PHARMACOLOGICAL PREVENTION OF DEMENTIA

A pharmacoepidemiological approach in The Rotterdam Study

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With respect to the **cover,** the author acknowledges Dr. Joe Rogers, Dr. Ron Strohmeyer and Dr. Scott Styren of the Sun Health Research Institute in Sun City, USA. The photo represents GFAP immunoreactive astrocytes co-localized with a neuritic plaque in the Alzheimer's disease cortex. The astrocytes appear as dark black and the plaque is labeled with thioflavine fluorescence and therefore has a white cotton ball appearance.

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Voor
Laure,
Jesse
en Mels

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Chapter 1

GENERAL INTRODUCTION

Dementia is a common and disabling disorder in the elderly. Because of the worldwide increase of the proportion of elderly in the population, dementia is of growing public health relevance.

Alzheimer's disease, the most common dementia subtype, is characterized by progressive loss of memory and cognitive function and affects an estimated 15 million people worldwide. The incidence increases sharply from 0.5% per year at the age of 65 to nearly 8 percent per year at the age of 85 (1). As people with Alzheimer's disease usually survive for approximately a decade, prevalence increases from 3% at 65 years of age to almost 50% at age 85 (1). With increasing longevity of the population and decreasing birth rates, the prevalence will continue to rise. In Alzheimer's disease several deficiencies of neurotransmitter systems, such as the cholinergic neurotransmission, have been found (2). Cerebral extracellular β-amyloid deposition as senile plaques and intraneuronal neurofibrillary tangles appear to represent critical processes in the development of these deficiencies (3).

Early treatment of Alzheimer's disease would be important as it might reduce cognitive and behavioural symptoms of this disease and it might slow disease progression, thereby alleviating some of the social and economic costs. However, currently available treatments for patients with Alzheimer's disease mainly focus on the cholinergic pathway. Because of the limited efficacy of these treatment modalities they must be viewed as palliative (4).

Knowledge on potential alternative therapeutic strategies for the prevention of Alzheimer's disease is mainly based on observational studies in subjects with prevalent dementia. As these studies often have methodological shortcomings valid risk estimates are scarce.

This thesis concerns the role of certain chronically used drugs in the development of Alzheimer's disease. The aim was to assess the contribution of different types of drugs in the prevention of Alzheimer's disease, and to determine candidate drugs for future investigation or preventive use. Hereto, the literature on Alzheimer's disease and potentially protective drug effects was reviewed (chapter 2). In chapter 3 the results of a study on the association between NSAID and risk of dementia are described, with a focus on duration of use (3.2 and 3.3) and misclassification of exposure (3.1 and 3.3). In chapter 4 the effects of antihypertensive drugs on dementia and its subtypes are discussed. Subsequently, in chapter 5, we report on the risk of Alzheimer's disease in women reporting prior use of hormone replacement therapy. All studies presented in chapters 3 to 5 were conducted in The Rotterdam Study, which is a prospective population-based cohort study of neurological, cardiovascular, locomotor, endocrinological and ophthalmological diseases in the elderly. The focus in chapter 6 is on the association between psychotropic drugs and cognitive function as examined in The Rotterdam Scan Study, a non-demented elderly sub-sample of two population-based studies. In chapter seven, after summarizing the main findings, we will discuss quantitative and qualitative problems, which are typical for

pharmacoepidemiological studies in dementia. In the end, we briefly discuss health care aspects, and potential directions for future research.

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Chapter 2

REVIEW

Pharmacological prevention of Alzheimer's disease

A review of the epidemiological evidence

ABSTRACT

In this chapter, we describe the current state of epidemiological studies on potentially efficacious drugs, not specifically designed or prescribed for the prevention or treatment of Alzheimer's disease. The focus is on the potential methodological pitfalls related to validity and precision of the various studies.

NSAID and to a lesser extent hormone replacement therapy (HRT) are the drugs which have most frequently been studied in relation to Alzheimer's disease. A protective effect was most consistently demonstrated for the long-term use of HRT. However, only two-third of the 15 studies have been positive and secondary prevention trials are inconsistent. If proven efficacious a further growth of its use seems likely. Although optimistic reviews, mainly based on studies in prevalent Alzheimer's disease, have been published on the potentially protective role of NSAID in Alzheimer's disease, not all prospective studies support this. Even when these drugs appear to be protective, large-scale preventive use in their current form is unlikely given their toxicity. However, these studies may boost the development of safer NSAID.

Studies on antihypertensive therapy and Alzheimer's disease are scanty but promising. As these drugs are of proven efficacy in cerebro- and cardiovascular disease, placebo controlled primary prevention trials are unethical and additional observational studies are needed to quantify their effect.

Free radical scavengers comprise a variety of substances. The most promising, next to HRT, are Ginkgo biloba, selegiline and vitamin C/E. Evidence is promising but too limited and too diverse to draw conclusions. However, given the good safety profile of a number of these agents, if proven efficacious, a further increase in their use is likely.

Epidemiological studies on glucocorticoids, other anti-inflammatory drugs, H2-antagonists, and benzodiazepines are inconsistent and insufficient to judge their potential contribution. As glucocorticoids are toxic and benzodiazepines addictive on long-term use, it is unlikely that these drugs will be of major value in the primary prevention of Alzheimer's disease, even when effective.

In conclusion, we are only just in the beginning of making valid and useful assessments of protective drug effects in Alzheimer's disease. Currently available studies are often vulnerable to a number of obvious and less obvious biases. Given this fact, for no agent preventive use is currently justified. For the future, placebo-controlled trials are needed but they may prove to be cumbersome. In the meantime there are a number of niches that will remain in which observational studies will be able to contribute. However, in order to further untangle these often difficult issues more uniform and more valid approaches are needed.

INTRODUCTION

Dementia is a neurodegenerative disorder characterized by changes in cognitive function and behavior. According to current diagnostic criteria, Alzheimer's disease is the most common subtype of dementia diagnosed in approximately two thirds of all cases of dementia (1). Other well known but less common forms are vascular dementia and Parkinson's dementia. Alzheimer's disease is characterized by a gradual and progressive decline of long-term episodic memory and of other cognitive domains of mental functioning (2). A diagnosis of Alzheimer's disease is considered probable when alternative causes of dementia are excluded (3, 4). Many cases of Alzheimer's disease may have important co-morbidity of clinical-, or magnetic resonance imaging detected cerebrovascular disease that could contribute to the dementia.

Age, depression, low educational level, atherosclerosis, vascular factors (5-7) and smoking (8) are associated with an increased risk of Alzheimer's disease. There are also a growing number of genetic factors that have been implicated in Alzheimer's disease, including dominant mutations (amyloid precursor protein, presenilins 1 and 2) and susceptibility genes (Apolipoprotein-E and others under investigation such as- α_2-macroglobulin) (9, 10).

Because a deficit of acetylcholine is an important characteristic of Alzheimer's disease, drug development and treatment of Alzheimer's disease has thus far primarily involved cholinesterase inhibitors, although drugs with a different mode of action are under investigation. The Food and Drug Administration approved the drugs tacrine, donepezil and rivastigmine (11). Other drugs such as selective muscarinic agonists are sometimes prescribed as supplements to these drugs.

In this review, we focus on medications not developed specifically for Alzheimer's disease but which have been reported in observational studies and trials to have a protective effect in Alzheimer's disease. We focus on primary prevention of Alzheimer's disease, not on related outcomes such as cognitive impairment, or other dementia such as vascular dementia. The drugs we examine are estrogens, in the form of hormonal replacement therapy (HRT); non-steroidal anti-inflammatory drugs (NSAID) and aspirin, steroids and other "anti-inflammatory agents"; antihypertensive agents; histamine-2-receptor (H2) antagonists; benzodiazepines; and free radical scavengers.

First, we discuss the methodological issues related to the interpretation of observational studies of drugs and the risk of Alzheimer's disease. Then, we discuss the putative biological mechanisms by which different drugs are thought to modulate Alzheimer's disease expression, and the relevant prevalence and incidence studies and trials for each class of drugs. Finally, we summarize the overall evidence and discuss possible implications for future development of pharmacological intervention against Alzheimer's disease.

METHODOLOGICAL CONSIDERATIONS

Validity

A number of biases have been described for epidemiological studies (12). There are, several biases that are particularly important to the interpretation of studies on drug exposure and Alzheimer's disease (13). Roughly they can be categorized as selection bias related to survival and to inclusion into the study; information bias by (mis)classification of exposure; and confounding by factors related to whether or not someone receives a medication (confounding by indication, severity or co-morbidity).

Selection bias

Selection bias may occur when the use of a drug leads to a difference in survival between cases and non-cases. For example, a drug may slow progression of disease that is differentially distributed between cases and controls. Or, inappropriate drug intake as a consequence of cognitive problems in the pre-clinical phase of Alzheimer's disease could lead to severe adverse effects and a lower survival. In a study based on prevalent cases this may lead to the conclusion that the drug protects against Alzheimer's disease. Selection bias may also occur if cases and controls are drawn from different source populations (14, 15). For example, studies based on cases referred to health services may be subject to selection bias if cases and controls differentially use one type of health service over another (16). Subjects taking a certain drug for other reasons may have other health-care-seeking behavior than Alzheimer's disease patients who do not have problems that require the drug.

Diagnostic bias is a special case of biased selection into a study population. In studies of Alzheimer's disease, persons taking drugs against cardio- or cerebrovascular disease may be excluded from a diagnosis of Alzheimer's disease a priori.

Information bias

A major concern is the potential for misclassification of exposure of drugs. Exposure includes drug compounds, frequency and duration of use, and route of administration. These are all elements involved in studying dose-response effects of medications. Another source of misclassification is a wrong definition of the biologically relevant exposure window relative to the onset of the disease. Alzheimer's disease is probably preceded by a long sub-clinical period, and it is very difficult to get reliable estimates of when clinical symptoms began. As a result it is difficult to determine whether the exposure preceded disease onset. One important potential source of misclassification is information from proxy informants differentially collected between cases and controls. Furthermore, ever/never drug use reported in a baseline interview is often used as an approximation of chronic use. As chronic use generally increases with age and age is the most important risk factor for Alzheimer's disease,

misclassification by such approximation may be differential. An additional source of exposure misclassification may be differences in compliance between Alzheimer's disease cases and non-cases.

Confounding by indication, severity or co-morbidity
These are of particular importance in studies of persons with compromised cognitive function. It is possible that doctors differentially prescribe drugs, depending on the patients' cognitive status. For example, cognitively intact patients may more assertively demand drugs with a putative beneficial effect against cognitive impairment. This may lead to a differential prescription of these drugs. Or, doctors may be reluctant to prescribe drugs with a high frequency of adverse reactions to cognitively impaired Alzheimer's disease patients. On the other hand, one could argue that diagnosis of cognitive impairment leads to more diagnostic tests and increased responsiveness from the patient and family members to get any preliminary promising drugs.

Bias in prevalence studies
Cross-sectional studies use existing cases and this may lead to biased estimates. Validity may be compromised by selective survival, an unclear temporal relationship, and because information is obtained from proxy informants.

Bias in incidence studies
Because of the absence of the so-called "prevalent-case bias", studies relying on incident cases of Alzheimer's disease are thought to be more valid with respect to strength and direction of the association. However, one problem that typically arises in incidence studies, is the competing risk for death. This may be an important alternative explanation for the finding that some drugs are inversely associated with onset of Alzheimer's disease. Users of certain drugs may have more co-morbidity and consequently a higher mortality rate than subjects who do not use the drugs. Users are then less frequently able to reach the endpoint of Alzheimer's disease and seem to be protected by the drug.

Precision

Sampling error is a potential problem that may arise in epidemiological studies on Alzheimer's disease, but is often not addressed. As most population-based epidemiological studies are multi-purpose and not specifically designed to study drug effects in Alzheimer's disease, sample size is often a limiting factor for studying drugs with low exposure. This is in particular a problem when dose-response is under investigation, as inability to show dose-response effects in Alzheimer's disease weakens conclusions regarding a beneficial effect.

EPIDEMIOLOGY OF DRUGS IN THE ONSET OF ALZHEIMER'S DISEASE

Hormone replacement therapy

Biological mechanism

HRT in the form of estrogen (in combination with progestins), is generally prescribed for estrogen dependent post-menopausal complaints and for the prevention and treatment of osteoporosis.

The assumption that estrogen may alter a person's risk of Alzheimer's disease is based on evidence that it directly affects neuronal function, growth and repair mechanisms (17-24). Estrogens may down-regulate β-adrenergic and serotonin 5-HT_2 receptors (25, 26), increase the release of endogenous catecholamines from the hypothalamus (27), inhibit monoamine oxidase (28) as well as enhance the amyloid precursor protein metabolism (28). Estrogen may also have antioxidant- (29) and anti-inflammatory properties (30). In addition, estrogen may alter brain activation patterns in postmenopausal women during the performance of verbal memory function (31). Finally, estrogen may be involved in the pathogenesis of Alzheimer's disease through its role in vascular disease (32).

Prevalence studies

There is evidence that the reduced production of estrogen may be linked to the onset of Alzheimer's disease. Several studies suggest that proxy measures of higher levels of exposure to estrogen -- a higher body mass index (33, 34), late age at menopause (35) and early age at menarche -- are inversely associated with the risk of Alzheimer's disease. Studies relating HRT to the risk of Alzheimer's disease have yielded inconsistent results (table 1). Initial case-control studies did show that estrogen use was inversely associated with Alzheimer's disease (36-39). However, these studies had limited measures of exposure (ever/recent), investigated the association in prevalent cases, and were designed to examine multiple risk factors. Furthermore, these earlier studies did not adequately control for potential confounders such as education and age at menopause. In later case-control studies (40-45) exposure was measured with relatively unbiased methods, for example by abstracting medical records (42). Only two studies (40, 46) were population based. These latter studies all suggested a risk reduction of approximately 50%.

Incidence studies (table 1)

In the Leisure World Cohort, an upper-middle-class elderly population, information on hormone use of non-demented women was collected during a baseline interview. Alzheimer's disease, dementia or senility were diagnosed on the basis of death certificates. Estrogen users had a significantly lower risk of Alzheimer's disease and associated disorders. The risk was lowest for those women that used HRT for the longest period in the highest dose (47). An important limitation of this study is that

TABLE 1
Studies on hormone replacement therapy (HRT).

Author/ year	Exposure	Exposure source	Design	Case source (n°)	Control source	RR/OR (95% CI) or probability
Studies in prevalent Alzheimer's disease						
Heyman 1984(38)	Ever last 3 months	Interview	Matched case-control	Epidemiologic study group (n = 28)	Community	2.32 NS
Amaducci 1986(37)	Ever HRT	Interview next-of-kin	Matched case-control	Seven centers (n = 116)	Hospital/population	Hospital 0.71 NS Population 1.67 NS
Graves 1990(39)	Ever HRT	Telephone interviews with patients and controls surrogates	Matched case-control	Clinic based (n = 60)	Friends and non-blood relatives.	1.15 (0.50-2.64)
Broe 1990(36)	Ever HRT	Interview	Matched case-control	Clinic based (n = 106)	General practice of corresponding case	0.78 (0.39-1.56)
Henderson 1994(43)	Ever HRT	Interview in non-demented and primary caregivers in AD	Case-control	Volunteer sample of consecutively enrolled women (n = 143)	Volunteer sample of consecutively enrolled women	0.33 (0.15-0.74)
Birge 1994(41)	Current use and duration of HRT	Interview	Matched case-control	Clinic (n = 158)	Clinic	0.07 (p<0.01)
Mortel 1995(42)	Ever HRT	medical record/ proxy informant	Case-control	306 subjects referred to clinic (n = 93)	Friend/relative	0.53 (0.27-0.94)
Lerner 1997(44)	Ever HRT	Interview in non-demented and primary caregivers in AD	Case-control	UK (n = 88)	UK	0.58 (0.25-0.91)
Balderischi 1998(40)	Ever HRT	Interview	Population based cohort	8 municipal population registers (n = 92)	8 municipal population registers	0.28 (0.08-0.98)
Slooter 1999(46)	Ever HRT	Interview next-of-kin	Matched case-control	All patients with early onset AD in two regions of the Netherlands (n = 109)	Municipal population register	0.44 (0.21-0.96)

Studies in incident Alzheimer's disease						
Brenner 1994(45)	All HRT before onset Oral HRT before onset	Computerized pharmacy data for maximum of 15 years	Case-control	Alzheimer's disease registry from health plan population (n = 107)	Stratified random sample of health plan population	1.1 (0.6-1.8) 0.7 (0.4-1.5)
Paganini-Hill 1996(62)	HRT ≥ 3 yrs HRT 4-14 yrs HRT ≥ 15 yrs	Interview (repetitive)	Nested matched case-control	Retirement community (n = 248)	Retirement community	0.83 (0.56-1.22) 0.50 (0.31-0.81) 0.44 (0.26-0.75)
Tang 1996(49)	HRT ≤ 1 yr HRT > 1	Interview	Prospective cohort	Medicare recipients, senior centers and elder-ly housing sites (n = 167)	Medicare recipients, senior centers and elder-ly housing sites	0.47 (0.2-1.10) 0.13 (0.02-0.92)
Kawas 1997(50)	HRT > 0-5 yr HRT 5-10 yr HRT >10 yr	Repetitive interviews	Cohort	Community volunteers (n = 34)	Community volunteers	0.44 (0.12-1.51) 0.34 (0.05-2.52) 0.50 NS
Waring 1999 (155)	HRT < 6 mos HRT ≥ 6 mos	Review of medical records	Matched case-control	Mayo clinic residents of Rochester (n = 222)	Sample from Rochester population.	0.85 (0.44-1.62) 0.42 (0.18-0.96)
Trials						
Schneider 1996 (56)	HRT/tacrine	NA	Randomized placebo-controlled secondary prevention trial	Multi-center (n = 318)	NA	Enhancement of tacrine effect by estrogens
Mulnard 2000 (57)	Randomization to placebo or estrogen Replacement Therapy (0.625/1.25 mg) for 1 year	NA	Randomized placebo-controlled secondary prevention trial in hysterectomized women	Multi-center (n = 120)	NA	Clinical Global Impression Scale (p=0.43)
Henderson 2000 (52)	Randomization to placebo or estrogen Replacement Therapy (1.25 mg) for 16 weeks	NA	Randomized placebo-controlled secondary prevention trial	Multi-center (n = 42)	NA	Alzheimer's Disease Assessment Scale NS

P = probability, NA = not applicable, NS = non-significant, UK = unknown, RR = relative risk, OR = odds ratio, CI = confidence interval.

Alzheimer's disease cases were identified on the bases of death certificates, which underestimate dementia (48).

Other prospective studies are based on clinically assessed Alzheimer's disease. In the Manhattan cohort, the relative risk of developing Alzheimer's disease for users of oral and transdermal estrogen was significantly lower after adjustment for education, ethnic group, sample source but not for other behavioral and medical risk factors. Women who had used estrogen for longer than a year had a greater reduction in risk, although confidence intervals overlapped with women who had used HRT for a shorter period of time (49). In this study, participants were sampled from Medicare recipients, senior centers and elderly housing sites. This may lead to biased estimates if a group with a different risk of Alzheimer's disease also had a different chance of getting HRT. In a sample of 472 peri- and postmenopausal women of the Baltimore Longitudinal Study of Aging, followed for up to 16 years, HRT use (45%) was prospectively documented during each visit. Although the number of cases was small (n = 34), the risk of Alzheimer's disease in users of HRT was significantly reduced; there was no effect of duration of therapy (50). In a study based on the Mayo clinic cohort there was a significantly inverse association between long-term (> 6 months) estrogen therapy and Alzheimer's disease adjusting for education and age at menopause. There was a significant trend of decreasing risk with increasing duration of use.

Trials

There are no published primary prevention data available on HRT and Alzheimer's disease. There are, however, ongoing primary prevention trials. The Women's Health Initiative Memory Study (51) is a multi-center trial designed to test the hypothesis that HRT reduces all-cause-dementia in women aged 65 years and older. This trial is designed to show a 40% risk reduction and it is anticipated that over 7500 women will be randomized. Other ongoing investigations are the Women's International Study of Long Duration Estrogen for Menopause and the Preventing Postmenopausal memory Loss and Alzheimer's with Replacement Estrogens study (52).

In several small secondary prevention trials there is some evidence that estrogen may be beneficial in improving specific cognitive domains (53-55), and that it modifies the effect of cholinesterase-inhibitors (56). These beneficial results were not confirmed in a larger more recent trial, in which a sixteen-week treatment did not improve symptoms. Moreover, in an even longer and larger trial, estrogen replacement therapy for 1 year did not slow disease progression nor did it improve global, cognitive or functional outcomes in women with mild to moderate Alzheimer's disease (57).

Although there is relatively consistent evidence of a protective effect of HRT one needs to consider the possibility of selection bias in observational studies using HRT as an exposure. Women taking HRT may be healthier in general (58-60) and subsequently have a reduced risk of Alzheimer's disease. Furthermore, a higher education

and socioeconomic status are associated with the use of HRT, both of which are associated with a reduced risk of Alzheimer's disease (61). Selection bias pertaining to HRT-users might arise from increased estrogen-related mortality due to breast cancer or trombotic complications. On the other hand if HRT has a positive prognostic effect on survival after onset of Alzheimer's disease, as suggested by some (47, 62), a prevalent series of Alzheimer's disease cases may over-represent women who use HRT. This would make it more difficult to find an association if one existed. The need for caution in interpreting results is highlighted in a large-scale secondary prevention trial on HRT-use and coronary heart disease (63). This study did not confirm a protective effect earlier found in a large number of observational studies. This suggests the possibility that undetected selection and observation biases could be responsible for the previously found lowered risk. On the other hand, the pathological substrate and therefore intervention strategies may be different once there is clinical disease.

Other problems not frequently addressed are the changing prescription habits and contents of HRT products over time. Today's HRT preparations contain more progestins (if any) than those prescribed in the last 20 years and are based on different types of estrogen. It is possible that these changes affect the efficacy of the drug.

Non-steroidal anti-inflammatory drugs and aspirin

Biological mechanism

Non-steroidal anti-inflammatory drugs (NSAID) are prescribed for a variety of conditions. The most important indications for chronic use are (inflammatory) joint diseases such as rheumatoid arthritis and osteoarthritis or other systemic diseases with joint manifestations. Short-term indications are sprains, headaches, dysmenorrhoea and dental complaints. NSAID include salicylates, phenylacetic acid derivatives, propionic acid derivatives, oxicam derivatives, pyrazolin derivatives and a small group of other compounds. At present the most frequently used NSAID are nonspecific inhibitors of both isoforms of cycloxygenase: COX-1 and COX-2.

A strong inflammatory response may be autotoxic to neurons, exacerbating the fundamental pathology in Alzheimer's disease (64). There are several theories on how NSAID (and aspirin) could alter this inflammatory course: the first is inhibition of inflammation perse through either a COX or a non-COX-dependent mechanism by directly activating the peroxisome proliferator gamma (PPAR-γ) nuclear transcription factor (65-67). This factor acts to suppress the expression of certain pro-inflammatory genes (66, 68). Another theory is that NSAID interfere in a process involving post-synaptic signaling events that use the arachidonic pathway (69).

Alzheimer's disease may also be a consequence of impaired vascular delivery of nutrients to the brain (70). Drugs like NSAID and aspirin exhibit anti-clotting properties and could thereby potentially improve disease course.

Prevalence studies

The association of anti-inflammatory therapy and Alzheimer's disease has been studied in a number of ways (table 2). Initial case-control studies examined the association indirectly by using proxies of anti-inflammatory drug use as exposure measure such as rheumatoid arthritis (36, 38, 39, 71-75). These studies have been reviewed extensively elsewhere (13, 76). Results from these studies were conflicting but also largely incomparable.

In other studies, the association between a history of anti-inflammatory drug therapy and Alzheimer's disease was studied. Several older case-control studies in which the use of analgesics (including acetaminophen) was examined were also inconclusive (37, 77). Two studies on subjects with a shared genetic background (twins and siblings) provided support for a protective role of NSAID in Alzheimer's disease (78, 79). In both studies there was evidence that (long-term) use of NSAID significantly reduced the risk of Alzheimer's disease.

A number of population-based studies on the cross-sectional association between NSAID and prevalent Alzheimer's disease show an inverse association (80-82) with an effect size ranging from 0.4 to 0.6.

Incidence studies (table 2)

Several incidence studies on the association between NSAID and Alzheimer's disease have been published (82-89). Some studies showed no association between NSAID use and the risk of Alzheimer's disease (82-84, 86, 89). Other studies showed a non-significant trend towards a reduced risk in persons with a history of NSAID use (87, 88). The relative risk of Alzheimer's disease was assessed among reported users of aspirin or other NSAID over a 16-year follow-up in the Baltimore Longitudinal Study of Aging. The risk of Alzheimer's disease decreased with increasing duration of NSAID use. Among those with two or more years of reported NSAID use, the relative risk was lower than for those with less than 2 years of NSAID use. Overall use of aspirin and acetaminophen was not associated with Alzheimer's disease (85).

Studies on NSAID are particularly vulnerable to misclassification of exposure. Because NSAID are often used periodically, and to a different extent in different age groups it is difficult to obtain reliable information on exposure. Reliable and valid data might be particularly difficult to obtain from proxy interviews.

