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Risk of Parkinsonism After Exposure to Different Types of Gadolinium-Based Contrast Agents: A Nationwide Population-Based Cohort Study of 222,977 Individuals

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Objective: This study aimed to assess the association between exposure to gadolinium-based contrast agents (GBCAs) and the risk of parkinsonism according to the GBCA type.

Materials and Methods: Individuals aged ≥40 years who underwent first-ever magnetic resonance imaging (MRI) examinations between 2011 and 2014 were identified from the Korean nationwide population-based health insurance claims database and followed up until 2022. Individuals were divided into those who underwent at least one GBCA-enhanced MRI, and those who underwent only non-enhanced MRI. GBCA-exposed individuals were further categorized into those exposed only to linear or macrocyclic GBCAs, after excluding those exposed to both types. The primary event of interest was all-cause parkinsonism. Secondary events included all-cause parkinsonism requiring medication, Parkinson's disease (PD), atypical parkinsonism, and secondary parkinsonism. Hazard ratios (HRs) were estimated using multivariable Cox proportional hazard regression models for exposure to linear and macrocyclic GBCAs, with the non-enhanced MRI group serving as a reference. The models were adjusted for age, sex, smoking status, alcohol consumption, regular exercise, body mass index, estimated glomerular filtration rate, and comorbidities. Subgroup analyses were performed according to age, sex, renal function, and history of cancer.

Results: A total of 222,977 individuals were included in this study. Among them, 92,230, 48,335, and 82,412 individuals underwent non-enhanced, linear GBCA-enhanced, and macrocyclic GBCA-enhanced MRI, respectively. Exposure to linear GBCAs slightly increased the risk of all-cause parkinsonism (adjusted HR, 1.13 [97.5% confidence interval, 1.08–1.19]), while exposure to macrocyclic GBCAs did not increase the risk (adjusted HR, 1.00 [97.5% confidence interval, 0.95–1.05]). The results were similar for all-cause parkinsonism requiring medication, PD, and secondary parkinsonism, whereas no significant association was observed for atypical parkinsonism.

Conclusion: Exposure to linear GBCAs may slightly increase the risk of parkinsonism in adults, whereas exposure to macrocyclic GBCAs may not. Caution should be exercised when using linear GBCAs until further evidence emerges.

Keywords: Gadolinium; Contrast; Linear; Macrocyclic; Magnetic resonance imaging; Brain; Parkinsonism; Parkinson's disease; Toxicity; Side effect

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INTRODUCTION

Gadolinium-based contrast agents (GBCAs) have been used in the enhancement studies of magnetic resonance imaging (MRI) since 1988 and were considered exceptionally safe until cases of nephrogenic systemic fibrosis (NSF) were reported in patients with renal failure in 2006 [1,2]. NSF is a rare but devastating disorder characterized by widespread fibrosis of the skin and connective tissues [3]. Most GBCAs are excreted mainly through the renal system [4] and consequently remain longer in patients with renal failure. With prolonged exposure, toxic gadolinium (Gd^{3+}) ions are readily released from unstable linear-type GBCAs and accumulate in tissues, triggering skin fibrosis [5,6]. Macrocyclic GBCAs that hold free gadolinium ions within rigid closed-ring cages are kinetically inert and less likely to dechelate in the body [7]. Accordingly, fewer toxic gadolinium ions are released and only a few cases of NSF have been associated with the use of macrocyclic GBCAs in patients with renal failure [8].

Although incident NSF markedly decreased after regulatory actions were taken to avoid linear GBCAs in patients with renal failure [9], gadolinium retention in the brains of patients with normal renal function has emerged as another safety issue. Similar to NSF, greater gadolinium retention is assumed in linear GBCAs than in macrocyclic GBCAs [10,11]. Most studies have consistently provided evidence that gadolinium accumulates in the globus pallidus and dentate nucleus [12]. Although less frequently described, other iron- or ferritin-rich regions [13,14] including the substantia nigra, posterior thalamus, red nucleus, colliculi, and superior cerebellar peduncle have also been reported as gadolinium deposition sites [15]. These regions are involved in motor control and have been implicated in various forms of parkinsonism, including secondary, atypical, and Parkinson's disease (PD) [16-23], raising the possibility that gadolinium retention in these areas negatively affects motor function and promotes parkinsonian symptoms.

Despite ample evidence of radiological and histological gadolinium retention in the brain, there are no established reports linking histological changes or adverse clinical outcomes to gadolinium exposure [4]. A previous population-based study [24] also failed to find a significant association between gadolinium exposure and incident parkinsonism. However, this study did not investigate how different types of GBCAs or varying levels of renal function affect the risk of parkinsonism after GBCA exposure [24]. Therefore, we aimed to assess the influence of GBCA exposure on the development of parkinsonism according to the GBCA type in a large nationwide population-based cohort in South Korea.

MATERIALS AND METHODS

Study Population

The Institutional Review Board of the Yonsei University Health System, Severance Hospital exempted the study protocol (IRB No. 4-2024-0623) and waived the requirement for written patient consent based on a fully de-identified database. This retrospective cohort study collected patient data recorded between 2002 and 2022 from the Korean National Health Insurance Service (NHIS) database (Supplementary Text 1). Among all individuals who underwent at least one MRI scan (Supplementary Table 1 for the list of MRI codes) between January 2011 and December 2014, we identified those who underwent their first MRI examination within the same period, excluding those who had prior MRIs before 2011. We tracked all available data for the included individuals until December 31, 2022 (Fig. 1).

