BRAIN COMMUNICATIONS

Creatinine and C-reactive protein in amyotrophic lateral sclerosis, multiple sclerosis and Parkinson's disease

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Serum creatinine and C-reactive protein have been proposed as potential biomarkers for neurodegenerative diseases, including amyotrophic lateral sclerosis, multiple sclerosis and Parkinson's disease. However, longitudinal studies investigating temporal patterns of these biomarkers, including the phase before diagnosis, are rare. We performed a case–control study including all newly diagnosed patients with amyotrophic lateral sclerosis ($N = 525$), multiple sclerosis ($N = 1815$) or Parkinson's disease ($N = 3797$) during 2006–2013 in Stockholm, Sweden, who participated in the Stockholm CREAtinine Measurements (SCREAM) project. For each case, we randomly selected up to five controls from SCREAM that were individually matched to the case by age, sex and county of residence ($N = 2625$ for amyotrophic lateral sclerosis, $N = 9063$ for multiple sclerosis and 18 960 for Parkinson's disease). We collected for both the cases and the controls testing results of serum creatinine and C-reactive protein performed by healthcare providers in Stockholm during the study period. Median levels of creatinine and C-reactive protein were visualized using locally weighted smoothing curves among cases and controls. A linear mixed model was also applied to explore temporal changes within an individual. Compared to controls, patients with amyotrophic lateral sclerosis had lower levels of creatinine from 2 years before diagnosis onwards. In contrast, patients with amyotrophic lateral sclerosis had lower levels of C-reactive protein before diagnosis but higher levels after diagnosis, compared to controls. Focusing the 2 years before to 2 years after diagnosis, patients with amyotrophic lateral sclerosis displayed statistically significantly decreasing level of creatinine from 1 year before diagnosis until 2 years after diagnosis, whereas increasing level of C-reactive protein from diagnosis until 2 years after diagnosis. There were no similar patterns noted among patients with multiple sclerosis or Parkinson's disease, or the controls of the three patient groups. Patients with amyotrophic lateral sclerosis display distinct temporal patterns of creatinine and C-reactive protein before and after diagnosis, compared to amyotrophic lateral sclerosis-free controls or patients with multiple sclerosis and Parkinson's disease.

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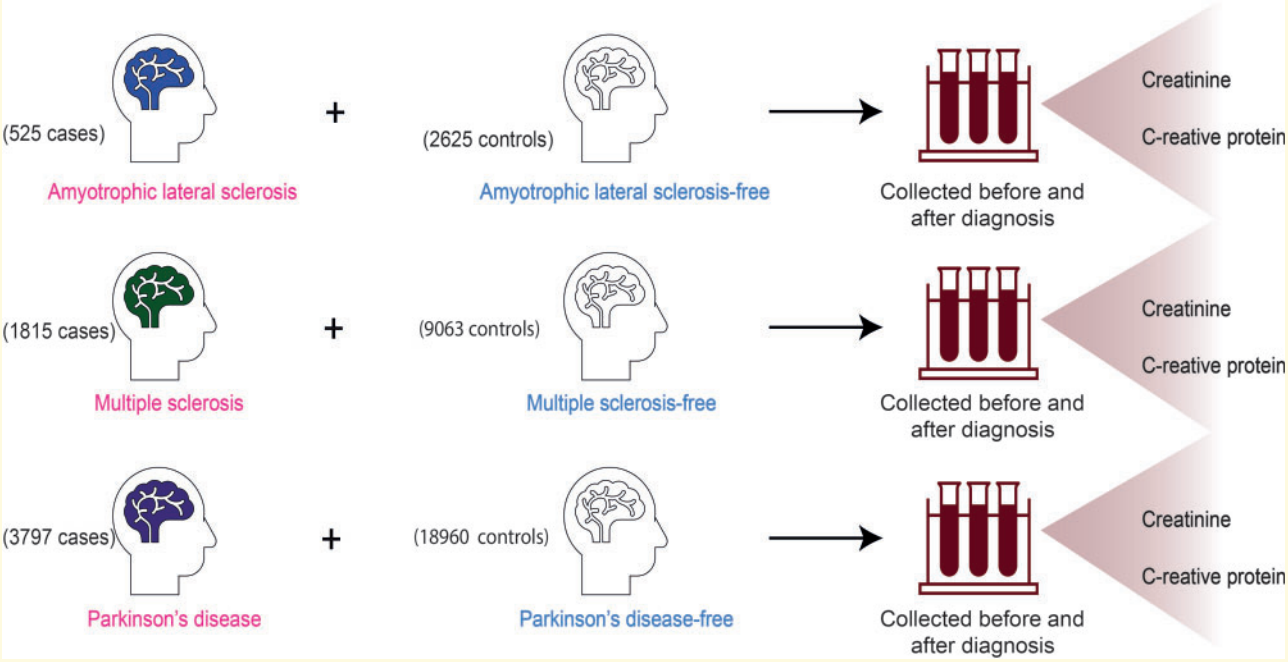
Abbreviations: ICD-10 = the 10th Swedish revision of the International Classification of Disease codes; LOESS = locally estimated scatterplot smoothing; SCREAM = the Stockholm CREAtinine Measurements project