Over the counter sales may decrease the validity of medical and pharmacy records as sources of drug exposure. In general, measurement of exposure has been a problem to some extent in all follow-up studies on NSAID. In some studies, duration was not taken into account at all (82-84, 86, 87, 89). In other studies, the methodology used to measure duration of exposure may have introduced misclassification bias. Repeated cross-sectional measurements could have led to an overestimation of drug use (85). In earlier analyses in The Rotterdam Study, the missing duration of individual prescriptions was imputed; this might have led to systematic or random misclassification (88). A problem in all these studies was that it was

unclear which particular NSAID was used by the subjects. Furthermore, only two studies (85, 88) took into account the timing of intake in relation to the time of onset; this may be important given the unknown duration of the pre-clinical period.

Finally, confounding by contraindication may be important. Due to the higher chance of adverse events in cognitively impaired subjects, doctors may be less likely to prescribe NSAID in the pre-clinical and clinical phase of Alzheimer's disease.

Trials

To our knowledge, there are no primary prevention trials published on anti-inflammatory drugs and Alzheimer's disease. A 6-month secondary prevention trial on indomethacin in Alzheimer's disease showed that patients performed significantly better after six months of therapy compared to placebo on a battery of cognitive tests (90). There were, however, a large number of participants with adverse effects and consequently there was a high dropout rate.

The efficacy and safety of diclofenac in combination with misoprostol was evaluated in 41 patients with mild-moderate Alzheimer's disease in a prospective 25-week, randomized, double-blind placebo-controlled trial (91). This small pilot study did not demonstrate a significant effect of NSAID treatment in Alzheimer's disease, but the trends observed justify further investigations with a larger number of participants. The combination of diclofenac and misoprostol seems safe in Alzheimer's disease patients, but its tolerability is not optimal. Before more definite conclusions can be drawn, results of studies on COX2-inhibitors (celicoxib/rofecoxib) have to be awaited (92, 93). It is, however, questionable whether it is valid to extrapolate findings of these trials to primary prevention. Therefore we have to await the results from a primary prevention trial currently pending (94).

Studies on aspirin have mainly focussed on stroke, showing a protective effect in secondary prevention of stroke (95). Whether and to what extent this protective effect can be extrapolated to non-vascular dementia and in particular to Alzheimer's disease remains to be elucidated.

Glucocorticoids and other anti-inflammatory drugs

Biological mechanism

Glucocorticoids are mainly used for the treatment of non-infectious inflammatory diseases and in the treatment of chronic obstructive pulmonary disease. These are potent anti-inflammatory/immunosuppressive drugs, which are also used to suppress inflammatory processes in the brain. They suppress the acute phase response neutrophil adherence and monocyte accumulation as well as inhibit prostaglandin production (30). However, doses commonly used to suppress secondary brain inflammation in other diseases are toxic on long-term treatment and lead to a high incidence of severe adverse effects like osteoporosis, behavioral disturbances and other problems (96, 97). It has been suggested that glucocorticoids may be toxic to the hip-

TABLE 2
Studies on anti-inflammatory drugs.

Author/ year	Exposure	Exposure source	Design	Case source (n°)	Control source	RR/OR (95% CI) or probability
Studies of prevalent Alzheimer's disease						
Heyman 1984(38)	Arthritis Ever use of analgesics	Interview	Matched case-control	Epidemiologic study group (n = 40)	Community	1.19 NS 1.23 NS
French 1985(72)	Arthritis Hayfever	Interview with random reconfirmation	Matched case-control	Veterans Administration Medical Center (n = 78)	Hospital- and non-hospital controls	0.62 (0.29-1.29) (HC) 2.75 (0.81-10.22)
Amaducci 1986(37)	Analgesics ever	Next-of-kin	Matched case-control	Consecutive AD patients of 7 neurology centers (n = 116)	Hospital Friend	1.21 NS 1.0 NS
Jenkinson 1989(73)	Rheumatoid arthritis	Presence of RA according to accepted criteria.	Case-control	Consecutive patients of geriatric unit (n=96)	Consecutive patients of geriatric unit	0.17 (P < 0.005)
Broe 1990(36)	Arthritis Allergies	Interview	Matched case-control	Clinic based (n = 170)	GP practice of corresponding case	0.56 (0.36-0.87) 0.97 (0.60-1.58)
Graves 1990(39)	History of steroid use Rheumatoid arthritis Hay fever	Telephone interviews with patients and controls surrogates	Matched case-control	Clinic based (n = 130)	Friends and non-blood relatives.	0.73 (0.38-1.38) 1.18 (0.35-3.91)
McGeer 1990(74)	Rheumatoid arthritis	Presence of RA	Incidence study	Clinic based (n = 4)	None but referenced to Canadian Study of Health and Aging	2.7% vs. 5.1%
Beard 1991(75)	Rheumatoid arthritis	Presence of RA	Incidence study	Clinic based (n = 23)	Reference to other clinical population	4.4% vs. 2.7%
McGeer 1992 (100)	Continuous dapsone use or closely related agents	Current use	Cohort	Living leprosy patients Japan (n = 151 all dementia)	Living leprosy patients Japan	0.63 (0.43-0.92)

Li 1992(71)	Arthritis (before onset) Analgesics (≥ 2 yrs use)	Interview of relatives	Matched case-control	Clinic based (n = 70)	Registration offices neighborhoods	0.2 (0.06-0.70) 1.0 (0.09-11.03)
Henderson 1992(77)	Analgesics (ever daily >6 mos)	Interview of an informant	Matched case-control	GP practice (n = 170) consecutive referrals	GP practice	1.4 (P = 0.05) early onset 0.5 NS late onset
Canadian Health Study 1994(80)	Arthritis NSAID Steroids.	Questionnaires completed by proxy respondents	Nested case-control	Communities and institutions (n = 224)	Communities and institutions	0.55 (0.37-0.82) 0.75 (0.39-1.46) 0.54 (0.36-1.46)
Breitner 1994(78)	Anti-inflammatory drugs (> 1 yr use; began > 2 yrs before onset)	Self-reporting or if not possible from surrogates	Co-twin control	Male and female twins from USA	Male and female twins from USA	1.0 (0.21-4.73) (male) 0.0 (0.01-0.43) (female)
Breitner 1995(79)	NSAID (duration) Steroids Aspirin	Interview of unaffected individuals and/or collateral information	Sibship study	Siblings (n=107)	Siblings	0.19 (0.06-0.64) 0.63 (0.12-2.63) 0.34 (0.14-0.84)
Rich 1995(156)	NSAID current/past 12 mos on daily basis	Interview	Cohort	Cohort of AD patients	NA	Better performance on MMSE, Boston Naming Test and others.
Andersen 1995(81)	NSAID (use in past week, dose)	Interview of subjects and/or proxy informants	Population based cohort study	Cohort (n = 339)	Cohort (total) Topical medication users (subgroup)	0.38 (0.15-0.95) 0.54 (0.16-1.78)
Endoh 1999 (101)	Dapsone, rifampicin, clofazimine, minomycin or ofloxacin	Medical files	Cohort	Leprosy patients of the national leprosarium in Tokyo (n = 35)	Leprosy patients of the national leprosarium in Tokyo	0.79 (0.53-1.84) 3.37 (1.87-5.97) <80 yrs
Studies of incident Alzheimer's disease						
Kukull 1994(83)	NSAID (5 years prior) Ever > 180 daily doses	Computerized pharmacy data	Case-control	AD patient registry HMO (n = 268)	Health Maintenance Organization	0.8 (0.6-1.2) 1.1 (0.7-1.8)

TABLE 2 – continued

Author/ year	Exposure	Exposure source	Design	Case source (n°)	Control source	RR/OR (95% CI) or probability
Fourrier 1996(83)	NSAID use (both at baseline and 1 year later)	Repetetive interviews	Prospective population based cohort study	Random sample of population of France (n = 47)	Random sample of population of France	0.98 (0.23-4.16)
BLSA(85)	NSAID (< 2yrs) NSAID (≥ 2 yrs) Aspirin (< 2yrs) Aspirin (≥ 2yrs)	Repetitive interviews	Nested Case-control in BLSA	Volunteers (n = 81)	Volunteers	0.65 (0.33-1.29) 0.40 (0.19-0.84) 0.58 (0.28-1.18) 0.82 (0.50-1.36)
Henderson 1997(86)	NSAID Aspirin	Interview	Prospective cohort study	Community	Community	NS
Beard 1998(87)	NSAID, aspirin for 7 or more days in 2 years before onset	Medical records	Matched case-control	Clinic based (n = 302)	Clinic	0.47 (0.20-1.10) NSAID 0.90 (0.51-1.59) NSAID +aspirin
Brooks 1998(82)	NSAID (current use) Aspirin	Interview	Prospective cohort study	Community (8.4 % = 53)	Community	NS
Cornelius 1998(89)	NSAID regularly taken	Interview	Prospective population based cohort study	Cohort (n = 110)	Cohort	0.8 (0.4-1.9)
In 't Veld 1999(88)	NSAID (in 10 years before diagnosis) < 2 months 2-6 months > 6 months	General practitioners medical records	Nested matched case-control study within Rotterdam Study	Cohort (n=101)	Cohort (population based)	 0.76 (0.37-1.57) 0.97 (0.44-2.17) 0.27 (0.05-1.51)
Trials						
Rogers 1993(90)	Randomization to placebo or indomethacin	NA	Placebo controlled secondary prevention trial	Volunteer AD cases (n = 44)	NA	Significantly better performance on cognitive tests (P < 0.003)

Scharf 1999(91)	Randomization to placebo or diclofenac/ misoprostol	NA	Placebo controlled secondary prevention trial	Volunteer AD cases (n = 41)	NA	Test-battery: no significant differences in intention to treat analyses
Aisen (104)	Randomization to placebo or prednisone 10 mg for 1 year	NA	Placebo controlled secondary prevention trial	Volunteer AD cases (n = 138)	NA	No difference on ADAS-cog (P = 0.16) Behavioral decline in treatment group

P = probability, NA= not applicable, NS= non-significant, UK= unknown,, RR= relative risk, OR= odds ratio, CI= confidence interval, RA= rheumatoid arthritis, ADAS-cog = Alzheimer's Disease Assessment cognitive subscale, HC= hospital control, GP= general practitioner, BLSA = Baltimore Longitudinal Study of Aging."exposure or exposure proxied by disease.

pocampus (98, 99), a vital structure in memory.

Prevalence studies

Thus far, there are only few epidemiological studies on the association between glucocorticoid use and Alzheimer's disease (table 2). In a twin study, the onset of Alzheimer's disease was inversely associated with prior concomitant use of corticosteroids or adrenocorticotropin (=ACTH) (78). In a larger study of siblings with a high risk of Alzheimer's disease, no significant difference in risk was found after exposure to glucocorticoids (79). Two other studies that were considerably larger (39, 80), one of which was population-based (80), did not find a significant association (table 2). In a recent review on the role of anti-inflammatory drugs in Alzheimer's disease, pooling of data from the above studies yielded a significant inverse association (OR 0.65) (76).

In a Japanese study on leprosy, the anti-inflammatory/bacteriostatic agent dapsone (= diaphenylsulfone) appeared to have a protective effect on dementia (100). In a more recent study from Japan of prevalent Alzheimer's disease cases in which a variety of anti-leprosy drugs were investigated this protective effect was not confirmed (101). In subjects below 80 years of age there was an increased risk of Alzheimer's disease in users. Finally, colchicine, normally prescribed for gout, has been proposed as a potential beneficial agent in Alzheimer's disease (102) and secondary prevention trials in Alzheimer's disease have been started.

Incidence studies and trials

No incidence studies have been published. Results from the secondary prevention "Multicenter Trial of Prednisone in Alzheimer's disease" (103) have recently become available (104). A total of 138 subjects were randomized either to placebo or to an initial dose of 20 mg prednisone tapered after four weeks to 10 mg and continued for a year. There were no differences in performance on the cognitive subscale of the Alzheimer's disease Assessment Scale. However, prednisone treated subjects showed behavioral decline compared to the placebo group.

Trials on other anti-inflammatory drugs, like hydroxychloroquine and colchicine have to be awaited.

Histamine-2-receptor blocking agents

Biological mechanism

H2-antagonists are frequently prescribed for duodenal ulcers, reflux esophagitis or ulcerative lesions caused by the use of NSAID. Histamine is a neurotransmitter in the brain, which has not been clearly implicated in major diseases. All histaminergic neurons reside in the posterior hypothalamus and innervate most brain areas, which is compatible with the idea that histamine is involved in general central regulatory mechanisms. A recent post-mortem study in humans suggested that a decrease

in brain histamine may contribute to the cognitive decline in Alzheimer's disease directly or through the cholinergic system (105). Furthermore, there is evidence that H2-antagonists can aggravate the neuronal damage in the hippocampus caused by ischemia (106). These latter data are in contrast to the hypothesis that H2-antagonists may inhibit the cascade leading to excitotoxic cell-death (79).

Prevalence studies

Until now, only two observational epidemiological studies have been published; one showed a protective effect of H2-antagonists independent of NSAID exposure (79), the other found no association (107) (table 3). It may be difficult to study the independent effect of H2-antagonists since previous NSAID and/or glucocorticoid use may induce the prescribing of H2-antagonists if gastrointestinal adverse effects occur.

Antihypertensives

Biological mechanism

Antihypertensives are mainly prescribed for hypertension but also after myocardial infarction to prevent the heart from remodeling (particularly angiotensin-converting-enzym inhibitors), and for post-menopausal complaints (clonidine). There is increasing evidence that hypertension may contribute to the development of cognitive impairment and dementia (108-111). This logically leads to the hypothesis that antihypertensive drugs might protect against the development of cognitive dysfunction and dementia. It is currently unclear, whether a protective effect on the brain is the consequence of the lowering of the high blood pressure or that also other mechanisms are involved (112). Another mechanism that was suggested is that some antihypertensives, i.e. calcium antagonists may beneficially influence calcium homeostasis of neurons thereby preventing or delaying onset of Alzheimer's disease (113).

Prevalence studies

Prevalence studies on the association between antihypertensive drugs and Alzheimer's disease are not available.

Incidence studies

There is little evidence of a beneficial effect of antihypertensive drugs on the risk of Alzheimer's disease (table 4). In the population-based Kungsholmen study of subjects aged 75 years and over, persons using antihypertensive medication or diuretic monotherapy at baseline had a reduced risk of developing dementia compared to non-users (114).

Observational studies on antihypertensives and Alzheimer's disease are seriously limited by confounding by indication and co-morbidity. Specific drugs are prescribed according to degree of severity and co-morbidity. Furthermore, this co-morbidity is

TABLE 3
Observational studies on H2-receptor blocking agents.

Author/ year	Exposure	Exposure source	Design	Case source (n°)	Control source	RR/OR (95% CI) or probability
Studies of prevalent Alzheimer's disease						
Breitner 1995(79)	H2-antagonists (duration)	Interview of unaffected individuals and/or collateral information	Sibship study	Siblings (n = 107)	Siblings	0.2 (0.1-0.7) 1-12 mos 0.06(0.0-0.3) > 12 mos
Launer(107)	H2-antagonists (use in past week, dose)	Interview	Population based cohort study	Cohort (n = 208)	Cohort	1.24 (0.52-2.98)

Mos = months,, RR = relative risk, OR = odds ratio, CI = confidence interval, H2-antagonists = histamine-2-receptor antagonists.

TABLE 4
Studies on antihypertensives.

Author/ year	Exposure	Exposure source	Design	Case source (n°)	Control source	RR/OR (95% CI) or probability
Studies of incident Alzheimer's disease						
Guo 1999(114)	Antihypertensive use in two weeks before interview	Interview	Prospective population based cohort study	Community cohort (n = 204 all dementia)	Community cohort	0.7 (0.6-1.0) all antihypertensives 0.6 (0.4-0.9) diuretics 0.6 (0.3-1.2) betablockers or calcium antagonists
Primary prevention trial						
Forette 1998(113)	Randomization to placebo or nitrendipine (+enalapril and/or hydrochlorothiazide if necessary)	Dispensed in trial	Randomized placebo controlled trial	People with systolic hypertension (n = 23)	NA	P = 0.05 50% lower risk

P = probability, NA= not applicable, RR= relative risk, OR= odds ratio, CI= confidence interval.

sometimes in itself associated with the occurrence of Alzheimer's disease (e.g. cardiac problems, diabetes mellitus and stroke) or death as competing risk. Another potential problem is that hypertension may lead to cognitive impairment, which appears to be associated with less compliant behavior and exposure misclassification (115). It may then be hard to determine what the actual effect of antihypertensive drugs is.

Trials

Currently, the only primary prevention trial on the association between antihypertensives use and the risk of dementia is the Systolic Hypertension in Europe Trial. In this trial of isolated systolic hypertension (160-219 mm Hg) subjects were treated with nitrendipine and, if blood pressure was not lowered sufficiently, enalapril and/or hydrochlorothiazide were added. They found that the incidence of dementia was 50% lower in the treatment group (113). It is, however, unclear whether this protective effect, if real, was a consequence of the lower blood pressure or of a specific neuroprotective effect of calcium channel-blockade (112). This was a small study, which needs to be replicated.

In a trial on stroke prevention by thiazide treatment (=diuretic) in older persons with isolated systolic hypertension, treatment significantly reduced the risk of stroke but not of cognitive impairment (116). In a secondary prevention trial sabeluzole, a new benzothiazole derivative (calcium channel-blocker), appeared to exert beneficial effects on memory in Alzheimer's disease patients (117).

It is now clear that both diastolic and systolic hypertension are associated with an increased risk of cardio- and cerebrovascular morbidity and mortality. Because of ethical problems, it is unlikely that future placebo controlled primary prevention trials will be initiated in subjects who fulfill the established criteria for treatment. Trials can only compare different antihypertensive agents, and not the overall effect of antihypertensive treatment. Large observational prospective population based studies will be needed to study the overall effect of antihypertensive drugs on Alzheimer's disease.

Benzodiazepines

Biological mechanism

Benzodiazepines are among the most frequently prescribed drugs in the elderly. Their clinical applications include administration as sedatives-hypnotics, anticonvulsants and anxiolytics. In animal models of cerebral ischemia, the inhibitory neurotransmitter γ-aminobutyric acid (GABA) and GABA-mimetic drugs (benzodiazepines) were reported to protect against neuronal damage (118-122). Benzodiazepines may protect neurons by reducing cerebral oxygen demand through reduction of synaptic transmission (123). A large number of experimental studies are available on the potential (short-term) reversible adverse effects of benzodiazepines on memory

performance (124-129). However, very little is known about the long-term cognitive effects of chronic benzodiazepine exposure.

There are no ***prevalence studies*** on the association of benzodiazepines and Alzheimer's disease. This may reflect the fact that benzodiazepines are often prescribed for behavioral and sleeping problems in Alzheimer's disease, making it impossible to study associations.

Incidence studies
The relation between the chronic use of benzodiazepines and incident dementia was examined in the Kungsholmen Study (130) (table 5). Users of benzodiazepines both at baseline and follow-up had a lower incidence of Alzheimer's disease compared to non-users, after adjusting for age, sex, education and use of NSAID and estrogen. As this is the first study on the association other studies are needed before any conclusion can be drawn. A potential threat to the validity in studies relating benzodiazepines to Alzheimer's disease is that pre-clinical symptoms in Alzheimer's disease such as sleeping problems may be treated with benzodiazepines, although such a bias would tend to overestimate the risk.

Free radical scavengers

Biological mechanism
Oxidative stress may play an important etiologic role in Alzheimer's disease (131, 132). Free radical scavengers are agents that sequester free radicals so that they do not initiate oxidative reactions that can lead to cellular damage. These free radical scavengers can be naturally occurring substances (Beta-carotene, vitamin C and E, estrogen (133, 134) and Ginkgo biloba) or synthetically prepared substances (selegiline, a monoamine-oxidase (MAO)-B inhibitor established in the therapy of Parkinson's disease, lazabemide another more selective MAO-B inhibitor (135, 136) and tenilsetam, which is believed to be an advanced glycation end products-inhibitor (137)).

Prevalence studies
Observational data on free radical scavengers and the risk of Alzheimer's disease are limited (table 6).

Incidence studies
In an analysis on data of the Rotterdam Study that included 58 subjects with incident dementia, dietary intake of anti-oxidants was not associated with a reduced incidence of dementia (133). Observational data on use of vitamin E and vitamin C supplements and incident Alzheimer's disease is reported in one study (134). In this prospective study of 633 persons of 65 years and older, a stratified random sample

TABLE 5
Studies on benzodiazepines.

Author/ year	Exposure	Exposure source	Design	Case source (n°)	Control source	RR/OR (95% CI) or probability
Studies of incident Alzheimer's disease						
Fastbom 1998(130)	benzodiazepines (regular)	Interview	Prospective population based cohort study	Cohort (n = 33)	Cohort	P = 0.012 (all benzodiazepines) P = 0.013 (hypnotics)

P = probability, RR= relative risk, OR= odds ratio, CI= confidence interval.

TABLE 6
Studies on radical scavengers and antioxidants.

Author/ year	Exposure	Exposure source	Design	Case source (n°)	Control source	RR/OR (95% CI) or probability
Studies of prevalent Alzheimer's disease						
Broe 1990(36)	Vitamin E by proxy informants	Interview	Case-control study	General practice (n = 170)	General practice	1.3 (0.6-1.65) vitamin E 1.17 (0.5-2.5) iron
Studies of incident Alzheimer's disease						
Morris 1998(134)	Vitamin C and E taken in previous two weeks	Interview with direct inspection	Prospective cohort study	Stratified sample of cohort of disease free subjects (n = 91)	Stratified sample of cohort of disease free subjects	P = 0.10 Vitamin C P = 0.04 Vitamin A
Kalmijn(157)	Anti-oxidants	Food questionnaire interview	Prospective population based cohort study	Cohort (n = 58)	Cohort	No reduction
Trials						
Haase 1996 (141)	EGb 761 i.v. 4 days per week for 4 weeks	NA	Randomized double blind secondary prevention trial	(Alzheimer, vascular, or mixed type)	NA	NAB P=0.05 CGI P=0.05 IADL
Sano 1997(142)	Selegiline (10 mg) and/or α-tocopherol (2000 IU)	NA	Randomized double blind secondary prevention trial	23 centers (n = 341)	NA	Significant delay until institution-alization for treat-ment group
Le Bars 2000 (140)	Egb 761 t.i.d. 40 mg	NA	Randomized double blind secondary prevention trial	Multicenter (n=309) (Alzheimer, vascular dementia)	NA	ADAS-cog P=0.04 GERRI P=0.007 CGI

P = probability, NA= not applicable, RR= relative risk, OR= odds ratio, CI= confidence interval. ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale, GERRI=Geriatric Evaluation by Relative's Rating Instrument, CGI= Clinical Global Impression of Change, NAB=Nurnberger-Alters-Beobachtungs-skala, IADL=Instrumental Activities of Daily Living.

was selected from a disease-free population. At baseline, all vitamin supplements taken in the previous 2 weeks were identified by direct inspection. After an average follow-up period of 4.3 years, 91 of the sample participants with vitamin information met accepted criteria for the clinical diagnosis of Alzheimer's disease. This study data suggest an inverse association between high vitamin E and vitamin C intake and Alzheimer's disease. However, further exploration is needed as this is the first longitudinal study and results were only significant for Vitamin C.

One of the reasons for the scarcity of observational studies may be the complicated assessment of exposure: some are in the form of over-the-counter supplements, herbs or food. High over-the-counter sales mean that medical or pharmacy records do not provide a valid measure of intake. In addition, similar to the use of HRT, the healthy user effect may hamper valid assessments.

Trials

Ginkgo biloba (138-141) and selegiline or α-tocopherol (vitamin E) have been studied as secondary protective agents against Alzheimer's disease (142). The largest Ginkgo biloba trial published thus far, in which primary outcome measures included the ADAS-Cog, the Geriatric Evaluation by Relative's Rating Instrument and the Clinical Global Impression of Change showed superiority of Ginkgo biloba extract over placebo. In comparison to the baseline values, the placebo group worsened statistically significantly on all domains of assessment, while the group receiving Ginkgo biloba extract was considered slightly improved on cognitive assessment and daily living and social behaviour. Regarding safety, no differences were observed. The recently started Ginkgo Evaluation of Memory Study may resolve the question whether or not these findings can be extrapolated to primary prevention.

The selegiline/α-tocopherol trial showed that in patients with moderately severe impairment from Alzheimer's disease, treatment with selegiline or α-tocopherol slowed the progression of disease. A potential limitation of this trial is that progression was defined as a non-specific outcome that included time until institutional placement, or loss of activity to perform basic activities of daily living, or severe dementia or death. There were no significant differences in any of the cognitive test scores. Furthermore, selegiline may act as an anti-depressant, which could lead to improved cognition. The results of trials with lazabemide have to be awaited (136).

Discussion and conclusion

In recent years, some progress has been made in unraveling presumed protective effects of drugs in Alzheimer's disease. There are several methodological problems that are encountered in epidemiological research on drug effects and Alzheimer's disease. The exposure definition of drug use is often imprecise and lacks uniformity over studies. When studying drug effects, an adequate definition of drug expo-

sure is needed that encompasses when the drug was used relative to the onset of the disease, at what dose, and for how long. Standardization of research criteria used to define Alzheimer's disease would also increase the comparability of studies. Although NINCDS-ADRDA criteria are frequently used, the use of different diagnostic criteria may lead to very different case populations (143) and potentially to non-comparable and different risk estimates. The time of first clinical symptoms should be well documented, as, for obvious reasons, exposure can only be preventive if it occurs before diagnosis of the disease. However, it is recognized that these are difficult data to obtain reliably. An additional problem in studies of Alzheimer's disease is the sub-clinical period of unknown duration, in which a drug may or may not influence progression. Since drug use or non-use could be associated with factors that are in itself associated with the risk of a disease, these factors should be equally well defined as the drug under study and correctly controlled for in the analysis (144).

