Different Exposures to Risk Factors Do Not Explain the Inverse Relationship of Occurrence Between Cancer and Neurodegenerative Diseases

An Italian Nested Case-control Study

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Abstract: Several studies reported that cancer is less frequent in persons with Alzheimer's and Parkinson's Diseases (AD/PD) and vice-versa. We evaluated whether a different distribution of known nongenetic risk factors for cancer and AD/PD, might explain their inverse relationship of occurrence. We nested 2 case-control studies in a subsample of a large cohort of 1,000,000 resident in Lombardy Region in Italy (n = 1515), followed-up for cancer and AD/PD occurrence since 1991 until 2012. Conditional logistic regression was performed to determine the odds ratios (OR) and 95% confidence intervals (CI) of AD/PD in subjects with and without cancer and the risk of cancer in those with and without AD/PD. A total of 54 incident cases of AD/PD and 347 cancer cases were matched with 216 and 667 controls, respectively. After controlling for low education, obesity, history of hypertension, diabetes, dyslipidemia, physical activity, smoking habit, alcohol consumption, and dietary habit, cancer was found inversely associated with the risk of AD/PD (OR, 0.66; 95% CI, 0.32-1.38), and the risk of cancer in AD/PD was similarly reduced (OR, 0.42; 95% CI, 0.20-0.91). Different exposures to nongenetic risk factors of both diseases do not explain their competitive relationship of occurrence.

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AD indicates Alzheimer's Diseases; AD/PD, Alzheimer's or Parkinson's Diseases; ATC, anatomic therapeutic chemicals classification; BMI, body mass index; FFQ, food frequency questionnaire; ICD-9 and ICD-10, International Classification of Diseases, Ninth and Tenth Revision coding system; MeDi, Mediterranean Diet; OR (95% CI), odds ratio (95% confidence intervals); PD, Parkinson's Diseases.

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Neurodegenerative disorders, particularly Alzheimer's Disease (AD) (the most common form of dementia) and Parkinson's Disease (PD), are the third leading cause of death in the elderly following cancer and vascular diseases.[1] Several previous studies reported that the risk of cancer is reduced in people with neurodegenerative diseases,[2–13] and vice-versa.[2–6,10,11,14] This finding might be explained by factors, possibly genetically based, that competitively could predispose to cancer or to AD/PD.[15] However, the negative association between the 2 diseases might be explained by different exposures to specific risk factors of persons with AD/PD or cancer in comparison to the general population.

AD incidence was found increased in subjects with vascular risk factors[16–19] and poor adherence to the Mediterranean Diet (MeDi).[20] In contrast, AD incidence was reported reduced in people who are highly educated and employed in cognitively stimulating activities,[21] and in those who are physically active.[22] Conversely, results on the direction of the association between smoking and AD are still conflicting.[23,24] Studies on PD reported a protective role of tobacco, physical exercise[25,26] and high adherence to the MeDi[27] whereas the role of vascular risk factors is more controversial.[28,29] Diabetes, smoking, overweight, low physical activity, and adherence to the MeDi are also positively associated with cancer occurrence.[30–32]

In our previous cohort study on approximately 1,000,000 subjects aged 60 years and older in Northern Italy, we evaluated the incidence of cancer in persons with AD and the incidence of AD in subjects with cancer by analyzing administrative data. When compared with the general population of the same age and sex, the risk of AD among individuals with cancer was reduced by 35% [relative risk (RR), 0.65, 95% confidence interval (CI), 0.56-0.76] and the risk of cancer among those with AD was decreased by 43% (RR, 0.57; 95% CI, 0.49-0.67).[5] The potential sources of bias because of underdiagnosis and life expectancy reduction in persons with AD or cancer were addressed by performing the analysis before and after the diagnosis of each disease, and stratifying by survivors and nonsurvivors. The main limitation was the lack of available information on clinical and lifestyle determinants of

cancer and AD. Therefore, we studied a smaller subsample of this large cohort clinically examined in 1991 to 1995. The aims of this were is to (i) verify the existence of an inverse relationship of occurrence between cancer and AD/PD as well as in this subcohort, and to (ii) evaluate whether a different distribution of variables representing risk factors of both diseases, might explain the competitive relationship of occurrence.

