LETTER

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

We have read with interest the recent publication of Perez-Pardo and colleagues reporting the role of the TLR4 in the gut–brain axis in Parkinson’s disease (PD). These findings prompted us to investigate the role of common GI infections (GIs) in the pathogenesis of PD. In this prospective cohort study, we assessed the risk of PD in patients who previously suffered from GIs compared with the control group not exposed to GIs (Table 1). At study entry (1 January 2005), the analysis sample from health claims data of the largest German health insurer consisted of 228,485 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 GIs 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 GI during the observation period between 2005 and 2015.

The most frequent GIs 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 GIs (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 GIs when compared with the control group (HR = 1.42; 95% CI 1.33 to 1.52). Subgroup analyses (Table 2) revealed positive associations of GIs 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).

Our findings suggest that GIs 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

### Table 1

| Characteristics | Not exposed to GIs; n=177,993 (77.9) | Exposed to GIs; 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) | 6,831 (13.5) |
| Intracranial injury | 7,835 (4.4)        | 3,422 (6.8)                      |
| n=228,485       |                                      |                                  |

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

### Table 2

| Types of Analysis | Not exposed to GIs | Exposed to GIs | Cox regression (ref.: not exposed to GIs) |
|-------------------|--------------------|----------------|-----------------------------------------|
|                   | 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.

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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.

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nucleus in the central nervous system (CNS). 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. 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 GLIs, may trigger aggregation 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. In line with this, oral challenge of rats with a wild-type Escherichia coli strain expressing the oral challenge of rats with a wild-type Escherichia coli strain expressing the alpha-synuclein to retrogradely deposit to the CNS. Several species of gut bacteria express amyloid curli led to deposition of pathological alpha-synuclein in their ENS and subsequently CNS. Another study in patients showed that expression of alpha-synuclein in enteric neurites of the GI tract was elevated in response to GLIs and VIIs. 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. Overall, our findings are consistent with the concept that in some patients PD may start in the GI tract.

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