Graphical Abstract



Introduction

Neurodegenerative diseases comprise a range of conditions where different forms of disease processes progressively affect the structure and function of central nervous system, including amyotrophic lateral sclerosis and Parkinson's disease (Inglese and Petracca, 2013). In contrast to conventional neurodegenerative diseases, multiple sclerosis is believed to be triggered by a dysregulated adaptive immune response; however, the disease also comprises a prominent neurodegenerative facet (Filippi *et al.*, 2018). Various hypotheses, such as protein misfolding, mitochondrial dysfunction, oxidative stress and metabolic dysfunction, have been proposed as potential mechanisms underlying different neurodegenerative diseases (Cai *et al.*, 2012; Chen *et al.*, 2012; Johri and Beal, 2012; Kempuraj *et al.*, 2016; Sweeney *et al.*, 2017). The causes of these diseases remain, however, largely unknown (Magalingam *et al.*, 2018) and no cure is currently available for any of these diseases (Heemels, 2016).

Biomarkers are important for the diagnosis and prognosis prediction of neurodegenerative diseases (Rachakonda *et al.*, 2004). Serum creatinine, a metabolite-based biomarker, is a surrogate of muscle mass and motor function (Patel *et al.*, 2013). Serum C-reactive protein, a biomarker of systemic inflammation (Koenig *et al.*, 1999), has also been suggested as a biomarker for neurodegeneration (Luan and Yao, 2018; Qiu *et al.*, 2019). The previous studies have found decreased levels of serum creatinine among patients with amyotrophic lateral sclerosis and progressive multiple sclerosis (Calabresi *et al.*, 2002; Chen *et al.*, 2014), but normal levels among patients with Parkinson's disease (Abou-Raya *et al.*, 2009). C-reactive protein, on the other hand, was shown to be elevated among patients with amyotrophic lateral sclerosis and Parkinson's disease (Keizman *et al.*, 2009; Ryberg *et al.*, 2010; Qiu *et al.*, 2019), but similar between patients with multiple sclerosis and their controls (Ristori *et al.*, 1998; Giovannoni *et al.*, 2001; Soilu-Hanninen *et al.*, 2005). Another study found C-reactive protein to be higher among multiple sclerosis patients during relapse compared to patients in remission, and among multiple sclerosis patients experiencing disease progression compared to patients with stable disease (Soilu-Hanninen *et al.*, 2005).

The longitudinal temporal patterns of these biomarkers, before and after diagnosis, have rarely been described among patients with amyotrophic lateral sclerosis, multiple sclerosis or Parkinson's disease.

The Stockholm CREAtinine Measurements (SCREAM) project is a repository of laboratory tests for residents of Stockholm County, Sweden, who had accessed healthcare and had at least one measurement of serum creatinine during 2006–2011 (Runesson *et al.*, 2016). Through cross-linking SCREAM to several regional and national health registers in Sweden, we performed a population-based case–control study to assess the temporal patterns of creatinine and C-reactive protein during the years before and after diagnosis of amyotrophic lateral sclerosis, multiple sclerosis and Parkinson's disease, in comparison to their respective controls.

Materials and methods

Study design

The SCREAM is a collection of laboratory data from the three main laboratory service providers in the county of Stockholm (Unilabs, Aleris and Karolinska), which together run the vast majority (>90%) of laboratory analyses for the sole healthcare provider of the county (Runesson *et al.*, 2016). It includes all individuals with a valid personal identifying number (Ludvigsson *et al.*, 2009) who were residing in the Stockholm county and had undertaken at least one measurement of serum creatinine in either primary, secondary or tertiary care during 2006–2011 ($N = 1\,344\,197$). The participants of SCREAM represent 66% of the total population in Stockholm and >90% of the population above 65 years during the study period. Due to the use of laboratory data through healthcare, SCREAM has very high coverage for chronic diseases. For instance, it includes 98% of all patients with cardiovascular disease and 97% of all patients with diabetes in Stockholm. In addition to creatinine, SCREAM includes information also on all other laboratory tests of the included individuals who were performed during the same period. For each test, we collected information on date of test, method of test, test result, unit of measurement and so on. Through the personal identifying numbers, SCREAM was cross-linked to different Swedish regional and national population and health registers to individually follow the included individuals from 1 January 2006 until migration out of Stockholm, death, or 31 December 2013, whoever came first.