METHODS

Study Population and Design

We nested 2 case-control studies in a subcohort of the larger one of 1,000,000 inhabitants registered in the administrative health registries of the Local Health Authority of the Region of Lombardy.[5] This subsample (n = 1604) aged 42 to 74 years old, participated in a population-based study that involved in-person examination and completion of a lifestyle questionnaire at baseline, from January 1, 1991 to January 1, 1995. Details on the recruitment procedures are reported elsewhere.[33] Excluding those subjects who reported an antecedent malignancy (n = 61) or cognitive decline (n = 28) during the visit, a final subset of 1515 subjects was followed-up for incident AD/PD and cancer over a median of 18.5 years. Flow-chart describing the steps involved in establishing the final study sample is showed in Figure 1. The review board of the National Research Council approved the original study protocol. All participants at baseline were informed about the scope of the study and provided voluntary responses to invitation by phone that served as informed consent. All the procedures were performed in agreement with the World Medical Association Declaration of Helsinki.

Assessment of Covariates

From the baseline visits data on sociodemographic characteristics (age, sex, and education), personal and family history of diseases, and use of drugs were obtained. Participants underwent a general clinical assessment that included anthropometric (height and weight) measurements. Blood samples after an overnight fast were drawn and high-density lipoprotein cholesterol (HDL-cholesterol) was determined with standardized laboratory techniques. Subjects were also investigated about their lifestyle habits, such as physical activity, smoking habits, alcohol consumption and dietary habits. Information about dietary data collection and data analysis are reported elsewhere.[33] Adherence to the MeDi score was computed according to the Trichopoulou algorithm.[34]

Cases Ascertainment

The methodology for identifying cases of AD/PD and cancer has been previously described.[5] Briefly, each member of the cohort was retrieved by means of the fiscal code (a unique identifying code), and prospectively followed-up, since study entry to October 31, 2012 (end of follow-up), in the administrative health registries of the Lombardy Region (Italy). AD/PD cases were retrieved by linking 4 different data sources: (1) the Pharmaceutical Prescriptions Registry from January 2001, (2) the Hospital Discharge Registry from January 1996, (3) the Mortality Registry from January 1999, and (4) exemption code for special diseases conditions. In these registries we identified the members of the cohort who received at least 1 prescription for an antidementia drug (donepezil, rivastigmine, galantamine, or memantine) or levodopa, as a drug-tracer for PD,[35] or who experienced at least 1 hospitalization or received an exemption code or died for AD or PD. AD/PD Cases were identified and classified according to the International Classification of Diseases, Ninth and Tenth Revision coding system (ICD-9 and ICD-10) and to the Anatomic Therapeutic Chemicals classification (ATC). The diagnostic algorithm used in identifying AD/PD cases is reported as supplementary material 1 (Supplemental Digital Content 1, http://links.lww.com/WAD/A173).

Cohort members were linked to the Regional Cancer Registry to identify cases of cancers.

