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Increased risk of dementia differs across cardiovascular diseases and types of dementia – Data from a nationwide study

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Aims. Dementia is a major health problem. Cardiovascular diseases (CVD) and risk factors are associated with incident dementia. However, whether there is an association among CVD, Alzheimer's disease (AD) and vascular dementia (VD) at the population level remains unclear.

Methods. We analysed the association between CVD (heart failure [HF], atrial fibrillation [AF], myocardial infarction [MI], peripheral arterial disease, stroke and transient ischemic attack) and the incidence of dementia using nationwide FinnGen data of 218,192 individuals. The last follow-up information on dementia was available from October 2021.

Results. The age at the end of the follow-up was 61.7 ± 17.1 years, and 53% were women. Overall, we observed 9701 (4.4%) dementia, 6323 (2.9%) AD and 1918 (0.7%) VD cases. Individuals with CVD had a higher risk of developing dementia than unexposed individuals. In the multivariable-adjusted Cox models, stroke was most strongly associated with dementia (hazard ratio [HR] 1.7, 95% confidence interval [CI] 1.6–1.8). CVD was more strongly associated with VD than with AD. Individuals with HF and MI had an increased risk of AD (HF: HR 1.11, 95% CI 1.04–1.19; MI: HR 1.10, 95% CI 1.02–1.18). AF was associated with VD (HR 1.58, 95% CI 1.42–1.77), but not with AD (HR 1.03, 95% CI 0.97–1.09). Clinical characteristics, such as diabetes, smoking and alcohol abuse, were associated with both types of dementia.

Conclusion. All major CVDs were associated with an increased risk of developing dementia, particularly VD. Therefore, CVD onset should prompt an assessment of cognitive decline and possible preventive measures.

Keywords: atrial fibrillation, cardiovascular disease, dementia, heart failure, outcomes, population epidemiology, stroke/TIA

Abbreviations: AD, Alzheimer's disease; AF, atrial fibrillation; CI, confidence interval; FDR, false discovery rate; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; TIA, transient ischemic attack; VD, vascular dementia

Introduction

Dementia has become the leading cause of death in older adults worldwide, after ischaemic heart disease, stroke and chronic obstructive pulmonary disease, owing to the increasing human survival rates and growing population [1–3]. Dementia imposes a great burden on the patient, their caregivers and society. The annual pecuniary costs of dementia are estimated to be more than €30,000 in Europe and the United States [4]. A comorbidity with cardiovascular disease (CVD) has been reported. In a Swedish longitudinal twin study,

non-stroke CVD was associated with the risk of late-life dementia [5]. By examining common non-stroke or transient ischemic attack (TIA) CVD separately, heart failure (HF) [6, 7], atrial fibrillation (AF) [8], myocardial infarction (MI) [9, 10] and symptomatic peripheral arterial disease [11] have been reported to be associated with cognitive impairment and dementia. However, the results of most clinical studies have been inconsistent [12]. CVD is more likely to be related to vascular dementia (VD); however, Alzheimer's disease (AD) and VD have often not been examined separately.

Classical CVD risk factors underlie the pathophysiology of common CVD. Risk factor trajectories have been associated with a decline in cognitive function and dementia onset [13]. Whether classical cardiovascular risk factors and CVD have different associations with AD or VD requires further investigation. A strong inflammatory component has been observed in patients with AD. Cardiovascular risk factors and CVD are characterized by chronic, subclinical systemic inflammation. Therefore, a pathophysiological link may exist between AD and VD onset and neuroinflammation due to systemic inflammation [14, 15]. Cardiovascular risk factors must be considered when evaluating the onset of dementia [16].

The population-based FinnGen cohort provides a resource for better understanding the epidemiological association of common CVD with future overall dementia and the major subtypes of AD and VD, accounting for stroke and TIA. As both classical risk factors and CVD clusters may be related to dementia onset, we examined risk factors that have been proposed as strong predictors of dementia and are available in the registry, such as hypertension, diabetes, obesity, excessive alcohol consumption and smoking [17]. The FinnGen cohort provides complete coverage across CVD and dementia outcomes and thus provides a unique opportunity to assess classical risk factors across the spectrum of CVD and CVD onset in relation to AD and VD.

