life events in adult life* (long-term illness or serious accident, having children with major educational problems, serious conflicts with adult children, marital problems, death or long-term illness in a close family member, and serious economic problems). The above questions were based on a shorter and modified version of the Social Readjustment Rating Scale.[18] A non-weighted sum of life events was calculated to assess the accumulation of life events within each domain of life. *Economic hardship* was defined as a self-reported annual household income at baseline <18,000 US\$ for subjects <67 years of age (retirement age). The structural aspects of social network covered *cohabitation* (living alone versus living with a partner/others), and *regularity of contact with family and friends* (more/less than a few times per month). The functional aspects included *availability of a confidant* ("Is there someone you can talk to about personal issues?") and *satisfaction with social network* (very/somewhat or not at all).

Pre-motor symptoms

Vital exhaustion is defined as a psychological response reflecting a breakdown of the adaption to stress, which include a complex of symptoms characterised by unusual fatigue, increased irritability, and feelings of demoralisation.[19] Thus, vital exhaustion somewhat overlaps with symptoms of depression, which has previously been observed to precede PD. [12–15, 20] However, studies of vital exhaustion and depression display significant disparities supporting a distinction between this symptom complex and depression.[21, 22] In this study vital exhaustion was assessed by 17 items based on the Vital Exhaustion Scale developed by Apples [19], which were summed into an item score and categorised into three groups (0, 1–7 and 8–17). Examples of items are: "Do you feel altogether weak?" and "Do little things irritate you more than they used to?" The full list of items can be assessed in Appendix 1. *Sleep impairment*: Information regarding daily/almost daily use of sleep medication was assessed as an indicator of any type of severe sleep impairment that may predate PD. This indicator has previously been shown to be highly correlated with excessive daytime sleepiness assessed by the commonly used Epworth Sleepiness Scale.[23, 24]

Covariates

Other covariates included sex, age, educational attainment (<8 years, 8–10 years, 11 years of formal schooling), and smoking (never-smoker, ex-smoker, smoker of 1–14 gram tobacco/day, smoker of 15–24 gram tobacco/day, and smoker of >24 gram tobacco/day).

Follow-up

Participants were followed from date of third examination until the date of first hospitalization (including emergency and out-patient visits) with PD (n=98), death from PD (n=10), death from other causes (n=4351), emigration out of Denmark (n=115), or end of follow-up on May5, 2011 (n=5381), with an average follow-up of 14 years and less than 2% loss to follow-up. In the following, hospitalization will refer to first-time hospitalization, emergency and out-patient visit with PD, and PD related deaths without prior hospitalization. Using the civil registry number, unique to every Danish citizen, first-time admissions with PD and PD deaths were identified through linkage to the Danish Hospital Discharge Registry and the Central Death Registry. The following International Classification of Disease codes were used to identify PD: ICD-8 342 and ICD-10 G20.

Statistical analyses

Data were analyzed by means of Cox proportional hazard models with age as the underlying time variable. Due to similarity of effects in the initial sex-specific analyses the analyses were combined for women and men. All variables met the assumption of proportional hazards. Initially, we estimated the age- and sex-adjusted hazard ratios (HR) and 95% confidence intervals (CI) for first-time hospitalization with PD in separate models for each exposure variable. A multivariate model was fitted to adjust for potential confounding from baseline covariates. We used prior knowledge and the methods of Directed Acyclic Graphs[25] to identify potential confounders, which included educational attainment, age, and sex. Smoking is most likely an intermediate variable between the psychosocial factors and PD, and was therefore controlled for in a separate model. In sensitivity analyses, we excluded PD deaths without prior PD hospitalization. Analyses were also confined to individuals >60 years of age to exclude patients with young-onset PD. In analyses with a five- and ten-year lag-time we hoped to prevent reverse causation and to explore how early the pre-motor symptoms would manifest prior to PD. Analyses restricted to primary diagnoses of PD were conducted in order to increase specificity and minimizing inclusion of parkinsonian disorders other than idiopathic PD.

RESULTS

Baseline characteristics

Among the 9555 eligible participants, 98 were hospitalized with PD during follow-up and 10 had a PD related death without prior hospitalization with the disease. The mean age of the study population was 59 years at baseline (range 21–94 years), and mean age at first-time hospitalization with PD was 78 years (range 54–91 years). Baseline characteristics of the population are shown in Table 1.

