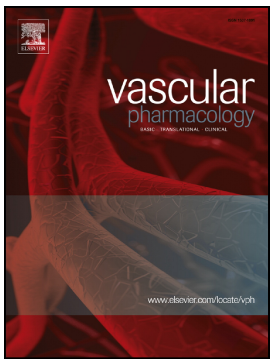

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Beta-Blocker Therapy and Risk of Vascular Dementia: a Population-Based Prospective Study

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Abstract

There are a few studies that report cognitive impairment as a complication of treatment with beta- blockers. We aimed to evaluate the longitudinal association between use of beta-blockers, as a class, and incident risk of all-cause dementia, vascular dementia, Alzheimer and mixed dementia in the prospective population-based Malmö Preventive Project. We included 18,063 individuals (mean age 68.2, males 63.4%) followed up for 84,506 person-years. Dementia cases were retrieved from the Swedish National Patient Register and validated by review of medical records and neuroimaging data. We performed propensity score matching analysis, resulting in 3,720 matched pairs of beta-blocker users and non-users at baseline, and multivariable Cox proportional-hazards regression. Overall, 122 study participants (1.6%) were diagnosed with dementia during the follow-up. Beta-blocker therapy was independently associated with increased risk of developing vascular dementia, regardless of confounding factors (HR: 1.72, 95%CI 1.01-3.78; p=0.043). Conversely, treatment with beta-blockers was not associated with increased risk of all-cause, Alzheimer and mixed dementia (HR:1.15; 95%CI 0.80-1.66; p=0.44; HR:0.85; 95%CI 0.48–1.54; P=0.59 and HR:1.35; 95%CI 0.56–3.27; p=0.50, respectively). We observed that use of beta-blockers, as a class, is associated with increased longitudinal risk of vascular dementia in the general elderly population, regardless of cardiovascular risk factors, prevalent or incident history of atrial fibrillation, stroke, coronary events and heart failure. Further studies are needed to confirm our findings in the general population and to explore the mechanisms underlying the relationship between use of beta- blockers and increased risk of vascular dementia.

Key words: vascular dementia; beta-blocker; Alzheimer; mixed dementia.

Introduction

Dementia is a general term for neurodegeneration marked by the development of multiple cognitive deficits such as the ability to memorize, learn, perceive and process information [1]. Since the number of people affected by dementia is expected to increase rapidly [2], the research to find different pathological mechanisms for prevention has been intensified [3]. Previous studies have revealed a possible relationship between blood pressure (BP) changes and the risk of developing dementia [4, 5]. A decline in blood pressure between middle-and advanced age, and lower BP in advanced age have been disclosed as independent risk factors of incident dementia [6]. A theory has been proposed that blood pressure reduction causes a decline in cerebral perfusion, which has previously been emphasized as an important factor in the pathology in vascular dementia[7].

Hence, antihypertensive treatment (AHT) which is commonly used among elderly individuals has been suggested to be implicated in dementia risk as the blood pressure lowering effect may reduce the cerebral perfusion [8]. A systematic review including fifteen randomized clinical trials studying the impact of different AHTs on cognition in older individuals without dementia reported an improvement in episodic memory in patients treated with angiotensin receptor blockers versus placebo or other types of antihypertensive drugs [9]. However, the knowledge is sparse on the adverse effects of AHT including potential harms such as orthostasis, fatigue, and depression, which can negatively impact daily functioning and quality of life [10]. Studies investigating the AHT effect on cognitive function have so far provided contradictory conclusions, as AHT have both shown to preserve the cognitive function and reduce it [11, 12]. Beta-blockers (BB) are commonly used as medication in hypertensive patients [13]. However, cerebral side effects, including sleep disturbances, dizziness, tiredness, depression, hallucinations, nightmares, low energy, somnolence/lethargy [14], have long been recognized as complication to beta blockade, particularly for the lipophilic

agents as propranolol [15]. Most studies appointing the linkage between treatment with beta blockers and cognition are focused on beta blockade risk to impair separate cognitive functions and not dementia [16]. Therefore, the aim of this study is to explore the relationship between beta blockade and dementia risk in older individuals.

