Published in final edited form as:

Alzheimer Dis Assoc Disord. 2010 ; 24(3): 213–219. doi:10.1097/WAD.0b013e3181d1b99b.

Non-Stroke Cardiovascular Disease and Risk of Alzheimer's Disease and Dementia

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Abstract

Unresolved issues in dementia research include 1) the association between non-stroke cardiovascular disease (CVD) and Alzheimer's disease (AD) and 2) whether the association between CVD and dementia is mediated by familial factors (i.e. genes and early life environment). We therefore conducted a study with both a longitudinal and a co-twin control design in 2,214 Swedish twins with clinical dementia evaluation and *APOE4* genotyping. The analyses were then replicated in a register-based cohort of 18,405 individuals. Results show that CVD increases the risk of AD in carriers (but not non-carriers) of the *APOE4* allele (Hazard Ratio [HR] 2.39, 95% confidence interval 1.15-4.96). CVD was also associated with an almost two-fold increased risk of developing late-life dementia (HR 1.83, 1.23-2.72). Within twin pairs, the dementia-affected twin was more likely to have had CVD than the non-demented twin partner (Odds Ratio 1.86, 1.11-3.13). In conclusion, this study shows that 1) non-stroke CVD increases the risk of late-life dementia but that it is only a risk factor for AD in carriers of the *APOE4* allele and 2) the association between CVD and dementia is not explained by genetic or early life environmental factors in common to both disorders.

Keywords

Alzheimer's disease; cardiovascular disease; risk factor; *APOE*; longitudinal; co-twin control

Introduction

Cardiovascular disease (CVD) and risk factors for CVD have been linked to cognitive impairment and dementia.¹⁻⁵ CVD is a well established risk factor for vascular dementia (VaD) but the association with Alzheimer's disease (AD) remains unclear.

The main underlying cause of CVD is atherosclerosis.⁶ It has been hypothesized that atherosclerosis-induced brain hypoperfusion, oxidative stress and/or inflammation could contribute directly to the development of the neuropathology in AD.⁷ However, CVD and AD are both prevalent diseases in elderly people and co-exist in a large proportion of individuals with late-onset dementia. Accordingly, many elderly persons with clinical dementia have both AD-type and vascular brain lesions.^{8,9} An alternative explanation is thus that CVD is simply a comorbid process that increases the likelihood of a dementia diagnosis in patients with sub-clinical AD pathology.¹⁰

The apolipoprotein E epsilon 4 allele (*APOE4*) is the most well-established genetic risk factor for sporadic AD.¹¹ However, the role of *APOE4* in the association between CVD and AD is still unclear. *APOE4* has been linked to CVD, although this association has recently come in to question.¹² Studies indicate that *APOE* contributes to AD pathology through direct effects on amyloid beta processing and neurotoxicity¹³ and not through enhanced atherosclerosis and cardiovascular disease.^{14,15} Some studies have also found that there is an interaction between *APOE4* and CVD on AD risk,^{16,17} while others have not.^{1, 3}

Familial factors are important in the development of both dementias and CVD and it has therefore also been proposed that an association between CVD and dementia could be explained by confounding from sharing of genetic or familial environmental risk factors.¹⁸ Twin pairs discordant for CVD and dementia provide an exceptional setting to control for such confounding; if the twin with dementia is more likely to have had CVD than the non-demented twin partner, this provides strong support for the explicit contribution of CVD on the development of dementia.

In this study we have analyzed a population-based sample of 2,214 twins who participated in longitudinal studies of aging that included clinical dementia evaluation. First, we estimated the impact of CVD on the risk of dementia and the major sub-types of dementia diagnosis, AD and VaD. Second, we evaluated whether the association between CVD and dementia is explained by *APOE4*-genotype. Third, to evaluate whether the association between CVD and dementia can be explained by familial predisposition to disease, we performed twin pair analyses. Fourth, in order to test whether the impact of CVD on dementia risk is detectable also at the population level, we replicated our analysis in a large register-based cohort of 18,405 individuals.