Methods

Study design and sample selection

FinnGen represents a public–private partnership that longitudinally collects and manages pseudonymous nationwide health information across Finland, including diagnoses, medications, clinical events, health registries and genomic data. FinnGen includes data from individuals of Finnish ancestry. Our study sample was drawn from the FinnGen data freeze 9 (end of follow-up, 11 October 2021), which consisted of patients from Finland's national hospital biobanks and randomly selected participants from Finnish cohort studies [18].

Standard protocol approvals and informed consent

All the participants provided written informed consent. The study protocol was approved by The Coordinating Ethical Committee of the Hospital District of Helsinki and Uusimaa, as described in the Supporting Information section.

Variables

The end point was defined as the first hospital admission for a given type of dementia (any dementia, AD or VD). The exposures of interest included HF, AF, MI, peripheral artery disease, stroke and TIA. Covariates included sex (inferred from genotype), birth year, smoking status, obesity, hyperlipidaemia, chronic kidney disease, hypertension, diabetes and alcoholism. The covariates were selected a priori because of their known associations with dementia. Clinical diagnoses were identified using the International Classification of Diseases (ICD) codes in the nationwide hospital discharge and causes-of-death registers and linked by personal nationwide identification codes. We used the first event for all outcomes. ICD code-based diagnoses were made by the attending physician and are listed in Table S1. The accuracy of these codes is robust and has been previously described in detail [19].

Statistical analyses

The start of follow-up in the present study was defined as birth or the year 1998, as complete coverage for all registers began in that year. The hospital discharge register, the main source of diagnoses, contained data from 1969 onward. If exposure occurred before 1998, the person was considered exposed, but the exposure time started from the start of follow-up. The analyses were based on register entries between 1964 (the start year of the drug reimbursement registry) and October 2021. Of the 377,277 genotyped FinnGen participants, the smoking status of 221,762 was known and included in the dataset. Therefore, 155,515 individuals with missing smoking statuses were excluded from the study. Other variables were considered to include complete data, as the coverage of the nationwide registers for cardiovascular

outcomes was >90% [19]. Accordingly, the absence of an event in relevant registries was defined as a non-event. The removal of prevalent dementia cases resulted in a final sample of 218,192 participants.

We generated Kaplan–Meier curves and evaluated Cox proportional hazards models to assess the association between CVD events and dementia. Hazard ratios (HR) and 95% confidence intervals (CI) were presented. In all survival models, age was used as a timescale, and participants were censored at the end of follow-up, death or at the time of the outcome event. Exposures and disease covariates were handled as time-varying variables. The proportional hazards assumption was validated visually by inspecting the log–minus-log plots, owing to the large sample size. In addition, secondary analyses with all exposures in the same model, with a 1-year lag time between exposure and dementia, and sex-stratified associations were performed. Further, we stratified the analyses by age at the start of the follow-up. To create age groups with an adequate number of dementia events in a relatively young study sample (mean age at baseline 40 ± 19 years), we used the fifth age quintile (57 years) as the threshold for dividing the participants into two groups. For all analyses, we used R software (v.4.2.1; packages: tidyverse, DataTable, survival, survminer, forestplot, gridExtra, kableExtra and tableone). False discovery rate-corrected two-sided p-value <0.05 was considered the threshold for statistical significance.

Table 1. *Main characteristics of the FinnGen cohort.*

Variable	Overall
N	218,192
Any dementia, *n* (%)	9701 (4.4)
Alzheimer's disease, *n* (%)	6323 (2.9)
Vascular dementia, *n* (%)	1619 (0.7)
End of follow-up age, years	61.7 ± 17.1
Women, *n* (%)	115,717 (53.0)
Birth year	1958 ± 19
Obesity, *n* (%)	12,411 (5.7)
Hyperlipidaemia, *n* (%)	75,658 (34.7)
Chronic kidney disease, *n* (%)	5077 (2.3)
Hypertension, *n* (%)	63,488 (29.1)
Diabetes, *n* (%)	36,944 (16.9)
Smoking, *n* (%)	109,462 (50.2)
Alcohol abuse, *n* (%)	10,274 (4.7)
Heart failure, *n* (%)	16,843 (7.7)
Atrial fibrillation, *n* (%)	27,140 (12.4)
Myocardial infarction, *n* (%)	16,186 (7.4)
Peripheral arterial disease, *n* (%)	10,496 (4.8)
Stroke, *n* (%)	15,442 (7.1)
TIA, *n* (%)	10,959 (5.0)

Note: In the present study, follow-up spanned from the year 1998 (or birth) to 2021, death or the outcome event. Events prior to first dementia are shown for exposures and covariates. Quantitative measures are presented as the mean ± SD.
Abbreviation: TIA, transient ischemic attack.