Material and Methods

Study population

The Malmo Preventive Project (MPP) was funded in the mid 1970s at the Malmo University Hospital in purpose to explore CV risk factors in general population [17]. Between 2002 and 2006, a total of 18,240 individuals from the original cohort were re-examined and beta blocker (BB) use, as well as other antihypertensive medications, was ascertained. Patients with prevalent stroke (n=61), incident stroke prior to dementia diagnoses (n=99), and prevalent dementia (n=17), were excluded from analyses. In a propensity score matching procedure, 7,440 representative individuals were included and represent the current study population. The study population was separated into 2 groups (Figure 1) with equal number of patients including BB users (n=3,720) and non-users (n=3,720). All participants who attended the rescreening program gave an informed consent and were thus eligible for the study of dementia [18]. The study complied with the Declaration of Helsinki, and the protocol was approved by the regional Ethical Review Board in Lund (LU 244-02).

Dementia diagnosis

Information about dementia diagnosis was requested from the Swedish National Patient Register (SNPR) and covered the period from baseline through Dec 31, 2009. The diagnoses in the register were coded according to the International Classification of Diseases (ICD 8th, 9th, and 10th revisions). Since 1987, SNPR includes all in-patient care in Sweden and, in addition, contains data on outpatient visits including day surgery and psychiatric care from

both private and public caregivers recorded not earlier than in 2001. Of note, primary care is not yet covered in the SNPR. Dementia diagnoses were validated by a thorough review of medical records as well as neuroimaging data when available. A research physician assigned the final diagnosis for each patient and a geriatrician specialized in cognitive disorders was consulted in unclear cases. All-cause dementia was diagnosed according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised (DSM-IIIR) [19]. Alzheimer dementia and vascular dementia diagnoses adhere to the DSM-IV criteria [20]. Mixed dementia was applied when both Alzheimer and cerebrovascular pathology were assumed to contribute to the symptoms. 471 individuals had a dementia diagnose registered in SNPR. Of these, 66 cases were classified as validated dementia diagnoses in the beta blockade group and 56 in the non-treatment group.

Statistical analysis

Quantitative variables were summarized as mean and standard deviation (SD) or median and interquartile range (IQR) according to their distribution. Qualitative variables were summarized as frequency and percentage. In order to compare outcomes between beta-blocker users (BB+) and beta blocker non-users (BB-), a propensity score matching procedure was performed using a multivariable logistic model with 8:1 greedy matching algorithm with no replacement [21]. All baseline variables included in the matching model are presented in Table 1. The adequacy of covariate balance in the matched sample was assessed via standardized mean differences between the two groups, with differences of less than 10% indicating a good balance [22]. Patients for whom no match was found, were discarded from the matched analyses. Rates of overall survival were estimated by means of the Kaplan–Meier method and were compared between beta-blocker users and non-users with the use of the log-rank test. The Schoenfeld residuals test was performed to check the proportional hazards

assumption. Cox proportional- hazards models were performed to estimate hazard ratios with 95% confidence interval (HR 95%CI). Two type of models were performed: the first predictive model of dementia status was performed with beta-blocker use as independent variable adjusted only for propensity score. The second model was performed in the same way, adding incident heart failure, incident atrial fibrillation and incident coronary event as covariates. Only the BMI variable had missing values (96 patients, 0.53%). Missing values were handled with multiple imputation technique using chained equations [23]. All variables used as covariate in the matching procedure were included in the imputation model. 2-tailed P-values less than .05 were considered significant. In order to perform a sensitivity analysis, the E-value for all models was computed, according to VanderWeel's formula[24-26]. The E-value is defined as the minimum strength of association that an unmeasured confounder would need to have with both the treatment and the outcome to fully explain away a specific treatment–outcome association, conditional on the measured covariates. The statistical analysis was performed using IBM SPSS Statistics v23.0 software (SPSS Inc. Chicago, Illinois, USA).