NSAID and to a lesser extent HRT are the drugs which have been most frequently studied in relation to Alzheimer's disease. For other drugs that have been studied, evidence is yet too scanty to evaluate their effect on the risk. A protective effect was most consistently demonstrated for the long-term use of HRT, although only 10 of 15 studies have been positive and secondary prevention trials are inconsistent. Because of beneficial effects on post-menopausal complaints, osteoporosis (145, 146) and atherosclerosis (147, 148), use of HRT is currently increasing in western society. In case a beneficial effect of HRT in Alzheimer's disease is demonstrated in (ongoing) clinical trials, the benefits may be considered so large that in spite of the increased risk of venous thrombo embolism (63) and breast cancer (149), a further increase of its use seems likely. This development will be further strengthened if selective estrogen receptor modulators, a new class of synthetic estrogens, really turn out to retain beneficial estrogenic effects in the brain without exhibiting mentioned adverse effects (150, 151).

Although optimistic reviews, mainly based on studies in prevalent Alzheimer's disease, have been published on the potentially protective role of NSAID in Alzheimer's disease, most prospective studies do not support this. In addition, currently available secondary prevention trials are inconclusive. These differences across studies may be the result of differences in study design, measurement of exposure, drug composition, ascertainment of cases (early/late onset, familial/sporadic). Given the high percentage of severe adverse-effects of the use of NSAID (90, 152), their potential role in the primary prevention of Alzheimer's disease is far less clear-cut (a disadvantage that also holds for the use of other anti-inflammatory drugs). It is questionable whether future developments of selective COX2-inhibitors and/or nitric oxide-releasing NSAID may change this (153, 154).

Although studies of antihypertensive therapy and Alzheimer's disease are scanty, the first results are promising. Research on the role of antihypertensives in Alzheimer's disease should probably focus on the potential mechanism and thus on the question whether a protective effect, if present, is solely explained by lowering of blood

pressure. Because of beneficial effects in cardio- and cerebrovascular disease in general, when proven effective in Alzheimer's disease, it is likely that treatment with antihypertensive drugs will be further intensified.

Given the low frequency of adverse effects of naturally occurring free radical scavengers their use will probably increase when proven beneficial. It will, however, be difficult to monitor their use because they are mainly obtained over the counter.

Because of the high risk of addiction, short-term memory problems and higher risk of fractures and accidents it is unlikely that benzodiazepines will ever be introduced as primary preventive agents in Alzheimer's disease.

In conclusion, we are only just in the beginning of making valid and useful assessments of protective drug effects in Alzheimer's disease and there is a long way to go. For the future, placebo-controlled trials for primary prevention may be very cumbersome. However, in the light of the developing large scale efforts (HRT, NSAID and Ginkgo) it may prove possible to study most of the suggested hypotheses. In order to be of help, how should observational studies contribute? Given the publicity regarding some of the drugs, and use of drugs for related co-morbidity, it may become more difficult to do observational studies. There are nevertheless a number of issues like the temporal relationship, the optimal dose level and the identification of particular risk groups that can and should be addressed in observational studies. However, in order to further untangle these difficult issues more uniform approaches are needed.

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Chapter 3

NSAID AND DEMENTIA

3.1

Risk estimation based on cross-sectional drug assessment at baseline in cohort studies may be biased by differential misclassification of exposure

ABSTRACT

Exposure to drugs is difficult to measure. In this study, we explored the effects of exposure misclassification on the association between reported and chronic use of NSAID and Alzheimer's disease. We included participants who were interviewed after January 1st, 1992, who were registered with one of the pharmacies that provided data to the Rotterdam Study and who provided baseline interview data on drug use (n=4402). Sensitivity, specificity, negative and positive predictive value of interview data as a measure of NSAID exposure compared to pharmacy data were used as outcome measures. In conclusion, baseline cross-sectional NSAID exposure is not a valid method for the assessment of chronic use of NSAID in the elderly. The validity of cross-sectional interview NSAID exposure data varies highly with age, sex and cognitive function. In our study, the misclassification resulted in a bias towards the null regarding the association between chronic use of NSAID and Alzheimer's disease. However, cross-sectional exposure assessment of NSAID use at baseline in a cohort study among elderly may yield risk estimates for Alzheimer's disease that can be biased in any direction since the degree of misclassification depends on age, gender and cognitive function at baseline. In order to prevent this we recommend the use of longitudinal pharmacy data for drug exposure assessment in epidemiological cohort studies.

Introduction

In epidemiological studies, specific and sensitive information on the type, dose and duration of exposure is essential (1). When compared to the usually rigorous validation and standardization of clinical measurements, the extent to which drug exposure is assessed in epidemiological studies is often poor. There are many examples of population-based cohort studies that have used cross-sectional interview data to assess drug exposure. Among those are controversial studies associating calcium channel blockers with cancer, myocardial infarction and gastro-intestinal bleeding (2-4), NSAID and aspirin with cancer (5), but also studies relating benzodiazepines

to hip fractures (6). Cross-sectional assessment of current drug exposure by means of interview may provide little insight into the duration of past or current drug exposure given the dynamic character of pharmacological treatment. Using such data as a measure of exposure may introduce serious exposure misclassification. Several authors who base their conclusions on this type of exposure measurement have acknowledged the potential for misclassification. However, it is often assumed that this misclassification will be non-differential and leads to a more conservative risk estimate, and that an observed significant observation therefore is a true one.

Triggered by some contradictory studies regarding the association between use of NSAID and the occurrence of Alzheimer's disease (7-10) we conducted a study to quantify the degree of misclassification introduced by using cross-sectional data, and to estimate the effects of exposure misclassification on the estimated risk of Alzheimer's disease associated with NSAID use.

Methods

Study population

The Rotterdam Study is a prospective population-based cohort study of neurological, cardiovascular, locomotor and ophthalmological diseases in the elderly and has been described extensively elsewhere (11). In brief, all inhabitants of Ommoord, a suburb of the city of Rotterdam in the Netherlands, aged 55 years or older and living in the district for at least one year were invited in 1990-1993 to participate in the study. Of the 10,275 eligible subjects, 7,983 (78%) participated and were interviewed. During the interview, a questionnaire was administered covering, among other topics, socioeconomic background, medical history and medication use. During subsequent visits to the research center, subjects underwent additional interviewing and clinical examinations, including screening for and diagnostic work-up of dementia (12, 13).

In Ommoord, seven computerized pharmacies that are all linked to one network serve the total population. These records were linked to the database of the Rotterdam Study. Over a 7-year period more than 95% of the study population had filled at least one prescription in these pharmacies.

All dispensed drugs have been filed since January 1st, 1991 and are available in computerized format. The population for the current study comprised all cohort members who were interviewed after January 1st, 1992 (to ensure at least 1 year of potential drug history) and who were labeled as clients of one of the pharmacies.

Automated pharmacy records containing all prescription medication histories of 7814 out of 7983 subjects (97.9%) were available. We excluded 4 subjects since they had no baseline interview data and 3408 subjects because the interview was conducted before January 1st, 1992. The study population therefore comprised 4402 subjects.

Drug exposure assessment

Interview data

At baseline, all participants were interviewed by a trained research assistant and were asked to show all vials of medications (either prescription or over-the-counter) that were used during the preceding week. Names or brands of drugs were recorded and classified according to their corresponding Anatomical-Therapeutical-Chemical-code (ATC-code) (14). For this study we used all information that was recorded pertaining to the use of NSAID (ATC: M01).

Pharmacy data

Medication histories included information on all filled prescriptions characterized by the name, ATC codes, amount dispensed and the dosage regimen. The legend duration of use of each NSAID prescription was calculated as the ratio of the dispensed number of tablets or capsules and the prescribed daily number.

We created several categories of NSAID exposure depending on the time and duration of use. Exposure to NSAID in the year prior to the baseline interview was characterized as non-use (no prescription), occasional use and chronic use. Persons were classified as chronic users of NSAID if the cumulative legend duration of NSAID amounted to at least 180 days in the 12 months before the baseline interview date (15). Use for less than 180 days in the 12 months before the baseline interview date was defined as occasional use

Analysis

We were interested in chronic NSAID use, because this type of exposure has been reported to protect against Alzheimer's disease (9). To quantify the validity of NSAID exposure as measured by means of cross-sectional interview data we calculated the sensitivity, specificity, positive and negative predictive value of the NSAID exposure classification between interview and pharmacy data. As at the time of measurement no NSAID were available without prescription, we considered the pharmacy data as the gold standard. We calculated these parameters for chronic use during the 1-year period preceding the baseline interview. We furthermore examined whether age, gender or low cognitive function, defined as a Mini Mental State Examination (MMSE) (16) of below 26, were associated with the validity of NSAID exposure assessment as a proxy of chronic use.

In addition, we performed a logistic regression analysis to determine whether these factors independently affected the validity while controlling for the other factors.

Finally, to explore the effects of potential misclassification on the association between use of NSAID and the occurrence of Alzheimer's disease, we examined the effect of exposure misclassification introduced by interview data on the asso-

ciation between NSAID use and Alzheimer's disease. To this purpose we compared the hazards between persons who developed Alzheimer's disease in the Rotterdam Study (17) and persons who remained free of Alzheimer's disease during follow-up, based on either interview data or pharmacy exposure data in persons who were non-demented at baseline. Age and gender adjusted hazard ratios were calculated by means of Cox' proportional hazards regression analyses.

Results

Of the 4402 subjects in our study population, 336 (7.6%) subjects reported NSAID use during the baseline interview. According to the pharmacy database, 994 (22.6%) of the study subjects used NSAID in the one year prior to the interview, of whom 131(3%) were chronic user (≥ 180 days in prior 12 months) and 863 (19.6%) subjects were occasional user (1-179 days in prior 12 months).

Table 1 shows the exposure classification of subjects according to interview and pharmacy data. Although the sensitivity and specificity were high for chronic use, the table shows also that only 31% of those reporting NSAID use at baseline were actual chronic users (positive predictive value).

Table 2 shows the validity for interview data according to age, gender and low cognitive function. The validity of assessment of NSAID use at interview as a proxy of chronic use by interview differed per age class. Despite a lower sensitivity and specificity in older age, the proportion of people that reported NSAID use at baseline and who were real chronic users increased significantly with age from 25% below 65 years to approximately 41% above 80 years of age (positive predictive value). Men and women did not significantly differ with respect to any of the validity measures. In subjects with low cognitive performance (MMSE < 26) sensitivity (57%) was significantly lower than in subjects with a normal cognitive function (88%). Additional analyses showed that higher age and the presence of cognitive impairment, but not

TABLE 1
Validity of a single interview-based exposure measurement for the assessment of chronic NSAID exposure in the year prior to the interview.

	User status Pharmacy				Validity status for Chronic use (n=131)	
User status Interview	Chronic user	Occasional user	Non-use	Total		
User	105	184	47	336	Sensitivity	80.2%
Non-user	26	679	3361	4066	Specificity	94.6%
Total	131	863	3408	4402	PPV	31.3%
					NPV	99.4%

PPV =positive predictive value, NPV =negative predictive value.

TABLE 2
Validity of a single interview based exposure measurement for the assessment of chronic NSAID exposure in the year preceding the interview, stratified by age, sex and cognitive function.

		VALIDITY PARAMETERS			
		Sensitivity	Specificity	PPV	NPV
AGE	55-64 yrs	100%	95.0% (93.9-96.1)	25.2% (17.7-32.7)	100%
	65-79 yrs	77.8% (66.7-88.9)	95.0% (94.0-96.0)	30.9% (23.1-38.7)	99.3% (98.9-99.7)
	≥80 yrs	70.2% (57.1-83.3)	92.5% (90.5-94.5)	40.7% (28.5-47.5)	97.7% (96.3-99.1)
SEX	Male	79.4% (71.8-87.0)	93.6% (92.6-94.6)	33.9% (27.8-40.0)	99.1% (98.7-99.5)
	Female	82.7% (68.7-96.7)	96.0% (95.1-96.9)	24.7% (15.9-33.5)	99.7% (99.4-100.0)
COGNITION	MMSE <26	66.7% (48.3-83.6)	93.3% (91.3-95.3)	31.6% (19.6-43.6)	98.4% (97.4-99.4)
	MMSE ≥26	92.5% (85.9-98.8)	94.5% (93.8-95.2)	25.4% (19.9-29.9)	99.8% (99.6-100.0)

PPV =positive predictive value, NPV =negative predictive value.

sex, independently and significantly modified the association between the baseline interview and chronic use according to the pharmacy data (data not shown).

To examine the potential consequences of the misclassification, we compared the risks of exposure to reported and chronic NSAID use between 117 incident Alzheimer patients and 3750 non-Alzheimer's disease patients. The age and sex adjusted hazard ratio for exposure to NSAID according to cross-sectional interview data was 0.81. According to pharmacy data the hazard ratio was 0.51 for subjects chronically exposed in the year prior to the interview.

Discussion

We found that cross-sectional assessment of NSAID exposure with baseline interview data is not a valid method for the estimation of preceding chronic NSAID use in the elderly. The amount of misclassification was inversely associated with age, which itself is a strong risk factor for Alzheimer's disease. This differential misclassification means that the effect on the relative risk can go into any direction. In our study a protective point estimate of 0.81 for NSAID use in Alzheimer's disease changed to 0.51 after making use of a chronic exposure estimate. Although the current study is by design not suitable to adequately address the true association between NSAID and Alzheimer's disease, these findings are important because in several epidemiological studies regarding Alzheimer's disease, drug exposure is measured cross-sectionally on the basis of current use (7, 8, 10, 18, 19). Interviews on current NSAID use lead to a high number of false positives when used as a proxy of chronic use. Because exposure will be overestimated in all subjects, but especially in younger subjects as their prevalence of chronic use is lower. Moreover, subjects with cognitive impairment significantly less often showed their NSAID vials, when in fact they had been chronic users in the past year. Since cognitive impairment may be a symptom of Alzheimer's disease this is one of the reasons why such a design should not be used in prevalent demented subjects.

In this study we have shown that misclassification of exposure is substantial when medication use in the past week is used as a proxy for "long-term" use. This is not new, since many authors have acknowledged this issue when outlining the limitations of their study. However, we quantified the effect and more importantly we have shown that the degree of misclassification changes with cognitive status and within strata of age.

In interpreting our results, we need to discuss the potential limitations of this study. Selection bias is not likely to be an issue as our study is population based and the exclusion of subjects was only dependent on the baseline interview date that was assigned randomly. We used drug exposure as recorded in pharmacy data as the gold standard in this study. In the Netherlands, because of the high insurance coverage of approximately 99.4% (20) there is no economic incentive for switching

among pharmacies. Pharmacy records are therefore considered virtually complete resources for drug exposure, and are often used to assess completeness of medical records or interview data (21, 22). On the basis of the pharmacy records we may have misclassified chronic exposure as a consequence of people not finishing their prescriptions. However, as it is highly improbable that people regularly fill prescriptions that they do not use we think that it is unlikely that this influenced the results. Moreover, as the mean duration of the cumulative prescriptions was 308 days in the year preceding and encompassing the interview date, subjects may have missed on average 1 in every three prescriptions and still be accurately classified as a chronic user. Even though the pharmacy data are a reliable source in determining chronic use, a limitation to our study is the simplification of the definition of this chronic use. By changing the definition, estimates of validity change. However, when chronic use was defined as use during 365 days per year, misclassification was similar and the effect on the risk estimate for prevalent Alzheimer's disease was comparable.

It is unclear to what extent our findings can be extrapolated to other populations. Although prescription patterns and patterns of use may be different, it is likely that age is a determinant of chronic drug use as it is the most important determinant of chronic disease in western society. Finally, it is important to note that the often intermittent pattern of use of NSAID is probably different from, for example, the pattern of use of antihypertensives, which are normally used chronically.

What are the implications of these findings on judging the existing studies of dementia and on the design of future studies? If misclassification of a dichotomous exposure is independent of disease status, e.g. non-differential, the risk estimate is biased towards the null. However, in studies on dementia, but also in other diseases, errors in exposure and disease may be associated and lead to differential misclassification. To what extent this misclassification may have happened in previous studies is unclear. It may be considerable but depends among other things on age and gender distribution, degree of co-morbidity and patterns of NSAID use. Because the potential effects of misclassification of exposure on the relative risk are complex and not easily generalized, each study should be evaluated individually (23). This potential for misclassification may be one of the contributing causes of the conflicting results that have been found in studies on NSAID and Alzheimer's disease. In conclusion, we think that in view of these results, cross-sectional exposure assessment at baseline in a cohort study may yield biased risk estimates of diseases, which are related to chronic drug exposure. As misclassification of exposure can not be dealt with by the methods used for control of confounding (24), we strongly recommend the use of continuously gathered drug exposure data in pharmaco-epidemiological studies instead of cross-sectional drug exposure information.

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3.2

NSAID and incident Alzheimer's disease

The Rotterdam Study

ABSTRACT

Recent studies suggest that the use of non-steroidal anti-inflammatory drugs (NSAID) may reduce the risk for Alzheimer's disease. We investigated the relation of NSAID use over a ten-year period and the risk for incident Alzheimer's disease using a nested case-control design in the population based Rotterdam Study. The study was performed in 306 subjects; 74 Alzheimer patients diagnosed according to NINCDS-ARDRA criteria and 232 age and sex matched controls. NSAID use was abstracted from general practitioners medical records and expressed as cumulative prescription days. The relative risk of Alzheimer's disease associated with long-term use (≥ 2 months) was 0.95 (95% CI: 0.46-1.99) as compared to non-users, after controlling for possible confounders. In a separate examination, subjects who had more than 6 months of prescription days had a reduced relative risk of Alzheimer's disease; 0.74 (95% CI: 0.20-2.72). In an age-stratified analysis the effect in long-term users was evident in those aged 85 and under; 0.53 (95% CI: 0.15-1.77). All risk estimates were lower when the last two years of exposure were excluded from the analyses. Our point estimates in subjects younger than 85 years and in subjects using NSAID for 6 months or more are consistent with the hypothesis that long-term use of NSAID reduces the risk of Alzheimer's disease. However, overall there was no association between NSAID use and the risk of incident Alzheimer's disease.

INTRODUCTION

Alzheimer's disease is a progressive age related dementing disorder, that increases in incidence from about 1 per 1000 person-years at age 65 to 80 per 1000 person-years in people aged 85 and over (1). Due to aging and the increased life expectancy in many populations an increase in the number of cases of Alzheimer's disease is expected, that has enormous medical and social consequences. Therefore, studies of determinants of Alzheimer's disease that could eventually lead to the development of preventive strategies are a priority. There are indicators of immune-mediated auto-destructive processes in brain tissue in Alzheimer's disease patients (2-5), sug-

gesting that inflammatory processes may play a role in Alzheimer's disease. It has been hypothesized that anti-inflammatory drugs, such as non-steroidal anti-inflammatory drugs (NSAID), might slow the onset or progression of Alzheimer's disease.

Studies of the association of NSAID with the risk for Alzheimer's disease have been inconclusive. Some showed a reduced risk (6,7) or a lower than expected frequency of Alzheimer's disease, in groups thought to be chronically exposed to NSAID (8-12); whereas other studies showed no association (13,14). Recently, a study, in the volunteer cohort of the Baltimore Longitudinal Study of Aging, showed an inverse relation between the duration of exposure to NSAID and the development of Alzheimer's disease over a 15 year period (15). We have previously reported an inverse association of recent NSAID use and Alzheimer's disease on prevalent cases detected in the population based Rotterdam Study (12). However, in that cross-sectional study information on duration of NSAID use was not available. Furthermore, that study was based on prevalent cases, and is therefore subject to survival bias. To address some of these weaknesses, we examined the association between incident Alzheimer's disease and NSAID use up to ten years prior to the onset using a nested case-control design based on the Rotterdam Study cohort.

Methods

Study population

The Rotterdam Study is a prospective population-based cohort study of neurological, cardiovascular, locomotor and ophthalmologic diseases in the elderly. All inhabitants of Ommoord, a suburb of Rotterdam in the Netherlands, aged 55 years or more and living in the district for at least one year were invited in 1990-1993 to participate in the study. Of the 10,275 eligible subjects, 7,983 (78%) participated and were interviewed at home; 7,129 (89%) of them made two follow-up visits to the research center. In the home interview, trained interviewers administered a questionnaire covering, among other topics, socio-economic background, medical history and medication use. During the center visits, subjects underwent additional interviewing and clinical examinations, including screening and diagnosis of dementia.

Case finding for dementia

At baseline, subjects were screened for dementia in a two step procedure. All subjects were screened on cognitive function using the Mini-Mental State Examination (MMSE)(16) and the Geriatric Mental State schedule (GMS) (17). Those scoring 25 or below on the MMSE or scoring 1 or more on the GMS were selected for further diagnostic evaluation. This included more detailed neuropsychologic testing and an informant interview based on the Cambridge Examination for Mental Disorders of

the Elderly (18), as well as neurologic examination. Some participants underwent brain imaging. A clinical diagnosis of dementia was made according to the DSM-III-R criteria for dementia (19) and possible and probable Alzheimer's disease was diagnosed according to NINCDS-ADRDA criteria (20).

Case and control selection

The 7046 subjects who were without dementia at baseline were eligible for the present study. Over a three-year period after baseline examination all new cases of dementia were assembled. New cases were identified in weekly computerized reports of relevant morbidity sent by the general practitioner, through the regional institute for outpatient mental Health care, or were detected in a second round of investigation three years after the initial one, according to the same schedule of investigations followed to identify prevalent cases. As of January 1995, 101 incident Alzheimer patients had been detected. These subjects form the case-group. The date of diagnosis was defined as the index date. For each case, three age- ($\pm$2 years) and sex-matched controls were drawn from the remainder of the cohort that did not have a diagnosis of dementia before January 1995. Prior to the start of the study, we calculated that this number of subjects was sufficient to detect a 50% reduction in risk (α=0.05, β=0.20), an estimate which was close to our earlier and to other studies (12,15).

Definition of NSAID use

In a 40-day period two medically trained students visited the general practitioners of all cases and controls and abstracted prescription data from medical records. In so far as was possible, the abstractors were blinded to case status. For each case, data on medication use were collected, from ten years till six months prior to the date of diagnosis (index-date). The six-month cut-off was used to reduce the possibility that prescription patterns were associated with the clinical expression of Alzheimer's disease. For each NSAID prescription, the drug was classified according to the corresponding Anatomical Therapeutical Chemical (ATC) code (21), generic name, prescription date, (calculated) end date, and dosage. Each new NSAID prescription was entered separately and directly into a computerized database. A new prescription was defined when a change in generic name or dosage was recorded or when the interval between start dates was longer than three months. For each prescription, the duration of exposure was calculated on the basis of the total number of capsules (tablets or suppositories) prescribed, divided by the number of units per day.

If the start date was present and stop date or prescription duration missing, then the prescription was regarded as incomplete. To minimize loss of information we supplemented general practitioner data with pharmacy filling information from the computerized database of the three Ommoord pharmacies. These data were available

on the Rotterdam Study cohort as of January 1991. Using approximately 25,000 complete NSAID prescriptions we calculated a mean prescription duration for each specific ATC-code. Subsequently these were used to replace missing durations for the prescriptions that had a start date.

To obtain the number of cumulative days exposed we added all prescription durations during the study period for each subject. This variable was then further categorized into, never users (35.2%), short term users (less then 2 months: 34.9%) and long term users (2 months or more: 29.7%). This two-month period was the median exposure duration of subjects who used NSAID.

Confounding variables

The following data were entered into the statistical models as to control for putative confounding: education (low, middle and high), smoking (never, former, current), alcohol use (none, ≤13.2 g/day, >13.2 g/day), living situation (independent, supported, nursing-home), self reported stroke (no/yes). These data were collected during the home interview prior to the onset of dementia. Alcohol intake was available only on community dwellers; a dummy variable indicating missing for this variable was incorporated into the model.

We also included salicylates (categorized in none, short-term and long-term use based on the median of ten months in users) and benzodiazepines (1 point for at least one prescription in every two years; 5 points when at least once in every two year a benzodiazepine was prescribed; categorical range 0-5) in the regression model. Data on the latter two were collected at the same time as the NSAID data.

Analytical sample

Of the initial 388 subjects, medical records could not be retrieved for 16 cases (mean age 88.5 yrs, 43% nursing home residents) and 35 controls (mean age 88.8 yrs, 48 % nursing-home residents). Furthermore, 11 cases and 20 controls had less than 10 years of medical history available. The analytical sample therefore comprised 306 subjects out of 388 eligible subjects, of whom 74 were cases and 232 controls. As some cases lost a control and vice versa we reallocated controls to different age and sex matched cases. This resulted in 14% male and 23% female cases respectively with 2 controls, and 33% male and 40% female cases with 4 controls.

Statistical analyses

Univariate comparisons between cases and controls were tested with the chi-square statistic, a linear test for trend and conditional logistic regression analysis. The relative risk for Alzheimer's disease associated with NSAID use was estimated by calculation of the odds ratios (95% confidence interval), using conditional logistic regression

analysis.

The main analysis was supplemented with three sub-analyses. We restricted the exposure window to 10-2 years prior to the index date. This was done to examine the possibility that the sub-clinical disease process already affected drug utilization patterns in an early phase and because the disease process may already have progressed to a stage at which NSAID are no longer protective (15). Secondly, an exposure of 2 months may be too short to see an effect. Therefore we split the group of long-term users into a group exposed 2-6 months and a group exposed for more than 6 months, which is approximately the upper 10% of use. Finally, we stratified NSAID exposure into two age classes, according to the median age of the cases: 85 years or younger (n=144) and those aged over 85 years (n=162). Multivariate conditional logistic regression was performed to adjust for the confounding variables. All analyses were done on a microcomputer using SPSS/PC 7.0 for Windows and EGRET.

