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Investigating Parkinson's disease risk across farming activities using data mining and large-scale administrative health data



Pascal Petit¹ ✉, François Berger², Vincent Bonneterre^{3,4} & Nicolas Vuillerme^{1,5}

The risk of Parkinson's disease (PD) associated with farming has received considerable attention, in particular for pesticide exposure. However, data on PD risk associated with specific farming activities is lacking. We aimed to explore whether specific farming activities exhibited a higher risk of PD than others among the entire French farm manager (FM) population. A secondary analysis of real-world administrative insurance claim data and electronic health/medical records (TRACTOR project) was conducted to estimate PD risk for 26 farming activities using data mining. PD cases were identified through chronic disease declarations and antiparkinsonian drug claims. There were 8845 PD cases among 1,088,561 FMs. The highest-risk group included FMs engaged in pig farming, cattle farming, truck farming, fruit arboriculture, and crop farming, with mean hazard ratios (HRs) ranging from 1.22 to 1.67. The lowest-risk group included all activities involving horses and small animals, as well as gardening, landscaping and reforestation companies (mean HRs: 0.48–0.81). Our findings represent a preliminary work that suggests the potential involvement of occupational risk factors related to farming in PD onset and development. Future research focusing on farmers engaged in high-risk farming activities will allow to uncover potential occupational factors by better characterizing the farming exposome, which could improve PD surveillance among farmers.

Parkinson's disease (PD) is the most common muscular functioning disorder and the second most common neurodegenerative disease after Alzheimer's disease (AD), which affects millions of adults worldwide^{1–8}. PD has a long prodromal phase (up to several decades), during which many possible protective and risk factors can contribute to the onset, development, and/or progression of PD^{4,9}. PD is a multifactorial disorder characterized by complex interactions between genetic, behavioral, and environmental factors^{1,4,6,10,11}. Most individuals diagnosed with PD have no family history of the disease, since genetics only accounts for 5–10% of the PD case^{1,3,4}. Some protective (e.g., cigarette smoking)^{4,6,8,12,13} and risk factors (e.g., alcohol consumption)⁴ are modifiable, while others are not (e.g., aging and being a male)^{6,14}. Identifying and understanding these factors is crucial to developing effective prevention strategies and interventions^{9,11}.

The PD risk associated with farming activities has received considerable attention, in particular for pesticide exposure^{2,7,15}, which involves low-dose cocktail effects¹⁶. The exposure to pesticides and other stressors (agricultural exposome¹⁷) strongly depends on the type of crops and livestock. Because of the broad range of farming activities, it is essential to study specific farming types that could act as a proxy for distinct agricultural exposome, as highlighted by several recent works^{15,17–19}. However, to our knowledge, studies examining the association between PD risk and specific farming activities are limited, with investigations typically covering only 4–18 different types of crops and animal farming^{18–26}. Most of these studies are not population-based and rely on a case-control design, which is prone to recall bias. They also focus on limited geographical areas, with few sex-specific analyses^{17,19}. Furthermore, the existing research has primarily been conducted in France ($n = 5$)^{18–22}, the US ($n = 2$)^{25,26}, and Canada ($n = 2$)^{23,24}.

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French studies include two nationwide ecological studies^{18,20} as well as one case-control study²², one cross-sectional study²¹, and one prospective cohort¹⁹, which were limited geographically. To complement these studies, large-scale administrative health data can be used. Administrative health data does not require additional time or effort for data collection and is population-based, with large sample sizes spanning multiple years^{27–29}.

This study aimed, for the first time, to explore, using data mining and nationwide administrative health data, whether and to what extent specific farming activities exhibited a higher risk of PD than others, both overall and by sex category, among the entire French farm manager (FM) population. A FM refers to an individual who owns and/or oversees a farm (farm/company managers, owners, and self-employed persons) while performing a broad range of activities directly in the field (e.g., pesticide application, tractor driving, harvesting, or milking)³⁰.

Results

Population characteristics

There were 1,088,561 FMs, among which 8845 FMs were identified as PD cases in the main analysis (Supplementary Table 1), resulting in an incidence rate of 0.28 [95% CI: 0.27–0.29] PD cases per 1000 persons-years, with 0.40 [0.38–0.41] cases per 1000 persons-years for males and 0.24 [0.23–0.25] cases per 1000 persons-years for females (Supplementary Table 2). All PD cases had a drug reimbursement, while only 3034 (34%) had a LTI (long-term illness) declaration and 317 (4%) had an ODC declaration (occupational disease covered under workers' compensation statutes) for PD induced by pesticide exposure (Supplementary Table 3). Overall, FMs with PD were older than FMs without PD (mean age of 55 years old vs. 47 years old) (Table 1).

PD risk associated with farming activities

Associations varied by types of crops and animal farming (Table 2, and Supplementary Table 4). Elevated HRs were observed for fruit arboriculture (HR = 1.35 [1.08–1.68]), pig farming (HR = 1.39 [1.16–1.68]), dairy farming (HR = 1.48 [1.40–1.57]), mixed cattle farming (HR = 1.58 [1.41–1.46]), and crop farming (HR = 1.67 [1.53–1.82]) (Table 2). Modestly elevated HR were found for cow farming (HR = 1.22 [1.14–1.30]), truck farming (HR = 1.22 [1.09–1.36]), and unspecified and mixed farming (HR = 1.09 [1.02–1.16]). A positive trend was observed in viticulture (HR = 1.07 [0.94–1.21]) and ovine and caprine farming (HR = 1.07 [0.96–1.20]) (Table 2).

By contrast, the lowest-risk group included FMs engaged in gardening, landscaping and reforestation companies (HR = 0.81 [0.69–0.95]), small animal farming (HR = 0.51 [0.39–0.67]), training, dressage and riding clubs (HR = 0.49 [0.35–0.71]), stud farming (HR = 0.48 [0.37–0.63]), and rural craftsperson (HR = 0.14 [0.06–0.34]) (Table 2). Most activities did not exhibit any sex difference, with the exception of viticulture and stud farming (Supplementary Table 5). In viticulture, male FMs (HR = 1.23 [1.05–1.43]) had a more elevated HR than females (HR = 0.89 [0.72–1.11]) (Supplementary Table 5).

All sensitivity analyses yielded similar results to the main analysis (Fig. 1, Supplementary Table 4). There were a few exceptions. When excluding PD cases diagnosed in 2012 (SA1), the positive association with fruit arboriculture disappeared (Supplementary Table 4). Regarding the sensitivity analysis for which PD cases were solely identified using ODC declaration for PD induced by pesticide exposure (SA2), positive associations were found only for pig farming (HR = 2.47 [1.31–4.64]), mixed cattle farming (HR = 2.14 [1.37–3.33]), viticulture (HR = 1.65 [1.15–2.38]), unspecified and mixed farming (HR = 1.42 [1.05–1.93]), and dairy farming (HR = 1.32 [0.99–1.77]) (Supplementary Table 4).

The bar plot consists of two panels. The left panel shows the main analysis, with each bar representing the negative log-transformed adjusted *p*-value (*x*-axis) for each farming activity (*y*-axis). Red bars indicate a higher PD risk (hazard ratio > 1), green bars a lower PD risk (hazard ratio < 1), and white bars denote activities where the hazard ratio 95% confidence interval includes 1. Vertical dashed lines mark the $-\log_{10}(0.05)$ threshold. The right panel presents a stacked bar plot showing the percentage of sensitivity

analyses out of 17 (*x*-axis) in which each farming activity (*y*-axis) was associated with higher (red), lower (green), or unchanged PD risk (white). Please refer to the Supplementary materials for more details about sensitivity analyses.

All analyses adjusted for sex (for “both sexes” only), age, farm establishment year, median farm surface, number of associates, unemployment status, farm count, family status, partner employment status, farm location, number of comorbidities, and performing a secondary activity.

Discussion

For the first time, the association between PD risk and multiple farming activities was examined, overall and by sex category, in the entire French FM population using data mining and large-scale real-world administrative health data. As suspected, the association between the risk of PD and farming highly varied depending on the activity considered, with a 3.4-fold range observed between the lowest and highest HRs. The highest-risk group included FMs engaged in pig farming, cattle farming, fruit arboriculture, viticulture, truck farming, and crop farming, while the lowest-risk group included all FMs engaged in activities involving horses and unspecified small animal farming, but also gardening, landscaping and reforestation companies. This PD risk heterogeneity suggests that part of the risk may possibly be attributable to specific farming practices, with a few sex-specific PD risks that could denote differences in occupational exposures and tasks between males and females, as previously suggested¹⁵. Potential hormonal disparities may also have played a role because several studies suggest a possible protective effect of female sex hormones (especially estrogen)^{31–34}. However, this study is only a preliminary work, which highlights the need for further research.

FMs with PD were older than FMs without PD, which is consistent with the literature as PD affects people late in life, usually starting after 50 years old^{2,5,7,35}. In line with previous works, the PD incidence rate increased with age, was higher for males than females^{4,5,7,19,21}, and was consistent with those of the entire French population³⁶ and other studies^{4,6,7,23}.

During farming activities, FMs can be exposed to numerous environmental co-occurring contaminants (agricultural exposomes)²⁹, some of which could be implicated in PD. Of particular interest are pesticides, which are used to protect crops and livestock from pest infestations and diseases^{16,37}. Numerous studies have reported an association between pesticide exposure and PD, but results are often inconsistent and limited, in particular for specific pesticide compounds, probably because of the large number of different pesticides each FM used throughout his/her career^{1,2,8,12,15,18,35}. The paraquat herbicide^{19,38–46}, 2,4-D herbicide^{7,44,47}, triazine (atrazine) herbicides^{2,44,48,49}, rotenone insecticide^{19,40,41,45,50}, fipronil insecticide^{2,44,51}, organophosphates (OPs)^{50,52–55}, organochlorines^{44,53,54,56,57}, pyrethroids^{40,44,49}, as well as the fungicides maneb^{19,39,46}, mancozeb^{12,19}, and ziram^{7,12,19,46} are among the most frequently incriminated pesticides.

While the pesticides used may sometimes be common between farming types, their amount, frequency, intensity, and mode of application also strongly vary and change over time^{18,19,21}. For instance, there is a higher use of pesticides in truck farming, crop farming, fruit arboriculture, and viticulture than in other farming activities¹⁸. Farms specialized in orchards rank first in terms of insecticide use, whereas viticulture uses mostly fungicides, and cereal crop farming employs insecticides, herbicides, and fungicides, but with lower frequency and intensity^{18,22}. Regarding the treatment of ectoparasites in animal husbandry, OP insecticides have preferentially been used on animals since the 1970s¹⁹, replacing the organochlorine insecticide lindane, before being substituted by pyrethroids and sometimes oral medications only (ivermectine). Hence, the farming type is a proxy of agricultural exposure that is easier to assess than specific pesticides²¹ and may better reflect the agricultural exposome²⁹, for which pesticide association plays a pivotal role, with a low-dose cocktail effect¹⁶.

Several French studies reported an association between PD and pesticide use and pesticide expenditures in vineyards^{18,22} or in regions with a greater presence of vineyards, cereal farming, fruit crops, fresh vegetable farming, and pig farming^{20,21}. Another French study (prospective cohort

Table 1 | Baseline characteristics of the study population, TRACTOR project, France, 2012–2016

	FM without PD (n = 1,079,716)	FM with PD (n = 8845)
<i>Main characteristics</i>	<i>n (%)</i>	<i>n (%)^a [overall %^b]</i>
Sex		
Male	745,798 (69.1)	5500 (61.2) [0.73]
Female	333,918 (30.9)	3345 (38.8) [0.99]
Age at baseline: 2012/01/01 (years)		
Mean (SD) [min-max]	46.5 (14.1) [18–96]	55.8 (12.6) [34–93]
Family status		
Single	465,923 (43.2)	3087 (34.9) [0.66]
As a couple	613,793 (56.8)	5758 (65.1) [0.93]
First year of the farm's establishment		
Median (IQR)	1994 (39)	1990 (39.9)
Farm surface (expressed in hectares)		
Median (IQR)	1.64 (14.0)	1.93 (14.1)
Farm location (region)		
Auvergne-Rhône-Alpes	116,588 (10.8)	840 (9.5) [0.72]
Bourgogne-Franche-Comté	65,323 (6.05)	541 (6.12) [0.82]
Bretagne	80,791 (7.48)	511 (5.78) [0.63]
Centre - Val de Loire	49,424 (4.58)	410 (4.64) [0.82]
Corse	5296 (0.49)	30 (0.34) [0.56]
Grand Est	81,022 (7.5)	732 (8.28) [0.90]
Hauts-de-France	47,908 (4.44)	490 (5.54) [1.01]
Île-de-France	13,978 (1.29)	106 (1.2) [0.75]
Normandie	79,917 (7.4)	721 (8.15) [0.89]
Nouvelle-Aquitaine	178,771 (16.6)	1612 (18.2) [0.89]
Occitanie	165,387 (15.3)	1438 (16.3) [0.86]
Provence-Alpes-Côte d'Azur	113,201 (10.5)	852 (9.63) [0.75]
Pays de la Loire	82,110 (7.6)	562 (6.35) [0.68]
Number of farms		
1 farm	1,053,455 (97.6)	8655 (97.9) [0.81]
>1 farm	26,261 (2.43)	190 (2.15) [0.72]
Farm type (farm clustering)		
Individual farm	750,001 (69.5)	6587 (74.5) [0.87]
Farm with work partners	329,715 (30.5)	2258 (25.5) [0.68]
Partner work status		
Perform task to help farm manager	126,923 (11.8)	1328 (15) [1.04]
Do not perform task to help farm manager	952,793 (88.2)	7517 (85) [0.78]
Number of associates		
0	829,228 (76.8)	7004 (79.2) [0.84]
≥ 1	250,488 (23.2)	1841 (20.8) [0.73]
Secondary farming activity[†]		
No secondary farming activity performed in in parallel to a main activity	678,780 (62.9)	7810 (88.3) [1.14]
At least one farming activity performed in in parallel to a main activity	400,936 (37.1)	1035 (11.7) [0.26]
Number of different yearly activities performed		
Only one activity during the observation period	971,334 (90.0)	8116 (91.8) [0.83]

Table 1 (continued) | Baseline characteristics of the study population, TRACTOR project, France, 2012–2016

	FM without PD (n = 1,079,716)	FM with PD (n = 8845)
Two activities during the observation period	101,735 (9.42)	704 (7.96) [0.69]
At least three activities during the observation period	6647 (0.62)	25 (0.28) [0.37]
Lack of job security		
Has never been unemployed during the observation period	1,077,605 (99.8)	8838 (99.9) [0.81]
Has been unemployed during the observation period	2111 (0.2)	7 (0.08) [0.33]
Median yearly insurance premium (euros)		
Median (IQR)	5166 (40818)	4592 (40877)
Employees		
No employee	783,007 (72.5)	7137 (80.7) [0.90]
At least one employee	296,709 (27.5)	1708 (19.3) [0.57]
Work status		
Working as a farm manager	814,203 (75.4)	6544 (74) [0.80]
Working as a solidarity contributor*	265,513 (24.6)	2301 (26) [0.86]
Retirement status		
Did not retired before the disease diagnosis or end of follow-up	761,653 (70.5)	2808 (31.7) [0.37]
Retired before the disease diagnosis or end of follow-up	318,063 (29.5)	6037 (68.3) [1.86]
Pre-existing disability		
Did not become disabled before the disease diagnosis or end of follow-up	1,075,485 (99.6)	8657 (97.9) [0.80]
Became disabled before the disease diagnosis or end of follow-up	4231 (0.39)	188 (2.13) [4.25]
Number of pre-existing comorbidities (long term illness)		
0 comorbidity before the disease diagnosis or end of follow-up	704,914 (65.3)	4602 (52) [0.65]
1 comorbidity before the disease diagnosis or end of follow-up	214,432 (19.9)	2464 (27.9) [1.14]
>1 comorbidity before the disease diagnosis or end of follow-up	160,370 (14.9)	1779 (20.1) [1.10]

Note: FM farm manager, IQR interquartile range, PD Parkinson's disease, SD arithmetic standard deviation.

^aPercentage of PD cases among all FMs with PD.

^bPercentage of PD cases among all FMs with the given characteristics.

[†]A secondary farming activity is defined as a farming activity (e.g., grassland farming) that a FM can perform in addition to its main activity (e.g., ovine farming). The nature of the secondary activity is however unknown.

*FMs who farm on a small surface (<12.5 ha) or who works less than 1200 h/year.

AGRICAN), including both FMs and farm workers from 13 French departments using self-administered questionnaires, reported that lifelong pesticide use was associated with an increased risk of PD in all types of activities (e.g., cattle, crop farming)¹⁹. This study, which included 1732 PD cases, also found positive associations between PD and farmers exposed to insecticides on animals, which were particularly strong for pig farming¹⁹. A Canadian case-control study with 403 PD cases reported a higher PD risk for ever-occupational contact with cattle and found a positive trend for swine²³.

Table 2 | Risks of Parkinson’s disease by agricultural activity, TRACTOR project, France, 2012–2016

Farming activity	Sex	Study population no. (%)	PD* no. (%)	Unexposed PD no.	HR [95% CI]†	p	adj. p
Crop farming (e.g., wheat, corn, and industrial grower)	Both sexes	317,458 (29.2)	2998 (33.9)	5847	1.67 [1.53–1.82]	5.0e–30	2.7e–29
	Female	106,016 (31.4)	1238 (37.0)	2107	1.74 [1.50–2.02]	3.4e–13	4.3e–13
	Male	211,442 (28.1)	1760 (32.0)	3740	1.67 [1.50–1.87]	3.5e–20	9.6e–20
Mixed cattle farming	Both sexes	31,309 (2.88)	324 (3.66)	8521	1.58 [1.41–1.76]	1.3e–15	2.1e–14
	Female	8206 (2.43)	116 (3.47)	3229	1.72 [1.43–2.07]	1.1e–08	3.0e–8
	Male	23,103 (3.08)	208 (3.78)	5292	1.47 [1.28–1.69]	7.0e–8	1.5e–07
Dairy farming	Both sexes	162,906 (15.0)	1412 (16.0)	7433	1.48 [1.40–1.57]	5.8e–40	3.2e–39
	Female	50,385 (14.9)	532 (15.9)	2813	1.45 [1.32–1.59]	2.4e–14	3.6e–14
	Male	112,521 (15.0)	880 (16.0)	4620	1.45 [1.35–1.56]	6.5e–23	2.4e–22
Pig farming	Both sexes	13,760 (1.26)	111 (1.25)	8734	1.39 [1.16–1.68]	5.2e–04	1.5e–03
	Female	3948 (1.17)	42 (1.26)	3303	1.62 [1.19–2.20]	1.9e–03	4.4e–03
	Male	9812 (1.31)	69 (1.25)	5431	1.25 [0.99–1.59]	0.06	0.07
Cow farming	Both sexes	113,244 (10.4)	1015 (11.5)	7830	1.22 [1.14–1.30]	6.0e–9	2.0e–7
	Female	33,603 (9.96)	371 (11.1)	2974	1.23 [1.11–1.37]	1.6e–04	4.8e–04
	Male	79,641 (10.6)	644 (11.7)	4856	1.20 [1.10–1.30]	2.0e–5	1.1e–04
Truck farming, floriculture/flower-growing	Both sexes	43,684 (4.01)	312 (3.53)	8533	1.22 [1.09–1.36]	6.5e–04	4.2e–03
	Female	13,350 (3.96)	122 (3.65)	3223	1.32 [1.10–1.58]	3.0e–3	9.6e–03
	Male	30,334 (4.04)	190 (3.45)	5310	1.16 [1.00–1.34]	0.05	0.06
Fruit arboriculture	Both sexes	25,090 (2.30)	201 (2.27)	8644	1.35 [1.08–1.68]	8.9e–03	0.03
	Female	7981 (2.37)	67 (2.00)	3278	1.34 [0.91–2.02]	0.12	0.15
	Male	17,109 (2.28)	134 (2.44)	5366	1.36 [1.04–1.79]	0.02	0.05
Unspecified and mixed farming (e.g., polyculture, mixed farming, diversified farming)	Both sexes	129,013 (11.9)	1013 (11.5)	7832	1.09 [1.02–1.17]	9.2e–03	0.04
	Female	39,914 (11.8)	396 (11.8)	2949	1.11 [1.00–1.23]	0.06	0.09
	Male	89,099 (11.9)	617 (11.2)	4883	1.07 [0.98–1.16]	0.13	0.17
Viticulture	Both sexes	122,713 (11.3)	1169 (13.2)	7676	1.07 [0.94–1.21]	0.3	0.31
	Female	43,370 (12.9)	492 (14.7)	2853	0.89 [0.72–1.11]	0.24	0.30
	Male	79,343 (10.6)	677 (12.3)	4823	1.23 [1.05–1.43]	9.2e–03	0.03
Ovine and caprine farming	Both sexes	49,061 (4.51)	330 (3.73)	8515	1.07 [0.96–1.20]	0.2	0.65
	Female	17,529 (5.20)	118 (3.53)	3227	0.96 [0.80–1.15]	0.64	0.82
	Male	31,532 (4.20)	212 (3.85)	5288	1.15 [1.00–1.32]	0.05	0.65
Wood production (e.g., lopping)	Both sexes	11,431 (1.05)	55 (0.62)	8790	1.11 [0.85–1.44]	0.46	0.79
	Female	303 (0.09)	2 (0.06)	3343	Not calculated		
	Male	11,128 (1.48)	53 (0.96)	5447	1.18 [0.90–1.55]	0.23	0.52
Garden center/tree nursery	Both sexes	5418 (0.50)	33 (0.37)	8812	1.09 [0.78–1.54]	0.61	0.79
	Female	1438 (0.43)	6 (0.18)	3339	0.66 [0.30–1.48]	0.31	0.79
	Male	3980 (0.53)	27 (0.49)	5473	1.28 [0.88–1.87]	0.2	0.79
Poultry and rabbit farming	Both sexes	25,863 (2.38)	124 (1.40)	8721	0.90 [0.75–1.07]	0.24	0.92
	Female	10,196 (3.02)	53 (1.58)	3292	0.87 [0.66–1.14]	0.3	0.92
	Male	15,667 (2.09)	71 (1.29)	5429	0.91 [0.72–1.15]	0.43	0.92
Unspecified large animal farming (e.g., ostrich, llama)	Both sexes	3020 (0.28)	16 (0.18)	8829	1.15 [0.70–1.87]	0.58	0.75
	Female	1458 (0.43)	6 (0.18)	3339	0.82 [0.37–1.83]	0.63	0.75
	Male	1562 (0.21)	10 (0.18)	5490	1.45 [0.78–2.70]	0.24	0.75
Agricultural work companies (e.g., pesticide applications, harvest reaping)	Both sexes	15,635 (1.44)	60 (0.68)	8785	0.90 [0.70–1.16]	0.4	1.0
	Female	1887 (0.56)	7 (0.21)	3338	0.77 [0.37–1.61]	0.49	1.0
	Male	13,748 (1.83)	53 (0.96)	5447	0.94 [0.72–1.23]	0.65	1.0