Results

Baseline characteristics

The study population included 18, 063 patients (mean age was 68.2±5.8 years; 63.4% males) (Table 1). Study participants who received dementia diagnosis were older (73.1 vs 68.1 years), more likely to be women (43.8% vs 36.5%) and more frequently treated with acetylsalicylic acids (ASA) and statins. The propensity score analysis resulted in 3,720 matched pairs of beta- blocker users and non-users at baseline (Figure 1, Table 2). In the unmatched population, BB+ were more frequently diabetic and more frequently users of angiotensin converting enzyme inhibitors, diuretics, aspirin, nitroglycerine and statins. After

matching, there were no differences in the baseline characteristics between the two groups (Table 2), with all standardized mean differences below 0.10.

Beta-blocker use and risk of incident dementia

During 84,506 person-years follow-up, 66 BB+ patients (1.8%) and 56 BB- patients (1.5%) received a diagnosis of dementia, as showed in Table 3. Interestingly, BB+ patients more frequently developed vascular dementia, as shown by the Kaplan-Meier estimate (Log-rank Test p-value=0.036) (Table 3 and Figure 2). In Cox proportional hazard models (Table 4), use of BB was independently associated with a two-fold increase in vascular dementia (HR:1.97; 95%CI 1.01-3.27, p= 0.046). These results were confirmed in the multivariate analysis after adjustment for incident atrial fibrillation, incident coronary event, incident stroke and incident hearth failure (HR:1.72; 95%CI 1.01-3.78, p=0.048). Conversely, treatment with BB was not associated with increased risk of all-cause, Alzheimer and mixed dementia (HR:1.15; 95%CI 0.80-1.66; p=0.44; HR:0.85; 95%CI 0.48–1.54; P=0.59 and HR:1.35; 95%CI 0.56–3.27; p=0.50, respectively).

Discussion

In this study we have observed that use of beta-blockers is associated with a two-fold increased risk of subsequent vascular dementia in the general elderly population. However, use of this class of medication did not increase the risk of other dementia subtypes, including Alzheimer and mixed dementia.

The prevalence of dementia increases exponentially with advancing age [27],whilst its prevention and treatment constitute a serious global health issue [28]. Cardiovascular (CV) risk factors such as smoking, dyslipidemia, and prevalent CV disease have been associated with increased incidence of dementia [29]. Further, hypertension in mid-life has been reported to

increase the risk of developing dementia in later life [30] and several studies have concluded that lowering the blood pressure have protective effects on cognition and reduce the risk of dementia development [12, 31]. Antihypertensive treatment (AHT) has therefore been suggested as an accessible strategy to reduce the incidence of dementia [12]. The protective role of AHT on dementia risk might be explained by reducing the risk of other cardiovascular morbidities associated with dementia including heart failure, stroke and vascular disease [32]. However, in patients with prevalent dementia, systemic blood pressure has been reported to be declined compared to healthy age-matched individuals, indicating that AHT might come with the adverse effect of aggravating the cognitive function rather than to improve it [33].

In this study, only treatment with beta blockade did significantly increase the risk of vascular dementia. Use of beta blockers implies a higher burden of cardiovascular disease which is the underlying pathology for vascular dementia. Therefore, the association between treatment with beta blockers and incident vascular dementia seen in the current study, might just indicate a higher prevalence of cardiovascular disease. Furthermore, increased survival due to effective AHT might conceal positive effects on cognition.