A nested case–control study was performed within the study base described above. We first identified 525 individuals with a newly diagnosed amyotrophic lateral sclerosis, 1815 individuals with a newly diagnosed multiple sclerosis and 3797 individuals with a newly diagnosed Parkinson's disease during 2006–2013, according to the VAL database, the regional subset of Swedish Patient Register in Stockholm, using the 10th Swedish revision of the International Classification of Disease (ICD-10) codes (G12.2 for amyotrophic lateral sclerosis, G35 for multiple sclerosis and G20 for Parkinson's disease). The Swedish Patient Register has been collecting nationwide complete information on hospital-based inpatient and outpatient care since 2006 in Sweden (Ludvigsson *et al.*, 2011). A patient with a first-ever hospital visit concerning amyotrophic lateral sclerosis, multiple sclerosis or Parkinson's disease was defined as an incident case, and the date of the first hospital visit was defined as the date of diagnosis. Such definitions of amyotrophic lateral sclerosis, multiple sclerosis and Parkinson's disease have been estimated previously, with a positive predictive value of 91% for amyotrophic lateral sclerosis (in Stockholm during 2013–2014) (Mariosa *et al.*, 2017), 92.5% for multiple sclerosis (in Sweden during 2001–2013) (Murley *et al.*, 2019) and 70.8% for Parkinson's disease (in Sweden during 1964–2009 based on inpatient care alone) (Feldman *et al.*, 2012). For each case, we then randomly selected five controls who were individually matched to the case by age, sex and county of residence, using the method of incidence density sampling. Date of diagnosis was used as the index date for the cases, whereas date of selection was used as the index date for controls. Controls had to be still at follow-up and free of the disease of their matched case on the index date.

We then collected information on all tests of serum creatinine and C-reactive protein available in SCREAM for both the cases and the controls. Creatinine was standardized to isotope dilution mass spectrometry standards. High-sensitivity C-reactive protein was measured by a validated high-sensitivity assay with the Behring nephelometer and reagent (Glynn *et al.*, 2009). Inter- and intra-laboratory variations were considered minimal, because the three laboratories are frequently audited for quality and harmonization by the national organization EQUALIS (www.equalis.se).

Statistical analysis

Baseline characteristics of the cases and controls were summarized as mean (standard deviation; SD) for continuous variables and number (%) for categorical variables.

To visualize the levels of creatinine and C-reactive protein, we first used boxplot to describe median levels of a biomarker in 3-month time windows. We then used the locally estimated scatterplot smoothing (LOESS) curves to show these median levels from the 7 years before to 6 years after index date. For patients with multiple values in a 3-month interval, only the median of these multiple values was taken into consideration. As a result, one patient could contribute only one value per 3-month time window. To construct the pointwise 95% confidence bands for the LOESS curves, we used the bootstrap

Table 1 **Baseline characteristics of patients with neurodegenerative diseases and their matched controls**

	Patients with amyotrophic lateral sclerosis	Controls of patients with amyotrophic lateral sclerosis	Patients with multiple sclerosis	Controls of patients with multiple sclerosis	Patients with Parkinson's disease	Controls of patients with Parkinson's disease
N	525	2625	1815	9063	3797	18 960
Age (mean ± SD)	65.90 ± 13.10	65.87 ± 13.09	44.70 ± 15.50	44.70 ± 15.50	73.51 ± 10.73	73.50 ± 10.74
Male (%)	302 (57.52)	1510 (57.52)	559 (30.80)	2793 (30.82)	2191 (57.70)	10 937 (57.68)

method by resampling with replacement 200 times from the entire data set. Individuals were the units of bootstrap resampling, and hence the statistical dependencies between the longitudinal measurements were preserved. We used all measurements of an individual when they were resampled. If the confidence bands did not overlap, we considered the observed difference statistically significant. This method is conservative and corresponds to hypothesis testing with alpha level <5%, but it is highly convenient in interpreting the graphical presentation of the results. Creatinine was plotted according to its original values, whereas C-reactive protein was plotted based on its natural logarithm transformation. Stratification analyses were conducted based on age at index date (categorized according to median) and sex to assess whether the results would differ by age and sex.

Finally, a linear mixed model was applied to assess the coefficient of change of creatinine and C-reactive protein with an individual. Because there was attrition of patients due to death after diagnosis, especially among patients with amyotrophic lateral sclerosis, and most of the different levels of creatinine and C-reactive protein were noted during the 2 years before and 2 years after index date between cases and controls, we estimated the coefficient with four 1-year time windows from 2 years before to 2 years after index date for both cases and controls. Random effects for the individuals and fixed effects for age at index and sex were used in the linear mixed models.

Data analyses and data visualization were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC) and R platform (version 3.6.0). All statistical tests were two sided with a significance level at $P < 0.05$. The study was approved by the Regional Ethical Review Board in Stockholm.

Data availability

Anonymized data that support the findings of this study are available on request from the corresponding authors, only for the purpose of procedures replication and results presentation in the article, in agreement with European regulations and Regional Ethical Review Board in Sweden.

Results

Table 1 summarizes the age and sex distributions of patients with amyotrophic lateral sclerosis, multiple sclerosis or Parkinson's disease and their matched controls. The mean age at diagnosis was 65.9 for amyotrophic lateral sclerosis, 44.7 for multiple sclerosis and 73.5 for Parkinson's disease. There were more males than females among patients with amyotrophic lateral sclerosis (57.5%) or Parkinson's disease (57.7%) but not multiple sclerosis (30.8%).

