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ORIGINAL ARTICLE

Retinal vein occlusion as an age-dependent marker of incident dementia in a long-term Danish national cohort

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Abstract

Purpose: The aim of this study was to investigate retinal vein occlusion (RVO) as an independent marker of incident dementia.

Methods: In a prospective nationwide cohort study, we identified 2 225 568 individuals through the Danish national health registers. Individuals older than 65 years, without unspecified retinal vascular occlusion or dementia were included from 1998 to 2020 and followed until 2022. We calculated the incidence rate (IR) and performed a Cox regression analysis with a hazard ratio (HR) and 95% confidence interval (CI) for RVO (exposure) as a marker of all-cause dementia adjusted for systemic comorbidity.

Results: We identified 19 669 individuals with RVO who had a higher prevalence of systemic comorbidity at inclusion compared to those without RVO (n = 2 185 483). We performed a Cox regression analysis for age-dependent exposure due to non-proportional hazards in the pre-planned analysis. Exposed individuals younger than 75 years had an increased risk of all-cause dementia (adjusted HR 1.09, 95% CI 1.01–1.18), whereas individuals older than 75 years had a decreased risk of all-cause dementia (adjusted HR 0.92, 95% CI 0.86–0.98).

Conclusion: Individuals with RVO had an age-dependent risk of dementia, with a 9% increased risk in individuals with RVO younger than 75 years and an 8% decreased risk in individuals older than 75 years at the time of exposure.

KEYWORDS
Alzheimer's disease, cohort study, dementia, ocular biomarkers, register-based study, retinal vein occlusion, vascular dementia

1 | INTRODUCTION

Retinal vein occlusion (RVO) is a common eye condition with a global 5-year incidence of 0.86% (Song et al., 2019). As a result of improved living conditions and an ageing population, an increase in disease burden is expected alongside other age-related diseases (Song et al., 2019). The most frequent symptom is acute painless loss of vision, and patients with RVO are more likely to have hypertension, dyslipidaemia, renal disease and diabetes mellitus (Ørskov et al., 2022).

Dementia is an umbrella term including, but not limited to, Alzheimer's disease (AD) and vascular dementia (VD; WHO, 2017). AD accounts for 62% of all dementia cases and is therefore the most frequent form of dementia, followed by VD (17%) and mixed dementia (10%; Prince et al., 2014). Dementia is a highly prevalent global health issue, affecting over 55 million people worldwide and ranks as the fourth leading cause of death and a substantial economic burden, with costs equivalent to 1.1% of the Gross National Product (Stapelfeldt & Gottrup, 2022).

While vascular pathology is a key component in the development of dementia (Kalaria, 2016), retinal vasculopathy is also associated with AD (Kusne et al., 2017; Liao et al., 2021; Shi et al., 2021). A possible association between RVO and dementia is plausible due to overlapping risk factors and a shared embryological origin between the retina and the central nervous system (Shi et al., 2021).

This leads to the theory that a higher incidence of dementia exists among individuals with an RVO, and that this cannot be sufficiently explained by shared risk factors. Some proof-of-concept for this theory is established, but so far studies have been limited by short follow-up (Nam et al., 2021), cross-sectional design (Chan et al., 2021), and a limited number of participants (Lee et al., 2021).

Although treatment options for dementia have so far been limited (Gauthier et al., 2016), evidence states that earlier diagnosis and implementation of prophylaxis are key features in preventing disease progression (Livingston, 2020). Likewise, new results on the antibody Lacenemab provides hope for better treatment options for early AD (van Dyck et al., 2023). Early diagnosis is therefore crucial for an optimal prognosis for individuals with dementia.

Hence, the aim of this study was to perform a long-term national cohort study to examine if RVO may act as an independent marker of incident dementia.

2 | MATERIALS AND METHODS

2.1 | Data sources

All Danish citizens are registered in the Civil Registration System with a unique personal identification number (Schmidt et al., 2014). The register provides information on date of birth, age, sex, marital and vital status, and the identification number enables linkage of information across registers.