For several decades, beta blockade treatment has been a crucial part of the routine treatment for hypertension, mainly through binding to adrenergic receptors (ADRs) and by that inhibiting central and peripheral effects of noradrenaline (NA) and adrenaline (AD) [13]. Adrenergic receptors are G-protein coupled receptors (GPCR) which are extensively expressed throughout the body and involved in multiple physiological processes including cardiac muscle contraction, airway reactivity, cognition, stress-related behavior, and inflammation [34]. There are three main ADR classes including beta 1-adrenergic receptor (B_1-ADR) which is mainly expressed in the heart and brain, beta 2-adrenergic receptor (B_2-ADR) found in various body tissues, and B_3 -adrenergic receptor (B_3 -ADR) which is expressed

mainly in adipose tissue [35]. The receptor subtypes differ from each other not only by location but also by involvement in diverse physiological processes [34]. The selectivity of different ADR binding agents is therefore of great importance in aim to find potential drug targets for prevention of diseases associated with NA and AD system dysfunction [34]. Hence, the beta blockade effect is not merely determined by location binding site throughout the body but also by which ADR subtype it attaches to. Entailed side effects of beta blockade treatment have been reported from the cardiovascular, respiratory and gastrointestinal systems [36]. The impact of beta blockade treatment on cognitive function has so far provided contradictory conclusions, as beta blockade has both shown to preserve the cognitive function and reduce it [16, 37, 38]. To illustrate this, attenuated memory ability has been observed in both rodents and humans treated with the selective B_1- ADR antagonist propranolol whereas infusion of B_1-ADR agonist led to memory enhancement [39]. In addition, stimulation of B-ARs in the dentate gyrus improves long-term potentiation and ameliorates the late-phase memory in the hippocampus [35]. To our knowledge, this study is the first to report that beta blockade increases the longitudinal risk of dementia in the general population. Our results are consistent with those of a recent observational study aimed to assess the functional decline in a population of long-stay nursing residents (mean age 84 years), treated or not with BB, after acute myocardial infarction [40]. Patients treated with beta-blockers showed a higher rate of functional decline compared with non-users. Interestingly, the observed risk was greater for nursing residents with moderate-to- severe cognitive impairment or functional disabilities at baseline [40]. Potential theories to explain these associations include both indirect effects on the cerebral hemodynamics but also direct effects mediated by the blockade of adrenergic signaling pathways in the central nervous system (CNS). By binding to beta adrenergic receptors in the heart, beta-blockers provide a negative chronotropic and inotropic effect resulting in decreasing blood pressure, heart frequency and cardiac output [41]. Declined cardiac

output caused by BB has been shown to reduce both cerebral blood flow and cerebral oxygenation [42]. Since vascular dementia occurs as a result of cerebral ischemia, the reduced cerebral oxygenation observed in individuals with beta blockade might serve as a possible explanation why beta blockade comes with higher risk of vascular dementia. With advancing age, the vascular elasticity and the arterial compliance is reduced leading to a failure of the autoregulatory capabilities of cerebral arteries [43]. The cerebral autoregulation is responsible to maintain the cerebral perfusion hence fluctuations of the blood pressure. The cerebral perfusion pressure is preserved between 60 and 160 mmHg of systemic MAP [44]. Below 60 mmHg, the cerebral autoregulation collapses and the reduction of blood flow is compensated for by enhanced oxygen extraction [45]. If the improved oxygen extraction fails to deliver enough amount of oxygen to cerebral tissues, cerebral hypoxia ensues which may result in irreversible tissue damage and development of dementia [46]. To illustrate this, nocturnal dips in diastolic blood pressure level has been associated with reduced cerebral perfusion [47].