Methods

Study population

The Swedish Twin Registry (STR) is a population-based national register including over 170,000 Swedish twins born from 1886 to 2000.¹⁹ For this study we included all 2,287 twins (henceforth referred to as the “clinical cohort”) with cognitive data from the three separate longitudinal studies of aging with clinical dementia evaluation that have been conducted within the STR: 1) The Swedish Adoption/Twin Study of Aging (SATSA)²⁰, 2) Origins of variance in the Old Old: Octogenarian Twins (OCTO-Twin)²¹ and 3) Aging in Women and Men (GENDER)²². All three studies have been described in detail elsewhere. In brief, SATSA is an ongoing study of like-sex pairs aged 50 years or more. The first face-to-face examination was conducted in 1986-1988 with follow-ups every three years (except for 1995-1997). There is now information on cognitive status on 1087 individuals. OCTO-Twin included 702 individuals from like-sex twin pairs where both had survived to the age of 80 years with a baseline examination in 1991-1994 and four follow-ups on a two-year rolling schedule. GENDER consists of cognitive testing of 498 twins from unlike-sex pairs born 1916-1925 with both members of the pair alive and willing to participate in 1995. Two follow-up occasions of testing took place in 1999-2001 and 2003-2004.

Assessment of dementia

Dementia was ascertained in the “clinical cohort” through a two-step procedure which entailed, first, a cognitive screening and, second, diagnostic assessment of each suspected case.²³ Screening and diagnostic assessment at baseline and follow-up occasions were similar in all three studies and have been described in detail previously.^{24, 25} In brief, the Mini-Mental State Examination (MMSE)²⁶ was used to screen for dementia. In SATSA, all twins who screened positive for suspicion of dementia (and their twin partners) were given a complete clinical work-up including physical and neurological evaluation, a complete history based on informant interviews, neuropsychological assessment, laboratory tests and neuroimaging. In OCTO-twin and Gender, the diagnostic assessment of dementia was based on reviews of medical records (from both in- and outpatient settings), the results on cognitive tests, biochemical blood values, and informant interviews. In all three studies, the final diagnoses of dementia were set at a multidisciplinary consensus conference. Dementia was diagnosed according to the criteria in the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised (DSM-III-R)²⁷ and fourth edition (DSM-IV)²⁸ and differentially diagnosed as AD (based on the NINCDS/ADRDA criteria)^{29, 30}, vascular dementia (based on the NINDS-AIREN criteria)³¹, mixed dementia (AD+VaD), other specified dementia, or unspecified dementia.

Assessment of CVD

Information on CVD was gathered through linkage to the National Patient Register (NPR). The NPR contains data on admission dates, primary diagnosis, secondary diagnoses and surgical procedures for all individuals admitted to hospital.³² The NPR was established in 1964 and reached complete nationwide coverage in 1987. CVD was assessed through extraction of all International Classification of Diseases (ICD) codes for angina pectoris (AP), myocardial infarction (MI), atherosclerosis, claudication, ischemic heart disease (IHD) and the surgical procedures coronary artery by-pass graft (CABG) and percutaneous transluminal coronary angioplasty (PTCA) (ICD codes 410-414, 420, 440, 443, 450, 453, I20-I25, I70, I73, 3068, 3127, 3141, 3158, FNC10-60, FNC96, FND10-20, FND96, FNE00-20, FNE96, 3080, 984, FNG00, FNG02, FNG05, FNG0). Analyses used two categories—total CVD (including MI) and MI alone—since MI is an acute condition that requires hospitalization and has been shown to have high sensitivity and specificity in the NPR.³³

Covariates

Age at baseline, sex, history of smoking (ever vs. never) and level of education (less than elementary school vs. more than elementary school) were based on self-reported data. Body mass index (BMI) (25 or more kg/m² vs. less than 25 kg/m²) was based on clinical measurements in twins who underwent clinical dementia evaluation. Data on diabetes and stroke were derived from the NPR, ICD-codes 260, 250, E10-E14 and 330-332, 334, 430, 431, 433, 434, 436, I60, I61, I63, I64, respectively. Information on *APOE* genotype (at least one *APOE4* allele vs. no *APOE4* alleles) was available for 1623 twins who had donated a blood sample. In total, there were 2,121 individuals with data on educational attainment, 1,921 individuals with smoking data and 1,662 individuals with BMI data.

