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Benzodiazepine use in relation to long-term dementia risk and imaging markers of neurodegeneration: a population-based cohort study.

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Background: Benzodiazepines have well-established acute adverse effects on cognition. However, long-term effects on dementia risk and imaging markers of neurodegeneration remain uncertain.

Methods: We included 5443 cognitively healthy participants (MMSE≥26) from the population-based Rotterdam Study (57.4% women, mean age 70.6 years). Benzodiazepine use from 1991 until baseline (2005-2008) was derived from pharmacy records, from which we determined type and cumulative dose. We determined the association with dementia risk until 2020 using Cox regression, and with neuroimaging markers during 5-yearly repeated MRI using linear mixed models.

Results: During a mean follow-up of 11.2 years, 726 participants (13.3%) developed dementia. Benzodiazepine use occurred in 1675 (30.8%) participants, of whom 845 (50.4%) had used anxiolytics, 390 (23.3%) had used sedatives, and 440 (26.3%) had used both. Current use of any type of benzodiazepine at baseline, but not former use, was associated with increased dementia risk during follow-up (HR[95%CI]: 1.56[1.17-2.09]). Excess risk in current users persisted after excluding a 2-year lag-time of use prior to baseline. Dementia risk was dependent on cumulative dose (>median: HR[95%CI] 1.31[1.05-1.63] vs. <=median: HR[95%CI] 1.01[0.78-1.31]). Use was not associated with volume of grey matter, white matter, hippocampus, amygdala or thalamus at baseline. During follow up, high cumulative dose was associated with accelerated decrease in hippocampal volume (p=0.021). Regarding drug type, dementia risk was increased with anxiolytics (overall HR[95%CI]: 1.37[1.10-1.71]), which was paralleled by accelerated grey matter atrophy (p=0.036), albeit no dose-response relationship was observed. Sedatives were not associated with dementia risk or brain atrophy. Combined use of anxiolytics and sedatives at baseline was associated with increased dementia risk (HR[95%CI]: 1.70[1.05-2.76]), but this attenuated after excluding use during a 2-year lag time (HR[95%CI]: 1.08[0.71-1.64]), and was not associated with brain atrophy.

Conclusion: Chronic use of benzodiazepines in a population of cognitively healthy older adults is associated with increased dementia risk.

Conflicts of interest to disclose: We declare no competing interests

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The impact of mental disorders during education on work participation: a register-based longitudinal study on young adults with 10 years follow-up.

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BACKGROUND. Mental disorders are a leading cause of disability and a major threat to work participation in young adults. This register-based longitudinal study aims to investigate the influence of mental disorders on entering and exiting paid employment among young graduates and to explore differences across socioeconomic groups.

METHODS. Register information on sociodemographics (age, sex, migration background) and employment status of 2,346,393 young adults who graduated from secondary vocational (n=1,004,395) and higher vocational education or university (n=1,341,998) in the period 2010-2019 was provided by Statistics Netherlands. This information was enriched with register information on the prescription of nervous system medication for mental disorders in the year before graduation as a proxy for having a mental disorder. Cox proportional hazards regression models were used to estimate the influence of mental disorders on (a) entering paid employment among all graduates and (b) exiting from paid employment among graduates who had entered paid employment.

RESULTS. Individuals with mental disorders were less likely to enter (HR: 0.69-0.70) and more likely to exit paid employment (HR: 1.41-1.42). Individuals using antipsychotics were the least likely to enter (HR: 0.44) and the most likely to exit paid employment (HR:1.82-1.91), followed by those using hypnotics and sedatives. The association between mental disorders and work participation was found across socioeconomic subgroups (i.e., educational level, sex and migration background).

DISCUSSION. Young adults with mental disorders are less likely to enter and maintain paid employment. These results ask for prevention of mental disorders and for a more inclusive labour market.