The Danish National Patient Register contains information on all somatic patient hospitalisations along with examinations and treatments since 1977. Psychiatric hospitalisations, emergency department and outpatient contacts have also been included in the register since 1995 (Schmidt et al., 2015). Diagnoses are registered according to the eighth revision of the International Classification of Diseases (ICD) until 1994 and the tenth revision from 1994 forward. The Danish National Prescription Registry holds data on prescription drugs sold in Danish pharmacies and used during hospitalisation registered according to the Anatomical Therapeutic Chemical Classification (ATC; Kildemoes et al., 2011).

2.2 | Study design

This study was a longitudinal, register-based cohort study including all Danish citizens older than 65 years from sampling start (1 January 1998) to end of inclusion (31 December 2020). Entry date was defined by sampling start (age older than 65 years on 1 January 1998) or the date of their 65th birthday, if this occurred during the inclusion period. End of study was 31 December 2022.

2.2.1 | Exposure

Participants with an RVO diagnosis (ICD 10 H348, including subcodes = *) in the study period were registered as exposed. To account for changes over time, we considered the exposure as a time-varying variable. This means that individuals switched from the unexposed to the exposed group on the date their RVO was first registered.

2.2.2 | Outcomes

The primary outcome was all-cause dementia, which included AD, VD, mixed and unspecified dementia defined by diagnostic codes (ICD 10 F00*, F01*, G30*, F03*). Secondary outcomes were AD (ICD 10 G30.0, G30.1, G30.9, F00.0, F00.1, F00.9) and VD (ICD 10 F01.0, F01.2, F01.3, F01.8, F01.9) as isolated endpoints. AD and VD are part of the all-cause dementia definition, but they do not make up the main outcome alone. We chose not to perform subanalyses for mixed and unspecified dementia, as we deemed these groups too heterogeneous.

2.2.3 | Exclusion criteria

We excluded participants if any registration of unspecified retinal vascular occlusion (ICD 10 H349) or dementia (ICD 8290.0, 290.1, 293.0, 293.1, 337.02-3 and ICD 10 G30*, F00*, F01*, F02*, or F03) was registered in the Danish National Patient Register before the entry date.

2.2.4 | Covariates

We selected covariates in our analysis from a priori knowledge. These were age in 5-year categories, sex (binary), marital status (never married, married/cohabiting or divorced/widowed) and medical conditions considered as possible confounders, including hypertension, dyslipidaemia, cardiovascular disease, chronic obstructive pulmonary disease (COPD), diabetes and chronic kidney disease (all binary). The definition of medical conditions, including diagnostic codes (ICD-8 and ICD-10) and ATC- codes was inspired by previous research (Frederiksen et al., 2022; Hvidberg et al., 2016; Thygesen et al., 2011). The definitions are available in Table S1.

We considered marital status and sex as fixed covariates at the entry date, while hypertension, dyslipidaemia, diabetes, chronic kidney disease and cardiovascular disease were considered time-varying covariates that were allowed to change during the follow-up period. We adjusted for COPD if ever registered, since this was a proxy for smoking, and we cannot justify using the date of diagnosis as the date of smoking exposure.

2.3 | Statistical analysis

Baseline characteristics were presented as numbers, percentages and medians with an interquartile range (IQR) and tested for differences using chi-square tests (categorical data) and k-sample tests for equality of medians (continuous data; Table 1).

We calculated the incidence rate (IR) and reported the primary outcome as the hazard ratio (HR) with a 95% confidence interval (CI) of a crude, a semi-adjusted (age and

TABLE 1 Baseline characteristics of overall cohort, and individuals exposed and unexposed with a retinal vein occlusion.