Analyses

Baseline was defined as January 1st, 1974 (more than half of the Swedish counties were then covered by the NPR).³⁴ From the 2,287 twins with cognitive data we excluded 12 individuals due to death or dementia prior to baseline and 61 twins whose dementia onset preceded their first record of CVD in the NPR, leaving 2,214 in the final study population (313 monozygous [MZ] pairs, 718 dizygous [DZ] pairs, 5 pairs with unknown zygosity and 142 single twins). A part of this sample, i.e. like-sexed pairs born 1903-1936 (N=1,053), is also included in the register-based study population (by design).

Statistical analyses—All analyses were performed using the statistical software package SAS v 9.1 and v 9.2. Relative risks were estimated as Hazard Ratios (HR) in a Poisson regression model (PROC GENMOD with DIST=Poisson and OFFSET=natural logarithm of time at risk). Time at risk was calculated as years from baseline to the date of the first record of dementia, last date of follow-up, other causes of dementia (e.g. hydrocephalus), or end of study on December 31st, 2003 (the last occasion the STR was updated against the causes of death register). The Lexis macro³⁵ was used to split the underlying time scale (time since entry into study). CVD was analyzed as a time-dependent variable, i.e. a person negative for CVD contributes time-at-risk to the CVD-negative group until the first record of CVD in the NPR, at which point that individual will start to contribute time-at-risk to the CVD-positive group. Testing the proportional hazards assumption revealed that the effect of CVD on dementia risk was affected by time since CVD and a second time scale (time since CVD) was therefore introduced. HRs were thus estimated by including (time since exposure)*CVD interaction terms (<= 3 years and >3 years since exposure) in the same model. We adjusted for correlated twin data using generalized estimating equations (GEE) (REPEATED SUBJECT=identification number unique to each twin pair, TYPE=exchangeable).

Co-twin control analysis—The co-twin control design capitalizes on pairs who are discordant for both the exposure and the outcome. In this longitudinal setting, pairs in which both twins eventually developed dementia were treated as discordant pairs; the twin with the earliest age of dementia onset was defined as the case and the partner (with a later age of onset) as the control. This is equivalent to a nested case-control study with age as the timescale and matched on twin pair. Only pairs where the partner to the demented proband was alive and non-demented at the time the proband developed dementia were included. CVD data on both twins in the pair were collected until the date the proband developed dementia. Twin pairs were analyzed using conditional logistic regression (PROC LOGISTIC with STRATA=identification number unique to each twin pair).

Register Cohort, N=18,405

We replicated our analysis in a large population-based sample of 18,405 twins (henceforth referred to as the “register cohort”) for whom dementia diagnoses were ascertained through register linkage. The register cohort included all twins born 1903-1936 that responded to a questionnaire in 1967 or 1973 regarding health related information with special attention to cardiovascular health. Cohort compilation and analyses were identical to those for the clinical cohort with the exceptions described below.

The outcome of interest was defined as hospitalization with dementia and was ascertained through linkage to the NPR and extraction of all primary and secondary diagnoses of AD (ICD codes 305, 290, 331, F00, G30), VaD (306, 293, 290E, F01) and other dementias not due to exogenous factors or tumors. Information on dementia was complemented with data from the Causes of Death Register (CDR). The CDR contains information on the date of death and underlying and contributory causes of death and the register has more than 99% overall completeness since 1961.³⁶ A “surrogate” date of dementia hospitalization was calculated for those twins who only had a dementia diagnosis in the CDR (N=153) (thus lacking a date of dementia hospitalization) by deducting three years from the date of death. Three years was the average time between the *first hospitalization with dementia* and *death with dementia* in those twins (N=273) who had a record of dementia in both the NPR and the CDR.