Conflicts of interest to disclose: We declare no competing interests

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Plasma Alzheimer's disease markers and MRI load of vascular pathology and neurodegeneration: the SMART-MR Study

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Introduction: Two of the main causes for dementia are Alzheimer's disease (AD) pathology and vascular pathology. Plasma biomarkers for AD pathology have recently emerged, including amyloid-beta, p-tau, neurofilament light (NfL), and glial fibrillary acidic protein (GFAP). Vascular pathology can be assessed on MRI via white matter hyperintensities (WMH) and infarcts. Our aim was to estimate the relationship between plasma AD biomarkers and MRI markers of vascular pathology and neurodegeneration in non-demented individuals with manifest arterial disease.

Methods: Data from 594 individuals (mean (SD) age: 64 (8) years; 17% female) were included from the SMART-MR Study, a prospective cohort study from the UMC Utrecht in the Netherlands. Vascular and neurodegenerative MRI markers included WMH volume, presence of infarcts (yes/no), total brain volume (TBV), and hippocampal volume (HV) assessed on 1.5T MRI. AD plasma markers (amyloid-beta 42/40 ratio, ptau-181, NfL, and GFAP) were assessed using Single Molecular Array (Simoa; Quanterix) assays. Linear regressions were performed for each plasma marker with WMH volume, TBV, and HV, correcting for age, sex, education, and ICV. Additionally, logistic regressions were performed for the presence of lacunar and cortical infarcts. Plasma AD levels were converted to z-scores.

Results: Higher ptau-181 was associated with larger WMH volume (β=0.16, 95% CI=0.06; 0.26, p=0.001). Higher NfL (β=-5.63, 95% CI=-8.95; -2.31, p=0.001) was associated with lower TBV. Higher NfL levels (OR=1.58, 95% CI=1.20; 2.08, p=0.001) and higher GFAP levels (OR=1.45, 95% CI=1.09; 1.92, p=0.010) were associated with cortical infarcts.

Conclusion: In our sample of patients with manifest arterial disease, NfL was related to both brain volume and infarcts. Further, an association between ptau-181 and WMH was found, as well as between GFAP and cortical infarcts. Plasma biomarkers offer the potential to easily measure a wider range of pathophysiological processes related to cognitive decline.

Conflicts of interest to disclose: We declare no competing interests

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Health-related Quality of Life during the first 4 years after Non-Muscle Invasive Bladder Cancer Diagnosis: Results of a Large Multi-centre Prospective Cohort

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Introduction: The health-related quality of life (HRQoL) of patients with non-muscle invasive bladder cancer (NMIBC) may be impaired due to the chronic and burdensome disease course, but longitudinal data is limited. Therefore, we aimed to evaluate HRQoL outcomes during the first 4 years after NMIBC diagnosis, and to compare HRQoL across clinical characteristics and to a normative population.

Methods: Patients with NMIBC (n=1,019) were included from the multi-centre prospective cohort study UroLife. Data were collected at 6 weeks (baseline), 3, 15, and 51 months after diagnosis. Longitudinal reference data were obtained from an age- and sex-matched normative population (n=490). Cancer-specific and NMIBC-specific HRQoL outcomes (range 0-100) were evaluated by the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30 and EORTC QLQ-NMIBC24 questionnaires, respectively. Linear mixed modelling was used to analyse HRQoL changes over time within groups and HRQoL differences across groups.

Results: Compared to baseline, statistically significant deteriorations of small clinical relevance were noted for appetite loss and diarrhoea at 51mo. In contrast, improvements were observed for insomnia and social functioning. We also found improvements for urinary symptoms, future worries and risk of contaminating a partner during sex. These three symptoms were more often reported in patients with high grade NMIBC and patients treated with BCG treatment. No differences were observed between patients with or without NMIBC recurrence/progression. In comparison to a normative population, clinically relevant worse scores were observed for cognitive and social functioning, dyspnoea, insomnia, appetite loss, and diarrhoea. Only the differences in appetite loss and diarrhoea remained until 51mo.

Conclusion: Most HRQoL outcomes were not affected during the first 4 years after NMIBC diagnosis. Only small deteriorations in diarrhoea and appetite loss persisted, also in comparison to normative data. The reason for this remains to be elucidated.

