

A population-based, retrospective, cohort study based on administrative data to evaluate the association between modifiable risk factors and dementia: The Prev-Ita-Dem study.

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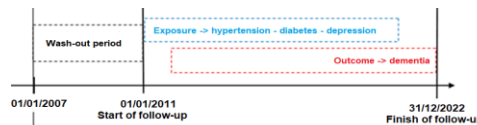


Figure 1. Study design.

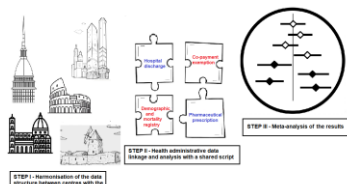


Figure 2. Methodological and analytical approach used within the NeuroEpiNet network.

INTRODUCTION.

In 2018, approximately 1.2 million individuals were living with dementia in Italy [1]. According to the Lancet Commission, up to 35% of dementia cases worldwide could be prevented or delayed by addressing modifiable risk factors. In Italy, a 20% reduction in these factors is projected to lower Alzheimer's disease incidence by 6.4% [2,3,4,5]. To investigate this, the PREV-ITA-DEM project, funded in 2022 by the Italian Ministry of Health (PNRR-MAD-2022-12375822), adopted a population-based design using Healthcare Utilization Databases to estimate dementia incidence in relation to diabetes, hypertension, and depression, with the goal of supporting prevention strategies.

MATERIAL AND METODES

This retrospective cohort study examined three distinct exposure cohorts, each defined by the presence of one of the following risk factors: hypertension, diabetes, or depression. The reference population comprised adults aged ≥ 50 years residing in, and receiving healthcare from, the metropolitan area of Turin, the Bologna Local Health Authority (AUSL), and the Lazio region. Incident cases were identified during the period 2011–2020, applying a four-year look-back window (2007–2010) to exclude prevalent cases. Follow-up extended for up to 12 years, beginning on January 1, 2011, and ending at the earliest occurrence of dementia diagnosis, migration, death, or study termination (December 31, 2022). A Common Data Model (CDM) framework was implemented, involving a harmonized study protocol, standardized database structures, and a common analytic script executed locally by each participating center, in accordance with Italian data protection regulations. Cohorts were established through record linkage of regional administrative health databases. Quantitative variables were summarized as means with standard deviations, while categorical variables were presented as absolute and relative frequencies. Incidence rates of dementia and exposures (hypertension, diabetes, and depression) were estimated as the number of incident cases per person-time, accounting for censoring due to death or migration. The association between each exposure and dementia risk was evaluated using Cox proportional hazards models, applied in both univariate and multivariable settings (the latter adjusted for relevant confounders), with exposures treated as time-dependent covariates. Results were reported as hazard ratios (HRs) with corresponding 95% confidence intervals (95% CIs). Statistical analyses were conducted using Stata and SAS software, with two-sided p-values < 0.05 considered statistically significant.

CONCLUSIONE AND DISCUSSION

During follow-up, incident dementia cases (table 2) among individuals with depression totaled 4,161 (12.3%) in Bologna, 15,412 (9.4%) in Lazio, and 6,775 (8.3%) in Turin. Among those with diabetes, dementia developed in 1,163 individuals (4.1%) in Bologna, 6,854 (3.6%) in Lazio, and 1,917 (2.1%) in Turin. For hypertension, incident dementia cases amounted to 6,729 (3.8%) in Bologna, 13,018 (1.0%) in Lazio, and 3,321 (1.5%) in Turin. In univariate analyses, depression was strongly associated with an increased risk of dementia across all study areas: Bologna (HR 6.0, 95% CI 5.6–6.4), Lazio (HR 5.06, 95% CI 4.88–5.25), and Turin (HR 7.56, 95% CI 7.1–7.94). Diabetes was also significantly associated with dementia: Bologna (HR 2.2, 95% CI 2.1–2.4), Lazio (HR 1.8, 95% CI 1.7–1.9), and Turin (HR 2.4, 95% CI 2.2–2.7). Hypertension showed a positive association in Bologna (HR 1.5, 95% CI 1.4–1.6) and Lazio (HR 1.06, 95% CI 1.0–1.1), whereas an inverse association was observed in Turin (HR 0.94, 95% CI 0.89–0.98). After adjustment for sex, age, and Charlson Comorbidity Index, depression remained strongly associated with dementia risk in all areas: Turin (HR 6.0, 95% CI 5.7–6.2), Bologna (HR 2.8, 95% CI 2.6–2.9), and Lazio (HR 2.58, 95% CI 2.49–2.68). Diabetes was significantly associated with dementia only in Turin (HR 1.7, 95% CI 1.5–1.8) and Bologna (HR 1.1, 95% CI 1.02–1.3), but not in Lazio (HR 0.98, 95% CI 0.93–1.03). Conversely, hypertension was inversely associated with dementia in all regions: Turin (HR 0.9, 95% CI 0.9–1.0), Bologna (HR 0.63, 95% CI 0.60–0.66), and Lazio (HR 0.80, 95% CI 0.78–0.82). These findings emphasize the need for prevention strategies targeting psychiatric and metabolic risk factors in adulthood, with potential benefits in mitigating dementia incidence.