Growing evidence suggests that ADRs located in the CNS possess important regulating abilities for cognitive and behavioral functions [48]. Noradrenaline containing neurons have proved to be highly involved in consolidation of the memory capacity through signaling in locus coeruleus and hippocampus [49]. Locus coeruleus which is the center of cells producing norepinephrine in the CNS is of great importance for many fundamental brain functions, including attention, sleep, arousal, mood regulation, learning, and memory [50]. From locus coeruleus, noradrenergic pathways are going to amygdala, hippocampus and neocortex, the foremost brain areas involved in AD [35]. Hypothetically these activities might be negatively affected by the use of lipophilic beta-blockers with the ability to cross the blood-brain barrier and bind to beta adrenergic receptors in the brain [51]. It has been recently reported that, in a rat model in which persistent long-term depression was achieved by perforant path-dentated gyrus stimulation, isoproterenol, a B-ADR receptor agonist, reinforced the duration of long-

term depression, a key process linked to memory processes, for over 24h [52]. In the same animal model, the infusion of propranolol, a non-selective highly lipophilic B-ADR receptor antagonist, counteracted the positive effect of beta-adrenergic pathway in hippocampus synaptic plasticity and information processing. In addition, B_1-ADRs have been suggested as potential therapeutic targets for treatment of cognitive dysfunction in Alzheimer dementia. Involved in the regulation of neuroinflammatory processes, B_1-ADR possess neuroprotective properties. By activating B_1-ADR in an AD animal model, cognitive function was improved and beta-amyloid burden decreased [34]. Interestingly, in a mouse model of AD chronic treatment with xamoterol, a selective B_1-ADR partial agonist reduced the increase of neuroinflammation induced using dsp4, a toxin which depletes NA neurons in the LC, by restraining microgliosis and astrogliosis [53]. Astrocytes, which are the most abundant cell types in the CNS [54], represent an important structural and functional component of the so called "neurovascular unit", with their end-feet specialized processes ensheathing brain arterioles and capillaries [55]. They are known to provide metabolic support to neurons, but also to play an active role in many neurophysiological and neuropathological events [56]. Astrocytes express high density of adrenergic receptors, including B-ADR [57], whose activation stimulate cAMP levels and mediate several NA effects including: i) attenuation of neuroinflammation; ii) increase in the production of neurotrophic factors; iii) modulation of glycogenolysis (absent in neurons) and iv) induction of morphological changes [58]; such events may modulate neuronal circuits and play a role in curbing the development and/or progression of cognitive impairment and dementia. Furthermore, lipophilic BBs, which are able to cross the blood-brain barrier, could also negatively affect the beneficial noradrenergic modulation of glial activation.

The mechanism behind BB-induced cognitive impairment has also been argued to be caused by reduced production of melatonin through inhibition of B_1-ADR. In two placebo-controlled studies exploring the association between beta blockade treatment and CNS side effects in hypertensive patients discovered that decreased melatonin concentration in urine was directly related to CNS side effects during BB treatment [59]. Interestingly a reduction in melatonin levels has also been reported to correlate with AD and melatonin supplementation has been shown to delay the progression of mild cognitive impairment patients to AD [60]. The role of melatonin in improving cognitive deficit has been recently described in an animal model of ischemic vascular dementia [61].

Finally, impaired angiogenesis in the brain has been proposed as a contributor to the progression of cognitive dysfunction, especially in AD and vascular dementia. Angiogenesis is under the influence of VEGF (vascular endothelial growth factor) which is reported with increased intrathecal concentrations in patients with vascular dementia compared to healthy controls [62]. Since administration of beta receptor antagonists have been shown to reduce VEGF concentrations it has been suggested that treatment with beta-blockers inhibit the angiogenesis [62].

Strengths and limitations

The principal strengths of this study include the large and well-characterized study population, the extensive follow-up time, as well as the reliability of the prospective data collection protocol of our registries. Since primary care is not covered in the SNPR, an underestimation of dementia cases is possible. The degree of such an underestimation has been reported in studies based on hospital discharge diagnosis, but not in the setting of hospital-based outpatient care[63, 64]. The number of dementia cases reported in these studies was indeed lower than in our study population. With regards to the identification of dementia

cases in the population, it has been shown that SNPR yields a sensitivity ranging between 23 and 55%.