Results

As a result of matching the mean age in both groups was almost equal: 85.3 years in cases and 84.7 years in controls (Table 1). There were significantly more female than male sets. Controls had a longer mean exposure than cases. The proportion of incomplete prescriptions was high, but similar in cases and controls. A significantly higher proportion of cases compared to controls were residents of a nursing home (35.1% vs. 19.3%, p=0.01) and cases were significantly more often current smokers. then controls (23% vs. 9%, p=0.008). Controls more frequently reported a stroke then cases (6% vs. 4%). Benzodiazepine and salicylate use was equally distributed between cases and controls over a 10 year period.

TABLE 1
Description of sample and prescription behavior for incident cases of Alzheimer's disease and matched controls: The Rotterdam Study

	Incident cases of Alzheimer's disease (n=74)	Controls (n=232)
Mean age (SEM)	85.3 (0.8)	84.7 (0.4)
Male (%)	27	27
Number of prescriptions	158	490
Mean number of prescription days (SE)	62.1 (11.7)	104.9 (19.8)
Subjects with all original prescriptions (%)	36	34
Prescriptions that were complete (% of all prescription)	26	25

TABLE 2
Risk of incident Alzheimer's disease and NSAID use over a ten year period: The Rotterdam Study

Prescription days for NSAID	Incident AD n=74	Controls n=232	Crude odds ratio (95% CI)	Adjusted odds ratio† (95% CI)
10-0.5 years before diagnosis				
None	24 (32.4%)	84 (36.2%)	1.0	1.0
< 2 months	27 (36.5%)	80 (34.5%)	1.17 (0.62-2.19)	1.08 (0.50-2.33)
2-6 months	19 (25,7%)	44 (19.0%)	1.36 (0.68-2.70)	1.03 (0.46-2.31)
≥ 6 months	4 (5.4%)	24 (10.3%)	0.68 (0.21-2.14)	0.74 (0.20-2.72)
10-2 years before diagnosis*				
None	32 (43.3%)	93 (40.0%)	1.0	1.0
< 2 months	24 (32.4%)	82 (35.3%)	0.83 (0.45-1.54)	0.76 (0.37-1.57)
2-6 months	16 (21.6%)	38 (16.4%)	1.19 (0.60-2.35)	0.97 (0.44-2.17)
≥ 6 months	2 (2.7%)	19 (8.2%)	0.32 (0.07-1.43)	0.27 (0.05-1.51)
2-0.5 years before diagnosis				
None	53 (71.7%)	185 (79.7%)	1.0	1.0
Users	21 (28.3%)	47 (20.3%)	1.53 (0.82-2.85)	1.41 (0.65-3.05)

* the last 2 years of NSAID exposure before diagnosis of Alzheimer's disease are excluded .
† adjusted for smoking, alcohol, living situation, education, benzodiazepine and aspirin use by means of multivariate conditional logistic regression analysis.

After controlling for smoking, alcohol use, residence, education, benzodiazepine and aspirin use no statistically significant difference between cases with Alzheimer's disease and controls was observed when short-term and long-term (mean use 273 days) NSAID users were compared to never users. Odds ratios in both comparisons hovered near 1. After excluding prescription data from 2 years to 6 months prior to diagnosis, the odds ratios in both short- and long-term users were lower although the confidence interval still included 1 (Table 2). Separate examination for the period from two years to 6 months suggested that compared to controls, cases had relatively more NSAID prescription days (36.5 days for controls and 59.5 for cases). In the additional analyses, in which we compared subjects with more than 6 months of NSAID use (mean use 720 days) to none users we found lower risk estimates, for the 10-0.5 year period: odds ratio 0.74 (95% CI: 0.20-2.72) as well as for the 10-2 year restricted exposure window: odds ratio 0.27 (95% CI: 0.05-1.51) (Table 2).

Stratification for age showed a non-significant reduced risk for long term users aged 85 years or under, for both the 10-0.5 year period: odds ratio 0.53 (95% CI: 0.15-1.77) as well as for the 10-2 year restricted exposure window: odds ratio 0.40 (95% CI: 0.11-1.44). Long-term users aged over 85 had odds ratios close to 1 (Table 3).

TABLE 3
Risk of incident Alzheimer's disease and NSAID use over a ten year period by age: The Rotterdam Study

Prescription days for NSAID	Incident AD cases	Controls	Crude odds ratio (95% CI)	Adjusted odds ratio† (95% CI)
AGE ≤ 85 YEARS	n = 33	n = 111		
10-0.5 years before diagnosis				
None	12 (36.4%)	40 (36.0%)	1.0	1.0
Short (< 2 months)	13 (39.4%)	38 (39.4%)	1.23 (0.50-3.04)	1.29 (0.48-3.46)
Long (≥ 2 months)	8 (24.2%)	33 (29.7%)	0.60 (0.20-1.75)	0.53 (0.11-1.43)
10-2 years before diagnosis*				
None	17 (51.5%)	45 (40.5%)	1.0	1.0
Short-term (<2 months)	9 (27.3%)	38 (34.2%)	0.77 (0.31-1.95)	0.69 (0.25-1.91)
Long-term (≥2 months)	7 (21.2%)	28 (25.2%)	0.38 (0.11-1.24)	0.40 (0.11-1.44)
AGE > 85 YEARS	n = 41	n = 121		
10-0.5 years before diagnosis				
None	12 (29.3%)	44 (36.4%)	1.0	1.0
Short (< 2 months)	14 (34.1%)	42 (34.7%)	1.43 (0.58-3.07)	1.86 (0.67-5.18)
Long (≥ 2 months)	15 (36.6%)	35 (28.9%)	1.33 (0.58-3.07)	1.32 (0.51-3.37)
10-2 years before diagnosis*				
None	15 (36.6%)	48 (39.7%)	1.0	1.0
Short-term (<2 months)	15 (36.6%)	44 (36.4%)	1.28 (0.56-2.94)	1.81 (0.72-4.54)
Long-term (≥2 months)	11 (26.8%)	29 (24.0%)	1.02 (0.43-2.42)	0.93 (0.35-2.47)

* the last 2 years of NSAID exposure before diagnosis of Alzheimer's disease were excluded.
† adjusted for smoking, alcohol, living situation, education, benzodiazepine and aspirin use by means of multivariate conditional logistic regression analysis.

Discussion

In this population based nested case-control study, overall there was no significant association of NSAID use with the risk for incident Alzheimer's disease. However, there was a non-significant tendency towards a risk reduction for subjects with at least six months of exposure. Furthermore, there was some evidence that a protective effect may be detectable in subjects younger than 85 years.

Several issues of validity need to be discussed when interpreting these results, i.e. potential selection bias, information bias and confounding. As the Rotterdam Study is population based with complete ascertainment of incident dementia, selection bias of cases is unlikely.

Misclassification of exposure may have affected our results. One major concern

in earlier cross-sectional and case-control designs was the potential for bias by misclassification due to underreporting by proxy informants of drug use among cases. To avoid this problem we used general practitioner records as an independent assessment of exposure. In the Netherlands, general practitioners, are the gatekeepers of health care, and prescribe the majority of NSAID. There are no published figures of over the counter NSAID use in relation to prescription use. However, it is likely that over-the-counter use in the elderly is minimal because all health insurance packages in the Netherlands reimburse for these drugs. Moreover, for the study period only ibuprofen could be obtained without prescription, but these had to be bought at a pharmacy. Salicylates were available during the study period for over-the-counter use. However, they only exhibit anti-inflammatory properties in high doses, which are normally obtained through prescriptions only. Medical specialists also prescribe NSAID. However, these specialists are required to report treatment to the general practitioners. As we are not aware of diseases that require chronic NSAID therapy that are etiologically associated with Alzheimer's disease, missing reports from specialists should not be different between cases and controls.

Despite the notable advantages to using medical records in the Netherlands, general practitioner records were not complete with regard to NSAID use. In a validation study we found that medical record data under-reported NSAID and aspirin prescriptions compared to pharmacy filling data (22). However, the number of incomplete prescriptions in our study was equally distributed over cases and controls, suggesting that systematic under-reporting by case status was minimal.

Another potential source of exposure misclassification may have been introduced by the method we used to impute exposure in incomplete prescriptions. We imputed exposure on a compound basis (i.e., by ATC code) using a large number of records. This large sample size should give us stable mean estimates. However, by applying a mean exposure to all incomplete prescriptions, we may have overestimated exposure in subjects using NSAID for an acute problem, and underestimated exposure among chronic users. The distribution of incomplete prescriptions was equal among cases and controls. Without knowing the proportion of chronic users in the case and control groups, it is not possible to determine the direction of the bias that might have been introduced by the imputation procedure. Examining pharmacy data from 1991-1996, thereby only partially overlapping the study period, we found that the fraction of subjects with longer-term prescriptions, ranging from 60 to 90 days (durations usually prescribed in chronic users), was similar in cases and controls. Therefore, we think that it is less likely that the application of an overall mean duration for a prescription with a missing duration can explain the results. However, we can not exclude the possibility that in this period the physician's prescription behaviour was influenced by the diagnosis of Alzheimer's disease.

Confounding by indication is an important issue in this type of study. Previously we hypothesized that sub-clinically demented individuals may not receive NSAID prescriptions because they would have an impaired ability to express complaints or

because doctors may be less eager to prescribe NSAID in case of an adverse event. In this study there is some evidence to the contrary. Comparisons of results in table 2 show a more frequent exposure to NSAID in cases within the 24-6 month period prior to diagnosis. This suggests that in the period preceding the presumptive diagnosis of Alzheimer's disease there may already be changes in behavior, that are subsequently related to whether or not the individual receives NSAID. This confounding would make it more difficult to detect an effect if one existed.

In conclusion in this population based nested case-control study, overall there was no significant association of NSAID use with the risk for incident Alzheimer's disease. However, there was a non-significant tendency towards a risk reduction for subjects with at a longer exposure which was more prominent subjects younger than 85 years. These inverse associations were stronger when the exposure-window was restricted to 10-2 years prior to the onset of Alzheimer's disease.

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NSAID and the risk of Alzheimer's disease and vascular dementia

The Rotterdam Study

ABSTRACT

A large number of observational studies on the association between NSAID and Alzheimer's disease have been published, but the results have been inconsistent. Almost all previous studies have obtained information on exposure to NSAID using methods vulnerable to misclassification. To examine the association between NSAID and aspirin use, and the long-term risk of incident Alzheimer's disease and vascular dementia we conducted a prospective cohort study using data from the population-based Rotterdam Study. The study population comprised all subjects (n=6989) who were non-demented at baseline and had data on drug use during the study period provided by the 7 pharmacies serving this population. Dementia screening took place in 1990-93, 1993-1994 and 1997-1999. In addition, the cohort was continuously monitored for incident cases of dementia. Proportional hazards regression analysis was used to estimate the risk of Alzheimer's disease in relation to the use of NSAID. NSAID use was defined as four mutually exclusive time varying exposure categories: no exposure, less than 1 month (incidental), 1-23 months (intermediate) and 24 months or more (long-term). Adjustments were made for age, gender, education and use of aspirin, H2-antagonists or anti-diabetic drugs. During 47498 person-years of follow-up, 394 subjects developed dementia, of whom 294 had Alzheimer's disease, 55 vascular dementia and 45 other types of dementia. Average follow-up was 6.8 years. Compared to non-use the relative risk of Alzheimer's disease was 0.95 (95% CI 0.70-1.29) in incidental users, 0.83 (95% CI 0.62-1.11) in intermediate users and 0.21 (95% CI 0.05-0.83) in those subjects that used NSAID for 2 years or more. The use and duration of NSAID use were not associated with the risk of vascular dementia. This study suggests that prolonged NSAID use may reduce the risk of Alzheimer's disease.

INTRODUCTION

Inflammatory processes play a role in the pathogenesis of Alzheimer's disease. The accumulation of microglia around plaques, the cytokine-mediated cerebral acute phase response and activation of the complement cascade, all contribute to the tissue destruction in Alzheimer's disease (1, 2). This inflammatory response may

be autotoxic to neurons, exacerbating the fundamental pathology in Alzheimer's disease (3). Non-steroidal anti-inflammatory drugs (NSAID) have been proposed as agents that could alter this inflammatory course. Suggested mechanisms are through inhibition of cyclo-oxygenase (COX) 1 and 2 and through activation of the peroxisome proliferator gamma (PPAR-γ) nuclear transcription factor (4-6), leading to inhibition of inflammation and inhibition of platelet aggregation.

Evidence from observational studies with regard to the association of NSAID use and Alzheimer's disease is inconsistent. Some studies suggested a protective effect whereas others did not (7, 8). However, almost all previous studies obtained information on NSAID exposure by either retrospective recall, surrogate interviews, repeated cross-sectional interviews or -as we did in an earlier study- by using medical records as exposure measure (9). These exposure measures are all vulnerable to misclassification. In The Netherlands, pharmacy records are considered virtually complete resources of drug exposure on a daily basis. These prospectively gathered automated data comprise quantitative and qualitative information on all filled prescription drugs and are extensively used for drug utilization and other types (10) of pharmaco-epidemiological studies (11-15). Linkage of these pharmacy data to the research database of the Rotterdam Study, provided us with the possibility to examine whether the use of NSAID and aspirin, was associated with a decreased risk of Alzheimer's disease or vascular dementia.

Methods

Setting

The Rotterdam Study is a prospective population-based cohort study of neurological, cardiovascular, locomotor, and ophthalmological diseases in the elderly that has been described extensively elsewhere (16). In brief, all inhabitants of Ommoord aged 55 years or older who were living in this suburb of Rotterdam were invited to participate in the study (1990-1993). Of the 10,275 eligible subjects, 7983 (78%) participated and were interviewed at home. During this visit, trained interviewers administered an extensive questionnaire covering, among other topics, socio-economic background, food intake, medical history and medication use. During subsequent visits to the research center, subjects underwent additional interviewing and clinical examinations, including screening and diagnosis of dementia. In addition, apolipoprotein E (APOE) genotyping was performed on coded DNA samples without knowledge of the diagnosis for subjects who developed dementia (17). The large majority of the participants (99.7%) were registered at one or more of the seven pharmacies serving the Ommoord area. These pharmacies are fully automated and currently comprise data as of January 1 1991 until January 1 1999. During the study period approximately 98% of the study population obtained at least one pre-

scription through one of these pharmacies.

Study population

In this cohort study, the potential study period consisted of the 8-year period between January 1 1991 and January 1 1999. We included all subjects who were free of dementia at baseline (n=7046). From this group, we excluded all subjects (n=17) who were not registered at one of the pharmacies, and all persons with a follow-up of less than 6 months medication history (n=40). During follow-up participants were screened for dementia in a second (1993-1995) and third (1997-1999) examination as described below. Every member of the study population (n=6989) was followed until death, dementia or the end of the study period whichever came first. The end of the study period was set at the date of the last examination unless this date fell in 1999 in which case the endpoint was set at December 31 1998.

Exposure definition

All prescriptions are available in automated form and include the product name, international non-proprietary name, the Anatomical Therapeutical Chemical (ATC) code (18), number of filled tablets/capsules or other dosage forms, the date of delivery, the prescribed daily number, the dosage, and the legend duration (prescription length). For dosage comparisons, we used the cumulative mean prescribed daily dosage expressed as defined daily dosage (DDD). The DDD is defined by the World Health Organization as the average dosage of a drug used by an adult for the main indication (19). NSAID were our primary interest and included all prescriptions for oral NSAID (ATC-code M01A; prescriptions for M01B were not filled). All prescriptions filled during follow-up were used to construct time-varying covariates. Separate variables were constructed for oral salicylate analgesics (ATC-code N02BA) and for the platelet-inhibiting salicylates acetylsalicylic acid (ATC-code B01AC06) and carbasalate calcium (ATC-code B01AC08).

Case ascertainment of dementia

Both at baseline and at the follow-up examinations, subjects were screened for dementia in a stepwise procedure. Subjects were screened for dementia with a combined Mini Mental State Examination (MMSE) (20) and the Geriatric Mental State schedule (GMS-A, organic level) (21). Those scoring 25 or below on the MMSE or scoring one or more on the GMS were selected for further diagnostic evaluation and were subsequently examined by a physician with the CAMDEX diagnostic interview, which includes an informant interview (22). Finally, subjects who were suspected of dementia were examined by a neurologist, a neuropsychologist and had a brain MRI. In addition to the dementia screening, the cohort is continuously monitored for inter-

val cases of dementia (23). A clinical diagnosis of dementia was made according to the DSM-III-R criteria for dementia by a panel that reviewed all existing information. A sub-diagnosis of Alzheimer's disease was made according to the NINCDS-ADRDA criteria (24). A sub-diagnosis of vascular dementia was made according to the NINDS-AIREN criteria (25). The date of dementia onset was defined, as midway the latest date a person was known to be non-demented and the first known date a person was diagnosed with dementia.

Analysis

For every cohort member we calculated duration of follow-up. Since drug exposure may vary over time, we calculated relative risks for dementia with a Cox proportional hazards model (26) with the exposure to drugs represented by time-varying covariates. In the Cox model age in days was used as the time axis, to ensure optimal controlling for age (27). The model compares each case of dementia with all subjects in the study who are alive and free of dementia at the age when the dementia case was diagnosed. For the Cox regressions, SAS Proc PHREG v6.12 was used to estimate the age specific incidence of Alzheimer's disease and vascular dementia in relation to the use of NSAID and aspirin. Next to a time-dependent comparison in which ever use was compared to never use, we also used a time-dependent categorical variable in four mutually exclusive categories for the duration of use (no use, less than 1 month, 1-23 months and 24 months or more). Cut-points were chosen to ensure an adequate number of subjects in each group; in addition, a 2-year exposure period has previously been reported as a cutoff of interest (28). The time-dependent categorical exposure variable was represented in the models by use of 3 dummy variables, with no use as reference category.

Potential confounders that were examined included gender, baseline age, educational status, and time varying use of anti-diabetics (as proxy for diabetes), antihypertensives, histamine-2 (H2)-antagonists and either aspirin or NSAID. All risk estimates were also adjusted for these factors.

As the strength of the anti-inflammatory effect of NSAID increases with an increasing dose, we stratified according to the use of low or high mean use, defined as either a DDD $\leq$ 1 or a DDD>1.

In an earlier study, we found that a risk reduction was particularly present in subjects aged less than 85 years (9). In additional analyses, we therefore examined whether baseline age modified the effect of NSAID on Alzheimer's disease. Finally, to investigate the possibility of pharmacogenetic interaction we examined whether effects of NSAID were different over strata of sex and APOE, comparing the effect of NSAID in subjects with a APOE2E4, APOE3E4 or APOE4E4 genotype with that of those with an APOE3E3 genotype.

Modeling the relationship between drug exposure and dementia using a small number of exposure categories has some shortcomings (29, 30). First, the probably

smooth dose response relation is approximated with an unrealistic step function with sudden jumps. Second, no use is made of the within category information. Third, results can be sensitive for the choice of the category cut-points. Taking a larger number of categories makes the estimates very unstable. Therefore, as an alternative way of representing exposure in the model, we modeled the duration relationship using restricted quadratic spline regression with four knots (29, 30). This allows a smooth continuous estimate of the duration response relationship, while no within category information is lost. In this analysis we also examined whether excluding either the last one or last two years of follow-up was suggestive for the presence of a latency time (28, 31-33). In addition we did a trend test for each of the three splines.

Results

During 47498 person-years of follow-up a total of 394 subjects were diagnosed with dementia (mean follow-up 6.8 years). Of these patients 294 had Alzheimer's disease, of whom 264 without and 30 with cerebrovascular disease, 55 had vascular dementia and 45 other types of dementia. Of the 6989 participants, 60% were women, and 87% of the subjects had a follow-up of 5 years or more. Thirty-four percent had more

TABLE 1
General profile of Rotterdam Study cohort members followed between January 1991 and January 1999.

Variable	Category	Number of subjects (n=6989)		Number of Person-years (n=47498)		Dementia cases (n=394)
		Number	%	Number	%	Number
Gender	Male	2795	40.0	19014	40.2	125
	Female	4194	60.0	28484	59.8	269
Education	< 6 yr.	4407	63.1	29635	62.3	271
	≥ 6 yr.	2379	34.0	16834	35.6	82
	Missing	203	2.9	1029	2.1	41
Baseline age	≤ 65 yr.	3162	45.2	23485	50.0	25
	66-75 yr.	2323	33.2	15776	33.4	127
	76-85 yr.	1504	21.5	8237	17.3	242
Follow-up	< 3 yr.	461	6.6	920	1.9	155
	3-4 yr.	478	6.8	1930	4.1	102
	5-6 yr.	1651	23.6	10604	22.3	131
	≥ 7 yr.	4399	62.9	34044	71.7	6
APOE genotype	33	3780	54.1	26027	54.8	166
	24/34/44	1793	25.6	12240	25.8	137
	Missing	536	7.7	3086	6.5	49

than 6 years of education and 23.1% had either an APOE3E4 or APOE4E4 genotype (Table 1).

Diclofenac, ibuprofen and naproxen together accounted for approximately eighty percent of the total number of prescriptions and seventy percent of the total number of NSAID prescription days (table 2). Relatively more women than men had used NSAID at any time during follow-up (68.5 vs. 56.9%). Of subjects who used NSAID, women had a higher exposure fraction than men (7.0% vs. 4.0% of the total number of person-days). Those with a lower education more frequently used NSAID at any time during follow-up than those with higher education (66 vs. 60%). The rate at which NSAID were obtained from the pharmacy was remarkably constant over time and varied between 37 and 40 days of exposure per 1000 person days over the 8 years of follow-up (table 3). Aspirin was predominantly prescribed as a platelet aggregation-inhibiting drug (± 83% of total). However, even when registered as an oral analgesic, approximately 95% of the remaining 17 % prescriptions were in fact prescribed in platelet aggregation inhibiting doses. We therefore decided to pool both types of exposure. In total, 2340 (33.4%) subjects had used aspirin, 616 (8.8%) subjects had used anti-diabetic medication, 4012 (57.4%) antihypertensives and 1778 (25.4%) subjects had used H2-antagonists at any time during follow-up

Ever versus never use of NSAID, defined as a binary time dependent variable, was associated with a non-significant lower risk of Alzheimer's disease (RR 0.86; 95% CI 0.66-1.09). In examining duration of use, compared to non-use, the relative risk of Alzheimer's disease was 0.95 (95% CI 0.70-1.29) in incidental users, 0.83 (95% CI 0.62-1.11) in intermediate users and 0.21 (95% CI 0.05-0.83) for those subjects that used NSAID for 2 years or more. There were no substantial differences in type of NSAID use between cases and reference subjects. No relation was found between NSAID use and risk of vascular dementia (Table 4). For aspirin users, we found no relation with risk of Alzheimer's disease and an increased risk of vascular dementia that increased with the duration of use (Table 4).

In the stratified analyses, long-term NSAID users with a high average prescribed daily dose had relative risks comparable to users with a low average dose. For the incidental and intermediate users risks were lower in the high-dose group (table 5). Men seemed to have somewhat lower relative risks than females, although confidence intervals overlapped. The stratified analysis for age revealed a significantly lower risk in the intermediate duration stratum in younger subjects. Stratification for APOE genotype showed that subjects with an APOE2E4, APOE3E4 or APOE4E4 genotype had relative risks comparable to the reference group with an APOE3E3 genotype.

The restricted quadratic spline regression in figure 1 shows that our results as obtained from the categorical analyses with the sudden jump at 2 years of exposure slightly exaggerates the protective effect. In addition the figure shows that there is indeed a trend towards a lower risk with longer exposure. This trend becomes more prominent and significant after lagging either the last one or two years of follow-up

TABLE 2
Type and numbers of NSAID used in years 1991-1998 in the Rotterdam Study cohort.

Drug type	Prescriptions (number)	Percentage of total	Cumulative duration (days)	Percentage of total
Diclofenac	9723	40.71	225813	33.86
Ibuprofen	5114	22.25	140608	21.08
Naproxen	4177	17.49	109760	16.46
Piroxicam	1579	6.61	65564	9.83
Indomethacin	1099	4.60	47409	7.11
Ketoprofen	592	2.48	27385	4.11
Diclofenac combination	512	2.14	13597	2.04
Nabumetone	309	1.29	12736	1.91
Azapropazone	222	0.93	6060	0.91
Sulindac	127	0.53	5896	0.88
Meloxicam	75	0.31	2420	0.36
Tiaprofenic acid	64	0.27	3299	0.50
Flurbiprofen	55	0.23	4711	0.71
Tolfenamic acid	16	0.07	1039	0.16
Phenylbutazon	11	0.05	353	0.05
Tenoxicam	8	0.03	225	0.03
Benzydamine	2	0.01	28	0.004

TABLE 3
NSAID use according to calendar year of prescription from 1991-1998 in the Rotterdam Study cohort.

Calendar year	No of person days exposed	Total no of person days	Exposure rate (exposed/ total)	Mean prescription duration (days)	Total number of prescriptions
1991	101083	2548517	0.040	31.4	3224
1992	101058	2509431	0.040	29.5	3430
1993	94643	2431136	0.039	28.1	3366
1994	87544	2342662	0.037	27.2	3215
1995	82795	2258329	0.037	26.5	3127
1996	83801	2159938	0.039	26.5	3160
1997	72117	1911849	0.038	26.3	2745
1998	43862	1186759	0.037	27.1	1618

TABLE 4
Relative risk of Alzheimer's disease and vascular dementia according to duration of NSAID or aspirin referenced to no exposure (95% confidence interval).