The health questionnaire data provided by the twins in 1967 or 1973 was used to 1) complement CVD data in the NPR with self-reported information on ever having had angina pectoris and/or a myocardial infarction in order to also include CVD occurring in younger ages and, 2) extract (self-reported) covariate information similar to that in the “clinical cohort”.

Twins in the “register cohort” were followed for dementia through linkage to the NPR and CDR from the age of 60 to 65 years (depending on when the NPR became complete in the county of residence) until December 31st, 2003. The upper limit of 65 years at baseline was imposed in order to minimize risk of including twins who had already developed dementia.

The study sample was compiled by including all 26,486 twins born from 1903 to 1936 who responded to questionnaires in 1967 or 1973. Individuals were then excluded due to one or more of the following: missing CVD data in the questionnaires (N=2,583), an age above 65 years at baseline (N=3,797), loss to follow-up (N=151), dementia at baseline (N=64), death prior to baseline (N=2,062) or dementia onset preceding the first record of CVD in the NPR (N=103), leaving 18,405 twins in the final study population (2767 MZ pairs, 4839 DZ pairs, 175 pairs with unknown zygosity and 2843 single twins).

Results

Population characteristics

Of the 2,275 twins initially included in the “clinical cohort”, 494 (21.7%) received a diagnosis of dementia, 251 at the first wave of dementia testing and 243 at follow-up. Of the twins with a dementia diagnosis, 133 (26.9%) were at some point hospitalized with CVD, 72 before dementia onset and 61 twins after dementia onset. Of the 72 twins with CVD *before* dementia, 48.6% received a diagnosis of VaD and 33.3% a diagnosis of AD. Of the 61 twins with CVD *after* dementia, 23.0% received a diagnosis of VaD and 62.3% received a diagnosis of AD ($p=.0006$). Twins diagnosed with AD were hospitalized with CVD on average 1.4 years *after* AD diagnosis whereas twins diagnosed with VaD were hospitalized with CVD on average 4.8 years *before* VaD diagnosis ($p<.0001$).

The sixty-one twins with a dementia onset preceding hospitalization with CVD were excluded, leaving 433 twins with dementia in the analysis. Dementia sub-type was available for all twins and the diagnosis were as follows: 242 possible or probable AD, 113 possible or probable VaD, 11 mixed (AD+VaD) and 67 not otherwise specified dementia (NOS) (Table 1).

During the follow-up period until 31st December 2003, 409 (18.5%) twins in the “clinical cohort” were admitted at least once to hospital with a primary or secondary diagnosis of CVD. AP and MI made up the largest proportion of CVD diagnoses, 115 (28.1%) had a diagnosis of both AP and MI, 134 (32.8%) had AP but not MI, 107 (26.2%) had an MI but not AP and 53 (13.0%) had only a diagnosis of atherosclerosis, claudication, IHD, CABG or PTCA. Stroke was not included in the CVD variable, but 105 (25.7%) individuals of those positive for CVD (N=409) were also hospitalized with stroke, compared to 207 (11.5%) of the non-CVD (N=1,805) part of the sample ($p<.0001$).

In order to evaluate if our findings were related to the effect of *APOE4* on the timing or severity of CVD, we looked at age at first hospitalization with CVD and the number of hospitalizations with CVD. We found no significant differences in timing of CVD between carriers and non-carriers of *APOE4*: *APOE4* carriers were on average 74.5 years at first hospitalization with CVD, non-carriers 74.8 years ($p=0.78$). Nor did we find a significant difference in the number of hospitalizations (in those ever hospitalized): *APOE4* carriers were hospitalized with CVD or stroke on average 4.5 times, non-carriers 4.4 ($p=0.89$).