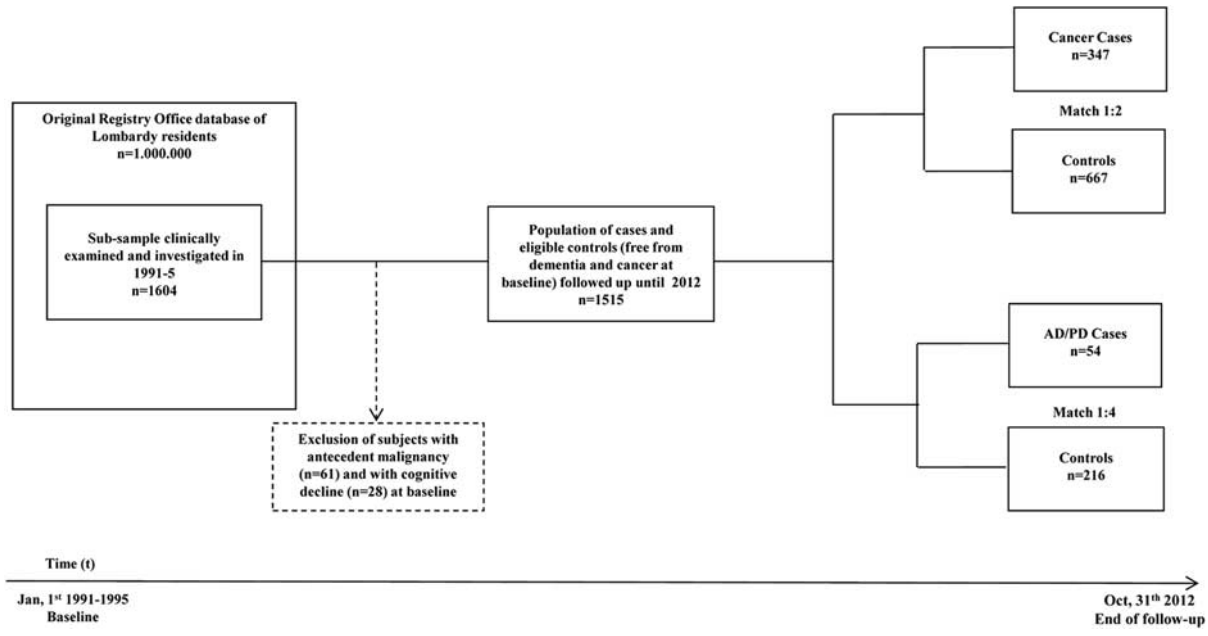

FIGURE 1. Study flow-chart describing the steps involved in the selection of cases and controls. AD indicates Alzheimer's Disease; PD, Parkinson's Disease.

Controls Selection

Each cancer case was matched with up to 2 control subjects and similarly 4 controls were randomly selected for each AD/PD case. Cases and controls were matched by 3-year baseline age group (50 y and below, 50 to 64 y, 64 + y), sex, and smoking habit (never and past/current). Matching variables were selected upon their potential confounding effect. We therefore defined 2 different study datasets: the first one (n = 270) included 54 AD/PD cases and 216 matched controls; the latter (n = 1014) was composed of 347 cancer cases and 667 controls.

Statistical Analyses

Descriptive statistics, expressed as frequencies and percentages, were used to describe the characteristics of the study population. Education was categorized in primary school or less and middle school or higher. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2) and categorized as normal ($\leq 24.9\,kg/m^2$), overweight (25 to $29.9\,kg/m^2$), and obese ($> 30\,kg/m^2$). HDL-cholesterol (mg/dL) was categorized using the median value as cut-off (< 56 mg/dL or above). Subjects reporting a history of hypertension, diabetes, or those treated with specific drugs for these diseases, were considered hypertensive and/or diabetics. Smoking habit was categorized as never and past, or current, and alcohol consumption as (i) none, (ii) up to 30 g per day or (iii) > 30 g per day; persons regularly engaged in at least 1 sport activity/week were classified as physically active. Finally, adherence to the MeDi was dichotomized as high (score higher than 5), and moderate/low.

To investigate the strength and statistical significance of the association between cancer and AD/PD and between AD/PD and cancer development, conditional logistic regression analysis was carried-out. The risk of cancer and of AD/PD in relation to controls was estimated as OR with 95% CI that was calculated from the standard errors of the regression. To take into account the different exposures, 2 models were applied: unadjusted and adjusted models which included education, BMI, HDL-cholesterol, history of hypertension and diabetes, physical activity, alcohol consumption, and adherence to the MeDi.

Smoking is a known risk factor for several types of cancers and, but it is a protective factor for PD, whereas the effects on AD are contradictory. To exclude that smoking, and some other exposures, could be differently distributed in subjects with AD and in those with PD, biasing the results when we combine the 2 outcomes, we compared the distribution of baseline characteristics between the 2 groups of diseases using χ^2 or t test statistics.