Levels of serum creatinine and C-reactive protein

Compared to controls, amyotrophic lateral sclerosis patients showed slightly lower levels of creatinine during the 2 years before diagnosis but markedly lower levels after diagnosis (Fig. 1). Amyotrophic lateral sclerosis patients had slightly lower levels of C-reactive protein from before diagnosis until 1 year after diagnosis, whereas higher levels of C-reactive protein, thereafter, compared to controls.

Compared to controls, patients with Parkinson's disease had slightly lower levels of creatinine from 1 year before diagnosis onwards. The patients with Parkinson's disease had lower levels of C-reactive protein from before diagnosis until 1 year after diagnosis, but higher levels from 3 years after diagnosis onwards, compared to controls.

When comparing the patients affected by multiple sclerosis to their controls, we found slightly lower levels of both creatinine and C-reactive protein during the 2 years before and 2 years after diagnosis, but not earlier or later.

These results were similar for younger and older individuals as well as between men and women (Figs. 2 and 3).

Changes in levels of creatinine and C-reactive protein

The patients with amyotrophic lateral sclerosis showed statistically significantly decreasing levels of creatinine from 1 year before until 2 years after diagnosis (Table 2). Controls of amyotrophic lateral sclerosis patients had, on the other hand, increasing levels of creatinine during large part of these 4 years, although the annual change was not always statistically significant. Patients with amyotrophic lateral sclerosis had increasing levels of C-reactive protein from diagnosis until 2 years after diagnosis (Table 3). Controls of patients with amyotrophic lateral

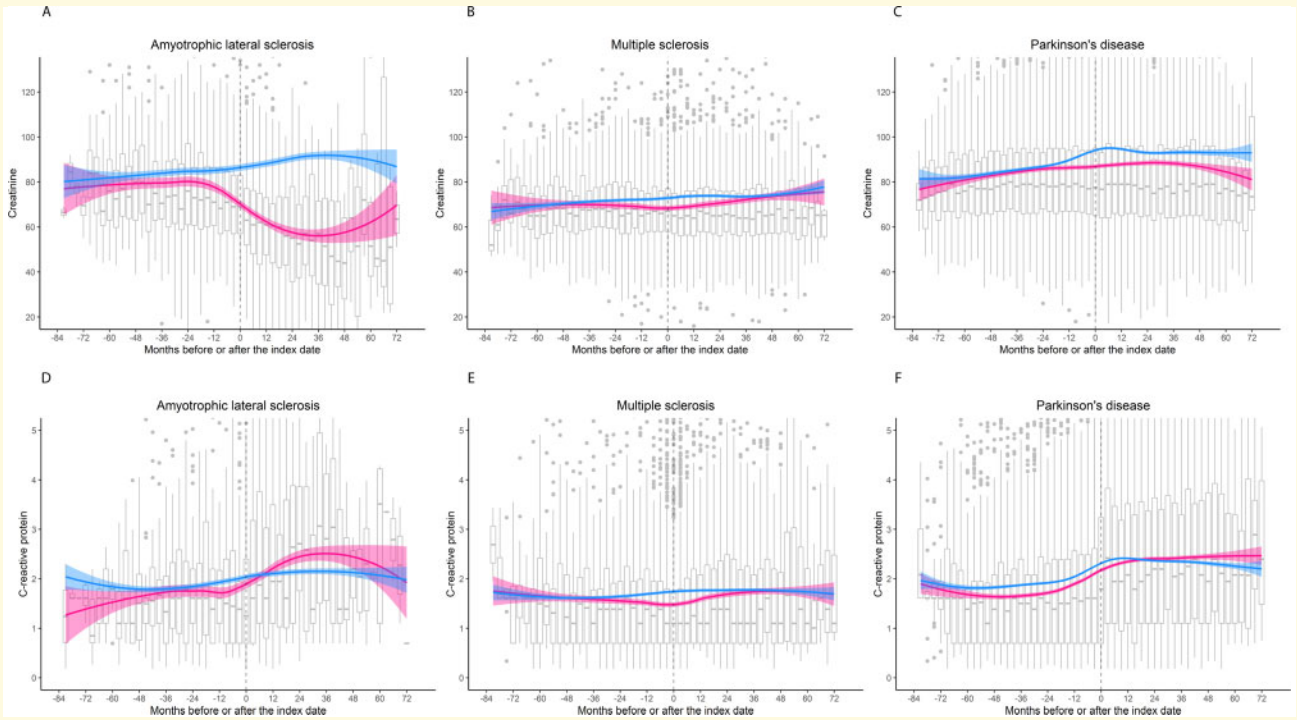


Figure 1 Distributions of creatinine and C-reactive protein before and after index date (date of diagnosis among cases and date of selection among controls). The boxplots show median values of creatinine or C-reactive protein in the 3-month time windows. The line inside the box denotes the median. The lower and upper edges of the box denote the first and third quartiles. Whiskers denote data points that are no more than 1.5 times the interquartile from the edge of the box. The gray points denote the extreme data points that are more than 1.5 times the interquartile from the edge of the box. Loess lines with 95% confidence intervals are shown for patients with amyotrophic lateral sclerosis/multiple sclerosis/Parkinson's disease (red) and their matched disease-free controls (blue). (**A–C**) Creatinine (unit: micromoles per liter). (**D–F**) C-reactive protein (unit: milligram per liter).

sclerosis demonstrated, however, no clear change of C-reactive protein during the 4 years.