Risk of dementia, AD and VaD

CVD was associated with an almost doubled risk of dementia (HR 1.83, 95% CI 1.23-2.72) during the first three years since the first hospitalization with CVD and a more than three-fold increased risk of a diagnosis of VaD (3.64, 2.01-6.57) whereas there was no significant increased risk of a diagnosis of AD (1.48, 0.83-2.64) (Table 2). Relative risk estimates

decreased with longer follow-up time since hospitalization with CVD (interaction term HR 0.97 per year, $p=0.22$).

APOE4—Including *APOE4*-genotype as a covariate in the model had no effect on the relative risk of CVD on dementia/AD. However, there was a significant interaction between *APOE4* and CVD on the risk of AD (interaction term HR 2.98, $p=0.05$) but not on all dementias (1.31, $p=0.40$) or VaD (0.76, $p=0.61$). Stratifying on *APOE4* genotype revealed that the association between CVD and dementia/AD during the first three years since hospitalization with CVD was present only among carriers of at least one *APOE4* allele, HR 2.37 (1.34-4.22) for all dementias and 2.39 (1.15-4.96) for AD (in *APOE4* non-carriers: 1.45 (0.76-2.75) and 0.76 (0.24-2.42) for all dementias and AD, respectively). Risk estimates for VaD were similar regardless of *APOE4*-status, 3.36 (1.15-9.79) and 3.90 (1.73-8.82) in the *APOE4* positive and negative and groups, respectively.

Age—Twins under the age of 75 years at the first hospitalization with CVD had a higher risk of any dementia (2.61, 1.25-5.44) and VaD (7.68, 3.26-18.08) compared to twins 75 years and older, 1.57 (0.99-2.51) and 2.08 (0.96-4.54) respectively. For AD, the trend was reversed HR 0.54 (0.08-3.90) before the age of 75 and 1.66 (0.93-2.99) thereafter.

We also performed additional analyses that had no effect on the relative risk estimates: 1) To evaluate an effect of CVD on dementia risk that is not mediated by stroke, we reran our analysis excluding prevalent stroke cases and censoring incident stroke. 2) We excluded fatal MIs (defined as death within a month of hospitalization with MI). 3) Adjustments for sex, educational level, BMI, smoking and diabetes in those with complete covariate information ($N=1,215$) had no effect on the HRs.

Risk of dementia, AD and VaD in co-twin control analyses

CVD was more likely to have been present in the twin who developed dementia than in the twin partner who survived to the same age (Tables 3 and 4). The results were very similar to those found in the survival analysis of the full “clinical cohort”; the most elevated ORs were observed for VaD and there were no significant findings for AD. Among identical twin pairs, no twin without CVD developed VaD. This result is consistent with the full twin sample, but makes it impossible to estimate an OR.

Register Cohort

Compared to the clinical cohort, the register cohort was 5.1 years older at baseline ($p<.0001$), 3.8 years younger at first CVD ($p<.0001$), 1.7 years younger at dementia onset ($p<.0001$), 7.8 years younger at death ($p<.0001$), had 8.1 years shorter follow-up time ($p<.0001$), a higher burden of CVD ($p<.0001$), a larger proportion of men ($p<.0001$) and ever smokers ($p<.0001$) (Table 1).

Age-adjusted HRs are shown in Table 2. CVD was associated with an almost doubled risk of dementia during the first three years since CVD and a 43% increased risk during the following 10 years. HRs decreased with longer follow-up time (interaction term HR 0.97 per year, $p<0.0001$) and the age-adjusted relative risk of dementia attributable to CVD after more than 13 years declined to 1.25 (1.04-1.50). Excluding individuals with a history of stroke at baseline and censoring follow-up time after an incident stroke had no effect on the associations between CVD and dementia. Including stroke as a covariate in survival analysis had a marginal effect on the estimates, HR of CVD on dementia decreased from 1.48 (1.14-1.94) to 1.42 (1.08-1.85) for the entire follow-up period.