All P-values are 2-tailed and we considered a $P < 0.05$ as statistically significant. All statistical analyses were performed using the software packages SPSS (IBM Corp; Version 22.0 Armonk, NY) and STATA (Version 11, StataCorp; College Station, TX).

RESULTS

During the follow-up period, 26,083.02 person-years were accrued and 54 AD/PD and 347 cancers occurred. Table 1 reports the distribution of known potential confounders among participants who developed AD/PD and cancer during follow-up. In comparison with subjects with AD/PD, those with cancer were slightly younger (59.2 vs. 62.1 y old), more frequently males (64.3% vs. 55.6%), and past or current smokers (56.2% vs. 31.5%). The 2 groups were quite similar in terms of education, BMI, HDL-cholesterol, history of hypertension and diabetes, physical activity, alcohol consumption, and adherence to MeDi (compare column of AD/PD cases in Table 2 with column of cancer cases in Table 3). We controlled for the potential confounding effect of age, sex, and smoking by matching.

TABLE 1. Distribution of Matching Variables Among Participants Who Developed AD/PD and Cancer During 18.5 Years of Follow-up

Characteristics	AD/PD Cases (N = 54)	Cancer Cases (N = 347)
Age at baseline (mean ± SD) (y)	62.1 ± 7.2	59.2 ± 7.7
Sex		
Male	30 (55.6)	223 (64.3)
Female	24 (44.4)	124 (35.7)
Smoking habit		
Never	37 (68.5)	152 (43.8)
Past or current	17 (31.5)	195 (56.2)

Values are numbers (percentages) unless stated otherwise.
AD indicates Alzheimer's disease; PD, Parkinson's disease.

Table 2 shows the baseline characteristics of AD/PD cases and controls and summarizes the unadjusted and adjusted OR with 95% CI from conditional logistic regression analysis. The frequency of cancer was less in AD/PD cases compared with controls (16.7% vs. 24.5%). The risk of cancer in AD/PD cases was reduced in relation to controls, with a non statistically significant unadjusted OR of 0.61 (95% CI, 0.29-1.29). The estimate was slightly increased when we included all the covariates in the model (OR, 0.66; 95% CI, 0.32-1.38). As far as the other exposures, only a borderline statistically significant negative association was observed between high levels of HDL-cholesterol and AD/PD risk (OR, 0.52; 95% CI, 0.25-1.08).

Baseline characteristics of cancer cases and controls, and unadjusted and adjusted OR with 95% CI, are shown in Table 3. In comparison to controls, cancer cases had a lower frequency of AD/PD (2.6% vs. 5.8%) and were less physically active (16.1% vs. 22.2%). Both the unadjusted and the adjusted risk of AD/PD in cancer cases in relation to controls, was significantly reduced by 58% (OR, 0.42; 95% CI, 0.20-0.91). Furthermore we found that practicing sport more than once per week was inversely associated with cancer risk (OR, 0.67; 95% CI, 0.48-0.95). No other significant associations between the considered exposures and cancer were found.

When we compared subjects who developed AD with those who developed PD on baseline characteristics, we did not find any statistically significant differences between the 2 groups. This makes us quite confident that the combination of the 2 outcomes did not affect the results (supplementary material 2, Supplemental Digital Content 2, http://links.lww.com/WAD/A174). To minimize potential selection bias, we performed a sensitivity analysis by excluding those controls that died before the index case had the event in both the case-control studies but the estimates did not change significantly. We found that the adjusted risk of cancer in AD/PD cases in relation to controls was nonsignificantly reduced by 40% (OR, 0.60; 95% CI, 0.26-1.42) and the adjusted risk of AD/PD in cancer cases as compared with controls was 0.39 (95% CI, 0.20-0.91).

