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Risk of amyotrophic lateral sclerosis and other motor neuron disease among men with benign prostatic hyperplasia: a population-based cohort study

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ABSTRACT

Objectives Amyotrophic lateral sclerosis (ALS) is a rapidly progressive neurodegenerative disorder. Sleep disturbance may interfere with clearance of abnormal proteins that aggregate in neurodegenerative diseases. The objective of this study was to examine the association between benign prostatic hyperplasia (BPH), a common disorder causing nocturia and sleep disturbance, and risk of ALS and other motor neuron disease (MND). We hypothesised that men with BPH, in comparison to men in the general population, would be at increased risk.

Design This is a nationwide, population-based cohort study.

Setting This study was conducted among the population of Denmark.

Participants We used linked Danish medical databases to identify all men with a first-time diagnosis of BPH between 1 January 1980 and 30 November 2013 and no prior diagnosis of MND (BPH cohort, n=223 131) and an age-matched general population comparison cohort of men without BPH or MND (n=1 115 642).

Primary outcome measure The primary outcome is diagnosis of MND after the BPH diagnosis (index) date, with follow-up until MND diagnosis, emigration, death or 30 November 2013.

Results We used Cox regression to compute adjusted HR, comparing men with and without BPH. After 34 years of follow-up, there were 227 cases of MND in the BPH cohort (incidence rate 0.13/1000 person-years) and 1094 MND cases in the comparison cohort (0.12/1000 person-years; HR 1.05, 95% CI 0.90 to 1.22). Risk did not vary by follow-up time.

Conclusions BPH is not associated with an increased risk of ALS and other MND. Future studies should examine the relation between other disorders that disrupt sleep and MND risk in men and women.

Strengths and limitations of this study

- This is the first study to examine the relation between a disorder with the potential to disrupt sleep on a chronic basis (benign prostatic hyperplasia (BPH)) and motor neuron disease (MND).
- The exposure (BPH) and outcome (MND) were determined from nationwide, population-based, linked medical registries in a country with national health service and universal access to care.
- The long follow-up and large sample size allow longer exposure, reduce concerns of reverse causality and increase precision of the results.
- The validity of the diagnosis of BPH in this population is not known; some men diagnosed with BPH may not have sleep disruption due to nocturia; some men in the general population comparison cohort may have had undiagnosed BPH; and some men diagnosed with MND may have had a different disorder.
- Our analyses were adjusted for factors associated with both BPH and MND, but results could have been affected by unrecognised confounding.

INTRODUCTION

Motor neuron disease (MND) includes amyotrophic lateral sclerosis (ALS) and closely related disorders such as progressive bulbar palsy. These are progressive neurodegenerative diseases that affect motor neurons in the spinal cord, brainstem and cerebrum.[1] Roughly half of patients with ALS die within 2.5 years of symptoms onset, mainly due to respiratory failure, and this illness carries a high economic burden.[2 3] Most cases are sporadic, with onset during middle or old age, and men are affected twice as often as women.[1] Apart from age and sex, there are few known risk factors.[2]

Similar to several other neurodegenerative diseases, MND is characterised by the accumulation of protein aggregates within vulnerable neurons.[1] The glymphatic system of the brain is a major pathway for the removal of toxic substances within the cerebrospinal and interstitial fluids. Its function is similar to that of the lymphatic system in the rest of the body, and glymphatic flow is increased during deep sleep.[4 5] Sleep disruption is linked, for example, to Alzheimer's disease, possibly through reduced clearance of amyloid-beta,[5 6]

a protein that accumulates in the brains of patients with Alzheimer's disease. Sleep disruption may also be a risk factor for MND,[4] but this association has not been previously investigated.

Benign prostatic hyperplasia (BPH) with lower urinary tract symptoms is a common, age-related disorder in men, with a lifetime prevalence of about 26%.[7] Nocturia, defined as two or more voids per night, causes sleep deprivation, sleep fragmentation and insomnia.[8] Approximately 70% of men with BPH suffer from nocturia.[9] In this study, we sought to evaluate whether there was an association between BPH and MND. Since BPH is a common, treatable condition that often interrupts sleep, an increased risk of MND in this population would support a pathogenetic role of sleep disruption in this disorder and could have public health implications.

We used Danish population-based medical and administrative registries with nationwide coverage and long-term follow-up to examine the association of BPH with ALS and other MND. We hypothesised that BPH would be associated with increased risk of these disorders.