Conflicts of interest to disclose: We declare no competing interests

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Using real-world general practitioner data to study the diagnosis and management of dementia: rationale and design

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Introduction: General practitioners (GPs) play a critical role in the early recognition and management of dementia. Timely diagnosis is important in light of potential disease-modifying therapies and to improve patient outcomes. We aimed to establish a real-world data cohort utilizing GP data of individuals with dementia as a starting point, with the goal of gaining insights into trajectories and management of dementia and patient outcomes. Here we describe the rationale and design.

Methods: We selected individuals with dementia using Dutch GP data from the PHARMO Data Network, which includes diagnoses, symptoms, examinations, prescriptions, and communication between GPs and specialists. Diagnosis of dementia was defined as a diagnosis or prescription of anti-dementia drugs between 2011 and 2020. We described the cohort in terms of demographics and screening tests for cognitive impairment.

Results: 52,911 individuals with dementia were selected from a population of 4.7 million persons. Mean age was 81 years (standard deviation [SD] = 8.65) and 59% were female. On average, patients have 8.6 years (SD = 4.09) of data available prior to diagnosis and can be followed-up for 2.8 years (SD = 2.19). Reason for end of follow-up was death for 32%, end of data availability for 40%, and 28% reached December 2020 (i.e., active). We found the Mini-Mental State Examination (MMSE) in GP records of 60% of all persons, and the Montreal Cognitive Assessment (MoCA) and Rowland Universal Dementia Assessment Scale (RUDAS) for only 3%, and <0.5%, respectively.

Conclusion: We created a cohort of 52,991 individuals with dementia, providing a starting point for further research on trajectories and management of dementia and patient outcomes. Next steps include matching the cohort with dementia-free controls, enriching the cohort by established linkages to other data sources (e.g. hospital data), and examining healthcare resource utilization, indicators of cognitive decline, treatment, and young-onset dementia.

Conflicts of interest to disclose: We declare no competing interests

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Psychosocial factors, health behaviors and the incidence of cancer: a summary of IPD meta-analyses by the PSY-CA consortium

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Introduction: Depression, anxiety and other psychosocial factors have long been theorized to increase cancer risk. We examined whether (i) psychosocial factors are associated with cancer incidence; (ii) psychosocial factors interact with or moderate the effects of health behaviors on cancer incidence; and (iii) health behaviors mediate the association between psychosocial factors and cancer incidence.

Methods: The PSYchosocial factors and CAncer incidence (PSY-CA) consortium involves 18 national and international cohorts (N= 437,827, cancer incidences= 36,961, person-years of follow-up= 4,749,481). We performed a series of two-stage, individual participant data (IPD) meta-analyses on the associations between psychosocial factors (depression diagnosis, depression symptoms, anxiety diagnosis, anxiety symptoms, perceived social support, loss events, general distress, neuroticism, relationship status) and cancer incidence (all cancers, smoking-related, alcohol-related, breast, lung, prostate, and colorectal cancers). Models were adjusted for sociodemographic factors, health behaviors and cancer-specific confounders. We examined interaction and mediation of health behaviors (smoking, alcohol use, physical activity, overweight, sedentary behavior, sleep quality, sleep duration).

Results: (i) Psychosocial factors were not associated with the incidence of any cancer, except for most psychosocial factors being associated with an increased incidence of lung and smoking-related cancers. These associations weakened when adjusting for health behaviors. (ii) Psychosocial factors did not interact with or moderate the effects of health behaviors on cancer incidence. (iii) The associations between psychosocial factors and the incidence of lung cancer/smoking-related cancers were mediated by smoking and, to a lesser extent, physical inactivity.

Conclusion: PSY-CA is the first IPD meta-analysis examining the association between several psychosocial factors and cancer incidence, and the first to analyze the interacting and mediating role of health behaviors. We showed that for many psychosocial factors there is no association with cancer incidence. One exception is that psychosocial factors are associated with increased smoking which subsequently increases risk of lung and smoking-related cancers.

Conflicts of interest to disclose: We declare no competing interests