Table 2 (continued) | Risks of Parkinson’s disease by agricultural activity, TRACTOR project, France, 2012–2016

Farming activity	Sex	Study population no. (%)	PD no. (%)	Unexposed PD no.	HR [95% CI] [†]	p	adj. p
Sylviculture/forestry (e.g., thinning, pruning)	Both sexes	2166 (0.20)	16 (0.18)	8829	1.10 [0.68–1.80]	0.7	0.96
	Female	361 (0.11)	6 (0.18)	3339	1.57 [0.71–3.50]	0.27	0.68
	Male	1805 (0.24)	10 (0.18)	5490	1.00 [0.54–1.85]	0.99	1.0
Company representative/authorized representative	Both sexes	1935 (0.18)	9 (0.10)	8836	1.22 [0.64–2.35]	0.55	0.64
	Female	1500 (0.45)	7 (0.21)	3338	1.20 [0.57–2.52]	0.63	0.69
	Male	435 (0.06)	2 (0.04)	5498	Not calculated		
Unspecified specialized farming (e.g., herbs, mushrooms)	Both sexes	6671 (0.61)	29 (0.33)	8816	0.82 [0.57–1.18]	0.28	0.6
	Female	2438 (0.72)	9 (0.27)	3336	0.63 [0.33–1.22]	0.17	0.5
	Male	4233 (0.56)	20 (0.36)	5480	0.93 [0.60–1.45]	0.75	0.89
Stationary sawmill (e.g., edging, trimming, decking, debarking)	Both sexes	791 (0.07)	6 (0.07)	8839	1.24 [0.56–2.76]	0.6	0.72
	Female	55 (0.02)	0 (0)	3345	Not calculated		
	Male	736 (0.10)	6 (0.11)	5494	1.41 [0.63–3.14]	0.4	0.6
Shellfish farming (e.g., oyster farming, scallop aquaculture)	Both sexes	3825 (0.35)	12 (0.14)	8833	0.65 [0.37–1.15]	0.14	0.59
	Female	736 (0.22)	3 (0.09)	3342	0.71 [0.23–2.21]	0.56	0.65
	Male	3089 (0.41)	9 (0.16)	5491	0.67 [0.35–1.29]	0.23	0.59
Salt works/salt evaporation pond	Both sexes	980 (0.09)	3 (0.03)	8842	0.59 [0.19–1.83]	0.36	0.48
	Female	220 (0.07)	1 (0.03)	3344	Not calculated		
	Male	760 (0.10)	2 (0.04)	5498	Not calculated		
Gardening, landscaping and reforestation companies	Both sexes	49,177 (4.52)	150 (1.70)	8695	0.81 [0.69–0.95]	0.01	0.05
	Female	2562 (0.76)	10 (0.30)	3335	0.91 [0.49–1.70]	0.77	0.88
	Male	46,615 (6.20)	140 (2.55)	5360	0.88 [0.74–1.04]	0.13	0.27
Unspecified small animal farming (e.g., frogs, snails, bees)	Both sexes	19,984 (1.84)	54 (0.61)	8791	0.51 [0.39–0.67]	7.7e–07	1.9e–05
	Female	8632 (2.56)	18 (0.54)	3327	0.39 [0.25–0.62]	7.3e–05	3.3e–04
	Male	11,352 (1.51)	36 (0.65)	5464	0.59 [0.43–0.82]	1.7e–03	2.7e–03
Stud farming	Both sexes	17,269 (1.59)	53 (0.60)	8792	0.48 [0.37–0.63]	1.3e–07	7.6e–07
	Female	7486 (2.22)	13 (0.39)	3332	0.28 [0.16–0.48]	4.8e–06	1.4e–05
	Male	9783 (1.30)	40 (0.73)	5460	0.64 [0.47–0.87]	4.5e–03	7.9e–03
Training, dressage, riding clubs	Both sexes	14,979 (1.38)	30 (0.34)	8815	0.49 [0.35–0.71]	1.2e–04	2.5e–03
	Female	6687 (1.98)	7 (0.21)	3338	0.29 [0.14–0.60]	9.6e–04	4.8e–03
	Male	8292 (1.10)	23 (0.42)	5477	0.63 [0.42–0.95]	0.03	0.05
Rural craftsperson (e.g., mason, mechanics)	Both sexes	7696 (0.71)	5 (0.06)	8840	0.14 [0.06–0.34]	1.3e–05	2.0e–5
	Female	283 (0.08)	0 (0)	3345	Not calculated		
	Male	7413 (0.99)	5 (0.09)	5495	0.15 [0.06–0.36]	2.1e–05	3.0e–5

Abbreviations: PD Parkinson’s disease, HR hazard ratio, m number of exposed PD cases, p p-value, adj. p p-value adjusted using the Benjamini-Hochberg approach.

[†]The percentages in brackets refer to the ratio of exposed PD cases in the study population to the total number of PD cases in the overall population.

[‡]Main analysis: adjusted for sex (for “both sexes” only), age, the first year of the farm’s establishment, farm surface, number of associates, unemployment status, total number of farms, family status, partner work status, farm location, number of comorbidities, and having a secondary farming activity.

Regarding animal farming, FMs can also be exposed to pesticides from animal manure and feeds, in particular for cattle and pigs^{14,23}, such as diethyltoluamide (35%), a repellent that has been implicated with PD¹⁴.

Interestingly, our findings for PD are different than those from a previous study conducted in the same population examining AD risk, in which only three farming activities were found to have a higher risk of AD (crop farming, fruit arboriculture, and viticulture), while all animal farming activities exhibited a lower risk of AD³⁰. This could suggest that different exposome and potentially pesticides with different mechanisms could be involved. One possibility could be that the site of initial misfolding events differs between both neurodegenerative diseases. The Braak and dual-hit hypotheses posit that PD may first initiate in the olfactory structures (olfactory bulb) and the gut enteric nerves (gut-to-brain pathway)^{9,58,59}. Hence, pesticides could gain access to the brain via the olfactory pathway or the vagus nerve, which could eventually trigger the spread of PD by a

templating mechanism in a prion-like manner^{9,59}. In contrast to PD, AD does not seem to be affected by the olfactory pathways^{59,60}.

The cocktail effect, involving a low-dose mixture of pesticides, is now considered a pivotal physiopathological issue¹⁶. It makes classical epidemiological study very challenging. Recently, large-scale screening on dopaminergic cells demonstrated the involvement of 53 pesticides and the impact of specific mixtures on PD¹⁶. These in vitro studies are not fully relevant for the in vivo occupational situation, as it is not known if these compounds can reach the dopaminergic cells in the brain and also what the relevant dose is associated with neurodegeneration⁶¹. Our finding of specific farming activities associated with higher PD risk probably reflects specific mixtures of pesticides and environmental factors (agricultural exposomes). It suggests that “real-life screening” should be synergistically associated with this new field of diseases^{61,62}. The chemical exposome^{62,63} needs to be better objectified in the future, using biological exposure monitoring (e.g., urine,

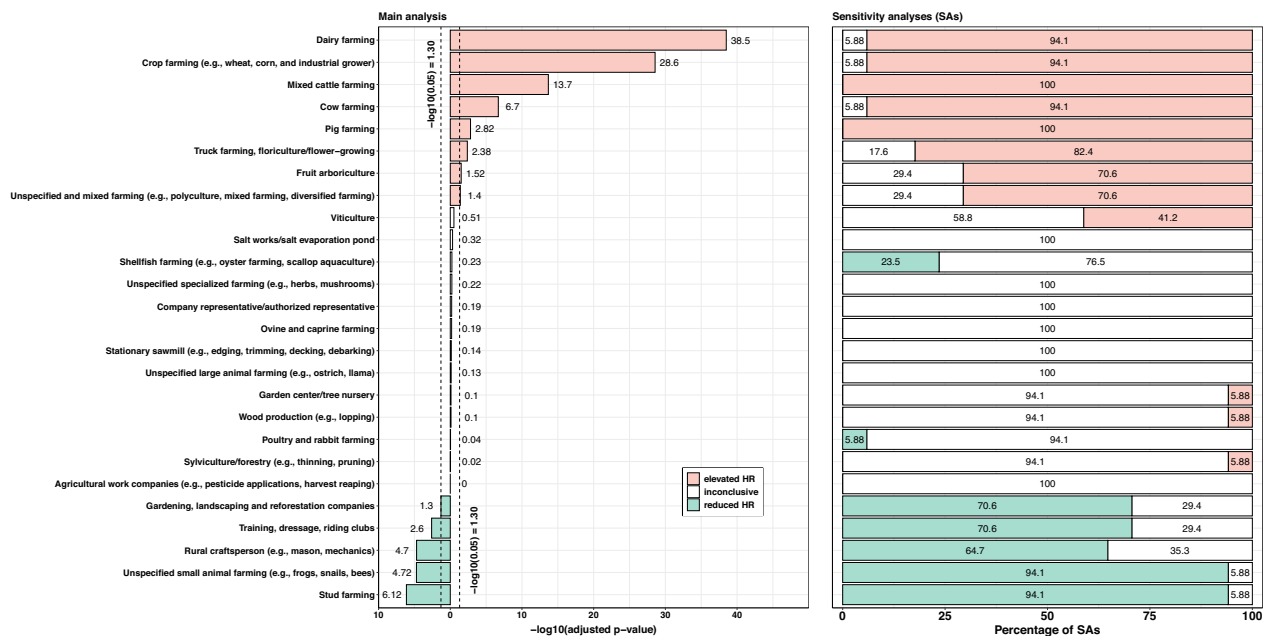


Fig. 1 | Farming activities and risks of PD, TRACTOR project, France, 2012–2016. Comparison of primary and sensitivity analyses.

blood, hair, or fat tissues) to help in the identification of specific mixtures of pesticides or environmental cocktails involved in PD neurodegeneration^{61,62}.

The microbiota is today hypothesized to play a key role in PD⁶⁴. Changes in gut microbiota can generate pro-inflammatory mediators and alpha-synuclein aggregation, which can be transported from the enteric nervous system to the brain via the vagus nerve (“Gut-Brain axis”). Some pesticides can disrupt the nasal and gut microbiome, cause mitochondrial dysfunction, affect lysosomal function, or exert neurotoxic effects, in particular pesticides composed of heavy metals such as manganese, zinc, aluminum, copper, and mercury^{5,14,18,49}. For instance, several fungicides contain metals, such as maneb (containing manganese), ziram (containing zinc), mancozeb (containing both zinc and manganese), or the Bordeaux mixture (containing copper), that were/are used in viticulture, crop, and fruit farming^{18,65}. Exposure to some pathogenic bacteria can cause epigenetic changes in several PD risk factor genes⁶⁴. The microbiome of farmers, and in particular livestock breeders, is completely altered by their specific occupational exposure, as shown by numerous studies conducted mainly in pig breeders^{66–70}. Contact with animals during breeding activities is associated with changes in the dermal, nasal, and gut microbiota, as the microbiome of the upper respiratory track is then swallowed. In particular, it has been shown that the microbiome and resistome of farmers are very similar to those of their animals^{66–70}.

Contact with animals can also expose FMs to zoonotic agents and endotoxins^{23,71,72}, in particular *Mycobacterium avium* ss. *paratuberculosis* (MAP), which could start as an enteric infection via the vagus nerve, as hypothesized by one study⁷³. Cattle farmers were also found to have a higher risk of both hypothyroidism and hyperthyroidism¹⁷ but also inflammatory bowel disease⁷⁴, which have been associated with PD risk^{64,75}.

Previous studies found evidence that alpha-synuclein’s activities can be affected by polystyrene and other particles found, for instance, in microplastics (MPs) and nanoplastics (NPs)^{76,77}. MPs/NPs represent emerging environmental pollutants, with up to 430,000 tons of MPs potentially entering agricultural fields annually in Europe^{78,79}. Pesticides and other toxic agents (e.g., infectious agents) can bind NPs that can act as carriers to facilitate blood-brain barrier crossing based on the “Trojan Horse” effect^{80,81}. There are many possible sources of MPs/NPs contamination in agriculture. Direct contamination sources include plastic mulching, the cover of plastic greenhouses, or polymer-based fertilizers⁷⁹. Indirect sources of contamination include the application of biosolids, the application of compost, or irrigation with waste-treated water^{78,79}.

Our study is the first to focus on the entire FM population. Strengths of our study include the largest sample of FMs ever studied, its population-based and nationwide design, the large number of exposed PD cases, sex-specific analyses, adjustments to several potential confounders (sex, age, geographical area, farm surface), as well as the wide range of agricultural exposures with detailed information on 26 farming activities. In addition, contrary to case control studies or studies using declarative data, the administrative nature of our data (farming type as a means of assessing exposure) was not prone to recall bias, which could have led to exposure misclassification^{1,18}. We chose to use a time-on-study approach instead of using age as timescale because several studies suggest that time-on-study models may be preferable, as they perform at least as well as left-truncated age scale models^{82–84}. Additionally, they tend to be more robust against misspecification of the underlying time scale and generally offer better predictive ability^{82–84}.

Our findings need to be considered in light of some limitations. First, the administrative nature of available data, which is characterized by a lack of accurate information on confounders and precise dates of disease onset^{4,29}. Indeed, the date of diagnosis or first treatment does not equate to the date of disease, in particular because there are no specific tests to detect PD and because individuals are most commonly diagnosed years after symptom onset once the motor symptoms (e.g., freezing of gait) set in^{1,4–6}. Potential PD case misidentification cannot be excluded because PD cases were identified with either the date of LTI declaration, ODC declaration, or first treatment reimbursement. However, diagnostic misclassifications are unlikely to depend on the farming type¹⁸, and several sensitivity analyses were conducted to address this bias, which yielded consistent results (Supplementary material). Clinical information on PD FMs (e.g., severity scales, non-motor symptoms, disease phenotypes) as well as genetic information (from both causal and at-risk genetic variants) were not available. This prevented us from accounting for these factors in the analysis, which is a limitation. Indeed, given the complex nature of PD, which is characterized by a dynamic interplay between genes and the environment, some genetic variants (e.g., ABCB1) may increase susceptibility to pesticide exposures associated with PD^{10,11,15,34,35,53,56,85}.

Because of the administrative nature of our data, some potential confounding factors of interest (e.g., cigarette smoking, genetic information, use of protective equipment) were not available^{17,30,74}. This could represent a bias if their absence confounds or masks the genuine relationship between

farming activities and PD. This is particularly true for cigarette smoking, which is a protective factor in PD^{4,6,8,12,13,35}. Even though FMs have the lowest smoking prevalence in the French population, some of the differences observed may be associated with smoking because the prevalence of active smoking varies from one farming activity to another^{86,87}. To address this bias, we conducted a sensitivity analysis, which yielded consistent results (Supplementary material). The possibility of residual confounding cannot be excluded because some farming activities are highly heterogeneous in nature, with, for instance, crop and fruit farming that involve a broad range of practices/tasks and pesticide usage depending on the type of crop (e.g., cereal, potatoes, barley, wheat) or fruit (e.g., walnut, apple). Residual confounding due to environmental exposure (e.g., air pollution in regions with a high density of industrial plants) should be limited because we adjusted for farm locations. While specific chemical, physical, or biological exposures were not available, farming activity serves as a relevant proxy for agricultural exposure that is easier to assess than specific pesticides or stressors^{15,18–21,29}. To address this limitation and complement this study, job and crop exposure matrices could refine exposure estimates by enabling cumulative exposure indexing for pesticides, heavy metals, and organizational factors^{88–92}. Undertaking such a task, which is beyond the scope of this study, would present major challenges, as it entails navigating various potential biases and limitations that must be carefully considered and addressed. The farming activity coding system used by Mutualité Sociale Agricole (MSA) is not an international classification, which may hinder the transcoding process. Some farming activities (e.g., crop farming) may be too broad (not descriptive enough) to allow for an accurate exposure assessment using crop or job exposure matrices. Finding relevant crop or job exposure matrices is also challenging due to the lack of a gold standard⁹³. In addition, crop or job exposure matrices have also some limitations that may bias risk estimates, such as an heterogeneity in performance depending on the exposure and outcome of interest as well as the assumption of homogeneity within jobs/categories^{88–90,93–95}. Ideally, the crop or job exposure matrix should define each farming activity as specifically as possible, with exposure estimates given for a minimal combination of the year, country, region, sex, work status (e.g., FMs or farm workers), and farming activity. However, to the best of our knowledge, such matrices do not exist, at least not in France. Because farming practices can differ from a country to another, as well as within countries, it is important to use crop and job exposure matrices that are comparable to the population studied. To our knowledge, no French job exposure matrix has been specifically designed for farming. Consequently, several crop or job exposure matrices would have to be used. However, each crop or job exposure matrix is created by potentially different experts, aims, and methodologies, which could make them not easily comparable and compatible with one another^{88–90,93–95}. In France, there are several crop and job exposure matrices, in particular Matgéné⁹⁶ and Pestimat⁸⁸. For Matgéné⁹⁶, exposure to pesticides is not provided, exposure estimates are not available for each sex and for each region, and exposure probabilities are provided as ranges. While French activity nomenclature (NAF) codes are available in both Matgéné⁹⁶ and MSA data, NAF codes from MSA are, however, not reliable due to their declarative nature and non-evolving nature (i.e., rarely updated). Regarding Pestimat⁸⁸, only exposure to pesticides is available, but not for the entire France and not for all types of crops⁹⁷. Exposure estimates are not available for each sex and for each region. In addition, exposure estimates are only known for crop, vegetable, and fruit farming activities. However, pesticides, and in particular insecticides, are used in animal farming as well¹⁹. Moreover, the farming activities (e.g., crop farming) in MSA data are too broad compared to the information from Pestimat⁸⁸ (e.g., potato farming), which would force us to consider that each crop farmer, regardless of the crops, is exposed to the same pesticides, which would introduce bias and exposure misclassification. Linking crop and job exposure matrices with MSA data is an issue that deserves to be explored in the future, as highlighted by a previous work⁹⁷. Standardizing or developing new matrices tailored to French agriculture is therefore essential. Another perspective would be to investigate whether FMs engaged in various farming activities have a higher PD risk compared to a non-farming population.

Because occupational data was only available between 2002–2016 and because the average age at baseline was 47 years old, the exposure characterization only took into account the most recent half of the individuals' careers. However, FMs have a relatively stable career because most FMs (90%) never changed their main activity between 2002–2016. Hence, the impact of this bias should be limited. The generalizability of our findings may be limited as farming practices and risk factors can differ between countries and populations (e.g., farm workers, FMs).

Our findings represent a preliminary work that suggests the potential involvement of occupational risk factors related to farming in PD onset and development. Our study could guide future research aiming to examine such factors by identifying vulnerable populations and potential research avenues. Future work should focus on farmers engaged in high-risk farming activities (i.e., pig farming, crop farming, cattle farming, mixed farming, viticulture, truck farming, and fruit arboriculture) to better characterize their exposure and potential association with PD because the combined exposure to multiple stressors (e.g., cocktail effect) may result in a synergistic adverse effect on PD risk, as alluded to by several studies in the literature. Confirmation of our findings in longitudinal studies and in other countries would also be valuable.

Methods

Data source

A secondary use of routinely collected data from Mutualité Sociale Agricole (MSA), the unique social security scheme of all French farmers, available to the TRACTOR (Tracking and monitoring occupational risks in agriculture) project was conducted^{17,30,74,98–100}.

Insurance claim data routinely collected through the completion of mandatory forms by FMs on an annual basis from 2002 to 2016 was available. These claims provide information on sociodemographic (e.g., age, sex, family status), farm characteristics (e.g., farm surface), and farming activities. Farming activities are coded into 26 categories (e.g., pig farming, viticulture) by MSA following a national thesaurus defined by French laws³⁰.