No clear change in either creatinine or C-reactive protein was noted among patients with Parkinson's disease or multiple sclerosis or their respective controls, apart from the increasing levels of creatinine and C-reactive protein from 1 year before until 2 years after the index date among controls of patients with Parkinson's disease (Supplementary Tables 1–4).

Discussion

This study explored the temporal patterns of serum creatinine and C-reactive protein among patients with amyotrophic lateral sclerosis, multiple sclerosis or Parkinson's disease, both before and after diagnosis, and demonstrated a distinct temporal pattern of creatinine and C-reactive protein among patients affected by amyotrophic lateral sclerosis, in contrast to amyotrophic lateral sclerosis-free controls as well as patients with multiple sclerosis or Parkinson's disease.

We found lower levels of serum creatinine among patients with amyotrophic lateral sclerosis, compared to controls. The difference was noted already during the 2 years before diagnosis and became more pronounced after diagnosis. Previous studies did also show a decreased level of circulating creatinine among clinically diagnosed patients with amyotrophic lateral sclerosis (Ikeda *et al.*, 2012; Chen *et al.*, 2014; Chio *et al.*, 2014; Lawton *et al.*, 2014). In the analysis of annual changes in creatinine with an individual focusing on the 2 years before and 2 years after index date, patients with amyotrophic lateral sclerosis had shown progressively declining levels of creatinine from 1 year before until 2 years after diagnosis, whereas their matched controls had shown gradually increasing levels during the entire 4 years, likely reflecting the deteriorating renal function along with ageing (Tiao *et al.*, 2002). Levels of creatinine in the blood reflect mainly the amount of muscle mass and renal function a person has, although creatinine is also influenced by age, sex, dietary protein intake, physical activity and so on. (Raman *et al.*, 2017). Because it is unlikely for the patients with amyotrophic lateral sclerosis to achieve increasing renal function around diagnosis, the decreasing level of creatinine is most likely attributable to the increasing muscle loss. Furthermore, although we had no information on lifestyle factors including diet and

