

GI infections are associated with an increased risk of Parkinson's disease

We have read with interest the recent publication of Perez-Pardo and colleagues¹ reporting the role of the TLR4 in the gut–brain axis in Parkinson's

Table 1 Characteristics of the study population by exposition to GIIs, no (%)

Characteristics	Not exposed to GIIs; n=177 993 (77.9)	Exposed to GIIs; n=50 492 (22.1)
Age (SD)*	67.5 (10.7)	68.6 (12.0)
Men	77 355 (43.5)	19 184 (38.0)
Women	100 638 (56.6)	31 308 (62.0)
Diabetes mellitus	72 574 (40.8)	24 629 (48.8)
Cerebrovascular diseases	64 749 (36.4)	24 176 (47.9)
Hypertension	147 078 (82.6)	45 612 (90.3)
Ischaemic heart diseases	78 948 (44.4)	28 347 (56.1)
Hypercholesterolaemia	67 242 (37.8)	22 590 (44.7)
Chronic obstructive pulmonary disease	40 208 (22.6)	15 159 (30.0)
Smoking-related cancers	19 839 (11.2)	6831 (13.5)
Intracranial injury n=228 485	7835 (4.4)	3422 (6.8)

*Mean age in years at 1 January 2005.
GIIs, GI infections.

disease (PD). These findings prompted us to investigate the role of common GI infections (GIIs) in the pathogenesis of PD. In this prospective cohort study, we assessed the risk of PD in patients who previously suffered from GIIs compared with the control group not exposed to GIIs (table 1). At study entry (1 January 2005), the analysis sample from health claims data of the largest German health insurer consisted of 2 28 485 individuals aged 50 years and older, which were followed for a mean time of 8.6 years (median=11.0 years; IQR=7.6 years). PD and GIIs were defined by ICD-10 codes as described in the supplementary material. Overall, 6195 individuals (2.7%) developed PD and 50 492 individuals (22.1%) were affected by any GII during the observation period between

2005 and 2015. The most frequent GIIs were those that caused infectious gastroenteritis and colitis of unspecified origin (IGCUs; 39 093 individuals, 17.1%), followed by viral intestinal infections (VIIs; 9328 individuals, 4.1%) and bacterial intestinal infections (BIIs; 9298 individuals, 4.1%). The cumulative incidence of PD was significantly higher among individuals with GIIs ($p<0.001$, online supplementary figure S1). Multivariable analyses (table 2) using Cox regression to compute HRs revealed an increased risk of PD in patients with GIIs when compared with the control group (HR=1.42; 95% CI 1.33 to 1.52). Subgroup analyses (table 2) revealed positive associations of GIIs for men (HR=1.48; 95% CI 1.34 to 1.63), women (HR=1.38; 95% CI 1.27 to

1.50), individuals aged 70 years or older (HR=1.25; 95% CI 1.04 to 1.49) and individuals with (HR=1.40; 95% CI 1.23 to 1.59) or without chronic obstructive pulmonary disease (HR=1.43; 95% CI 1.33 to 1.54). To solidify our results, we performed sensitivity analyses and found no remarkable changes compared with our primary analysis (online supplementary table S1). In a secondary analysis, where we considered GIIs separately (online supplementary table S2), BIIs (HR=1.30; 95% CI 1.12 to 1.50), VIIs (HR=1.31; 95% CI 1.14 to 1.50) and IGCUs (HR=1.34; 95% CI 1.24 to 1.44) were each associated with an increased risk of PD.

Our findings suggest that GIIs are associated with an increased risk of PD. In sporadic PD, Lewy pathology defined by aggregated alpha-synuclein is first observed in the olfactory bulb and the enteric plexuses from where it propagates via the vagus nerve to the dorsal motor nucleus in the central nervous system (CNS).² This prion-like ability of pathological alpha-synuclein to retrogradely spread from the periphery to the CNS is supported by a growing body of experimental work in rodents.³⁻⁵ In the light of these findings, our results point to the missing link of what may cause alpha-synuclein pathology in the enteric nervous system (ENS): bacterial and viral pathogens, which breach the mucosal lining of the GI tract during GIIs, may trigger aggregation

Table 2 Incidence rates* and HRs of PD for the total sample and subgroups

Types of Analysis	Not exposed to GIIs			Exposed to GIIs			Cox regression (ref.: not exposed to GIIs)			
	Events	Person years	IR	Events	Person years	IR	Cr. HR	95% CI	Adj. HR	95% CI
Overall†	5020	1 704 049	2.95	1175	250 573	4.69	1.42	1.33 to 1.52	1.42	1.33 to 1.52
Men‡	2327	724 388	3.21	493	93 896	5.25	1.48	1.34 to 1.63	1.48	1.34 to 1.63
Women‡	2693	979 661	2.75	682	156 677	4.35	1.38	1.27 to 1.50	1.38	1.27 to 1.50
Age <70 years§	1062	862 501	1.23	162	114 127	1.42	1.17	0.99 to 1.38	1.17	0.99 to 1.38
Age ≥70 years§	3958	841 548	4.70	1013	136 446	7.42	1.25	1.04 to 1.49	1.25	1.04 to 1.49
Without COPD¶	4051	1 438 104	2.82	858	191 598	4.48	1.65	1.53 to 1.78	1.43	1.33 to 1.54
With COPD¶	969	265 945	3.64	317	58 975	5.38	1.51	1.33 to 1.72	1.40	1.23 to 1.59
Without SRC¶¶	4650	1 613 378	2.88	1065	230 044	4.63	1.66	1.55 to 1.78	1.40	1.35 to 1.55
With SRC¶¶	370	90 671	4.08	110	20 529	5.36	1.93	1.59 to 2.33	1.20	0.96 to 1.48

N=228 485; PD cases=6195.

*Per 1000 person years.

†HRs were adjusted for gender, age, diabetes mellitus, cerebrovascular diseases, hypertension, ischaemic heart diseases, hypercholesterolaemia, chronic obstructive pulmonary disease and intracranial injury.

‡HRs were adjusted for age, diabetes mellitus, cerebrovascular diseases, hypertension, ischaemic heart diseases, hypercholesterolaemia, chronic obstructive pulmonary disease and intracranial injury.

§HRs were adjusted for gender, diabetes mellitus, cerebrovascular diseases, hypertension, ischaemic heart diseases, hypercholesterolaemia, chronic obstructive pulmonary disease and intracranial injury.

¶HRs were adjusted for gender, age, diabetes mellitus, cerebrovascular diseases, hypertension, ischaemic heart diseases, hypercholesterolaemia and intracranial injury.

Adj. HR, adjusted HR; COPD, chronic obstructive pulmonary disease; Cr. HR, crude HR; GII, GI infections; IR, incidence rate; PD, Parkinson's disease; SRC, smoking-related cancers.

of alpha-synuclein in enteric neurons and initiate its retrograde transport to the CNS. Several species of gut bacteria express amyloid proteins, which could potentially cross-seed aggregation of alpha-synuclein.⁶ In line with this, oral challenge of rats with a wild-type *Escherichia coli* strain expressing the extracellular amyloid curli led to deposition of pathological alpha-synuclein in their ENS and subsequently CNS.⁷ Another study in patients showed that expression of alpha-synuclein in enteric neurites of the GI tract was elevated in response to BIIIs and VIIIs.⁸ Also, biopsy samples from intestinal allograft subjects after a norovirus infection showed elevated alpha-synuclein expression in enteric neurons that persisted months after the virus was no longer detected.⁸ Overall, our findings are consistent with the concept that in some patients PD may start in the GI tract.

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