Results

The study sample comprised 218,192 individuals (53% women). The characteristics of the study sample are shown in Table 1 and Tables S2 and S3. We observed 9701 (4.4%) of dementia, 6323 (2.9%) of AD and 1918 (0.7%) of VD cases.

The Kaplan–Meier curves for age at first dementia, AD or VD in each exposure group are shown in Fig. 1. The curves tended to separate most clearly from the age of 70 years for overall and VD. Multivariable-adjusted Cox model plots are shown in Fig. 2. After adjusting for sex, birth year and comorbidities, individuals with CVD had a higher risk of developing dementia than unexposed individuals. The association with any dementia was strongest for stroke (HR 1.7, 95% CI 1.6–1.8). Another study reported that CVD was associated with an increased risk of dementia. CVD showed a stronger association with VD than AD. Patients with HF and MI had an increased risk of AD (HF: HR 1.11, 95% CI 1.04–1.19; MI: HR 1.10, 95% CI 1.02–1.18). AF was associated with an increased risk of VD, but not AD. Diabetes, smoking and alcohol abuse are associated with both types of dementia. Hypertension was also significantly associated with VD only (Table S4). No statistically significant interactions according to sex were observed after correcting for multiple comparisons (Figs. S1 and S2). Analyses stratified by age at the start of follow-up and at 57 years of age yielded similar results (Figs. S3 and S4). Baseline characteristics according to age are shown in Table S4. Table S5 shows the incidence of dementia per 1000 person-years according to the exposure category. Sensitivity analysis with a 1-year lag time between CVD events and dementia showed similar, although somewhat weaker, results than the main analysis (Figs. S5 and S6). Table S6 shows the multivariable-adjusted Cox models for