Electronic health/medical records from 2012–2016 were also available. These records provide information on declared chronic illnesses (LTIs), such as PD (LTI n°16), that grant full coverage of health care expenditures to FMs who hold them. Electronic health/medical records also pertain to ODCs, such as “PD induced by pesticide exposures” (ODC n°RA 58 in the agricultural scheme table). Since 2012, in France, PD can be considered a work-related disease in farmers under specific conditions, including a diagnosis confirmed by a neurologist and occupational exposure to pesticides for 10 years or more⁷. Data on drug reimbursements was also available. Each LTI and ODC is assigned an ICD-10 code (10th revision of the International Statistical Classification of Diseases and Related Health Problems), while each drug is assigned an ATC code (Anatomical Therapeutic Chemical classification system). January 1st, 2012, was defined as the baseline time point (i.e., time zero), and December 31st, 2016, as the follow-up end. The Kaplan-Meier reverse method was used to determine the median follow-up.

The data was analyzed from September 2023 to September 2024. The variables used for this study were complete. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) was used as reporting guidelines (Supplementary Table 6).

Ethics approval

This study was conducted in accordance with the Declaration of Helsinki, and ethics approval was obtained from the French independent administrative authority responsible for safeguarding privacy and personal data (CNIL) (authorization number: MMS/SBM/AE171001). The need for informed consent was waived by CNIL (i.e., ethics committee) for the TRACTOR project because data analyses were only descriptive and results were reported at a large collective scale (i.e., farming activity level), because data were pseudonymized, and because measures were undertaken to prevent the risk of reidentification of individuals.

Study population and outcome

All FMs who performed at least one of the 26 activities once (1 yearly declaration to MSA) between 2002 and 2016 were included. The farming activity was considered a proxy for occupational exposure (agricultural activity exposomes), as previously done in other works^{17–21}. The FMs' degree of involvement in the daily tasks was unknown (not recorded by MSA). The duration of exposure for each activity was determined by calculating the number of years in which a FM engaged in the activity based on the yearly declarations made to MSA during the period from 2002 to 2016.

PD cases were identified using ICD-10 codes for FMs declared with PD through the LTI and ODC insurance declaration schemes, as well as with ATC codes for PD drugs given to FMs (with or without LTI or ODC)^{20–22,101}. FMs were considered to have PD if they had at least one LTI declaration for PD (ICD-10 code G20 or F02), one ODC declaration for PD, or one reimbursement of any drugs solely used to treat PD (i.e., all anti-parkinsonian agents, with the exception of pramipexole, rotigotine, amantadine, and lisuride) (Supplementary Table 7). In addition, FMs only on anticholinergics (trihexyphenidyl, biperiden, and tropatepine) and neuroleptics (drug-induced parkinsonism) were not considered as PD cases.

Statistical analysis

All statistical analyses were performed with R software 4.3.1[®] (R Core Team, Vienna, Austria) for Windows 10©. When the number of exposed PD cases was ≥ 3 , Cox proportional hazards models and associated hazard ratios (HRs) were used to investigate whether specific farming activities exhibited a higher risk of PD than others, both overall and by sex category (i.e., one separate model for each sex). Because we did not have access to the general population nor to other occupational sectors not related to agriculture, a separate model was created for each of the 26 farming activities, comparing FMs who had not previously engaged in a given farming activity from 2002 to 2016 with those who had prior experience (leave-one-group-out approach).

For each model, the dependent variables were the timescale (continuous) and the PD diagnosis (two categories: yes or no). The time to the oldest PD insurance declaration (LTI or ODC) or PD drug reimbursement was used as the underlying timescale. In addition, the farming activity was parameterized as a time-dependent variable to account for potential immortal time bias.

Overall analyses were adjusted for sex, with interaction tests conducted to assess potential sex differences. All analyses were adjusted for age, first year of the farm's establishment, median farm surface, number of associates, unemployment status, total number of farms, family status, partner work status, farm location, number of comorbidities, and performing a secondary farming activity (Supplementary Table 8). We ensured that the included variables were non-collinear (variance inflation factor ≤ 2.5). A covariate*time interaction was added to the model when the assumption of a proportional hazard rate, assessed by the independence of scaled Schoenfeld's residuals and time, was not met. Multiple testing was accounted for using the Benjamini-Hochberg approach.

Seventeen sensitivity analyses (SAs) were undertaken to test hypotheses and address potential sources of bias (Supplementary Table 8). For example, PD cases diagnosed in 2012 were excluded to increase the likelihood that identified PD cases were incident cases (SA1). In another SA (SA2), the PD case identification was based solely on ODC declarations. Please refer to the Supplementary material for more details.

Data availability

The data that supports the findings of this study is not publicly available. A reasonable request to the Mutualité Sociale Agricole (MSA) can be made, but restrictions apply to the availability of these data due to both the individual and medical nature of the data, which requires approval from both the MSA and the French independent administrative authority protecting privacy and personal data (CNIL). Further information is available from the corresponding author upon request.

Code availability

The underlying code for this study is not publicly available for proprietary reasons but can be made available upon reasonable request.

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Competing interests

The authors declare no competing interests.

Additional information

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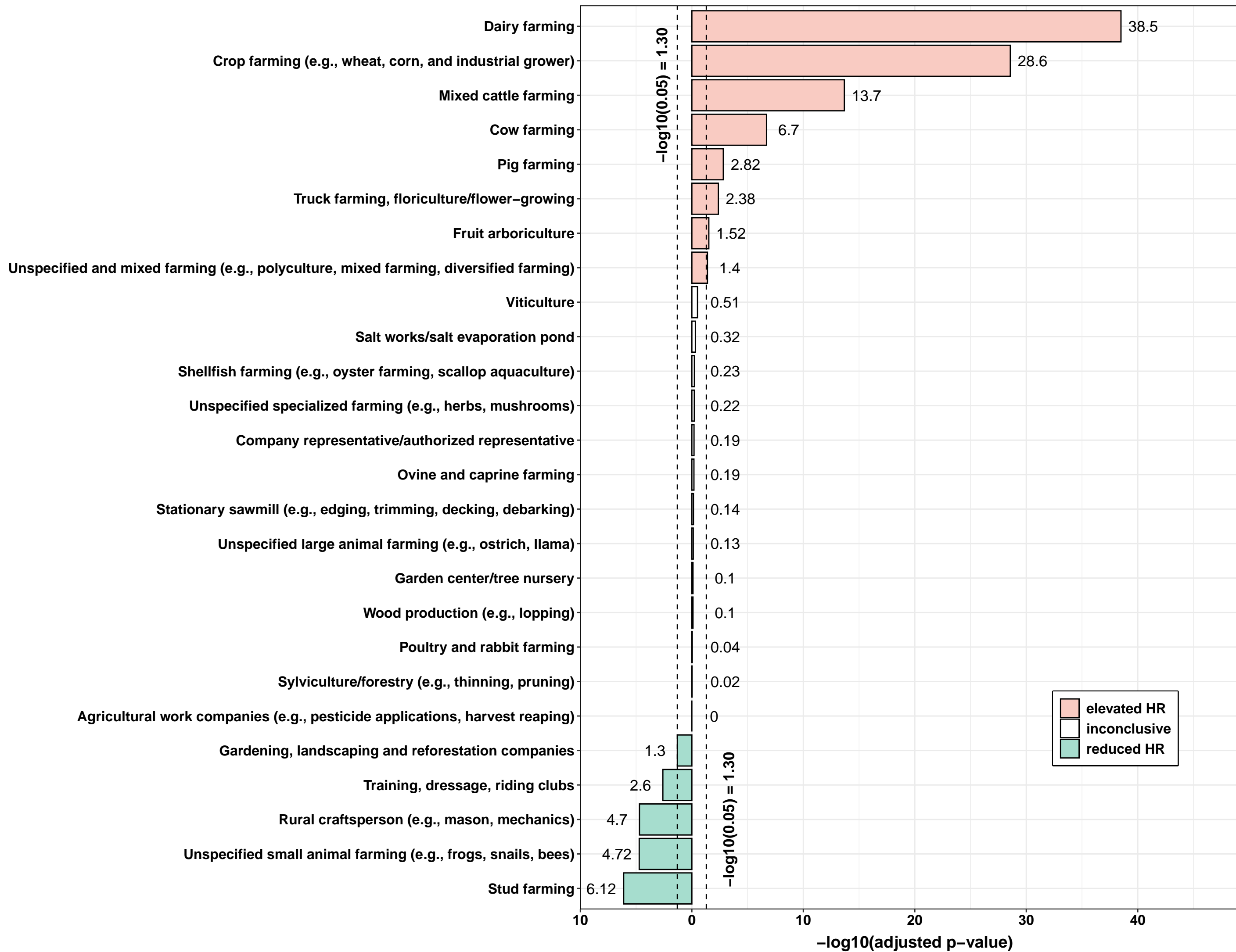
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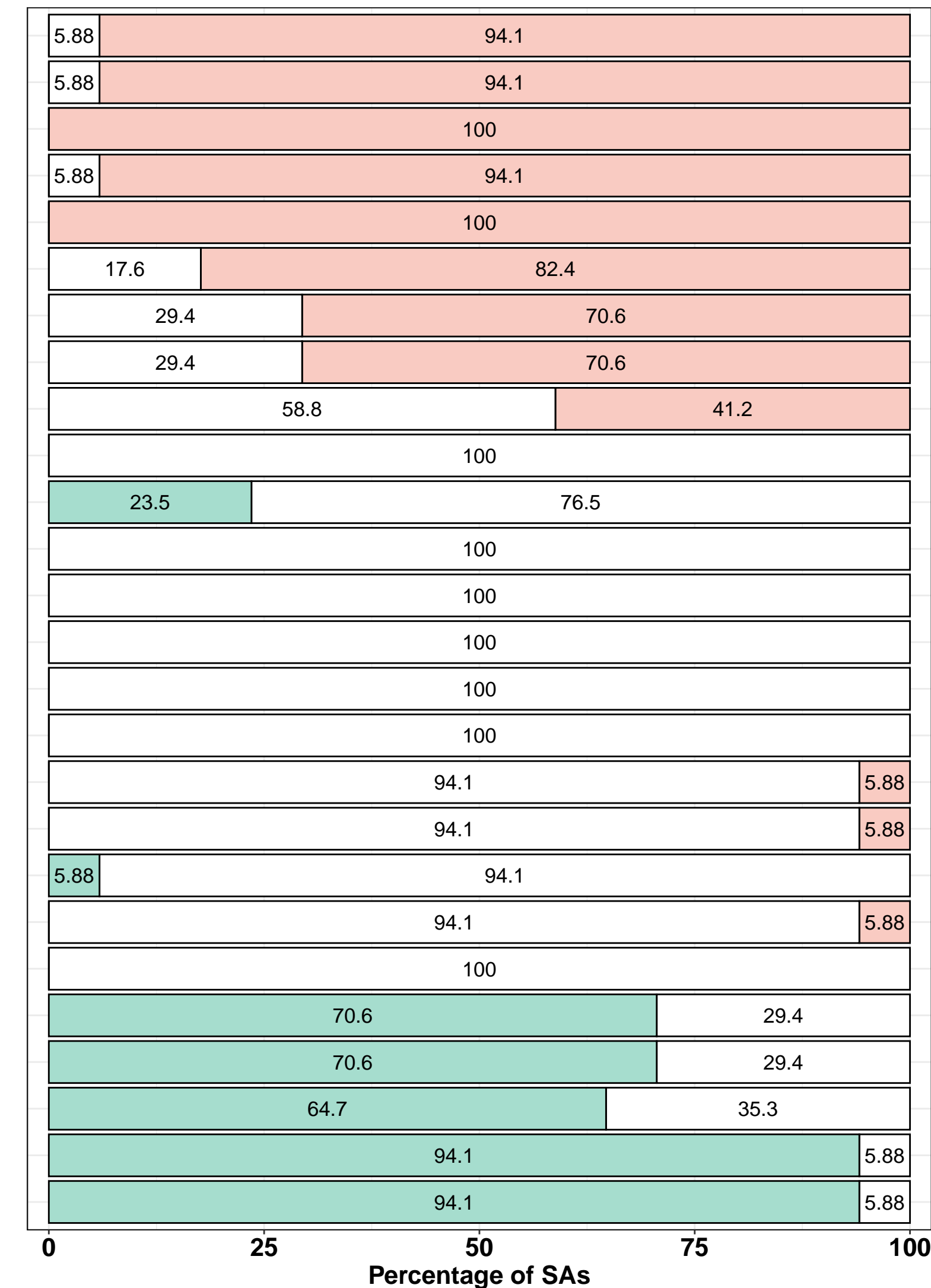
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Main analysis



Sensitivity analyses (SAs)



Supplementary material

Title

Investigating Parkinson's disease risk across farming activities using data mining and large-scale administrative health data

Authors

Pascal Petit, François Berger, Vincent Bonneterre, Nicolas Vuillerme

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1 **Supplementary Table 1:** Number of farm managers and identified PD cases for each analysis conducted

Analysis	FMs without PD No. (%)	FMs with PD No. (%)	Total number of FMs
Main analysis	1079716 (99.2%)	8845 (0.81%)	1088561
Sensitivity analysis 1 - excluding PD cases diagnosed in 2012	1079716 (99.4%)	5910 (0.54%)	1085626
Sensitivity analysis 2 - PD identification only using ODC declaration data	1088244 (99.9%)	317 (0.03%)	1088561
Sensitivity analysis 3 - only including FMs ≥ 40 years	715050 (98.9%)	7893 (1.09%)	722943
Sensitivity analysis 4 - only including FMs ≥ 50 years	446334 (98.6%)	6388 (1.41%)	452722
Sensitivity analysis 5 - only including FMs ≥ 60 years	165468 (98.1%)	3206 (1.90%)	168674
Sensitivity analysis 6 - PD identification only using ODC and LTI declaration data	1085439 (99.7%)	3122 (0.29%)	1088561
Sensitivity analysis 7 - PD identification only using drug reimbursement data	1080343 (99.2%)	8218 (0.76%)	1088561
Sensitivity analysis 8 - excluding FMs with ADRD (LTI declaration)	1080113 (99.2%)	8448 (0.78%)	1088561
Sensitivity analysis 9 - PD identification only using LTI declaration data (G20, G21)	1085449 (99.7%)	3112 (0.29%)	1088561
Sensitivity analysis 10 - PD identification only using LTI declaration data (F02, G20, G21)	1085534 (99.7%)	3027 (0.28%)	1088561
Sensitivity analysis 11 - considering drug reimbursement not solely used for PD	1078438 (99.1%)	10123 (0.93%)	1088561
Sensitivity analysis 12 - PD identification using LTI, ODC or ≥ 2 drug reimbursements	1081419 (99.3%)	7142 (0.66%)	1088561
Sensitivity analysis 13 - PD identification using LTI, ODC or ≥ 3 drug reimbursements	1081951 (99.4%)	6610 (0.61%)	1088561
Sensitivity analysis 14 - PD identification using LTI, ODC or ≥ 6 drug reimbursements	1082990 (99.5%)	5571 (0.51%)	1088561
Sensitivity analysis 15 - using only one farming activity as reference	1079716 (99.2%)	8845 (0.81%)	1088561
Sensitivity analysis 16 - adjusting on smoking	1079716 (99.2%)	8845 (0.81%)	1088561
Sensitivity analysis 17 - control of other diseases not related to farming exposure	530961 (98.4%)	8845 (1.64%)	539806

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3 Abbreviations: ADRD: Alzheimer’s disease and other related dementias, F02: ICD-10 code for dementia in other diseases classified elsewhere, FM: farm manager, G20: ICD-10 code for
4 Parkinson’s disease, G21: ICD-10 code for secondary parkinsonism, ICD-10: 10th revision of the International Statistical Classification of Diseases and Related Health Problems, LTI: long-term
5 illness, No: number of, ODCs: occupational diseases covered under workers’ compensation statutes, PD: Parkinson’s disease.

6 **Supplementary Table 2: Incidence rate per analysis**

Analysis	Both sexes		Male		Female	
	n	IR [95%CI] ^a	n	IR [95%CI] ^a	n	IR [95%CI] ^a
Main analysis	8845	0.28 [0.27-0.29]	5500	0.40 [0.38-0.41]	3345	0.24 [0.23-0.25]
Sensitivity analysis 1 - excluding PD cases diagnosed in 2012	5910	0.19 [0.18-0.20]	3713	0.26 [0.25-0.27]	2197	0.16 [0.15-0.17]
Sensitivity analysis 2 - PD identification only using ODC declaration data	317	0.01 [0.009-0.02]	285	0.01 [0.009-0.02]	32	0.004 [0.003-0.005]
Sensitivity analysis 3 - only including FMs ≥ 40 years	7893	0.49 [0.48-0.50]	4718	0.59 [0.57-0.61]	3175	0.44 [0.43-0.46]
Sensitivity analysis 4 - only including FMs ≥ 50 years	6388	1.04 [1.02-1.07]	3575	1.09 [1.06-1.13]	2813	0.98 [0.95-1.02]
Sensitivity analysis 5 - only including FMs ≥ 60 years	3206	1.72 [1.66-1.78]	1544	1.62 [1.54-1.71]	1662	1.82 [1.73-1.91]
Sensitivity analysis 6 - PD identification only using ODC and LTI declaration data	3122	0.10 [0.08-0.11]	2083	0.12 [0.11-0.13]	1039	0.09 [0.08-0.10]
Sensitivity analysis 7 - PD identification only using drug reimbursement data	8218	0.26 [0.25-0.27]	5104	0.37 [0.36-0.38]	3114	0.22 [0.21-0.23]
Sensitivity analysis 8 - excluding FMs with ADRD (LTI declaration)	8448	0.27 [0.26-0.28]	5302	0.37 [0.36-0.39]	3146	0.23 [0.22-0.24]
Sensitivity analysis 9 - PD identification only using LTI declaration data (G20, G21)	3112	0.11 [0.08-0.12]	2077	0.12 [0.11-0.13]	1035	0.09 [0.08-0.10]
Sensitivity analysis 10 - PD identification only using LTI declaration data (F02, G20, G21)	3027	0.10 [0.09-0.12]	1994	0.12 [0.11-0.13]	1033	0.09 [0.08-0.10]
Sensitivity analysis 11 - considering drug reimbursement not solely used for PD	10123	0.32 [0.31-0.33]	6206	0.47 [0.45-0.48]	3917	0.27 [0.26-0.28]
Sensitivity analysis 12 - PD identification using LTI, ODC or ≥ 2 drug reimbursements	7142	0.23 [0.22-0.24]	4481	0.32 [0.30-0.33]	2661	0.20 [0.19-0.21]
Sensitivity analysis 13 - PD identification using LTI, ODC or ≥ 3 drug reimbursements	6610	0.21 [0.20-0.22]	4163	0.29 [0.28-0.30]	2447	0.18 [0.17-0.19]
Sensitivity analysis 14 - PD identification using LTI, ODC or ≥ 6 drug reimbursements	5571	0.18 [0.17-0.19]	3641	0.25 [0.24-0.26]	2130	0.16 [0.15-0.17]
Sensitivity analysis 15 - using only one farming activity as reference	8845	0.28 [0.27-0.29]	5500	0.40 [0.38-0.41]	3345	0.24 [0.23-0.25]
Sensitivity analysis 16 - adjusting on smoking	8845	0.28 [0.27-0.29]	5500	0.40 [0.38-0.41]	3345	0.24 [0.23-0.25]
Sensitivity analysis 17 - control of other diseases not related to farming exposure	8845	0.81 [0.79-0.83]	5500	1.00 [0.96-1.03]	3345	0.73 [0.71-0.75]

7
8 Abbreviations: ADRD: Alzheimer's disease and other related dementias, F02: ICD-10 code for dementia in other diseases classified elsewhere, FM: farm manager, G20: ICD-10 code for
9 Parkinson's disease, G21: ICD-10 code for secondary parkinsonism, ICD-10: 10th revision of the International Statistical Classification of Diseases and Related Health Problems, IR: incidence
10 rate, LTI: long-term illness, ODCs: occupational diseases covered under workers' compensation statutes, PD: Parkinson's disease, PR: prevalence.
11 ^a incidence rates (IRs) are expressed as cases per 1000 persons-years.

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Supplementary Table 3: Number of farm managers with a LTI, ODC or ATC code of interest

A. Number of PD farm managers with a PD drug reimbursement based on the drug name

ATC code	Drug name	Indication*	Number of FMs No. (%)
N04	Anti-parkinson drugs	PD and other disorders (cf. below)	10123 (0.93)
N04	Anti-parkinson drugs solely used for PD	PD only (cf. below)	8845 (0.81)
N04BA02	Levodopa and decarboxylase inhibitor	PD only	2698 (0.25)
N04BC08	Piribedil	PD only	2286 (0.21)
N04BC05	Pramipexole	PD, restless legs syndrome	2056 (0.19)
N04BC04	Ropinirole	PD only	1468 (0.13)
N04BD02	Rasagiline	PD only	1300 (0.12)
N04AA01	Trihexyphenidyl	PD, parkinsonism	1125 (0.10)
N04AA12	Tropatepine	PD, parkinsonism	1009 (0.09)
N04BA03	Levodopa, decarboxylase inhibitor and COMT inhibitor	PD only	873 (0.08)
N04BC09	Rotigotine	PD, restless legs syndrome	416 (0.04)
N04BB01	Amantadine	PD, influenza A, postherpetic neuralgia	253 (0.02)
N04AA02	Biperiden	PD, parkinsonism	168 (0.02)
N04BX02	Entacapone	PD only	110 (0.01)
N04BC07	Apomorphine	PD only	102 (0.01)
N04BD01	Selegiline	PD only	32 (2.9e-03)
N04BC01	Bromocriptine	PD only	19 (1.7e-03)
N04BX01	Tolcapone	PD only	9 (8.3e-04)
N02CA07	Lisuride	PD, hyperprolactinaemia disorders	0
N04BA01	Levodopa	PD only	0
N04BC02	Pergolide	PD only	0

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Abbreviations: COMT: catechol-O-methyltransferase, FM: farm manager, No: number of, PD: Parkinson's disease.