TABLE 2. Distribution of Baseline Characteristics Among Participants Who Developed AD/PD and Matched Controls, Unadjusted and Adjusted OR (n = 270)

Characteristics	AD/PD Cases (N = 54)	Controls (N = 216)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Cancer cases	9 (16.7)	53 (24.5)	0.61 (0.29-1.29)	0.66 (0.32-1.38)
Educational level				
Primary school or less	33 (61.1)	145 (67.1)	1.00	1.00
Middle school or higher	21 (38.9)	71 (32.9)	1.31 (0.67-2.55)	1.33 (0.63-2.80)
Body mass index (kg/m^2)				
Normal weight	19 (35.2)	65 (30.1)	1.00	1.00
Overweight	22 (40.7)	107 (49.5)	0.70 (0.38-1.31)	0.56 (0.27-1.14)
Obese	13 (24.1)	44 (20.4)	1.03 (0.45-2.31)	1.10 (0.42-2.88)
HDL-cholesterol (mg/dL)†				
< 56	21 (38.9)	64 (29.6)	1.00	1.00
≥ 56	22 (40.7)	96 (44.4)	0.66 (0.35-1.22)	0.52 (0.25-1.08)
History of hypertension	18 (33.3)	77 (35.6)	0.90 (0.49-1.66)	1.04 (0.55-1.98)
History of diabetes	3 (5.6)	23 (10.6)	0.49 (0.14-1.71)	0.53 (0.14-2.05)
Practicing sport activity				
Less than once/week	41 (75.9)	168 (77.8)	1.00	1.00
More than once/week	13 (24.1)	48 (22.2)	1.16 (0.53-2.35)	1.24 (0.51-2.64)
Alcohol intake (g/die)				
None	15 (27.8)	60 (27.8)	1.00	1.00
< 30	7 (13)	35 (16.2)	0.80 (0.30-2.14)	0.76 (0.29-2.03)
≥ 30	32 (59.3)	121 (56)	1.05 (0.53-2.08)	1.06 (0.51-2.20)
MeDi adherence‡				
High (6-9)	9 (16.7)	43 (19.9)	1.00	1.00
Moderate or low (0-5)	38 (70.4)	125 (57.9)	1.43 (0.67-3.06)	1.55 (0.67-3.58)

Values are numbers (percentages).

*Adjusted for educational level, BMI, HDL-cholesterol, history of hypertension and diabetes, practicing sport activity, alcohol intake, and adherence to MeDi.

†Sixty-seven subjects with missing laboratory data.

‡Fifty-five subjects with missing dietary data.

AD indicates Alzheimer's disease; HDL-cholesterol, high-density lipoprotein cholesterol; MeDi, Mediterranean Diet; OR, odds ratio; PD, Parkinson's disease.

DISCUSSION

Main Findings

This study adds to and supports the existing evidence of an inverse relationship of occurrence between cancer and neurodegenerative diseases, demonstrating that their association was independent from exposure to risk factors related to both diseases. Our findings agree with our previous results[5] and are consistent with other observational studies on AD[3–8,10–12,14] and PD.[9]

We used a nested case-control study design to verify whether the lower occurrence of AD/PD in people with cancer and vice-versa could be explained by some confounding related to a different distribution of risk factors in the comparison groups. Cases of cancer and AD/PD were significantly different in terms of age, sex, and smoking, and we controlled the potential confounding effect of these variables by matching. When we compared AD/PD and cancer cases with controls, we observed that persons with cancers had a lower frequency of AD/PD as well as the frequency of cancers was lower in those with AD/PD. In the unadjusted model, people with cancer had a significant 58% lower risk of AD/PD and those with AD/PD had a 38% lower risk of cancer, although this reduction was not statistically significant. However, because of the small number of identified cases of AD/PD (n = 54), it is possible that this study had a low statistical power in detecting differences between AD/PD cases and controls. When controlling for education, BMI, HDL-cholesterol, history of hypertension and diabetes, physical activity, alcohol consumption, and adherence to MeDi, the risks estimated did not change substantially, indicating that the observed relationship between cancer and AD/PD was not because of differences of exposures to these variables. These findings suggest that the negative association between cancer and neurodegenerative disorders is not explained by a different exposure to nongenetic risk factors of AD/PD or cancer.

