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Major life events and risk of Parkinson's disease

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Abstract

Background—Major life events such as divorce, death of a spouse or a child, or long-term unemployment are stressful to most people and animal models have suggested a link between stress and onset of Parkinsonian symptoms. In a large case-control study based on nationwide registries, we aim to address whether major life events are risk factors for Parkinson's disease.

Methods—Between 1986–2006, we identified 13,695 patients with a primary diagnosis of Parkinson's disease in the Danish National Hospital Register. Each case was frequency matched by age and gender to five population controls. Information on major life events prior to onset of Parkinson's disease was ascertained from national registries.

Results—Among men, number of life events was associated with risk of Parkinson's disease in an inverse dose-response manner ($P < 0.0001$). Compared to no events, three or more events were associated with a 42% lower risk of Parkinson's disease ($OR = 0.58$; 95 % CI: 0.34–0.99). Life events were not associated with Parkinson's disease in women. In contrast, a higher risk of Parkinson's disease was observed among women who had never been married (1.16; 1.04–1.29) and among men (1.47; 1.18–1.82) and women (1.30; 1.05–1.61) who have never been employees.

Conclusions—Major life events were not associated with increased risk of Parkinson's disease. The lower risk of Parkinson's disease among men who had experienced life events was unexpected but might suggest a general 'risk avoidance behavior' in Parkinson's patients.

Keywords

Life change events; Parkinson disease; Psychological stress

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Authors roles

Naja Hulvej Rod contributed to the conception and design of the study, the analysis and interpretation of data, and the drafting of the article. Beate Ritz and Eva Schernhammer contributed to the conception and design of the study and to critically revise the article. Johnni Hansen contributed to the design of the study, the acquisition of data, and to critically revise the article. Naja Hulvej Rod takes responsibility for the integrity of the data and the accuracy of the data analysis.

INTRODUCTION

Parkinson's disease is a movement disorder characterized by bradykinesia, resting tremor, stiffness, postural instability and a broad spectrum of non-motor features such as sleep problems and autonomous nervous system dysfunction, depression and dementia.^{1,2} Surprisingly little is known about the etiologic factors contributing to Parkinson's disease even though it is one of the most common neurodegenerative disorders in the elderly population and it represents a considerable personal and societal burden in the form of loss of quality of life and high health and nursing care costs. The human body responds to stress by activating the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis, resulting in increases in the release of catecholamines and glucocorticoids. Stress can also increase the secretion of dopamine and glutamate.³ This is critical for the brain's adaptive response to stress. However, both neurotransmitters have the ability to be neurotoxic and could potentially play a role in the loss of dopaminergic neurons underlying Parkinson's disease.⁴ Chronic stress and elevated corticosterone levels have been found to exaggerate functional deficits and accelerate loss of dopamine-producing neurons in a rat model of Parkinson's disease.⁵ Based on these observations, stress may also be hypothesized to increase the risk of human Parkinson's disease, but the relation between both chronic and acute stress and Parkinson's disease remains to be studied in human populations. One exception is a study of Parkinson's disease mortality in British men who had been prisoners of war in the Far East and, thus, been exposed to intense and chronic psychological stress in addition to overall extreme deprivation and potential neurotoxic exposures.⁶ These prisoners did not exhibit higher deaths rates from Parkinson's disease than the general population, however, the comparison of an extreme survivor population to men in the general population may not be appropriate.

The objective of the present study is to evaluate whether several types of major life events (death of a spouse, divorce, death of a child, and long-term unemployment) in a regular population are potential risk factors for Parkinson's disease. For this purpose, we conducted a large record-linkage study based on nationwide registries in Denmark. To our knowledge, this is the first population-based study to address the etiological role of major and common life events in Parkinson's disease.

METHODS

Study population

Cases of Parkinson's disease were identified from the Danish Hospital Register, which was instituted on 1 January 1977. The Register contains individual information on all admissions for medical conditions other than psychiatric diseases to hospitals in Denmark.⁷ For each patient the information is computerized and kept even after the patients have died, including codes for hospital department, dates of admission and discharge, diagnosis (ICD-8 until 1993 and ICD-10 afterwards), and a unique 10-digit personal identification number. The latter includes information on date of birth, sex and a control digit, and it permits exact linkage between information from administrative and research registries in Denmark. Information on outpatient visits, including visits to emergency rooms, was added to the Register in 1995. A total of 13,734 patients were identified with a first hospitalization of Parkinson's disease (ICD-8 code 342, and ICD-10 code G20) during the period 1986–2006. We only included Parkinson's disease cases recorded after 1986 in the analyses, because our data indicated that cases from 1986 and onward were more likely incident cases.⁸ After the exclusion of patients who had emigrated from Denmark (n=9) and patients who were younger than 35 years at the time of hospitalization (n=56), since Parkinson's disease is unlikely below this age, we were left with a case-group of 13,695 patients (7423 men and 6272 women). We chose the earliest admission or outpatient visit with a diagnosis of