Exposures

Individuals who underwent at least one GBCA-enhanced MRI were considered exposed to GBCAs, whereas those who underwent only non-enhanced MRI during the study period were considered unexposed. Individuals exposed to GBCAs were further divided into those exposed only to either linear or macrocyclic GBCAs, after excluding individuals who were exposed to both types during the study period. The first GBCA-enhanced or non-enhanced MRI was defined as the index MRI, and the index MRI examination was set as the index date (Supplementary Text 1, Supplementary Table 2).

We excluded individuals who were <40 years old on the index date; those with index MRI of the brain or spine; those diagnosed with parkinsonism before or within one year after the index date to adequately wash out the individuals with prevalent parkinsonism; those who did not participate in the National Health Screening Program (NHSP), which provide information on covariables, within

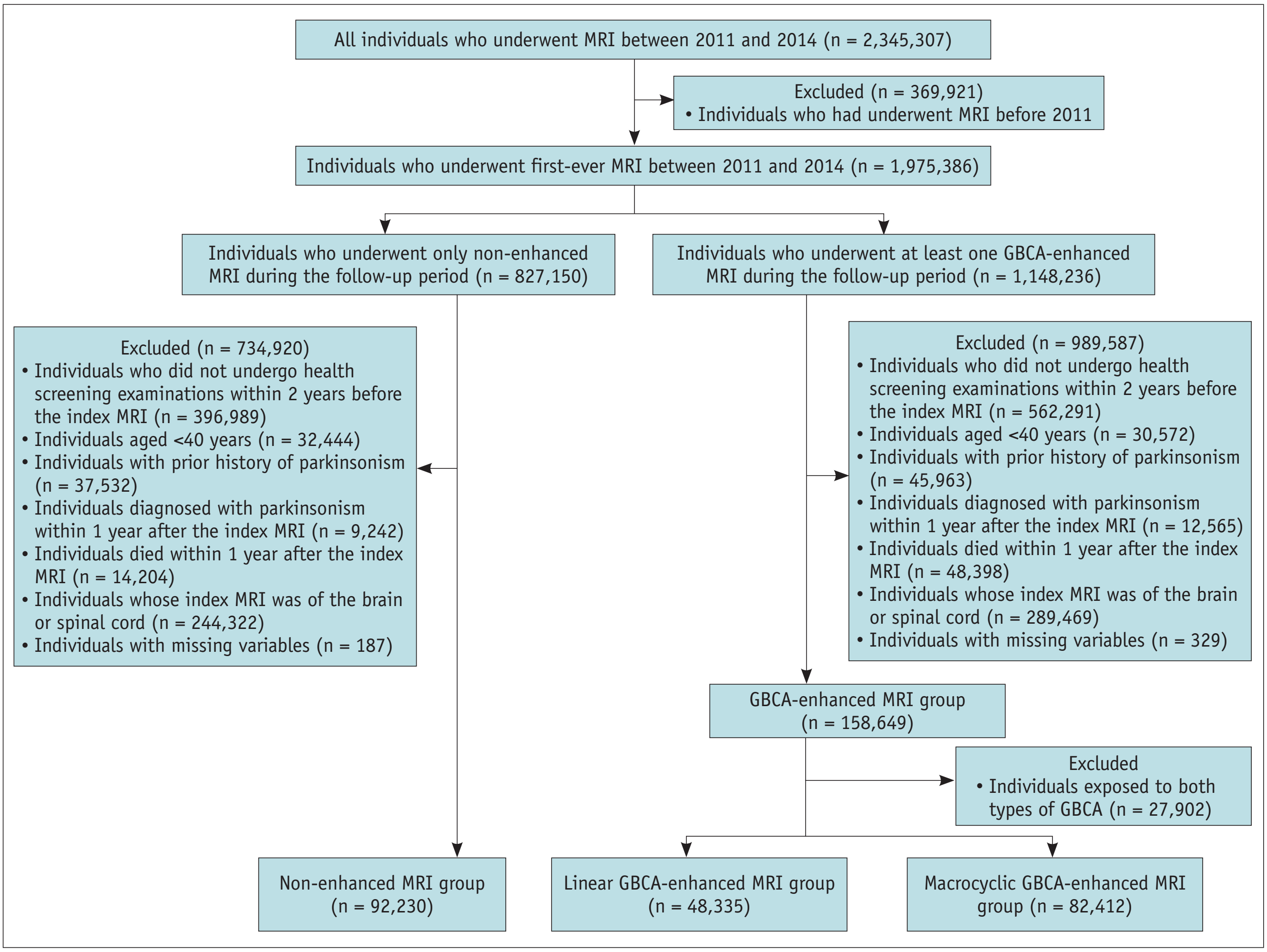

Fig. 1. Selection flowchart for the study population. MRI = magnetic resonance imaging, GBCA = gadolinium-based contrast agent

two years prior to the index date (missing NHSP data); those who died within one year after the index date; and those with any missing variables.

Events

The primary event of interest was incident all-cause parkinsonism defined by any of the following International Classification of Diseases, 10th revision (ICD-10) diagnosis codes: G20-3, G25, or G26. Secondary events included incident all-cause parkinsonism requiring medication, PD, atypical parkinsonism, and secondary parkinsonism. PD was defined in two ways: by the ICD-10 code G20 (without any codes of G21-3, G25, or G26) with anti-PD medication and by the same ICD-10 code with the PD registration code used in the rare and intractable disease registration program in Korea. Atypical parkinsonism was defined by G23 without any codes of G20-2, G25, or G26, and secondary parkinsonism was defined by G21, G22, G25, or G26 without G20 or G23 (Supplementary Text 1, Supplementary Tables 3, 4). The study population was followed up from the index date until the date of death, date of the first reported event, or December 31, 2022, whichever occurred first.