Biologic Plausibility

Cancer and neurodegenerative disorders are 2 age-related chronic diseases. However, theoretically they can be considered 2 diametric diseases: cancer is characterized by uncontrolled cellular proliferation, whereas neurodegeneration is marked by a progressive neuronal death.[36] It is very likely that cancer and neurodegenerative disorders share genetic and biologic pathways that are inversely regulated in the 2 diseases.[37] Therefore, a genetic predisposition against cellular senescence or apoptosis might protect people from cancer but in contrast might predispose them to neurodegeneration.[15,38] Growing evidence suggests that an over-expression of Pin1, which is involved in cell proliferation and survival, may promote neuroprotection but increases cancer risk. Whereas the up-regulation of the tumor suppressor gene P53 protects against cancer but promotes apoptosis and cellular senescence.[37] The WNT and the ubiquitin-proteasome signaling pathways, which are involved in cell cycle, cellular survival, and proliferation, also show opposite regulation in cancer and neurodegenerative disorders.[39] Beyond the differential regulation of common genetic factors, cancer and neurodegenerative disorders share many common age-related pathophysiological processes as mitochondrial dysfunction, oxidative stress, and DNA damage and repair that drive both diseases but with opposite ends.[15] Neurons present high energy demands

TABLE 3. Distribution of Baseline Characteristics Among Participants Who Developed Cancer and Matched Controls, Unadjusted and Adjusted OR (n = 1014)

Characteristics	Cancer Cases (N = 347)	Controls (N = 667)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
AD/PD cases	9 (2.6)	39 (5.8)	0.42 (0.20-0.89)	0.42 (0.20-0.91)
Educational level				
Primary school or less	193 (55.6)	387 (58.0)	1.00	1.00
Middle school or higher	154 (44.4)	280 (42.0)	1.10 (0.85-1.42)	1.11 (0.85-1.47)
Body mass index (kg/m^2)				
Normal weight	103 (29.7)	208 (31.2)	1.00	1.00
Overweight	176 (50.7)	308 (46.2)	1.18 (0.87-1.61)	1.13 (0.82-1.56)
Obese	68 (19.6)	151 (22.6)	0.92 (0.63-1.36)	0.89 (0.60-1.34)
HDL-cholesterol (mg/dL)†				
< 56	135 (38.9)	240 (37.4)	1.00	1.00
≥ 56	148 (42.7)	266 (39.9)	1.05 (0.77-1.44)	1.03 (0.75-1.42)
History of hypertension	113 (32.6)	207 (31.0)	1.07 (0.81-1.41)	1.06 (0.79-1.42)
History of diabetes	29 (8.4)	48 (7.2)	1.15 (0.71-1.86)	1.15 (0.68-1.93)
Practicing sport activity				
Less than once/week	291 (83.9)	419 (77.8)	1.00	1.00
More than once/week	56 (16.1)	148 (22.2)	0.68 (0.48-0.95)	0.67 (0.48-0.95)
Alcohol intake (g/die)				
None	89 (25.6)	176 (26.4)	1.00	1.00
< 30	63 (18.2)	132 (19.8)	0.90 (0.59-1.35)	0.90 (0.59-1.37)
≥ 30	195 (56.2)	359 (53.8)	1.04 (0.75-1.45)	1.05 (0.75-1.46)
MeDi adherence‡				
High (6-9)	50 (14.4)	116 (17.4)	1.00	1.00
Moderate or low (0-5)	244 (70.3)	434 (65.1)	1.30 (0.91-1.87)	1.21 (0.82-1.78)

Values are numbers (percentages).

*Adjusted for educational level, BMI, HDL-cholesterol, history of hypertension and diabetes, practicing sport activity, alcohol intake and adherence to MeDi.

†Two hundred twenty–five subjects with missing laboratory data.