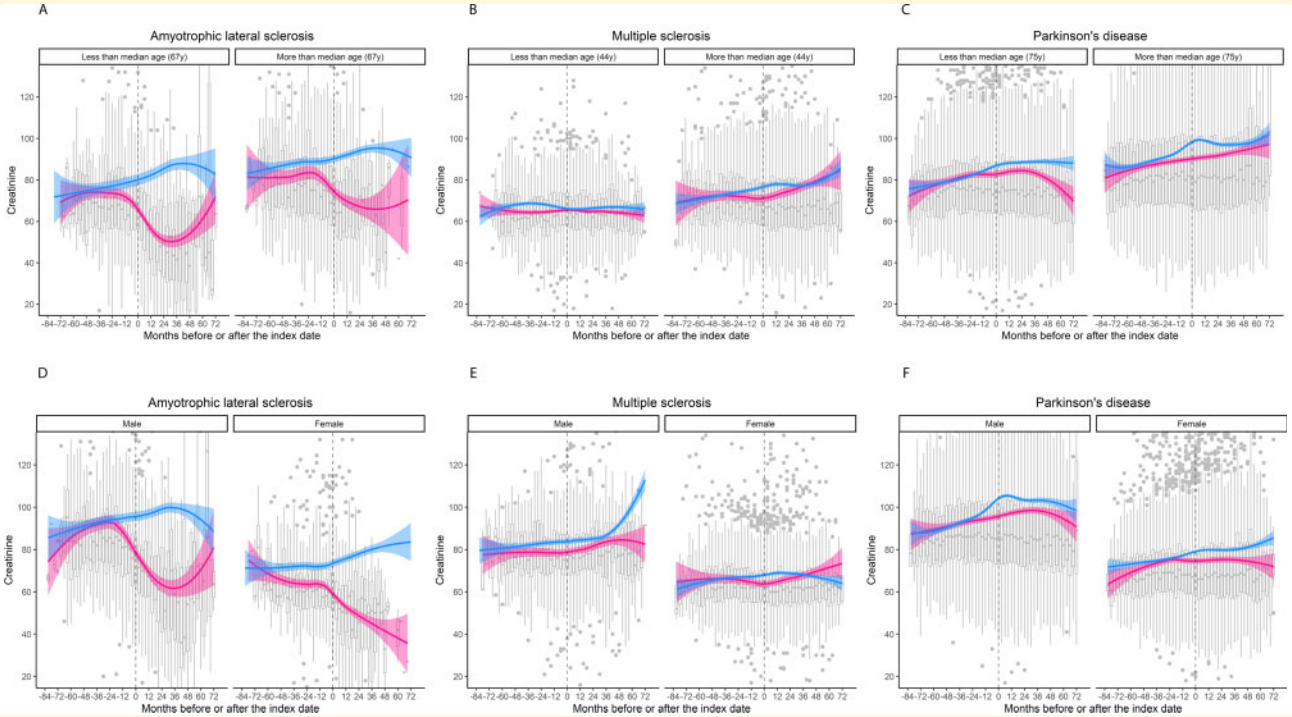


Figure 2 Distributions of creatinine before and after index date (date of diagnosis among cases and date of selection among controls), by median age at index date and sex. The boxplots show median values of creatinine in the 3-month time windows. The line inside the box denotes the median. The lower and upper edges of the box denote the first and third quartile. Whiskers denote data points that are no more than 1.5 times the interquartile from the edge of the box. The gray points denote the extreme data points that are more than 1.5 times the interquartile from the edge of the box. Loess lines with 95% confidence intervals are shown for patients with amyotrophic lateral sclerosis/multiple sclerosis/Parkinson's disease (red) and their matched disease-free controls (blue). Unit of creatinine: micromoles per liter.

physical activity, the similar results noted in the stratified analyses by age and sex precluded age and sex as important confounders.

Our finding might have different implications. First, because creatinine exists in equilibrium with creatine, which is proposed to protect the structure and function of mitochondria in muscle (Viollet *et al.*, 2009), and creatine supplement is suggested to increase muscle strength in patients with amyotrophic lateral sclerosis (Mazzini *et al.*, 2001), this finding adds further evidence to the involvement of mitochondrial dysfunction in the pathogenesis of muscle atrophy in amyotrophic lateral sclerosis. Second, the dynamic change of creatinine before diagnosis might indicate an active disease course of amyotrophic lateral sclerosis before clinical onset. The average diagnostic delay of amyotrophic lateral sclerosis was estimated to be around 1 year in Stockholm (Longinetti *et al.*, 2018). The fact that patients with amyotrophic lateral sclerosis started to demonstrate declining levels of creatinine from 1 year before diagnosis corroborates the time frame of diagnostic delay. Taken together, serum creatinine might be an important biomarker in monitoring disease course before symptom onset, for example among high-risk individuals. Finally, because both our latest study and previous studies have suggested an inverse relationship between creatinine level and amyotrophic lateral sclerosis progression (Chio *et al.*, 2014; Lanznaster *et al.*, 2019; Sun *et al.*, 2020) and proposed creatinine as a potential biomarker to assess treatment effects in amyotrophic lateral sclerosis clinical trials (van Eijk *et al.*, 2018), the clinical use of serum creatinine as a biomarker for diagnosis and prognosis prediction of amyotrophic lateral sclerosis needs to be further discussed.

To a smaller extent than in amyotrophic lateral sclerosis, patients with Parkinson's disease had also shown slightly lower levels of creatinine from 2 years before diagnosis onwards, compared to their matched controls. There was, however, no significant declining level of creatinine during the 2 years before and the 2 years after diagnosis among patients affected by Parkinson's disease, indicating that creatinine level was rather stable around Parkinson's disease diagnosis. In contrast to these findings, two previous studies failed to show any difference in creatinine levels between patients with Parkinson's disease and their controls (Sun *et al.*, 2012; Hu *et al.*, 2016). Varying study populations and sample sizes might have contributed to the different results. For instance, given the relatively small absolute differences in creatinine levels noted between patients with Parkinson's disease and their controls in this study, a large sample size is needed to achieve statistical significance. We did not