Parkinson's disease as the index date representing the first report of Parkinson's disease to the Hospital Register. For each Parkinson's disease patient five control subjects were chosen at random from the Danish Central Population Register from among all inhabitants of the same sex and year of birth who were alive, living in Denmark and free of hospitalization with Parkinson's disease at this index date of their respective case (density sampling). Even though we aimed to recruit five control subjects per case, 26 cases were matched to either two, three or four control subjects, yielding a total of 68,445 controls

Register information on life events

Cases and controls were re-linked to various registers in order to obtain information on major life events that occurred prior to the index date. The Danish Central Person Register was instituted on April 1, 1968 and the register includes all residents being alive at that date and all persons born thereafter. We used this register to ascertain information on death of a spouse, divorce, and death of a child occurring after this date. The registry only includes valid informations on children for persons born after 1930; the analysis for the event 'deaths of a child' will therefore be restricted to persons born after this date. Information on job titles for cases and controls was also derived from the Danish Central Person Registry and coded according to five socioeconomic categories: I (executives and/or academics); II (middle managers and/or having more than 3–4 years of further education); III (other white collar workers); IV (skilled blue collar workers); V (semi- or unskilled blue collar workers). The Pension Database was instituted in 1964 and membership in a pension plan is compulsory for all employees and wage-earners with at least 8 hours of employment a week; this data includes information about all employments on a company level, including dates of start and end of each employment. Information is kept in the registry even when a person has retired, died or emigrated. We used this register to obtain information on long-term (> 1 year) unemployment after 1964 defined as periods of at least one year duration during which a person was not a member of the Pension Fund given that this person had been a member both before and afterwards. We only included persons born after 1930 in the analysis of unemployment to guarantee that we have information on employments for most of their working life. We also excluded all life events five years prior to the index date in order to prevent reverse causality.

Statistical methods

We evaluated the associations between number and type of major life event and Parkinson's disease using unconditional logistic regression models. Multivariate analyses were adjusted for age, sex, and baseline morbidity. We constructed the Charlson comorbidity score, a weighted index of 19 medical conditions, with a lag-time of five years prior to index date as an indicator of baseline morbidity.⁹ This score was based on information from the Danish Hospital Register. In secondary analyses, we stratified on sex, early (< 60 yrs) versus late onset of Parkinson's disease, and according to timing of the major life events (5–20 years or >20 years prior to index date). Seventeen percent of the population lacked information on socio-economic status and we evaluated the change in estimates after adjustment for socio-economic status in a reduced study population with complete information for this variable. We also evaluated the association between number of life events and risk of Parkinson's disease after excluding those who had never been married, had no children and had never been employed. Finally, we evaluated the relation between life events and Parkinson's disease in a reduced population of those born after 1930 in order to ensure complete register information for the majority of their adult lives.

RESULTS

Baseline characteristic

More men than women developed Parkinson's disease (Table 1). The average age at first known hospitalization with Parkinson's disease was 73 years for men and 74 years for women, and the majority of the patients were reported between ages 65 and 85. More than three-fourths of the patients were born before 1930. Slightly more patients than controls had high socio-economic status while there were no differences in the proportions outside the labour market or with missing informations on socio-economic status. About 80 percent of both cases and controls had no baseline disease, defined as no hospitalization with conditions included in the Charlson comorbidity score between 1977 and five year prior to index/diagnosis date. Forty-eight percent of patients and 51 percent of controls had experienced one or more major life events. Slightly more controls than patients had experienced death of a spouse and long-term unemployment, while there were no differences in the proportions of patients and controls who had experienced divorce or death of a child. Among those who had experienced one or more major life events, unemployment was the most frequent event in men and widowhood the most frequent event in women; these major life events happened on average 15–25 years prior to the index date (data not shown).