In this study, the follow-up time from betablocker identification to dementia diagnosis was rather short. It can be assumed that covert VaD pathology might have been present for several years before a clinical diagnosis could be done, and that beta blockade treatment could have been administered to individuals with concealed dementia. Importantly, no mechanistic conclusions can be drawn on how beta blockade might contribute to the increased risk of vascular dementia.

The association between beta blocker treatment and incident dementia was on the verge of statistical significance; however, the matching procedure and the E-value analysis would make a false positive result less likely. In the re-screened subset of the MPP cohort (n=18,240) that constituted our study population, we obtained information regarding use of different antihypertensive medications, but only beta blocker treatment demonstrated a significant relationship with incident dementia in the Cox regression models. The objective in the current study was to explore how beta blocker treatment was related to incident dementia. As dementia due to stroke is common we decided to exclude participants with stroke in order to handle confounding. Furthermore, we cannot rule out residual confounding. No information was available regarding polypharmacy[65], use of anticholinergics[66], and subclasses of beta-blocker, hence the observed relationship between BB and dementia may not necessarily fall into a "class effect", but rather be a distinct "molecular effect". To the best of our knowledge, there is no previous studies reporting the possible effect of different beta blocker classes on dementia risk.

Furthermore, we acknowledge that despite the matching procedure, unmeasured confounders might still affect the results, including the certainty of the diagnosis, the lack of information

about other type of treatments, the selection of participants into the cohort and the nonuniform follow-up.

Finally, the study population is of European ancestry and the results are not generalizable to other ethnic groups.

Conclusions

We observed that beta-blocker treatment among older adults is independently associated with higher risk of incident vascular dementia, but not with increased risk of other dementia subtypes, including Alzheimer and mixed dementia. Further investigations are needed to confirm our findings in the general population and to study the mechanistic underpinnings of the complex interactions of beta-blocker medications in the central nervous system both in appropriate animal models of cerebral hypoperfusion and Alzheimer dementia, and in significant cell systems.

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Competing interests: The authors declare no competing interests.

Ethical approval: The study was approved by the Regional Ethical Review Board in Lund (LU 244-02).

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Tables

Table 1. Baseline characteristics of study population.

Baseline characteristics	Study population (n=18,063)	Dementia + (n=249)	Dementia - (n=17,814)
Age, mean±SD	68.2±5.8	73.1±4.4	68.1±5.7
BMI, mean±SD	27.2±4.4	25.7±3.9	27.2±4.4
Gender, n (%)			
Male	11,447 (63.4)	140 (56.2)	11,307 (63.5)
Female	6,616 (36.6)	109 (43.8)	6,507 (36.5)
Medical history, n (%)			
Current smoker	2,453 (13.6)	32 (12.9)	2,421 (13.6)
Diabetes	2,004 (11.1)	31 (12.4)	1,973 (11.1)
Prior Heart Failure event	1 (0.0)	-	1 (0.0)
Prior atrial fibrillation/flutter	16 (0.1)	-	16 (0.1)
Prior coronary event	23(0.1)	-	23 (0.1)
Drugs, n (%)			
Beta-blocker	3,839 (21.3)	67 (26.9)	3,772 (21.2)
ACEI	2,953 (16.3)	39 (15.7)	2,914 (16.4)
CCB	1,796 (9.9)	27 (10.8)	1,769 (9.9)
Diuretics	2,341 (13.0)	41 (16.5)	2,300 (12.9)
ASA	3,535 (19.6)	78 (31.3)	3,457 (19.4)
Digoxin	173 (1.0)	4 (1.6)	169 (0.9)
Nitrates	662 (3.7)	14 (5.6)	648 (3.6)
Statin	3,574 (19.8)	69 (27.7)	3,505 (19.7)

ACEI, angiotensin converting enzyme inhibitor; ASA, acetylsalicylic acid; BMI, body mass index; CCB, calcium channel blocker; SD, standard deviation.

Table 2. Propensity score matching model.