	All	RVO	No RVO	
	n = 2 205 152	*n* = 19 669	*n* = 2 185 483	*p*-Value[a]
Sex, *n* (%)				
Female	1 180 739 (54)	10 309 (52)	1 170 430 (54)	0.001
Male	1 024 413 (46)	9360 (48)	1 015 053 (46)	
Age at index date, median years (IQR)	65.0 (65.0;70.3)	65.0 (65.0;69.6)	65.0 (65.0;70.3)	0.008
Civil status, *n* (%)				
Never married	793 227 (36)	7096 (36)	786 131 (36)	0.005
Married/cohabiting	1 135 530 (51)	9967 (51)	1 125 563 (51)	
Divorced/widowed	276 395 (13)	2606 (13)	273 789 (13)	
Comorbidity, *n* (%)				
Hypertension	844 821 (38)	9222 (47)	835 599 (38)	<0.001
Dyslipidaemia	358 871 (16)	3587 (18)	355 284 (16)	<0.001
Diabetes	159 875 (7)	1731 (9)	158 144 (7)	<0.001
COPD	63 272 (3)	464 (2)	62 808 (3)	<0.001
Chronic kidney disease	11 786 (1)	170 (<1)	11 616 (<1)	<0.001
Cardiovascular comorbidity	262 294 (12)	2468 (13)	259 826 (12)	0.004
Obstructive sleep apnoea	26 708 (1)	224 (1)	26 484 (1)	0.035
Glaucoma	19 241 (1)	864 (4)	18 377 (1)	<0.001

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, inter quartile range; RVO, Retinal vein occlusion.
[a]*p*-Value for χ^2 test (categorical) or k-sample test (continuous variables).

sex) and a fully adjusted Cox proportional hazards regression model (all covariates) of individuals exposed to RVO compared to unexposed individuals (data not shown). We tested for proportional hazards using the Fine-Grey test, but the assumptions of proportional hazards were not met.

Due to violations of the proportional hazards assumption, we tried to modify the covariates included in the model, splitting age into categories. As this did not solve the violations of the assumption, we decided to estimate the time-varying effects of the exposure and found that the effect was age-dependent. To account for this, we performed the Cox regression analyses in the three models of individuals exposed to RVO according to their age at exposure. Statistical significance was defined as a 95% CI not including 1.0 and *p*-values < 0.05.

Participants were followed from the entry date until the date of (i) the first dementia diagnosis, (ii) death, (iii) emigration or (iv) end of the study (31 December 2022), whichever came first. Individuals registered with unspecified retinal vascular occlusion (H349) or dementia in other diseases classified elsewhere (ICD 10 F02*) during the follow-up period were censored the day before the diagnosis was registered. ICD 10 F02* includes, among others, Creutzfeldt-Jakob, Huntington's and Parkinson's disease. We expect individuals registered with these dementia forms not to be registered with a potential underlying or subsequent AD and therefore an unreliable outcome.

2.4 | Supplementary analyses

We tested for interaction with age at exposure, sex, obstructive sleep apnoea and glaucoma. We included specialty requirements on dementia and RVO in a sensitivity analysis to accommodate the risk of misclassification by incorrect diagnostic code registration. In this analysis, individuals with a registration of RVO in other than an ophthalmologic department were censored from the day before diagnosis registration. Likewise, dementia diagnoses had to be registered at either a neurologic, geriatric, psychiatric or internal medicine department.

We performed the analyses using Stata version 17.0 (StataCorp LLC).

2.5 | Ethics

Data were available via the Danish Excellence Centre in Ophthalmic Epidemiology (DECODE-EYE) study (Grauslund et al., 2020), and data management was conducted in collaboration with the Open Patient data Explorative Network (OPEN) at Odense University Hospital. The handling of personal information was in accordance with the General Data Protection Regulation, which ensured that this study complied with national laws and guidelines cf. the Danish Health Care Act. Relevant permission to conduct this study was obtained from the Region of Southern Denmark's record of data processing activities (Journal no. 19/7775). The Danish Health Authorities granted permission to access register data (FSEID-00004087). Register-based studies in Denmark need no permission from the Danish National Committee on Health Research Ethics.