Major life events and Parkinson's disease

The larger the number of major life events experienced, the lower was the risk of Parkinson's disease among men (inverse dose-response, p-value for trend: <0.0001) (Table 2). The odds ratio for men who had experienced three or more major life events was 0.58 (95% CI: 0.34–0.99) for developing Parkinson's disease when compared to men who had not experienced any major life events. However, there was no association between number of life events and Parkinson's disease in women. When addressed as individual events neither divorce nor death of a child or long-term unemployment were associated with increased risk of or protection against Parkinson's disease in men or women. Compared to married men, men who had lost a wife appeared to be at lower risk of developing Parkinson's disease (OR=0.85; 95 % CI: 0.79–0.93). While being widowed was not associated with Parkinson's disease risk in women, a higher risk of Parkinson's disease was observed among women who had never been married (OR=1.16; 95 % CI: 1.04–1.29) as well as among both men (OR=1.47; 95 % CI: 1.18–1.82) and women (OR=1.30; 95 % CI: 1.05–1.61) who have never been employed in the period from 1964 to the index date.

Subgroup analyses

Ten percent of the male patients and seven percent of the female patients were hospitalized with Parkinson's disease before the age of 60. The inverse association between major life events and Parkinson's disease risk in men was similar when we stratified by early and late onset of Parkinson's disease, although the risk estimates were unstable for early onset Parkinson's disease due to the small number of cases (data not shown). In women, there was no clear association between number of major life events and risk of Parkinson's disease independently of age at onset. The major life events happened on average 15–25 years prior to index date. When considering timing of the event, the Parkinson's disease risk associated with different types of life event were in general similar whether they had happened 5–20 years or more than 20 years prior to index date (Table 3). The only difference was that women who had been divorced more than 20 years prior to index date had a slightly higher risk of Parkinson's disease (OR=1.12; 95 % CI: 1.01–1.25). Further adjustment for socio-economic status in the subgroup of the population with information for this variable did not markedly change the risk estimates (data not shown). Also, the inverse association between number of stressful life events and Parkinson's disease in men remained stable in a

sensitivity analysis when we excluded men who had never been married, had no children or had never been employed as well as in a sensitivity analysis where we only included those born after 1930.

DISCUSSION

In this population-based case-control study of more than 13,000 patients with Parkinson's disease, we observed a lower risk of Parkinson's disease among men who had experienced one or more major life events compared to men who had not experienced any events. There was no support for any relation between major life events and Parkinson's disease in women. In contrast, women who had never been married and both men and women who have never been employed had a slightly higher risk of Parkinson's disease.

The lower risk of Parkinson's disease among men who had experienced major life events was unexpected and might, in part, be due to certain personality characteristics of individuals who will develop Parkinson's disease later in life. Parkinson's disease patients are often described as having premorbid personalities that make them seem more cautious, rigid, stoic, serious, and nonimpulsive.^{10–12} These personality traits might be a possible explanation to why Parkinson's disease patients experienced less major life events than controls, for example, they may choose a job with low risk of unemployment and may be more reluctant to seek a divorce. A more conservative personality type may also explain the higher risk of Parkinson's disease observed among women who had never been married and among men and women outside the labour market. In support of this theory, the event 'death of a child', a major life event that cannot be attributed to personality characteristics, was not associated with a lower Parkinson's disease risk. A lower risk of Parkinson's disease among widowed men on the other hand is also unlikely to be explained by personality, but since women play an important role in men's contact with the health care system, widowed men may be less likely to get diagnosed with Parkinson's disease.

An alternative explanation for our unexpected finding of a lower risk of Parkinson's disease in men with multiple events could be an association between life events and higher smoking prevalence. Facing a major life event, smoking may be used as a stress control device to reduce the negative effects of loss.¹² In a recent pooled analysis, smoking was found to protect against Parkinson's disease in a dose-response manner.¹³ Thus, a higher smoking prevalence among men who have experienced major life events may be a possible explanation for the observed lower risk of Parkinson's disease. The prevalence of smoking is lower among older women in Denmark, and may partly explain the lack of an association seen in women.

Denmark went through a financial crisis starting in the early 1970s and ending in the mid 1990s with unemployment rates as high as 13%; this may explain the high proportion of long-term unemployment observed in this population. About eight percent of the study population had not been registered as employees since the initiation of the Pension Database in 1964; the major reasons are likely to be retirement, unemployment, being a house wives, chronic illness, or being self-employed (especially farmers, tradesmen, and small shopkeepers). Exposure to environmental toxins in some of the professions with high proportions of self-employed (e.g. farmers) may partly explain the higher risk of Parkinson's disease observed in this group.