	Unmatched Population (n=18,063)		Matched Population (n=7, 440)		Standardized mean difference
	BB+ (n=3,839)	BB- (n=14,224)	BB+ (n=3,720)	BB- (n=3,720)	
Age, mean±SD	69.4±5.7	67.9±5.7	69.4±5.7	69.6±5.7	-0.03
BMI, mean±SD	28.3±5.4	26.9±4.0	28.2±4.4	28.1±4.4	0.01
Gender, n (%)					-0.04
Male	2,540 (66.2)	8,907 (62.6)	2,458 (66.1)	2,382 (64.0)	
Female	1,299 (33.8)	5,317 (37.4)	1,262 (33.9)	1,338 (36.0)	
Medical history, n (%)					
Current smoker	386 (10.1)	2,067 (14.5)	379 (10.2)	381 (10.2)	-0.00
Diabetes	715 (18.6)	1,289 (9.1)	678 (18.2)	655 (17.6)	0.02
Prior Heart Failure	-	1 (0.0)	-	-	-
Prior atrial Fibrillation or Flutter	6 (0.2)	10 (0.1)	6 (0.2)	6 (0.2)	0.00
Prior coronary event	10 (0.3)	13 (0.1)	7 (0.2)	8 (0.2)	-0.01
Drugs, n (%)					
ACEI	1,255 (32.7)	1,698 (11.9)	1,172 (31.5)	1,128 (30.3)	0.03
CCB	807 (21.0)	989 (7.0)	744 (20.0)	753 (20.2)	-0.01
Diuretics	1,096 (28.5)	1,345 (9.8)	1,016 (27.3)	983 (26.4)	0.02
ASA	1,694 (44.1)	1,841 (12.9)	1,596 (42.9)	1,496 (40.2)	0.05
Digoxin	98 (2.6)	75 (0.5)	89 (2.4)	68 (1.8)	0.04
Nitrate	409 (10.7)	253 (1.8)	310 (8.3)	232 (6.2)	0.09
Statin	1,679 (43.7)	1,895 (13.3)	1,575 (42.3)	1,487 (40.0)	0.05

ACEI, angiotensin converting enzyme inhibitor; ASA, acetylsalicylic acid; BMI, body mass index; CCB, calcium channel blocker; SD, standard deviation.

Table 3. Treatment with beta-blockers across different subtypes of dementia.

Dementia subtypes	BB+ n (%)	BB- n (%)	p-value*
Overall Dementia	66 (1.8)	56 (1.5)	0.332
Vascular Dementia	26 (0.7)	13 (0.3)	0.034
Alzheimer Dementia	20 (0.5)	26 (0.7)	0.392
Mixed Dementia	20 (0.5)	17 (0.5)	0.249

*Log-rank Test.

Table 4. Relationship between beta blocker treatment and risk of dementia subtypes in unadjusted and multivariable-adjusted Cox regression model.

Dementia subtypes	Model 1		p-value[1]	E-value	Model 2		p-value[1]	E-value
	β (SE)	HR (95%CI)			β (SE)	HR (95%CI)		
Overall Dementia	0.17 (0.18)	1.18 (0.83-1.69)	0.102	1.64 (1.33-2.77)	0.13 (0.19)	1.15 (0.80-1.66)	0.442	1.57 (1.00-2.71)
Vascular Dementia	-0.68 (0.34)	1.97 (1.01-3.27)	0.046	3.35 (1.11-5.99)	0.51 (0.35)	1.72 (1.01-3.78)	0.048	2.83 (1.11-7.02)
Alzheimer Disease	0.25 (0.30)	0.78 (0.44-1.40)	0.406	1.88 (1.00-3.97	-0.15 (0.30)	0.85 (0.48-1.54)	0.599	1.63 (1.00-3.59)
Mixed Dementia	0.17 (0.33)	1.18 (0.62-2.25)	0.617	1.64 (1.00-3.93)	0.14 (0.34)	1.35 (0.56-3.27)	0.501	2.04 (1.00-5.99)

Model 1: Beta-blocker use and propensity score as independent variables.
Model 2: Beta-blocker use, propensity score, incident stroke, incident atrial fibrillation, incident coronary event and incident hearth failure as independent variables.
[1]: p-value referred to beta-blocker use.