3 | RESULTS

A flowchart on inclusion and grouping of participants is shown in Figure 1. We identified 2 225 568 individuals living in Denmark and being 65 years or older within

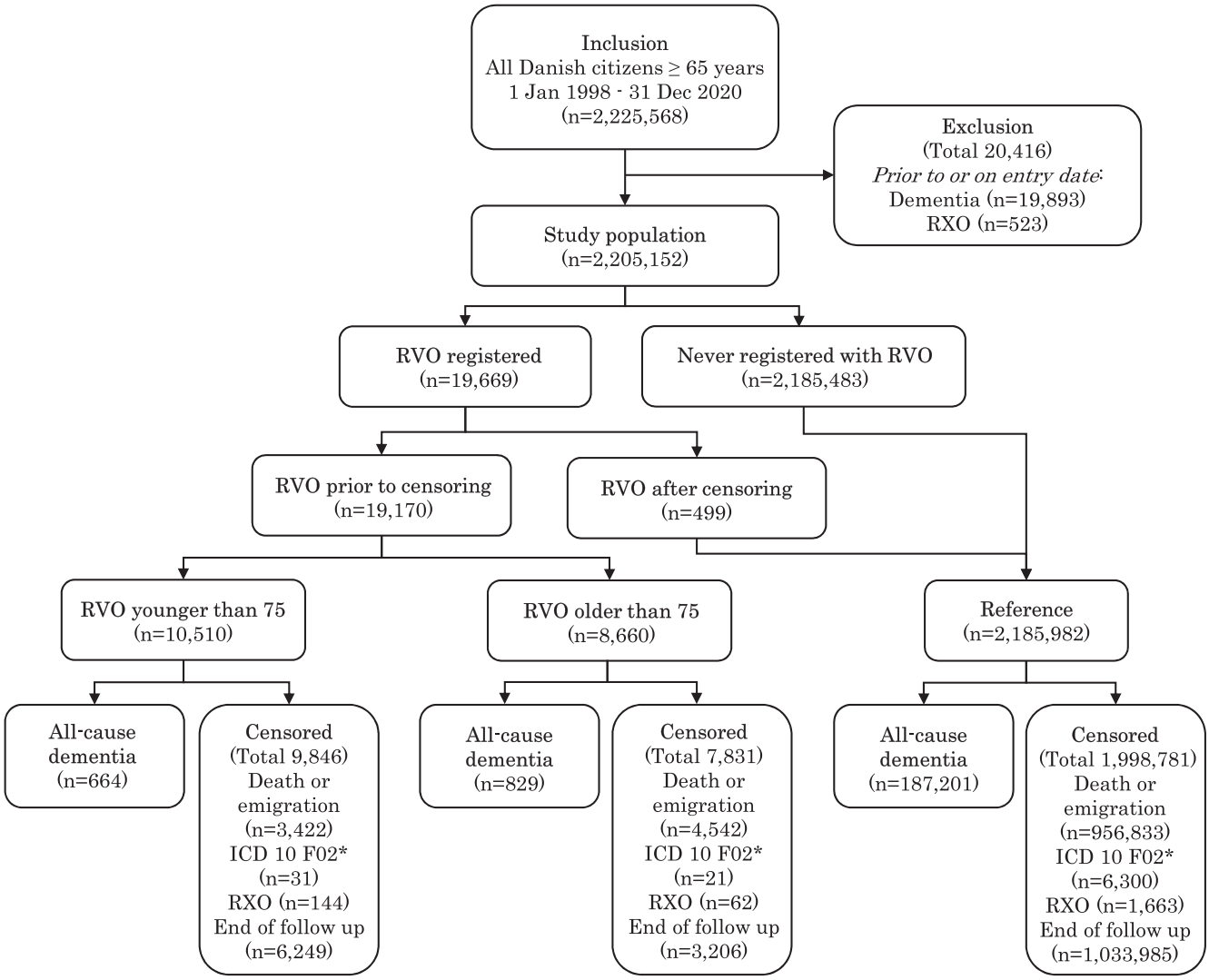

FIGURE 1 Flow chart of the study participants. ICD, International Classification of Diseases; RVO, retinal vein occlusion; RXO, unspecified retinal vascular occlusion. Due to the time-varying structure, an RVO after a censoring event is not included as an exposure. Therefore, the 499 individuals only contribute risk time to the reference group.

TABLE 2 Incidence rate and hazard ratio with 95% confidence interval for all-cause dementia, Alzheimer's disease and vascular dementia according to age-dependent exposure status.

Outcome	Exposure status	No of events/PYR	IR[a]	Crude HR (95% CI)	Semi-adjusted[b] HR (95% CI)	Fully adjusted[c] HR (95% CI)
All-cause dementia	No RVO	187 201/22 926 436	8.17	1.00 Ref	1.00 Ref	1.00 Ref
	RVO younger than 75	664/83 949	7.91	1.10 (1.02;1.19)	1.11 (1.02;1.19)	1.09 (1.01;1.18)
	RVO older than 75	829/42 842	19.35	0.92 (0.86;0.98)	0.92 (0.86;0.99)	0.92 (0.86;0.98)
Alzheimer's disease	No RVO	79 525/23 318 843	3.41	1.00 Ref	1.00 Ref	1.00 Ref
	RVO younger than 75	291/85 445	3.41	1.09 (0.97;1.22)	1.10 (0.98;1.23)	1.10 (0.98;1.23)
	RVO older than 75	334 / 44 599	7.49	0.94 (0.84;1.05)	0.95 (0.85;1.05)	0.95 (0.85;1.05)
Vascular dementia	No RVO	26 434/23 543 351	1.12	1.00 Ref	1.00 Ref	1.00 Ref