*According to the Vidal (<https://www.vidal.fr/>), Thesorimed (<https://theso.prod-un.thesorimed.org/monographie>) and BCB databases (<https://www.bcb.fr/v2/app/recherche.jsp>).

B. Number of PD farm managers with a LTI or ODC declaration based on the ICD-10 code

ICD-10 code	Definition	Number of FMs No. (%)
G20	Parkinson's disease	3034 (0.28)
G21	Secondary parkinsonism	98 (9.0e-03)
F02	Dementia in other diseases classified elsewhere	12 (1.1e-03)

Abbreviations: ICD-10: 10th revision of the International Statistical Classification of Diseases and Related Health Problems, FM: farm manager, No: number of, ODCs: occupational diseases covered under workers' compensation statutes, PD: Parkinson's disease.

26 **Supplementary Table 4:** Farming activities and risks of PD, TRACTOR project, France, 2012-2016. Comparison of the main analysis with all sensitivity analyses for all sex
27 categories.

28 Please refer to the MS Excel file entitled *Supplementary Tables 4 and 5*, in the tab named “*Supplementary Table 4*”.

29

30 **Supplementary Table 5:** Comparison of results from the interaction tests regarding the sex between the main analysis and all sensitivity analyses.

31 Please refer to the MS Excel file entitled *Supplementary Tables 4 and 5*, in the tab named “*Supplementary Table 5*”.

32 **Supplementary Table 6: STROBE Statement Checklist**

33

	Item No	Recommendation	Page
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3, 4
Methods			
Study design	4	Present key elements of study design early in the paper	14, 15
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	14, 15
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	14, 15
		(b) For matched studies, give matching criteria and number of exposed and unexposed	DNA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	15-17, suppl
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	15-17, suppl
Bias	9	Describe any efforts to address potential sources of bias	16,17, suppl
Study size	10	Explain how the study size was arrived at	14-16
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	15-17, suppl
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	15-17, suppl
		(b) Describe any methods used to examine subgroups and interactions	15-17, suppl
		(c) Explain how missing data were addressed	15-17, suppl
		(d) If applicable, explain how loss to follow-up was addressed	DNA
		(e) Describe any sensitivity analyses	16, 17, suppl
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study-e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, and analyzed	4
		(b) Give reasons for non-participation at each stage	DNA
		(c) Consider use of a flow diagram	DNA
Descriptive data	14*	(a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders	4, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	DNA
		(c) Summarize follow-up time (e.g., average and total amount)	4, suppl
Outcome data	15*	Report numbers of outcome events or summary measures over time	4, suppl
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	4-7, suppl
		(b) Report category boundaries when continuous variables were categorized	DNA
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	DNA
Other analyses	17	Report other analyses done-e.g., analyses of subgroups and interactions, and sensitivity analyses	5-7, suppl
Discussion			
Key results	18	Summarize key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8, 12-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8, 12-14
Generalizability	21	Discuss the generalizability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

34 *Give information separately for exposed and unexposed groups.

35 DNA: does not applied, suppl: supplementary material.

36 **Supplementary Table 7:** ICD-10 and ATC codes used for identifying PD cases among farm managers depending on the analysis

Data origin	Classification system	Code	Definition	Drug Indication§	Analysis
Long-term illness scheme/declaration (requirement to be considered as a PD case: at least one declaration of any of these three ICD-10 codes)	ICD-10	F02	Dementia in other diseases classified elsewhere	/	MA, SA1, SA3-6, SA8, SA10-17
	ICD-10	G20	Parkinson's disease	/	MA, SA1, SA3-6, SA8-17
	ICD-10	G21	Secondary parkinsonism	/	SA6, SA9-11
Occupational disease scheme (requirement to be considered as a PD case: at least one declaration for PD induced by pesticides)	ODC	RA 58	PD induced by pesticide exposure	/	MA, SA1-6, SA8, SA11-17
Drug reimbursement for PD (requirement to be considered as a PD case: at least one reimbursement of any of these ATC codes)	ATC	N04BA01	Levodopa	PD only	MA, SA1, SA3-5, SA7-8, SA11-17
	ATC	N04BA02	Levodopa and decarboxylase inhibitor	PD only	MA, SA1, SA3-5, SA7-8, SA11-17
	ATC	N04BA03	Levodopa, decarboxylase inhibitor and COMT inhibitor	PD only	MA, SA1, SA3-5, SA7-8, SA11-17
	ATC	N04BD01	Selegiline	PD only	MA, SA1, SA3-5, SA7-8, SA11-17
	ATC	N04BD02	Rasagiline	PD only	MA, SA1, SA3-5, SA7-8, SA11-17
	ATC	N04BX01	Tolcapone	PD only	MA, SA1, SA3-5, SA7-8, SA11-17
	ATC	N04BX02	Entacapone	PD only	MA, SA1, SA3-5, SA7-8, SA11-17
	ATC	N04BC01	Bromocriptine	PD only	MA, SA1, SA3-5, SA7-8, SA11-17
	ATC	N04BC04	Ropinirole	PD only	MA, SA1, SA3-5, SA7-8, SA11-17
	ATC	N04BC07	Apomorphine	PD only	MA, SA1, SA3-5, SA7-8, SA11-17
	ATC	N04BC08	Piribedil	PD only	MA, SA1, SA3-5, SA7-8, SA11-17
	ATC	N04AA01	Trihexyphenidyl*	PD, parkinsonism	MA, SA1, SA3-5, SA7-8, SA11-17
	ATC	N04AA02	Biperiden*	PD, parkinsonism	MA, SA1, SA3-5, SA7-8, SA11-17
	ATC	N04AA12	Tropatepine*	PD, parkinsonism	MA, SA1, SA3-5, SA7-8, SA11-17
	ATC	N02CA07	Lisuride	PD, hyperprolactinemia disorders	SA11
	ATC	N04BB01	Amantadine	PD, influenza A, postherpetic neuralgia	SA11
	ATC	N04BC05	Pramipexole	PD, Restless Legs Syndrome	SA11
	ATC	N04BC09	Rotigotine	PD, Restless Legs Syndrome	SA11

37 *Abbreviations:* ATC: Anatomical Therapeutic Chemical classification system, COMT: catechol-O-methyltransferase, ICD-10: 10th revision of the International Statistical Classification of
38 Diseases and Related Health Problems, MA: main analysis, ODCs: occupational diseases covered under workers' compensation statutes, PD: Parkinson's disease, SA: sensitivity analysis.

39 * Farm managers only on anticholinergics and neuroleptics (drug-induced parkinsonism) were not considered.

40 § According to the Vidal (<https://www.vidal.fr/>), Thesorimed (<https://theso.prod-un.thesorimed.org/monographie>) and BCB databases (<https://www.bcb.fr/v2/app/recherche.jsp>).

41 **Supplementary Table 8:** List of covariates considered in the statistical analyses

Dependent variable	Modality
PD diagnosis (LTI declaration or drug reimbursement)	2 categories: yes or no
Time to first PD insurance declaration, or drug reimbursement	continuous
Independent variables	
Activity	2 categories: yes or no
Sex	2 categories: female or male
Age	continuous
First year of the farm's establishment, years	continuous
Median yearly farm surface, hectares	continuous
Median yearly insurance premium, euros	continuous
Number of associates	continuous
Unemployment status	2 categories: never unemployed or had been unemployed at least once over the period 2002-2016
Number of farms	2 categories: 1 or > 1
Family status	2 categories: single or as a couple
Partner work status	2 categories: perform or do not perform task to help farm manager
Having a secondary farming activity [†]	2 categories: yes or no
Number of pre-existing medical comorbidities	continuous
Farm location	96 categories: 96 metropolitan French administrative geographical areas (departments)

42 *Abbreviations:* LTI: long-term illness, PD: Parkinson's disease.

43 Categorical variables with more than two categories were converted to binary variables by applying the one-hot encoding approach, with the exclusion of one category to prevent multicollinearity.

44 For each binary variable (e.g., activity), the reference was set as the 'no' or '0' modality.

45 *The analysis was adjusted on sex only for "both sexes"; otherwise, sex was used for subgroup analyses.

46 † A secondary farming activity is defined as a farming activity (e.g., grassland farming) that a FM can perform in addition to its main activity (e.g., ovine farming). The nature of the secondary
47 activity is, however, unknown.

48 **Sensitivity analysis**

49 Thirteen sensitivity analyses (SAs) were undertaken to test hypotheses and address potential sources of bias.

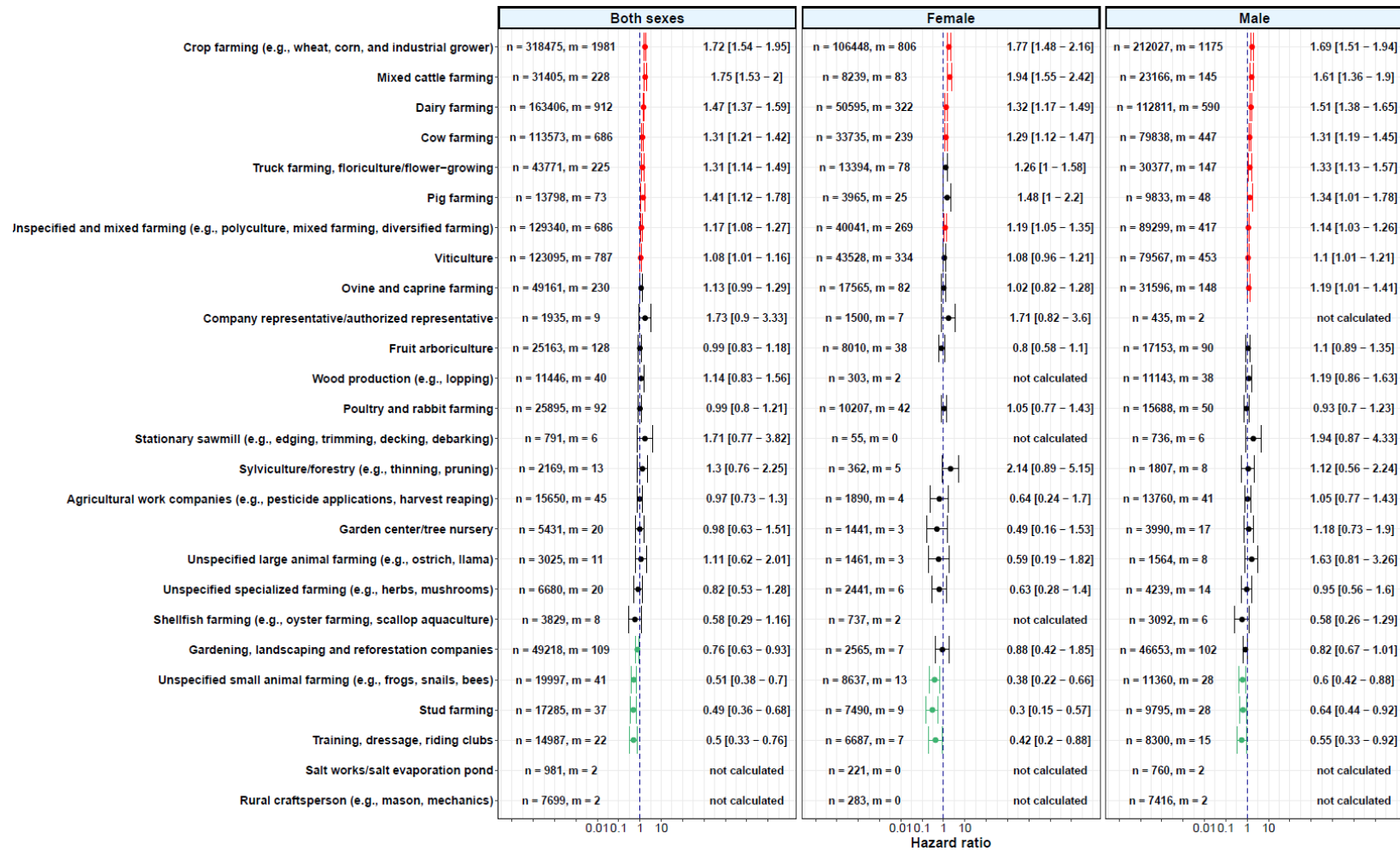
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51 *Sensitivity analysis 1 - excluding PD cases diagnosed in 2012*

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53 To increase the likelihood that identified PD cases were incident cases, a sensitivity analysis was conducted by
54 excluding PD cases diagnosed in 2012. Similarly to the main analysis, for this sensitivity analysis, FMs were
55 considered to have PD if they had at least one LTI declaration for PD (ICD-10 code G20 or F02), one ODC
56 declaration for PD, or one reimbursement of any drugs solely used to treat PD (i.e., all antiparkinsonian agents,
57 with the exception of pramipexole, rotigotine, amantadine, and lisuride) (Supplementary Table 7). However, FMs
58 only on anticholinergics (trihexyphenidyl, biperiden, and tropatepine) and neuroleptics (drug-induced
59 parkinsonism) were not considered PD cases.

60 The highest-risk group included FMs engaged in crop farming, mixed cattle farming, dairy farming, truck farming,
61 pig farming, viticulture, unspecified and mixed farming (Supplementary Table 4, Supplementary Figure 1). A
62 positive trend was also observed for ovine and caprine farming. By contrast, the lowest-risk group included FMs
63 engaged in gardening, landscaping and reforestation companies, small animal farming, training, dressage and
64 riding clubs, and stud farming. No farming activities exhibit a sex difference.



65

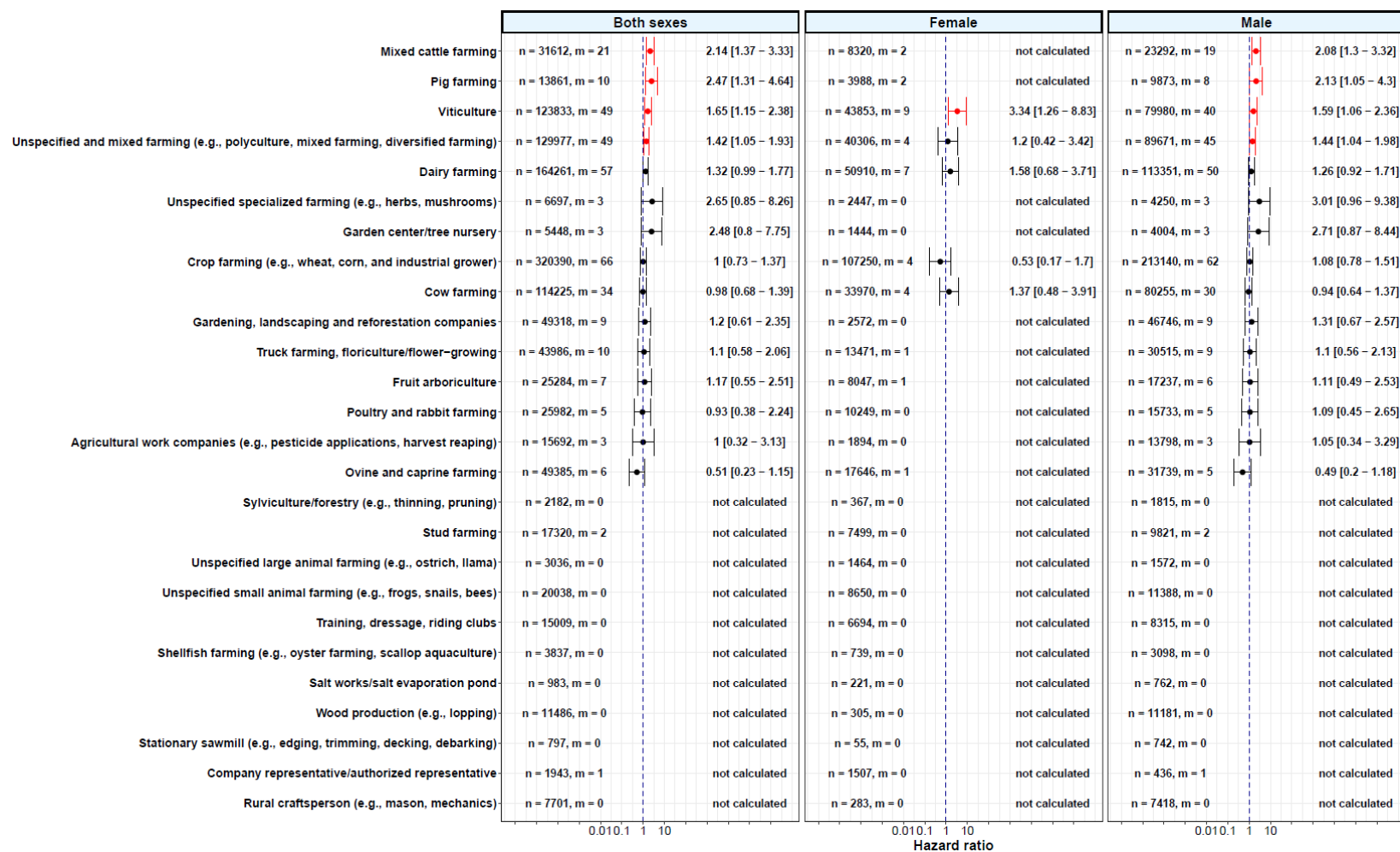
66 **Supplementary Figure 1:** Farming activities and risks of Parkinson’s disease, TRACTOR project, 2012-2016 – sensitivity analysis 1

67 Multivariable Cox regression models for Parkinson’s disease according to each agricultural activity (y-axis) are displayed when the number of exposed cases was sufficient (m ≥ 3). The hazard
68 ratio is represented by a point (x-axis), while error bars represent the 95% confidence interval. The red error bars refer to a higher risk of Parkinson’s disease while the green error bars represent a
69 lower risk of Parkinson’s disease. The black error bars indicate situations where there is no difference in risk of Parkinson’s disease among the farm managers engaged in the considered activity
70 compared to the population of farm managers not performing the considered activity. All analyses were adjusted for sex (for “both sexes” only), age, first year of the farm’s establishment, median
71 farm surface, number of associates, unemployment status, total number of farms, family status, partner work status, farm location, number of comorbidities, and performing a secondary farming
72 activity. n, number of exposed farm managers; m, number of exposed Parkinson’s disease cases.

73 *Sensitivity analysis 2 – PD identification using only ODC declaration data*

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75 In this sensitivity analysis, the PD case identification was based solely on ODC declarations for PD induced by
76 pesticide exposures, knowing that compensation for PD as an occupational disease among long-term pesticide
77 users, with causality presumption, only started in May 2012 in France¹. The highest-risk group included FMs
78 engaged in mixed cattle farming, pig farming, viticulture, and unspecified and mixed farming (Supplementary
79 Table 4, Supplementary Figure 2). By contrast, no activity had reduced HRs, probably because of the small number
80 of PD cases (317 in total) identified for this analysis. Viticulture was the only farming activity that exhibited a sex
81 difference, with a PD risk around two times higher in females than males.



82

83 **Supplementary Figure 2:** Farming activities and risks of Parkinson’s disease, TRACTOR project, 2012-2016 – sensitivity analysis 2

84 Multivariable Cox regression models for Parkinson’s disease according to each agricultural activity (y-axis) are displayed when the number of exposed cases was sufficient (m ≥ 3). The hazard
85 ratio is represented by a point (x-axis), while error bars represent the 95% confidence interval. The red error bars refer to a higher risk of Parkinson’s disease while the green error bars represent a
86 lower risk of Parkinson’s disease. The black error bars indicate situations where there is no difference in risk of Parkinson’s disease among the farm managers engaged in the considered activity
87 compared to the population of farm managers not performing the considered activity. All analyses were adjusted for sex (for “both sexes” only), age, first year of the farm’s establishment, median
88 farm surface, number of associates, unemployment status, total number of farms, family status, partner work status, farm location, number of comorbidities, and performing a secondary farming
89 activity. n, number of exposed farm managers; m, number of exposed Parkinson’s disease cases.