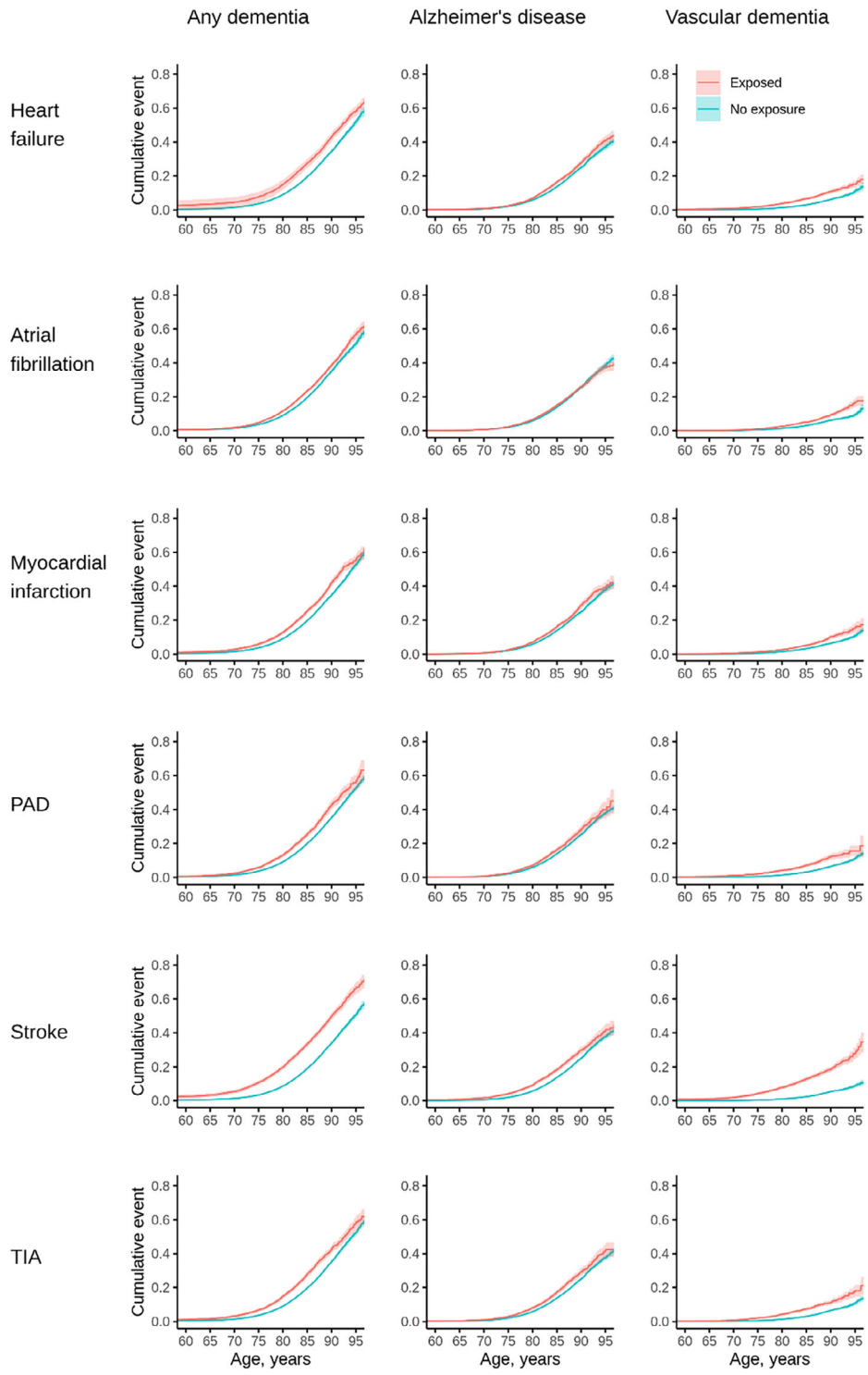

Fig. 1 *Visualization of raw data using Kaplan–Meier curves for any dementia, Alzheimer's dementia and vascular dementia for major cardiovascular diseases: heart failure, atrial fibrillation, myocardial infarction, peripheral arterial disease (PAD), stroke and transient ischemic attack (TIA). 95% confidence intervals are shown.*