Figure 1. Flow diagram of the study population.

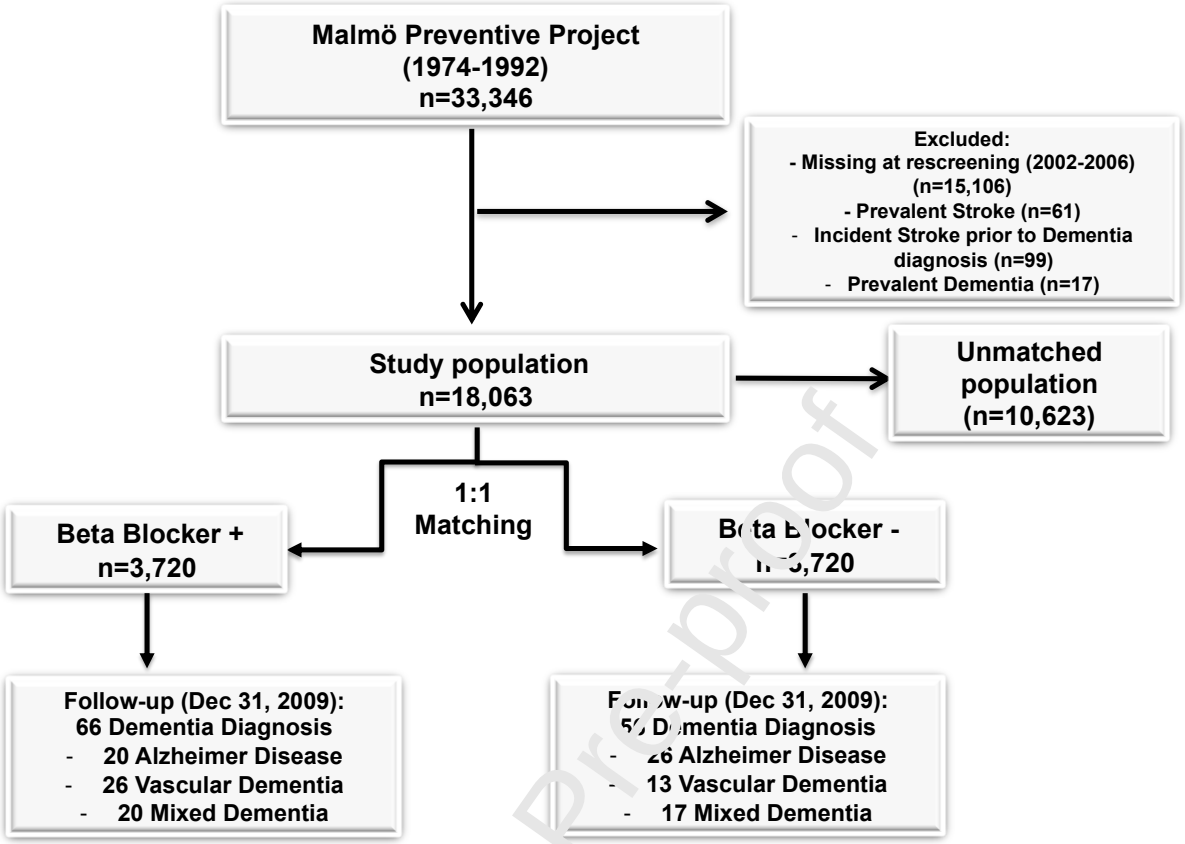

Figure 2. Kaplan-Meier curves for cumulative incidence of A) all-cause dementia B) vascular dementia C) Alzheimer dementia and D) mixed dementia incidence by use of beta-blocker medications.