Type of dementia and cumulative duration of NSAID or aspirin use	RR (95% CI)* of AD (n=294)	RR (95% CI)* of VaD dementia (n=55)
NSAID		
No exposure	1 (reference)	1 (reference)
≤ 1 month	0.95 (0.70-1.29)	1.25 (0.63-2.53)
> 1-23 months	0.83 (0.62-1.11)	1.36 (0.70-2.64)
≥ 24 months	0.21 (0.05-0.83)	0.99 (0.13-7.58)
Aspirin		
No exposure	1 (reference)	1 (reference)
≤ 1 month	0.76 (0.31-1.84)	-
> 1-23 months	1.30 (0.97-1.74)	2.99 (1.57-5.71)
≥ 24 months	0.76 (0.49-1.19)	4.88 (2.38-10.0)

*Adjusted for age, gender, education and use of H2-antagonists, antihypertensives, anti-diabetic medication and either aspirin or NSAID as time varying exposure. AD=Alzheimer's disease; VaD=vascular dementia.

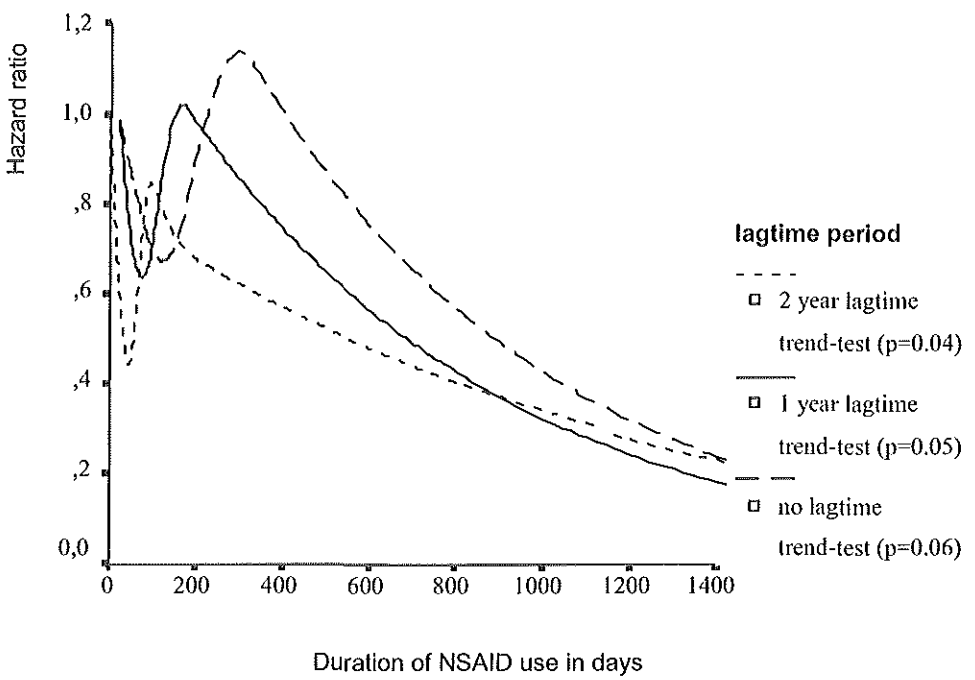

FIGURE 1
Duration of NSAID use and risk of Alzheimer's disease.

TABLE 5
Risk of Alzheimer's disease stratified for defined daily dose (DDD), baseline age, gender and APOE genotype according to duration of NSAID use (referenced to no exposure).

Strata (AD cases)	RR (95% CI)* of AD for < 1 month use	RR (95% CI)* of AD for 1-23 months of use	RR (95% CI)* of AD for ≥ 24 months of use
Average Daily Dose			
≤ 1 DDD	1.18 (95% CI 0.82-1.70)	1.04 (95% CI 0.73-1.49)	0.17 (95% CI 0.02-1.22)
> 1 DDD	0.77 (95% CI 0.50-1.19)	0.78 (95% CI 0.54-1.14)	0.25 (95% CI 0.03-1.78)
Baseline age			
< 80 years (n=152)	0.97 (95% CI 0.66-1.53)	**0.57 (95% CI 0.37-0.90)**	0.23 (95% CI 0.03-1.71)
≥ 80 years (n=142)	0.85 (95% CI 0.52-1.39)	1.14 (95% CI 0.77-1.69)	0.18 (95% CI 0.03-1.31)
Gender			
Male (n=81)	0.80 (95% CI 0.46-1.80)	**0.44 (95% CI 0.21-0.91)†**	
Female (n=213)	0.99 (95% CI 0.69-1.33)	0.95 (95% CI 0.69-1.40)	**0.23 (95% CI 0.06-0.94)**
APOE Genotype**			
24/34/44 (n=111)	0.85 (95% CI 0.52-1.39)	0.73 (95% CI 0.45-1.19)†	
33 (n=127)	1.07 (95% CI 0.71-1.63)	0.94 (95% CI 0.63-1.40)	0.41 (95% CI 0.10-1.72)

*Adjusted for age, gender, education and use of H2-antagonists, antihypertensives, anti-diabetic medication and either aspirin or NSAID as time varying covariates.
**Subjects with a different genotype and subjects of whom the genotype was unknown were excluded.
† Risks for combined period as there were no demented subjects in the long-term exposure category.

before the diagnosis.

Discussion

In this prospective population based cohort study, we found an increasing risk reduction of Alzheimer's disease with duration of NSAID use. This risk reduction was significant in subjects that used NSAID for more than two years. The risk reduction was more prominent when excluding the last two years, suggesting that NSAID may be less effective in the late pre-clinical stage. We found no relation between aspirin use and Alzheimer's disease. NSAID did not reduce the risk of vascular dementia.

In the prospective Rotterdam Study cohort, information on drug use was registered prospectively and independently of patient characteristics like age, sex and mental status. Using information gathered in this way avoided the limitations of earlier studies using information from interviews or medical records. Although the prospective cohort design effectively minimizes bias inherent to most cross-sectional and case-control studies, several aspects of validity need to be discussed that may affect our results.

Selection bias is unlikely, as our study is prospective and population-based with a high response rate (78%). During follow-up, however, pre-clinical dementia may be associated with a higher frequency of GP or specialist visits and therefore with a greater chance of finding indications for NSAID. If present this phenomenon would have led to an underestimation of a protective effect, as NSAID will spuriously be associated with an increased risk of Alzheimer's disease. Moreover, one would expect the same effect in people with Alzheimer's disease and in people with vascular dementia, which is not the case.

The main concern in almost all earlier studies was the potential for misclassification of exposure. In order to overcome this problem we used pharmacy records as exposure measure. These records provide indirect, independent and more reliable information regarding drug exposure, in particular when it comes to dose and duration. A limitation of our study is that NSAID therapy may have been initiated (and stopped) before 1991. It is likely, that some subjects that were incidentally exposed before 1991 may not have been exposed in the years after 1991 and vice versa. It is also likely, that some intermediate users were in fact long-term users. In case of a true protective effect this may be an explanation for the rather steep decline in risk early in the spline curve (fig. 1). An alternative explanation for this early decline may be random variation. Leaving subjects with less than 1 or 2 years of follow-up out of the analysis strengthened the trend towards a risk reduction, suggesting that this kind of misclassification may lead to an underestimation of a protective effect. With respect to chronic use, it is unlikely that former chronic users became non-users as diseases for which NSAID are prescribed chronically, rarely subside spontaneously.

The findings on aspirin are not straightforward to interpret. The validity of all

analyses depends on the assumption that a prescription is independent of the subsequent probability of dementia. However, low dose aspirin is generally prescribed for vascular problems that may contribute to, or precede the development of vascular dementia and possibly also of Alzheimer's disease (34,35). The increased risks found in our study in vascular dementia associated with the use of mainly low dose aspirin are thus likely to be a consequence of protopathic bias or of confounding by indication. To a lesser extent the same may have occurred in Alzheimer's disease. Therefore, it is too early to state that inhibition of platelet aggregation is not important in the prevention of Alzheimer's disease.

A problem in dose or duration response studies in dementia is the decision about biologically plausible categorizations. The arbitrary categorization may explain the large difference in risk below and above 2 years of NSAID exposure. To overcome this problem we used spline regression to describe NSAID use as a continuous variable. These analyses also suggested a tendency towards a risk reduction with increasing duration of use.

Our results strongly suggest that NSAID use is associated with a reduced risk of Alzheimer's disease. Suggested mechanisms are through inhibition of COX 1 and 2, thereby suppressing the arachidonate cascade leading to prostaglandin synthesis. Accumulating evidence indicates that COX-2 protein levels are increased in Alzheimer's disease brain and may correlate with levels of Aβ-peptide (36). In addition, some NSAID have been shown to attenuate inflammatory processes in a non-COX-dependent manner by directly activating the peroxisome proliferator gamma (PPAR-γ) nuclear transcription factor (4-6). This factor acts to suppress the expression of certain pro-inflammatory genes (5, 37). Alzheimer's disease has also been suggested to be a consequence of impaired vascular delivery of nutrients to the brain (38). The evidence indicates that cerebral capillary transport of vital nutrients is disturbed in brains of patients with Alzheimer's disease due to abnormal hemodynamic flow. An additional explanation for the link between NSAID and Alzheimer's disease may therefore be that NSAID and aspirin partly protect through their anti-clotting properties.

An alternative explanation is that either the indication for NSAID use or an other factor related to NSAID use may be associated with the occurrence of Alzheimer's disease, rather than NSAID use itself. However, we could not think of any such factor that could explain the observed risk reduction.

A comparison with existing data shows that the observed risk reduction is in line with evidence from immunological and histopathological studies suggesting that inflammatory mechanisms may be important in the pathophysiology of Alzheimer's disease. The results are also in line with some (28, 39) but not all longitudinal studies (9, 40-43) on the effects of NSAID in the prevention of Alzheimer's disease. Our results are closest to the Baltimore Longitudinal Study of Aging (28). In this study Alzheimer's disease risk was reduced in subjects using NSAID for more than 2 years

(RR 0.4; 95% CI 0.19-0.84). Overall use of aspirin and acetaminophen was not associated with Alzheimer's disease. Although, the results of this latter study are in accordance with our findings of a protective effect of NSAID in Alzheimer's disease, NSAID use was based on extrapolated cross-sectional interview data acquired during biennial examinations. Exposure gathered in this way is probably more vulnerable to (non)differential misclassification than when using pharmacy records, in particular when it comes to duration and dose of NSAID use.

In conclusion, the evidence from our study is consistent with a beneficial effect of NSAID used prior to the onset of Alzheimer's disease. Although there is some evidence from secondary prevention trials that NSAID may be effective in slowing cognitive decline (44, 45), this evidence is inconclusive. Moreover, it is questionable whether secondary prevention can be compared to primary prevention of Alzheimer's disease, given the huge damage, which exists once Alzheimer's disease is clinically present. Therefore in order to draw more definite conclusions we have to await results of primary prevention trials.

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Chapter 4

ANTIHYPERTENSIVES AND DEMENTIA

Antihypertensive drugs and incidence of dementia

The Rotterdam Study

ABSTRACT

There is increasing evidence that hypertension may contribute to the development of dementia. We investigated the relation of antihypertensive drug use and the risk of dementia in the cohort of the population based Rotterdam Study. The study cohort included 7046 elderly, free of dementia at baseline. Dementia was diagnosed in a stepwise procedure. First, participants were screened. Screen positives were further tested. Those suspected of dementia underwent a diagnostic work-up. Dementia and its subtypes were diagnosed according to prevailing criteria. A Cox proportional hazards regression analysis was used to estimate relative risks. After a mean follow-up of 2.2 years, subjects taking antihypertensive medication at baseline (n=2015) had a lower incidence of dementia (adjusted relative risk, 0.76; 95% confidence interval 0.52-1.12) than subjects without antihypertensive treatment. This risk reduction was most pronounced for vascular dementia, (adjusted relative risk, 0.30; 95% confidence interval 0.11-0.99). For Alzheimer's disease the relative risk was 0.87, but not significant. The risk of vascular dementia may be reduced by antihypertensive treatment. In order to confirm any association with Alzheimer's disease larger observational studies with longer follow-up are needed.

INTRODUCTION

There is increasing evidence that hypertension may contribute to the development of cognitive impairment and dementia (1-4), although there is certainly no general agreement on the mechanism (5). This logically leads to the hypothesis that lowering of the blood pressure with antihypertensive treatment might protect against the development of cognitive dysfunction and dementia.

In the Framingham Heart Study, there was no longitudinal association between cognitive function and blood pressure among subjects using antihypertensive drugs after more than 15 years of follow-up. However, in untreated subjects both higher systolic and diastolic blood pressure, were associated with a poor cognitive performance later in life (6). In a recently published 20-year follow-up study, it was also

shown that the association between hypertension at baseline and the development of cognitive dysfunction was strongest in untreated men (4).

Until now, however, evidence of a beneficial effect of antihypertensive treatment on the development of dementia in epidemiological studies is scarce. In the prospective population-based Kungsholmen study in subjects aged 75 years and older, use of antihypertensive medication was studied in relation to the onset of Alzheimer's disease. Among the non-demented subjects, persons with antihypertensive medication in general and diuretic monotherapy at baseline had a significantly reduced risk of developing both total dementia and Alzheimer's disease (7, 8). Other evidence comes from the Systolic Hypertension in Europe trial (Syst-Eur), in which treatment of isolated systolic hypertension with nitrendipine was associated with a borderline significant protective effect for total dementia. However, follow-up time was short (median 2 years) and numbers of demented subjects were very small in this study (9).

It is now clear that treatment of hypertension leads to a risk reduction of both cardiovascular morbidity and mortality. A possible consequence is that ethical problems will arise in the design and conduct of future clinical trials to assess the effect of blood pressure lowering on the risk of dementia. Therefore we investigated the association between use of antihypertensives and the incidence of dementia in the Rotterdam Study, a large observational prospective population-based study.

Methods

Study population

The Rotterdam Study is a prospective population-based cohort study of neurological, cardiovascular, locomotor and ophthalmological diseases in the elderly. After approval of the Medical Ethics Committee, all inhabitants of Ommoord, a suburb of Rotterdam in The Netherlands, aged 55 years or more and living in the district for at least one year were invited in 1990-1993 to participate in the study. Of the 10,275 eligible subjects, 7,983 (78%) participated and signed informed consent. During the home interview, trained interviewers administered a questionnaire covering, among other topics, socio-economic background, medical history and medication use. During subsequent visits to the research center, subjects underwent additional interviewing and clinical examinations, including screening and diagnosis of dementia. Complete data on dementia were available from 7,528 subjects. A diagnosis of dementia was made in 482 persons. The remaining 7,046 non-demented subjects were followed for an average of 2.2 years until the second round of examinations in 1993 and 1994. At these examinations, 5,571 (79%) participants were actively screened for dementia. Of 999 (14%) subjects who were not re-examined and 476 (7%) who died during follow-up, information on cognitive function was obtained

from close informants and general practitioners.

Drug exposure and other baseline measurements

At baseline participants were asked to report and show all medication used during the preceding week. Subsequently, all drugs were classified according to their corresponding Anatomical-Therapeutical-Chemical-code (ATC-code) (10). For the current study, a classification was made according to the nature of the drug-class: diuretics, beta-blockers, ACE-inhibitors, calcium channel blockers and other antihypertensives. We assumed that drugs with antihypertensive properties were used chronically, as hypertension rarely subsides spontaneously. At the research center height and weight were measured. Blood pressure was measured in the sitting position at the right upper arm with a random-zero sphygmomanometer and calculated as the mean of two consecutive measurements. Diabetes mellitus was defined as the use of anti-diabetic medication or at least one blood-glucose assessment higher than 11 mmol/l, according to WHO-criteria for epidemiological studies (11). A history of stroke was assessed during the baseline interview and verified with medical records by a neurologist. The ratio of the systolic blood pressure at the ankle to the systolic blood pressure at the arm was calculated for each leg. Peripheral arterial disease was considered present when this ankle-arm index was lower than 0.9 on at least one side (12).

In addition, prescription-filling data, provided by the 7 pharmacies in the Ommoord region, were available for approximately 99% of the cohort as of January 1991. These data comprise quantitative information on each individual prescription.

Case ascertainment of dementia

Both at baseline and at the follow-up examination, subjects were screened for dementia in a stepwise procedure. Subjects were screened on cognitive function using the Mini-Mental State Examination (MMSE) (13) and the Geriatric Mental State schedule (GMS) (14). Those scoring 25 or below on the MMSE or scoring 1 or more on the GMS were selected for further diagnostic evaluation. This included more detailed neuropsychological testing and an informant interview based on the Cambridge Examination for Mental Disorders of the Elderly (15), as well as a neurological examination. Some participants underwent magnetic resonance imaging of the brain. A clinical diagnosis of dementia was made according to the DSM-III-R criteria for dementia by a panel that reviewed all existing information. A sub-diagnosis of Alzheimer's disease was made according to the NINCDS-ADRDA criteria (16). A sub-diagnosis of vascular dementia was made according to the NINDS-AIREN criteria (17). After a mean follow-up of 2.2 years, a total of 162 demented subjects, including 116 (73%) subjects with Alzheimer's disease, of which 15 also had cerebrovascular disease, and 22 (14%) subjects with vascular dementia, were diagnosed.

Confounding variables

The following variables were considered possible confounders and were therefore entered into the statistical models: age, gender, diastolic and systolic blood pressure (mm Hg), and history of stroke and diabetes mellitus. Additional adjustments were made for body mass index (BMI: kg/m^2), smoking (never, former, current), education (<7 years, ≥7 years), living situation (independent, home for the elderly), baseline MMSE and peripheral arterial disease.

Statistical analyses

Analysis of covariance adjusted for gender and age was used to compare characteristics of subjects with and without antihypertensives at baseline. We used Cox proportional hazards regression analysis to calculate relative risks with 95% confidence intervals (95% CI) for total dementia, Alzheimer's disease with and without cerebrovascular disease and vascular dementia during use of antihypertensive drugs. For categorical data with missing values we incorporated missing indicator variables in the model.

Subsequently, we excluded 622 subjects of whom 376 had a missing blood pressure measurements, 243 a missing Mini Mental State Examination (MMSE) and 404 a missing body mass index (BMI). The mean age in this excluded group was higher than in the remainder of the population (77.6 vs. 68.6 years), they were more often females (71.9% vs. 58.7%) and were far more often inhabitants of homes for the elderly (36.7% vs. 4.7%).

To reduce the possibility of differential reporting of drug use because of potential pre-clinical dementia at baseline, we did an additional analysis in which we excluded subjects who were diagnosed with dementia within one year after baseline examination.

The risk of dementia in subjects with hypertension and associated co-morbidity may be different from subjects without hypertension. In a second sub-analysis, we therefore excluded all untreated subjects without hypertension according to the WHO criteria (18) and calculated relative risks of treatment for dementia (sub) types. According to the WHO hypertension is defined as a diastolic blood pressure of at least 95 mm Hg and/or a systolic blood pressure of at least 160 mm Hg.

Next, we studied the effect of gender. We examined whether gender modified the relation by calculating relative risks for men and women separately.

To examine confounding by indication we stratified according to monotherapy with first- (diuretics/beta-blockers) and second-line antihypertensive treatment (remaining drugs and combinations of drugs).

In order to examine whether misclassification of exposure was important in our study, we examined a sub-population of our cohort that had a first time examination after June 30 1991 (n=5101) and were not living in a home for the elderly. We used

this cut-off, as pharmacy data were only available as of January 1991. We then calculated the percentage of subjects that reported both antihypertensive drug use at baseline and filled an antihypertensive prescription at the pharmacy in the 6 months before baseline examination. As the duration of a prescription is normally limited to 3 months it is likely that most drugs were captured using a six month period.

Results

Of the 6,416 subjects included in the present study, 118 subjects developed dementia, of whom 82 had Alzheimer's disease, 18 vascular dementia and 18 other forms of dementia. In table 1, baseline characteristics are given for subjects with and without exposure to an antihypertensive drug. Mean age, diastolic- and systolic blood pressure and BMI were significantly higher in users of antihypertensive drugs. Furthermore, relatively many women were users and users more frequently had diabetes mellitus, peripheral arterial disease and a history of stroke. Finally, users were less often current smokers than non-users. The mean MMSE, grade of education and the proportion of subjects living independently were comparable between groups.

TABLE 1
General characteristics of participants at baseline.

Baseline measurements	Non-users N=4401	Users of anti-hypertensive drugs N=2015	Ancova*
Mean age (yrs)	67.4	71.4	P<0.001
Female gender	57.0%	62.5%	P=0.003
MMSE	27.6 (17-30)	27.6 (16-30)	Ns
Body mass index	25.8	27.4	P<0.001
Mean diastolic blood pressure (mm Hg)	73.1	75.1	P<0.001
Mean systolic blood pressure (mm Hg)	137.7	142.5	P<0.001
Smoking			
Current	24.6%	18.8%	P<0.001
Education of more than 6 years	36.1%	35.6%	NS
Diabetes mellitus	8.1%	14.2%	P<0.001
Housing			
Ho me for the elderly	4.5%	5.2%	NS
Markers of vascular disease			
Peripheral arterial disease	15.5%	21.1%	P<0.001
History of stroke	1.6%	3.9%	P<0.001

*Age and gender adjusted analysis of covariance.

TABLE 2
Use of any type of antihypertensive drug at baseline and the risk of dementia expressed as relative risk (95% confidence interval).

Dementia type	Number of demented subjects	Relative risk* N=6416	Relative risk† N=6416
Total dementia††	118	0.76 (0.52-1.12)	0.67 (0.45-1.00)
Total AD	82	0.87 (0.56-1.37)	0.77 (0.49-1.24)
AD without vascular pathology	68	0.94 (0.57-1.53)	0.83 (0.49-1.39)
AD with vascular pathology	14	0.64 (0.21-1.91)	0.63 (0.20-1.93)
Vascular Dementia	18	0.33 (0.11-0.99)	0.30 (0.09-0.92)

* Cox proportional hazards regression analysis adjusted for age, gender, diastolic and systolic blood pressure, diabetes mellitus and stroke.
† Additional adjustment for body mass index, baseline MMSE, smoking, education, living situation and peripheral atherosclerotic disease.
†† This includes 18 subjects with an other type of dementia: Parkinson's dementia (n=4), other type (n=13) and undetermined (n=3)

Of the 6.416 subjects 31.3% used antihypertensive medication of which 21.1% used monotherapy, 8.5% used two drugs and 1.7% used three or more drugs. In total 14.6 % reported use of beta-blockers, 15.3 % reported use of diuretics, 5.9 % reported use of calcium antagonists, 5.7 % reported use of ACE-inhibitors and 1.9 % reported use of other antihypertensives.

Table 2 shows a non-significant risk reduction for dementia in general in users of antihypertensive drugs. The risk reduction was significant and most prominent for vascular dementia. Furthermore, it was present independent of adjustments made for potential confounders. Risk reduction was similar when we excluded those subjects (n=27) with a diagnosis of dementia in the first year of follow-up or a follow-up of less than a year (data not shown). For Alzheimer's disease the reduction in risk was, although not significant, most prominent in those with vascular pathology. The exclusion of untreated subjects without hypertension revealed comparable risk estimates (table 3).

Stratified analysis revealed larger risk reductions for men (RR 0.52; 95% CI 0.22-1.20) than for women (RR 0.93; 95% CI 0.59-1.46) and for first line therapy than second line therapy (data not shown) for total dementia. However, in both instances confidence intervals overlapped largely. Stratification for individual drugs could not confirm the earlier suggestion that calcium-channel blockers (RR 0.70; 95% CI 0.32-1.52) and diuretics (RR 0.83; 95% CI 0.33-1.30) in particular are protective against dementia.

In those living independently at baseline the concordance between reported use and actually filled prescriptions in the pharmacy was high and not significantly different for both healthy subjects (n=4703: 94.6%) and demented subjects at follow-up (n=40: 92.9%).

TABLE 3
Relative risk of dementia according to drug use after exclusion of all normotensive subjects (diastolic blood pressure <95 mmHg and/or systolic blood pressure <160 mmHg) without treatment.

Dementia type	Number of demented subjects	Relative Risk (95% CI)*
Total dementia	61	0.67 (0.35 to 1.32)
Total AD	45	0.99 (0.47 to 2.12)
Vascular Dementia	10	0.11 (0.02 to 0.74)

*Cox proportional hazards regression analysis adjusted for age, gender, diastolic and systolic blood pressure, stroke, diabetes mellitus.

Of the 622 subjects excluded from the analysis because of missing values, approximately 40% reported use of blood pressure lowering drugs and the overall incidence of dementia was 29.9/1000 person years.

Discussion

In this population based prospective cohort study, we found a risk reduction of dementia in users of antihypertensive drugs. This risk reduction was most prominent and significant for vascular dementia and more pronounced in males. Risk reduction for Alzheimer's disease was, although not significant, most prominent in those with concomitant vascular disease.

Several issues of validity need to be discussed when interpreting these results, in particular potential information bias and confounding by indication.

First, we should consider whether misclassification of exposure may have affected our results. A major concern in earlier, cross-sectional or retrospective, drug studies on dementia was the potential for bias due to underreporting of drug use among cases by proxy informants. Although our study only comprised subjects who were not demented at baseline, one might fear subtle impairment of memory in the pre-clinical phase of dementia and therefore less reliable answers and potentially different health related behavior. A spurious protective effect might then be the consequence of underreporting of antihypertensive drug use in cases. To assess this problem we performed separate analyses for a sample restricted to those not demented in the first year of follow-up and found similar risk estimates.