Covariables

Smoking status, alcohol consumption, physical activity, body mass index (BMI), and estimated glomerular filtration rate (eGFR), defined based on NHSP data collected within two years prior to the index date, as well as a history of hypertension, diabetes mellitus, dyslipidemia, and cancers of any form before the index date, were used as covariables (Supplementary Text 1, Supplementary Table 4).

Statistical Analysis

Baseline demographic and clinical characteristics were compared among the non-enhanced MRI, linear GBCA-enhanced MRI, and macrocyclic GBCA-enhanced MRI groups

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using one-way analysis of variance or the Kruskal–Wallis test for continuous variables, and the chi-square test for categorical variables. Post-hoc pairwise comparisons were performed using Student's *t*-test, Mann–Whitney U test, or chi-square test with Bonferroni correction for multiple comparisons when appropriate. The incidence rate of parkinsonism was calculated as the number of events per 1,000 person-years of follow-up.

Cox proportional hazards regression analyses were conducted to evaluate the associations between GBCA exposure and parkinsonism according to the type of GBCA, and risks were expressed as hazard ratios (HRs) with 97.5% confidence intervals (CIs), with Bonferroni correction for multiple comparisons. Analyses were conducted with and without adjustment for covariables including age, sex, smoking, alcohol consumption, regular exercise, BMI, eGFR, and comorbidities. Multivariable-adjusted survival curves were plotted based on multivariable Cox proportional hazards regression models to visualize the event-free survival. Additional subgroup analyses stratified according to age (<65 vs. ≥65 years), sex (male vs. female), eGFR (<60 vs. ≥60 mL/min/1.73 m^2), and history of cancer were also conducted. These analyses included all the covariables used in the multivariable models. Multiple-comparison correction was not applied, and the results are presented as 95% CI.

A two-tailed $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Study Cohort

A total of 222,977 individuals who underwent MRI were included in this study. Among them, 92,230, 48,335, and 82,412 individuals underwent non-enhanced MRI, linear GBCA-enhanced MRI, and macrocyclic GBCA-enhanced MRI, respectively (Fig. 1). The demographic and clinical characteristics of the study cohort are summarized in Table 1.

Risk of Parkinsonism According to GBCA Exposure

Individuals who were exposed only to linear GBCAs had a slightly higher risk of all-cause parkinsonism than those who underwent non-enhanced MRI (adjusted HR, 1.13 [97.5% CI, 1.08 to 1.19]), while those who were exposed only to macrocyclic GBCAs showed no increased risk (adjusted HR, 1.00 [97.5% CI, 0.95 to 1.05]) (Table 2). The multivariable-adjusted survival curve showed a lower all-cause parkinsonism-free survival rate in individuals exposed only to linear GBCAs than in those unexposed to GBCA and those exposed only to macrocyclic GBCAs (Fig. 2).

Table 1. Demographic and clinical characteristics of the study cohort

Characteristics	Non-enhanced MRI (n = 92,230)	Linear GBCA-enhanced MRI (n = 48,335)	Macrocyclic GBCA-enhanced MRI (n = 82,412)	*P**	Post hoc analysis	
					P1†	*P2*‡
Age, yr	56.8 ± 10.9	60.4 ± 10.6	58.9 ± 11.1	<0.001	<0.001	<0.001
Sex, male	48,523 (52.6)	28,822 (59.6)	31,465 (38.2)	<0.001	<0.001	<0.001
Current smoker	19,499 (21.1)	10,866 (22.5)	10,369 (12.6)	<0.001	<0.001	<0.001
Alcohol drinker	40,846 (44.3)	18,908 (39.1)	27,574 (33.5)	<0.001	<0.001	<0.001
Regular exercise	13,519 (14.7)	7,123 (14.7)	12,316 (14.9)	0.231	0.692	0.092
BMI, kg/m^2	24.6 ± 3.2	24.0 ± 3.1	23.9 ± 3.2	<0.001	<0.001	<0.001
eGFR, mL/min/1.73 m^2	87.5 ± 42.9	87.6 ± 40.4	87.0 ± 37.4	0.007	0.420	0.013
Comorbidities						
Hypertension	39,418 (42.7)	23,615 (48.9)	36,505 (44.3)	<0.001	<0.001	<0.001
Diabetes mellitus	15,380 (16.7)	10,848 (22.4)	14,443 (17.5)	<0.001	<0.001	<0.001
Dyslipidemia	33,420 (36.2)	17,017 (35.2)	32,190 (39.1)	<0.001	<0.001	<0.001
Cancer	5,144 (5.6)	28,085 (58.1)	61,671 (74.8)	<0.001	<0.001	<0.001
Follow-up duration, yr	9.6 [8.5–10.7]	9.0 [4.7–10.5]	9.0 [8.1–10.2]	<0.001	<0.001	<0.001
Death during follow-up	9,096 (9.9)	16,370 (33.9)	15,853 (19.2)	<0.001	<0.001	<0.001

Values are presented as numbers (%), and as mean ± standard deviation or median [interquartile range].
*Comparison between non-enhanced MRI, linear GBCA-enhanced MRI, and macrocyclic GBCA-enhanced MRI groups, †Comparison between non-enhanced MRI and linear GBCA-enhanced MRI groups; significant at $P < 0.025$ after multiple-comparison correction, ‡Comparison between non-enhanced MRI and macrocyclic GBCA-enhanced MRI groups; significant at $P < 0.025$ after multiple-comparison correction.
MRI = magnetic resonance imaging, GBCA = gadolinium-based contrast agent, BMI = body mass index, eGFR = estimated glomerular filtration rate