Additional adjustments for sex, educational level, smoking, BMI and diabetes had little effect on the estimates. The multi-adjusted relative risk (HR with 95% CI) of dementia during the first three years since CVD was 1.65 (1.27-2.13) and during the following 10 years 1.42 (1.17-1.74).

Discussion

In two large population-based samples with long-term follow-up we were able to show that non-stroke cardiovascular diseases (CVD) can double the risk of late-life dementia. However, non-stroke CVD was only a significant risk factor for a diagnosis of Alzheimer's disease (AD) in individuals carrying the *APOE4* allele. Also, by using a co-twin control design, we could show that a twin with dementia is more likely to have had CVD than is his or her non-demented identical twin partner, suggestion that the association between CVD and dementia is not confounded by genetic and early life environmental factors. We were also able to show, consistent with findings from the Rotterdam study,³ that the relative risk of dementia due to CVD is attenuated over time, perhaps as a consequence of the impact of CVD on mortality risk.

Recent data show that late-life dementia often represents a mix of AD and vascular pathology.^{37, 38} Our results raise a question whether CVD might skew differential diagnosis of dementia towards VaD. In our sample, one fourth of twins diagnosed with AD were at some point in life hospitalized with CVD, but less than 40% of them had been hospitalized *before* their AD diagnosis compared to VaD, where more than 70% were hospitalized before their VaD diagnosis. It is thus possible that the impact of CVD on the clinical manifestation of AD is underestimated due to diagnostic bias.

In this study we were interested in estimating an effect of atherosclerotic disease on the risk of dementia/AD that is not mediated by the acute trauma to the brain that is stroke.³⁹ Thus, we did not include stroke in our definition of CVD. However, given that coronary heart disease and peripheral vascular disease are associated with stroke incidence⁴⁰, we also performed additional analyses to adjust for the possible indirect effect of stroke on our estimates. We excluded prevalent stroke cases, censored incident stroke cases, and also included stroke as a covariate in the model. None of these adjustments had a substantial effect on our risk estimates. Our data thus suggest that CVD is not only a risk factor for dementia/AD in that it is associated with stroke but that, even in the absence of stroke, atherosclerotic disease appears to be a risk factor for dementia/AD.

Our study suggests that CVD increases the risk of dementia through the cardiovascular disease per se. Similar results in the cohort analyses and the within twin pair analyses suggest that the association between CVD and dementia is not confounded by genetic or early life environmental factors. If confounding was present and the association was attributable to genes or early life exposures in common to both diseases, any (false) positive associations found in the cohort analyses would not be seen in the co-twin control analyses.

The role of *APOE4* in the association between CVD and AD has long been subject to debate. In line with previous findings,^{14,15} this study supports the hypothesis that *APOE4* is a risk factor for AD through other pathways than CVD since the three-fold elevated risk of AD attributable to *APOE4* remained also when adjusting for CVD (data not shown). However, we did find evidence that *APOE*-genotype modifies the effect of CVD on AD risk (CVD was only a risk factor for AD in *APOE4* carriers). This effect modification was not attributable to indicators of CVD severity, such as an earlier onset of CVD or more frequent hospitalizations for CVD; there were no significant differences in age at hospitalization with CVD or the number of hospitalizations with CVD between *APOE4* carriers and non-carriers. Our interpretation of

these findings is that carriers of the *APOE4* allele are more vulnerable to the burden of CVD and less resilient to withstand the impact of atherosclerotic disease on cognition.

There are some limitations to this study that deserve mentioning. Given the relatively high age of the study population at the beginning of follow-up, it is likely that a proportion of those classified as negative for CVD at baseline are, in fact, CVD-positive. If such misclassification is present, the true relative risk of dementia due to CVD would be higher than what we have presented here. Furthermore, twins had to survive to a certain age to be eligible for participation. Since it is likely that individuals affected by both CVD and dementia will be removed from the source population at a faster rate than individuals with only one (or none) of the diseases, it is possible that we have underestimated the proportion of individuals with both CVD and dementia.