Sensitivity analyses 3 to 5 – age restrictions

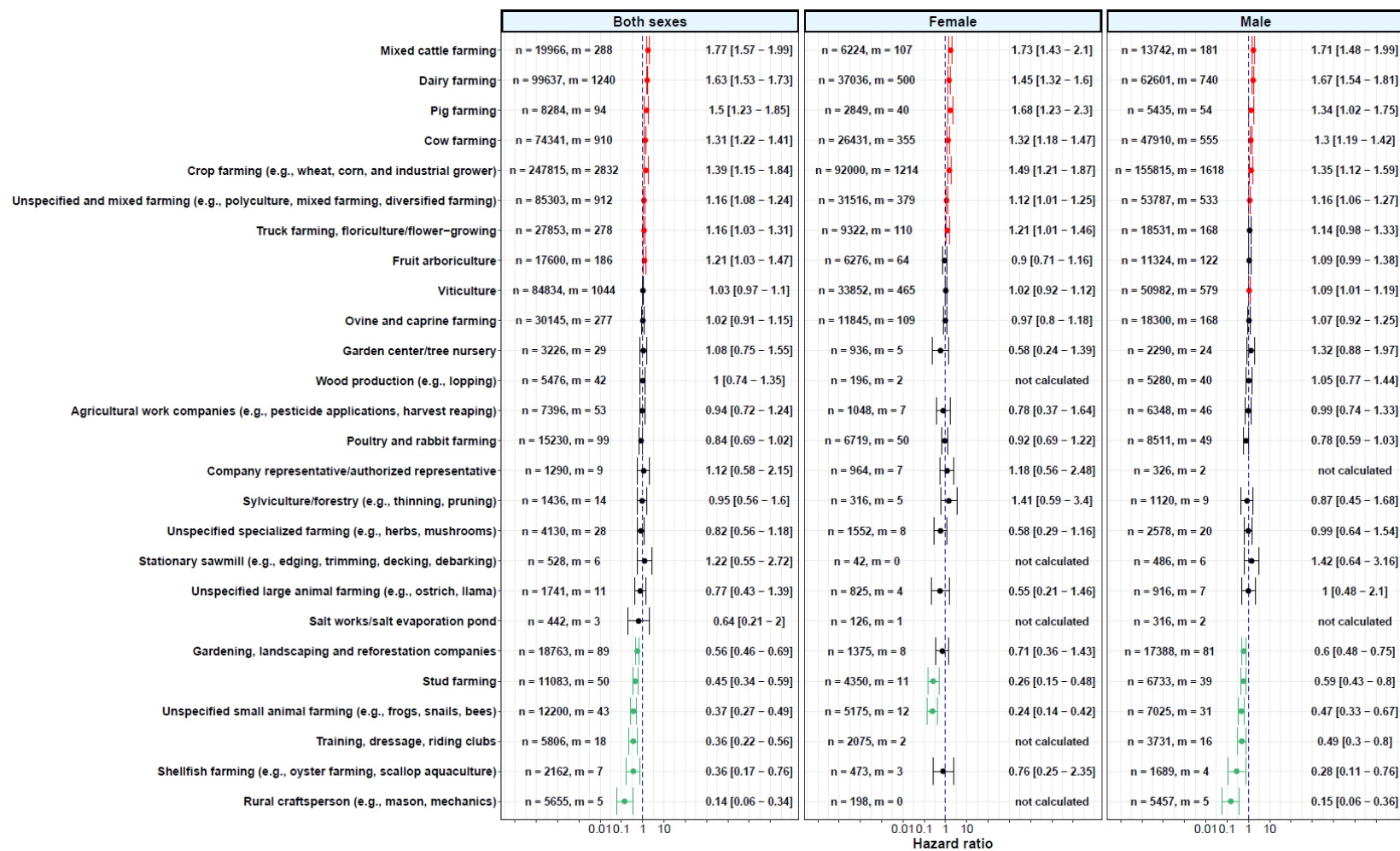
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Because PD is not common before age 40¹⁻³, one SA was restricted to FMs who were 40 years and older (SA3), another one to FMs who were 50 years and older (SA4), and a third to FMs who were 60 years and older (SA5), respectively. Similarly to the main analysis, for these sensitivity analyses, FMs were considered to have PD if they had at least one LTI declaration for PD (ICD-10 code G20 or F02), one ODC declaration for PD, or one reimbursement of any drugs solely used to treat PD (i.e., all antiparkinsonian agents, with the exception of pramipexole, rotigotine, amantadine, and lisuride) (Supplementary Table 7). However, FMs only on anticholinergics (trihexyphenidyl, biperiden, and tropatepine) and neuroleptics (drug-induced parkinsonism) were not considered PD cases.

Regarding the sensitivity analysis restricted to FMs ≥ 40 years (SA3), the highest-risk group included FMs engaged in mixed cattle farming, pig farming, dairy farming, cow farming, crop farming, unspecified and mixed farming, truck farming, and fruit arboriculture (Supplementary Table 4, Supplementary Figure 3). A positive trend was also observed for viticulture and ovine and caprine farming. By contrast, the lowest-risk group included FMs engaged in gardening, landscaping and reforestation companies, small animal farming, training, dressage and riding clubs, stud farming, shellfish farming and rural craftsperson. Dairy farming and stud farming were the only activities exhibiting a sex difference, with male FMs having a higher risk than females.

Regarding the sensitivity analysis restricted to FMs ≥ 50 years (SA4), the highest-risk group included FMs engaged in mixed cattle farming, dairy farming, crop farming, pig farming, cow farming, and truck farming (Supplementary Table 4, Supplementary Figure 4). A positive trend was also observed for viticulture and unspecified and mixed farming. By contrast, the lowest-risk group included FMs engaged in gardening, landscaping and reforestation companies, small animal farming, training, dressage and riding clubs, stud farming, shellfish farming and rural craftsperson. Four activities exhibited a sex difference, with male FMs having a higher risk than females for dairy farming, pig farming, and stud farming; while female FMs engaged in crop farming had a higher risk than males.

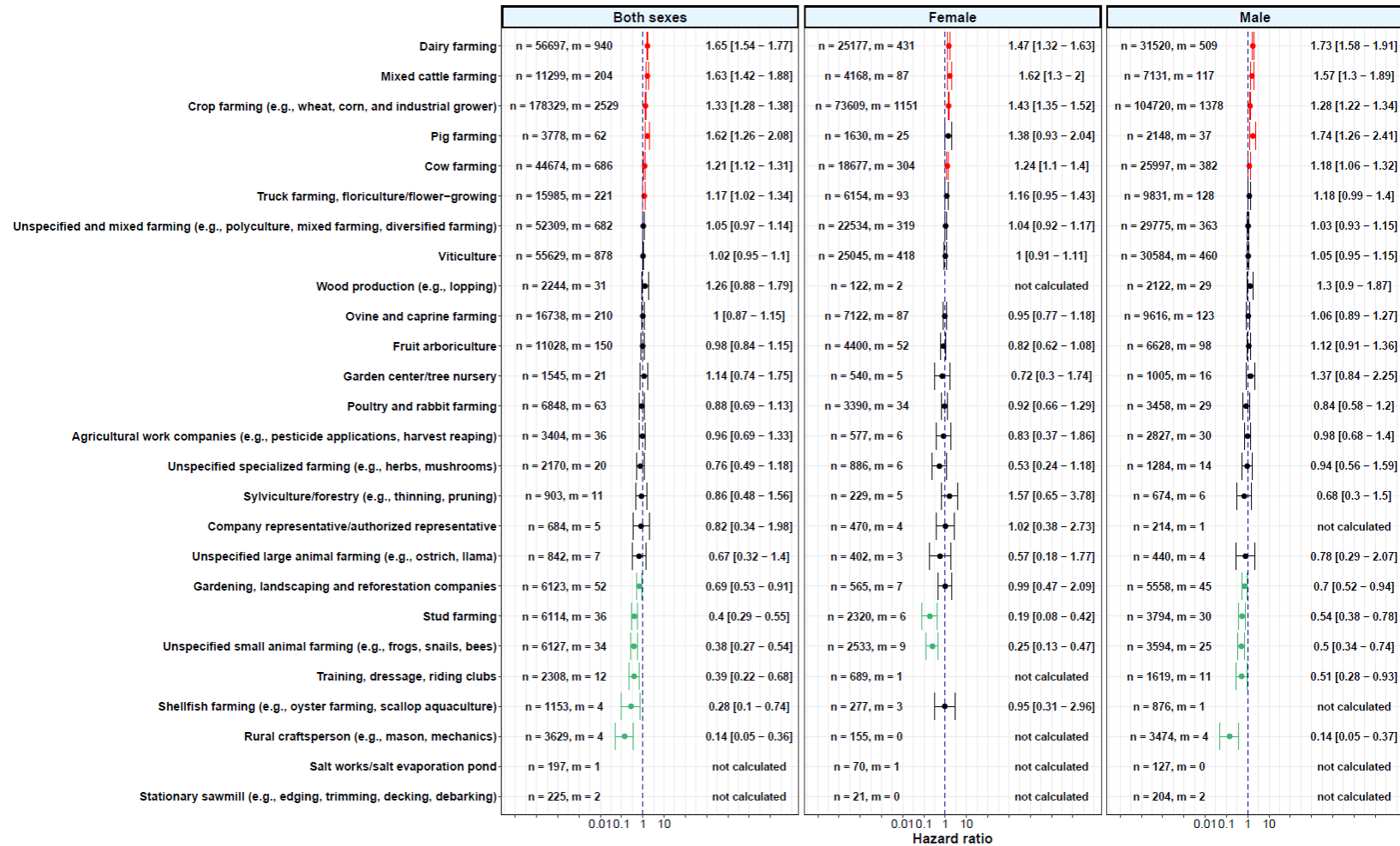
Regarding the sensitivity analysis restricted to FMs ≥ 60 years (SA5), the highest-risk group included FMs engaged in dairy farming, mixed cattle farming, pig farming, fruit arboriculture, cow farming, and crop farming (Supplementary Table 4, Supplementary Figure 5). A positive trend was also observed for viticulture and truck farming. By contrast, the lowest-risk group included FMs engaged in stud farming and small animal farming. Three activities exhibited a sex difference, with male FMs having a higher risk than females for fruit arboriculture, pig farming, and stud farming.



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124 **Supplementary Figure 3:** Farming activities and risks of Parkinson’s disease, TRACTOR project, 2012-2016 – sensitivity analysis 3

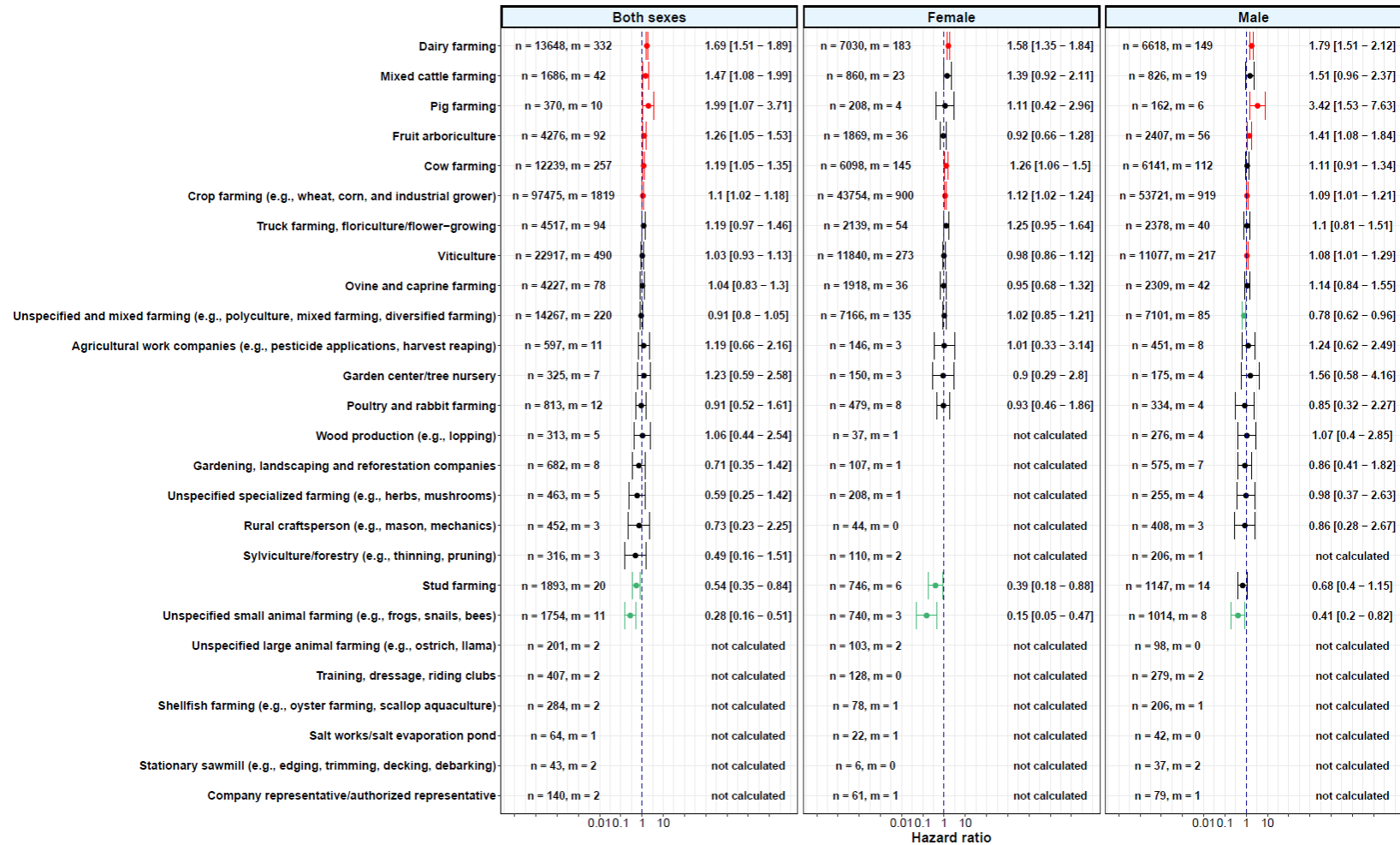
125 Multivariable Cox regression models for Parkinson’s disease according to each agricultural activity (y-axis) are displayed when the number of exposed cases was sufficient ($m \geq 3$). The hazard
 126 ratio is represented by a point (x-axis), while error bars represent the 95% confidence interval. The red error bars refer to a higher risk of Parkinson’s disease while the green error bars represent a
 127 lower risk of Parkinson’s disease. The black error bars indicate situations where there is no difference in risk of Parkinson’s disease among the farm managers engaged in the considered activity
 128 compared to the population of farm managers not performing the considered activity. All analyses were adjusted for sex (for “both sexes” only), age, first year of the farm’s establishment, median
 129 farm surface, number of associates, unemployment status, total number of farms, family status, partner work status, farm location, number of comorbidities, and performing a secondary farming
 130 activity. n, number of exposed farm managers; m, number of exposed Parkinson’s disease cases.



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132 **Supplementary Figure 4:** Farming activities and risks of Parkinson’s disease, TRACTOR project, 2012-2016 – sensitivity analysis 4

133 Multivariable Cox regression models for Parkinson’s disease according to each agricultural activity (y-axis) are displayed when the number of exposed cases was sufficient (m ≥ 3). The hazard
 134 ratio is represented by a point (x-axis), while error bars represent the 95% confidence interval. The red error bars refer to a higher risk of Parkinson’s disease while the green error bars represent a
 135 lower risk of Parkinson’s disease. The black error bars indicate situations where there is no difference in risk of Parkinson’s disease among the farm managers engaged in the considered activity
 136 compared to the population of farm managers not performing the considered activity. All analyses were adjusted for sex (for “both sexes” only), age, first year of the farm’s establishment, median
 137 farm surface, number of associates, unemployment status, total number of farms, family status, partner work status, farm location, number of comorbidities, and performing a secondary farming
 138 activity. n, number of exposed farm managers; m, number of exposed Parkinson’s disease cases.



139

140 **Supplementary Figure 5:** Farming activities and risks of Parkinson’s disease, TRACTOR project, 2012-2016 – sensitivity analysis 5

141 Multivariable Cox regression models for Parkinson’s disease according to each agricultural activity (y-axis) are displayed when the number of exposed cases was sufficient (m ≥ 3). The hazard
 142 ratio is represented by a point (x-axis), while error bars represent the 95% confidence interval. The red error bars refer to a higher risk of Parkinson’s disease while the green error bars represent a
 143 lower risk of Parkinson’s disease. The black error bars indicate situations where there is no difference in risk of Parkinson’s disease among the farm managers engaged in the considered activity
 144 compared to the population of farm managers not performing the considered activity. All analyses were adjusted for sex (for “both sexes” only), age, first year of the farm’s establishment, median
 145 farm surface, number of associates, unemployment status, total number of farms, family status, partner work status, farm location, number of comorbidities, and performing a secondary farming
 146 activity. n, number of exposed farm managers; m, number of exposed Parkinson’s disease cases.

Sensitivity analyses 6 to 14 – addressing potential case misclassification

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To address potential case misclassification due to the potential lack of specificity of health data, ten sensitivity analyses with varying stringency were conducted (Supplementary Table 7). For instance, the LTI declaration for G21 (secondary Parkinsonism) was considered as PD cases in several sensitivity analyses. The rationale behind this decision is that, sometimes, differentiating primary Parkinson’s disease (G20) from secondary Parkinsonism (G21) can be challenging, especially in the early stages. If only G20 is used to identify Parkinson’s disease cases, there may be a risk of under-capturing relevant cases that are initially coded as G21 but may later transition to G20. This inclusion could avoid missing cases where secondary parkinsonism was initially misdiagnosed but later identified as primary PD, or where a person exhibits features of both.

The first one, SA2, was described previously.

For SA6, FMs were considered PD cases if they had either at least one LTI (F02, G20, G21) or ODC declaration. The highest-risk group included FMs engaged in crop farming, mixed cattle farming, dairy farming, pig farming, fruit arboriculture, truck farming, unspecified and mixed farming, and cow farming (Supplementary Table 4, Supplementary Figure 6). By contrast, the lowest-risk group included FMs engaged in gardening, landscaping and reforestation companies, small animal farming, and stud farming. Viticulture was the only farming activity exhibiting a sex difference, with male FMs having a higher risk than females.

For SA7, FMs were considered PD cases if they had at least one drug reimbursement of any anti-Parkinson drugs solely used to treat PD. However, FMs only on anticholinergics (trihexyphenidyl, biperiden, and tropatepine) and neuroleptics (drug-induced parkinsonism) were not considered as PD cases. The highest-risk group included FMs engaged in mixed cattle farming, dairy farming, crop farming, cow farming, pig farming, truck farming, unspecified and mixed farming, and viticulture (Supplementary Table 4, Supplementary Figure 7). A positive trend was also observed for ovine and caprine farming. By contrast, the lowest-risk group included FMs engaged in gardening, landscaping and reforestation companies, small animal farming, training, dressage and riding clubs, stud farming, shellfish farming and rural craftsperson. Pig farming was the only farming activity exhibiting a sex difference, with female FMs having a higher risk than males.

For SA8, FMs who had at least one drug reimbursement of any anti-Parkinson drugs solely used to treat PD and also a LTI declaration for Alzheimer’s disease and other related dementias (ADRD) that corresponded to ICD-10 codes F00 (“dementia in Alzheimer’s disease”), F01 (“vascular dementia”), F02 (“dementia in other diseases classified elsewhere”), F03 (“unspecified dementia”), and G30 (“Alzheimer’s disease”) were not considered PD cases. In addition, FMs only on anticholinergics (trihexyphenidyl, biperiden, and tropatepine) and neuroleptics (drug-induced parkinsonism) were not considered as PD cases. The highest-risk group included FMs engaged in mixed cattle farming, crop farming, dairy farming, pig farming, cow farming, unspecified and mixed farming, and truck farming (Supplementary Table 4, Supplementary Figure 8). A positive trend was also observed for viticulture and ovine and caprine farming. By contrast, the lowest-risk group included FMs engaged in gardening, landscaping

186 and reforestation companies, small animal farming, training, dressage and riding clubs, stud farming, shellfish
187 farming and rural craftsperson. No activity exhibited a sex difference.

188
189 For SA9, FMs were considered PD cases if they had one LTI declaration with either the ICD-10 code G20
190 (“Parkinson’s disease”) or G21 (“secondary parkinsonism”). The highest-risk group included FMs engaged in crop
191 farming, mixed cattle farming, dairy farming, pig farming, fruit arboriculture, cow farming, unspecified and mixed
192 farming, and truck farming (Supplementary Table 4, Supplementary Figure 9). A positive trend was also observed
193 for viticulture and silviculture. By contrast, the lowest-risk group included FMs engaged in gardening, landscaping
194 and reforestation companies, small animal farming, training, dressage and riding clubs, and stud farming. Only
195 viticulture exhibited a sex difference, with male FMs having a higher risk than females.

196
197 For SA10, FMs were considered PD cases if they had one LTI declaration with either the ICD-10 code F02, G20,
198 or G21. The highest-risk group included FMs engaged in crop farming, mixed cattle farming, dairy farming, fruit
199 arboriculture, viticulture, pig farming, cow farming, unspecified and mixed farming, and truck farming
200 (Supplementary Table 4, Supplementary Figure 10). A positive trend was also observed for silviculture. By
201 contrast, the lowest-risk group included FMs engaged in gardening, landscaping and reforestation companies,
202 small animal farming, and stud farming. Only viticulture exhibited a sex difference, with male FMs having a higher
203 risk than females.