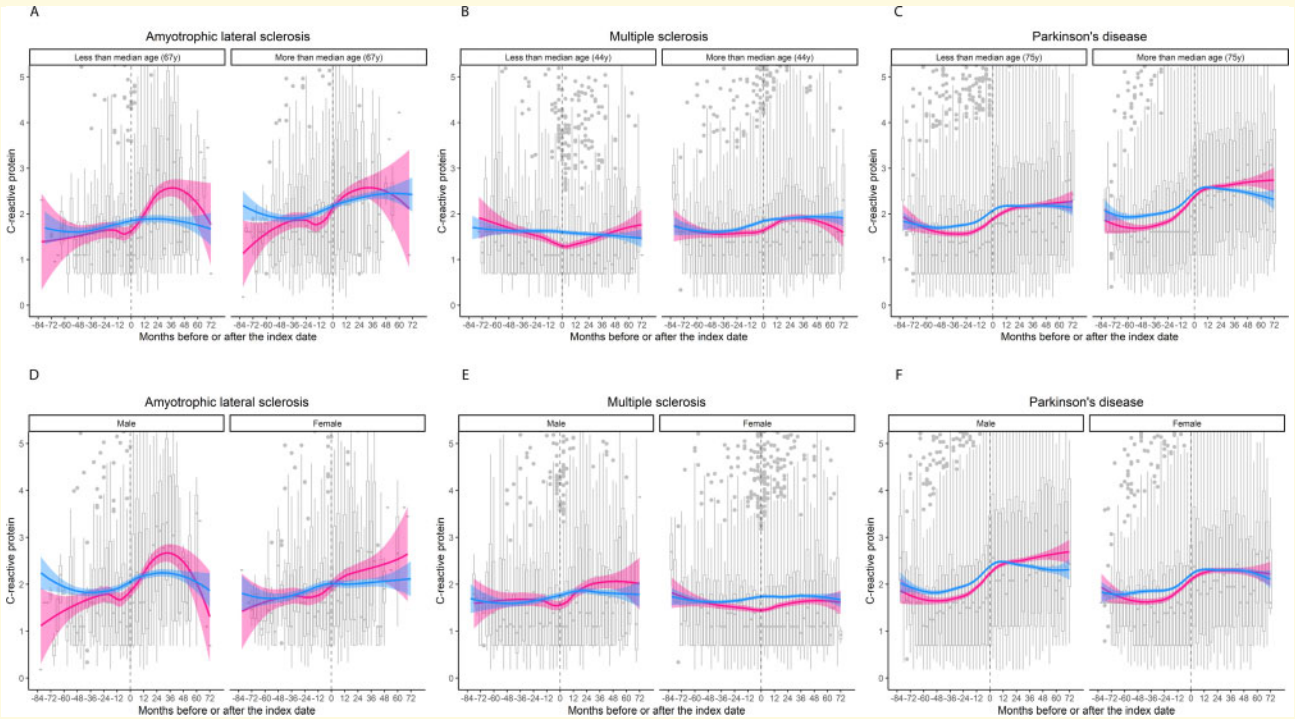


Figure 3 Distributions of C-reactive protein before and after index date (date of diagnosis among cases and date of selection among controls), by median age at index date and sex. The boxplots show median values of C-reactive protein in the 3-month time windows. The line inside the box denotes the median. The lower and upper edges of the box denote the first and third quartiles. Whiskers denote data points that are no more than 1.5 times the interquartile from the edge of the box. The gray points denote the extreme data points that are more than 1.5 times the interquartile from the edge of the box. Loess lines with 95% confidence intervals are shown for patients with amyotrophic lateral sclerosis/multiple sclerosis/Parkinson's disease (red) and their matched disease-free controls (blue). Unit of C-reactive protein: milligram per liter.

Table 2 **Temporal changes of creatinine levels from 2 years before to 2 years after diagnosis among patients with amyotrophic lateral sclerosis and their matched controls**[a]

Group	Months before or after amyotrophic lateral sclerosis diagnosis	Estimate	Std.Error	t Value	*P* value
Patients with amyotrophic lateral sclerosis	−24 to −12	−0.6085	0.3217	−1.89	0.0591
	−12 to 0	−0.5753	0.1761	−3.27	0.0011
	0 to 12	−0.9714	0.1181	−8.22	<0.0001
	12 to 24	−0.8492	0.1945	−4.37	<0.0001
Controls	−24 to −12	−0.1041	0.1998	−0.52	0.6025
	−12 to 0	0.2357	0.1982	1.19	0.2345
	0 to 12	0.5339	0.3731	1.43	0.1525
	12 to 24	0.9668	0.2659	3.64	0.0003

detect lower levels of creatinine among multiple sclerosis patients, compared to their controls, apart from some small differences noted during the 2 years before and 2 years after diagnosis. Lower-than-expected creatinine levels have previously been reported among patients with progressive multiple sclerosis (Calabresi *et al.*, 2002).

We found that patients with amyotrophic lateral sclerosis to have lower levels of C-reactive protein before diagnosis until 1 year after diagnosis, but higher levels, thereafter, compared to controls. The observation of lower C-reactive protein levels before diagnosis is novel and may be explained by different reasons. For instance, patients with amyotrophic lateral sclerosis are known to be physically fit and active, which may result in lower C-reactive protein levels (Plaisance and Grandjean, 2006). On the other hand, the higher levels of C-reactive protein from 1 year after diagnosis onwards corroborates prior studies which reported elevated C-reactive protein levels

Table 3 **Temporal changes of C-reactive protein levels from 2 years before to 2 years after diagnosis among patients with amyotrophic lateral sclerosis and their matched control[a]**

Group	Months before or after amyotrophic lateral sclerosis diagnosis	Estimate	Std.Error	t Value	P value
Patients with amyotrophic lateral sclerosis	−24 to −12	0.005483	0.02011	0.27	0.7854
	−12 to −0	0.01452	0.01303	1.11	0.2657
	0 to 12	0.03039	0.01128	2.69	0.0072
	12 to 24	0.06342	0.02262	2.80	0.0053
Controls	−24 to −12	−0.00860	0.009272	−0.93	0.3537
	−12 to 0	0.006584	0.008713	0.76	0.4500
	0 to 12	0.01240	0.008863	1.40	0.1619
	12 to 24	0.01031	0.009786	1.05	0.2921

among clinically diagnosed patients with amyotrophic lateral sclerosis compared to controls (Keizman *et al.*, 2009; Ryberg *et al.*, 2010). Increased C-reactive protein levels have also been shown in the cerebrospinal fluid of patients with amyotrophic lateral sclerosis (Ryberg *et al.*, 2010).