The strengths of our study include identification of patients from a national hospital register, unbiased selection of controls from a population registry, ascertainment of information on life events independently of case status, and the large size of the study. The limitations of the study include lack of information on diagnostic details for patients with Parkinson's

disease, lack of information on the date of first symptoms of Parkinson's disease, and in particular that the information on major life events was only available from the time of first initiation of the registries we employed. Because we lack information about life events occurring prior to the initiation of the registries some individuals who have e.g. been divorced before the registries were initiated will be classified as not having been divorced. This may partly explain the lack of an association between each of the major life events and risk of Parkinson's disease, but it is unlikely to explain the inverse association between number of life events and Parkinson's disease observed in men assuming that this type of misclassification occurs for cases and controls to a similar degree.

We were only able to include patients who were hospitalized with Parkinson's disease in the case group. Since Parkinson's disease is mainly an outpatient disease, especially in the early phases, this may be of concern. Say that people who have experienced major life events such as divorce or long-term unemployment are less likely to become hospitalized if they develop Parkinson's disease then such differential misclassification could explain some of the observed inverse association between life events and Parkinson's disease. A community based study of the relation between major life events and incidence of Parkinson's disease would be preferable, but probably not feasible due to the rarity of both the exposure and the disease.

It is important to distinguish between stressors and stress. A stressor is an external stimulus that can potentially cause stress depending on the individual's perception of the threat the stressor poses. We used information on major life events that are expected to create stress in most individuals regardless of personality, coping styles and social support. However, for some individuals the event itself may reduce stress, such as for example a divorce from an abusive spouse or the expected death of a spouse who suffered from long-time illness. Also, major life events may be conceptually different from the more chronic low-key stress of everyday life and the bodily response is most likely different,¹⁴ which may partly explain why our results do not correspond to those observed in animal models of chronic stress. Each of our life event measures may only account for a fraction of an individual's stress burden. Also, some studies have suggested that most people can successfully handle a stressful life event, but that problems arise when stressors accumulate.¹⁵ Thus, an 'ideal' study that measures the full stress burden for each individual comprehensively over extended periods during life may have shown different results.

The present results which support no causal role of some serious but common life events in the etiology of Parkinson's disease might help prevent attribution and self-blaming in Parkinson's disease patients who are pondering what events and life circumstances may have caused or contributed to their disease.

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REFERENCES

1. Burch D, Sheerin F. Parkinson's disease. *Lancet*. 2005; 365:622–627. [PubMed: 15708109]
2. Pfeiffer RF. Non-motor parkinsonism. *Parkinsonism Relat Disord*. 2007; 13:S211–S220. [PubMed: 18267238]
3. Smith AD, Castro SL, Zigmond MJ. Stress-induced Parkinson's disease: a working hypothesis. *Physiol Behav*. 2002; 77:527–531. [PubMed: 12526994]
4. Metz GA. Stress as a modulator of motor system function and pathology. *Rev Neurosci*. 2007; 18:209–222. [PubMed: 18019607]
5. Smith LK, Jadavji NM, Colwell KL, Katrina PS, Metz GA. Stress accelerates neural degeneration and exaggerates motor symptoms in a rat model of Parkinson's disease. *Eur J Neurosci*. 2008; 27:2133–2146. [PubMed: 18412632]
6. Gale CR, Braidwood EA, Winter PD, Martyn CN. Mortality from Parkinson's disease and other causes in men who were prisoners of war in the Far East. *Lancet*. 1999; 354:2116–2118. [PubMed: 10609817]
7. Andersen TF, Madsen M, Jorgensen J, Mellekjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull*. 1999; 46:263–268. [PubMed: 10421985]
8. Olsen JH, Friis S, Frederiksen K, McLaughlin JK, Mellekjaer L, Moller H. Atypical cancer pattern in patients with Parkinson's disease. *Br J Cancer*. 2005; 92:201–205. [PubMed: 15583688]
9. Hall WH, Ramachandran R, Narayan S, Jani AB, Vijayakumar S. An electronic application for rapidly calculating Charlson comorbidity score. *BMC Cancer*. 2004; 4:94. [PubMed: 15610554]
10. Evans AH, Lawrence AD, Potts J, et al. Relationship between impulsive sensation seeking traits, smoking, alcohol and caffeine intake, and Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2006; 77:317–321. [PubMed: 16484638]
11. Menza M. The personality associated with Parkinson's disease. *Curr Psychiatry Rep*. 2000; 2:421–426. [PubMed: 11122991]
12. Nystedt P. Marital life course events and smoking behaviour in Sweden 1980–2000. *Soc Sci Med*. 2006; 62:1427–1442. [PubMed: 16162388]
13. Ritz B, Ascherio A, Checkoway H, et al. Pooled analysis of tobacco use and risk of Parkinson disease. *Arch Neurol*. 2007; 64:990–997. [PubMed: 17620489]
14. McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med*. 1998; 338:171–179. [PubMed: 9428819]
15. Miller, T. The assessment of stressful life events. In: Goldberger, L.; Breznitz, S., editors. *Handbook on stress. Theoretical and clinical aspects*. New York: The Free Press; 1993. p. 161-173.

