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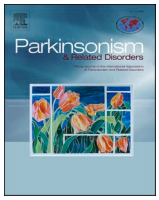

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Parkinsonism in people with intellectual disability

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Many adults with intellectual disability (ID) manifest parkinsonism due to use of antipsychotic medication and other drugs [1]. However, despite suggestions of premature aging in people with ID [2], knowledge on the occurrence of Parkinson's disease (PD) and other causes of non-drug-induced parkinsonism in the broader population of people with ID is practically non-existing.

Based on our clinical experience and the fact that parkinsonism is reported as a manifestation of several genetic neurodevelopmental disorders associated with ID [3], we predicted to find an increased risk of parkinsonism in people with ID as compared to the general population, regardless of medication use. To test this hypothesis, we conducted exploratory analyses to examine the presence of parkinsonism in people with and without ID in: 1) a large database of Dutch primary care patients, representative of the general population, and 2) the Dutch national mortality registry.

First, we extracted administrative healthcare data of 1,428,178 primary care patients from the Netherlands Institute for Health Services Research (NIVEL) database who were registered between January 1, 2019 and December 31, 2021. NIVEL collects data from general practitioners that are recorded routinely in their electronic health records system, with diagnoses coded according to the International Classification of Primary Care (ICPC) [4]. For all patients, we recorded the presence/absence of an active episode of parkinsonism, i.e.: ICPC code N87 parkinsonism/PD. Second, we extracted data from a Dutch mortality registry concerning 1,057,163 individuals who died between January 1, 2015 and December 31, 2021. Data regarded all-cause mortality and parkinsonism-related mortality. For this, we, used a population-based database from Statistics Netherlands (CBS). In both datasets, individuals with ID were identified through linkage with a database for chronic care and a database for welfare support. This method has previously demonstrated its merits and is described in detail elsewhere [5].

Subsequently, we calculated odds (OR) and hazard ratios (HR) with 95 % confidence intervals (95 % CI) to assess the relative risk differences for parkinsonism between people with and without ID using regression analyses and corrected for differences in age and sex. Within the NIVEL primary care cohort as well as the deceased population, 1.5 % had an ID, in line with international estimates [5].

In the cohort of primary care patients, the occurrence of parkinsonism was similar for people with and without ID; i.e., 0.4 %. However, when considering the younger age distribution of the ID population, individuals with ID exhibited higher odds of parkinsonism (OR 2.45, 95 % CI 1.99–3.00). Similar to the general population, a majority of ID patients with parkinsonism were male, and they were on average 8 years younger than their counterparts without ID (see Table 1).

In the mortality statistics, parkinsonism accounted for a smaller proportion of all deaths in the ID population (109 out of 16,528; 0.7 %) compared to the general population (12,608 out of 514,397; 1.2 %), largely due to the substantial overall mortality disparity faced by individuals with ID (all-cause mortality HR 3.27; see Table 1), leading to more competing causes of death. However, when we again considered the different demographic profile (age and sex) of the ID population, individuals with ID were found to be at a higher risk of mortality from parkinsonism compared to individuals of the same age and sex in the general population; with the vast majority registered as primary parkinsonism (HR 1.48, 95 % CI 1.23–1.79). On average, individuals with ID who died from parkinsonism were 10 years younger than those dying from parkinsonism in the general population (see Table 1).

The findings of these analyses are in line with a study on primary healthcare data on 1,424,378 adults in Scotland that reported a similar OR (2.83, 95 % CI 1.95–4.13) for parkinsonism in people with ID [6]. Expanding on this, the Dutch mortality data suggested, for the first time, that forms of parkinsonism other than drug-induced parkinsonism (i.e., 97.8 % of deaths attributed to parkinsonism concerned primary parkinsonism; See Table 1) may be more common in ID as compared to the general population.

The implications of our observations may be manifold. On an individual level, increased awareness may inform a timely diagnosis (which is presently often not the case in our experience) and tailored treatment (assuming that at least some persons with ID will prove to have parkinsonism that is responsive to dopaminergic medication) [3], which could ultimately improve quality of life. Individuals with ID, caregivers, and professionals involved in their care will need to be informed of the risk of developing parkinsonism, in order to promote early detection, diagnosis, and treatment. Periodic neurologic enquiry and motor assessments may be considered for all adults with ID. Video recordings and

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Table 1
Parkinsonism in a cohort of Dutch primary care patients and in the Dutch mortality registry.