Table 2. Risk of all-cause parkinsonism according to type of GBCA

GBCA use and type	No.	Events	Person-years	Incidence rate (95% CI)*	Crude hazard ratio (97.5% CI)	Adjusted hazard ratio (97.5% CI)†
Non-enhanced MRI	92,230	7,257	846,626	8.57 (8.38–8.77)	1 [reference]	1 [reference]
Linear GBCA-enhanced MRI	48,335	3,744	375,437	9.97 (9.66–10.30)	1.19 (1.14–1.25)	1.13 (1.08–1.19)
Macrocyclic GBCA-enhanced MRI	82,412	5,975	696,075	8.58 (8.37–8.80)	1.02 (0.98–1.06)	1.00 (0.95–1.05)

*Incidence per 1,000 person-years, †Adjusted for age, sex, smoking, alcohol drinking, regular exercise, body mass index, estimated glomerular filtration rate, and comorbidities.
GBCA = gadolinium-based contrast agent, CI = confidence interval, MRI = magnetic resonance imaging

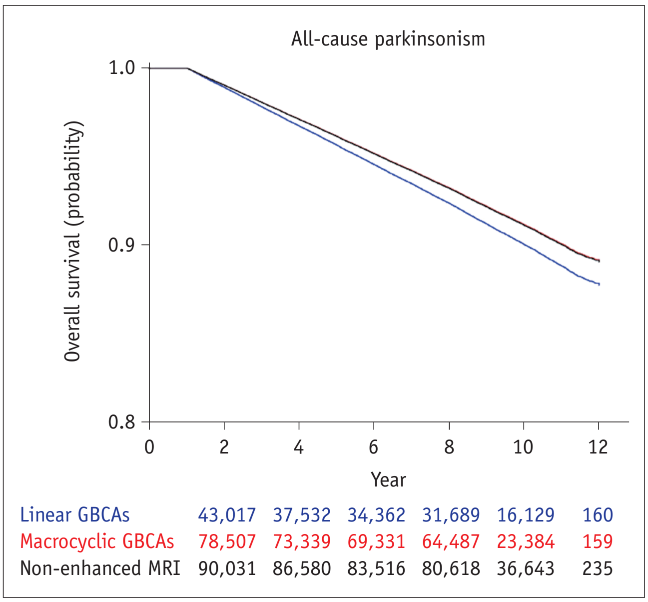

Fig. 2. Multivariable-adjusted survival curve comparing all-cause parkinsonism-free survival among individuals who underwent non-enhanced MRI (black), linear GBCA-enhanced MRI (blue), and macrocyclic GBCA-enhanced MRI (red). Adjusted for age, sex, smoking, alcohol drinking, regular exercise, body mass index, estimated glomerular filtration rate, and comorbidities. The curves for non-enhanced MRI and macrocyclic GBCA-enhanced MRI overlap almost completely. MRI = magnetic resonance imaging, GBCA = gadolinium-based contrast agent

A slightly increased risk associated with exposure only to linear GBCAs was similarly observed for all-cause parkinsonism requiring medication (adjusted HR, 1.08 [97.5% CI, 1.01 to 1.16]). The risk of PD also slightly increased after exposure to linear GBCAs only when PD was defined based on ICD-10 code and registration code (adjusted HR, 1.29 [97.5% CI, 1.06 to 1.57]), whereas no significant association was observed when PD was defined based on ICD-10 code and medication criteria. A slightly increased risk associated with exposure only to linear GBCAs was maintained for secondary parkinsonism (adjusted HR, 1.13 [97.5% CI, 1.07 to 1.19]), but not for atypical parkinsonism. In contrast, individuals exposed only to macrocyclic GBCAs did not have an increased risk of any of the secondary events compared to the non-enhanced group (Table 3). The corresponding multivariable-adjusted survival curves are shown in Figure 3.

Risk of All-Cause Parkinsonism After GBCA Exposure According to Subgroup

The results are summarized in Table 4. The slightly increased risk of all-cause parkinsonism after exposure to linear GBCAs was maintained regardless of sex (adjusted HR, 1.16 [95% CI, 1.09 to 1.24] for male and 1.10 [95% CI, 1.03 to 1.17] for female). The slightly increased risk from exposure to linear GBCAs was also maintained in individuals ≥65 years old (adjusted HR, 1.20 [95% CI, 1.13 to 1.28]), those with normal renal function (adjusted HR, 1.14 [95% CI, 1.04 to 1.20]), and those who had no history of cancer (adjusted HR, 1.14 [95% CI, 1.08 to 1.20]). However, individuals aged <65 years, those with decreased renal function, and those with a history of cancer did not show increased risks. The risk of all-cause parkinsonism slightly decreased when female individuals were exposed to macrocyclic GBCAs (adjusted HR, 0.93 [95% CI, 0.88 to 0.98]) compared to those who underwent non-enhanced MRIs.