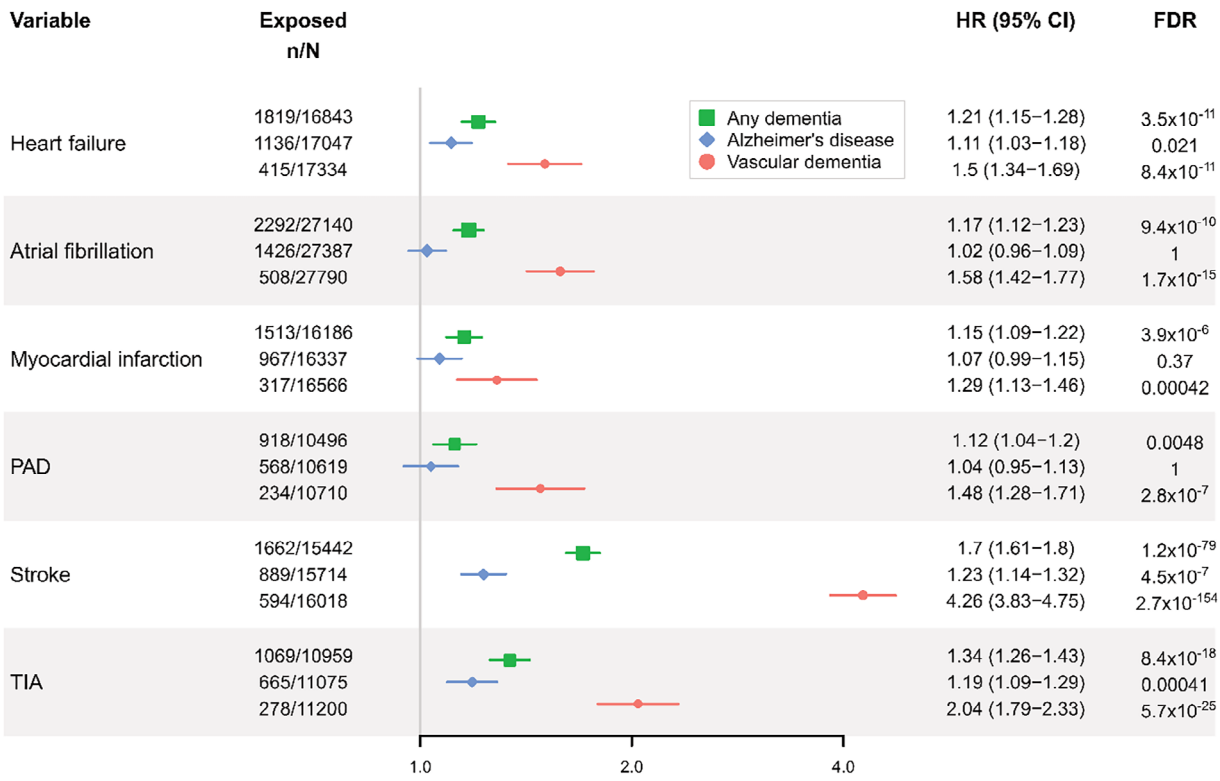

Fig. 2 *Forest plot of multi-variable-adjusted Cox models for time-dependent cardiovascular disease and incident dementia, Alzheimer's dementia and vascular dementia for major cardiovascular diseases: heart failure, atrial fibrillation, myocardial infarction, peripheral arterial disease (PAD), stroke and transient ischemic attack (TIA). Multi-variable-adjustment comprised birth year, sex, smoking, obesity, hyperlipidaemia, chronic kidney disease, hypertension, diabetes and alcohol abuse. Exposures and disease covariates were treated as time-varying variables. The number of exposed individuals with an outcome event and all exposed individuals are denoted as n and N, respectively. FDR-corrected p-values are shown. FDR, false discovery rate.*

incident dementia, AD and VD, with disease variables treated as time-dependent covariates.

Discussion

In our contemporary population-based cohort, all common CVDs were related to dementia onset and were more strongly related to VD than to AD. As expected, CVD risk factors were stronger predictors of VD than AD. Some risk factors, such as hypertension and hyperlipidaemia, were only significantly related to VD. We did not observe interactions by sex, although MI was not significantly associated with dementia or VD in women compared to men.

Classical risk factors and dementia

Compared with other CVDs, cardiovascular risk factors only account for approximately 40% of dementia risk [17]. The results of controlling risk factors to decrease dementia onset remain inconsistent. Whereas a meta-analysis of randomized controlled trials indicated that hypertension treatment lowers the risk of incident dementia or cognitive impairment [20], and targeting cardiovascular risk factors at older age was not sufficient to significantly reduce dementia onset over 12 years in the Prevention of Dementia by Intensive Vascular Care randomized clinical trial [21]. Therefore, strong CVD risk factors, such as hypertension, obesity, chronic kidney disease, and hyperlipidaemia, were not significantly associated with the overall incidence of dementia in multivariable-adjusted models. However, smoking and diabetes were associated with both AD and VD. Hypertension was only significantly associated with VD. Notably, alcohol abuse was among the strongest modifiable risk factors for dementia, with 1.6- and

2.2-fold increased risks of AD and VD, respectively. Targeting these risk factors should be considered to reduce the risk of dementia. Our observations also indicate that a better understanding of the pathobiology of the diseases is required to identify additional risk factors that may modulate dementia risk.

CVD and dementia

Although all the investigated CVD are predictors of TIA or stroke [22], which directly cause cerebral damage, resulting in cognitive impairment, mechanisms more specific to individual diseases have been suggested. The pathophysiology behind the observed association between MI and VD appears to be apparent, with shared risk factors and an underlying systemic vascular and atherosclerotic disease [10], with a longer latency for dementia to become clinically overt. Left ventricular impairment and the development of AF in patients post-MI overlapped with those of the other two diseases. Micro- and macroemboli from the hypokinetic regions and left atrial thrombi may lead to TIA or stroke. However, even after adjusting for clinically overt ischaemic cerebral events, the strongest association with incident dementia, particularly VD, was observed in patients with HF and AF. Repeated cerebral microembolization and ischaemia, which are not detected by conventional imaging, may also play a substantial role. In AF, oral anticoagulation intake, even in patients with low stroke risk, appears to be beneficial in preventing dementia [23, 24]. In addition, chronic hypoperfusion has been suggested as a causal factor in CV-related cerebral injury. The latter is supported by the observation of a dose–response relationship between cognitive decline and more severe HF [25]. In AF, the irregularity of the heartbeat and delayed adaptation to tachy- and bradycardic phases by cerebral autoregulation have been proposed as mechanisms of cerebral impairment [26].