	RVO younger than 75	121/86 055	1.41	1.36 (1.14;1.63)	1.34 (1.12;1.61)	1.14 (0.96;1.37)
	RVO older than 75	132/45 485	2.90	1.14 (0.96;1.35)	1.13 (0.95;1.34)	1.04 (0.88;1.23)

Abbreviations: CI, confidence interval; COPD: chronic obstructive pulmonary disease; HR, hazard ratio; IR, incidence rate; PYR, person-years at risk; RVO: retinal vein occlusion.

[a]Per 1000 person-years.

[b]Adjustments for sex.

[c]Adjustments for sex, marital status, cardiovascular disease, diabetes, dyslipidaemia, COPD, hypertension and chronic kidney disease.

the inclusion period (1 January 1998 until 31 December 2020). Of these, 20 416 were excluded due to dementia (n = 19 893) or unspecified retinal vascular occlusion (n = 523) prior to or on date entry, leaving a final study population of 2 205 152 individuals. Median follow-up time was 9.72 years (IQR 5.13–14.92).

Overall, 19 669 individuals obtained a RVO diagnosis in the study period (Table 1). These individuals were more likely to be older at inclusion ($p=0.008$, k-sample test), to have cardiovascular diseases ($p=0.004$, χ^2 test), COPD ($p<0.001$), obstructive sleep apnoea ($p=0.035$), chronic kidney disease ($p<0.001$), dyslipidaemia ($p<0.001$), arterial hypertension ($p<0.001$), diabetes ($p<0.001$), glaucoma ($p<0.001$) and to be divorced/widowed and never married ($p=0.005$). Individuals with RVO were more frequently female ($p=0.001$), but the difference in sex between exposed and unexposed was minor (Table 1).