Furthermore, in a study on the concordance of reported cardiovascular drug use at baseline and the actually filled prescriptions in the pharmacy an overall high correspondence was found for participants of the Rotterdam Study (19). For the present study, we examined a subset of the analytical sample and found no major differences between demented and non-demented at follow-up with respect to reported

use and filled prescriptions in the local pharmacy. Although we have no information on compliance, it seems unlikely that differential misclassification of antihypertensive drug use may explain the results. A second possibility of misclassification of exposure may have occurred because patients were not asked how long they had been treated. As demented subjects were older, the probability of detection of hypertension over time may have been higher and therefore also the probability of treatment may have been higher. If present, however, such a bias would have led us to underestimate the actual effect.

Misclassification of hypertension may also have happened as a consequence of the disease, as it has been suggested that blood pressure drops in the pre-clinical phase of Alzheimer's disease (20). When such a pressure drop happened before baseline this might theoretically have led to discontinuation of antihypertensive treatment and therefore to an underestimation of long-standing treatment of hypertension at baseline in subjects who became demented, resulting in a potential overestimation of the protective effect. However, it is not common practice to stop antihypertensive treatment, and we consider it unlikely that this kind of misclassification has affected our results.

In a study on the effects of antihypertensives on dementia confounding by indication is an important issue as there is evidence that long-standing hypertension could lead to dementia (1-4). Although we tried to minimize this problem by adjusting for a number of putative confounders, we can not exclude the possibility that there may be some residual confounding. However, residual confounding by indication would tend to underestimate a truly protective effect of antihypertensives in dementia. This could thus explain the lack of a statistically significant effect in Alzheimer's disease but not the observed risk reduction in VD. An alternative explanation for finding no significant effect in Alzheimer's disease may be the lack of power at the relative risk that we observed, in particular for the stratified analyses. However, given the 50 % risk reduction in the Syst-Eur trial and given the number of exposed and unexposed and an expected 2.5% occurrence of disease we had over 80% power to detect a significant risk reduction.

Given the existing evidence how should our study be valued? In contrast to the Syst-Eur (21) trial and the Kungsholmen study (7) we did not find a significantly reduced risk of dementia. However, although not significant, in the overall analyses we found a risk reduction of approximately 30%, which equals the reduction found in the Kungsholmen Study. An explanation for the lack of significance in our study is the higher mean age in the Kungsholmen Study leading to a higher exposure prevalence, a higher incidence of dementia and therefore a greater power.

Although it is known that treatment of hypertension reduces associated morbidity, to our knowledge no prior study has shown a risk reduction of vascular dementia. Moreover, our results do not indicate that there are harmful effects with respect to the occurrence of the dementia subtypes. Our results underline the importance of adequate antihypertensive treatment.

In conclusion, our results are supportive of a protective role of the use of antihypertensive medication in relation to the onset of dementia. Results were, however, based on a short-term follow-up and were only significant for vascular dementia. As future placebo controlled trials in subjects fulfilling established criteria for treatment are not likely to be executed because of ethical complications, studies with longer follow-up, a larger sample of demented subjects and longitudinal exposure data are needed to further explore this association.

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Chapter 5

ESTROGEN AND ALZHEIMER'S DISEASE

Hormone replacement therapy and risk of Alzheimer's disease

The Rotterdam Study

ABSTRACT

We report on the association between HRT use and the risk of Alzheimer's disease as observed in the Rotterdam Study. The study population comprised all women who were non-demented and had data on HRT exposure as provided during a baseline interview. Exposure to HRT use was defined either as ever use or as short-term (1-11 months) and long-term use (≥ 12 months). Dementia screening took place in 1990-93, 1993-1994 and 1997-1999; in addition, the cohort was continuously monitored for incident cases of dementia. Cox proportional hazards regression analyses were used to estimate the hazard function of Alzheimer's disease in relation to the use of HRT. Of the 3066 women in the study sample, 397 reported prior use of HRT. During a total of 17551 person-years of follow-up a total of 179 women developed Alzheimer's disease. We found no evidence of a risk reduction for Alzheimer's disease in HRT users with a relative risk of 0.83 (95% CI 0.45-1.51). This observation was present adjusted for age, age at menopause, artificial menopause, education, systolic blood pressure and smoking. There was no evidence of a dose response effect of HRT. In conclusion, our results are not supportive of a protective effect of HRT on Alzheimer's disease.

Introduction

In recent years, it has been hypothesized that decreasing levels of circulating estrogen after menopause might increase the risk of Alzheimer's disease and that substitution may postpone or even prevent the onset of the disease. Indeed, neurobiological and behavioral studies suggest that estrogens improve brain function. Proposed biological mechanisms by which estrogen might attenuate neuronal injury are through direct stimulation of cholinergic neurons, development of gliacytes, antioxidative properties, and down-regulation of the amyloid-β-42 production and also through a decrease in excitotoxicity (1-7).

Several epidemiologic studies examined the association between use of postmenopausal hormone replacement therapy (HRT) and the risk of Alzheimer's disease (8,

9). Some of these studies showed a lower risk of Alzheimer's disease in former HRT users, yet selection and observation bias could usually not be excluded. Furthermore, in some studies confounding of the association of estrogen use and Alzheimer's disease by lifestyle and demographic characteristics might have been present.

In the absence of results from primary prevention trials there is a need for prospective population based cohort studies, which are less vulnerable to bias. Therefore, we studied the association between HRT use and incident Alzheimer's disease in the population based Rotterdam Study.

Methods

Study population

The Rotterdam Study is a prospective population-based cohort study of neurological, cardiovascular, locomotor and ophthalmological diseases in the elderly. After approval of the Medical Ethics Committee, all inhabitants of Ommoord, a suburb of Rotterdam in The Netherlands, aged 55 years or more and living in the district for at least one year were invited in 1990-1993 to participate in the study (10). In the Rotterdam Study, 4853 post-menopausal women participated.

During a home interview, trained interviewers administered a questionnaire covering, among other topics, socio-economic background, medical history and medication use. During subsequent visits to the research center, subjects underwent additional interviewing and clinical examinations, including screening of dementia.

Assessment of exposure to hormone replacement therapy

During the baseline interview (1990-1993) questions on ever use of female hormones for menopausal complaints and duration of use were asked by trained interviewers. Women who reported the use of female hormones for menopausal complaints were considered to be exposed and included in the study as ever user. Women who reported the use of female hormones as contraceptive drug or for other reasons were excluded. Women reporting no prior use of female hormones were considered to be non-exposed and were defined as never users.

Case ascertainment of dementia

Both at baseline (1990-1993) and at the first (1993-1994) and second (1997-1999) re-examination, subjects were screened for dementia in a stepwise procedure. First participants were screened with a combined Mini Mental State Examination (MMSE) (11) and the Geriatric Mental State schedule (GMS-A, organic level) (12). Those scoring 25 or below on the MMSE or scoring one or more on the GMS were selected

for further diagnostic evaluation, comprising a CAMDEX diagnostic interview, which includes an informant interview (13). Finally, a neurologist, a neuropsychologist, examined subjects who were suspected of dementia and if possible a brain MRI was made. In addition to the dementia screening, the cohort is continuously monitored for interval cases of dementia (14). A clinical diagnosis of dementia and sub-diagnoses were made according to internationally accepted criteria (14, 15) by a panel that reviewed all existing information. In case of dementia, the date of onset was assumed to be midway the last date of the examination that the individual was known to be non-demented and the date of examination at which the individual was diagnosed as demented.

Measurement of potential confounders

Data included in the interviews were medical history, current medication, age at menopause defined as the cessation of menses for 1 year or more, type of menopause (natural or artificial), smoking habits, highest attained level of education. Height and weight were measured and a body mass index (BMI: kg/m^2) calculated. Blood pressure was measured twice with a random zero sphygmomanometer with the subject in sitting position, and averaged. Apolipoprotein E (APOE) genotyping was performed on coded DNA samples (16).

Statistical analysis

Of the 4221 non-demented women in this study, 4026 women had valid data on female hormone use. Of these, 2669 reported no prior use of female hormones, 397 reported a history of use of HRT, 854 reported use of female hormones as a contraceptive drug and 106 women used the drug for different reasons. After exclusion of these latter 960 women the analytical sample comprised 3066 women.

Analyses of covariance and chi-square statistics were used to compare baseline characteristics of ever HRT-users and never HRT-users. The strength of the association between Alzheimer's disease and HRT use was studied as a hazard rate using Cox proportional hazards regression analysis (17), with age as time axis and presented with 95% confidence intervals (95% CI). End points were death, dementia or the end of the study period, whichever came first. The multivariate analyses further included age at menopause, BMI, diastolic and systolic blood pressure, smoking, and type of menopause (natural/artificial). In these analyses, missing data on missing continuous covariates were imputed using the EM algorithm of SPSS 9.0. For missing data on categorical variables we used missing indicators.

To examine the effect of duration of HRT exposure, we compared the incidence of dementia in 3 strata: non-use, 1-11 months of use and 12 or more months of HRT use, in women reporting duration of hormone use.

Because it has been suggested that there may be a pharmacogenetic interaction

between APOE genotype and HRT use (18, 19), a separate analysis was done to test for effect modification by APOE genotype. To examine this, the study-population was divided into the following four groups: APOE4- (APOE2E2, APOE2E3 and APOE3E3) without HRT (reference), APOE4+ (APOE2E4, APOE3E4 or APOE4E4) with and without HRT and APOE4- with HRT.

In order to examine the potential effect of the excluded subjects (reporting use for contraceptive or other reasons) on risk estimates, a sensitivity analysis was performed in which the excluded subjects were assumed to be either exposed or unexposed.

Results

Users of HRT were younger, had significantly more often an artificial menopause

TABLE 1
Age-adjusted baseline characteristics of never vs. ever users of HRT. Values are means (SE) or proportions.

Characteristics	Never users of HRT (n=2669)	Ever users of HRT (n=397)	P-value*
Age	72.7 (0.18)	67.5 (0.38)	P<0.001
Body mass index	27.0 (0.08)	26.6 (0.21)	P=0.14
Age at menopause (yrs)	48.6 (0.01)	48.4 (0.15)	P=0.46
Systolic blood pressure (mmHg)	142.2 (0.43)	141.3 (1.11)	P=0.72
Diastolic blood pressure (mmHg)	73.7 (0.23)	73.5 (0.59)	P=0.43
Artificial menopause	20.1%	33.2%	P<0.001
Education			P=0.08
Primary education	33.6%	25.8%	
Primary vocational training	15.4%	17.8%	
Secondary education MAVO	18.2%	18.6%	
Secondary vocational training	9.9%	11.3%	
Secondary education HAVO/VWO	16.9%	20.6%	
College HBO	1.9%	2.3%	
University	3.9%	3.6%	
Other	0.3%	-	
APOE genotype			
E2/4, E3/4 and E4/4	26.4%	29.5%	P=0.22
Smoking			
Never smoking	59.1%	48.3%	P<0.001
Former smoker	25.2%	33.2%	
Current smoking	15.7%	18.4%	

Missing values in percentage of total: age at menopause = 3.4%; APOE=9.6%; blood pressure=5.2%; education=2.5%; smoking=1.4%; natural menopause=0.5%; BMI=7.7%. *Analysis of covariance adjusted for age or chi-square statistics when applicable.

and were significantly more often former and less often never smokers (Table 1). No significant age-adjusted differences were seen in BMI, age at menopause, blood pressure, and distribution of highest attained education and APOE genotype. Excluded subjects were younger (mean 62.6 years) than those included and had a lower incidence of dementia.

During 17751 person-years of follow-up (mean follow-up 5.7 years), 179 women developed Alzheimer's disease. The age and education adjusted analysis showed no effect of HRT on Alzheimer's disease (Table 2). Additional adjustment for blood pressure, smoking, BMI, age at menopause and type of menopause did not markedly change these results. A subsequent analysis, among subjects with data on the duration of HRT use (88%) showed no association between duration of HRT use and risk of Alzheimer's disease.

We did not observe a clear interaction of an APOE4+ genotype with HRT use. Compared to never users with an APOE4- genotype, a protective effect of HRT, if any, seemed to be limited to APOE4- carriers. In the APOE4+ group the risk of Alzheimer's disease was significantly higher both in ever and in never users. Ever HRT use was not associated with a protective effect within the APOE4+ group.

TABLE 2
Use and duration of hormonal replacement therapy and the risk of Alzheimer's disease expressed as relative risk (95% confidence interval).

HRT exposure	Cases	Relative risk* (95% CI)	Relative risk† (95% CI)
Never use	167	1.0 (reference)	1.0 (reference)
Ever use	12	0.82 (0.45-1.48)	0.83 (0.46-1.52)
Never use	167	1.0 (reference)	1.0 (reference)
1-11 months	6	0.89 (0.36-2.19)††	0.90 (0.37-2.21)††
≥ 12 months	5	1.0 (0.31-3.17)††	1.03 (0.32-3.30)††

* Cox proportional hazards regression analysis adjusted for baseline age and education.
† Cox proportional hazards regression analysis adjusted for baseline age, education, body mass index, smoking, blood pressure, age at menopause and type of menopause.
†† 52 women with missing duration excluded.

TABLE 3
Risk of Alzheimer's disease stratified by use of hormonal replacement therapy and APOE genotype.

HRT exposure and APOE genotype	APOE4-	APOE4+
Never HRT	1.0 (reference)	2.25 (1.60-3.18)
Ever HRT	0.43 (0.14-1.37)	3.21 (1.52-6.78)

Cox proportional hazards regression analysis adjusted for age and education. APOE4- denotes the APOE2E2, APOE2E3 or APOE3E3 genotype; APOE4+ means APOE2E4, APOE3E4 or APOE4E4. Subjects of whom APOE genotype was unknown were excluded (n=300).

The sensitivity analyses in which we examined the effect of the exclusion of women reporting use of female hormones for other purposes then HRT yielded an RR of 0.73 (0.44-1.23) when all excluded subjects were considered to be ever users of HRT and an RR of 0.88 (0.49-1.23) when all were considered to be never users of HRT.

Discussion

In this population-based study we found no evidence for a risk reduction of Alzheimer's disease in ever users of HRT. However, prior to interpreting the results, several methodological issues need to be addressed.

The main limitation of our study was the low exposure prevalence. Overall exposure to HRT was low in the age range where Alzheimer's disease incidence is highest (5.9% in subjects of over 75 years). The consequence of this low exposure prevalence is a lack of power. Therefore we could not evaluate with sufficient precision the role of duration, or effect modification by the various APOE genotypes.

The Rotterdam Study is a population based cohort study that by its prospective design reduces the potential for a number of biases, which may occur in case-control studies on HRT. Furthermore, it is representative of the general population in terms of socioeconomic status, education and HRT use.

Selection bias could be a problem. However, our study is population-based with a high response rate (78%) and very low loss to follow-up. Furthermore, additional sensitivity analyses on excluded subjects did not affect the risk estimate to a large extent. A number of studies have shown that estrogen users are healthier than never users. As a consequence, their risk of Alzheimer's disease may be lower independent of the pharmacological effect of HRT. As we adjusted for a number of proxies for health-status and moreover as we found no effect of HRT we feel confident that such selection did not contribute to the observed risk estimates. Therefore, we think that our findings are not likely to be explained as a consequence of selection bias.

A second potential hazard is that of information bias, as use of HRT was assessed by interview. Although all prevalent demented subjects were excluded there is a possibility of differential misclassification of exposure, as the agreement between self-reported HRT use and actual use may decrease with age and increasing age is associated with a higher risk of Alzheimer's disease. If such differential underreporting would be present this may lead to bias suggestive of a protective effect. However, a study on the agreement between interview information and physician records on history of menopausal estrogen use was not suggestive for such differential misclassification (20). The reported frequency of HRT use (13.0%) was comparable to that of another follow-up study from the Netherlands in which 12% of the women between 45 and 60 used HRT (21). In studies on HRT and Alzheimer's disease, timing of HRT intake may also be important. In our study, we were not

informed about the exact age at intake. In the past, however, HRT was usually started during menopause and there is no reason to assume differences with respect to this timing of HRT use between subjects who developed Alzheimer's disease and those who did not. Moreover, we adjusted for time of onset of menopause. Another source of misclassification may be the varying contents of HRT. According to data from the Dutch Institute of Medical Statistics the most frequently prescribed HRT in the study period were unopposed estrogens in a dose of 0.0625 mg daily (22). Besides conjugated equine estrogens, also estradiol was prescribed. Progestins were added in 0.6% of prescriptions in 1970, gradually increasing to 11% of prescriptions in 1986. As it is unknown if and how these progestins influence the Alzheimer's disease process, it is unclear how this could have affected our results.

Finally, we dealt with the issue of confounding, by adjusting for known risk factors for Alzheimer's disease. We measured the status of these risk factors at baseline, and applied them on HRT use before baseline. As most potential confounders are (relatively) stable, we do not expect these changes of covariates to have a large impact on our results.

How do our results compare to existing findings? Although studies have shown beneficial effects of estrogen on cognition and memory, evidence from epidemiological studies in Alzheimer's disease is limited and inconsistent. Of the published studies on late onset Alzheimer's disease, two-third suggested a decreased risk whereas the remaining studies showed no effect. Of the former studies only two were prospective cohort studies, both claiming a protective effect (18, 23). A "meta-analysis" of 10 observational studies, including the latter 2 studies, suggested a 29% decreased risk of developing dementia among estrogen users, but the findings of the studies are heterogeneous. This 29% reduction is different from our risk estimate of 0.83, but probably also not comparable. As our risk estimate was far from significant, our results are more compatible with no effect of HRT on Alzheimer's disease.

Existing evidence with regard to differences in HRT effect over various APOE genotypes is scanty and not in line with our findings (18, 19). However, these stratified analyses lacked sufficient power. In conclusion, our results are not supportive of a protective effect of HRT on the development of Alzheimer's disease. Whether or not HRT is preventive will probably not be definitely elucidated until the ongoing primary prevention trials are published. However, the results of two recently published secondary prevention trials in which the efficacy of estrogen did not differ from placebo, are also not very promising (24, 25).

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Chapter 6

PSYCHOTROPIC DRUGS AND COGNITIVE FUNCTION

Antidepressants and anticholinergic drugs, but not benzodiazepines, are associated with cognitive impairment

ABSTRACT

We describe a study on the relationship between the use of psychotropic drugs and cognitive function under everyday circumstances. In a population-based study of 1077 non-demented elderly subjects, data on the use of benzodiazepines, antidepressants, and drugs with anticholinergic properties were obtained during a structured interview. Cognitive function was assessed by a series of neuropsychological tests aimed to measure multiple cognitive domains, including global cognitive function (MMSE), memory function, mental processing speed and overall cognitive function. The results from linear regression analyses suggested that users of selective serotonin re-uptake inhibitors performed worse on memory tasks (-1.14 SD; 95% CI -2.08 to -0.19), and overall cognitive function (-0.87 SD; 95% CI -1.54 to -0.19) than non-users of investigated psychotropic drugs. Users of anticholinergic drugs and more in particular of tricyclic antidepressants performed worse on mental processing speed (-0.54 SD; 95% CI -1.0 to -0.09), on memory tasks (-0.57 SD; 95% CI -1.11 to -0.02) and on overall cognitive function (-0.55 SD; 95% CI -0.95 to -0.16), as compared to non-users. Benzodiazepine users did not differ significantly from non-users with respect to any of the cognitive scores. All results were adjusted for age, sex, educational level, CES-D (depression) score, concomitant use of other psychotropic drugs, as well as timing and validity of cognitive tests. In conclusion, in this study users of anticholinergic drugs and antidepressants performed significantly worse on tests measuring memory performance, mental processing speed and overall cognitive performance, whereas this was not found for benzodiazepine users.

INTRODUCTION

Benzodiazepines, selective serotonin re-uptake inhibitors (SSRIs), and tricyclic antidepressants (TCAs), are commonly associated with an increased risk of accidents in the elderly (1-5). Several factors have been proposed as important in the etiology of these potential drug-induced effects, such as dose and duration of administration, binding affinity and molecular structure (6, 7). As for the treatment of insomnia, there has been a trend towards the use of short-acting benzodiazepines and lower

doses. An example of this is the relatively new class of halogenated-5-aryl- (H5A) benzodiazepines (including triazolobenzodiazepines) (7). The use and development of these short-acting benzodiazepines has led to questions regarding safety, focusing on impairment of memory functions and speed of mental processing (8-16).

Mainly because of a more beneficial safety profile, antidepressive therapy has shifted from the use of TCAs to an increased use of SSRIs. TCAs have been associated with impairment of short-term memory and psychomotor speed (17, 18), which has been attributed to α-receptor blockade, to antihistaminic properties as well as to their anticholinergic properties. SSRIs are supposed to exert these effects to a lesser extent and sometimes even improve cognitive dysfunction (18). Anticholinergic drugs form a less homogenous group and are prescribed for various indications, like COPD, cardiac problems and depression. As a relative acetylcholine deficit is, for example, seen in Alzheimer's disease (19), anticholinergic drugs are expected to impair both memory and psychomotor performance.

In large database studies, investigating drug related accidents, moderate attention has been paid to potential confounders such as underlying depression, cognitive impairment or co-morbidity. On a population level little effort has been put into unraveling potential mechanisms of the use of psychotropic drugs and the increased risk of accidents. We hypothesized that an impairment of cognitive function and speed of mental processing may underlie this increased risk in users of psychotropic drugs. Although these drug effects have extensively been studied in healthy individuals in an experimental setting, much less is known of their impact under everyday therapeutic conditions. The aim of the present study was to determine whether the use of psychotropic drugs is associated with alterations in memory performance, speed of mental processing, and overall cognitive functioning in a non-demented elderly population under everyday circumstances and to study to what extent these associations are influenced by potential confounders.

We examined these associations in the population-based Rotterdam Scan Study in which data on drug use were collected without knowledge of the current study hypothesis and independently of neuropsychological tests (20).

Methods

Study population

The Rotterdam Scan Study is a population-based study of causes and consequences of age-related brain changes. Details concerning this study have been described elsewhere (20). The study was approved by the local ethics committee. Subjects were sex and age matched and eligible when they were aged between 60 and 90 years, not demented or blind, and as the Rotterdam Scan Study included cerebral MRI assessment, subjects did not have a MRI contraindication. Examinations took place

in 1995/96 and included a structured interview on medical history including drug use assessment and cognitive testing. Of 1717 eligible subjects, 1077 (62.5%) participated, and gave written informed consent. Participants were younger, with a mean age difference of 3.8 years ($p<0.001$), more often had a university degree (5% difference, $p=0.05$), and had higher baseline MMSE-scores (age and gender adjusted mean difference 0.4 points, $p<0.001$) than non participants.

Drug use assessment

Participants were asked to bring and report all currently used medication to the interview. At the research center, all drugs were classified according to their corresponding Anatomical-Therapeutical-Chemical-code (ATC-code) (21). All drugs coded as N05BA (anxiolytics), N05CD (hypnotics), N06AA (TCAs), and N06AB (SSRIs) or as drugs with anticholinergic properties were studied. Benzodiazepines were furthermore classified into H5A-benzodiazepines and non-H5A-benzodiazepines according to the presence of a halogenated 5-aryl group in the molecule. The prescribed H5A-benzodiazepines were lorazepam, flurazepam, flunitrazepam, lormetazepam, midazolam, and loprazolam. Non-H5A-benzodiazepines prescribed were diazepam, chlordiazepoxide, oxazepam, temazepam, nitrazepam and bromazepam. Eighty subjects received drugs with anticholinergic properties. Drugs prescribed in this group were mainly digoxine (41.3%), ipratropium (30%) and TCAs (imipramin, clomipramin, amitryptilin) (11.3%). The only SSRI prescribed was paroxetine. Participants and investigators had no knowledge of the research hypothesis when they recorded and classified the medication.

Measurement of cognitive function

To assess speed of mental processing, memory function and global cognitive function several neuropsychological tests were performed in each participant as described previously (20). To evaluate speed of mental processing four tests were used: an abbreviated Stroop test consisting of three subtasks (22), the Paper-and-Pencil Memory Scanning Task consisting of three subtasks (23, 24), the Letter-Digit Substitution Task, and a verbal fluency test in which as many animals as possible had to be named within sixty seconds. Memory performance was assessed by using a validated verbal word learning task (25). As a measure of global cognitive function we used the Mini Mental State Examination (MMSE) (26). Trained investigators administered the tests. We obtained compound scores for speed of mental processing, memory function and overall cognitive function by transforming raw test data into Z-scores. The compound score for speed of mental processing was calculated as the mean Z-scores of the 1-letter sub-task of the Paper-and-Pencil Memory Scanning Task, the naming sub-task of the Stroop test and the Letter-Digit Substitution task. The compound score for memory function was calculated as the mean Z-scores

for the immediate and delayed recall subtasks of the word-learning test. An overall compound for cognitive function was calculated as the weighted mean of the two other compounds (20). During testing, the reliability of the test results was coded. Codes for invalid test results comprised codes for lack of motivation, presence of cognitive or physical handicap, or deviation from the instructions. For 99% of all participants scores could be calculated of whom 90.5% had valid test-results for all neuropsychological tests.

Potential confounders

Data on potentially confounding factors including sex, age, level of education and mood disturbances according to the Center of Epidemiological Studies on Depression (CES-D) (27), were collected at the interview. Finally, we took into account the time of testing (morning or afternoon) and reliability of the neuropsychological test result.