METHODS

Setting and design

Denmark has a tax-funded healthcare system, with universal access to general practice and hospital-based care.[10] Residents are assigned a unique personal identification number in the Danish Civil Registration System at birth or immigration. This number permits accurate patient-level linkage of data from all Danish registries.[10]

BPH cohort

We used the Danish National Patient Registry (DNPR) to identify a cohort of all men with a first-time diagnosis of BPH, seen as inpatients or outpatients in Danish hospitals between 1 January 1980 and 30 November 2013 (the BPH cohort). The DNPR has recorded all inpatient diagnoses and procedures since 1977 and all outpatient clinic visits and emergency room visits since 1995.[11] Diagnoses in the DNPR were coded according to the *International Classification of Diseases*, 8th revision (ICD-8) from 1977 to 1993 and 10th revision (ICD-10) since 1994.[11] The index date was the date of BPH diagnosis.

General population comparison cohort

Using the Danish Civil Registration System, we assembled a matched general population comparison cohort of men who were alive and without a diagnosis of BPH or ALS or other MND at the index date of the corresponding patient with BPH. From this pool, we randomly sampled, with replacement, up to five men for each man with BPH, matching on year of birth (the general population comparison cohort).

Outcomes

The outcome of interest was incident MND, based on first-time inpatient diagnoses (from 1980 onwards) or outpatient hospital diagnoses (from 1995 onwards) in the DNPR.

Covariables

Components of the metabolic syndrome are associated with risks of both BPH[12 13] and MND[14 15] and might therefore act as confounders or as their markers. We used inpatient and outpatient DNPR records to identify diagnoses of diabetes, obesity, hypertension and hyperlipidaemia before the index date among the members of both cohorts. Diagnostic codes used in this study are given in table 1.

Statistical analyses

We characterised the BPH cohort and the general population comparison cohort with respect to age, index year and specified comorbidities. We followed all men from their index dates until the diagnosis of MND, emigration, death or 30 November 2013, and we calculated incidence rates of MND per 1000 person-years in each cohort. We used Cox proportional-hazards regression analysis to compute HRs and associated 95% CIs for MND, comparing men with BPH with men in the general population comparison cohort, while controlling for age and calendar time by study design. In the regression model, we adjusted for diagnoses of diabetes, obesity, hypertension and hyperlipidaemia. We constructed cumulative incidence curves, accounting for the competing risk of death.

We assessed period effects in stratified analyses according to calendar period of BPH diagnosis (before 1994, ICD-8 coding; 1994 and later, ICD-10 coding). We calculated the risk of MND during follow-up of up to 34 years and also during follow-up times of 0–2, >2–10 and >10–34 years. The proportionality-of-hazards assumption was deemed fulfilled by inspection of log-log plots in each follow-up interval and in both intervals combined.

Bias analysis

To test the robustness of the results, we conducted a bias analysis. This study was based on patients with a first-time

Table 1 *International Classification of Diseases* codes used in the study

Diagnosis	ICD-8 codes	ICD-10 codes
Benign prostatic hyperplasia	600	N40.9
Amyotrophic lateral sclerosis and other motor neuron disease	348	G12.2
Diabetes	249, 250	E10, E11
Obesity	277	E65-E68
Hypertension	400–404	I10-I15, I67.4
Hyperlipidaemia	249, 279.00	E78

ICD-8, *International Classification of Diseases*, 8th edition; ICD-10, *International Classification of Diseases*, 10th edition.

diagnosis of BPH made during an inpatient or outpatient hospital encounter. However, patients treated solely by their general practitioners are not captured in the DNPR. For this analysis, we assumed that such patients might account for 60% of the total BPH population. Also, we recognised that a few patients diagnosed with BPH in the DNPR may not have BPH. This potential misclassification of BPH status would be non-differential with respect to later MND status but could have diluted the observed association. Therefore, our bias analysis assumed a 40% sensitivity and a 90% specificity for a diagnosis of BPH in the DNPR.

All statistical analyses were performed using SAS V.9.4.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for the design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. We have no plans to disseminate results of the research to study participants or relevant patient communities.

RESULTS

BPH and MND

Between 1 January 1980 and 30 November 2013, the prevalence of BPH was 10.8% among Danish men aged 50 years and older, based on 221 978 first-time DNPR diagnoses from an at-risk cumulative population of 2 057 854 men. A total of 223 131 men (1 752 270 person-years at risk) had a first-time diagnosis of BPH, after excluding 103 men with BPH and a diagnosis of ALS or other MND before the index date (figure 1). We identified 1 115 642 (8 774 610 person-years at risk) matched men in the general population comparison cohort (figure 1). The median age was 71.6 (IQR 64.5 to 78.1) years in both cohorts. The median follow-up time was 6.4 (IQR 2.7 to 11.6) years in the BPH cohort and 6.6 (IQR 3.0 to 11.4) years in the general population comparison cohort. Table 2 shows characteristics of the men in the two cohorts.