3.1 | RVO as a marker of incident dementia

In a post-hoc analysis, we evaluated the risk of dementia according to age at exposure due to the non-proportional hazards of the main analysis. IR and HR with a 95% CI for all three outcomes according to exposure status are presented in Table 2. IR was higher in the group of exposed individuals older than 75 years as expected in an age-related disease.

Individuals who were younger than 75 years when exposed to a RVO had an increased risk of all-cause dementia (adjusted HR 1.09, 95% CI 1.01–1.18), whereas individuals older than 75 years when exposed to a RVO had a decreased risk of all-cause dementia (adjusted HR 0.92, 95% CI 0.86–0.98).

For individuals with RVO younger than 75 years, there was a tendency towards a higher risk of AD (adjusted HR 1.10, 95% CI 0.98–1.23), as opposed to the group of older individuals with RVO (adjusted HR 0.95, 95% CI 0.85–1.05). The HR did not differ between the three models for the AD analysis (Table 2).

Individuals with RVO in both age groups did not have a statistically significant increased risk of VD compared to unexposed individuals when adjusting for systemic comorbidity (HR 1.14, 95% CI 0.96–1.37 and HR 1.04, 95% CI 0.88–1.23 for the young and older individuals exposed to RVO, respectively), although individuals younger than 75 years at exposure had an increased risk in the crude analysis (crude HR 1.36, 95% CI 1.14–1.63; Table 2). Opposite to all-cause dementia and AD, the individuals exposed to a RVO after 75 years of age had a tendency to have a higher risk of VD compared to the unexposed individuals.

3.2 | Supplementary analyses

We found no interaction with sex, glaucoma or obstructive sleep apnoea. The sensitivity analysis with requirements for departments to register the diagnoses showed the same tendency as the main analysis (Table S2). The planned competing risk analysis was not computationally feasible due to the size of the cohort.

4 | DISCUSSION

We found important differences in the risk of all-cause dementia according to age at RVO debut in this national cohort of more than 2 million individuals. RVO was associated with a 9% increased risk of all-cause dementia in individuals aged below 75 years. This increased risk was not affected by systemic comorbidity, as the HR did not differ between the crude and fully adjusted analysis. On the other hand, being older than 75 years at exposure was associated with an 8% lower risk of all-cause dementia. The group of exposed individuals, when older than 75 years, is per study design not previously registered with a dementia diagnosis and have a cognitive capacity good enough to recognise visual impairment and search for medical attention. This forms a group of exposed individuals who are in lower risk of dementia, which is not a product of the exposure but a result of selection. This leads us to the theory that the young individuals exposed to RVO are more susceptible to developing cerebral vascular dysfunction, whereas the older individuals are exposed to RVO due to an increasing age with no effect on the risk of dementia. This correlates with the incidence rates, which are higher in the group of exposed individuals older than 75, although their HR is below one. The factors that account for the young individuals increased risk of dementia cannot be derived from this study. Factors inducing or allowing a more rapid breakdown of the blood-retina and blood-brain barrier can possibly explain this connection.

RVO was not associated with AD in any analysis, demonstrating that this form of dementia must be linked to other pathophysiological pathways, although the same tendencies as the HR's from the main analysis are repeated for AD. In the subanalysis with VD as the endpoint, we reported a 36% increased risk of VD among individuals younger than 75 years at exposure in the crude analysis, while the older group had a non-significant 14% increased risk of VD. RVO was not associated with VD after adjustments for systemic comorbidity, which was in contrast to a previous cohort study by Nam et al. (2021). This indicates that the increased risk can be ascribed to the shared risk factors of the fully adjusted model. However, the power of this subanalysis is limited by the rarity of the disease, with only 121 and 132 events of VD in each group. More worldwide data could maybe narrow the confidence intervals and establish if individuals with RVO have an increased risk independently from these shared risk factors. It is furthermore important to acknowledge that in a clinical setting, this 36% increased risk holds significant importance, with the individual's risk being evident regardless of pathophysiological explanations.