Table 1

Descriptive characteristics of the 13,695 Parkinson's disease patients (1986–2006) and population controls

	Patients with Parkinson's disease (n = 13,695)	%	Population controls (n = 68,445)	%
Sex				
Men	7423	54	37,101	54
Women	6272	46	31,344	46
Age at index date, years				
35–44	138	1	682	1
45–54	473	3	2362	3
55–64	1557	11	7779	11
65–74	4402	32	22,006	32
75–84	5849	43	29,238	43
85–94	1257	9	6283	9
95–99	19	0	95	0
Year of birth				
<1900	54	0	270	0
1900–1909	1406	10	7030	10
1910–1919	4749	35	23,741	35
1920–1929	4379	32	21,887	32
1930–1939	2044	15	10,218	15
1940–1949	819	6	4089	6
1950–1959	194	1	965	1
1960–1969	50	0	245	0
Socio-economic status				
I. Executives/academics	935	7	3701	5
II. Middle managers/white collar workers with further education	868	6	4060	6
III. Other white collar workers	1675	12	8303	12
IV. Skilled blue collar workers	2508	18	12,713	19
V. Semi- or unskilled blue collar workers	2321	17	12,725	19
No employments	2357	17	11,744	17
No job title	3031	22	15,199	22
Baseline disease*				
No	11,199	82	55,731	81
Yes	2496	18	12,714	19
Number of major life events				
0	7006	52	33,716	49
1	5289	39	27,345	40
2	1352	10	7101	10
3	47	0	278	0
4	1	0	5	0
Death of a spouse				
Never married	1094	8	5027	7

	Patients with Parkinson's disease (n = 13,695)	%	Population controls (n = 68,445)	%
Married, not widowed	9757	71	48,181	70
Married, widowed	2844	21	15,237	22
Divorce				
Never married	1094	8	5027	7
Married, not divorced	11,143	81	56,145	82
Married, divorced	1458	11	7273	11
Death of a child**				
No children	514	17	2302	15
Children, no deaths	2499	80	12,771	82
Children, death(s)	94	3	444	3
Long-term unemployment**				
Not in the labour market	278	9	1026	7
No unemployment	1252	40	6432	41
Unemployment(s) for >1 year	1577	51	8059	52

* Baseline disease is based on the Charlson comorbidity score, a weighted index of 19 medical conditions.