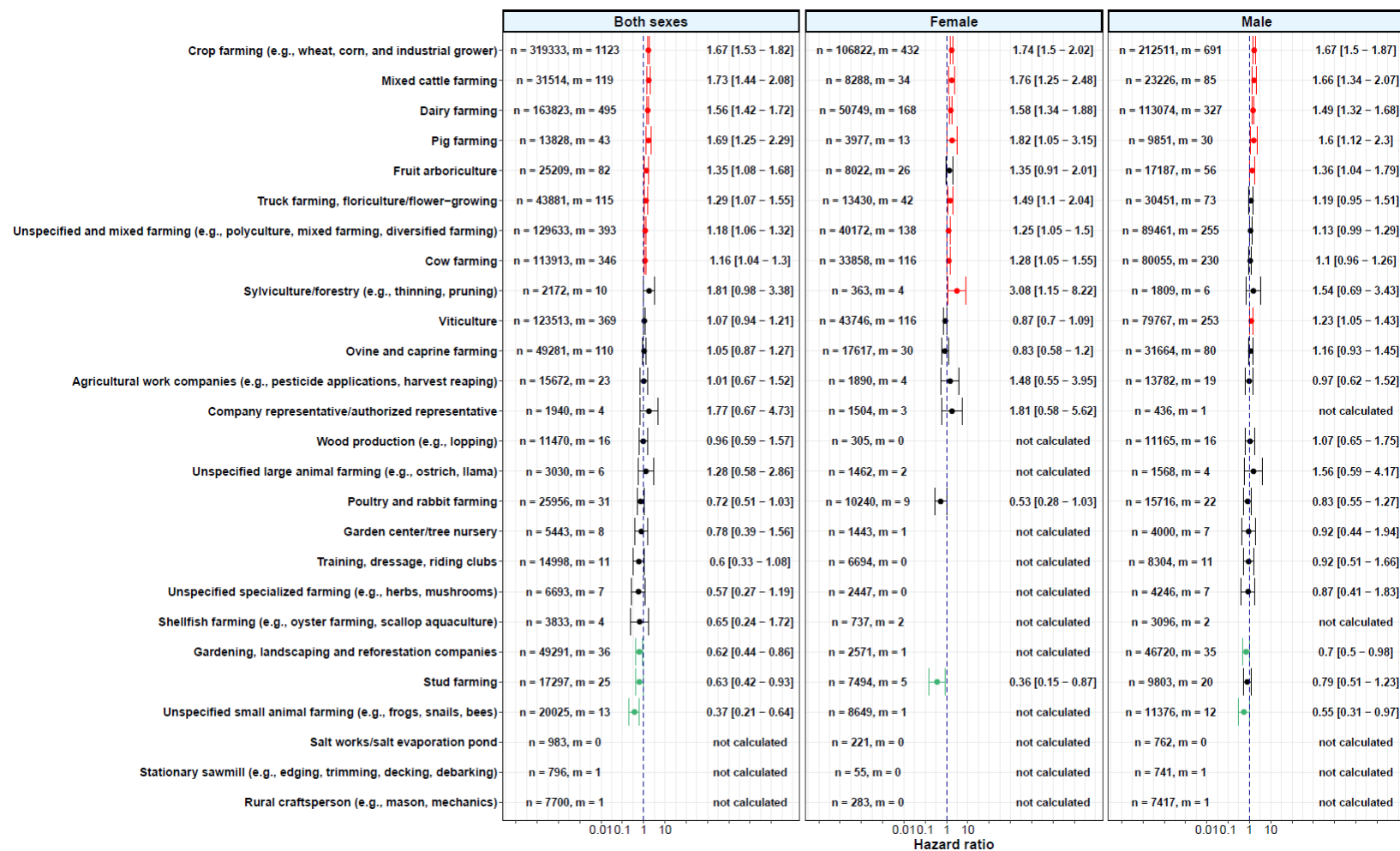
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205 For SA11, FMs were considered PD cases if they had either at least one LTI declaration (F02, G20, G21), one
206 ODC declaration, or one drug reimbursement of any anti-Parkinson drugs even, if the drug is not solely used for
207 PD. The highest-risk group included FMs engaged in crop farming, dairy farming, mixed cattle farming, pig
208 farming, fruit arboriculture, cow farming, viticulture, unspecified and mixed farming, and truck farming
209 (Supplementary Table 4, Supplementary Figure 11). A positive trend was also observed for ovine and caprine
210 farming and wood production. By contrast, the lowest-risk group included FMs engaged in small animal farming,
211 training, dressage and riding clubs, stud farming, and rural craftsperson. Three activities exhibited a sex difference,
212 with male FMs having a higher risk than females for viticulture and stud farming; while female FMs engaged in
213 mixed cattle farming had a higher risk than males.

214
215 For SA12, FMs were considered PD cases if they had either at least one LTI (F02, G20), one ODC declaration, or
216 two drug reimbursements of any anti-Parkinson drugs solely used to treat PD. However, FMs only on
217 anticholinergics (trihexyphenidyl, biperiden, and tropatepine) and neuroleptics (drug-induced parkinsonism) were
218 not considered as PD cases. The highest-risk group included FMs engaged in crop farming, dairy farming, mixed
219 cattle farming, cow farming, pig farming, truck farming, and fruit arboriculture (Supplementary Table 4,
220 Supplementary Figure 12). A positive trend was also observed for unspecified and mixed farming, viticulture, and
221 ovine and caprine farming. By contrast, the lowest-risk group included FMs engaged in gardening, landscaping
222 and reforestation companies, small animal farming, training, dressage and riding clubs, stud farming, and rural
223 craftsperson. Viticulture and stud farming were the only two farming activities exhibiting a sex difference, with
224 male FMs having a higher risk than females.

225

226 For SA13, FMs were considered PD cases if they had either at least one LTI (F02, G20), one ODC declaration, or
227 three drug reimbursements of any anti-Parkinson drugs solely used to treat PD. However, FMs only on
228 anticholinergics (trihexyphenidyl, biperiden, and tropatepine) and neuroleptics (drug-induced parkinsonism) were
229 not considered as PD cases. The highest-risk group included FMs engaged in crop farming, dairy farming, mixed
230 cattle farming, pig farming, cow farming, truck farming, and fruit arboriculture (Supplementary Table 4,
231 Supplementary Figure 13). A positive trend was also observed for unspecified and mixed farming, viticulture, and
232 ovine and caprine farming. By contrast, the lowest-risk group included FMs engaged in gardening, landscaping
233 and reforestation companies, small animal farming, training, dressage and riding clubs, and stud farming. A
234 negative trend was also observed for shellfish farming. Viticulture, stud farming and gardening, landscaping and
235 reforestation companies were the only farming activities exhibiting a sex difference, with male FMs having a
236 higher risk than females, with the exception of gardening, landscaping and reforestation companies.

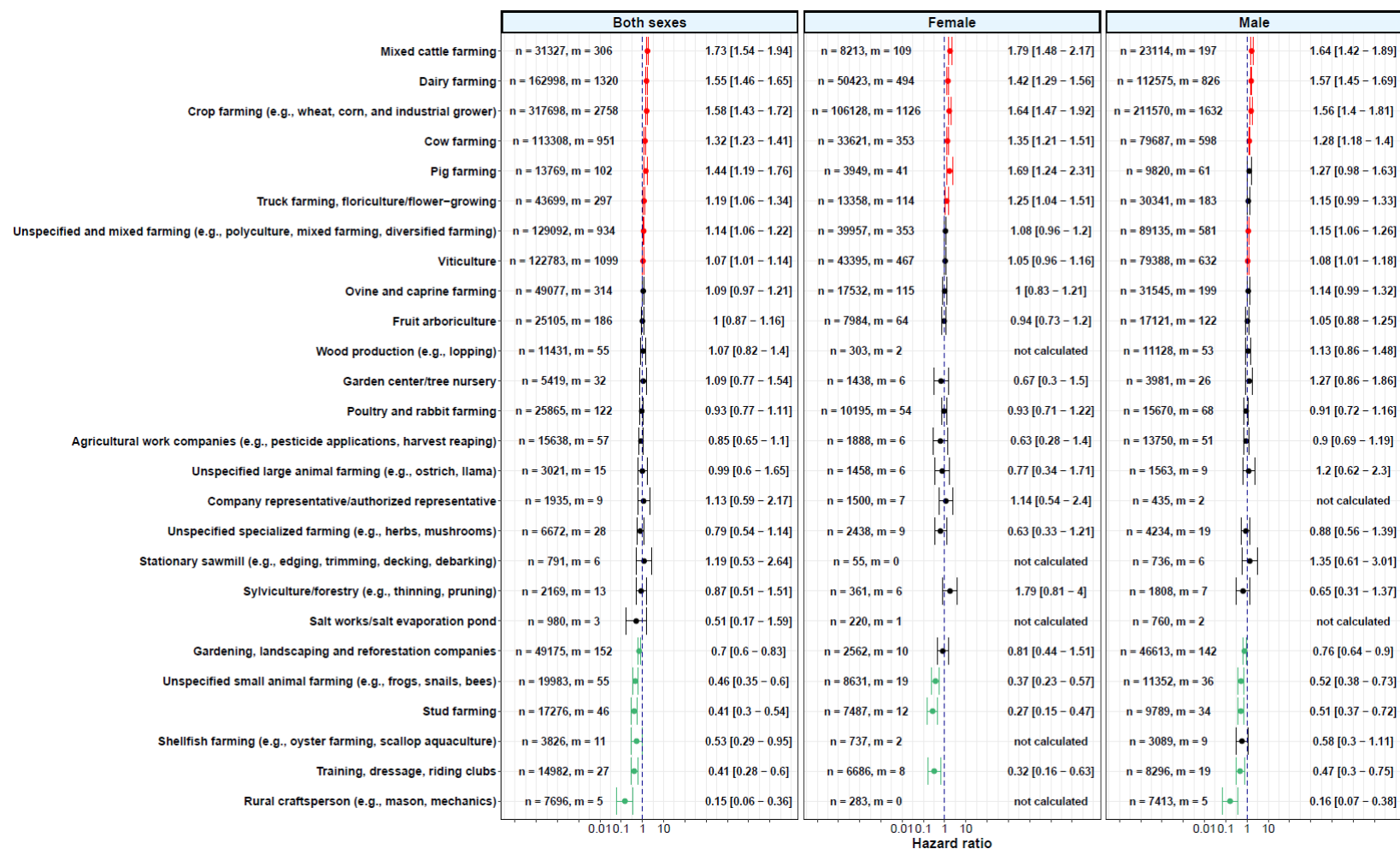
237
238 For SA14, FMs were considered PD cases if they had either at least one LTI (F02, G20), one ODC declaration, or
239 six drug reimbursements of any anti-Parkinson drugs solely used to treat PD. However, FMs only on
240 anticholinergics (trihexyphenidyl, biperiden, and tropatepine) and neuroleptics (drug-induced parkinsonism) were
241 not considered as PD cases. The highest-risk group included FMs engaged in dairy farming, crop farming, mixed
242 cattle farming, pig farming, cow farming, fruit arboriculture, and unspecified and mixed farming (Supplementary
243 Table 4, Supplementary Figure 14). A positive trend was also observed for truck farming, and viticulture. By
244 contrast, the lowest-risk group included FMs engaged in poultry and rabbit farming, gardening, landscaping and
245 reforestation companies, small animal farming, training, dressage and riding clubs, and stud farming. Viticulture
246 and training, dressage, riding clubs were the only farming activities exhibiting a sex difference, with male FMs
247 having a higher risk than females. A trend was also observed for unspecified specialized farming and stud farming,
248 with risk higher for males than females. In contrast, a trend with higher risk among females than males was
249 observed for both truck farming and shellfish farming.



250

251 **Supplementary Figure 6:** Farming activities and risks of Parkinson’s disease, TRACTOR project, 2012-2016 – sensitivity analysis 6

252 Multivariable Cox regression models for Parkinson’s disease according to each agricultural activity (y-axis) are displayed when the number of exposed cases was sufficient (m ≥ 3). The hazard
 253 ratio is represented by a point (x-axis), while error bars represent the 95% confidence interval. The red error bars refer to a higher risk of Parkinson’s disease while the green error bars represent a
 254 lower risk of Parkinson’s disease. The black error bars indicate situations where there is no difference in risk of Parkinson’s disease among the farm managers engaged in the considered activity
 255 compared to the population of farm managers not performing the considered activity. All analyses were adjusted for sex (for “both sexes” only), age, first year of the farm’s establishment, median
 256 farm surface, number of associates, unemployment status, total number of farms, family status, partner work status, farm location, number of comorbidities, and performing a secondary farming
 257 activity. n, number of exposed farm managers; m, number of exposed Parkinson’s disease cases.



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259 **Supplementary Figure 7:** Farming activities and risks of Parkinson's disease, TRACTOR project, 2012-2016 – sensitivity analysis 7

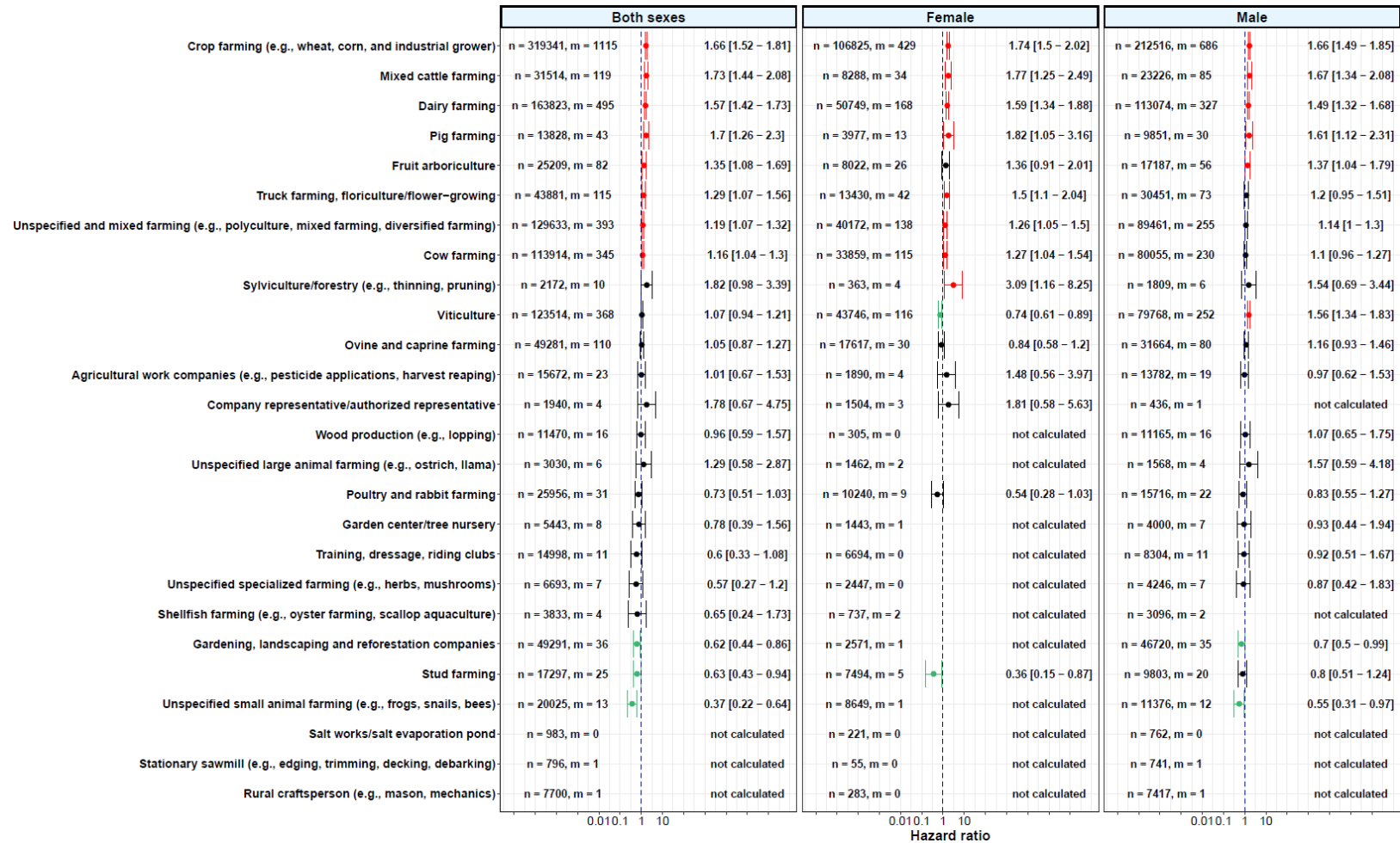
260 Multivariable Cox regression models for Parkinson's disease according to each agricultural activity (y-axis) are displayed when the number of exposed cases was sufficient ($m \geq 3$). The hazard
 261 ratio is represented by a point (x-axis), while error bars represent the 95% confidence interval. The red error bars refer to a higher risk of Parkinson's disease while the green error bars represent a
 262 lower risk of Parkinson's disease. The black error bars indicate situations where there is no difference in risk of Parkinson's disease among the farm managers engaged in the considered activity
 263 compared to the population of farm managers not performing the considered activity. All analyses were adjusted for sex (for "both sexes" only), age, first year of the farm's establishment, median
 264 farm surface, number of associates, unemployment status, total number of farms, family status, partner work status, farm location, number of comorbidities, and performing a secondary farming
 265 activity. n, number of exposed farm managers; m, number of exposed Parkinson's disease cases.



266

267 **Supplementary Figure 8:** Farming activities and risks of Parkinson's disease, TRACTOR project, 2012-2016 – sensitivity analysis 8

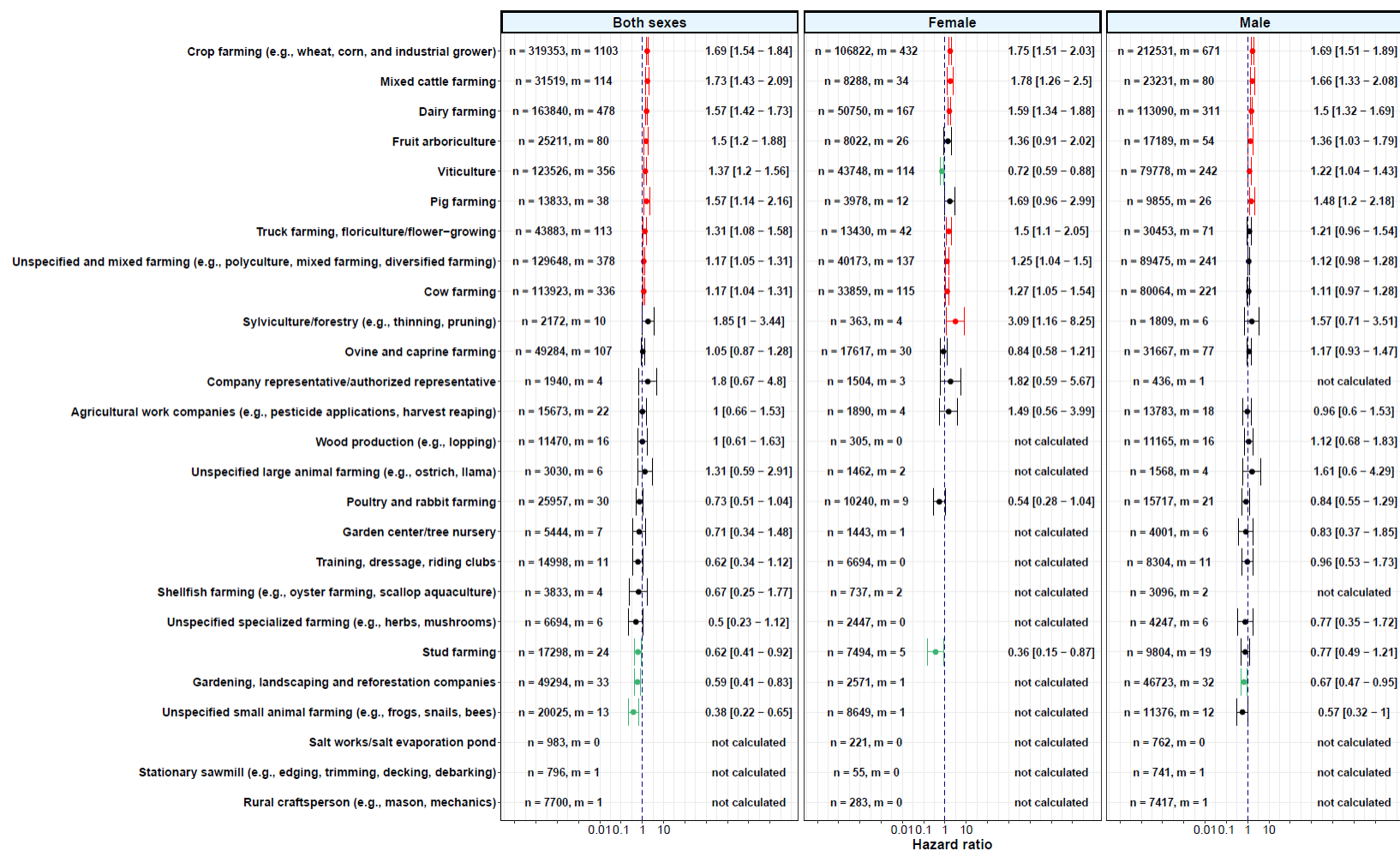
268 Multivariable Cox regression models for Parkinson's disease according to each agricultural activity (y-axis) are displayed when the number of exposed cases was sufficient ($m \geq 3$). The hazard
 269 ratio is represented by a point (x-axis), while error bars represent the 95% confidence interval. The red error bars refer to a higher risk of Parkinson's disease while the green error bars represent a
 270 lower risk of Parkinson's disease. The black error bars indicate situations where there is no difference in risk of Parkinson's disease among the farm managers engaged in the considered activity
 271 compared to the population of farm managers not performing the considered activity. All analyses were adjusted for sex (for "both sexes" only), age, first year of the farm's establishment, median
 272 farm surface, number of associates, unemployment status, total number of farms, family status, partner work status, farm location, number of comorbidities, and performing a secondary farming
 273 activity. n, number of exposed farm managers; m, number of exposed Parkinson's disease cases.