Limited publications exist concerning the association between RVO and dementia. A Korean nationwide matched cohort study included 46 259 individuals exposed to RVO with a mean follow-up time of 6.6 years (Nam et al., 2021). A 16% increased risk of incident all-cause dementia, a 15% increased risk of AD and a 24% increased risk of VD were reported among individuals exposed to RVO after adjustment for confounding variables (Nam et al., 2021). The study population differed from ours in regards to ethnicity, which might affect both the risk of RVO and dementia (Jonas et al., 2017; Kornblith et al., 2022), and follow-up time in our study was on average almost twice as high.

The association between RVO and dementia was stronger among individuals younger than 65 years in the Korean study, which supports our findings with RVO as an age-dependent risk factor.

In a cross-sectional study of 37 208 individuals from California, USA, Chan et al. found a higher prevalence of dementia in those with retinal vascular occlusion. However, comparisons to our study are difficult, as longitudinal data were not available and RVO was not differentiated from retinal artery occlusion as a separate exposure (Chan et al., 2021).

A small American cohort study investigated the association between retinal vascular occlusions and VD and AD, again combining retinal artery and vein occlusions (Lee et al., 2021). Although participants in the study with the apolipoprotein ε4 genotype had a three-fold risk of vascular dementia when exposed to a RVO, this was not the case for non-apolipoprotein ε4 carriers. Neither of the groups had an association between RVO and AD, which supports the findings in our study.

4.1 | Strengths and limitations

A major strength of this study was its design as a register-based prospective cohort study, which allowed inclusion of an entire nation with a long follow-up period and no loss of follow-up. The AD diagnosis is highly specific in Denmark (Phung et al., 2007). We accounted for the less valid VD diagnosis by performing a sensitivity analysis with requirements for departments who register the diagnoses and found no different hazard ratio in the Cox regression analysis, thus supporting our findings.

Diagnosing dementia in Denmark is centred in specialised centres at the hospitals rather than at primary care, which allowed us to retrieve the diagnostic codes. A delay in diagnosis registration is approximately 1 year, depending on residence, due to waiting time for dementia assessment (Stapelfeldt & Gottrup, 2022). We did not expect this delay to affect the results, as a long median follow-up of 9.7 years allowed the participants to develop symptoms of dementia and undergo diagnosis.

Limitations in the study exist. First, due to the register-based nature of the study, we had no access to information about the study population's lifestyle factors like body mass index, exercise levels and smoking status, which may result in residual confounding. However, we adjusted for COPD as a proxy for smoking. Second, comorbidities only treated by primary care physicians may be underestimated, as we could only retrieve information from hospitals. We partially accounted for this by including registered prescription medicines for dyslipidaemia, hypertension and diabetes.

Third, even though a previous American study argue that apolipoprotein E status has an impact on the effect of RVO on the risk of dementia (Lee et al., 2021), we had no information about genome predisposition to investigate this association.

Fourth, competing risks of death could have influenced our reported estimates. Due to the large cohort size, it was not computationally feasible to perform a sensitivity analysis taking competing risks of death into account in this study.

5 | CONCLUSION

This study establishes that individuals with a RVO debut before 75 years of age have an independently increased risk of incident all-cause dementia. Individuals older than 75 years when diagnosed with a RVO are at lower risk of all-cause dementia, but this should be interpreted with care. RVO is not independently associated with AD or VD, but the exposed individuals have a higher incidence, indicating the need for risk factor assessment and treatment in patients seen at hospitals with a RVO.

AUTHOR CONTRIBUTIONS

JG initiated the study. ARC and LS had full access to all data in the study and take responsibility for the data integrity and accuracy of the data analysis. ARC drafted the manuscript. All authors contributed to the design of the study, interpretation of data and revision of the manuscript.

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DISCLAIMER

The funders had no influence on the study, and all researchers were independent from the funders. Data cannot be shared due to the General Data Protection Regulation.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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