DISCUSSION

This nationwide population-based longitudinal study examined the association between GBCA exposure and the risk of parkinsonism according to the type of GBCA. In this study, we found that exposure to linear GBCAs was associated with a slightly increased risk of all-cause parkinsonism, whereas there was no significant association between macrocyclic GBCA exposure and the risk of parkinsonism. Sex did not affect the association between linear GBCA exposure and all-cause parkinsonism. The effect of linear GBCAs on the development of all-cause parkinsonism was maintained only in individuals aged ≥65 years, with normal renal function, and without a history of

Table 3. Risk of secondary events according to type of GBCA

Events, GBCA use and type	No.	Events	Person-years	Incidence rate (95% CI)*	Crude hazard ratio (97.5% CI)	Adjusted hazard ratio (97.5% CI)†
All-cause parkinsonism requiring medication						
Non-enhanced MRI	92,230	3,801	861,911	4.41 (4.27–4.55)	1 [reference]	1 [reference]
Linear GBCA-enhanced MRI	48,335	1,929	383,024	5.04 (4.82–5.27)	1.17 (1.10–1.25)	1.08 (1.01–1.16)
Macrocyclic GBCA-enhanced MRI	82,412	3,005	708,038	4.24 (4.09–4.40)	0.98 (0.93–1.03)	0.94 (0.88–1.01)
PD defined by diagnosis code and medication						
Non-enhanced MRI	92,230	929	874,010	1.06 (1.00–1.13)	1 [reference]	1 [reference]
Linear GBCA-enhanced MRI	48,335	538	388,944	1.38 (1.27–1.51)	1.34 (1.19–1.51)	1.14 (0.99–1.30)
Macrocyclic GBCA-enhanced MRI	82,412	845	716,541	1.18 (1.10–1.26)	1.13 (1.02–1.26)	1.03 (0.90–1.18)
PD defined by diagnosis and registration codes						
Non-enhanced MRI	92,230	415	875,704	0.47 (0.43–0.52)	1 [reference]	1 [reference]
Linear GBCA-enhanced MRI	48,335	266	389,911	0.68 (0.61–0.77)	1.49 (1.25–1.77)	1.29 (1.06–1.57)
Macrocyclic GBCA-enhanced MRI	82,412	417	717,941	0.58 (0.53–0.64)	1.26 (1.08–1.47)	1.14 (0.94–1.38)
Atypical parkinsonism						
Non-enhanced MRI	92,230	135	876,636	0.15 (0.13–0.18)	1 [reference]	1 [reference]
Linear GBCA-enhanced MRI	48,335	68	390,515	0.17 (0.14–0.22)	1.17 (0.84–1.64)	1.15 (0.80–1.65)
Macrocyclic GBCA-enhanced MRI	82,412	104	718,931	0.14 (0.12–0.18)	0.96 (0.72–1.29)	1.03 (0.72–1.48)
Secondary parkinsonism						
Non-enhanced MRI	92,230	6,450	849,640	7.59 (7.41–7.78)	1 [reference]	1 [reference]
Linear GBCA-enhanced MRI	48,335	3,283	377,125	8.71 (8.41–9.01)	1.17 (1.12–1.23)	1.13 (1.07–1.19)
Macrocyclic GBCA-enhanced MRI	82,412	5,241	698,581	7.50 (7.30–7.71)	1.00 (0.96–1.04)	0.99 (0.94–1.04)

*Incidence per 1,000 person-years, †Adjusted for age, sex, smoking, alcohol drinking, regular exercise, body mass index, estimated glomerular filtration rate, and comorbidities.
GBCA = gadolinium-based contrast agent, CI = confidence interval, MRI = magnetic resonance imaging, PD = Parkinson's disease

cancer. The slightly increased risk associated with exposure to linear GBCAs was maintained for the development of all-cause parkinsonism requiring medication, PD, and secondary parkinsonism, but not for atypical parkinsonism. The relatively small number of individuals diagnosed with atypical parkinsonism could have resulted in a lower statistical power, which may partly explain this non-significant finding.

Because gadolinium deposition in the brain has been observed even in patients with normal kidney function after GBCA exposure, its effects on motor function have been evaluated in several preclinical and clinical studies. Thus far, the prevailing view is that the deposited gadolinium does not induce structural brain damage or have a significant clinical impact [25]. Animal studies have failed to demonstrated any significant effects of GBCA exposure on motor function, even at doses up to an 80 times higher than those used in humans [26-29]. Autopsy studies also revealed no notable histological changes associated with GBCA deposition in the brain [28,30,31]. Additionally, a population-based study reported no significantly increased risk of incident parkinsonism after GBCA exposure [24]. However, in vitro studies have suggested that gadolinium may be neurotoxic, acting as a calcium antagonist, because of its similar atomic radius [32,33]. Because calcium is essential for neuronal functions, including neurotransmission, energy metabolism, and synaptic signaling [25], the possibility of neuronal dysfunction due to retained gadolinium remains a concern. Supporting this, a previous study [34] showed decreased metabolism in the globus pallidus and dentate nucleus regions associated with GBCA deposition, motor control, and parkinsonian symptoms in the GBCA-exposed group [12,16,21-23], although caution is required when interpreting these results because of the small sample size and younger control group. Given that linear GBCAs exhibit lower kinetic stability and are therefore more prone to release free gadolinium and demonstrate neurotoxicity at lower concentrations than macrocyclic GBCAs, as observed in in vitro experiments [35], their clinical impact should be more thoroughly investigated.

Our results showed that linear, but not macrocyclic, GBCAs slightly increased the risk of all-cause parkinsonism in individuals aged ≥40 years. The clinical impact of sex on gadolinium retention remains unclear with inconsistent