	General population						Individuals with ID[a]							
Primary care patients[b]	Total		Male sex		Age[c]		Total		Male sex		Age[c]		OR[e]	95 % CI
	n	%	n	%	M	SD	n	%	n	%	M	SD		
Total cohort	1,428,178	100	697,292	48.8	50.7	19.2	21,520	100	12,407	57.5	42.0	16.5	2.45	1.99–3.00
Patients with parkinsonism[d]	6,106	0.4	3,740	61.3	76.2	10.0	96	0.4	62	64.6	68.0	11.6		
Mortality registry	Total		Male sex		Age at death		Total		Male sex		Age at death		HR[e]	95 % CI
	n	%	n	%	M	SD	n	%	n	%	M	SD		
All-cause mortality	1,057,163	100	514,397	48.7	79.0	12.6	16,528	100	9,478	57.3	63.6	13.9	3.27	3.22–3.32
Parkinsonism-related mortality[f]	12,608	1.2	7,472	59.3	81.6	7.2	109	0.7	69	63.3	71.8	10.0	1.48	1.23–1.79

95 % CI = 95 % confidence interval, HR = hazard ratio, ICPC = International Classification of Primary Care, ID = intellectual disability, M = mean, OR = odds ratio, SD = standard deviation.

[a] ID prevalence 1.5 %.

[b] Selection based on all patients who were 18 years or older in 2021 and registered at a general practitioner service for a minimum of 3 months between 2019 and 2021 (mean registration duration of 2.1 (SD 0.9) versus 2.0 (SD 0.9) years).

[c] Refers to age in years in 2021.

[d] Record of chronic episode containing ICPC code N87 parkinsonism/PD, diagnosed at any time.

[e] Adjusted for age and sex. General population is reference group.

[f] Underlying cause of death primary (ICD-10 code G20, 97.8 % of all cases) or secondary (ICD-10 code G21, 2.2 % of all cases) parkinsonism.

validated screening and rating scales may aid in this regard. On a societal level, medical professional societies, healthcare facilities and policy makers will need to better prepare for appropriate guidelines that focus on the recognition of parkinsonism and installation of appropriate care. This is particularly relevant in light of the increase in life expectancy in people with ID [7].

To interpretate our findings properly, several methodological limitations should be considered. First, individuals with ID whose medical care is included in their long-term support package are likely to be underrepresented in the Dutch general practitioner data, given that patients with ID in residential settings not all had a general practitioner involved in their medical care [8]. This group was however included in the mortality statistics. Second, people with mild ID may be under-identified as they are less likely to utilize the long-term support services of which data were used for identification purposes. Third, the diagnostic information from primary care was restricted to 3-position ICPC-codes, which did not allow us to differentiate between PD and other forms of parkinsonism, as this distinction is defined by subcodes [4]. Fourth, information on use of medication that may cause parkinsonism was not available. However, even if that information were available, it must be taken into account that drug-induced parkinsonism and other causes of parkinsonism are not mutually exclusive, and that dopaminergic imaging would be required to establish a more definitive diagnosis. Fifth, while large population-based datasets were used to identify a broad spectrum of individuals with ID, these datasets lacked information on ID aetiology, which could help to further understand the causal pathways. Lastly, errors due to data handling should be considered. Accuracy of the diagnostic information in the records of a general practitioner depends on information provided by the medical specialist, as well as the quality of the registration by general practitioners [9].

In conclusion, our exploratory analyses support the idea that people with ID are at increased risk for developing parkinsonism, that may not only be related to their use of antipsychotics or other drugs. Future research will be necessary to confirm the findings, and to identify any genetic or other subgroups at risk.

CRediT authorship contribution statement

Erik Boot: Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Agnies M. van Eeghen:** Writing – review & editing, Investigation. **Bas R. Bloem:** Writing – review & editing, Investigation. **Bart P. van de Warrenburg:** Writing – review & editing, Investigation. **Maarten Cuypers:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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