Psychosocial risk factors and PD hospitalization

Overall the number of major life events was not associated with PD hospitalization, although a slightly higher risk was seen in participants who reported more life events in work life (HR=1.40; 95% CI: 0.69–2.85) (Table 2). Likewise, a higher risk of PD hospitalization was indicated in participants suffering economic hardship (HR=1.40; 95% CI: 0.62–3.16). Due to limited statistical power the confidence intervals are too wide to draw any firm conclusions. No associations were observed between social network and PD. Restricting the analyses to primary diagnosis of PD did not change the findings markedly. While hampered by small numbers, the suggested association with economic hardship strengthened in the analyses confined to those with a primary PD diagnosis (HR=1.95; 95% CI: 0.79–4.80). Analyses including a five-year lag-time, showed that participants without regular contact to friends had an approximately 50% higher risk (HR=1.51; 95% CI: 0.97–2.37) of later PD hospitalization. This association remained even after a 10-year lag-period (data not shown). Exclusion of early onset cases of PD resulted in a slight increase in the effect of major life events in work life (HR=1.70; 95% CI: 0.80–3.58) in participants experiencing two or more life events vs. none. Exclusion of the 10 PD cases only identified at death did not affect the estimates.

Pre-motor symptoms and PD hospitalization

Vital exhaustion was associated with a higher risk of PD hospitalization in an exposure dependent manner ($p_{\text{trend}}=0.001$). Participants in the highest category of vital exhaustion had a 2.5 times higher risk of being hospitalized with PD (HR=2.50, 95% CI: 1.28, 4.89) compared to those with the lowest score (Table 3). The association strengthened after adjustment for smoking, which is most likely due to some of the effect being mediated

through smoking. The results also suggested a higher risk in participants reporting a daily intake of sleep medication at baseline (HR=1.49; 95% CI: 0.87–2.56) relative to participants with less frequent use. However, small numbers yielded limited power to assess this association. Sensitivity analyses with a five-year lag-time attenuated the effect of vital exhaustion, with a HR of 1.54 (0.63–3.75) observed in participants with the highest vs. lowest level of vital exhaustion. Increasing the lag-time to 10 years removed the association (Table 4). In contrast, the estimated effect of sleep impairment strengthened with inclusion of a 10-year lag-time, with participants reporting a daily intake of sleep medication experiencing twice the risk of a PD hospitalization 10 to 20 years after baseline (HR=2.10; 95% CI: 0.91–4.85). Neither restriction to primary PD diagnoses, to participants >60 years of age, nor to PD hospitalizations (excluding PD deaths) notably altered the associations.

DISCUSSION

Psychosocial risk factors and PD hospitalization

In this prospective cohort study, with comprehensive measures of psychosocial factors, we did not observe associations between PD and most of the psychosocial risk factors. However, the accumulation of life events in work life, economic hardship and being somewhat socially isolated might contribute to PD risk. It could be worthwhile to re-examine this in studies with larger sample sizes.

We did not find consistent effects of experiencing multiple major life events throughout different domains of life on the risk of PD hospitalization. This is in agreement with the results of the aforementioned Danish linkage study which did not find a positive associations between major life events and PD.[3] However, inclusion of only a shorter list of predefined life events without the appraisal of these, could have contributed to an underestimation of effects due to misclassification of events.

Most previous studies on socioeconomic factors in PD have focused on the economic consequences of the disease. However, recent studies support an association between income and adherence to prescribed treatment and progression of the disease,[26, 27] adding potential mechanisms through which income could affect the course of PD rather than the development of disease per se. Hence, the higher risk of PD hospitalizations that we observed among participants suffering economic hardship could be a result of a generally more adverse course of disease, a higher symptom burden and earlier PD diagnosis. Moreover, individuals suffering economic hardship may have fewer resources to deal with the disease and thus seek medical assistance earlier in disease progression.