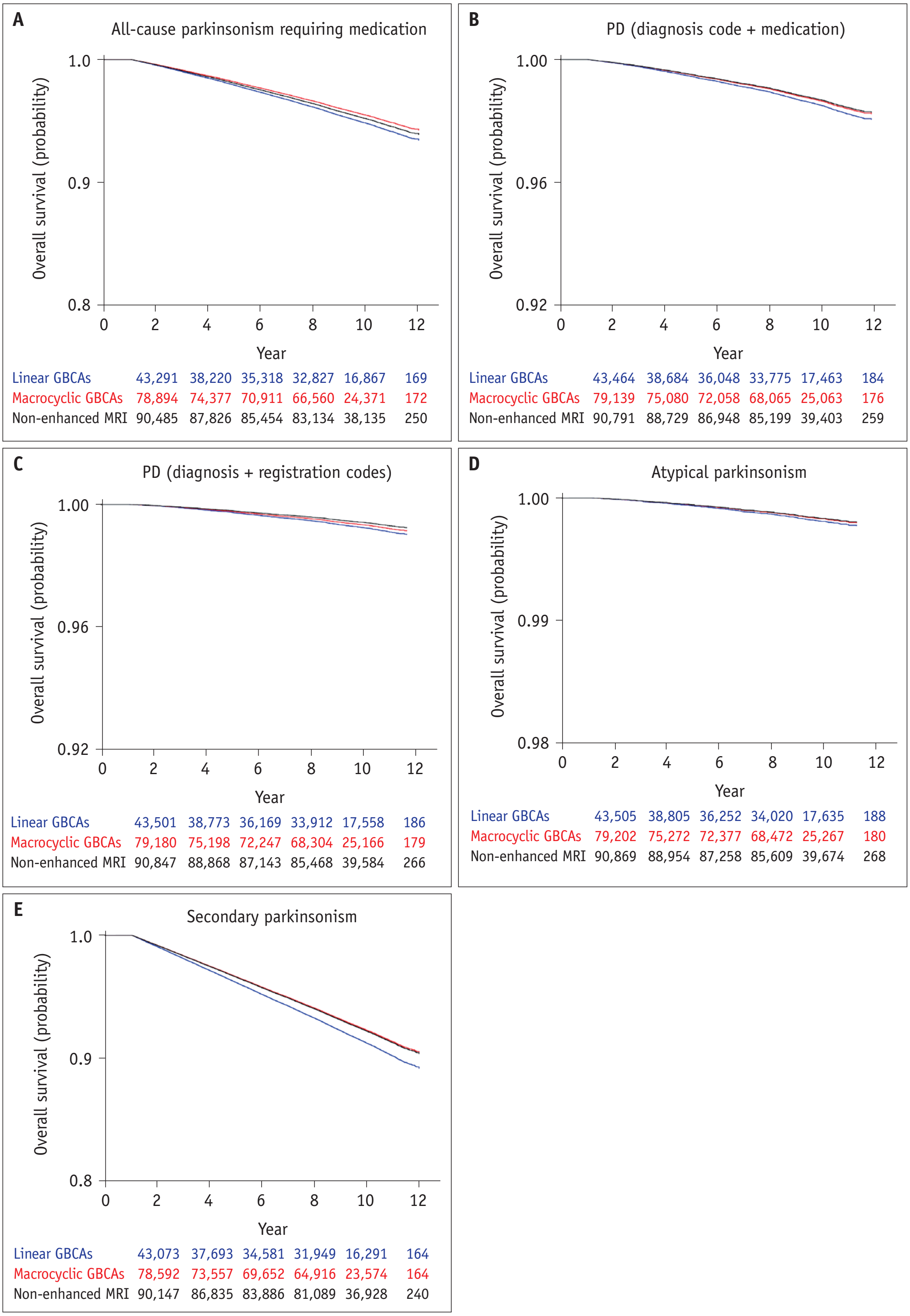

Fig. 3. Multivariable-adjusted survival curves comparing secondary event-free survival among individuals who underwent non-enhanced MRI (black), linear GBCA-enhanced MRI (blue), and macrocyclic GBCA-enhanced MRI (red). **A-E:** Adjusted for age, sex, smoking, alcohol drinking, regular exercise, body mass index, estimated glomerular filtration rate, and comorbidities. In the graphs for PD defined by diagnosis code and medication **(B)**, atypical parkinsonism **(D)**, and secondary parkinsonism **(E)**, the curves for non-enhanced MRI and macrocyclic GBCA-enhanced MRI show substantial overlap. MRI = magnetic resonance imaging, GBCA = gadolinium-based contrast agent, PD = Parkinson's disease

Table 4. Risk of all-cause parkinsonism after GBCA exposure according to age, sex, and renal function, and history of cancer