Epidemiological research using national disease registers such as the NPR and CDR offers the advantage of cost-effective large population-based studies over a long period. For acute conditions, like MI, the register data has both high sensitivity and specificity³³ but for non-acute conditions, like dementia, the sensitivity is usually lower. However, validation studies suggest that the registers are suitable for studies of dementia but that presence of false negative cases (low sensitivity) might dilute the risk estimates towards the null.⁴¹

In conclusion, the present study shows that non-stroke CVD is a risk factor for AD in genetically vulnerable individuals carrying the *APOE4* allele. With twin analyses, we have also shown that the association between CVD and dementia is not mediated by genetic or early life environmental factors in common to both disorders. However, we think it is important to separate the etiological from the clinical implications of this study. Given that 1) dementia often represents a mix of AD- and vascular pathology and 2) patient *APOE* genotype is not usually known, cardiovascular disease prevention should be of interest in all individuals as a possible means of reducing risk for dementia, irrespective of dementia sub-type.

Acknowledgments

This study was supported by grants from the National Institutes of Health (AG08861, AG04563, AG10175, AG08724), the Swedish Council on Social Research, the MacArthur Foundation Research Network on Successful Aging, the Axel and Margaret Ax:son Johnsons Foundation, the Swedish Foundation for Health Care Sciences and Allergy Research, and the Swedish Research Council.

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Table 1

Basic demographics

	CLINICAL COHORT N=2,214			REGISTER COHORT N=18,405		
	All dementias N=433	Alzheimer's Disease N=242	Vascular dementia N=113	No dementia N=1,781	No dementia N=17,211	All dementias N=1,194
CVD	72 (16.6)	24 (9.9) *	35 (31.0) *	337 (18.9)	5,271 (30.6)	370 (31.0)
MI	37 (8.6)	10 (4.1) *	21 (18.6) *	185 (10.4)	3,083 (17.9)	197 (16.5)
women	299 (69.1) *	186 (76.9) *	60 (53.1)	1,038 (58.3)	9,536 (55.4)	759 (63.6) *
education (low)	307 (78.1) *	180 (83.7) *	78 (72.9) *	1,072 (62.0)	9,974 (63.2)	701 (69.8) *
smoking (ever)	116 (33.8) *	58 (32.0) *	39 (40.6)	701 (44.4)	8,493 (50.1)	526 (44.1) *
BMI (>25)	121 (47.1)	62 (40.5) *	27 (49.1)	713 (50.8)	5,651 (33.3)	456(38.7) *
diabetes (ever)	64 (14.8) *	26 (10.7)	27 (23.9) *	174 (9.8)	1,937 (11.3)	178 (14.9) *
APOE4	163 (48.5) *	106 (53.0) *	31 (37.8) *	328 (25.5)	—	—
age at baseline	61.4 (6.9) *	62.4 (6.7) *	59.8 (7.2) *	53.8 (10.7)	60.4 (1.0)	60.7 (1.3) *
follow-up time	19.3 (6.4) *	18.0 (6.5) *	20.9 (5.7) *	25.2 (5.5)	15.8 (7.0)	18.1 (6.4) *
age at CVD in NPR	74.2 (7.7)	78.9 (4.7) *	71.5 (7.5)	74.4 (9.5)	70.4 (9.1)	73.4 (8.0) *
age at dementia onset	80.7 (6.9)	80.4 (7.5)	80.8 (6.0)	—	—	78.8 (6.7)
age of death	87.5 (5.8) *	88.3 (6.0) *	86.1 (5.4) *	85.0 (7.9)	77.3 (8.5)	82.6 (6.2) *

Abbreviations: CVD, Cardiovascular Disease; MI, Myocardial Infarction; BMI, Body Mass Index; APOE4, apolipoprotein E4; NPR, National Patient Register. Number of exposed individuals (percent of number of individuals with covariate data) for binary variables and mean age/time in years (SD) for continuous variables.

* Significant difference compared to the No dementia group, alpha=0.05.