Statistical Analyses

Demographic characteristics and depression variables were compared over various age groups using analysis of variance or chi-square statistics when appropriate.

Comparisons between benzodiazepine users and non-benzodiazepine users were made for benzodiazepine users in general, for benzodiazepines classified as hypnotics or anxiolytics and classified as benzodiazepines with or without a halogen molecule on position 5 of the aryl ring. In these two latter analyses subjects using both classes were excluded. Similar comparisons were made for users of anticholinergic drugs in general, TCAs, and SSRIs.

Subsequently, we performed multiple linear regression analysis to obtain the adjusted mean difference in cognitive function conditional on psychotropic drug user status. In this analysis we adjusted for age, sex, educational level, CES-D score, concomitant use of other psychotropic drugs, as well as timing and validity of cognitive tests.

Results

Basic characteristics of all 1077 participants according to three age strata are given in table 1. With increasing age, level of education and average MMSE score decreased and CES-D score increased. The use of psychotropic drugs, in particular the non-H5A-benzodiazepines, the hypnotic benzodiazepines and anticholinergic drugs increased with advancing age (table 1).

The relations between drug user-status and neuropsychological-test outcome are given in Table 2. There were no significant differences between any of the drug expo-

TABLE 1
Characteristics and drug use of the Rotterdam Scan Study Participants by age category.

Characteristics (N=1077)	AGE (YEARS)			p-value*
	60-69 (N=465	70-79 (N=416	80-89 (N=196)	
Age (SD)	65.2 (2.6)	74.7 (2.8)	83.7 (2.7)	-
Female	239 (51.4%)	211 (50.8%)	104 (52.7%)	Ns
Only primary education	140 (30.1%)	140 (33.7%)	96 (49.0%)	p<0.001
Mean MMSE (range)	27.8 (21-30)	27.4 (19-30)	26.8 (19-30)	p<0.001
Mean CES-D (SD)	5.3 (5.9)	6.2 (6.1)	6.5 (7.0)	p=0.021
Test-time after 13.00 hr	253 (54.4%)	257 (61.8%)	108 (55.1%)	Ns
Benzodiazepines†				
non-H5A	22 (4.7%)	30 (7.2%)	24 (12.2%)	p=0.002
H5A	5 (1.1%)	9 (2.2%)	7 (3.6)	Ns
Benzodiazepines††				
Anxiolytics	16 (3.4%)	20 (4.8%)	8 (4.1%)	Ns
Hypnotics	10 (2.2%)	19 (4.6%)	23 (11.7%)	p<0.001
Anticholinergic drugs	22 (4.7%)	25 (6.0%)	29 (14.8%)	P<0.001
Antidepressants				
SSRI	1 (0.2%)	2 (0.5%)	-	Ns
TCA	4 (0.9%)	3 (0.7%)	2 (1.0%)	Ns

*Tested with chi-square statistics or analysis of variance. NS=non-significant. † four subjects using both types excluded. †† five subjects using both types excluded

sure groups in global cognitive function as measured with the MMSE. The use of benzodiazepines had no significant relation to any of the cognitive measures. Users of anticholinergic drugs (n=80) in general, and in particular users of TCAs (n=9) performed significantly worse on measures for speed of mental processing and overall cognitive function as compared to non-users. In addition, TCA users performed significantly worse on measures of memory function. SSRI users (n=3) performed significantly worse on measures of memory function, as well as on overall cognitive function.

TABLE 2
The relation between drug use and neuropsychological-test outcome.

Test (compound score)	Difference in test result compared to non users (95% confidence interval)*			
	Mini Mental State Examination score	Mental processing speed (Z-score)	Memory performance (Z-score)	Overall cognitive performance (Z-score)
All benzodiazepine users (n=101)	0.06 (-0.54 to 0.42)	-0.08 (-0.24 to 0.08)	0.14 (-0.06 to 0.33)	0.04 (-0.10 to 0.17)
Benzodiazepines				
Non-H5A (n=76)†	0.10 (-0.59 to 0.40)	-0.10 (-0.28 to 0.07)	0.09 (-0.11 to 0.30)	-0.05 (-0.15 to 0.14)
H5A (n=21)	0.35 (-1.14 to 1.86)	0.28 (-0.23 to 0.80)	0.52 (-0.10 to 1.14)	0.40 (-0.04 to 0.85)
Benzodiazepines				
Anxiolytics (n=44)†	-0.20 (-0.87 to 0.47)	-0.15 (-0.37 to 0.08)	0.01 (-0.28 to 0.28)	-0.08 (-0.28 to 0.13)
Hypnotics (n=52)	0.03 (-0.58 to 0.63)	-0.05 (-0.26 to 0.15)	0.23 (-0.02 to 0.48)	0.09 (-0.09 to 0.27)
Anticholinergic drugs (n=80)	0.20 (-0.28 to 0.68)	***-0.17 (-0.33 to –0.04)***	-0.15 (-0.33 to 0.05)	***-0.16 (-0.30 to -0.01)***
Tricyclic anti-depressants (n=9)	-0.37 (-1.80 to 1.06)	***-0.54 (-1.0 to -0.09)***	***-0.57 (-1.11 to -0.02)***	***-0.55 (-0.95 to -0.16)***
Selective Serotonin Reuptake Inhibitors (n=3)	-0.40 (-2.85 to 2.05)	-0.60 (-1.39 to 0.18)	***-1.14 (-2.08 to -0.19)***	***-0.87 (-1.54 to -0.19)***

* Regression coefficients and 95% CI controlling for age, gender, educational level, CES-D score, co-medication, timing of the tests and test-status.
† Concomitant users excluded.

Discussion

In this population-based study, we found that the use of TCAs as well as of SSRIs was associated with an impaired function on multiple cognitive domains. These associations were independent of the subjects' depression score. We found that the use of benzodiazepines was not associated with impaired performance on any of the studied cognitive domains. This lack of association was found for the sub-classifications of anxiolytics and hypnotics, and did not depend on the presence of a halogen group in the molecule.

Major threats to the validity of any study consist of selection bias, information bias and confounding. Although in our study, as in any population based study, health status was an important determinant of participation, this was probably independent of preferential prescribing of pharmacotherapeutic subtypes of psychotropic drugs. Because the Dutch health insurance system provides the large majority of drugs without extra payment by patients, bias by preferential prescribing of drug-subtypes is unlikely. Because participants were asked to bring along their actual medication instead of merely reporting the used drugs, differential reporting of the use of drugs was excluded. Moreover, because no one was aware of the study hypothesis at the time of data collection, it is unlikely that over- or underreporting would be selective among drug-user groups, hereby limiting the extent of information bias that could have occurred. Misclassification of drug-use may have affected our results as no information was gathered on dose- and duration at the interview. Subjects on chronic treatment may have adapted better to pharmacological effects on performance than subjects who recently started. If so this may have led to an underestimation of the observed effects.

The indication for a specific drug prescription is a potential confounder in this study. As cognitive impairment, depression and sleeping problems often coincide, preferential prescribing of antidepressants and benzodiazepines to subjects with an impaired cognitive function, or vice versa, to depressive subjects could have occurred. To limit this bias we excluded subjects with dementia and adjusted the analyses for the score on the CES-D.

We found no relation between the use of benzodiazepines and cognitive function. Although it is possible that the used compound scores for cognitive function were not sensitive enough to reflect subtle differences in speed or memory tasks, we consider this unlikely as also in the separate neuropsychological tests no association was found between cognitive performance and the use of benzodiazepines (data not shown).

To our knowledge, this is one of the first population-based studies to report and quantify the association between psychotropic drug use and memory performance, speed of mental processing and overall cognitive functioning. Although the cross-sectional nature and small numbers of this study necessitate confirmation in larger

longitudinal studies, we found evidence that the use of antidepressants (SSRIs and TCAs) may contribute to cognitive impairment. In contrast, this was not found for users of benzodiazepines.

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Chapter 7

General discussion

Although dementia was early recognized as a distinct syndrome (1), for a long time it was thought to be an inevitable consequence of aging. The fact that age is indeed by far the most important known risk indicator for dementia may have contributed to the fact that research in this area has been relatively neglected. However, in recent years some light has been shed on the prevalence and incidence of dementia and its subtypes (2). Also a number of risk factors for dementia (3-8) have been identified. However, because of a naturally occurring order in scientific research in which identification of potentially beneficial agents usually follows the identification and evaluation of potential risk factors, evidence on the efficacy and effectiveness of these agents is still limited.

The studies described in this thesis were triggered by the perception that dementia and in particular Alzheimer's disease will be an increasingly important health problem in the coming decades and moreover, by the awareness that preventive agents and beneficial treatment modalities were largely absent.

The population-based Rotterdam Study, a single center prospective follow-up study of 7983 subjects, aged 55 years or over (9), that started in 1990 provided, and still provides, a unique opportunity to gain more knowledge on the epidemiology of dementia and also on the role of certain potentially beneficial pharmacological agents.

In this thesis, several of these agents have been studied. The rationale for investigating these agents is that inflammatory processes (10, 11), vascular (12-14), neuroprotective (15) and oxidative factors (16-18) and hormonal deficiencies (19-21) may play a role in the pathogenesis of dementia. All agents that we studied are drugs and therefore modifiable risk factors. This is important as this may create the possibility of modulating disease progression, postpone the onset of dementia or even prevent dementia. In addition, our research may provide new clues and ideas for future research.

After a brief description of the main findings, we will discuss some methodological problems, earlier discussed in chapter 2, which are typical for pharmacoepidemiological studies in dementia. In addition, we briefly discuss health care aspects and the clinical relevance of our findings. Finally, several potential dimensions of future research will be addressed.

Main findings

The main results on pharmacological agents and risk of dementia are extensively described in the earlier chapters of this thesis. In brief, we found a consistent inverse association between the long-term use of non-steroidal anti-inflammatory drugs (NSAID) and Alzheimer's disease. This finding is in line with existing evidence from immuno-histochemical, biochemical, molecular studies and observational studies indicating that inflammatory processes may be important in the pathophysiology of

Alzheimer's disease.

Following from the observation that hypertension may also contribute to the development of cognitive impairment and dementia (14, 22, 23), we examined the role of antihypertensive drugs. We found evidence for a beneficial effect of antihypertensive agents in the prevention of dementia, in particular in the prevention of vascular dementia but also in subjects with Alzheimer's disease in the presence of vascular disease.

In contrast to the results of a number of observational studies but in alignment with evidence from recent secondary prevention trials (24, 25), we found no evidence of a substantial beneficial effect of Hormone Replacement Therapy in Alzheimer's disease.

Next to these studies on dementia, we found anti-depressants and anticholinergic drugs, but not benzodiazepines, to be associated with impairment on multiple cognitive domains, in the cohort of the Rotterdam Scan Study of which the participants were free of dementia at the time of measurement.

Triggered by contradictory studies regarding the association between use of NSAID and the occurrence of Alzheimer's disease based on cross-sectional NSAID exposure and for a better understanding of the validity of these studies, we investigated the degree of measurement error induced by the use of interview data on NSAID in estimating chronic use. We showed that this type of information is an invalid measure for estimating chronic use in a population based cohort and moreover that these data should not be used in studies on Alzheimer's disease.

Methodological considerations

Validity

A number of biases have been described that apply to epidemiological studies in general (26). There are, however, certain types of bias that are particularly important for the interpretation of studies on drug exposure and Alzheimer's disease (27) and other types of dementia. Roughly they can be categorized as selection bias related to survival and to inclusion into the study; information bias by misclassification of exposure; and confounding by factors related to whether or not someone receives a medication (confounding by indication, severity or co-morbidity).

Selection bias

Selection bias may occur when the use of a drug leads to a difference in survival between cases and non-cases. For example, a drug may slow progression of a fatal disease that is differentially distributed between cases and controls. Or, inappropriate drug intake as a consequence of cognitive problems in the pre-clinical phase of dementia could lead to severe adverse effects and a lower survival. In both instances

in a study based on prevalent cases this may lead to the conclusion that the drug protects against dementia. Selection bias may also occur if cases and controls are drawn from different source populations (28, 29). Biased selection into a study population in studies of dementia may also occur when persons taking drugs against cardio- or cerebrovascular disease are in- or excluded from a diagnosis of Alzheimer's disease a priori.

Information bias

A major concern is the potential for misclassification of exposure to drugs. Adequate exposure assessment includes: type of drug compound, daily dose, duration and timing of use, and route of administration. These are all elements involved in studying dose-response effects of medications and therefore a potential source of misclassification.

Alzheimer's disease and to a certain extent also other types of dementia, are probably preceded by a long sub-clinical period, and it is very difficult to get reliable estimates of the exact time of onset. Different drugs may exhibit their beneficial properties at different times in the disease process. For example, antihypertensives may be protective in a very early phase or even before disease onset. When initiated in a late pre-clinical phase, however, these drugs may even be hazardous (30). In case of anti-inflammatory drugs there has to be inflammation in order to suppress it, whereas once given at a stage in which there are too many end stage lesions the effect may be minimal or even absent. An important potential source of misclassification is a difference between cases and controls, regarding the collected information from proxy informants. Furthermore, ever/never drug use reported in a baseline interview is often used as an approximation of chronic use. As chronic use generally increases with age and age is the most important risk factor for dementia, misclassification by such approximation may be differential and can not be adjusted for. An additional source of exposure misclassification may be differences in compliance between dementia cases and non-cases in the pre-clinical stage.

Confounding by indication, severity or co-morbidity or other forms of differential prescribing are particularly important in studies of persons with compromised cognitive function. It is possible that drugs are differentially prescribed, depending on the patients' cognitive status. For example, cognitively intact patients may more assertively demand drugs with a putative beneficial effect against cognitive impairment. This may lead to a differential prescription of these drugs and to an overestimation of its protective effect. Or, doctors may be reluctant to prescribe drugs with a high frequency of adverse reactions to cognitively impaired patients. An approach to reduce this problem in incidence studies on dementia with longitudinal exposure data is to use the method of lagging (31, 32). It is probable that drug usage patterns several years before clinical onset are less likely to be affected by the early symptoms of dementia.

Bias in prevalence studies

Cross-sectional studies use prevalent cases and this may lead to biased estimates. Validity may be compromised by selective survival, by an unclear exposure-disease sequence and by the fact that information is obtained from proxy informants.

Bias in incidence studies

Because of the absence of the so-called "prevalent-case bias", studies relying on incident cases of dementia are thought to be more valid with respect to strength and direction of the association. However, a problem typically arising in incidence studies, is the competing risk for death or dementia. This may be an alternative explanation for the finding that some drugs are inversely associated with onset of dementia. Users of certain drugs may have more co-morbidity and consequently a higher mortality rate than subjects who do not use these drugs. Users are then less frequently able to reach the endpoint of dementia because they die and appear to be protected by the drug. This may in particular be a problem in studies on drugs used in diseases with a high mortality rate.

Precision

Insufficient power is a potential problem that may arise in epidemiological studies on dementia, but is often not addressed. As most population-based epidemiological studies are multi-purpose and not specifically designed to study drug effects in Alzheimer's disease, sample size is often a limiting factor for studying drugs with a low exposure prevalence. This is in particular a problem when dose-response is under investigation, as inability to show dose-response effects limits the possibility to strengthen the likelihood of an association. Although power may be a real problem, an alternative explanation may be type of analysis that is used. Most frequently, the relationship between drug exposure and dementia is modeled using a small number of exposure categories. This method, however, has some shortcomings (33, 34). First, the probably smooth dose response relation is approximated with an unrealistic step function with sudden jumps. Second, no use is made of the within-category information. Third, results can be sensitive to the choice of the category cut-points. Taking a larger number of categories makes the estimates very unstable. Therefore, it may be better to use an alternative type of analytical method, such as spline regression (33, 34). This allows a smooth continuous estimate of the duration response relationship, while no within-category information is lost.

Clinical relevance and health care aspects

For all drugs studied in observational studies, it is currently unknown to what extent they really prevent or delay onset of dementia. Clinical and public health implica-

tions are therefore unclear and can only be discussed in very general terms. How could "society" benefit from these potential therapies? Costs of dementia depend on the perspective from which they are considered. Viewed from society, both direct and indirect costs are important. However, from the perspective of insurance companies and most pricing authorities, indirect costs are not or only marginally taken into account and usually not reimbursed. In contrast, from the viewpoint of policy makers indirect costs are of major importance, as these costs outweigh short-term direct costs. Next to these macro-economic costs (financial costs) also from the perspective of caregivers, "costs" are important. In a recent trial, the effect of metrifronate (a cholinesterase inhibitor) treatment on the psychological burden of caregivers was examined. The results suggested that beneficial drug therapy for patients could also have benefits for their caregivers (35). Brookmeyer et al. visualized the enormous potential impact of efficacious therapies that would delay Alzheimer's disease onset. They calculated that an average delay of Alzheimer's disease for one year, comparable with a 10% risk reduction, could in the USA lead to annual savings of $10 billion after a period of 10 years. An average risk reduction of 50% would lead to a decrease of an estimated 4 million demented subjects after a period of 50 years (36). Effective treatment and effective prevention would therefore have an enormous potential to reduce both direct and indirect costs associated with dementia.

Although trials for primary prevention are cumbersome, more intensive efforts by pharmaceutical companies might show whether some of these drugs could contribute to the prevention or treatment of Alzheimer's disease. Currently, such primary prevention studies appear to originate from outside the pharmaceutical industry. It is nevertheless, too easy to blame the pharmaceutical industry as it is doubtful whether they are provided with the incentives needed to invest in primary prevention. An additional problem follows from the growing awareness that dementing illnesses and cardiovascular disease may, at least in part, have a common etiology. This is important, as ethics committees may not easily approve adequately sized placebo-controlled primary prevention trials with existing drugs of proven efficacy. If for instance antihypertensives, besides lowering blood pressure, would decrease the risk of dementia it would be unethical to include a placebo-controlled arm in patients with hypertension. Finally, these committees will be reluctant to approve trials in healthy subjects using drugs with a high likelihood of adverse reactions.

Recommendations for future research

Several areas of future research can be identified:

• ***Development of pharmaco-epidemiological methods and analytical techniques***
Most observational studies of drugs in dementia, but also in other diseases, make use of cross-sectional drug exposure data or a history of drug use. As earlier men-

tioned, these type of data oversimplify exposure patterns and are analyzed accordingly. In order to more validly assess these associations the use of more reliable exposure data from pharmacy databases or from automated medication dispensing systems in combination with the use of more sophisticated analytical techniques should be encouraged.

• *Uniformity of diagnosis and development of diagnostic tools*

In current dementia research, incidence rates tend to vary over different populations. These differences are small in an absolute sense but large in a relative sense (2). Age specific differences in prevalence and incidence over various populations seem to reflect methodological rather than real differences (2). There is a tendency to use DSM III-R criteria and uniform additional criteria for sub-diagnoses of Alzheimer's disease (37) and vascular dementia (38). However, because of changing specificity and sensitivity application of these criteria to different populations may lead to different estimates of prevalence and incidence of dementia. Estimations of future absolute prevalence of dementia in the population are sensitive to assumptions about age-specific incidence rates and are therefore rather uncertain. The prevalence of Alzheimer's disease is expected to quadruple over the next 50 years in the USA and probably also in other western countries. Because of the expected high prevalence relatively large amounts of money will have to be allocated. Inappropriate allocation of these resources as a consequence of uncertainties in the estimated prevalence of dementia therefore carries a potential of important medical and social consequences. Therefore, there is a need to further optimize comparability of studies and to increase the standardization of screening and diagnostic tools.

• *Future contributions of observational studies*

Currently available therapy for Alzheimer's disease is mainly based on cholinergic augmentation. However, this type of drugs targets only one of several dysfunctional neurobiological systems. Cholinergic therapy improves cognition and reduces behavioral symptoms only slightly and in only 15 to 40% of patients with Alzheimer's disease (39, 40). There has been much debate as to the clinical relevance of currently available strategies (41, 42) as the ideal drug would improve memory and cognitive deficits and would simultaneously halt disease progression. Basic research has suggested new exciting therapeutic possibilities. Examples of these are anti-inflammatory, anti-amyloid and neuroprotective drugs addressing other aspects of the underlying neuropathology in Alzheimer's disease. As also shown in this thesis, these strategies may prove useful in slowing progression in an early phase.

Although in the end randomized trials are needed to really address the different hypotheses, observational studies may contribute by further exploration of the timing and mechanism of potential drug effects, by establishing the best outcome measure to study the effects of the interventions, by determining the optimal dose

level and the development of (genetic) techniques in order to be able to identify high-risk subjects (43). A highly important contribution of observational studies may come from areas in which it is no longer ethical to do placebo-controlled trials. A typical example is the potential effect of antihypertensive treatment on dementia. An important limitation of observational studies is that they only permit the exploration of the potential effects of existing drugs. This is important as currently available drugs only target a small minority of all receptors.

To develop meaningful strategies that reduce incidence or address progression of dementia, a further contribution of observational studies will be needed. This contribution in particular will have to come from studies in the post-marketing phase of new chemical entities. These studies, that will probably focus on effectiveness, are needed because the effects of drugs in large unselected populations under everyday circumstances are usually different from the effects that were expected on the basis of research in small selected trial populations, in which subjects are often followed for only a relatively short period of time. In the last few years, unforeseen safety issues, often detected by regulatory authorities, have led to a relatively large number of new drugs that had to be withdrawn from the market. These extremely costly affairs have already led to the recognition, by some, that in order to be optimally prepared there is a necessity of industry-initiated post marketing studies that address these issues. In the near future also pricing and regulatory authorities will more frequently be demanding these studies on effectiveness in order to get the drug reimbursed, respectively re-registered after 5 years.

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Chapter 8

SUMMARY / SAMENVATTING

8.1
Summary

The incidence of dementia rises exponentially after age 55. Several factors have been proposed as risk factor for this poly-etiological disease, although only few are really established. On the basis of these proposed risk factors several types of drugs have been proposed as being potentially efficacious in dementia.

The first part of this thesis focuses on what is known from observational studies on protective drug effects and discusses aspects of validity and precision. In the second part of this thesis the association of non-steroidal anti-inflammatory drugs (NSAID), aspirin, estrogen and antihypertensive use with dementia is examined and described. In addition, the association between cognitive function and the use of psychotropic medication in non-demented subjects is described.

In **Chapter 2** we review the existing epidemiologic studies on the effects of currently used drugs on AD, which have not specifically been designed for the prevention or treatment of Alzheimer's disease. The focus is on the potential methodological pitfalls related to validity and precision of the various studies.

NSAID and to a lesser extent hormone replacement therapy (HRT) are the drugs which have most frequently been studied in relation to Alzheimer's disease. A protective effect was most consistently demonstrated for the long-term use of HRT. However, only two-third of all published studies have been positive and secondary prevention trials are inconsistent. If proven efficacious a further growth of its use seems likely. Although optimistic reviews, mainly based on studies in prevalent Alzheimer's disease, have been published on the potentially protective role of NSAID in Alzheimer's disease, not all prospective studies support this. Even when these drugs appear to be protective, large-scale preventive use of these drugs in their current form is unlikely given their toxicity. However, these studies may boost the devel-

opment of safer NSAID.

Studies on antihypertensive therapy and Alzheimer's disease are scanty but promising. As these drugs are of proven efficacy in cerebro- and cardiovascular disease, placebo controlled primary prevention trials are unethical and additional observational studies are needed to quantify their effect.

Free radical scavengers comprise a variety of substances. The most promising, are Ginkgo biloba, selegiline and vitamin C/E. Evidence is promising but too limited and too diverse to draw conclusions. However, given the good safety profile of a number of these agents, if proven efficacious, a further increase in their use is likely.

Epidemiological studies on glucocorticoids, other anti-inflammatory drugs, H2-antagonists, and benzodiazepines are inconsistent and insufficient to judge their potential contribution. As glucocorticoids are toxic and benzodiazepines addictive during long-term use, it is unlikely that these drugs will be of major value in the primary prevention of Alzheimer's disease, even when effective.

In conclusion, we are only just in the beginning of making valid and useful assessments of protective drug effects in Alzheimer's disease. Currently available studies are often vulnerable to a number of obvious and less obvious biases. Given this fact, for no single agent preventive use is currently justified. For the future, placebo-controlled trials are needed but they may prove to be difficult. In the meantime, there are a number of niches that will remain in which observational studies will be able to contribute. However, in order to further untangle these often difficult issues more uniform and more valid approaches are needed.

In **chapter 3.1** a study on the validity of cross-sectional interview data as a measure of chronic use of non-steroidal anti-inflammatory drugs (NSAID) is described. We explored the effects of exposure misclassification on the association between reported and chronic use of NSAID and Alzheimer's disease. In this retrospective cohort study within the population-based Rotterdam Study, participants who were interviewed after January 1st 1992, who were registered with one of the pharmacies that provided data to the Rotterdam Study and who provided baseline interview data on drug use (n=4402) were included in the study. Sensitivity, specificity, negative and positive predictive value of interview data as a measure of NSAID exposure compared to pharmacy data were used as outcome measures. In conclusion, cross-sectional assessment of NSAID exposure is not a valid method for the assessment of chronic use of NSAID in the elderly. The validity of cross-sectional interview NSAID exposure data varies highly with age, sex and mental status. In our study the misclassification resulted in a bias towards the null regarding the association between chronic use of NSAID and Alzheimer's disease. However, cross-sectional exposure assessment of NSAID at baseline in a cohort study among elderly may yield risk estimates for Alzheimer's disease that can be biased in any direction since the amount of misclassification depends on age, gender and cognitive function at baseline. In

order to prevent this we recommend the use of longitudinal pharmacy data for drug exposure assessment in analytical epidemiologic cohort studies.