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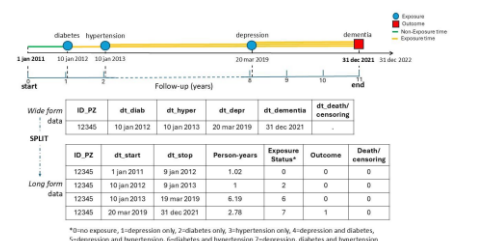


Figure 3. Time-dependent variables with multiple exposure.

Pathologies	Drug prescription (ATC-code)	Hospital discharge in primary or secondary diagnosis (ICD-9-code)	Emergence in pathology
Dementia	All least from prescriptions in one year: INDICAZIONE DINDICAZIONE DINDICAZIONE DINDICAZIONE	30P7.30.2; 39A.0; 39A.21; 303.02; 303.0; 303.2; 303.5; 303.7; 303.8; 303.9; 304.1	031; 039
Depression	All least 100 days of antidepressants prescriptions in one year: SIRKAA; SIRKAB; SIRKAC	296.20-296.23; 296.50-296.53; 300.4; 311; 304.1; 296.2; 296.3; 296.4; 300.0; 300.1; 300.2	031
Diabetes	All least from prescriptions in one year of all antidiabetic drug: A10A; A10B	250P	031
Hypertension	All least from prescriptions in one year: C02; C03; C03C; C09	401*; 402*; 403*; 404*; 405*; 30211	031

Table 1. Algorithm definition for Dementia, Depression, Diabetes and Hypertension running on health administrative databases 278 (drug prescription, hospital discharge and exemption for pathology)

	Bologna	Lazio	Piemonte	Toscana
Diabete				
Coorte	327,352	1,917,145	1,744,377	1,460,050
Incidenza esposizione	28,207 (8.6%)	204,662 (10.6%)	89,891 (5.2%)	135,096 (9.3%)
Incidenza di demenza dopo esposizione	1,163 (4.1%)	6,854 (3.6%)	1,917 (2.1%)	6,995 (5.2%)
Depressione				
Coorte	333,829	2,053,635	1,788,974	1,473,707
Incidenza esposizione	35,445 (10.6%)	163,489 (8.0%)	79,349 (4.4%)	170,305 (11.5%)
Incidenza di demenza dopo esposizione	4,161 (12.3%)	15,412 (9.4%)	6,775 (8.5%)	22,320 (13.5%)
ipertensione				
Coorte	313,819	1,227,941	1,080,595	1,012,162
Incidenza di esposizione	179,379 (57.2%)	455,071 (37.0%)	226,314 (20.9%)	303,648 (30%)
Incidenza di demenza dopo esposizione	6,729 (3.8%)	13,018 (1.0%)	3,321 (1.5%)	12,162 (4.0%)

Table 2. Incidence cases for diabetes, depression, and hypertension in specific cohorts.

REFERENCES.

1. Europe, A. (2019). Estimating the prevalence of dementia in Europe. *Alzheimer Europe*, 54-55.
2. Mayer, F., Di Pucchio, A., Lacorte, E., et al. An estimate of attributable cases of Alzheimer disease and vascular dementia due to modifiable risk factors: the impact of primary prevention in Europe and in Italy. *Dementia and geriatric cognitive disorders extra*. 2018; 8(1), 60-71.
3. Rolandi E, Zaccaria D, Vaccaro R, et al. Estimating the potential for dementia prevention through modifiable risk factors elimination in the real-world setting: a population-based study. *Alzheimers Res Ther*. 2020; Aug 7;12(1):94.
4. Rolandi E, Zaccaria D, Vaccaro R, Abbondanza S, Pettinato L, Davin A, Guaita A. Estimating the potential for dementia prevention through modifiable risk factors elimination in the real-world setting: a population-based study. *Alzheimers Res Ther*. 2020 Aug 7;12(1):94. doi: 10.1186/s13195-020-00661-y.
5. Bacigalupo, L, Lombardo, F, L, Bargagli, A, M., et al. Identification of dementia and MCI cases in health information systems. An Italian validation study. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, 2022, 8(1), e12327.