Regarding the role of social networks, previous studies have been confined to issues of social support to PD patients and their caregivers, and have not addressed the potential risk of PD associated with different dimensions of social network. However, studies have reported a higher occurrence of depression, stress, and physical disabilities in PD patients with insufficient social support [28, 29]. As such, lack of support may affect the course of disease and risk of hospitalization in undiagnosed people with PD. We did not find consistent associations between social network and hospitalization with PD, but an effect of being somewhat socially isolated was suggested in sensitivity-analyses including a 5- and 10-year lag-time, and in analyses confined to primary PD cases. A potentially higher risk of PD in more socially isolated people is also in line with the proposed pre-morbid personality of PD sufferers encompassing social introversion.[4]

Pre-motor symptoms and PD hospitalization

In this study, we found more than twice the risk of PD hospitalization in participants who reported high vital exhaustion. Although this is the first study to assess the relation between

vital exhaustion and development of PD, previous studies on depression have shown a high correlation with PD. The strong association between vital exhaustion and PD was mainly confined to the five years before PD hospitalization, which is likely an expression of this symptom being a preclinical manifestation of the ongoing neurodegenerative process – paralleling earlier findings for depression, with more depression diagnoses primarily two to five years before PD diagnosis.[13, 15, 20]

Similarly, it is plausible that the tentative association between PD and intake of sleep medication in our study may result from sleep impairment being a pre-clinical manifestation rather than risk factor for developing PD. However, the strengthening of the association in >10-year lag-time analyses suggests that sleep impairment could be either a very early disease marker or a potential etiologic risk factor for PD. Within the last decade interest into the predictive nature of some specific sleep disorders for PD, especially REM-sleep behavior disorders, has grown. Recent reviews highlight that although sleep disorders become more frequent as motor symptoms progress, some may be an initial expression of the disease.[8, 10, 11, 30] Most previous studies have been small and restricted to clinical settings or retrospective in design. In fact, to the best of our knowledge, only one prospective population-based study previously reported on sleep disturbances prior to PD onset.[9] In the Honolulu Asian Aging study of elderly Japanese-American men they found that within seven years of follow-up excessive daytime sleepiness was associated with a threefold excess in PD risk. Thus, our study provides additional support for the hypothesis that impaired sleep and not just REM-sleep disorders may be a pre-motor marker of PD.

Strengths and limitations

This study is among the first prospective studies to address the relation between several dimensions of psychosocial stress and first-time hospitalization with PD in a large cohort of women and men without previous hospitalization with PD. The prospective design ensured temporality between the psychosocial exposures and PD. Linkage of civil registry numbers to nationwide population-based registers enabled identification of first-time hospitalization for PD and PD related deaths and allowed for nearly complete long-term follow-up.

We used hospital admission with PD as a proxy for incidence of PD, but hospital admission may, in addition to incidence, reflect a greater likelihood of hospitalization per se. For example people's social network might affect their medical treatment seeking behavior when experiencing symptoms of disease. This is supported by previous research showing that people with an insufficient social network are less inclined to seek medical assistance when needed. In this case, detection-bias could have contributed to an underestimation of the potential effect of social network on PD incidence. Additionally, PD is mainly an out-patient disease, especially in the early phases, and cases may have been diagnosed by specialists in private practices years before having their first PD hospitalization. In fact, we previously showed that PD patients in Denmark were prescribed PD medication on average three years prior to their first hospitalization with the disease.[31] Moreover, the average age of PD hospitalization was 78 in the current study, which is approximately 5 years older than the age of average onset.[32] Information on diagnostic details for patients with PD and date of first symptoms was not available in this study, but inclusion of out-patient visits may have reduced this problem by shortening the time from diagnosis to registration in disease registries. Although addressing multiple aspects of psychosocial stress, we are aware that the included exposures do not fully capture life-time exposure to adverse psychosocial circumstances.

We lacked detailed information on type and duration of sleep medication, which made this a very crude measure of sleep impairment. In the CCHS the self-reported measure of sleep medication has, however, previously been found to be highly correlated with high scores on

the Epworth Sleepiness Scale[23], which is a commonly used measure of excessive daytime sleepiness and has previously proven helpful in diagnosis of sleep disorders.

In conclusion, we find little support for the stress hypothesis generally promoted by experimental studies. Our study, however, provides some evidence that symptoms of vital exhaustion are predictive of PD onset possibly within the 5 years prior to first-time PD hospitalization. If these findings can be confirmed it could be relevant to include vital exhaustion in questionnaires attempting to screen for early pre-motor symptoms, which are needed for prevention and treatment efforts that target people at high risk of developing PD.