** Among those born after 1930 (men: 1824 cases and 9112 controls; women: 1283 cases and 6405 controls)

Table 2

Adjusted risk of Parkinson's disease by type of major life event

	Men			Women		
	No. Cases / Controls (7423 / 37,101)	Age-adjusted OR (95 % CI)	Multiple* -adjusted OR (95 % CI)	No. Cases/ Controls (6272 / 31,344)	Age-adjusted OR (95 % CI)	Multiple* -adjusted OR (95 % CI)
Number of major life events						
0	4552 / 22,037	1 (reference)	1 (reference)	2454 / 11,679	1 (reference)	1 (reference)
1	2361 / 12,153	0.94 (0.89–0.99)	0.94 (0.89–0.99)	2928 / 15,192	0.92 (0.86–0.97)	0.89 (0.84–0.95)
2	495 / 2786	0.86 (0.77–0.95)	0.86 (0.77–0.95)	857 / 4315	0.95 (0.87–1.03)	0.92 (0.85–1.00)
3+	15 / 125	0.58 (0.34–0.99)	0.58 (0.34–0.99)	33 / 158	0.99 (0.68–1.45)	1.07 (0.80–1.43)
P-value for trend		<0.0001	<0.0001		0.04	0.05
Type of major life event						
Death of a spouse						
Never married	586 / 2860	1.01 (0.92–1.11)	0.99 (0.90–1.10)	508 / 2167	1.16 (1.05–1.29)	1.16 (1.04–1.29)
Married, not widowed	6077 / 29,907	1 (reference)	1 (reference)	3680 / 18,274	1 (reference)	1 (reference)
Married, widowed	760 / 4334	0.86 (0.79–0.93)	0.85 (0.79–0.93)	2084 / 10,903	0.94 (0.89–1.01)	0.95 (0.89–1.02)
Divorce						
Never married	586 / 2860	1.02 (0.92–1.12)	0.99 (0.90–1.10)	508 / 2167	1.20 (1.08–1.32)	1.16 (1.04–1.29)
Married, not divorced	6077 / 30,283	1 (reference)	1 (reference)	5066 / 25,862	1 (reference)	1 (reference)
Married, divorced	760 / 3958	0.96 (0.88–1.04)	0.96 (0.88–1.04)	698 / 3315	1.08 (0.98–1.17)	1.07 (0.97–1.17)
Death of a child**						
No children	322 / 1409	1.17 (1.03–1.34)	1.09 (0.92–1.28)	192 / 893	1.09 (0.92–1.29)	1.07 (0.89–1.29)
Children, no deaths	1451 / 7451	1 (reference)	1 (reference)	1048 / 5320	1 (reference)	1 (reference)
Children, death(s)	51 / 252	1.04 (0.76–1.41)	1.04 (0.77–1.42)	43 / 192	1.14 (0.81–1.59)	1.15 (0.82–1.61)
Long-term unemployment**						
Not in the labour market	126 / 431	1.52 (1.23–1.88)	1.47 (1.18–1.82)	152 / 595	1.29 (1.04–1.59)	1.30 (1.05–1.61)
No unemployment	887 / 4602	1 (reference)	1 (reference)	365 / 1830	1 (reference)	1 (reference)
Unemployment(s) for >1 year	811 / 4079	1.03 (0.93–1.14)	1.02 (0.92–1.14)	766 / 3980	0.96 (0.84–1.10)	0.96 (0.84–1.11)

* Adjusted for age, baseline disease (Charlson comorbidity score) and other types of major life events

** Among those born after 1930 (men: 1824 cases and 9112 controls; women: 1283 cases and 6405 controls)

Table 3

Adjusted* OR and 95 % CI of Parkinson's disease by type of major life event according to timing of event

	5–20 years prior to index date		> 20 years prior to index date	
	Men	Women	Men	Women
Death of a spouse				
Never married	1.00 (0.90–1.10)	1.18 (1.06–1.31)	1.01 (0.91–1.11)	1.17 (1.06–1.31)
Married, not widowed	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Married, widowed	0.87 (0.80–0.96)	0.98 (0.92–1.05)	0.83 (0.69–0.99)	0.93 (0.84–1.03)
Divorce				
Never married	0.99 (0.90–1.09)	1.14 (1.03–1.27)	1.00 (0.90–1.10)	1.16 (1.04–1.30)
Married, not divorced	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Married, divorced	0.90 (0.80–1.01)	0.97 (0.84–1.11)	1.01 (0.91–1.13)	1.12 (1.01–1.25)
Death of a child**				
No children	1.09 (0.92–1.29)	1.07 (0.89–1.29)	1.09 (0.92–1.28)	1.06 (0.88–1.28)
Children, no deaths	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Children, death(s)	1.17 (0.80–1.73)	1.23 (0.81–1.89)	0.88 (0.54–1.44)	1.02 (0.59–1.75)
Long-term unemployment**				
Not in the labour market	1.47 (1.18–1.80)	1.36 (1.12–1.65)	1.46 (1.18–1.80)	1.26 (1.03–1.55)
No unemployment	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Unemployment(s) for >1 year	1.01 (0.88–1.16)	1.13 (0.96–1.32)	1.02 (0.90–1.14)	0.90 (0.79–1.02)

* Adjusted for age, baseline disease (Charlson comorbidity score) and other types of major life events

** Among those born after 1930 (men: 1824 cases and 9112 controls; women: 1283 cases and 6405 controls)