Notably, in our study, HF was also related to AD, which has been reported in some earlier studies [27, 28] but not consistently in other investigations, such as a Danish nationwide registry [29]. Although proteotoxicity of misfolded, deposited proteins has been suggested as a common mechanism, it requires further evidence [30].

Clinical implications

Cognitive impairment and dementia are associated with a poor prognosis in patients with CVD and should be prevented [31]. In contrast, the onset of CVD may provide an opportunity for screening for cognitive decline and dementia. Early signs of cognitive impairment may be present after the onset of CVD. Further, mild impairments may affect rehabilitation and further CVD treatments. According to a Swedish registry, excess healthcare costs were incurred as early as 10 years before the formal diagnosis of dementia [32]. Importantly, in a recent meta-analysis, AF was found to be a strong risk factor for dementia in adults aged <70 years, in whom preventive measures may result in a large number of quality-adjusted life years [33]. Consistently, in our relatively young cohort, analyses stratified by age at the start of follow-up provided comparable results in both subgroups. Earlier identification of mild types of cognitive decline and a high risk of incident dementia may focus on prevention and care for this disabling disease and thus possibly prevent or delay disease onset. An interdisciplinary patient assessment that could be triggered by a CVD event, which usually leads to a medical encounter, may be required. Subsequently, patients with CVD would undergo closer monitoring for cognitive impairment than patients without CVD or cardiovascular risk factors, although evidence on the timing of repeated assessments for cognitive status is yet unavailable. In addition, patients' concerns about developing dementia, which are usually feared more than CVD outcomes, may be used to highlight the need for lifestyle changes and medication adherence in secondary CVD prevention [34].

Strengths and limitations

Our analyses were limited to hospital discharge registry data from a relatively young cohort of patients with age-related diseases with a mean age of 61 years at the end of follow-up. A more detailed assessment of cognitive function may show subtle changes in cognitive function and decline, which could show even a greater dimension of the problem in the population. Therefore, the number of dementia cases may have been underestimated in our sample, resulting in a bias. We focused on the most common types of dementia, AD and VD, which reduces the generalizability of our findings for other dementia subtypes. The incidence of AF and peripheral arterial disease, which can also be diagnosed outside the hospital, may have been underreported and may have affected these associations. For example, in individuals aged ≥65 years, a single time-point electrocardiogram

identified 1.44% of new AF cases in the population that were likely oligo- or asymptomatic [35]. The risk of dementia in AF increases independently of symptom status [33]. Therefore, the study results may be biased towards the null with missed AF cases. Furthermore, the risk factor assessment was restricted to coded cardiovascular risk factors, which reduced the number of potential confounding variables. However, the most commonly known CVD risk factors were also considered. A large proportion of FinnGen participants were recruited from hospital biobanks and disease-based cohorts, which may lead to an overestimation of disease risk. Finally, the bidirectional relationship between CVD and dementia must be considered. A pre-existing diagnosis of dementia has been associated with adverse outcomes in the CVD spectrum [36–38]. Strengths of the study include the population-wide source of information with complete coverage since 1998, lifelong follow-up, the good ability to examine AD and VD separately and the estimation of sex differences. In contrast to previous studies that examined different CVDs separately and often in diseased individuals, we further had the opportunity to perform parallel analyses across all major CVDs.

Conclusions

In population-based health register data, all major CVDs were associated with a significant increase in the risk of dementia, particularly VD. Apart from stroke and TIA, which have a direct pathophysiological link to cerebral damage and cognitive decline, AF and HF were most strongly related to incident dementia. However, the underlying biological mechanisms require further investigation. From a clinical perspective, our findings indicate that CVD onset should prompt the treating physician to assess the cognitive status and take measures to prevent dementia onset. If required, a multidisciplinary approach should be adopted to reduce the burden of dementia on the population.