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Table 1

Baseline Characteristics of the 9955 women and men from Third Wave of the Copenhagen City Heart Study according to Vital Exhaustion score

	Total population (n=9955)	Vital exhaustion score		
		0 (n=2880)	1–7 (n= 5522)	8–17 (n=1263)
No of Parkinson's Disease cases ^a , n (%)	108 (1)	21 (0.73)	67 (1.21)	15 (1.19)
Mean age at baseline (SD)	58 (15)	59 (15)	57 (16)	60 (15)
Women, n (%)	5,603 (56)	1385 (48)	3165 (57)	859 (68)
Education < 8 yrs, n (%)	3,481 (35)	963 (33)	1804 (33)	567 (45)
Current smoker, n (%)	4,841 (49)	1274 (44)	2704 (49)	730 (58)

^aThe number of Parkinson's Disease cases in the total population was 108, but because of missing values on vital exhaustion, the number of cases for this variable only adds up to 103.

Psychosocial Risk Factors and Parkinson's Disease Hospitalization among the 9955 women and men from the Third Wave of the Copenhagen City Heart Study

Table 2

	No. of cases ^a	IR/10,000 yrs	Age- & gender-adjusted HR (95% CI)	Multiple adjusted ^b HR (95% CI)	+Smoking adjusted HR (95% CI)
Major Life Events					
Major life events in childhood					
0	58	9	1 (reference)	1 (reference)	1 (reference)
1	24	6	0.75 (0.46–1.20)	0.75 (0.47–1.21)	0.75 (0.47–1.21)
2+	17	6	0.89 (0.51–1.53)	0.90 (0.52–1.55)	0.90 (0.52–1.55)
<i>P</i> _{trend}			0.44	0.47	0.47
Major life events in work life					
0	63	7	1 (reference)	1 (reference)	1 (reference)
1	26	7	1.35 (0.86–2.14)	1.37 (0.86–2.17)	1.39 (0.88–2.21)
2+	9	5	1.40 (0.69–2.84)	1.40 (0.69–2.85)	1.43 (0.70–2.91)
<i>P</i> _{trend}			0.17	0.16	0.14
Major life events in adult life					
0	29	7	1 (reference)	1 (reference)	1 (reference)
1	38	8	1.25 (0.77–2.03)	1.24 (0.76–2.02)	1.25 (0.77–2.03)
2+	32	7	1.14 (0.68–1.89)	1.13 (0.68–1.88)	1.15 (0.69–1.92)
<i>P</i> _{trend}			0.63	0.95	0.59
Economic Hardship					
Household income <18,000 US\$					
No	39	4	1 (reference)	1 (reference)	1 (reference)
Yes	7	6	1.34 (0.59–3.01)	1.40 (0.62–3.16)	1.45 (0.64–3.28)
Retired (age > 67yr)	59	18	0.86 (0.52–1.44)	0.87 (0.52–1.46)	0.86 (0.52–1.45)
Structural aspects of Social Network					
Cohabitation					
Yes	60	7	1 (reference)	1 (reference)	1 (reference)
No	48	10	1.11 (0.74–1.66)	1.11 (0.74–1.67)	1.12 (0.75–1.68)
Regular contact to family					
Yes	87	7	1 (reference)	1 (reference)	1 (reference)

	No. of cases ^a	IR/10,000 yrs	Age- & gender-adjusted HR (95% CI)	Multiple adjusted ^b HR (95% CI)	+Smoking adjusted HR (95% CI)
No	13	11	1.19 (0.66–2.14)	1.20 (0.67–2.16)	1.19 (0.66–2.15)
Regular contact to friends					
Yes	65	6	1 (reference)	1 (reference)	1 (reference)
No	35	10	1.20 (0.79–1.81)	1.22 (0.80–1.85)	1.23 (0.81–1.87)
Functional aspects of Social Network					
Having a confidant					
Yes	102	8	1 (reference)	1 (reference)	1 (reference)
No	6	7	0.72 (0.32–1.65)	0.73 (0.32–1.67)	0.74 (0.32–1.68)
Satisfaction with social network					
Very	69	7	1 (reference)	1 (reference)	1 (reference)
Somewhat/not at all	31	7	1.18 (0.77–1.81)	1.19 (0.78–1.82)	1.20 (0.78–1.83)

^aThe total number of Parkinson's Disease hospitalizations was 108, but because of missing values, the number of cases does not add up to the totals.