‡One hundred seventy subjects with missing dietary data.

AD indicates Alzheimer's disease; HDL-cholesterol, high-density lipoprotein cholesterol; MeDi, Mediterranean Diet; OR, odds ratio; PD, Parkinson's disease.

compared with the other cells and rely it primarily on oxidative phosphorylation rather than glycolysis, because of the reduced activities of some glycolytic enzymes. This is accompanied by an accumulation of oxidative damage with age and further DNA damage that accelerates neuronal apoptosis. This mechanism is recognized as the inverse of the "Warburg effect" that characterizes most cancer cells which rely on energy primarily of glycolysis.[36,40] Thus, a predisposition towards glycolysis might protect neurons from neurodegeneration but increase the risk of cancer.[15]

Strengths and Limitations of the Study

Some limitations of our study should be considered. AD/PD and cancer cases were ascertained using registries that were not created for epidemiological purposes. This approach is likely to have high specificity but might be less sensitive than an analytical study. Indeed, it is possible that some AD/PD or cancer patients were unrecognized as untreated or nonhospitalized, and have never benefited from an exemption code resulting in a number of false negatives cases in our study. The lack of sensitivity of our method of case ascertainment could lead to a misclassification of both outcomes and/or of exposure according to the specific analysis (cancer as exposure when AD/PD is considered the index disease and AD/PD as exposure when cancer is the outcome). We cannot exclude that a potential selective under-diagnosis of cancer in patients with AD/PD, and of AD/PD in patients with cancer, might be occurred. Although, when we considered the larger cohort of people from whom this case-control study was nested, we showed that the inverse association was present also restricting the analysis to those subpopulations were the preferential misclassification, reasonably, could not take place. We also acknowledge the possible impact of survival bias in our study. Even though, when we performed the analyses separately for survivors and nonsurvivors in the whole cohort,[5] the inverse relationship of occurrence persisted. Accordingly, we do not believe that potential bias introduced by life expectancy reduction in persons with AD/PD or cancer in this subsample, might have affected the results. Another weakness of the study is the relative low number of the ascertained AD/PD cases that limited the precision of our estimates. Unfortunately we have not the power to look at the relationship between AD/PD and cancer types, although we previously found similar results within different types of cancers classified by tissue of origin and sites, suggesting that the lower risk of AD/PD in patients with cancer and vice-versa is not confounded by some conditions or specific characteristics of cancer typology.[5] Finally, as no information is available in the time window during which subjects were recruited and the first available registry (Hospital Discharge from 1996), we cannot exclude that a portion of cases of AD/PD or cancer was not identified during this time span. Nevertheless, because these are almost always chronic long-term diseases, multiple contacts with the healthcare system, are often required. Actually, when we looked at number of AD/PD patients retrieved in single and multiple data sources, we found that 25.9% (n = 14) were retrieved in Hospital Discharge registry only, twelve patients (22.2%) only in drug prescription registry, and the remainder (51.9%) were retrieved in > 1 data source.

The major strength of our study is the effort to account for a wide number of potential confounders, as clinical and

lifestyle factors, that are not usually available in a large administrative dataset. In addition, all the exposures were recorded in midlife, several years before the onset of the diseases, excluding possible recall bias because of the systematic difference between cases and controls in the accuracy of the information reported. Furthermore, we prospectively defined cases of AD/PD and cancer in the cohort. Therefore, represent incident cases of disease. Another advantage of the study is the case-control nested design, where cases and controls arise from the same source population, minimizing the potential selection bias, and enhancing the generalizability of the results to the target population. Finally, the matched case-control approach was an efficient procedure for controlling the variables considered potential confounders, such as age, sex and smoking.

In conclusion, our data support the evidence of an inverse relationship of occurrence between the 2 diseases independently from exposure to nongenetic risk factors related to both diseases. Future large epidemiological and genetic studies will be needed to explore and clarify the underlying biologic mechanisms of this relationship with the aim to develop new therapeutic and preventive strategies.

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