Author contributions

Anni Kauko: Conceptualisation; formal analysis; methodology; data curation; visualisation; writing – original draft. **Daniel Engler:** Project administration; writing – review and editing. **Alfredo Ortega-Alonso:** Methodology; supervision; validation; writing – review and editing. **Teemu Niiranen:** Funding acquisition; supervision; validation; writing – review and editing. **Renate B. Schnabel:** Funding acquisition; supervision; validation; writing – original draft.

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Conflict of interest statement

RBS received consulting fees and speaker honoraria from BMS/Pfizer. VS reports personal fees from Sanofi and a grant from Bayer Ltd. outside the submitted work.

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Data availability statement

Due to the sensitive nature of the data collected for this study, requests to access the dataset may be submitted through the Finnish Biobanks Finngenious Portal (https://site.fingenious.fi/en/).

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1: Coding of variables and diagnoses in FinnGen.
Table S2a: The characteristics table of the study sample by exposures for any dementia. Follow-up spanned from the year 1998 (or birth) to the year 2021, death or to the outcome event.
Table S2b: The characteristics table of the study sample by exposures for the Alzheimer's disease. Follow-up spanned from the year 1998 (or birth) to the year 2021, death or to the outcome event.
Table S2c: The characteristics table of the study sample by exposures for the vascular dementia. Follow-up spanned from the year 1998 (or birth) to the year 2021, death or to the outcome event.
Table S3: The characteristics table of the study sample by sex. Events prior to the first dementia diagnosis are shown for exposures and covariates.
Table S4: The characteristics table of the study sample by the age at the start of follow-up. Individuals have been divided to two groups by the end of fourth quintile (57 years). Events prior to the first dementia are shown for exposures and covariates.
Table S5: Incidence of dementia per 1000 person-years by exposure category.
Table S6: Multivariable-adjusted Cox models for incident dementia, Alzheimer's dementia, and vascular dementia. Disease variables were treated as time dependent covariates. Provided are hazard ratios (HR) and 95% confidence intervals (CIs).
Figure S1: Visualization of raw data by Kaplan-Meier curves for any dementia, Alzheimer's dementia, and vascular dementia for major cardiovascular diseases: atrial fibrillation, heart failure, myocardial infarction, stroke, TIA, peripheral arterial disease by sex.
Figure S2: Forest plot of multi-variable-adjusted Cox models for time-dependent cardiovascular disease and incident a) dementia, b) Alzheimer's dementia, c) vascular dementia for major cardiovascular diseases: atrial fibrillation, heart failure, myocardial infarction, stroke, TIA, peripheral arterial disease by sex.
Figure S3: Visualization of raw data by Kaplan-Meier curves for any dementia, Alzheimer's dementia, and vascular dementia for major cardiovascular diseases: atrial fibrillation, heart failure, myocardial infarction, stroke, TIA, peripheral arterial disease by age. Individuals were divided into two groups by the end of fourth quintile: a) Start of follow-up <57 years and b) start of follow-up ≥ 57 years.
Figure S4: Forest plot of multi-variable-adjusted Cox models for time-dependent cardiovascular disease and incident dementia, Alzheimer's dementia, vascular dementia for major cardiovascular diseases: atrial fibrillation, heart failure, myocardial infarction, stroke, TIA, peripheral arterial disease by the age. Individuals were divided into two groups by the end of fourth quintile: a) Start of follow-up <57 years and b) start of follow-up ≥ 57 years.
Figure S5: Visualization of raw data by Kaplan-Meier curves for any dementia, Alzheimer's dementia, and vascular dementia for major cardiovascular diseases: atrial fibrillation, heart failure, myocardial infarction, stroke, TIA, peripheral

arterial disease with one-year lag time. Individual was removed from the analysis, if time between exposure event and dementia or other end of follow-up was less one year.

Figure S6: Forest plot of multi-variable-adjusted Cox models for time-dependent cardiovascular disease and incident dementia, Alzheimer's dementia, vascular dementia for major cardiovascular diseases: atrial fibrillation, heart failure, myocardial infarction, stroke, TIA, peripheral arterial disease with one-year lag time. Individual was removed from the analysis, if time between exposure event and dementia or other end of follow-up was less one year. ■