Over a follow-up period of up to 34 years, we identified 227 cases of ALS or other MND in the BPH cohort (incidence rate 0.13 (95% CI 0.11 to 0.15) per 1000 person-years at risk) and 1094 cases of MND among the matched members of the general population cohort (incidence rate 0.12 (95% CI 0.12 to 0.13) per 1000 person-years at risk) (table 3). The median age of diagnosis for MND was 74.7 years (IQR 68.8 to 79.9 years) for men in the BPH cohort and 75.0 years (70.2 to 79.9) in the comparison cohort. The cumulative incidence of MND over 34 years is shown in figure 2. The 34-year risk of MND was 0.16% (95% CI 0.13% to 0.18%) for men in the BPH cohort and 0.16% (95% CI 0.15% to 0.17%) for men in the general population comparison cohort. The adjusted HR was 1.05 (95% CI 0.90 to 1.22). The unadjusted HR was similar to the adjusted (HR 1.04, 95% CI 0.89 to 1.21).

After 10 years of follow-up, men with BPH had a similar risk of ALS or other MND when compared with men in the general population comparison cohort (table 3). When stratified by year of BPH diagnosis, we found similar risks for men diagnosed with BPH during 1980–1993 and for men diagnosed during 1994–2013 (table 3).

Bias analysis

The bias analysis that considered misclassification of the exposure and outcome yielded an unadjusted HR of 1.10

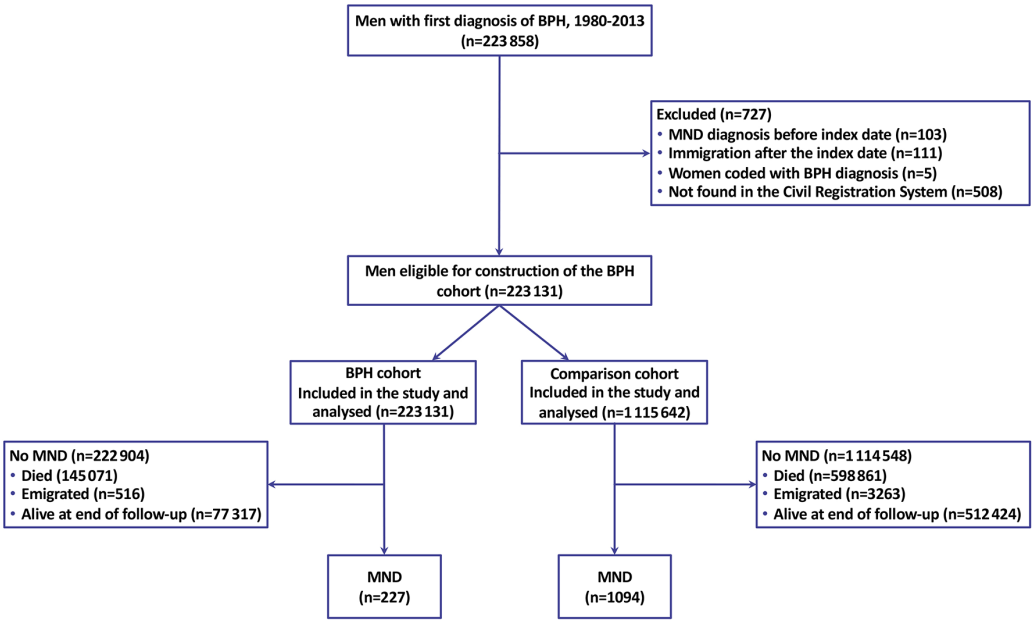

Figure 1 Flowchart for the benign prostatic hyperplasia (BPH) cohort and the general population comparison cohort. MND, motor neuron disease.