^bAdjusted for age, gender, and educational attainment.

Pre-motor Symptoms of Parkinson’s Disease Hospitalization among the 9955 women and men from the Third Wave of the Copenhagen City Heart Study

Table 3

	No. of cases ^a	IR/10,000 yrs	Age- & gender-adjusted HR (95% CI)	Multiple adjusted ^b HR (95% CI)	+ Smoking adjusted HR (95% CI)
Vital exhaustion score					
0	21	5	1 (reference)	1 (reference)	1 (reference)
1–7	67	8	2.19 (1.34–3.58)	2.20 (1.35–3.61)	2.26 (1.38–3.70)
8–17	15	9	2.45 (1.26–4.78)	2.50 (1.28–4.89)	2.67 (1.36–5.25)
P _{trend}			0.002	0.001	0.001
Daily intake of sleep medication					
No	90	7	1 (reference)	1 (reference)	1 (reference)
Yes	16	17	1.48 (0.86–2.54)	1.49 (0.87–2.56)	1.52 (0.88–2.62)

^aThe total number of Parkinson’s Disease hospitalizations was 108, but because of missing values, the number of cases does not add up to the totals.

^bAdjusted for age, gender, and educational attainment.

Table 4

No lag-time, 5-yr lag-time and 10-yr lag-time from *Pre-motor Symptoms* to Parkinson's Disease Hospitalization among the 9955 men and women from the Third Wave of the Copenhagen City Heart Study

		No lag-time		5-yr lag-time		10-yr lag-time			
	No. of cases ^a	IR/10,000 yrs	Multiple adjusted ^d HR (95% CI)	No. of cases ^b	IR/10,000 yrs	Multiple adjusted ^d HR (95% CI)	No. of cases ^c	IR/10,000 yrs	Multiple adjusted ^d HR (95% CI)
Vital exhaustion score									
0	21	5	1 (reference)	17	6	1 (reference)	14	9	1 (reference)
1–7	67	8	2.20 (1.35–3.61)	55	10	2.28 (1.32–3.93)	26	9	1.33 (0.69–2.56)
8–17	15	9	2.50 (1.28–4.89)	7	7	1.54 (0.63–3.75)	3	5	0.86 (0.24–3.03)
<i>P</i> _{trend}			0.001			0.043			0.77
Daily intake of sleep medication									
No	90	7	1 (reference)	71	8	1 (reference)	36	7	1 (reference)
Yes	16	17	1.49 (0.87–2.56)	12	21	1.56 (0.84–2.92)	7	25	2.10 (0.91–4.85)

^aThe total number of Parkinson's Disease hospitalizations with no lag-time was 108, but because of missing values, the number of cases does not add up to the totals.

^bThe total number of Parkinson's Disease hospitalizations after a 5 yr lag-time was 84, but because of missing values, the number of cases does not add up to the totals.

^cThe total number of Parkinson's Disease hospitalizations after a 10 yr lag-time was 44, but because of missing values, the number of cases does not add up to the totals.

^dAdjusted for age, gender, and educational attainment.

Appendix 1

The included Vital Exhaustion items^a

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- Do you often feel tired?
 - Do you feel altogether weak?
 - Do you feel you have not accomplished much recently?
 - Do you, at the moment, feel that you do not have what it takes?
 - Do you think you have come to a dead end?
 - Do you lately feel listless?
 - Do you have feelings of hopelessness recently?
 - Do you lately have difficulty concentrating?
 - Do little things irritate you more than they used to?
 - Do you feel that you want to give up?
 - Do you feel fine (no)?
 - Do you sometimes feel that your body is like a battery running out?
 - Do you sometimes wish you were dead?
 - Do you sometimes have difficulty coping?
 - Do you feel dejected?
 - Do you sometimes just feel like crying?
 - Do you ever wake up with a feeling of exhaustion?
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^aFrom: Appels A, Hoppener P, Mulder P. A questionnaire to assess premonitory symptoms of myocardial infarction. *Int J Cardiol* 1987 Oct;17(1): 15–24.