Table 2
Hazard Ratios from Poisson regression

	CLINICAL COHORT N=2,214			REGISTER COHORT N=18,405
	<i>AD</i>	<i>VaD</i>	<i>All dementias</i>	<i>All dementias</i>
CVD				
first 3 yrs after exposure	1.48 (0.83-2.64)	3.64 (2.01-6.57)	1.83 (1.23-2.72)	1.98 (1.57-2.49)
>3 yrs after exposure	0.67 (0.37-1.21)	2.63 (1.62-4.25)	1.32 (0.95-1.83)	1.43 (1.20-1.72)
MI				
first 3 yrs after exposure	0.91 (0.35-2.35)	4.64 (2.40-8.96)	1.88 (1.15-3.09)	2.22 (1.69-2.91)
>3 yrs after exposure	0.64 (0.27-1.53)	2.17 (1.09-4.31)	1.07 (0.64-1.79)	1.29 (1.01-1.65)

Age-adjusted hazards ratios (HR) with 95% confidence interval (CI) from Poisson regression with a (time since exposure)*CVD interaction.
Abbreviations: AD, Alzheimer's disease; VaD, vascular dementia; CVD, cardiovascular disease; MI, myocardial infarction; yrs, years.

Table 3

Discordant twin pairs

		CLINICAL COHORT						REGISTER COHORT	
		AD		VaD		All dementias		All dementias	
		MZ + DZ	MZ	MZ + DZ	MZ	MZ + DZ	MZ	MZ + DZ	MZ
CVD	Tot number of twin pairs, N	20	7	26	6	63	18	195	58
	Dementia in twin with CVD, N (%)	11 (55)	4 (57)	20 (77)	6 (100)	41 (65)	12 (67)	110 (56)	37 (64)
	Dementia in twin without CVD, N (%)	9 (45)	3 (43)	6 (23)	0 (0)	22 (35)	6 (33)	85 (44)	21 (36)
MI	Tot number of twin pairs, N	11	3	18	6	37	13	131	39
	Dementia in twin with MI, N (%)	7 (64)	2 (67)	16 (89)	6 (100)	26 (70)	9 (69)	69 (53)	27 (69)
	Dementia in twin without MI, N (%)	4 (36)	1 (33)	2 (11)	0 (0)	11 (30)	4 (31)	62 (47)	12 (31)

Total number of twin pairs discordant for both CVD and dementia and the distribution of dementia within the pair.

Abbreviations: AD, Alzheimer's disease; VaD, vascular dementia; MZ, monozygous twin pairs; DZ, dizygous twin pairs; CVD, cardiovascular disease; MI, myocardial infarction.

Table 4
Odds ratios from co-twin control analyses

CLINICAL COHORT										REGISTER COHORT					
AD					VaD					All dementias			All dementias		
MZ + DZ		MZ		HRs	MZ + DZ		MZ		HRs	MZ + DZ		MZ		HRs	95% CI
HRs	95% CI	HRs	95% CI		HRs	95% CI	HRs	95% CI		HRs	95% CI	HRs	95% CI		
CVD	1.22 (0.51-2.95)	1.33 (0.30-5.96)	3.33 (1.34-8.30)							1.86 (1.11-3.13)	2.00 (0.75-5.33)	1.29 (0.98-1.72)	1.76 (1.03-3.01)		
MI	1.75 (0.51-5.98)	2.00 (0.18-22.06)	8.00 (1.84-34.79)							2.36 (1.17-4.78)	2.25 (0.69-7.31)	1.11 (0.79-1.57)	2.25 (1.14-4.44)		

Odds ratios (OR) with 95% confidence interval (CI) by dementia subtype and zygosity groups.
* Among identical twin pairs, no twin without CVD developed VaD which makes it impossible to estimate an OR. Abbreviations: AD, Alzheimer's disease; VaD, vascular dementia; MZ, monozygous twin pairs; DZ, dizygous twin pairs; CVD, cardiovascular disease; MI, myocardial infarction.