Table 2 Descriptive data for men in the benign prostatic hyperplasia cohort and the general population comparison cohort

	Benign prostatic hyperplasia cohort		General population comparison cohort	
	n	%	n	%
Number	223 131	100.0	1 115 642	100.0
Age, years				
<60	30 305	13.6	151 659	13.6
60–69	67 920	30.4	339 850	30.5
70–79	82 734	37.1	413 462	37.1
80+	42 172	18.9	210 671	18.9
Index year				
1980–1994	96 951	43.5	484 752	43.5
1995–2003	65 893	29.5	329 464	29.5
2004–2013	60 287	27.0	301 426	27.0
Diabetes				
No	210 577	94.4	1 068 017	95.7
Yes	12 554	5.6	47 625	4.3
Obesity				
No	219 348	98.3	1 102 758	98.8
Yes	3783	1.7	12 884	1.2
Hypertension				
No	201 750	90.4	1 037 374	93.0
Yes	21 381	9.6	78 268	7.0
Hyperlipidaemia				
No	216 962	97.2	1 089 501	97.7
Yes	6169	2.8	26 141	2.3

(95% CI 0.76 to 1.60), similar to the HR found in our primary analysis.

DISCUSSION

In this nationwide, population-based cohort study, we did not find an association between BPH and ALS and other MND during follow-up of up to 34 years. The association was notably absent in the follow-up period of 10 to 34 years, when prolonged nocturia and sleep disruption from BPH might be expected to have the greatest effect on disease risk. Our findings thus do not support the hypothesis that BPH increases the risk of MND. These results imply that sleep disruption during middle age and older age linked to BPH does not substantially increase the risk of this neurodegenerative disorder. This research involved inhabitants of a developed country where economic and health disparities are relatively low, but the observed association between BPH and MND should be similar in other settings.

MND is characterised by the death of motor neurons, preceded by the accumulation of protein aggregates within these cells.[1] Proteins and other wastes are removed from the central nervous system in part via the glymphatic system, primarily during sleep. The role of sleep disruption has been best studied in relation to Alzheimer's disease pathogenesis.[5 6] The glymphatic system entails the influx of cerebrospinal fluid along the Virchow-Robin periarterial spaces driven by pulsations generated by arterial smooth muscle cells, flow through the basal lamina surrounding capillaries, the rapid interchange of cerebrospinal fluid and interstitial fluid in the perivenous space, and efflux through the cervical lymph system.[4 5] Our study was designed to investigate whether BPH—a common medical condition with the propensity to disrupt sleep on a chronic basis—is associated with the risk of MND. Our null results fail to support this association.

Strengths and limitations of the study

Our study has important strengths. We derived risk estimates from a population-based cohort study in a setting with a national health service and universal access to healthcare, which largely removed referral and diagnostic bias. Other strengths of this research include the large sample size, longitudinal design, prospective and routine accumulation of the data, and complete follow-up.

There are also limitations. Although most men with BPH suffer from nocturia,[9] which in turn leads to sleep deprivation and sleep fragmentation,[8] the correspondence between BPH and sleep disturbance is imperfect. Also, MND registration by hospital codes may be subject to misclassification. A Danish validation study estimated

Table 3 Incidence rates, HRs and associated 95% CIs for ALS and other MND, comparing men in the BPH cohort to men in a matched general population cohort

	ALS and other MND, N	Incidence rate per 1000 person-years (95% CI)	HR (95% CI)	
			Unadjusted	Adjusted*
Follow-up period				
0–34 years				
Comparison cohort	1094†	0.12 (0.12 to 0.13)	Reference	Reference
BPH cohort	227†	0.13 (0.11 to 0.15)	1.04 (0.89 to 1.21)	1.05 (0.90 to 1.22)
0–2 years				
Comparison cohort	246	0.12 (0.11 to 0.14)	Reference	Reference
BPH cohort	57	0.14 (0.11 to 0.18)	1.18 (0.89 to 1.58)	1.20 (0.90 to 1.61)
>2–10 years				
Comparison cohort	570	0.12 (0.11 to 0.13)	Reference	Reference
BPH cohort	117	0.12 (0.10 to 0.15)	1.07 (0.87 to 1.32)	1.08 (0.88 to 1.33)
>10–34 years				
Comparison cohort	278	0.15 (0.13 to 0.17)	Reference	Reference
BPH cohort	53	0.13 (0.10 to 0.17)	0.82 (0.58 to 1.15)	0.82 (0.58 to 1.16)
Year of BPH diagnosis				
1980–1993				
Comparison cohort	479	0.11 (0.10 to 0.12)	Reference	Reference
BPH cohort	103	0.12 (0.10 to 0.15)	1.07 (0.85 to 1.35)	1.06 (0.84 to 1.34)
1994–2013				
Comparison cohort	615	0.13 (0.12 to 0.15)	Reference	Reference
BPH cohort	124	0.14 (0.11 to 0.16)	1.02 (0.83 to 1.25)	1.03 (0.84 to 1.26)