Subgroup	GBCA use and type	No.	Events	Person-years	Incidence rates (95% CI)*	Adjusted hazard ratio (95% CI)†
Age, yr						
<65	Non-enhanced MRI	69,922	4,304	667,002	6.45 (6.26–6.65)	1 [reference]
	Linear GBCA-enhanced MRI	30,880	1,712	259,554	6.60 (6.29–6.91)	1.05 (0.99–1.11)
	Macrocyclic GBCA-enhanced MRI	55,272	2,974	489,633	6.07 (5.86–6.30)	0.97 (0.91–1.03)
≥65	Non-enhanced MRI	22,308	2,953	179,624	16.4 (15.9–17.0)	1 [reference]
	Linear GBCA-enhanced MRI	17,455	2,032	115,883	17.5 (16.8–18.3)	1.20 (1.13–1.28)
	Macrocyclic GBCA-enhanced MRI	27,140	3,001	206,441	14.5 (14.0–15.1)	0.99 (0.93–1.06)
Sex						
Male	Non-enhanced MRI	48,523	2,938	446,273	6.58 (6.35–6.83)	1 [reference]
	Linear GBCA-enhanced MRI	28,822	2,009	212,413	9.46 (9.06–9.88)	1.16 (1.09–1.24)
	Macrocyclic GBCA-enhanced MRI	31,465	2,584	251,059	10.3 (9.91–10.7)	1.03 (0.96–1.10)
Female	Non-enhanced MRI	43,707	4,319	400,353	10.8 (10.5–11.1)	1 [reference]
	Linear GBCA-enhanced MRI	19,513	1,735	163,024	10.6 (10.2–11.2)	1.10 (1.03–1.17)
	Macrocyclic GBCA-enhanced MRI	50,947	3,391	445,016	7.62 (7.37–7.88)	0.93 (0.88–0.98)
eGFR, mL/min/1.73 m^2						
<60	Non-enhanced MRI	6,544	778	53,568	14.5 (13.5–15.6)	1 [reference]
	Linear GBCA-enhanced MRI	3,874	383	27,308	14.0 (12.7–15.5)	1.03 (0.90–1.18)
	Macrocyclic GBCA-enhanced MRI	6,329	631	49,143	12.8 (11.9–13.9)	0.93 (0.81–1.05)
≥60	Non-enhanced MRI	85,686	6,479	793,058	8.17 (7.97–8.37)	1 [reference]
	Linear GBCA-enhanced MRI	44,461	3,361	348,129	9.65 (9.34–9.98)	1.14 (1.09–1.20)
	Macrocyclic GBCA-enhanced MRI	76,083	5,344	636,932	8.26 (8.04–8.48)	1.00 (0.96–1.05)
Cancer						
No	Non-enhanced MRI	87,086	6,827	805,045	8.48 (8.28–8.68)	1 [reference]
	Linear GBCA-enhanced MRI	20,250	1,758	171,843	10.2 (9.77–10.7)	1.14 (1.08–1.20)
	Macrocyclic GBCA-enhanced MRI	20,741	1,706	180,574	9.45 (9.01–9.90)	1.02 (0.97–1.08)
Yes	Non-enhanced MRI	5,144	430	41,580	10.3 (9.41–11.4)	1 [reference]
	Linear GBCA-enhanced MRI	28,085	1,986	203,593	9.75 (9.34–10.2)	1.04 (0.94–1.16)
	Macrocyclic GBCA-enhanced MRI	61,671	4,269	515,500	8.28 (8.04–8.53)	0.91 (0.82–1.01)

*Incidence per 1,000 person-years, †Adjusted for age, sex, smoking, alcohol drinking, regular exercise, body mass index, eGFR, and comorbidities for all subgroup analyses.
GBCA = gadolinium-based contrast agent, eGFR = estimated glomerular filtration rate, CI = confidence interval, MRI = magnetic resonance imaging

findings. Some studies have reported no sex differences in gadolinium retention in animal or human brains [27,36], whereas others have suggested potential sex-specific differences [37,38]. Although it is well known that females are less vulnerable to neurotoxins that induce parkinsonism, at least in part due to the neuroprotective effects of estrogen [39], the slightly increased risk of all-cause parkinsonism after exposure to linear GBCAs was statistically significant not only in males but also in females in our study. However, we unexpectedly observed that females had a slightly lower risk of all-cause parkinsonism after exposure to macrocyclic GBCAs, and this association is difficult to explain using currently available knowledge.

In this study, individuals younger than 65 years, those with decreased renal function, and those with a history of cancer did not show any significant association between linear GBCA exposure and the development of all-cause parkinsonism. To date, few studies on the effect of age on gadolinium retention have focused on differences between adult and pediatric or immature brains [27,37]. While a study in adults reported the effect of age on gadolinium retention on MRI, the direction of the association differed across brain regions [40]. Furthermore, as the signal intensities of the globus pallidus and dentate nucleus change with age, defining the effect of age on gadolinium retention using MRI is complicated [41]. The typical motor symptoms of PD occur when there is 60% loss of nigral dopaminergic neurons and 80% loss of striatal dopamine

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[42,43]. Similar to the age-related decline in the number and function of nigral dopaminergic neurons [44,45], reduced brain reserves in regions with gadolinium retention may make older adults more susceptible to parkinsonian symptoms, as preexisting neuronal loss could lower the threshold for environmental toxins, such as free gadolinium ions, to induce parkinsonism.

Because NSF mainly occurs in patients with renal failure after exposure to linear GBCA [1,2], longer retention of GBCAs, more dechelation of free gadolinium ions, and higher deposition of free gadolinium in various tissues are expected in patients with renal dysfunction. Therefore, we expected a higher risk of parkinsonism in individuals with lower eGFR. However, previous studies have reported inconsistent results regarding the association between renal dysfunction and gadolinium deposition. Some studies have reported that renal dysfunction promotes gadolinium retention [46], whereas others have reported either only a short-term effect [47] or no significant effect [48,49]. In our study, a slightly increased risk of all-cause parkinsonism after exposure to linear GBCAs was observed in individuals with normal renal function but not in those with decreased renal function. The lower statistical power due to fewer subjects included in this subgroup may explain why the significant association disappeared. When we stratified individuals using a different cutoff (eGFR ≥90 vs. <90 mL/min/1.73 m^2), resulting in more balanced subgroup size, the significant effect of linear GBCAs persisted in both subgroups (Supplemental Table 5). Moreover, if patients undergo GBCA-enhanced MRI despite impaired renal function, it is likely that they have more severe disease, such as malignancy or infection, where the presence of contrast enhancement would be helpful for diagnosis. As death from a more severe state of disease is a competing risk factor for the development of parkinsonism in this subgroup, survival bias might also explain the lack of a significant association. Additionally, because a lower eGFR may predispose individuals to parkinsonism through systemic inflammation and oxidative stress [50,51], this baseline vulnerability could result in a ceiling effect or residual confounding, attenuating the apparent impact of gadolinium exposure in the low-eGFR group. Further studies should be conducted to reach a more definitive conclusion regarding the relationship between renal dysfunction and gadolinium retention, and its clinical impact.