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275 **Supplementary Figure 9:** Farming activities and risks of Parkinson’s disease, TRACTOR project, 2012-2016 – sensitivity analysis 9

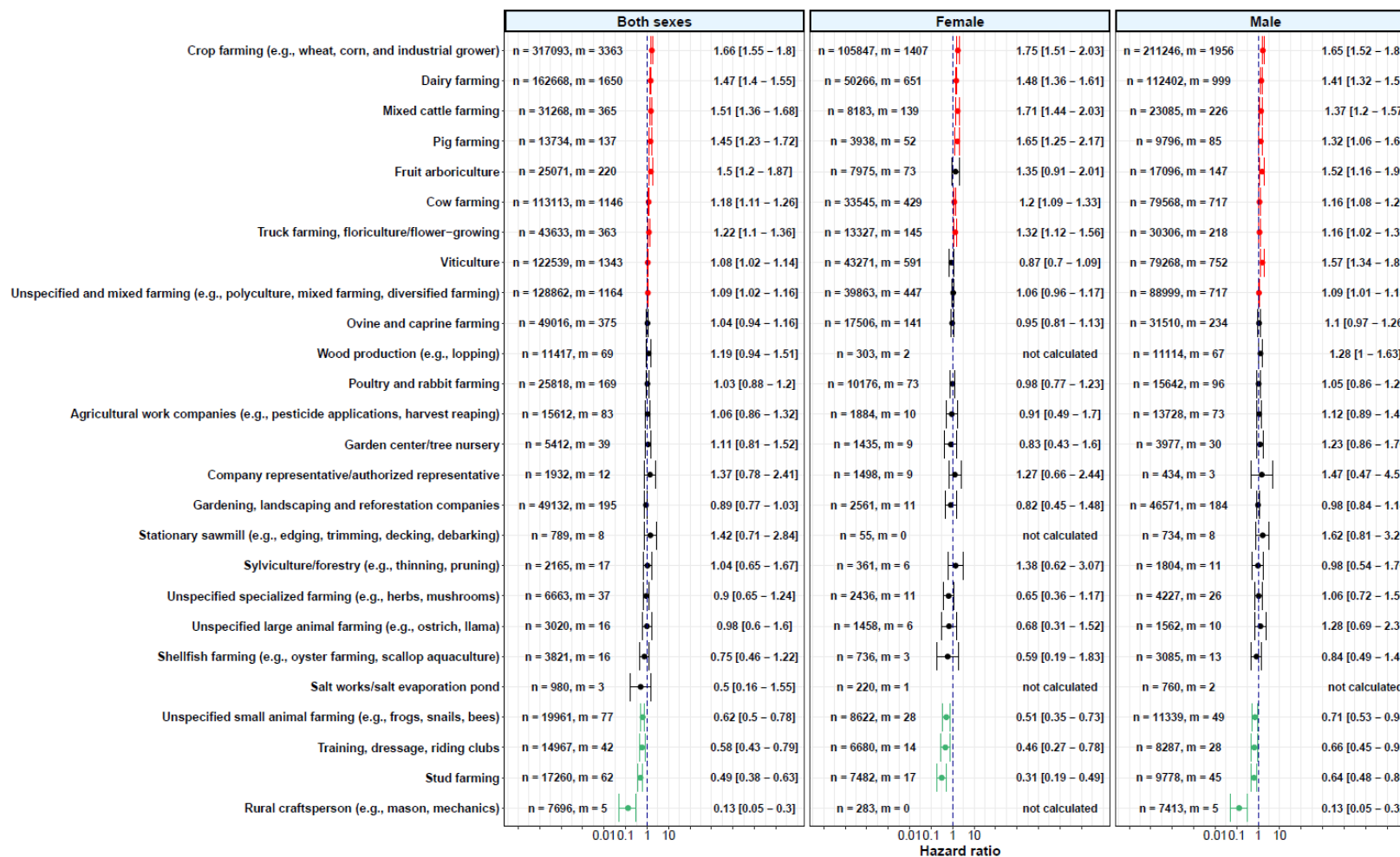
276 Multivariable Cox regression models for Parkinson’s disease according to each agricultural activity (y-axis) are displayed when the number of exposed cases was sufficient (m ≥ 3). The hazard
 277 ratio is represented by a point (x-axis), while error bars represent the 95% confidence interval. The red error bars refer to a higher risk of Parkinson’s disease while the green error bars represent a
 278 lower risk of Parkinson’s disease. The black error bars indicate situations where there is no difference in risk of Parkinson’s disease among the farm managers engaged in the considered activity
 279 compared to the population of farm managers not performing the considered activity. All analyses were adjusted for sex (for “both sexes” only), age, first year of the farm’s establishment, median
 280 farm surface, number of associates, unemployment status, total number of farms, family status, partner work status, farm location, number of comorbidities, and performing a secondary farming
 281 activity. n, number of exposed farm managers; m, number of exposed Parkinson’s disease cases.



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283 **Supplementary Figure 10: Farming activities and risks of Parkinson's disease, TRACTOR project, 2012-2016 – sensitivity analysis 10**

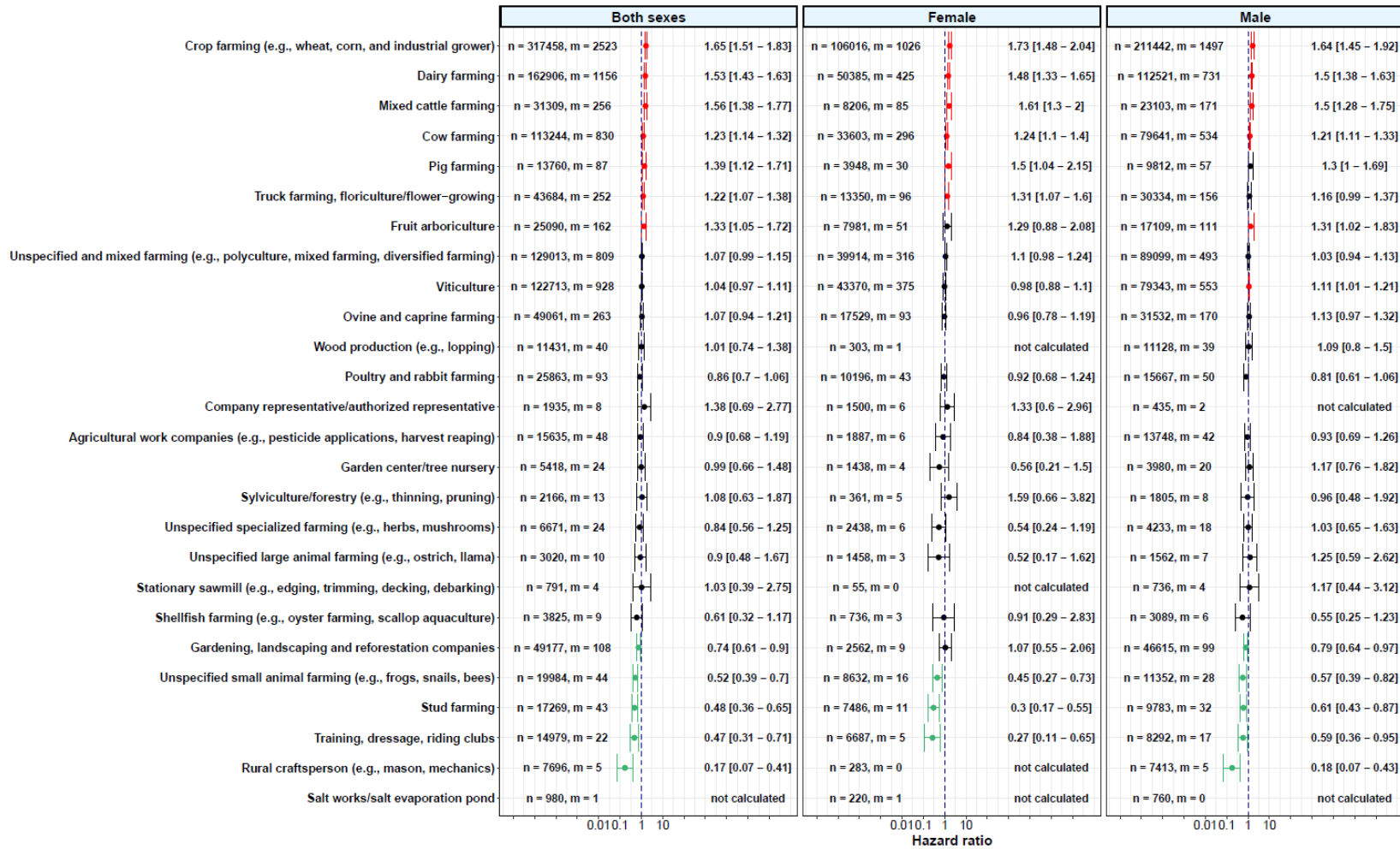
284 Multivariable Cox regression models for Parkinson's disease according to each agricultural activity (y-axis) are displayed when the number of exposed cases was sufficient (m ≥ 3). The hazard
 285 ratio is represented by a point (x-axis) while error bars represent the 95% confidence interval. The red error bars refer to a higher risk of Parkinson's disease, while the green error bars represent a
 286 lower risk of Parkinson's disease. The black error bars indicate situations where there is no difference in risk of Parkinson's disease among the farm managers engaged in the considered activity
 287 compared to the population of farm managers not performing the considered activity. All analyses were adjusted for sex (for "both sexes" only), age, first year of the farm's establishment, median
 288 farm surface, number of associates, unemployment status, total number of farms, family status, partner work status, farm location, number of comorbidities, and performing a secondary farming
 289 activity. n, number of exposed farm managers; m, number of exposed Parkinson's disease cases.



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291 **Supplementary Figure 11:** Farming activities and risks of Parkinson's disease, TRACTOR project, 2012-2016 – sensitivity analysis 11

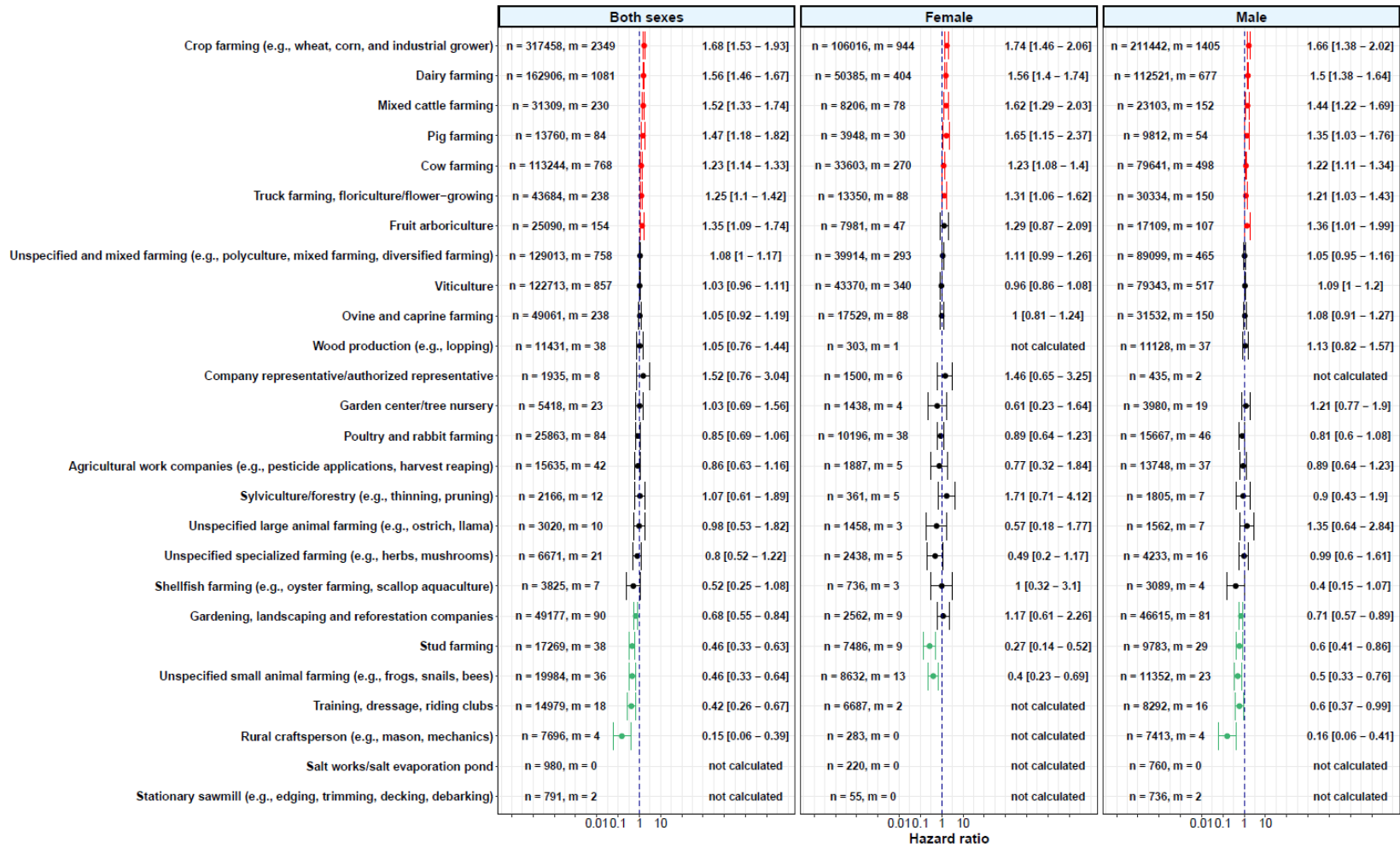
292 Multivariable Cox regression models for Parkinson's disease according to each agricultural activity (y-axis) are displayed when the number of exposed cases was sufficient ($m \geq 3$). The hazard
 293 ratio is represented by a point (x-axis), while error bars represent the 95% confidence interval. The red error bars refer to a higher risk of Parkinson's disease while the green error bars represent a
 294 lower risk of Parkinson's disease. The black error bars indicate situations where there is no difference in risk of Parkinson's disease among the farm managers engaged in the considered activity
 295 compared to the population of farm managers not performing the considered activity. All analyses were adjusted for sex (for "both sexes" only), age, first year of the farm's establishment, median
 296 farm surface, number of associates, unemployment status, total number of farms, family status, partner work status, farm location, number of comorbidities, and performing a secondary farming
 297 activity. n, number of exposed farm managers; m, number of exposed Parkinson's disease cases.



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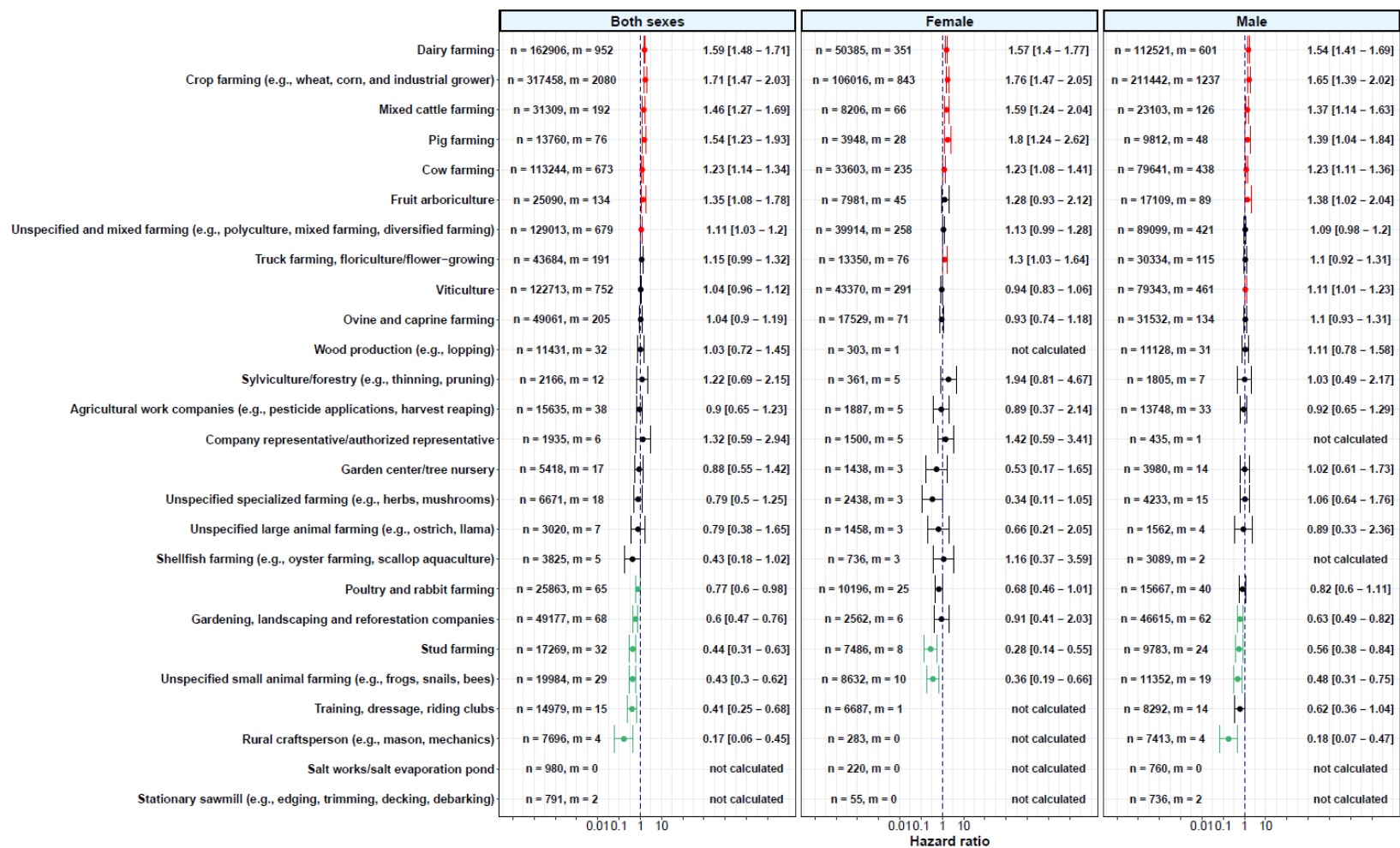
Supplementary Figure 12: Farming activities and risks of Parkinson's disease, TRACTOR project, 2012-2016 – sensitivity analysis 12

Multivariable Cox regression models for Parkinson's disease according to each agricultural activity (y-axis) are displayed when the number of exposed cases was sufficient ($m \geq 3$). The hazard ratio is represented by a point (x-axis), while error bars represent the 95% confidence interval. The red error bars refer to a higher risk of Parkinson's disease while the green error bars represent a lower risk of Parkinson's disease. The black error bars indicate situations where there is no difference in risk of Parkinson's disease among the farm managers engaged in the considered activity compared to the population of farm managers not performing the considered activity. All analyses were adjusted for sex (for "both sexes" only), age, first year of the farm's establishment, median farm surface, number of associates, unemployment status, total number of farms, family status, partner work status, farm location, number of comorbidities, and performing a secondary farming activity. n, number of exposed farm managers; m, number of exposed Parkinson's disease cases.



306
307 **Supplementary Figure 13:** Farming activities and risks of Parkinson’s disease, TRACTOR project, 2012-2016 – sensitivity analysis 13

308 Multivariable Cox regression models for Parkinson’s disease according to each agricultural activity (y-axis) are displayed when the number of exposed cases was sufficient (m ≥ 3). The hazard
309 ratio is represented by a point (x-axis), while error bars represent the 95% confidence interval. The red error bars refer to a higher risk of Parkinson’s disease while the green error bars represent a
310 lower risk of Parkinson’s disease. The black error bars indicate situations where there is no difference in risk of Parkinson’s disease among the farm managers engaged in the considered activity
311 compared to the population of farm managers not performing the considered activity. All analyses were adjusted for sex (for “both sexes” only), age, first year of the farm’s establishment, median
312 farm surface, number of associates, unemployment status, total number of farms, family status, partner work status, farm location, number of comorbidities, and performing a secondary farming
313 activity. n, number of exposed farm managers; m, number of exposed Parkinson’s disease cases.



314
315 **Supplementary Figure 14:** Farming activities and risks of Parkinson’s disease, TRACTOR project, 2012-2016 – sensitivity analysis 14

316 Multivariable Cox regression models for Parkinson’s disease according to each agricultural activity (y-axis) are displayed when the number of exposed cases was sufficient ($m \geq 3$). The hazard
317 ratio is represented by a point (x-axis), while error bars represent the 95% confidence interval. The red error bars refer to a higher risk of Parkinson’s disease while the green error bars represent a
318 lower risk of Parkinson’s disease. The black error bars indicate situations where there is no difference in risk of Parkinson’s disease among the farm managers engaged in the considered activity
319 compared to the population of farm managers not performing the considered activity. All analyses were adjusted for sex (for “both sexes” only), age, first year of the farm’s establishment, median
320 farm surface, number of associates, unemployment status, total number of farms, family status, partner work status, farm location, number of comorbidities, and performing a secondary farming
321 activity. n, number of exposed farm managers; m, number of exposed Parkinson’s disease cases.