*Adjusted for diagnoses of diabetes mellitus, obesity, hypertension and hyperlipidaemia.
†For ALS and other MND, the most common ICD-8 diagnosis was ALS (156 in the comparison cohort, 42 in the BPH cohort), and the most common ICD-10 diagnosis was MND (763 in the comparison cohort, 149 in the BPH cohort). Other ICD-8 diagnoses in these cohorts were other and unspecified MND (37), progressive bulbar paralysis (20), progressive spinal paralysis (10) and other progressive muscular atrophy (2). Other ICD-10 diagnoses were ALS (129), progressive bulbar paralysis (8), progressive spinal paralysis (2), Duchenne-Aran muscular atrophy (2) and progressive spinal muscular atrophy (1).
ALS, amyotrophic lateral sclerosis; BPH, benign prostatic hyperplasia; ICD-8, *International Classification of Diseases*, 8th edition; ICD-10, *International Classification of Diseases*, 10th edition; MND, motor neuron disease.

that 88% of patients coded with MND have ALS (68%) or another MND (20%), 8% have Parkinson's disease and 4% have no final diagnosis.[16] Whereas the validity of a BPH diagnosis in our population is unknown, we would expect some men in the general population comparison cohort to have undiagnosed BPH. Outpatient diagnoses by general practitioners are not captured in the DNPR, although lower urinary tract symptoms would presumably be less severe for men diagnosed solely by general practitioners and nocturia less common. Among Danish men aged 50 years and older, the 10.8% prevalence of BPH is similar to that reported in the Third National Health and Nutrition Examination Survey[17] but lower than that in some other representative cohorts.[18] However, our bias analysis showed robust results after correction for potential exposure misclassification. Nonetheless, misclassification of BPH or MND could dilute our HR estimates, and we could have failed to detect a modest association, if present.

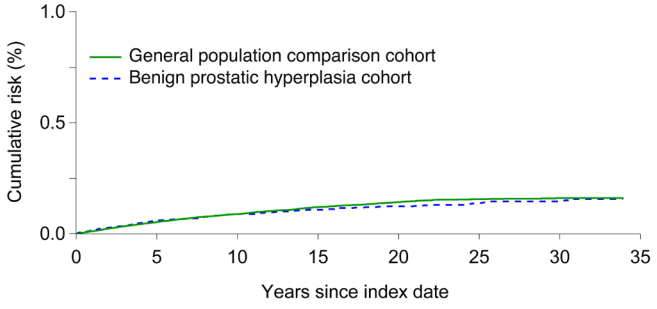

Figure 2 Cumulative incidence of amyotrophic lateral sclerosis and other motor neuron disease in the benign prostatic hyperplasia cohort and in the general population comparison cohort.

MND is itself associated with poor sleep quality.[19] Although sleep disturbance caused by MND might in some instances precede a diagnosis of MND and perhaps increase the likelihood of BPH diagnosis, MND is not known to have a long presymptomatic phase, and risk estimates were not elevated during follow-up intervals

of >2–10 or >10–34 years. We adjusted our estimates for individual diagnoses related to the metabolic syndrome, which may be associated with both BPH and MND. Physical activity is a well-known but controversial risk factor for ALS.[2 20] We were unable to adjust for this directly, but we adjusted for obesity, which in turn is linked to physical activity. We are unaware of other shared risk factors, but as in any observational study, our results could be affected by unrecognised confounding.

Comparison with other studies

We are unaware of other studies that have examined the relation between sleep disruption and ALS and other MND.

Implications and conclusions

We found no evidence of an increased risk of ALS and other MND among men with diagnosed BPH compared with men from the general population. This finding implies that sleep disruptions resulting from nocturnal awakenings in middle-age and older men with BPH are not substantially associated with risk of MND. However, several factors could have biased associations towards the null. The validity of a BPH diagnosis in the Danish population is not known; some men in the general population comparison cohort may have had undiagnosed BPH; and some men diagnosed with MND may have had some other disorder. Estimates from our bias analysis, however, showed results similar to those of our primary analysis. Future studies should examine other causes of sleep disruption in relation to MND risk in both men and women.

Contributors TTS and VWH conceived and designed the study. EH-P performed the statistical analyses. TTS prepared the first draft of the article. TTS, EH-P, MN, VE and VWH contributed substantially to reviewing and interpreting data and to critically appraising the draft article for content, accuracy and integrity. All authors approved the final submitted version. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study was approved by the Danish Data Protection Agency (record no. 1-16-02-1-08).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data may be obtained from a third party and are not publicly available.

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