This finding might have two implications. First, C-reactive protein, as a systemic inflammation marker, is involved in the disease course of amyotrophic lateral sclerosis, but likely only in later disease stages. It has been shown that the peripheral immune cell profiles, including lymphocytes such as CD4+ T cells, CD8+ T cells and pro-inflammatory monocytes, are altered only after, but not before, onset of amyotrophic lateral sclerosis symptoms (Figueroa-Romero *et al.*, 2020). It may be speculated that amyotrophic lateral sclerosis-associated immune responses first present as activation of resident glial cells in the central nervous system before presenting in the periphery (McCauley and Baloh, 2019). Second, our findings provide additional support for C-reactive protein as a biomarker for amyotrophic lateral sclerosis diagnosis and prognostic prediction. One earlier study found increased C-reactive protein levels in the cerebrospinal fluid samples of patients with amyotrophic lateral sclerosis, compared to healthy controls or patients with Alzheimer's disease (Ryberg *et al.*, 2010). Another study showed a positive association between C-reactive protein levels and disease progression among patients with amyotrophic lateral sclerosis (Lunetta *et al.*, 2017). Our recent study also found an association between increasing level of C-reactive protein and a higher mortality among patients with amyotrophic lateral sclerosis, further strengthening the prognostic value of C-reactive protein in amyotrophic lateral sclerosis (Sun *et al.*, 2020).

Patients with Parkinson's disease had lower levels of C-reactive protein from before diagnosis until 1 year after diagnosis and higher levels from 3 years after diagnosis onwards, compared to controls, but the differences were not as pronounced as in patients with amyotrophic lateral sclerosis. A systematic review and meta-analysis concluded a positive association between increased C-reactive protein levels and Parkinson's disease risk (Qiu *et al.*, 2019). The difference between the present findings and the meta-analysis might be because most of the previous studies measured C-reactive protein after clinical diagnosis of Parkinson's disease, that is among prevalent cases, and we indeed found higher levels of C-reactive protein from 3 years after Parkinson's disease diagnosis onward in this study. Patients with multiple sclerosis had slightly lower levels of C-reactive protein during the 2 years before and 2 years after diagnosis, but not earlier or later, compared to controls. Previous studies have mostly failed to demonstrate a clear correlation between C-reactive protein and multiple sclerosis (Ristori *et al.*, 1998; Giovannoni *et al.*, 2001; Soilu-Hanninen *et al.*, 2005).

Strengths of our study include a population-based design, long and complete follow-up, and the prospectively and independently collected information on creatinine and C-reactive protein as well as the clinical diagnoses of neurodegenerative diseases, minimizing therefore most of the systemic errors due to selection and information biases. There are also limitations. First, SCREAM includes 66% of the total population in Stockholm (>90% of the ones above 65 years) during the study period (Runesson *et al.*, 2016). We might have missed a few patients with multiple sclerosis (if they did not receive any creatinine test), although the problem is likely negligible for amyotrophic lateral sclerosis and Parkinson's disease because of their late ages at diagnosis. Similarly, although the controls of patients with amyotrophic lateral sclerosis or Parkinson's disease were likely representative of the general Stockholm population, this was unlikely true for the controls of patients with multiple sclerosis. Creatinine and C-reactive protein tests were taken in connection to a healthcare encounter, and number of tests varied between individuals. Patients with neurodegenerative diseases had on average more tests compared to controls (data not shown). We therefore used the median value of all tests performed within each 3-month time window to decrease this influence.

Furthermore, because of the high fatality rate after amyotrophic lateral sclerosis diagnosis, the result beyond 3 years after diagnosis might be over-represented by patients with better survival. We, therefore, in the linear mixed model focused only on the 4-year period around diagnosis. Finally, we lacked detailed information on clinical characteristics and treatments for patients with amyotrophic lateral sclerosis, multiple sclerosis and Parkinson's disease, precluding the possibility to examine whether the observed temporal patterns of creatinine and C-reactive proteins would differ for patients with different clinical characteristics or treatments.

Conclusion

Patients with amyotrophic lateral sclerosis had shown distinct temporal patterns of creatinine and C-reactive protein concentrations both before and after diagnosis, compared to amyotrophic lateral sclerosis-free controls. Similar temporal patterns were also noted among patients with Parkinson's disease, but to a much smaller extent, and were largely absent among patients with multiple sclerosis. Taken together, serum creatinine and C-reactive protein might reflect disease processes not commonly shared by neurodegenerative and neuroinflammatory diseases, in general.

Supplementary material

Supplementary material is available at *Brain Communications* online.

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Competing interests

The authors report no competing interests.

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