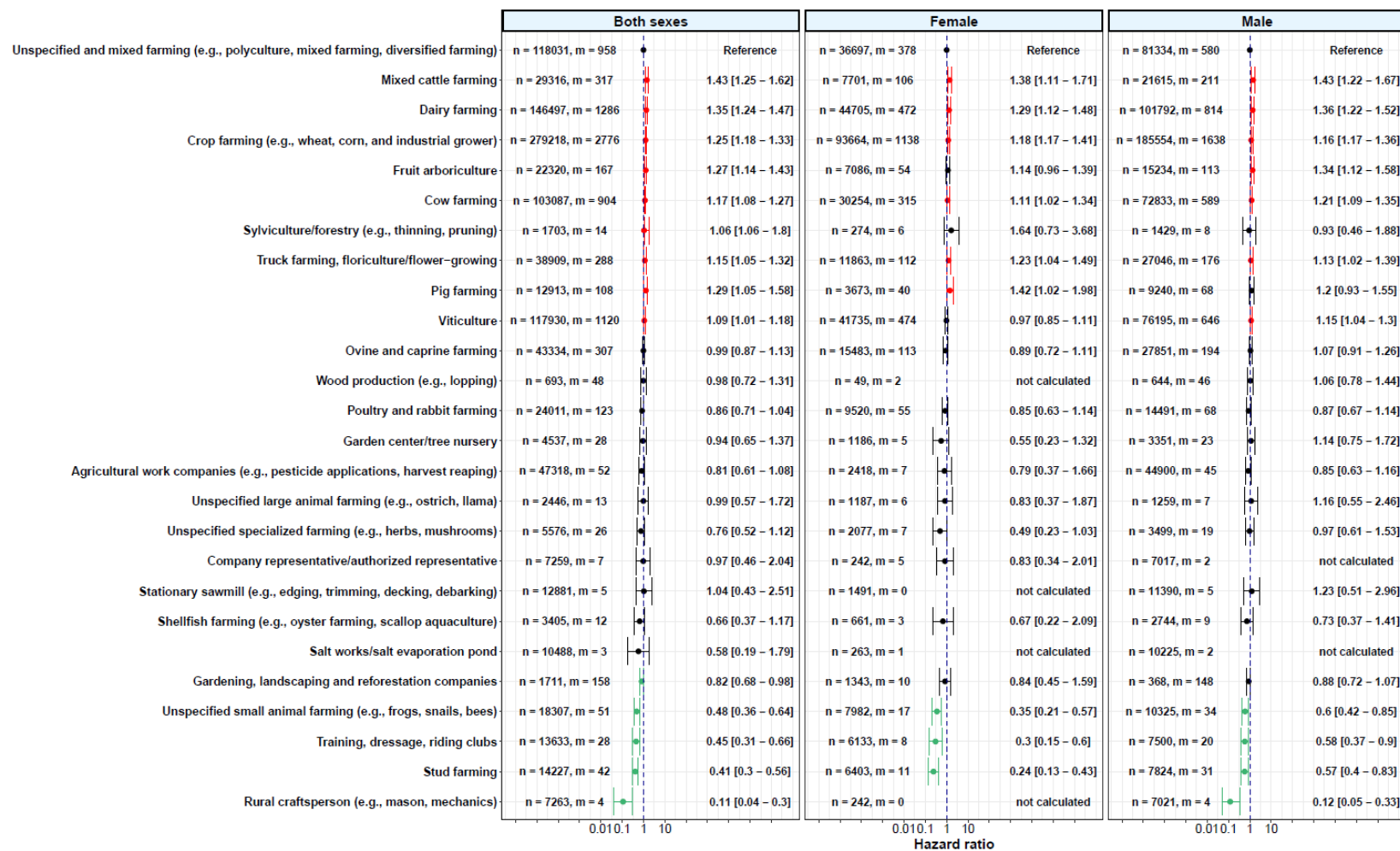
322 *Sensitivity analysis 15 – using only one farming activity as reference*

323

324 In the main analysis and other sensitivity analyses, we considered farm managers to be exposed to a given farming
325 activity if they had been engaged in this activity at least once between 2002 and 2016 (1 yearly declaration to
326 MSA). Instead, in this sensitivity analysis, each farm manager was considered to be engaged solely in their longest
327 farming activity ever practiced in terms of number of years. In case the longest exposure corresponded to several
328 farming activities (e.g., 4 years as a dairy farmer, then 4 years as crop farmer), only the oldest farming activity
329 (e.g., dairy farming in the previous example) was considered.

330 Similarly to the main analysis, for this sensitivity analysis, FMs were considered to have PD if they had at least
331 one LTI declaration for PD (ICD-10 code G20 or F02), one ODC declaration for PD, or one reimbursement of any
332 drugs solely used to treat PD (i.e., all antiparkinsonian agents, with the exception of pramipexole, rotigotine,
333 amantadine, and lisuride) (Supplementary Table 7). However, FMs only on anticholinergics (trihexyphenidyl,
334 biperiden, and tropatepine) and neuroleptics (drug-induced parkinsonism) were not considered PD cases.

335 The highest-risk group included FMs engaged in mixed cattle farming, dairy farming, crop farming, fruit
336 arboriculture, cow farming, silviculture, truck farming, pig farming, and viticulture (Supplementary Table 4,
337 Supplementary Figure 15). By contrast, the lowest-risk group included FMs engaged in gardening, landscaping
338 and reforestation companies, small animal farming, training, dressage and riding clubs, stud farming, and rural
339 craftsperson. Two activities exhibited a sex difference, with male FMs having a higher risk than females for
340 viticulture and stud farming.



341

342 **Supplementary Figure 15:** Farming activities and risks of Parkinson's disease, TRACTOR project, 2012-2016 – sensitivity analysis 15

343 Multivariable Cox regression models for Parkinson's disease according to each agricultural activity (y-axis) are displayed when the number of exposed cases was sufficient ($m \geq 3$). The hazard
 344 ratio is represented by a point (x-axis), while error bars represent the 95% confidence interval. The red error bars refer to a higher risk of Parkinson's disease while the green error bars represent a
 345 lower risk of Parkinson's disease. The black error bars indicate situations where there is no difference in risk of Parkinson's disease among the farm managers engaged in the considered activity
 346 compared to the population of farm managers not performing the considered activity. All analyses were adjusted for sex (for "both sexes" only), age, first year of the farm's establishment, median
 347 farm surface, number of associates, unemployment status, total number of farms, family status, partner work status, farm location, number of comorbidities, and performing a secondary farming
 348 activity. n, number of exposed farm managers; m, number of exposed Parkinson's disease cases.

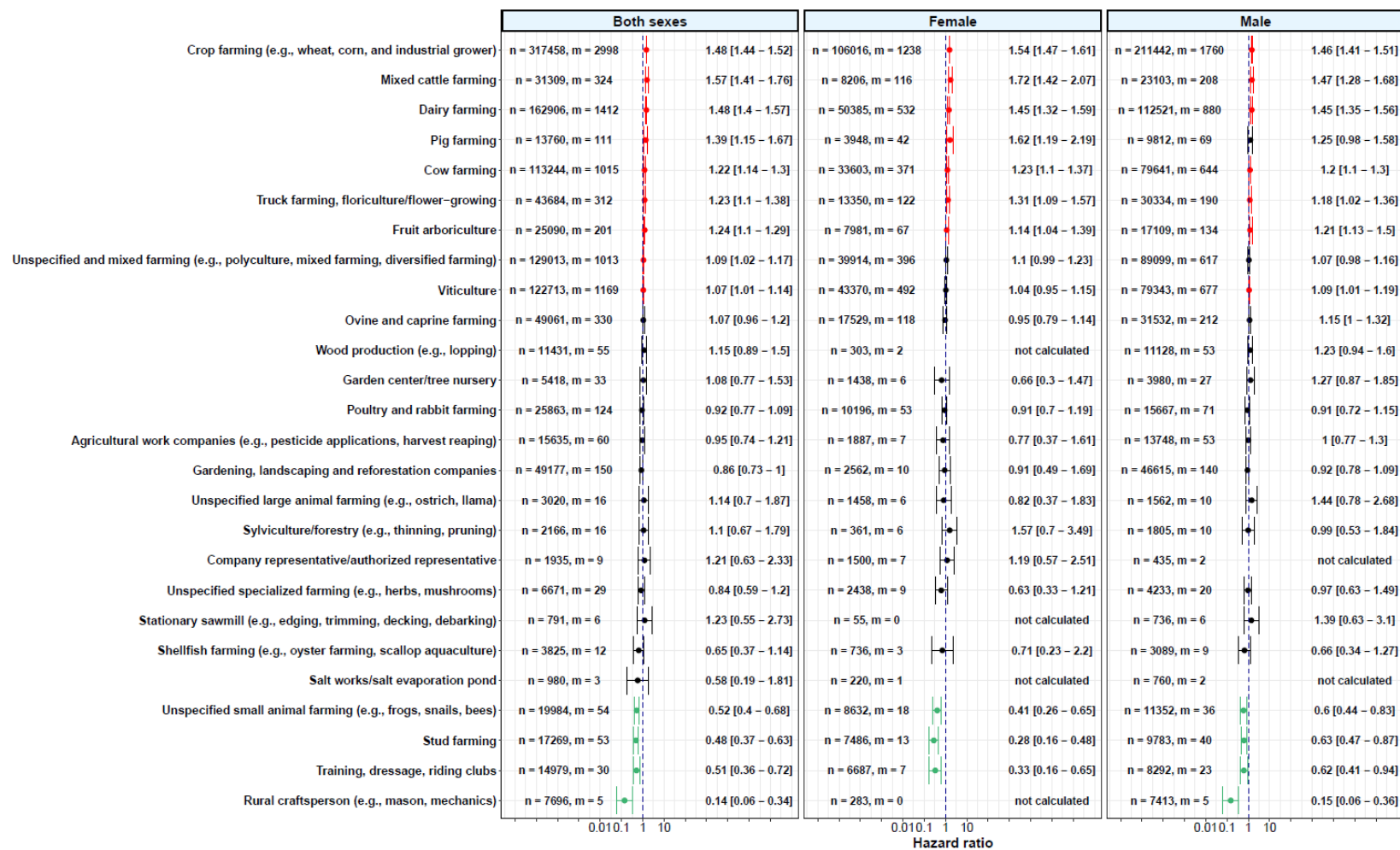
349 *Sensitivity analysis 16 – adjusting for smoking*

350

351 Because we did not have smoking data, we performed a sensitivity analysis adjusting for smoking. To that end,
352 we randomly generated the smoking status (current smokers/non-smokers) by assuming that there was a prevalence
353 of current smokers of 19% for crop farming, 9% for cattle farming, 6% for pig farming, 15% for poultry farming,
354 and 18% for all other farming activities. These prevalences were based on a cross-sectional study conducted in
355 3787 French farmers affiliated with MSA in 2013⁴.

356 Similarly to the main analysis, for this sensitivity analysis, FMs were considered to have PD if they had at least
357 one LTI declaration for PD (ICD-10 code G20 or F02), one ODC declaration for PD, or one reimbursement of any
358 drugs solely used to treat PD (i.e., all antiparkinsonian agents, with the exception of pramipexole, rotigotine,
359 amantadine, and lisuride) (Supplementary Table 7). However, FMs only on anticholinergics (trihexyphenidyl,
360 biperiden, and tropatepine) and neuroleptics (drug-induced parkinsonism) were not considered PD cases.

361 The highest-risk group included FMs engaged in crop farming, mixed cattle farming, dairy farming, pig farming,
362 cow farming, truck farming, fruit arboriculture, unspecified and mixed farming, and viticulture (Supplementary
363 Table 4, Supplementary Figure 16). A positive trend was also observed for ovine and caprine farming. By contrast,
364 the lowest-risk group included FMs engaged in small animal farming, training, dressage and riding clubs, stud
365 farming, and rural craftsperson. Stud farming was the only farming activity exhibiting a sex difference, with male
366 FMs having a higher risk than females.



367

368 **Supplementary Figure 16:** Farming activities and risks of Parkinson’s disease, TRACTOR project, 2012-2016 – sensitivity analysis 16

369 Multivariable Cox regression models for Parkinson’s disease according to each agricultural activity (y-axis) are displayed when the number of exposed cases was sufficient (m ≥ 3). The hazard
370 ratio is represented by a point (x-axis), while error bars represent the 95% confidence interval. The red error bars refer to a higher risk of Parkinson’s disease while the green error bars represent a
371 lower risk of Parkinson’s disease. The black error bars indicate situations where there is no difference in risk of Parkinson’s disease among the farm managers engaged in the considered activity
372 compared to the population of farm managers not performing the considered activity. All analyses were adjusted for sex (for “both sexes” only), age, smoking, first year of the farm’s establishment,
373 median farm surface, number of associates, unemployment status, total number of farms, family status, partner work status, farm location, number of comorbidities, and performing a secondary
374 farming activity. n, number of exposed farm managers; m, number of exposed Parkinson’s disease cases.

375 *Sensitivity analysis 17 – control of other diseases not related to farming exposure*

376

377 To ensure that any observed effect may be specific to the exposure being studied (i.e., farming-related factors
378 potentially associated with Parkinson’s disease) and not confounded by general health or morbidity, SA17 was
379 restricted to farm managers (non-PD cases) with no known disease or only those with at least one of the following
380 health conditions:

- 381 • Metabolic disorders (ICD-10 codes: E70-E88; LTI #17)
- 382 • Diabetes mellitus (ICD-10 codes: E08-E13; LTI: #8)
- 383 • Overweight, obesity, and other hyperalimentation (ICD-10 codes: E65-E68)
- 384 • Schizophrenia (ICD-10 codes: F20-F29)
- 385 • Diseases of the eye and adnexa (ICD-10 codes: H00-H59)
- 386 • Diseases of the ear and mastoid process (ICD-10 codes: H60-H95)
- 387 • Hypertension (ICD-10 code: I10; LTI #12)
- 388 • Coronary and ischemic heart diseases (ICD-10 codes: I20-I25; LTI: #3, 5 and 13)
- 389 • Cerebrovascular disease (ICD-10 codes: I60-I69; LTI: #1)
- 390 • Arthrosclerosis (ICD-10 code: I70)
- 391 • Anemia (ICD-10 codes: D63, D64)
- 392 • Gout (ICD-10 code: M10)
- 393 • Psoriasis (ICD-10 code: L40)
- 394 • Hepatitis (ICD-10 codes: B15-B19)
- 395 • HIV (LTI #7)
- 396 • Hypercholesterolemia (≥ 3 drug reimbursements; ATC codes: C10AA, C10AB, C10B)
- 397 • Hemoglobinopathies, chronic constitutional, or severe acquired hemolysis (LTI #10)
- 398 • Hemophilias or severe constitutional disorders of hemostasis (LTI #11)
- 399 • Cystic fibrosis (LTI #18)
- 400 • Severe chronic kidney disease or primary nephrotic syndrome (LTI #19)
- 401 • Medullary insufficiency or other chronic cytopenias (LTI #2)
- 402 • Progressive idiopathic structural scoliosis (LTI #26)
- 403 • Organ transplant consequences (LTI #28)
- 404 • Complicated bilharziasis (LTI #4)
- 405 • Chronic active liver disease or cirrhosis (LTI #6)
- 406 • No known disease

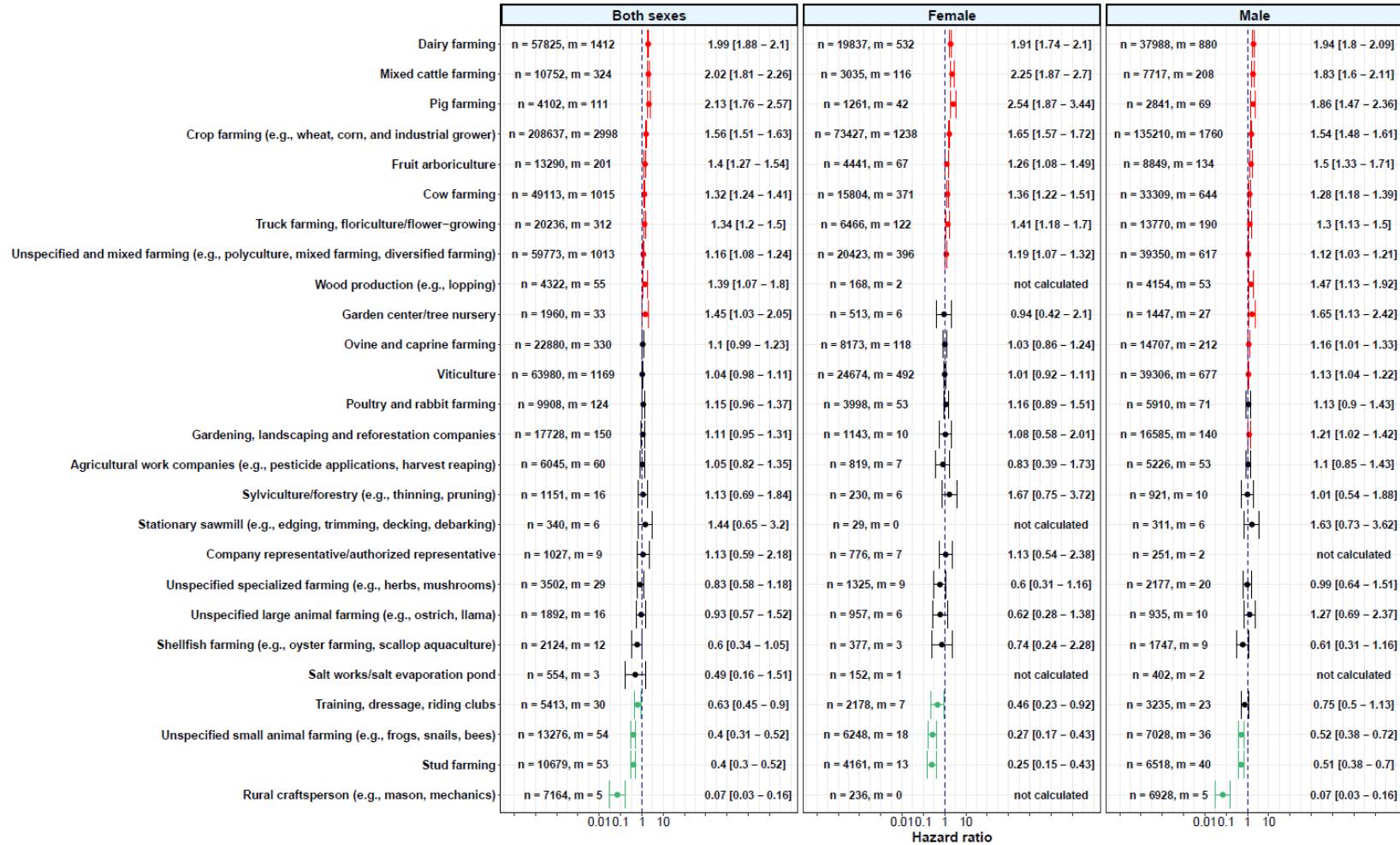
407

408 In summary, SA17 aimed to ensure that the farm managers without Parkinson’s disease might exhibit other health
409 conditions that are unrelated to the exposure under investigation. This approach may help clarify whether the
410 exposure has a specific influence on Parkinson’s risk, as opposed to a general health effect that might predispose
411 individuals to various unrelated diseases. Nonetheless, while these unrelated diseases were carefully selected based
412 on expert judgment, their inclusion may have introduced other biases or confounding factors into the model that

413 are challenging to evaluate. The criteria for identifying Parkinson's disease cases remained the same as in the
414 primary analysis.

415

416 Results from SA17 showed that the highest-risk group included FMs engaged in dairy farming, mixed cattle
417 farming, pig farming, crop farming, fruit arboriculture, cow farming, truck farming, unspecified and mixed
418 farming, wood production, and tree nursery (Supplementary Table 4, Supplementary Figure 17). A positive trend
419 was also observed for ovine and caprine farming, viticulture, poultry and rabbit farming, and gardening,
420 landscaping and reforestation companies. By contrast, the lowest-risk group included FMs engaged in small animal
421 farming, training, dressage and riding clubs, stud farming, and rural craftsperson. Tree nursery, stud farming and
422 gardening, landscaping and reforestation companies were the only farming activities exhibiting a sex difference,
423 with male FMs having a higher risk than females.



424

425 **Supplementary Figure 17:** Farming activities and risks of Parkinson's disease, TRACTOR project, 2012-2016 – sensitivity analysis 17

426 Multivariable Cox regression models for Parkinson's disease according to each agricultural activity (y-axis) are displayed when the number of exposed cases was sufficient ($m \geq 3$). The hazard
 427 ratio is represented by a point (x-axis), while error bars represent the 95% confidence interval. The red error bars refer to a higher risk of Parkinson's disease while the green error bars represent a
 428 lower risk of Parkinson's disease. The black error bars indicate situations where there is no difference in risk of Parkinson's disease among the farm managers engaged in the considered activity
 429 compared to the population of farm managers not performing the considered activity. All analyses were adjusted for sex (for "both sexes" only), age, first year of the farm's establishment, median
 430 farm surface, number of associates, unemployment status, total number of farms, family status, partner work status, farm location, number of comorbidities, and performing a secondary farming
 431 activity. n, number of exposed farm managers; m, number of exposed Parkinson's disease cases.

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433

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