An inverse relationship between cancer and PD has been consistently reported. Patients with PD have a low risk of developing cancer [52-55], whereas those with cancer have a low risk of developing PD [56,57]. These two conditions involve similar cellular processes but in opposite directions with respect to cell cycle control. Increased cell proliferation and apoptosis resistance in cancer cells may have a protective effect against neurodegenerative changes characterized by increased cell death. This protective effect might mitigate the harmful effects of linear GBCA on the brain. Moreover, patients with cancer who undergo GBCA-enhanced MRI may also suffer from more severe disease such as distant metastasis, than those who undergo non-enhanced MRI. Therefore, survival bias may also explain the lack of a significant association between exposure to linear GBCAs and the development of all-cause parkinsonism in individuals with a history of cancer in our study.

Recently, a population-based cohort study reported associations between GBCA exposure and the development of PD, considering the type of GBCA, for the first time [58]. According to this study, the GBCA-exposed group showed a higher incidence of PD than the non-exposed group, regardless of the GBCA type. While all GBCA-exposed groups were assumed to have undergone MRI, the authors did not consider MRI examination status when defining the non-exposed group. Furthermore, the authors did not consider the body regions examined by MRI. To appropriately define the control group in our study, we investigated the association of MRI examination and MRI body regions with the incidence of PD. According to this preliminary analysis, individuals who underwent MRI, even only non-enhanced MRI, and individuals who underwent brain or spine MRI showed almost four times and twice a higher risk of PD compared to those who had not undergone MRI and those who underwent other body region MRI, respectively (Supplementary Text 2, Supplementary Fig. 1, Supplementary Tables 6-8). Individuals with prodromal symptoms (e.g., hyposmia, sleep disorder) of PD [59] or symptoms associated with risk factors (e.g., head trauma) for PD development [60] might undergo MRI, particularly brain and spine MRI, more often; the increased risk of PD noted in the previous study might be an overestimation [58]. To minimize the possibility of these confounders, we defined the control group as individuals who underwent only non-enhanced MRI and excluded individuals who underwent an index MRI of the brain or spine from the analysis. Exposure to any GBCA, regardless of the type, was not significantly associated with the risk of parkinsonism, consistent with findings from a previous study [24] (Supplementary Tables 9, 10). Therefore, we believe that our findings, which suggest that linear but not

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macrocyclic GBCAs may have an adverse clinical impact on the brain, are more reliable.

Our study has several limitations. First, we might have missed GBCA exposures or MRI examinations that took place before January 1, 2002, and outside our country. Second, individuals who did not participate in NHSPs within two years prior to the index MRI were excluded because covariable information was unavailable. This exclusion may have introduced a selection bias and decreased the statistical power, limiting the generalizability of our findings to the full population. Third, the follow-up duration after GBCA exposure might not have been long enough to fully assess the relationship between exposure and the development of parkinsonism. Fourth, data on the indications for MRI were lacking. Although we excluded individuals with PD or other parkinsonism diagnosed before or within one year after the index date and individuals with index MRIs of the brain and spine, some with prodromal stages of PD or parkinsonism might have undergone GBCA-enhanced MRI. However, the neurotoxic effects of free gadolinium ions may render individuals at risk or with subclinical disease more susceptible to symptom manifestations and earlier diagnosis, rather than to the development of the disease itself. Therefore, the inclusion of individuals in the prodromal stage in our study population may not necessarily be a major limitation, as linear GBCA exposure may have facilitated the clinical manifestation of preexisting subclinical pathology. Fifth, information on the dose and route (e.g., intravenous, intrathecal, or intra-articular) of the injected GBCAs was unavailable. Therefore, we could not estimate individual GBCA doses or assess the potential differences in neurotoxicity by injection route. Sixth, our primary analysis excluded individuals exposed to both linear and macrocyclic GBCAs to avoid an inherent immortal time bias. This bias arises because, for a patient to be classified into the mixed-exposure group, they must survive without the event for the period after their first GBCA exposure until they receive a different type of GBCA. This exclusion is a limitation as it precluded the assessment of any potential synergistic or independent effects from combined exposure. Although a supplementary time-dependent analysis of this group suggested an increased risk associated with exposure to both types of GBCAs (Supplementary Table 11), the interpretation of this subgroup remains complex and warrants caution. Finally, some types of parkinsonism, including drug-induced parkinsonism, are not treated with anti-PD medications. Therefore, in this study, we defined incident all-cause parkinsonism without considering medication as the primary event of interest to include as many individuals with any type of parkinsonism as possible. To improve the specificity of diagnostic ascertainment, we also defined incident parkinsonism requiring medication, PD, atypical parkinsonism, and secondary parkinsonism as secondary events. However, the possibility of misclassification due to the use of claims data remains an inevitable limitation. This must be considered when interpreting and applying our results.

In conclusion, our findings suggest that exposure to linear GBCAs may slightly increase the risk of parkinsonism in adults, whereas macrocyclic GBCAs may not confer this risk. Therefore, until further evidence emerges, caution should be exercised when using linear GBCAs.

Supplement

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Availability of Data and Material

The datasets generated or analyzed during the study are not publicly available. The datasets were retrieved from the Korean National Health Insurance Service (NHIS) database specifically for this study. The original and retrieved datasets, which contain pseudonymised records at the individual level, are stored in a secure digital research environment at NHIS. These data are accessible to researchers following approval of specific study protocols by an official review committee (fees apply).

Conflicts of Interest

Kyunghwa Han, Statistical Consultant of the *Korean Journal of Radiology*, was not involved in the editorial evaluation or decision to publish this article. The remaining authors have declared no conflicts of interest.

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