In **chapter 3.2** we present a study on the association between NSAID use over a ten year period and the risk for incident Alzheimer's disease using a nested case-control design in the population based Rotterdam Study. This study was performed as recent studies suggested that the use of non-steroidal anti-inflammatory drugs (NSAID) might reduce the risk of Alzheimer's disease. The study was performed in 306 subjects; 74 Alzheimer patients diagnosed according to NINCDS-ARDRA criteria and 232 age and sex matched controls. NSAID use was abstracted from general practitioners medical records and expressed as cumulative prescription days. The relative risk for Alzheimer's disease associated with long-term use (≥ 2 months) was 0.95 (95% CI: 0.46-1.99) as compared to non-users, after controlling for potential confounders. In a separate examination, subjects who had more than 6 months of prescription days had a non-significant reduced relative risk for Alzheimer's disease; 0.74 (95% CI: 0.20-2.72). In an age-stratified analysis the effect in long-term users was evident in those aged 85 and under; 0.53 (95% CI: 0.15-1.77). All risk estimates were lower when the last two years of exposure were excluded from the analyses. Our point estimates in subjects younger than 85 years and in subjects using NSAID for 6 months or more are consistent with the hypothesis that long-term use of NSAID reduces the risk of Alzheimer's disease. However, overall there was no significant association between NSAID use and the risk for incident Alzheimer's disease.

In **chapter 3.3** we examined the association between NSAID and Alzheimer's disease in more detail using a larger sample of demented subjects and more detailed and more reliable exposure data. A large number of observational studies on the association between NSAID and Alzheimer's disease have been published, but the results have been inconsistent. Almost all previous studies have obtained information on exposure to NSAID using methods vulnerable to misclassification. To examine the association between NSAID and aspirin use and the long-term risk of incident Alzheimer's disease and vascular dementia we conducted a prospective cohort study using data from the population-based Rotterdam Study. The study population comprised all subjects (n=6989) who were non-demented at baseline and had complete data on drug use during the study period provided by the 7 pharmacies serving this community. Dementia screening took place in 1990-93, 1993-1994 and 1997-1999. In addition, the cohort was continuously monitored for incident cases of dementia. Proportional hazards regression analysis was used to estimate the risk of Alzheimer's disease in relation to the use of NSAID. NSAID use was defined as four mutually exclusive time varying exposure categories: no exposure, less than 1 month (incidental), 1-23 months (intermediate) and 24 months or more (long-term). Adjustments were made for age, gender, education and use of aspirin, H2-antagonists, antihypertensives and anti-diabetic drugs. During 47498 person-years of follow-up,

394 subjects developed dementia, of whom 294 had Alzheimer's disease, 55 vascular dementia and 45 other types of dementia. Average follow-up was 6.8 years. Compared to non-use the relative risk of Alzheimer's disease was 0.95 (95% CI 0.70-1.29) in incidental users, 0.83 (95% CI 0.62-1.11) in intermediate users and 0.21 (95% CI 0.05-0.83) for those subjects that used NSAID for 2 years or more. The use and duration of NSAID use were not associated with the risk of vascular dementia. This study suggests that prolonged NSAID use may reduce the risk of Alzheimer's disease.

There is increasing evidence that hypertension may contribute to the development of dementia. In **chapter 4** we investigated the relation of antihypertensive drug use and the risk of dementia in the cohort of the population based Rotterdam Study. The study cohort included 7046 elderly, free of dementia at baseline. Dementia was diagnosed in a stepwise procedure. Participants were first screened. Screen positives were further tested. Those suspected of dementia underwent a diagnostic work-up. Dementia and its subtypes were diagnosed according to internationally accepted criteria. A Cox proportional hazards model was used to estimate relative risks. After a mean follow-up of 2.2 years, subjects taking antihypertensive medication at baseline (n=2015) had a reduced incidence of dementia (adjusted relative risk, 0.76; 95% confidence interval 0.52-1.12). A significant risk reduction was confined to vascular dementia (adjusted relative risk, 0.30; 95% confidence interval 0.11-0.99). For Alzheimer's disease the risk estimate was 0.87, but not statistically significant. In conclusion our results suggest that the risk of vascular dementia may be decreased by antihypertensive treatment. In order to investigate such a relation in Alzheimer's disease, larger observational studies with longer follow-up are needed.

Approximately fifteen studies on the association between hormonal/estrogen replacement therapy (HRT) and Alzheimer's disease (Alzheimer's disease) have been published, but the results have been inconsistent. Most previous studies, however, were either not population based or not prospective, leaving room for uncertainty because of potential bias inherent to the type of study. In **chapter 5** we report on the association between HRT use and the risk of Alzheimer's disease as observed in the Rotterdam Study. The study population comprised all women who were non-demented and had data on HRT exposure as provided during a baseline interview. Exposure to HRT use was defined either as ever use or as short-term (1-11 months) and long-term use (≥ 12 months). Dementia screening took place in 1990-93, 1993-1994 and 1997-1999; in addition, the cohort was continuously monitored for incident cases of dementia. Cox proportional hazards regression analyses were used to estimate the hazard function of Alzheimer's disease in relation to the use of HRT. Of the 3066 women in the study sample, 397 reported prior use of HRT. During a total of 17551 person-years of follow-up a total of 179 women developed Alzheimer's disease. We found no evidence of an important risk reduction for Alzheimer's disease in HRT users; relative risk 0.83 (95% CI 0.45-1.51). This observation was present adjusted

for age, age at menopause, artificial menopause, education, systolic blood pressure and smoking. There was no evidence of a dose response effect of HRT. In conclusion, our results are not supportive of a protective effect of HRT on risk of Alzheimer's disease.

In **chapter 6** we describe a study on the relationship between the use of psychotropic drugs and cognitive function under everyday circumstances. In a population-based study of 1077 non-demented elderly subjects, data on the use of benzodiazepines, antidepressants, and drugs with anticholinergic properties were obtained during a structured interview. Cognitive function was assessed by a series of neuropsychological tests aimed to measure multiple cognitive domains, including global cognitive function (MMSE), memory function, mental processing speed and overall cognitive function. The results from linear regression analyses suggested that users of selective serotonin re-uptake inhibitors performed worse on memory tasks (-1.14 SD; 95% CI -2.08 to -0.19), and overall cognitive function (-0.87 SD; 95% CI -1.54 to -0.19) than non-users of investigated psychotropic drugs. Users of anticholinergic drugs and more in particular of tricyclic antidepressants performed worse on mental processing speed (-0.54 SD; 95% CI -1.0 to -0.09), on memory tasks (-0.57 SD; 95% CI -1.11 to -0.02) and on overall cognitive function (-0.55 SD; 95% CI -0.95 to -0.16), as compared to non-users. Benzodiazepine users did not differ significantly from non-users with respect to any of the cognitive scores. All results were adjusted for age, sex, educational level, CES-D (depression) score, concomitant use of other psychotropic drugs, as well as timing and validity of cognitive tests. In conclusion, in this study users of anticholinergic drugs and antidepressants performed significantly worse on tests measuring memory performance, mental processing speed and overall cognitive performance, whereas this was not found for benzodiazepine users.

Finally, **chapter 7** briefly reflects our main findings. Our studies on NSAID and antihypertensives are suggestive of a beneficial effect whereas the study on HRT is not. However, these results should be confirmed in other studies, preferably in primary prevention trials. Subsequently, we discuss some methodological problems typical for pharmacoepidemiological studies in dementia. In addition, we briefly discuss health care aspects and clinical relevance of our findings. Lastly, several potential dimensions and proposals for future research are addressed, such as the further development of pharmacoepidemiological methods and analytical techniques, the promotion and stimulation of uniformity in diagnosis and development of diagnostic tools and lastly what the future contributions of observational studies should be.

8.2
Samenvatting

De incidentie van dementie stijgt exponentieel na het 55e jaar. Diverse factoren zijn geopperd als mogelijke risicofactor voor deze aandoening, hoewel het van slechts enkele vaststaat dat ze dat ook daadwerkelijk zijn. Op basis van deze voorgestelde risicofactoren is met betrekking tot een aantal geneesmiddelen verondersteld dat ze effectief zijn bij de behandeling of preventie van dementie.

Het eerste deel van dit proefschrift richt zich op hetgeen bekend is uit observationele studies omtrent de beschermende effecten van geneesmiddelen bij de ziekte van Alzheimer en behandelt aspecten van validiteit en precisie. In het tweede gedeelte van het proefschrift wordt het verband beschreven tussen dementie en het gebruik van respectievelijk *non-steroidal anti-inflammatory drugs (NSAID)*, aspirine, oestrogenen en antihypertensiva, zoals werd bestudeerd in het Erasmus Rotterdam Gezondheid en Ouderen (ERGO) onderzoek. Daarnaast wordt het verband beschreven tussen het gebruik van psychotrope medicatie en de cognitieve functie van niet demente ouderen.

In **hoofdstuk 2** bespreken wij de bestaande epidemiologische studies naar de effecten van geneesmiddelen in relatie tot het ontstaan van de ziekte van Alzheimer. Het hoofdstuk concentreert zich met name op de methodologische valkuilen in de diverse studies met betrekking tot validiteit en precisie.

NSAID en in mindere mate hormonale substitutie therapie vormen de medicamenteuze behandelwijzen die het meest uitgebreid zijn bestudeerd in relatie tot de ziekte van Alzheimer. Een beschermend effect lijkt het meest consistent aanwezig bij langdurig gebruik van hormonale substitutie therapie. Echter, slechts tweederde van alle observationele studies was suggestief voor een beschermend effect. In de ERGO-populatie vonden wij geen aanwijzingen voor een beschermend effect. Ook

secundaire preventie *trials* blijken tot op heden geen duidelijk beschermend effect aan te tonen. Wanneer hormonale substitutie therapie effectief zou blijken te zijn, is een verdere groei van het gebruik echter waarschijnlijk. Hoewel optimistische epidemiologische overzichtsartikelen zijn gepubliceerd over de mogelijk beschermende rol van NSAID bij de ziekte van Alzheimer zijn deze gegevens voornamelijk gebaseerd op dwarsdoorsnede onderzoek en worden de resultaten niet in alle prospectieve studies bevestigd. Alhoewel deze geneesmiddelen echt lijken te beschermen tegen de ziekte van Alzheimer, is grootschalig gebruik in de huidige vorm onwaarschijnlijk, gegeven het hoge risico op bijwerkingen bij chronisch gebruik. Anderzijds zou de ontwikkeling van nieuwe NSAID met een gunstiger balans werkzaamheid/schadelijkheid hier verandering in kunnen brengen.

Studies naar de effectiviteit van antihypertensieve therapie in relatie tot de ziekte van Alzheimer zijn schaars maar veelbelovend. Omdat deze geneesmiddelen effectief zijn bij cerebro- en cardiovasculaire ziekten, zijn placebo gecontroleerde primaire preventie *trials* onethisch en zijn additionele observationele studies noodzakelijk om het effect te kwantificeren.

Het begrip "vrije radicalen vangers" omvat een variëteit aan substanties. De meest veelbelovende zijn Ginkgo biloba, selegiline en vitamine C/E. De resultaten van studies naar de toepassing van deze potentiële geneesmiddelen bij dementie zijn nog onvoldoende en te divers om een goed oordeel te kunnen vormen. Gegeven het aanvaardbare veiligheidsprofiel van een aantal van deze middelen is een verdere groei van het gebruik bij bewezen effectiviteit zeer waarschijnlijk.

Epidemiologische studies naar de effecten op dementie van glucocorticoiden, andere anti-inflammatoire middelen, H_2-antagonisten en benzodiazepinen zijn te inconsistent en/of te schaars om hun potentiële rol te kunnen beoordelen. Gegeven het feit dat glucocorticoiden toxisch en benzodiazepinen gewennend zijn bij langdurig gebruik is het onwaarschijnlijk dat deze geneesmiddelen van grote betekenis zullen zijn voor de preventie van de ziekte van Alzheimer, zelfs wanneer ze werkzaam zijn.

Concluderend kan worden gesteld dat slechts onlangs een begin is gemaakt met de uitvoering van valide en bruikbare studies naar de beschermende effecten van geneesmiddelen bij de ziekte van Alzheimer en andere vormen van dementie. De nu beschikbare studies zijn vaak gevoelig voor een aantal duidelijke en minder duidelijke *biases* (vertekeningen). Gegeven dit feit is er op dit moment geen rechtvaardiging voor het chronisch gebruik van een van de bovengenoemde geneesmiddelen bij de preventie van dementie, tenzij overige indicaties (bijvoorbeeld antihypertensiva bij patiënten die tevens hypertensie hebben) het gebruik van deze geneesmiddelen noodzaakt. Eerst zullen de effecten in placebo gecontroleerde studies moeten worden bevestigd, ook al zullen deze soms moeilijk zijn uit te voeren. Tot die tijd zijn er een aantal onderzoeksterreinen waaraan observationele studies een bijdrage kunnen leveren.

In **hoofdstuk 3.1** wordt een studie beschreven naar de validiteit van interviewgegevens uit dwarsdoorsnede onderzoek als maat voor chronisch gebruik van NSAID. Wij onderzochten de effecten van misclassificatie van expositie met betrekking tot het verband tussen de ziekte van Alzheimer en gerapporteerd en chronisch gebruik van NSAID. In deze cohort studie binnen het ERGO-onderzoek werden deelnemers geïncludeerd wanneer zij waren geïnterviewd na januari 1991, geregistreerd waren bij een van de deelnemende apotheken en interviewgegevens hadden met betrekking tot het geneesmiddelgebruik (n=4402). Om de concordantie tussen interview- en apotheekgegevens te meten gebruikten wij als uitkomstmaten de sensitiviteit, specificiteit en de positief- en negatief-voorspellende waarde. Concluderend kan gesteld worden dat huidig gebruik ten tijde van een interview geen goede maat is voor chronisch gebruik van NSAID bij ouderen. De uitkomstmaten van de interviewgegevens variëren sterk met leeftijd, geslacht en cognitieve functie. In onze studie resulteerde deze misclassificatie in een risicoschatting met een vertekening in de richting van geen beschermend effect van NSAID op de ziekte van Alzheimer. Het probleem is echter dat een expositiemeting op basis van dergelijke gegevens uit dwarsdoorsnede onderzoek risicoschattingen kan geven, die zowel tot een overschatting als tot een onderschatting van het effect kunnen leiden. Dit omdat de mate van misclassificatie afhangt van leeftijd, geslacht en cognitieve functie. Om dit te voorkomen raden wij aan in analytische epidemiologische cohort studies zoveel mogelijk gebruik te maken van longitudinale apotheekgegevens voor het vaststellen van geneesmiddelexpositie.

In **hoofdstuk 3.2** presenteren we een studie naar het verband tussen het gebruik van NSAID gedurende een periode van 10 jaar en het risico op de ziekte van Alzheimer. Hierbij maakten wij gebruik van een patiënt-controle onderzoek genest in het ERGO-onderzoek. De studie werd uitgevoerd omdat recente studies suggereerden dat gebruik van deze geneesmiddelen mogelijk het risico op de ziekte van Alzheimer zou verminderen. De studie werd uitgevoerd bij 306 personen waarvan bij 74 patiënten de diagnose was gesteld volgens NINCDS-ADRDA criteria, en bij 232 op leeftijd- en geslacht gematchte controles. Het geneesmiddelgebruik werd vastgesteld aan de hand van huisartsgegevens. Het relatieve risico op de ziekte van Alzheimer bij langdurig gebruik (≥2 maanden) was 0.95 (95%-betrouwbaarheidsinterval [95%BI]: 0.46-1.99) vergeleken met niet-gebruikers na correctie voor mogelijke confounders. Personen met een gebruik van meer dan 6 maanden hadden een risico van 0.74 (95%BI:0.20-2.72). In een - op leeftijd gestratificeerde - analyse was het effect bij de langdurig gebruikers meer uitgesproken bij personen tot 85 jaar. Alle risicoschattingen waren lager wanneer de laatste twee jaar van expositie werden uitgesloten. De risicoschattingen bij mensen jonger dan 85 jaar en bij langdurig geëxponeerden zijn consistent met de hypothese dat langdurig gebruik van NSAID beschermt tegen de ziekte van Alzheimer. Er was echter geen sprake van een significant beschermend verband tussen het gebruik van NSAID en de ziekte van Alzheimer. De lage aantallen en de matige registratie van geneesmiddelgebruik in de huisartsgegevens hebben

hier waarschijnlijk in belangrijke mate aan bijgedragen.

In **hoofdstuk 3.3** onderzochten we het verband tussen NSAID en de ziekte van Alzheimer in meer detail, met grotere aantallen en met betrouwbaarder expositiegegevens. Genoemde associatie is in een groot aantal observationele studies onderzocht, echter met tegenstrijdige resultaten. Bijna alle eerdere studies maakten gebruik van informatiebronnen voor vaststelling van expositie die gevoelig zijn voor misclassificatie. Om de relatie tussen het gebruik van NSAID en aspirine en de ziekte van Alzheimer en vasculaire dementie te onderzoeken verrichtten wij een prospectieve cohort studie waarbij gebruik werd gemaakt van de gegevens van het ERGO-onderzoek. De studiepopulatie omvatte 6989 mensen die bij aanvang van de studie niet dement waren en complete geneesmiddelexpositiegegevens hadden gedurende de follow-up volgens de 7 apotheken in Ommoord. Screening van dementie vond plaats in 1990-93, 1993-94 en in 1997-99. Daarnaast werd het cohort continu gevolgd om tussentijdse gevallen van dementie op te sporen. Gebruik van NSAID werd gedefinieerd als vier wederzijds uitsluitende expositie-categorieën: geen blootstelling, minder dan een maand (incidenteel), 1-23 maanden (intermediair) en 24 maanden of meer (langdurig). Analyses werden gecorrigeerd voor leeftijd, geslacht, hoogst behaalde opleiding, gebruik van aspirine, H_2-antagonisten, antihypertensiva en antidiabetica. Gedurende 47498 persoonsjaren ontwikkelde 394 mensen dementie waarvan 294 de ziekte van Alzheimer hadden, 55 vasculaire dementie en 45 een ander type dementie. De gemiddelde follow-up was 6.8 jaar. Vergeleken met niet gebruikers hadden incidentele gebruikers een relatief risico van 0.95(95%BI: 0.70-1.29), intermediare gebruikers 0.83 (95%BI: 0.62-1.11) en diegenen die NSAID gedurende 2 jaar of langer gebruikten een relatief risico van 0.21 (95%BI: 0.05-0.83). Voor vasculaire dementie werd geen risicovermindering waargenomen. Deze studie suggereert dat langdurig gebruik van NSAID de kans op de ziekte van Alzheimer verkleint.

Er zijn steeds meer aanwijzingen dat hypertensie bijdraagt aan de ontwikkeling van dementie. In **hoofdstuk 4** onderzochten we het verband tussen het gebruik van antihypertensiva en het risico op dementie in het ERGO onderzoek. De cohortstudie omvatte 7046 niet-demente ouderen. Dementie werd gediagnosticeerd in een stapsgewijze procedure. Deelnemers werden eerst gescreend waarna de screen-positieven verder werden onderzocht en getest. Dementie en subtypes van dementie werden gediagnosticeerd volgens internationaal aanvaarde criteria. Na een follow-up van gemiddeld 2.2 jaar bleken personen die bij aanvang van de studie antihypertensiva gebruikten (n=2015) een lager risico op dementie te hebben dan niet behandelden, corresponderend met een relatief risico van 0.76 (95%BI: 0.52-1.12). Een significant verlaagd risico van 0.30 (95%BI: 0.11-0.99) werd alleen gezien voor vasculaire dementie. Het relatieve risico op de ziekte van Alzheimer was met 0.87 niet significant verlaagd. Onze resultaten suggereren dat het risico op vasculaire dementie ver-

laagd wordt door het gebruik van antihypertensiva. Om een dergelijk verband bij de ziekte van Alzheimer te kunnen onderzoeken zijn grotere en langere observationele studies noodzakelijk.

Tot op heden zijn ongeveer 15 studies gepubliceerd waarin het verband tussen oestrogeen substitutie therapie en de ziekte van Alzheimer wordt beschreven, maar de resultaten van deze studies zijn niet eenduidig. Op de meeste van deze studies is wel iets aan te merken, ofwel omdat ze niet *population-based* zijn, ofwel niet prospectief zijn uitgevoerd zodat vertekening mogelijk is. In **hoofdstuk 5** beschrijven wij het verband tussen het gebruik van oestrogeen substitutie en het risico op de ziekte van Alzheimer, zoals dat werd gevonden binnen het ERGO onderzoek. De studiepopulatie omvatte alle vrouwen die bij het begin van de studie niet dement waren en van wie gegevens bekend waren met betrekking tot oestrogeen substitutie, zoals verkregen middels een interview bij aanvang van de studie. Blootstelling aan oestrogenen werd gedefinieerd als ooit of als kortdurend (1-11 maanden) en langdurend (12 maanden of meer). Screening van dementie vond plaats in 1990-93, 1993-94 en in 1997-99. Daarnaast werd het cohort continu gevolgd om tussentijdse gevallen van dementie op te sporen. Van de 3066 vrouwen in de studiepopulatie rapporteerden er 397 gebruik van oestrogeen substitutie. Gedurende 17551 persoonsjaren ontwikkelden 179 vrouwen de ziekte van Alzheimer. Wij vonden geen aanwijzingen voor een belangrijke risico reductie. Het relatieve risico op de ziekte van Alzheimer bij gebruikers was 0.83 (95%BI: 0.45-1.51). Deze risicoschatting was aanwezig na correctie voor leeftijd, leeftijd waarop de menopauze intrad, hoogste opleiding, systolische bloeddruk en roken. Er waren geen aanwijzingen voor een dosiseffect relatie. De belangrijkste conclusie is dat oestrogeen substitutie na de menopauze niet lijkt te beschermen tegen de ziekte van Alzheimer.

In **hoofdstuk 6** beschrijven wij een studie naar de relatie tussen het gebruik van psychotrope geneesmiddelen en cognitieve functie onder alledaagse omstandigheden. In een populatie-onderzoek bij 1077 niet demente personen werden bij aanvang middels een gestructureerd interview gegevens verzameld met betrekking tot het gebruik van benzodiazepinen, antidepressiva en geneesmiddelen met anticholinerge effecten. De cognitieve functie werd bepaald met behulp van een aantal neuropsychologische tests gericht op een aantal domeinen van de cognitie, waaronder algemene cognitieve functie (MMSE), geheugenfunctie, mentale verwerkingssnelheid en globale cognitieve functie. De resultaten van de lineaire regressie analyses toonden dat gebruikers van selectieve serotonine heropname remmers slechter presteren op het gebied van geheugen (-1,14 SD; 95%BI: -2.08 tot -0.19) en globale cognitieve functie (-0.87 SD; 95%BI: -1.54 tot -0.19) dan niet gebruikers van genoemde psychotrope geneesmiddelen. Gebruikers van anticholinerge geneesmiddelen - in het bijzonder van tricyclische antidepressiva - scoren slechter op verwerkingssnelheid (-0.54 SD; 95%BI: -1.0 tot -0.09), geheugen (-0.57 SD; 95%BI: -1.11 tot -0.02) en globale cognitieve

functie (-0.55 SD; 95%BI: -0.95 tot -0.16). Gebruikers van benzodiazepines hadden scores die vergelijkbaar waren met die van personen die geen psychotrope geneesmiddelen gebruikten. Deze resultaten werden gecorrigeerd voor leeftijd, geslacht, hoogste opleiding, CES-D (depressie) score, gelijktijdig gebruik van andere psychotrope geneesmiddelen alsmede de timing en validiteit van de tests.

In **hoofdstuk 7** ten slotte worden onze voornaamste bevindingen beschreven. Onze studies naar NSAID en antihypertensiva suggereren een beschermend effect tegen het optreden van dementie, terwijl geen significant beschermend effect werd waargenomen voor oestrogeen substitutie. Deze resultaten zullen echter bevestigd moeten worden door andere studies, bij voorkeur door middel van prospectief gerandomiseerd onderzoek. In dit hoofdstuk wordt tevens een aantal methodologische problemen besproken die zich vaak voordoen bij farmacoepidemiologische studies op het gebied van dementie. Daarnaast bespreken wij kort de consequenties voor de gezondheidszorg en de klinische relevantie van onze bevindingen. Ten slotte worden enkele voorstellen voor toekomstig onderzoek gedaan, zoals een verdere ontwikkeling van farmacoepidemiologische methoden en analyse technieken en de bevordering van eenvormigheid in het stellen van de diagnose dementie. Voorts wordt besproken welke de toekomstige bijdragen van observationele studies zouden moeten zijn.

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Bas in 't Veld was born on August 13, 1966 in Leiden, The Netherlands. He graduated in 1984 from secondary school (Atheneum B, 'Nijmeegse Scholen Gemeenschap', Nijmegen). In that same year he started his medical studies. In 1993, he obtained his medical degree and subsequently worked in various hospitals as a resident in neonatology, pediatrics, cardiology, and emergency medicine and in intensive care medicine. In 1996 he started his research project, described in this thesis at the department of Epidemiology and Biostatistics, Erasmus Medical Center Rotterdam (chair: Professor A. Hofman). At the same time he was appointed as Drug Safety Inspector at the Inspectorate for Health Care. During his research he was trained as an epidemiologist at the Netherlands Institute of Health Sciences in Rotterdam (MSc in Clinical Epidemiology). As of August 2000 he will start his training as anaesthesiologist at the Leiden University Medical Center.
He is married to Wendy. They have three children named Mels, Jesse and Laure.